concePTION
SAFETY EVIDENCE ECOSYSTEM

Protocol for DP 1.2

Exposure to SSRI/SNRI and depression in pregnancy and long-term childhood outcomes: the effect of modifying factors.

This study will be conducted within the ConcePTION project of the Innovative Medicines Initiative under grant agreement No 821520.

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PASS information

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Research question and objectives	This study is based on electronic health care data from health care databases in six European countries and congenital anomaly registry data from 14 countries between 1995 and 2019. The primary objectives are to: 1) develop algorithms to identify and validate maternal depression, neurodevelopmental outcomes and breastfeeding in healthcare data sources. 2) describe patterns of SSRI/ SNRI antidepressant use before, during, and after pregnancy and during lactation. This includes describing co-medication patterns, predictors of discontinuation, switching patterns, and trajectories of use over time. 3) assess the association between in utero exposure to SSRI / SNRIs and neurodevelopmental outcomes and major congenital anomalies (CA). It will examine the potential additional impact of maternal depression, breastfeeding and concomitant exposure to P-gp or BCRP transporter substrates/inhibitors on risk of major CAs and neurodevelopmental outcomes in children.
Country(-ies) of study	Finland (Nationwide), France (Haute-Garonne), Germany (Nationwide sample), Italy (regional: Tuscany and E. Romagna), Norway (Nationwide), UK (Wales), and pan-European (EUROmediCAT) – *pending on results from the data characterisation (WP7).*

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1. List of abbreviations

AD Antidepressant

ADHD Attention deficit hyperactivity disorder

AED Antiepileptic drug

ASD Autism spectrum disorders

ATC Anatomical Therapeutic Chemical

BCRP Breast Cancer Resistance Protein

BMI Body Mass Index

CA Congenital Anomaly

CDM Common Data Model

DAG Directed Acyclic Graph

DAP Data Access Provider

DDD Defined Daily Dose

DSM-V Diagnostic and Statistical Manual of Mental Disorders 5th Edition

EFEMERIS Evaluation chez la Femme Enceinte des MEdicaments et de leurs RISques

ENCePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ETL Extract, Transform, and Load

FDA Food and Drug Administration

GDPR General Data Protection Regulation

GePaRD German Pharmacoepidemiological Research Database

HPA Hypothalamic–Pituitary–Adrenal

HV Health Visitor

ICD International Classification of Diseases

ID Intellectual development

IMD Index of Multiple Deprivation

IMI Innovative Medicines Initiative

IPTW Inverse-Probability-of-Treatment Weighting

LMP Last Menstrual Period

MCA Major Congenital Anomalies

MPR Medication Possession Ratio

NCARDRS National Congenital Anomaly and Rare Disease Registration Service

OHDSI Observational Health Data Sciences and Informatics

P-gp P-glycoprotein

PDC Percent Days Covered

POMME PrescriptiOn Médicaments Mères Enfants

RWD Real World Data

RWE Real World Evidence

SAP Statistical Analysis Plan

SES Socioeconomic status

SGA Small for Gestational Age

SNRI Serotonin-Norepinephrine Reuptake Inhibitor

SSRI Selective Serotonin Reuptake Inhibitor

TOPFA Terminations of Pregnancy for Fetal Anomaly

WCBA Women of Child-Bearing Age

2. Responsible parties

DP leads: Maria Loane and Florence Coste

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Team: Rebecca Bromley, Sue Jordan, Sandra Lopez-Leon, Heli Malm, Helen Dolk.

Development of algorithms: Elsie Grace, Anasofia Afonso

WP7 representatives: Claudia Bartoloni, Olga Paoletti (SAP review, R coding and SAP analytics)

Statistical expert: Joan Morris

Data Access Providers (DAPs):

- Finland, Finnish Registries: Maarit Leinonen, Visa Martikainen and Mika Gissler
- France, EFEMERIS and POMME: Christine Damase-Michel and Anna-Belle Beau
- Germany, GePaRD, Leibniz Institute for Prevention Research and Epidemiology – BIPS (BIPS): Tania Schink
- Italy, Agenzia Regionale di Sanita, ARS, Tuscany: Rosa Gini*
- Italy, Emilia Romagna: Amanda Neville and Elisa Ballardini
- Italy, Tuscany CA registry: Anna Pierini and Alessio Coi
- Norway, Norwegian Registries: Hedvig Nordeng and Angela Lupattelli
- Spain, Valencian Region: Clara Cavero
- UK, Wales (SAIL): Sue Jordan, Daniel Thayer
- Europe, EUROmediCAT Central Database: Maria Loane

Data from the following DAPs may be included in this study pending the availability of data:

- UK, Public Health Scotland: Rachel Wood and Marion Bennie

* Protocol review lacking

Due Date (Month 27)

Version 1.0 (01 October 2021)

3. Abstract

Title: Exposure to SSRI/SNRI and depression in pregnancy and long-term childhood outcomes: the effect of modifying factors

Rationale and background:
Approximately, 10-20% of pregnant women suffer from depression and 4-10% use selective serotonin reuptake inhibitor (SSRI) antidepressants during some stage of pregnancy. There is conflicting evidence regarding the risk of congenital anomalies and long-term neurodevelopmental outcomes such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) associated with in utero exposure to SSRI and serotonin and norepinephrine reuptake inhibitors (SNRI). Existing studies in the literature often lack the power to assess the effect of time varying confounders such as variation in maternal disease status, breastfeeding, and transient or chronic interactions with other medications on risk of adverse outcomes, and few examine other aspects of neurodevelopment. This study will help create evidence-based clinical guidelines on risks and benefits of antidepressant treatment in pregnancy.

Research question and objectives:
This study has 3 parts. Part 1 will develop algorithms to identify and validate maternal depression, neurodevelopmental outcomes and breastfeeding in healthcare data sources for use in the **medication utilisation study** (Part 2) and in the **medication safety study** (Part 3).

The objective of the **medication utilisation study** (Part 2) is to describe patterns of SSRI/ SNRI medication use before, during, and after pregnancy and during lactation. This includes describing co-medication patterns, predictors of discontinuation, switching patterns, and trajectories of use over time.

The objective of the **medication safety study** (Part 3) is to assess the association between in utero exposure to SSRI / SNRIs and neurodevelopmental outcomes. It will examine the potential additional impact of maternal depression, breastfeeding and concomitant exposure to P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) transporter inhibitors/substrates on neurodevelopmental outcomes in children. A second objective is to perform a **EUROmediCAT safety study** to assess the risk of major congenital anomalies associated with exposure to SSRI / SNRIs in the first trimester of pregnancy, and to evaluate the impact of co-medication with P-gp or BCRP transporter substrates on risk.

Study design
Medication utilisation and safety studies: These studies are multinational cohort studies using secondary data sources.
EUROmediCAT safety study: This is a case-malformed control study.

Population
Medication utilisation and safety studies: The study population will be all pregnant women aged between 15 and 49 years during the study period in each European data source contributing to these studies.

Sub-studies will include all women of child-bearing age, aged between 15 and 49 years, during the study period in European data sources with this information.
EUROmediCAT safety study: All live births, fetal deaths from 20 weeks gestational age and terminations of pregnancy for fetal anomaly (TOPFA) with a major congenital anomaly recorded in each registry/ health care database contributing to this study.

Variables:
Disease: Depression
Exposure: SSRI/SNRI antidepressants prescribed or dispensed during the exposure windows of interest.
P-gp and BCRP substrate and inhibitor status of individual SSRI/SNRI antidepressants.
Valproic acid (positive control).
All medications will be identified using the Anatomical Therapeutic Chemical classification system (ATC).
Outcomes: Neurodevelopmental outcomes (ADHD, ASD, Learning disability/intellectual development disorders and delayed infant language/motor development).
Major congenital anomalies (overall and by organ system).
Covariates: Maternal age at birth, calendar year of birth, parity, maternal marital status (if available), socioeconomic status, maternal education, maternal occupation, smoking status at start of pregnancy (if available), breastfeeding (if available), co-medications and co-morbidities.

Data sources:
The **medication utilisation and safety studies** are based on electronic health care data from health care databases in six European countries: Finland (Nationwide), France (Haute-Garonne), Germany (Nationwide sample), Italy (regional: Tuscany and Emilia Romagna), Norway (Nationwide) and UK (Wales).
The **EUROmediCAT safety study** is based on data from 17 registries and 3 healthcare databases in 14 European countries.

Study size:
We estimate that the six data sources contributing to the **medication utilisation study** will include 5.6 million pregnancies with medication exposures in the study period and over 6 million births, between 1996 and 2019.
In the **medication safety study,** power calculations show that if 1% of women use SSRI/SNRIs during pregnancy, we would require a sample size of around 360,000 children to detect a 50% increased risk for ASD/intellectual development disorders; and a sample size of 68,000 children to detect a 50% increased risk for ADHD. If 5% of women use SSRI/SNRIs during pregnancy, we would require a sample size of around 75,000 children to detect a 50% increased risk for ASD/intellectual development disorders, and a sample size of 14,000 children to detect a 50% increased risk for ADHD.
In the **EUROmediCAT safety study,** we estimate that we will have over 300,000 congenital anomaly cases (live births, fetal deaths from 20 weeks gestational age, and TOPFA), between 1995 and 2019.

Data analysis:
Medication utilisation studies: We will estimate the prevalence of medications used to treat depression among pregnant women 3 months before, during, and 3 months after pregnancy

and the prevalence in women of childbearing age. We will also provide prevalence estimates of placental transporter substrate and inhibitor co-medications during pregnancy. We will describe breastfeeding in a subset of the study population (defined by data availability) in relation to use of SSRI/SNRIs up to 1 year of age.

Medication safety studies: We will estimate the risk of adverse neurodevelopmental outcomes up to a maximum age of 18 following exposure to SSRIs/SNRIs during pregnancy. The women exposed to SSRIs/SNRIs during pregnancy will be compared with 2 main comparator groups:

- women who discontinued antidepressants (+/- a diagnosis of depression) at least three months before pregnancy or who had a depression diagnosis with no exposure to antidepressants before or during pregnancy (unmedicated disease comparator)
- women with no history of depression or mental health medications.

Each DAP will conduct univariate and multivariate logistic, poisson, or linear regression, Kaplan-Meier or Cox proportional hazards regression with robust standard errors as appropriate. Analysis will also include advanced confounder adjustment methods such as marginal structural models. We will use appropriate meta-analytic methods to pool effect estimates using random-effects models. The meta-analyses on aggregate data will allow for adjustment for country-optimized covariates.

EUROlinkCAT safety study: A case-malformed control analysis will be performed to estimate the risk (odds ratio) of a specific anomaly associated with first trimester exposure to SSRIs/SNRIs.

4. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	Date	Text	Text	Text
…	Date	Text	Text	Text

5. Milestones

Milestone	Planned date
Registration in the EU PAS register	October 2021
Study progress report 1 (Internal) –Final list of DAPs included in study; Part 1 results	March 2022
Statistical Analysis Plan (SAP)	April 2022
Study progress report 2 (Internal) -Part 2 results; Interim results for Part 3	March 2023
Final report of study results	March 2024

6. Rationale and background

The study described in this protocol is performed within the framework of the IMI project ConcePTION (https://www.imi-conception.eu/) Work package 1, Task 1.5. The core goal of Work Package 1 is to develop methods for better use of routinely collected healthcare data. The goal of Task 1.5 is to execute five demonstration projects (DP) for established and newly marketed products to tackle methodological or data source issues where progress and innovation are needed. This protocol addresses Demonstration project #1.2.

Serotonin and brain development

Approximately 10-20% of pregnant women suffer from depression and 1-10% use selective serotonin reuptake inhibitor (SSRIs) or serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants during some stage of pregnancy (Gorman, Kao and Chambers, 2012; Charlton *et al.*, 2015; Zoega *et al.*, 2015; Molenaar *et al.*, 2020). SSRIs/SNRIs pass through the placenta (Hendrick *et al.*, 2003; Rampono *et al.*, 2009; Merwood *et al.*, 2014; Pogliani *et al.*, 2017) and appear in cord blood (Laine *et al.*, 2003; Salisbury *et al.*, 2009) in proportion to the dose administered (Hendrick *et al.*, 2003).

Serotonin plays an important role in neurogenesis (Sodhi and Sanders-Bush, 2004). It has been suggested that prenatal exposure to SSRIs could potentially alter the development of the neuronal architecture, manifesting as poorer neurodevelopmental outcomes including cognitive and behavioural disorders in childhood, adolescence, or adulthood (Migliarini *et al.*, 2013; Sprowles *et al.*, 2016; Gingrich *et al.*, 2017). This may be the mechanism underlying delays in fine motor development at 3 years (Handal *et al.*, 2016) or autistic-like behaviours secondary to increased serotonin post-partum (Gemmel *et al.*, 2018), although research evidence has not been consistent. Prenatal exposure to SSRIs may also affect monoamine metabolism in the foetus, resulting in neonatal problems such as restlessness, tremor and incoordination (Laine *et al.*, 2003; Sprowles *et al.*, 2016). Epigenetic changes, activation of the hypothalamic–pituitary–adrenal (HPA) axis and transfer of cortisol and other mediators to the foetus are associated with both maternal depression and antidepressants (Kendall-Tackett and Hale, 2010; Gentile and Fusco, 2017) and their impacts on neurodevelopment are difficult to disentangle (Gemmel *et al.*, 2018).

Assessments of neurodevelopmental harms associated with exposure to antidepressants during foetal life are largely derived from observational cohort studies which collect primary data and population-based cohort studies using secondary data. Both have inherent methodological limitations. Traditional observational cohort studies recruit pregnant women with depression directly within hospital or community-based health care settings and the participants are followed up using study-specific standardised protocols often utilising sensitive assessments, administered in a blinded fashion (Hanley, Brain and Oberlander, 2015). However, such methodologies often offer low statistical power to detect adverse neurodevelopmental outcomes, and short follow-up periods (typically only up to pre-school age). The latter is a major limitation as brain development continues into adolescence, and some functions cannot be assessed until children have reached an age where more complex tasks are demanded. Cohorts derived from population-based electronic records alternatively, offer large numbers of exposed children often across a broader range of maternal indications and may follow children to adolescence. The use of such data poses a methodological challenge however, due to a reliance on diagnostic codes or service referrals (Mansournia *et al.*, 2017a) and multiple assessors who may not be blinded to the medication exposure history of the child.

A recently published systematic review of the literature on human studies on neurodevelopmental outcomes after prenatal medication exposures found highly

inconsistent results (Hjorth *et al.*, 2019): some link antidepressants to adverse neurodevelopmental outcomes such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and motor- and cognitive dysfunction. Others do not, and have attributed observed effects to the underlying illness, other residual confounding, differences in study populations, sample heterogeneity or short follow-up time. Specifically, there is conflicting evidence regarding the risk of ASD (Kobayashi *et al.*, 2016; Brown *et al.*, 2017; Mezzacappa *et al.*, 2017; Sujan *et al.*, 2019), ADHD (Morales *et al.*, 2018; Uguz, 2018; Halvorsen *et al.*, 2019) motor and language skills (Rotem-Kohavi and Oberlander, 2017) associated with in utero exposure to SSRIs. Conflicts are likely due to the methodological variation observed across different studies. For example, even in large population-based datasets it is important that children should have been followed up long enough for outcomes to be measured/identified and the average age of diagnosis may vary across countries. The follow-up period should be at least 2 years for infant psychomotor outcomes and at least 7 years, and preferably 12 years, for ADHD (to cover the time period when most children are diagnosed with ADHD). However, the longer the follow up period, the smaller the available study population with the required years of follow up data. Conversely, a shorter follow-up period may lead to bias towards the more severe cases.

Time varying confounders

The conflicting evidence to date for neurodevelopmental outcomes may in part be explained by time varying confounders such as variation in recording of maternal disease status, breastfeeding, and transient or chronic interactions with other medications. Underlying maternal mental illness in pregnancy and/or the postpartum period has been shown to be associated with suboptimal behavioural, cognitive, and socio-emotional development in the child (Field, 2011; Kingston, Tough and Whitfield, 2012; Kingston and Tough, 2014; Kobayashi *et al.*, 2016; Kaplan *et al.*, 2017; Wood *et al.*, 2018; Halvorsen *et al.*, 2019). Both maternal depression and SSRIs/SNRI use may alter and even resolve over time (Lupattelli *et al.*, 2018), hence maternal depression has the potential to be a time-varying confounder (Mansournia *et al.*, 2017b).

Directed acyclic graphs (DAG) showing confounding and time varying confounding are shown in Appendix 1. There are two distinct types of time-varying confounders: (1) time-varying confounding not affected by prior treatment, and (2) time-varying confounding affected by prior treatment (Burcu and Oehrlein, 2016). Conventional statistical methods can introduce bias in the presence of time varying confounding (Mansournia *et al.*, 2017b) particularly time-varying confounding affected by prior treatment (Burcu and Oehrlein, 2016). This can happen due to over-adjustment bias, which occurs as a result of blocking the effect of past exposure on outcome, mediated through later confounders, leading to a downward bias (underestimation of the effect) and selection (also known as collider stratification) bias, which occurs by inappropriately adjusting for a time varying confounder that may share a common cause with the outcome (Mansournia *et al.*, 2017b).

Effects of breastfeeding

It has been reported that children who were breastfed, particularly those breastfed for at least 6 months, when compared with children never breastfed, have lower rates of ADHD (Orsolini and Bellantuono, 2015), lower rates of ASD diagnosis (Al-Farsi *et al.*, 2012; Ravi *et al.*, 2016; Cheng *et al.*, 2019; Tseng *et al.*, 2019; Ghozy *et al.*, 2020), better cognitive outcomes (Orsolini and Bellantuono, 2015), higher IQ (Kramer *et al.*, 2008; Horta, de Sousa and de Mola, 2018), higher school achievement, and higher income in adulthood (Horta, de Sousa and de Mola, 2018). This effect persists after controlling for maternal IQ (Horta, Loret De Mola and Victora, 2015). Women with major depressive disorder who take antidepressants during pregnancy are less likely to intend to breastfeed and to initiate

breastfeeding (Gorman, Kao and Chambers, 2012; Lewis *et al.*, 2016; Leggett *et al.*, 2017) which may result in risk of poorer outcomes for their children. Furthermore, for women who continue to take SSRIs/SNRIs while breastfeeding there is the potential for the child to be exposed through breastmilk by an average of 3-5% (with a maximum of 10%) of maternal dose (Merlob and Schaefer, 2015). Unmedicated depression is also associated with increased exclusive formula feeding at 6-8 weeks (Jordan *et al.*, 2019). Breastfeeding therefore has potential to be both a confounding factor and a mediator for neurodevelopment in relation to maternal depression and SSRI/antidepressant use (Jordan *et al.*, 2021).

Effect of co-medications

A further factor which may alter levels of SSRI exposure in the womb is commonly used medications which may interact with placental passage of SSRIs. P-glycoprotein (P-gp, encoded by ABCB1 gene) and breast cancer resistance protein (BCRP, encoded by ABCG2 gene) are considered the two most important efflux medication transporters in the human placenta, restricting transfer of medications that are substrates for these transporters from mother to foetus. Their presence in the placenta suggests an important barrier function, preventing medications from entering the fetal circulation and protecting the foetus from exogenous chemicals. The function of these efflux transporters is inhibited by several medications which are commonly used during pregnancy (proton pump inhibitors, several antihistamines and macrolide antibiotics, among others) (Ellfolk *et al.*, 2020). Concomitant use of SSRIs or SNRIs that are transporter substrates with these inhibitors may increase fetal exposure to the antidepressant. As teratogenesis is a dose dependent phenomenon, higher exposure to a potentially harmful agent may result in an increased risk of fetal adverse effects (Jelínek, 2005). While little is known about the clinical significance of placental transporter protein mediated medication interactions, recent research suggests that these interactions may be associated with an increased risk of congenital anomalies (CA) (Ellfolk *et al.*, 2020). The impact of placental transporter protein mediated medication interactions on a range of neurodevelopmental outcomes is not known.

First trimester exposure to SSRIs and SNRIs has been associated with increased risk of major congenital anomaly (MCA), particularly severe cardiac defects (Myles *et al.*, 2013; Bérard *et al.*, 2016; Zhang *et al.*, 2017; Gao *et al.*, 2018). The evidence is conflicting however (Wang *et al.*, 2015) and evidence for an impact of placental transporter medicated proteins would contribute to the evidence base.

Determinants of antidepressant use

Age, sex and socioeconomic factors, such as education and income, as well as the interaction between these factors, can influence patient health and well-being and have an impact on access to, and use of, health care services and prescription drugs (Elseviers *et al.*, 2016). A study in Norway reported that apart from education level of parents, all indicators of low socioeconomic status were related to higher rates of antidepressant prescription, which could be due to the association of low socioeconomic status with higher levels of anxiety and depression (von Soest *et al.*, 2012). A study in Finland collected data on living arrangements and concluded that people who live alone were more likely to have material and psychosocial problems, which might have contributed to excess mental health problems in this population group (Pulkki-Råback *et al.*, 2012). Several sociodemographic and lifestyle factors have been associated with antidepressant use in pregnancy. These include age, maternal smoking habits, ethnicity, educational level, marital status, occupation, geographic region of residence, country of residence, parity, body weight and social class (Elseviers *et al.*, 2016); and heavy alcohol use and substance misuse referral (Jordan *et al.*, 2016).

Other determinants relate to the health care systems within countries, disease patterns, types of antidepressants used, prescribing guidelines issued by professional associations, pharmaceutical marketing practices, reimbursement/financing systems and the availability of non-pharmaceutical alternatives.

This Demonstration Project will help create evidence-based clinical guidelines on risks and benefits of antidepressant treatment in pregnancy and to establish appropriate methods for dealing with confounders/moderators in relation to long term neurodevelopmental outcomes.

7. Research question and objectives

The project will be organized in three parts:

- **Part 1.** Develop algorithms to identify exposures and outcomes
- **Part 2.** Medication utilisation study
- **Part 3.** Medication safety study

The results from Part 1 will inform Parts 2 and 3.

Part 1. Develop algorithms to identify exposures and outcomes

Part 1 will develop algorithms to identify and validate maternal depression, neurodevelopmental outcomes and breastfeeding in healthcare data sources for use in Parts 2 and 3. As the study uses secondary data it is not possible to use a gold standard when evaluating algorithms. Instead, where available, results will be compared to relevant published prevalence rates.

Maternal depression

Aims:

1. To compare a range of algorithms to identify depression before, during and after pregnancy.
2. To determine how the prevalence of depression varies in the pre-pregnancy, pregnancy and post-natal periods based on the algorithms used to identify depression.

Maternal depression will be identified based on the following codes (see Appendix 2):

- ICD-9: Major Depressive Disorder, single episode (296.2), Major Depressive Disorder, recurrent episode (296.3), Dysthymic Disorder/neurotic depression (300.4) Depressive Disorder not elsewhere Classified (311), Mental disorders complicating pregnancy childbirth or the puerperium (648.4).
- ICD-10: depressive episode (F32), Recurrent depressive disorder (F33), dysthymia (F34.1), mixed anxiety and depressive disorder (F41.2), postnatal/postpartum depression (F53.0).
- ICPC2: It is not possible to distinguish those who had just depression in ICPC2. Depressive disorder code includes depressive neurosis/psychosis; mixed anxiety and depression; puerperal/postnatal depression; reactive depression) (P76).
- Read codes: depression diagnosis, symptom and review codes.

Neurodevelopmental outcomes

Aim: Develop algorithms to identify neurodevelopmental outcomes.

The neurodevelopmental outcomes included in this demonstration project are based on work in ConcePTION Task 1.2 (Damase-Michel *et al.*, 2020) and will be finalised following assessment of their validity (**Part 1**) and quality and completeness (WP7 data characterisation). The neurodevelopmental outcomes of interest are:

1. ADHD: characterized by a persistent pattern (at least 6 months) of inattention and/or hyperactivity-impulsivity, with onset during the developmental period, typically early to mid-childhood (World Health Organisation, 2021). This will be based on:
    - ICD-10, ICD-9, ICPC-2 or Read codes (see Appendix 3)
    - Childhood medication use: Stimulant medication use will be used as a surrogate for ADHD diagnosis (Wong *et al.*, 2019): amphetamine/amfetamine (N06BA01), dexamfetamine sulfate (N06BA02), Methylphenidate (N06BA04), atomoxetine (N06BA09), dexmethylphenidate (N06BA11), lisdexamfetamine (N06BA12), guanfacine (C02AC02) and racemic amphetamine sulfate.
2. ASD: characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behaviour and interests (Ousley and Cermak, 2014; Masi *et al.*, 2017).
    - ICD-10, ICD-9, ICPC-2 or Read codes (see Appendix 4).
3. Learning disability or intellectual development (ID) disorders: characterized by significantly below average intellectual functioning and adaptive behaviour that are approximately two or more standard deviations below the mean (approximately less than the 2.3rd percentile), based on appropriately normed, individually administered standardized tests (Centers for Disease Control and Prevention, 2020).
    - ICD-10, ICD-9, ICPC-2 or Read codes (see Appendix 5).
4. Delayed infant development:
    - Motor developmental outcomes assessed at 24 months in France (EFEMERIS/POMME), (see Appendix 6).
    - Locomotion, manipulation, behaviour and speech development assessed by health visitors at 27-30 months - Wales.
    - Gross motor skills, fine motor skills, language, perception/cognition, social/emotional competence or interaction/communication problems if coded, e.g., based on ‘early detection examinations’, which are recommended and in some federal states mandatory, at 21-24 months using ICD codes – GePaRD.

Objectives:

a) To identify ADHD, ASD, ID disorders and delayed infant development in data sources
b) To characterise the outcomes by type of measurement used to assess neurodevelopment.
c) To calculate annual background prevalence of the ADHD, ASD, ID disorders and delayed infant development in each of the specific datasets.
d) To calculate the distribution of age of diagnosis or measurement in each of the specific datasets.

Breastfeeding

Aims:

1. Examine the availability, status, provenance and validity of breastfeeding data at any postnatal age in the databanks used in the demonstration projects.
2. Investigate selected factors associated with breastfeeding status including specified prescription medications and diagnoses.

Objectives:

a) Examine the availability, status, provenance and validity of breastfeeding data at any postnatal age in the DAPs used in this demonstration project
b) Report on the definitions and terminology used when recording infant feeding in each data source.
c) Compare breastfeeding rates and other data with external sources.

Part 2. Medication utilisation study

Part 2 will describe patterns of SSRI/ SNRI medication use before, during, and after pregnancy and during lactation. This includes describing co-medication patterns, predictors of discontinuation, switching patterns, and trajectories of use over time.

Research Questions:

1. What are the maternal characteristics associated with SSRI/ SNRI antidepressant medication use in pregnancy?
2. What are the predictors of SSRI/ SNRI antidepressant medication discontinuation?
3. What medications are commonly used concomitantly with SSRI/ SNRI antidepressants (co-prescriptions)?
4. How does SSRI/ SNRI antidepressant medication prescribing / dispensing change over the course of pregnancy and lactation?

Objectives:

a) determine the prevalence of recorded diagnoses of depression in women before, during, and after pregnancy. We expect the time window to be 12 months before and 12 months after pregnancy, but this is dependent on the findings from Part 1.
b) describe the pattern of SSRI and SNRI use in women 3 months before, during, and 3 months after pregnancy.
c) describe variation in prevalence of depression and SSRI/SNRI use by DAP, and by maternal characteristics such as age, parity, socioeconomic and/or educational status (where available) and trends over time in pregnant women.
d) describe patterns of P-gp or BCRP transporter substrates used concomitantly with SSRIs/SNRIs in women 3 months before, during, and 3 months after pregnancy.
e) identify predictors of SSRI and SNRI medication discontinuation.

In data sources with information on women of childbearing age (WCBA):

i. describe the incidence of pregnancy among WCBA using the medications of interest.
ii. describe the pattern of SSRI and SNRI use in WCBA
iii. describe patterns of breastfeeding in the study population in relation to use of SSRI/SNRIs up to 1 year of age.

Part 3. Medication safety study

Part 3 will assess the association between in utero exposure to SSRI / SNRIs and a) neurodevelopmental outcomes and b) major congenital anomalies (MCA). It will examine the potential additional impact of maternal depression, breastfeeding and concomitant exposure to P-gp or BCRP transporter substrates or inhibitors on neurodevelopmental outcomes in children. It will also examine the potential additional impact of P-gp or BCRP transporter substrates/inhibitors on risk of MCA.

Research Questions

Is SSRI/SNRI medication exposure during pregnancy associated with increased risk of adverse neurodevelopmental outcomes or MCA in children?

Objectives:

a) Is prenatal exposure to SSRIs / SNRIs 3 months before and during pregnancy associated with an increased risk of ASD, ADHD, ID disorders or delayed infant language or motor development in children, after taking into account maternal depression during and after pregnancy, and breastfeeding status (at 4-8 weeks).
b) whether comedication with prescribed P-gp or BCRP transporter substrates (S) or inhibitors (I) affects the risk of ASD, ADHD, ID disorders and delayed infant language and motor development.
c) whether in utero exposure to SSRI and SNRIs in the first trimester of pregnancy is associated with an increased risk of MCA, subgroups of MCA and signal anomalies identified in the literature and if there is additional impact of co-medication with P-gp or BCRP transporter substrates/inhibitors
d) investigate factors putatively associated with breastfeeding status including specified prescription medications and diagnoses.
e) whether prenatal exposure to SSRIs and SNRIs is associated with an increased rate of exclusive formula feeding after taking into account maternal depression during and after pregnancy and relevant covariates, using a subsample of data sources.

8. Research methods

8.1. Study design

Part 1 Develop algorithms: Algorithms will be developed to identify and validate data in the data sources contributing to this demonstration project.

Part 2 Medication utilisation study: Non-interventional longitudinal cohort study conducted with secondary data obtained from population-based registries, electronic medical records, or administrative healthcare databases in different European countries.

Part 3 Medication safety study:

Cohort study: A multinational European retrospective cohort study using secondary data sources.

Case-control study, with malformed controls: A multinational European case-control study, with malformed controls, using the EUROmediCAT central database and three health care databases.

8.2. Setting

In Part 1: Develop algorithms, validation of neurodevelopmental outcomes and depression diagnoses will be conducted on data sources from the following six countries: Finland, France, Germany, Italy, Norway, and UK (Wales). Breastfeeding data will be characterised in France (Haute-Garonne), Italy (Tuscany) and the UK (Wales) (**Table 1**).

Results of data validation and data characterisation (WP7) will determine the optimal combination of data years/ data sources to be included in the drug utilisation and safety studies.

In Part 2: Medication utilisation study, data from the following six countries will be included: Finland, France, Germany, Italy, Norway, and UK (Wales). The analysis of WCBA will be limited to data from Italy, Germany, Norway, UK, and the analysis of breast-feeding data will be limited to France, Italy (Tuscany) and Wales, UK, **Table 1.**

In part 3: Medication safety study, the cohort study on neurodevelopmental outcomes will include data from six countries (Finland, France, Germany, Italy, Norway, and UK), (**Table 1**). The sub-study exploring the impact of breastfeeding as a mediator/confounder will be conducted in three countries with neurodevelopmental and breastfeeding data: France, Italy (Tuscany) and the UK (Wales), **Table 1**. The **case-malformed control study** will use data from 17 EUROmediCAT congenital anomaly registries, and three health care databases (the English National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), Sweden and France (EFEMERIS)) covering 14 countries, see Table 2.

Table 1 *Region, number of pregnancies and availability of data on medication exposures, depression, neurodevelopmental outcomes and breastfeeding (pending data characterisation results)*

Region	Pregnancies per year (1,000)	Pregnancies with medication exposure in period covered (1,000)	Medication exposure[1] (Utilisation and safety studies)	Depression diagnosis (Validation, utilisation, safety[2])	Neurodevelopmental outcomes[2] (Validation, and safety studies)	Breast-feeding data (Validation, utilisation and safety studies)
			Years with available data			
Finland[3]	53	1,575	1996-2019	1996-2019	1996-2019	-
France Haute-Garonne (EFEMERIS)[3]	10	156	2004-2019	2004-2019	2004-2019	2004-2019
France Haute-Garonne (POMME)[3]	10	18	2010-2019 cohort 2015-2019 cohort	July 1st, 2010 - June 30th, 2011 July 1st, 2015 - June 30th 2016	2010-2019 cohort 2015-2019 cohort	2010-2019 cohort 2015-2019 cohort
Germany, GePaRD[4]	135	1,200	2006-2019	2004-2019	2006-2019	-
Italy Emilia Romagna	36	573	2004-2019	2004-2019	2010-2019	-
Italy Tuscany	30	480	2003-2019	2003-2019	2010-2019	2003-2019
Norway	60	890	2004 -2019	2008-2019	2008 -2019	-
Wales	33	726	1998-2020	2000-2020[5]	2000-2020	2005-2020

[1] Maternal medication or child ADHD medication.
[2] Primary care or hospital in/outpatient database sources. The table shows the **first year data** are available in a data source e.g. in Finland, hospital data starts 1996 and primary care starts in 2013; the table shows 1996 as the first year that information on neurodevelopmental outcomes is available. Please note that this is not the birth year.
[3] Finland and France do not have information on women of childbearing age in this study.
[4] GePaRD covers 20% of national population; n=about 180,000 pregnancies per annum, but successful mother-child link is expected in 135,000.
[5] Primary care data available for 79% of population.

*Table 2 Data sources contributing to the **Part 3** Case-control study*

Centre	Years	Births covered	Number of MCA cases
EUROmediCAT registries			
Belgium, Antwerp	1997-2017	408,928	10,785
Croatia, Zagreb	1995-2017	142,525	2,669
Denmark, Odense	1995-2018	124,430	3,466
France, Brittany	2011-2018	276,715	10,302
France, Paris	2001-2017	445,975	14,351
Germany, Mainz	1996-2015	65,174	3,019
Germany, Saxony-Anhalt	2000-2018	331,942	10,482
Ireland, Cork and Kerry	1996-2018	205,376	5,675
Italy, Emilia Romagna	1995-2018	807,695	18,407
Italy, Tuscany	1995-2018	664,325	14,698
Malta	1996-2017	93,510	2,988
Netherlands, Northern	1995-2018	433,311	12,157
Poland, excluding Wielkopolska	1999-2018	6,144,011	87,631
Poland, Wielkopolska	1999-2018	744,714	18,838
Spain, Valencian Region	2007-2017	501,943	12,866
Switzerland, Vaud	1997-2018	171,812	6,459
UK, Wales	1998-2018	699,612	25,718
Health care databases contributing aggregate data			
France, EFEMERIS	2005-2019	145,303	3,661
Sweden	2007-2016	1,106,663	30,368
UK, NCARDRS (Northern England)	2021	628,171	13,408
Total	1995-2021	**14,142,135**	**307,948**

Study period

Part 3 Cohort study: The study period will include data from 1 January 1996 or the first year pregnancy, medication AND subsequent neurodevelopmental outcomes are available (whichever is latest) and will end at the most recent date of the data source where medication AND subsequent neurodevelopmental outcome data are available. For example, if medication exposure in pregnancy is available from 2000 but infant neurodevelopmental outcome measured at 24 months is not available until 2009 only pregnancies from 2007 will be included in the study.

If data were extracted in December 2021 but the lag time for information about birth outcomes is more than a year, then the study period will end in December 2020.

The study period is the same for Part 2 (medication utilisation study) and Part 3 (medication safety study).

Part 3 Case-control study: The study period will include births from 1st January 1995 or the first year registries have medication data coded using Anatomical Therapeutic Chemical (ATC) classifications (whichever is latest) and will end in 2019. NCARDRS will contribute data for births born in 2021.

Study population

Part 1 (Develop algorithms):

Maternal depression

The population will include all WCBA aged between 15 and 49 during the study period and women with a pregnancy in each of the databases. For Finland and EFEMERIS/POMME only those with a pregnancy during the study period will be included. See **Table 1**.

Neurodevelopmental outcomes

The study population will consist of all children aged between 6 months and up to 18 years during the study period in each of the databases. Only children who can be linked to maternal exposures will be included.

Breastfeeding

All live births during the study period with survival of mother and infant to the time point breastfeeding is recorded.

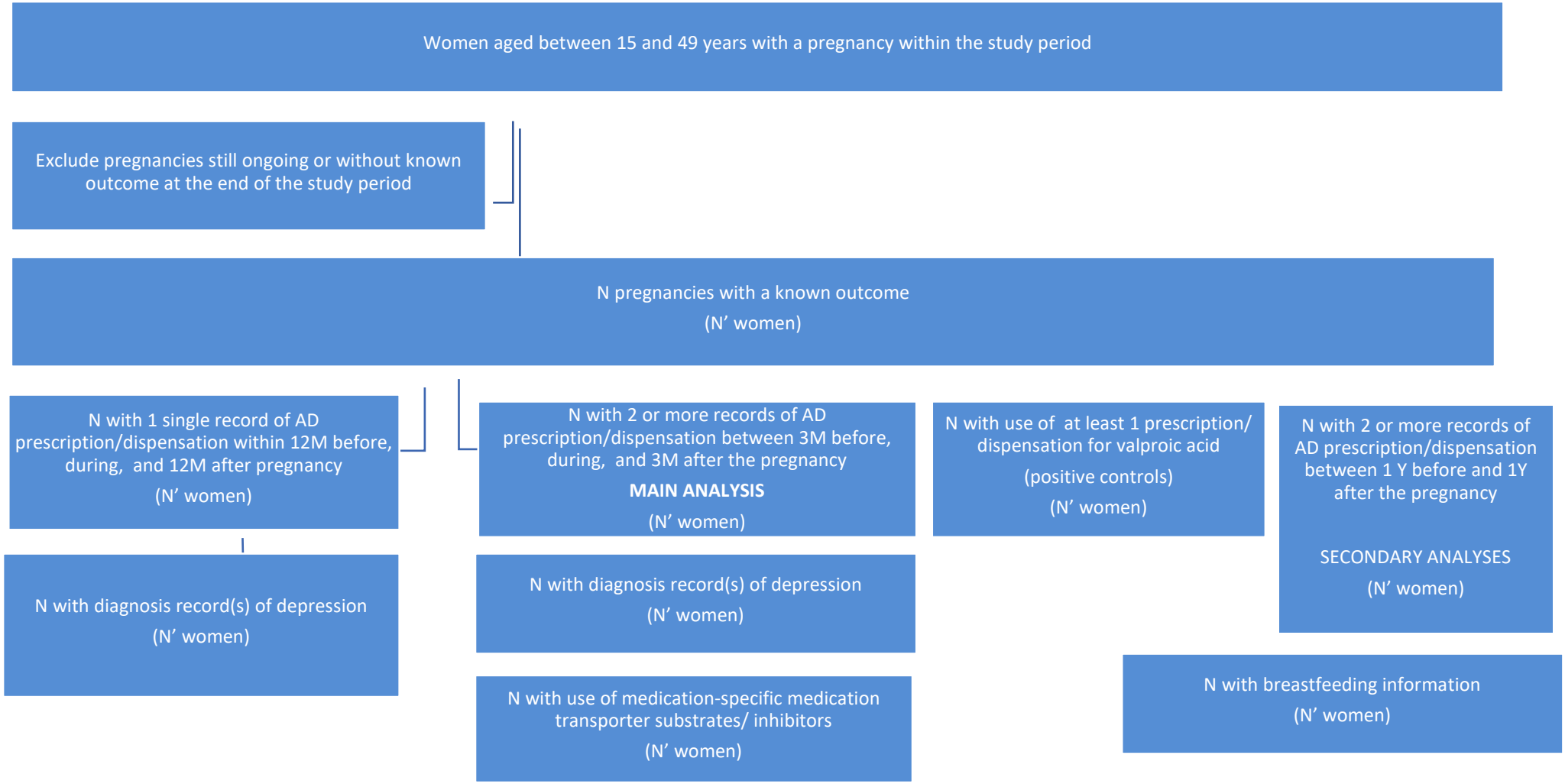
Part 2 Medication utilisation study

Study population for the main analyses: Establish a cohort of women present in each data source from 12 months before to 12 months after pregnancy with pregnancy outcome(s) identified during the study period. The main analyses will be based on this cohort i.e. pregnant women with at least 2 antidepressant prescriptions or dispensations between 12 months before, during, and 12 months after pregnancy, with or without a diagnosis of depression, see Figure 1. The date of the first record of antidepressant medication prescription or dispensation will define the index date.

Study population for secondary analyses: based on data sources with data on WCBA (15-49 years) (see Figure 1).

The index date for valproic acid derivative exposed pregnancies is the date of the first prescription for valproate recorded between 3 months before to the end of pregnancy. The index date for the population comparison group, i.e. women without any antidepressant prescription records or diagnosis of depression within one year prior or during pregnancy, is one year before pregnancy.

Figure 1 Flow chart of the main / secondary study cohorts



AD=Antidepressant

Exclusions

Maternal exclusions

A number of exclusions will be made.

1. Teratogenic medication exposure 3 months before to end of pregnancy or maternal conditions (see list in Appendix 7)

Child exclusions (due to increased risk of ASD and ADHD in these children).

1. Neurological or genetic conditions such as Tuberous Sclerosis

Note: Valproic acid exposures are included as positive controls in this study so they will not be excluded in this DP.

Where exposures associated with adverse outcomes cannot be determined in the data sources, this will be listed in the study limitations e.g. substance misuse & heavy alcohol use referrals.

Part 3: Medication safety study

Study population for the cohort study: The study population will include all women pregnant during the study period linked with a live birth. Where the datasets allow (some only have medication exposure 3 months pre-pregnancy), women must have been in the database for at least 12 months before they became pregnant in order to identify a depression diagnosis. (We expect this to be 12 months before pregnancy, but this is dependent on the findings from Part 1).

The population will be divided into the following:

1. Pregnant women with at least two antidepressant medication prescriptions/dispensations 3 months before pregnancy through to the end of pregnancy with or without a depression diagnosis ("**Exposed population**")
2. Pregnant women with a depression diagnosis or special reimbursement for "depression as a long term disability" before pregnancy with no exposure to antidepressants before or during pregnancy OR pregnant women with or without a diagnosis of depression who discontinued antidepressants at least 3 months before pregnancy and during pregnancy ("**Unmedicated disease population**")
3. Pregnant women with at least one prescription for valproic acid in the three months before pregnancy through to the end of pregnancy ("**Valproic acid positive control group**")
4. Pregnant women with no mental health medication, mental health diagnosis, special reimbursement for "depression as a long term disability" or valproic acid exposure at any time before or during pregnancy ("**Population comparison group**")

Exclusions

Exclusions will be as per **Part 2.**

For the case-malformed control study: The study population will include **r**egistries that record, or can link to, medication exposures in pregnancy using ATC classifications.

Cases of congenital anomaly ("registrations"):

Cases of major congenital anomaly include livebirths, fetal deaths (stillbirths and spontaneous abortions) from 20 weeks gestational age, and TOPFA (at any gestational age). Henceforth, these will be referred to as "registrants" so that the distinction can be made between cases and controls in the analysis.

Registrations will be classified into EUROCAT subgroups (see EUROCAT Guide 1.4 https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en#inline-nav-2 (EUROCAT Central Registry, 2013)) for analysis, and genetic syndromes will be analysed separately as controls, see below.

Exclusion criteria:

- registrations with a record of exposure to established teratogens: maternal epilepsy or antiepileptic exposure; maternal diabetes or insulin exposure; other established teratogenic exposure as detailed in Appendix 7**.**
- registration with teratogenic syndromes (congenital infections, valproate and other antiepileptic drug (AED) syndromes, diabetic embryopathies).
- registrations with a record of exposure to the medication(s) of interest but where timing of the exposure in the first trimester is unknown.
- TOPFA in registries where medication exposure is not recorded for TOPFA: Emilia Romagna, Valencian Region, Sweden
- Cases with minor anomalies only according to EUROCAT Guide 1.4.

8.3. Variables

Variables will be defined according to recommendations developed in the ConcePTION project (ConcePTION deliverable D1.2). The information items of interest to this project are shown in Appendix 8.

Exposure definition

Part 1 (Develop algorithms):

Maternal depression

Maternal depression may be identified based on medication exposure (see below), depression diagnoses (primary care, inpatient or outpatient diagnosis), special reimbursement status for depression as a chronic illness (the method used is dependant on the data source). See Appendix 2 for more detail.

Neurodevelopmental outcomes

ADHD, ASD and ID disorders will be identified based on primary care or outpatient diagnoses. ADHD may also be identified based on medication use. Infant developmental assessments are recorded as part of child developmental assessments in routine care. See Appendix 9 for more detail.

Breastfeeding

Many databases do not capture breastfeeding data, and across those which do there is no single standardised recording method. Both breastfeeding pattern and duration are of interest. Ideally the below information would be available (World Health Organization, 2018):

- early initiation of breastfeeding within one hour after birth
- any breastfeeding at 4–6 weeks
- exclusive breastfeeding at 4–6 weeks
- any breastfeeding at 6 months
- exclusive breastfeeding at 6 months
- giving any additional foods or fluids in the first 2 days after birth – as Indication of struggling to breastfeed.
- use of artificial teats and bottles in the first 6 months – to distinguish formula feeding from other feeding e.g. solids

The available breastfeeding data, in data sources contributing to this study, will be characterised in this validation exercise but variables of interest would include child age at breastfeeding assessment, duration of breastfeeding and how infant feeding is recorded (breastfeeding yes/no, exclusive breastfeeding etc.). Since few data sources collect breastfeeding information with optimal detail, some assumptions may need to be made, e.g. that an infant breastfed at 6 months is likely to have been breastfed at earlier ages. Decisions on the categories above will be made when we have access to the WP7 data characterisation results on breastfeeding data, see Appendix 10.

Part 2 and Part 3 cohort study

Medication exposure can be identified by prescription (prescribed, dispensed or reimbursed) records. The timing and dose (where available) of SSRIs and/or SNRIs (individually **and/or** as a class) will be defined by algorithms according to the quantity supplied (e.g. number of tablets), strength of unit dispensed (tablet) and prescription/dispensing dates.

The exposure sub-categories of interest are:

1. Any antidepressant

2. Any SSRI and/or SNRI

3. Any SSRI

4. Any SNRI

5. Individual substance observed among the top 3 (or 5) most frequent within a class

6. Any antidepressant other than SSRI or SNRI.

Medications will be classified according to the ATC classification system and the Defined Daily Dose (DDD). To quantify medication exposure, the quantities of medications prescribed or dispensed will be transformed in the standard units of measurement of the WHO DDD, defined as the average adult dose recommended for the main indication. DDD scores are thus measures of treatment intensity (drug burden). The duration of treatment and the dates of exposure will be estimated based on the frequency, amount and duration of exposure (representing the cumulative exposure). Medications prescribed/dispensed during the three months before the beginning of pregnancy will be included.

The medications investigated are listed in Table 3.

Table 3 Medications to be examined, ATC codes, name and defined daily dose (DDD)

	ATC	International non-proprietary name	DDD	DDD unit	Route
Any antidepressant medication	N06A				
SSRI	N06AB03	fluoxetine	20	mg	O
	N06AB04	citalopram	20	mg	O
			20	mg	P
	N06AB05	paroxetine	20	mg	O
	N06AB06	sertraline	50	mg	O
	N06AB08	fluvoxamine	100	mg	O
	N06AB10	escitalopram	10	mg	O
SNRIs	N06AX16	venlafaxine	100	mg	O
	N06AX17	milnacipran	100	mg	O
	N06AX21	duloxetine	60	mg	O
	N06AX23	desvenlafaxine	50	mg	O
Other antidepressant medications	N06 other than SSRI/SNRI listed above				

O=oral, P=parenteral

Concomitant medication use - P-gp and BCRP substrate and inhibitor status

Co-medication with medication-specific medication transporter substrates/ inhibitors have been identified from the University of Washington Metabolism and Transport Drug Interaction Database (UW Metabolism and Transport Drug Interaction Database, DIDB 2015) and previously published literature based on the DIBD data (Ellfolk *et al.*, 2020). The DIBD database is a manually curated knowledge base containing both in vitro and in vivo medication-medication interaction data developed by University of Washington's Department of Pharmaceutics, School of Pharmacy. In the Ellfolk et al. study, approximately 100 most commonly used medications in the pregnant cohort were identified for their P-gp and BCRP substrate/ inhibitor status (Ellfolk *et al.*, 2020). The transporter substrate/ inhibitor status for individual SSRIs and other SNRI antidepressants obtained from the DIDB are presented in Table 4 below.

Table 4 P-gp and BCRP substrate (S) and inhibitor (I) status of individual SSRIs and SNRI antidepressants included in the study, according to previous research (Ellfolk et al., 2020)

SSRI	P-gp	BCRP
Citalopram (N06AB04)	(S), (I)	
Fluvoxamine (N06AB08)	(I)	
Sertraline (N06AB06)	(I)	
Paroxetine (N06AB05)		(S; metabolite)

SSRI/SNRIs not listed above were not identified as P-gp or BCRP substrates or inhibitors in the DIBD 2015 database.

A list of medications, with their P-gp and BCRP substrate and inhibitor status, was included in (Ellfolk et al., 2020), see Appendix 11. This list will be updated for the SSRIs and SNRIs to take into account subsequent evidence from the literature.

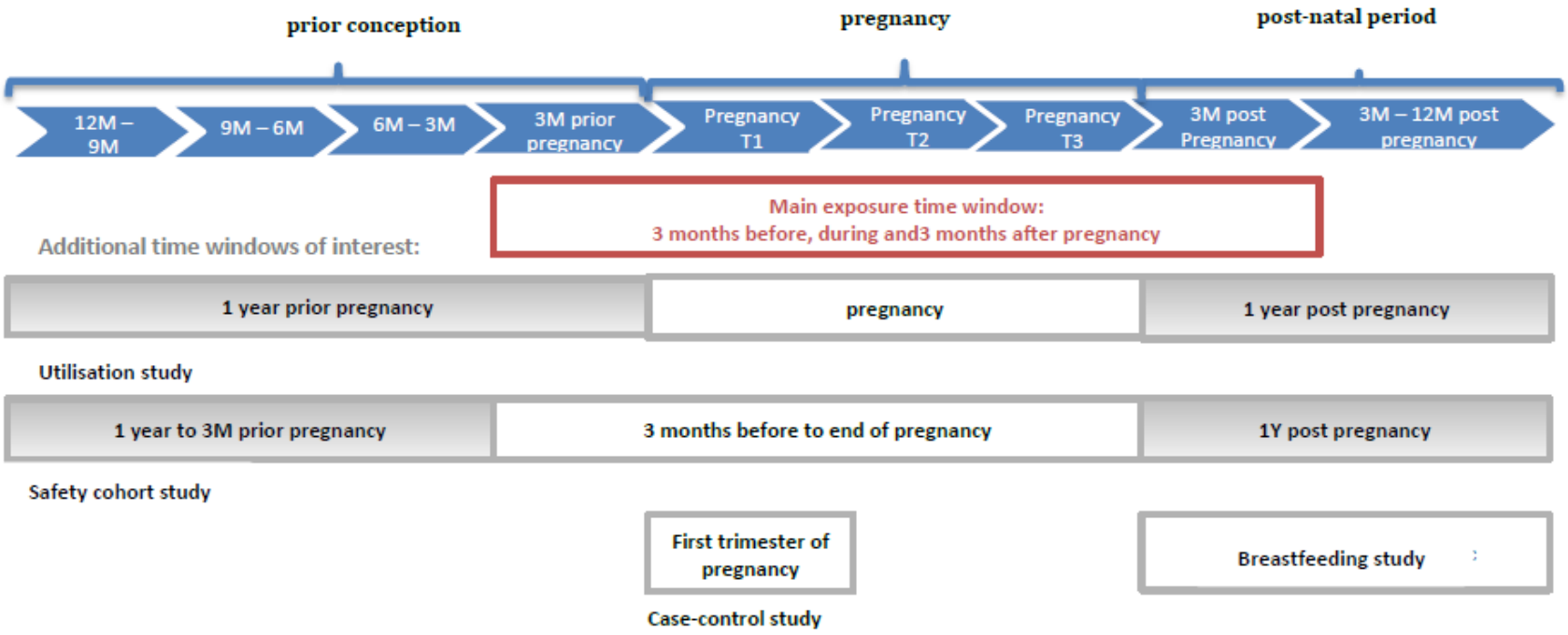
Valproic acid exposure

A single VPA exposure with or without antidepressants or other AEDs in the 3 months before to the end of pregnancy..

Exposure window

Various time windows will be considered for the exposure to medications or presence of depression or breastfeeding information (see Figure 2). The main exposure window in both the utilisation and safety studies is 3 months before pregnancy and during pregnancy. The case-control study will only examine first trimester exposures.

Figure 2 Time periods of interest in Part 2 (medication utilisation) and Part 3 (safety cohort study)



Part 3 case-control study

In EUROmediCAT, first trimester medication exposure is coded to the WHO ATC classification. Medication exposure is usually obtained from medical records created during pregnancy, but some registries use additional sources such as maternal interview, or prescription records (EUROmediCAT Central Database, 2017). Exposure is recorded if there is evidence that the woman took the medication in the first trimester – generally, preconception exposures for a medication with a long half-life are not recorded, although this may be specified in the text information (e.g. for drugs with long half-life like isotretinoin, fluoxetine/ norfluoxetine).

SSRI/SNRI exposures to be investigated are listed in Table 3.

Outcomes of utilisation study

The following estimates will be generated from the overall population of WCBA:

- prevalence of use of antidepressant medication, overall and by calendar year of birth

The following estimates will be generated from the population of women with a pregnancy, overall, by time period of interest (defined below) and by sub-population defined in Figure 1.

- prevalence of SSRI/SNRI use in the 3 months before pregnancy until 3 months after the end of pregnancy, overall and by calendar year.
- prevalence of SSRI/SNRI use and depression diagnosis in the 3 months before pregnancy until 3 months after the end of pregnancy, overall and by calendar year.
- prevalence of antidepressant use within the year following pregnancy, overall and by calendar year
- prevalence of antidepressant use and depression diagnosis within the year following pregnancy, overall and by calendar year

<u>Utilisation patterns of antidepressant medication</u>:

Patterns of medication use (details to be provided in Statistical Analysis Plan (SAP)) will be evaluated across various time periods. The main time period of interest is 3 months before the estimated pregnancy start until the end of pregnancy (whatever the outcome is), as well as the split between pregnancy exposure trimesters e.g. last menstrual period (LMP) to day 97 (trimester 1); day 98 after LMP to day 195 (trimester 2); day 196+ (trimester 3).

Other time periods of interest will be considered according to data availability, as per below:

- the pre-pregnancy exposure window: within 365 to 90 days before pregnancy estimated start date, and split by 90-day interval (pre1, pre2, etc)
- the post-pregnancy exposure window: within 365 days after estimated pregnancy end (whatever the pregnancy outcome is)
- Combination of the pre-pregnancy exposure window and the main time period OR/AND the main time period and the post-pregnancy exposure window

The issue of overlapping pregnancies (where the post pregnancy period in the first pregnancy overlaps with the pre-pregnancy period in the second pregnancy) will be dealt with in sensitivity analysis i.e. we will restrict analysis to a single pregnancy for women with more than one pregnancy in the study period.

Chronic use: repeated prescription/dispensing records without discontinuation, number of prescriptions fills, and sum of DDDs i.e. each ATC code has a DDD which gives the amount of active ingredients. These can be added up to give the cumulative exposure based on the frequency, amount and duration of exposure. The total medication exposure can subsequently be transformed into number of DDD per month of pregnancy (or per trimester of pregnancy). We will liaise with DAPs to get their definition of repeat prescriptions to identify chronic use. We will calculate:

- percentage of women receiving (prescribed/issued/dispensed) an SSRI or SNRI (= number of deliveries in which the woman received an SSRI prescription during the period of interest / total number of deliveries, overall and by time period of interest.

Discontinuation: the number of days without coverage by prescription/ dispensation is DAP specific. For instance, in Wales or Finland, 3 months (90 days) would be considered appropriate, whereas in Italy, only 2 packets of the same medication can be dispensed in one day. We will liaise with DAPs to get their country definition of discontinuation. We will calculate the:

- percentage of women who discontinued before pregnancy and did not restart i.e. there were no prescription records for SSRIs/ SNRIs during or after pregnancy
- percentage of women who discontinued before pregnancy and a prescription/ dispensation was recorded during trimester 2 or trimester 3
- percentage of women who discontinued before pregnancy and a prescription/ dispensation was recorded after delivery (or pregnancy end), see Figure 1
- percentage of women who discontinued during trimester 1 and did not restart i.e. there were no further prescription/ dispensation records for SSRIs/ SNRIs throughout the rest of the pregnancy or after pregnancy
- percentage of women who discontinued during trimester 1 and a prescription/ dispensation was recorded after delivery (or pregnancy end)
- percentage of women who had no prescription/ dispensation recorded during trimester 2 or trimester 3
- percentage of women with continuous use (i.e. without discontinuation) throughout pregnancy and three months post pregnancy

Switching:

A switch in antidepressant medication is defined as a discontinuation of the index (or first-line) medication, a prescription of a new (second-line) medication, and no renewal of the index medication. Patients who have a change in antidepressant medication together with a consecutive repeat prescription of the index one or with an overlap of the two medications for >30 days would be categorised as augmentation rather than a treatment switch (Mars *et al.*, 2017).

The occurrence of switching or augmenting will be expressed as a proportion of the population of pregnant women, overall and by trimester and after birth.

Adherence:

Adherence is a broad term defined as the extent to which a person's drug-taking behaviour corresponds with agreed recommendations from a health care provider (Grégoire and Moisan, 2016). For this study, the outcomes of interest to characterize adherence will be:

• Non-renewal: the extent to which a newly prescribed drug treatment is undertaken i.e.: proportion of women with a single record of antidepressant prescription/dispensation within 3 months before and 3 months after pregnancy (sometimes referred to as non-initiation).

• Persistence: the extent to which the treatment is taken for the recommended duration (based on local DAP knowledge). The percent days covered (PDC) and the number of discontinuation or treatment gaps (as defined above) observed during pregnancy are proposed as proxies of persistence.

For this calculation, we assume that all women use the drug in the defined daily dose, as we do not have access to information on what dosage was prescribed. The information available is number of DDDs dispensed and number of days between dispensations. We will allow for DAP-specific number of days of non-overlap (grace period) before we consider a period as uncovered (=discontinuation). A PDC cut-off of 0.8 is suggested to distinguish between treatment adherence and non-adherence.

Trajectory methods (modelling to be performed by DAPs using individual case data):

The intensity of drug exposure may be estimated using the longitudinal K means clustering algorithm. For the analysis, clusters of mothers with homogenous trajectories of medication exposure will be identified. The longitudinal K means clustering algorithm will be applied to create K clusters with homogenous trajectories, as empirically driven by the data. No assumption about the number of clusters is made prior to running the algorithm. Mean DDD trajectories will be plotted for each cluster and the shape described. It is anticipated that several clusters will be identified with homogenous trajectories of exposure around the pregnancy time period. Then, descriptive statistics will summarise distribution of exposure to each SSRI/SNRI as a class within each cluster (Hurault-Delarue et al. 2016).

Breastfeeding

Outcomes specific to the sub-population with breast-feeding information available:

The following estimates will be generated from the main population with a pregnancy episode:

- prevalence of breast-feeding in women with at least 2 records of antidepressant medication prescription or dispensation, stratified by presence of diagnosis of depression, overall and by calendar year, at the time of birth and during the post-natal period
- prevalence of breast-feeding in women without any antidepressant medication, stratified by presence of diagnosis of depression, at birth and during the post-natal periods, overall and by calendar year
- prevalence of breastfeeding at birth and in the post-natal period according to exposure to potential covariates, as outlined in Appendix 10.

Use of other medications:

The following estimates will be generated from the main population with a pregnancy episode:

- use of valproic acid (at least 1 prescription/dispensation) in pregnant women (three months before to the end of pregnancy), overall and by calendar year.

Concomitant exposure to SSRI/SNRI and to the following categories of substances will be described:

P-gp substrate/ inhibitor

Monotherapy with an SSRI/SNRI which is a P-gp substrate (SSRI/SNRI-P-gp-S) and an SSRI/SNRI-P-gp-S, and another medication which is a P-gp substrate or inhibitor:

- Citalopram monotherapy (allowing other medications prescribed so long as they are not listed as P-gp substrates or inhibitors)
- Citalopram co-prescribed with a medication that is a P-gp substrate or inhibitor (allowing one or more medications that are P-gp substrates or inhibitors)

Monotherapy with an SSRI/SNRI that is a P-gp substrate (SSRI/SNRI-P-gp-S) and an SSRI/SNRI-P-gp-S and another medication that is a P-gp inhibitor:

- Citalopram monotherapy (allowing other medications prescribed so long as they are not listed as P-gp substrates or inhibitors)
- Citalopram co-prescribed with a medication that is a P-gp inhibitor (allowing one or more medications that are P-gp inhibitors)

BCRP substrate/ inhibitor

Monotherapy with an SSRI/SNRI that is a BCRP substrate (SSRI/SNRI -BCRP-S) and an SSRI/SNRI-BCRP-S and another medication that is a BCRP substrate or inhibitor:

- Paroxetine monotherapy (allowing other medications prescribed so long as they are not listed as BCRP substrates or inhibitors)
- Paroxetine co-prescribed with a medication that is a BCRP substrate or inhibitor (allowing one or more medications that are BCRP substrates or inhibitors*)*

Monotherapy with an SSRI/SNRI that is a BCRP substrate (SSRI/SNRI -BCRP-S) and an SSRI/SNRI-BCRP-S and another medication that is a BCRP inhibitor:

- Paroxetine monotherapy (allowing other medications prescribed so long as they are not listed as BCRP substrates or inhibitors)
- Paroxetine co-prescribed with a medication that is a BCRP inhibitor (allowing one or more medications that are BCRP inhibitors)

A list of P-gp substrate/ inhibitors and BCRP substrate/ inhibitors is included in Appendix 11. This list will be updated before the analysis commences and may provide more information on individual SSRI/SNRI substrate/inhibitor status.

Outcomes of the Safety cohort and cross-sectional studies

Primary outcomes - Neurodevelopmental outcomes

The neurodevelopmental outcomes will be based on **Part 1**, see Appendix 9 .

Secondary outcomes

Major congenital anomalies

EUROmediCAT registries record all MCA in their registry area following EUROCAT definitions. Children with only minor anomalies are excluded (EUROCAT Central Registry, 2013). EFEMERIS, NCARDRS and Sweden will contribute aggregate data rather than individual level data. Sweden and NCARDRS record MCA using EUROCAT definitions.

EFEMERIS records diagnoses using ICD codes and these will be converted into the corresponding EUROCAT subgroups using a Stata script developed as part of the EUROlinkCAT project (Morris *et al.*, 2021).

Part 2 (Medication utilisation): Co-variates

The following maternal factors will be considered as covariates and included according to availability in each data source (see Appendix 12):

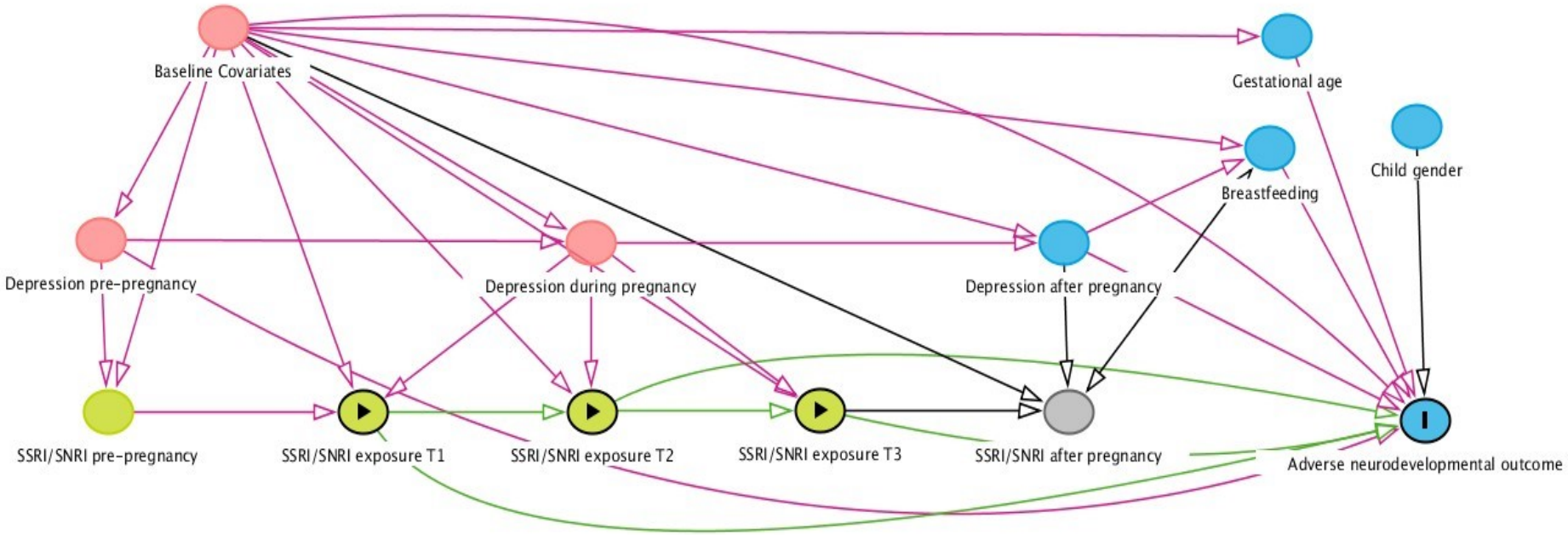
- Country, region and area (where applicable)
- Maternal age at birth in completed years
- Calendar year at index date
- Parity (as primiparous/ multiparous)
- Maternal marital status
- Maternal education
- Maternal occupation
- Socioeconomic status (SES)
- Smoking status – at start of pregnancy
- Multiple birth
- Other pregnancy(ies) in study period

Part 3 (Medication safety) Co-variates: confounders, mediators, moderators

Cohort study

A minimal sufficient adjustment set of covariates will be defined using DAGs (Greenland and Pearl, 2011) informed by literature review, see Figure 3 below for a preliminary example and Appendix 12 for covariates available across data sources.

Figure 3 A preliminary DAG



Baseline covariates would include for example maternal age, socioeconomic status and highest level of education. T1 – trimester 1, T2 – trimester 2, T3 – trimester 3.

Maternal depression

Maternal depression will be identified based on **Part 1**, see Appendix 2.

Breastfeeding

Breastfeeding status will be based on the information provided in Part 1, see Appendix 10.

Child factors

- Year of birth
- Sex
- Gestational age in completed weeks based on the best obstetric estimate. If the estimate is not available, gestational age will be calculated based on birth date and date of LMP
- Birth weight
- Small for Gestational Age (SGA), defined as <10th centile. We will use the <3rd centile, where available as this is clinically important.
- Neonatal adaptation problems, low Apgar scores <7 or treatment in NICU

Maternal factors

Information from the Utilisation study (Part 2) will inform the selection of maternal factors included in the Safety study

- Maternal age at birth in completed years.
- Parity
- Highest maternal education
- Socioeconomic status (SES) at birth, or at the start of pregnancy (dependent on when measured in DAP sources)
- Smoking status – at start of pregnancy: Non-smoker, smoker
- Substance misuse (where available) – based on referrals for addiction/treatment
- Alcohol use during pregnancy - yes/no (non-abstainer/abstainer).
- Heavy alcohol use (yes/no)
- Pre-pregnancy/first antenatal visit BMI

Case- control study

Covariates available in the case-control study are:

- Registry
- Birth year
- Maternal age at birth in completed years
- Co-medication
- Maternal illness before and during pregnancy

8.4. Data sources

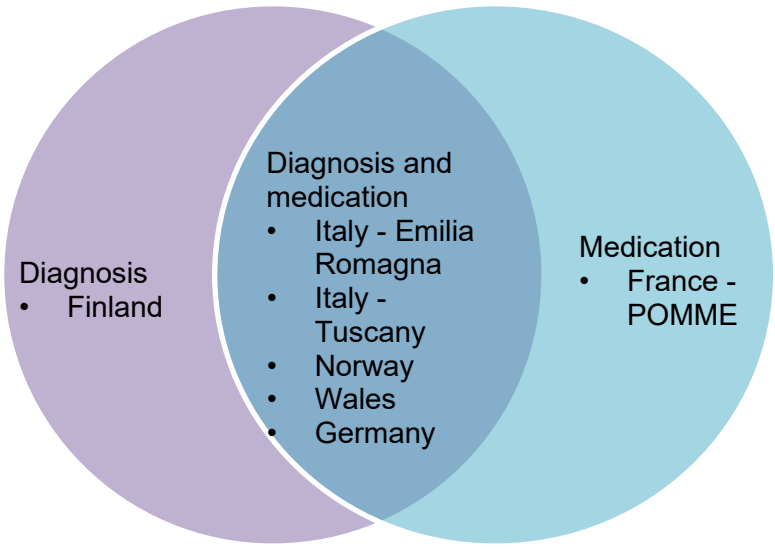
Data from healthcare and administrative databases will be used where available. Databases will be selected based upon availability of variables and data quality results from data characterisation undertaken when creating the IMI ConcePTION FAIR Data Catalogue. Different data sources may be used for different aspects of the project. **Table 1** shows the

time period and number of pregnancies covered for the potential data sources contributing to the medication utilisation study (pending data characterisation results).

Details of the neurodevelopmental outcomes available from each data source are shown in Table 5. ADHD may be identified based on 1) diagnosis only, 2) medication use and diagnosis and 3) medication use only, depending on the data source, as shown Figure 4 below. The rates of ADHD diagnosis produced using these three methods to identify cases will be compared in Part 1 and based on this a decision will be made whether to include all these data sources when examining risk of ADHD. We will also examine heterogeneity to assess if the results should be combined i.e. it is not valid to combine results if heterogeneity is high.

To increase the specificity of ASD and ADHD, a diagnosis should be present in a child's records at least once if it is recorded by a specialist and at least twice if it is recorded by a non-specialist before the child is considered as having that diagnosis. This will exclude the instances where a child is evaluated to rule out a diagnosis (Hjorth et al., 2019). For ADHD two recorded diagnoses by a non-specialist or a single diagnosis combined with a prescription for an ADHD medication would be sufficient. Where possible any diagnoses with an explicit qualifier "ruled out" or "suspected" will be excluded.

Figure 4 Identification of ADHD across data sources[6]



[6] EFEMERIS has no information on ADHD.

Table 5 Details of neurodevelopmental outcomes available in each data source

DAP	Infant development at 24 months		ASD, ADHD and ID diagnoses up to 7 years of age				ADHD medication use up to 7 years of age	
			Primary care diagnoses ICD-10, Read, ICPC-2		Hospital outpatient/mental health service diagnoses ICD-10			
	Years available	Children (1,000)	Years available	Children with 7 years of follow-up (1,000)	Years available	Children with 7 years of follow-up (1,000)	Years available	Children with 7 years of follow-up (1,000)
Finland			2012-2019	53	1996-2019	848		
EFEMERIS database	2004-2019[7]	136						
POMME database	2010 and 2015[7]	18					2010	8
Italy – Emilia Romagna					2010-2019	114	2004-2019	324
Italy - Tuscany					2010-2019	90	2003-2019	300
Norway					2008-2019	300	2004-2019	540
Wales[8]	2000-2020[9]	660	2000-2020	365	2000-2020	462	2000-2020	365
Germany	2006-2019[10]	1,335	Primary care does not exist in health system		2006-2019	555	2006-2019	555
Total sample		**2,131**		**418**		**2,369**		**2,110**

[7] Certificates completed at 24 months by a general practitioner or a paediatrician - include 14 items designed to detect children at risk of psychomotor development abnormalities
[8] Sample sizes assume GP data available for 79% of population
[9] Health Visitor child health developmental examinations at 27 months which assess vision, audio, locomotion, manipulation, behaviour and speech. Assessments are recorded as satisfactory, problem, observe, treatment, referral or not done
[10] ICD-10 codes recorded during standard care or 'early developmental assessments'.

The data sources with breastfeeding data, and how and when this is measured, are listed in Table 6 along with the neurodevelopmental outcomes available in the subset of data sources contributing to the breastfeeding sub-study. As can be seen from this table the breastfeeding information is available for the same or fewer years than neurodevelopmental outcomes.

Table 6 Details of breastfeeding measurement in each data source, years and number of children with breast feeding information available, years and number of children with both breastfeeding and neurodevelopmental outcome(s) available

Country	Breastfeeding information	Breastfeeding Years (1,000 children)	ND outcome(s) available	Breastfeeding and ND outcome(s) available Years (1,000 children[11])
France	Health certificates completed during mandatory medical examinations at 8 days, 9 months and 24 months old record breastfeeding (Yes/No), duration of breastfeeding (in weeks) and duration of exclusive breastfeeding (weeks)	2004-2019 (156)	Infant motor development at 2 years ADHD medication use	EFEMERIS 2004-2019 (136) POMME 2010 and 2015 cohorts (18)
Italy – Tuscany	How the new-born was fed during the hospital stay. Only breast milk; breast milk with the addition of water or other liquids other than milk, breast milk and infant formula, infant formula.	2003-2019 (480)	ASD, ADHD, ID disorders (ICD diagnosis) ADHD medication use	2010-2019 (90) 2003-2019 (300)
Wales	Health visitors record at birth, 10 days, 6 weeks and 6 months - 'any' breastfeeding	2005-2020 (630)	Infant development ASD, ADHD and ID disorder (ICD diagnosis) ADHD medication use	2005-2019 (540) 2005-2019 (Outpatient – 315) (Primary care diagnoses 249) 2005-2019 (Primary care medication use – 249)

The individual registries which contribute to the EUROmediCAT central database, and which have agreed to take part in ConcePTION are listed in Table 2 along with the years covered and number of CA cases.

[11] Estimates assume infant development assessed at 2 years with 7 years of follow-up for ADHD and ASD.

Table 7 gives an overview of data sources and their contribution to the different parts of the study.

Table 7 Data sources and their contribution to aspects of the study

		Medication utilisation (Cohort study)	Risk of adverse ND outcomes (Cohort study)	Risk of MCA (Case-control study with malformed controls)
Germany	GePaRD	✔	✔	
Finland	Care Register for Health Care, Register of Primary Health Care visits, Prescription Registry, Medical Birth Register, Register of Congenital Malformations	✔	✔	
France	EFEMERIS database	✔ ‡ BF	✔ BF	✔
	POMME database (France)	[12]	✔ BF	
Italy Emilia Romagna	SINPIA ER (Neuropsychiatry service for childhood and young people), SISM (regional mental health service), CEDAP (births), AFO/FED (dispensation of medications in community pharmacies/dispensations of medications from hospital pharmacies for outpatient use), SDO Scheda di dimissione ospedaliera (Hospital Discharge Record), CA registry (Emilia Romagna)	✔	✔	✔
Italy Tuscany	SALM – mental health services, CAP and CAP2 – birth registry, SPF – dispensation of medications in community pharmacies, FED – dispensations of medications from hospital pharmacies for outpatient use (Tuscany, Italy), CA registry (Tuscany)	✔ BF	✔ BF	✔
Norway	Norwegian Patient Registry (NPR), Norwegian Prescription Database (NorPD), Medical Birth Registry of Norway (MBRN)	✔	✔	

[12] Not included in the medication utilisation study as POMME is a subsample of EFEMERIS.

UK Wales	In-patient and out-patient PEDW records, Primary Care GP dataset, National Community Child Health Database (NCCHD), CARIS congenital anomaly registry (Wales, United Kingdom)	✔ BF	✔ BF	✔
	EUROmediCAT Central Database (Multi-National)			✔

BF= Breastfeeding sub study

8.5. Study size

Despite having a source population of more than six million births in **Part 2** (Medication utilisation, **Table 1**) sample size will be an issue in **Part 3 (Medication safety).** See **Section 8.9** study power.

Neurodevelopmental outcomes are available for a more limited time period than medication exposure in pregnancy, reducing the available sample size (**Table 1**). Delayed infant development requires at least two years of follow-up. ASD, ADHD and learning disability or disorders of intellectual development require a much longer follow-up period.

Breastfeeding data are available in a limited number of data sources and the available sample in the breastfeeding sub-study will be severely limited with at most two data sources containing information on the same neurodevelopmental outcome and breastfeeding (see Table 6).

Some subgroups of MCA are rare and the risk of MCA will only be examined in subgroups with at least 3 exposed cases. With fewer exposed cases a case series will be conducted.

8.6. Data management

All data have been prospectively recorded and are available via electronic health databases or administrative systems. In some countries several registries are linked using the personal identification number of each citizen in the country (Finland, Norway) or anonymisation of this (Wales).

ConcePTION will work using a distributed network approach, with a common protocol for data characterization, a common data model and common analytics. Individual case data will remain with the local data access providers (DAPs). Analysis scripts written in Stata, and double coded in R, will be sent to the DAPs to run on their local data. The results of the analysis scripts consisting of only highly aggregated results or effect estimates will be submitted by the DAPs to the ConcePTION Secure Data Platform. This platform can only be accessed by ConcePTION members taking part in the study.

For **Part 3** two forms of data will be included in the EUROmediCAT Central Database: a) individual case data transmitted yearly to the EUROmediCAT Central Database (most participating registries) and b) aggregate data tables requested for this study to supplement the central database. The latter data are being requested from NCARDRS for England, from Sweden, and from EFEMERIS in France. These aggregate tables will be combined with the individual level data for the analysis at Ulster University.

8.7. Data analysis

Each DAP will run the centrally produced analysis scripts on their own data, and upload **aggregated results or effect estimates** to the ConcePTION platform for meta-analyses by the postdoc researcher.

Part 1: Develop algorithms to identify exposures and outcomes

Descriptive statistics will be used to characterise the contents of variables containing information on maternal depression, adverse neurodevelopmental outcomes and breastfeeding. Algorithms will be developed and then used to determine the prevalence of maternal depression or adverse neurodevelopmental outcomes in each data source. These will be stratified by factors which may influence the ability of an algorithm to identify the outcome such as year, age, gender. See Appendix 2, Appendix 9 and Appendix 10 for more detail.

Part 2 (Medication utilisation)

Descriptive analysis: categorical variables will be summarized by frequencies and proportions of each modality, including the proportion of missing data. Mean, standard deviation and error, median and interquartile range will be provided for continuous variables. 95% Confidence intervals (CI) will be estimated [using Normal approximation for quantitative relevant parameters]. Cells with small numbers will be collapsed. See Table 8 below for an overview of the population groups and measures of disease/ exposures to be included in analysis.

Each DAP will conduct univariate and multivariate logistic regression locally based on an agreed SAP. The SAP will provide more details on modelling, including the longitudinal k-means clustering, described in **Section 8.3.**

Table 8 Overview of the population groups and measures of disease/ exposures to be included in analysis

Objective	Population	Measures of disease/exposure	Stratification
Depression in the WCBA population	WCBA with at least 2 records of antidepressant medication prescription or dispensation / WCBA without depression or treatment	Prevalence rate, (95% CI) (use of antidepressant medication)	Overall, by calendar year and by type of SSRI/SNRI
Pregnancy in the population with depression	Pregnant women with at least 2 records of antidepressant medication prescription or dispensation in 3 months before, during and 3 months after pregnancy / WCBA with depression or treatment	Incidence rate, (95% CI) (pregnancy among WCBA	Overall and by calendar year
Single record of antidepressant medication	Pregnant women with a single record of antidepressant medication prescription or dispensation i.e. non-renewal (or refilling) of prescription/ dispensation)	Prevalence rate, (95% CI)	Presence of depression diagnosis. Overall and by calendar year

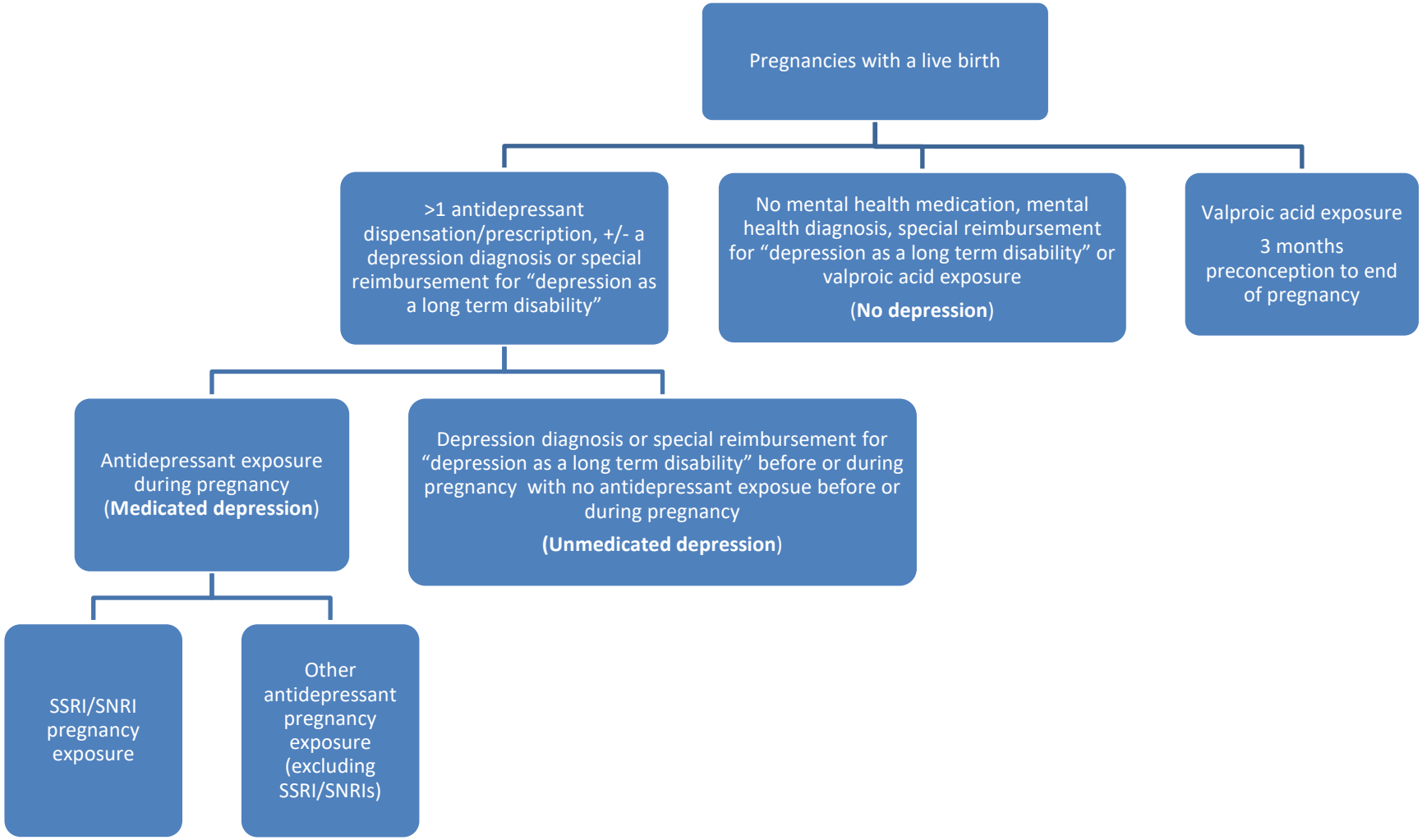
Use of antidepressant medication among pregnant women	(MAIN POPULATION) Pregnant women with at least 2 records of antidepressant medication prescription or dispensation in 3 months before, during and 3 months after pregnancy / Pregnant women without depression or treatment (general population of pregnant women)	Prevalence rate, (95% CI) (depression (with or without a diagnosis record) among pregnant women, before, during and after pregnancy)	Presence of depression diagnosis, Time windows of interest Overall, by calendar year and by type of SSRI/ SNRI
Utilisation patterns among pregnant women	MAIN POPULATION	Discontinuation Switching Adherence	By SSRI type

Part 3 (Medication safety)

Cohort study

The study population will be divided into a number of groups. medicated depression, unmedicated depression and no depression, see Figure 5 below.

Figure 5 Population groups of interest



Descriptive analysis

Maternal baseline characteristics (e.g. age, SES, smoking status, parity) will be summarized for each data source and for each group/cohort using descriptive statistics. Frequency tables including numbers and proportions will be generated for categorical variables. Mean, standard deviation, median and interquartile range and range will be provided for continuous variables.

Primary analysis

Each DAP will conduct univariate and multivariate logistic, poisson, or linear regression and Cox proportional hazards regression on their data source, based on an agreed SAP and a common script. If possible within the ConcePTION platform, this will also include advanced confounder adjustment methods, including propensity score methods, marginal structural models and inverse-probability-of-treatment weighting (IPTW) as appropriate to mitigate measured confounding.

When combining data from multiple DAPs, meta-analysis will be used to pool effect estimates using the random-effects model. The meta-analysis on aggregate data will allow for adjustment for country-optimized covariates (See Appendix 13).

Comparison groups

The risk of adverse neurodevelopmental outcomes following:

- SSRI/SNRI pregnancy exposure: Pregnancies with SSRI/SNRI exposure, with or without a depression diagnosis/special reimbursement for “depression as a long term disability”, three months before through to the end of pregnancy
- Other antidepressant pregnancy exposure: Pregnancies with other antidepressant exposure (Non-SSRI/SNRI), with or without a depression diagnosis/special reimbursement, from three months before pregnancy through to the end of pregnancy

will be compared with:

1. Pregnant women with a depression diagnosis or special reimbursement for “depression as a long term disability” before pregnancy with no exposure to antidepressants before or during pregnancy OR pregnant women with or without a diagnosis of depression who discontinued antidepressants at least 3 months before pregnancy and during pregnancy (“Unmedicated disease comparator”)
2. Pregnancies with no history of mental health medication, valproate exposure, or mental health diagnosis from a year before pregnancy through to the end of pregnancy (“Population comparison group”)

Valproic acid exposure three months before and during pregnancy will be used as a positive control, see later section on ‘**Valproic acid’**.

Some DAPs may not be able to use diagnosis information when creating the ‘unmedicated disease comparator’ and will rely on pre-pregnancy antidepressant exposures to create this group.

Analysis of Time varying confounders

Maternal depression is a time varying confounder affected by prior SSRI/SNRI treatment. If it is possible to identify maternal depression, over time, in the administrative datasets, and if possible within the ConcePTION platform, methods such as inverse-probability-of-treatment weighting, will be used to adjust for the confounding effect of depression, but not for the effect of SSRI/SNRI exposure on depression. This is dependent on whether the algorithms to identify maternal depression, developed in Part 1, can identify common time intervals across the data sources for e.g. 6 months or a year before pregnancy.

Ever/never exposure analysis

To estimate associations with "ever being exposed to SSRI/SNRI" in pregnancy and adverse neurodevelopmental outcomes crude and weighted analyses will be used. In the weighted analysis, adjustment for a sufficient set of confounders (defined using literature search and DAGs) will be done via the use of the inverse probability of treatment weight (IPTW), using the propensity score. Logistic regression models will be fitted to estimate the probability of 'SSRI/SNRI ever exposure', relative to the two comparison groups, given the set of sufficient confounders. If data allow, the hazard ratio (HR) for adverse neurodevelopmental outcomes, crude and weighted Cox regression analyses with robust standard errors, will be conducted using child age as time scale.

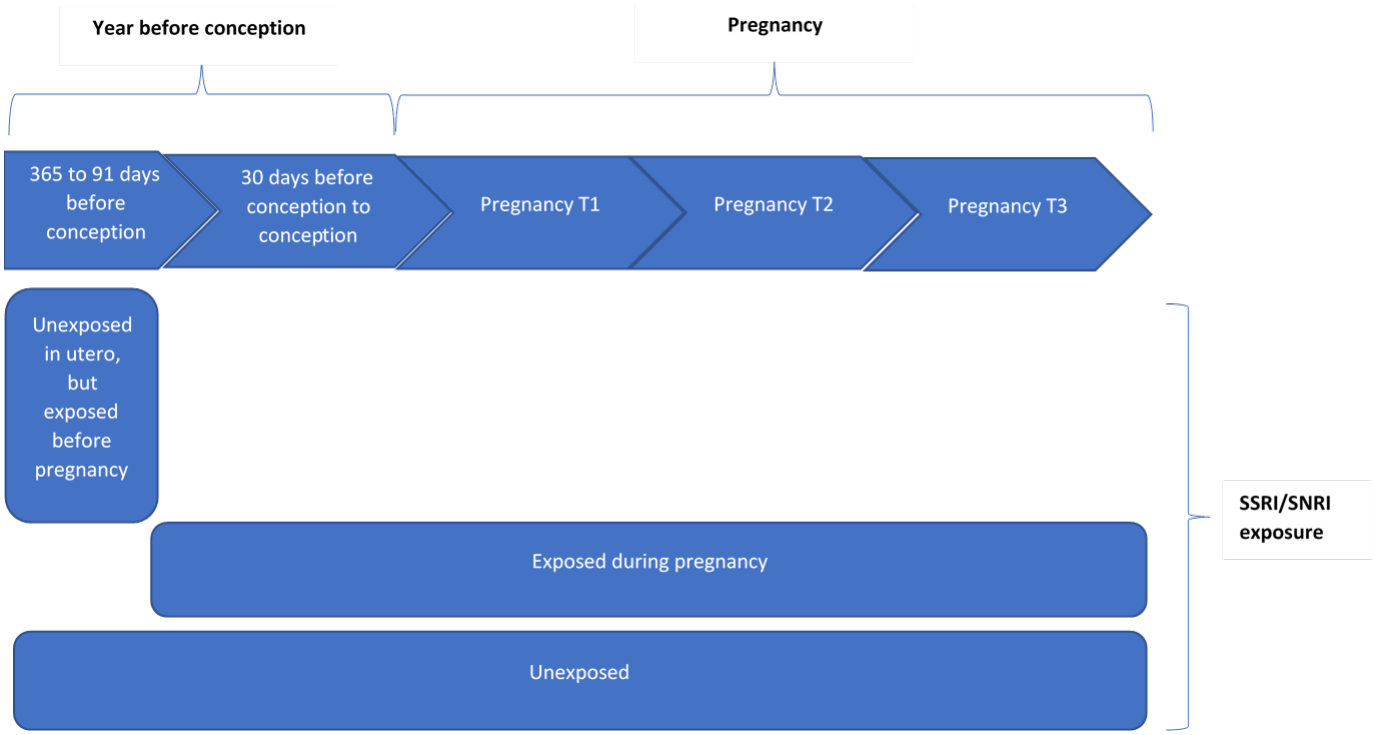
Timing of exposure analysis

To estimate associations by timing of exposure (see Figure 6), we will fit marginal structural models (MSM) to account for i) time-varying SSRI/SNRI exposure; ii) time-varying confounders (i.e. depression diagnosis) which are affected by prior SSRI/SNRI treatment. We will estimate the probability of SSRI/SNRI treatment using a pooled logistic regression in which the outcome is current treatment with an SSRI/SNRI in early, mid or late pregnancy, and covariates are maternal baseline factors, time-varying and time-fixed confounders. If data allow, we will then derive stabilized IPTW for each pregnancy at each time point. Marginal structural Cox models with robust standard errors will be fitted applying the IPTW, as described earlier.

Duration of exposure analysis

To estimate associations by duration of exposure, both crude and weighted analyses will be conducted, as for the ever/never exposure analysis. Logistic regression models will be first fit to estimate the probability of 'SSRI/SNRI exposure' identified in **part 2** relative to the two comparison groups, given the set of sufficient confounders. Cox models with robust standard errors will be fit applying the IPTW, as described earlier.

Figure 6 Exposure time periods for use in negative control and disease comparator analysis



Sub-analyses

P-gp substrate/ inhibitors and BCRP substrate/ inhibitors

The list of P-gp substrate/ inhibitors and BCRP substrate/ inhibitors associated with SSRI/SNRI exposures will be updated during the project. Based on the information available to date, within those exposed to SSRI/SNRI during pregnancy the impact of P-gp substrate/ inhibitors and BCRP substrate/ inhibitors on the risk of adverse neurodevelopmental outcomes will be assessed by examining the risk of adverse outcomes in the below groups, where exposure numbers allow.

P-gp substrate/ inhibitors

Monotherapy with an SSRI/SNRI which is a P-gp substrate (SSRI/SNRI-P-gp-S) vs. an SSRI/SNRI-P-gp-S, and another medication which is a P-gp substrate or inhibitor:

- Citalopram monotherapy (allowing other medications prescribed so long as they are not listed as P-gp substrates or inhibitors) compared with…
- Citalopram co-prescribed with a medication that is a P-gp substrate or inhibitor (allowing one or more medications that are P-gp substrates or inhibitors)

Monotherapy with an SSRI/SNRI that is a P-gp substrate (SSRI/SNRI-P-gp-S) vs. an SSRI/SNRI-P-gp-S and another medication that is a P-gp inhibitor:

- Citalopram monotherapy (allowing other medications prescribed so long as they are not listed as P-gp substrates or inhibitors) compared with…
- Citalopram co-prescribed with a medication that is a P-gp inhibitor (allowing one or more medications that are P-gp inhibitors)

BCRP substrate/ inhibitors

Monotherapy with an SSRI/SNRI that is a BCRP substrate (SSRI/SNRI -BCRP-S) vs. an SSRI/SNRI-BCRP-S and another medication that is a BCRP substrate or inhibitor:

- Paroxetine monotherapy (allowing other medications prescribed so long as they are not listed as BCRP substrates or inhibitors) compared with…
- Paroxetine co-prescribed with a medication that is a BCRP substrate or inhibitor (allowing one or more medications that are BCRP substrates or inhibitors*)*

Monotherapy with an SSRI/SNRI that is a BCRP substrate (SSRI/SNRI -BCRP-S) vs. an SSRI/SNRI-BCRP-S and another medication that is a BCRP inhibitor:

- Paroxetine monotherapy (allowing other medications prescribed so long as they are not listed as BCRP substrates or inhibitors) compared with….
- Paroxetine co-prescribed with a medication that is a BCRP inhibitor (allowing one or more medications that are BCRP inhibitors)

At present no analysis of the P-gp inhibitors (fluvoxamine or sertraline) is planned but this may change once the list of P-gp substrate/ inhibitors and BCRP substrate/ inhibitors is updated.

Missing data

The proportion of missing data will be described for each variable by birth year and patterns of missingness will be explored by cross-tabulating variables with missing data against exposure and outcome (Lupattelli, Wood and Nordeng, 2019). Depending on the pattern of missing data, and what is feasible within the ConcePTION platform, complete case analysis or imputation of missing values, such as single imputation or multiple imputation, will be used (Sterne *et al.*, 2009; Lupattelli, Wood and Nordeng, 2019).

Sensitivity analyses

Several sensitivity analyses will be performed to assess the robustness of results. It is anticipated that the below will be conducted but additional sensitivity analyses may be needed once data are characterised and preliminary results available.

- Restrict analysis to those exposed 30 days before LMP to end of pregnancy – instead of 90 days before LMP to end of pregnancy
- Restrict to the first pregnancy for women with more than one pregnancy in the study period
- Include those with a single diagnosis of ASD or ADHD (instead of at least two diagnoses or one diagnosis and no ADHD medication)
- Include pregnant women with one SSRI/SNRI in the exposure window (3 months before, and throughout pregnancy)
- Restrict to those who used SSRIs/SNRIs between 365 and 182 days before conception (instead of 365-90 days before conception) to allow for possible epigenetic changes by drug exposures.

Table 9 gives an overview of the data analysis for the cohort study. It should be noted that the analysis for the cohort study is dependent on the results from Part 1 as well as the ability of DAPs to run analyses on individual data. Limited resources and time constraints may affect the amount of analysis that can be performed by each DAP, so we will prioritise what can be done in the time available.

Table 9 Overview of data analysis according to objective in Part 3

Objective	Study design	Cohorts	Outcome	Exposure	Stratification	Statistical method	Measure of association
Main analysis[13]							
a	Cohort	Pregnant women with depression	Adverse ND outcomes	SSRI/SNRIs (as defined in Exposure section 8.3)	By type of SNRI/SNRI	Logistic regression, Poisson regression, Kaplan-Meier and Cox proportional-hazard regression model	Odds Ratio (OR and 95%CI, Relative Risks (RR) and 95% CI and Hazard Ratio (HR) and 95% CI
b	Cohort	Pregnant women with SSRI/SNRIs exposure	Adverse ND outcomes	SSRI/SNRIs (as defined in Exposure section 8.3)	Co-medication with P-gp substrate/ inhibitors or BCRP substrate/ inhibitors	Logistic regression, Poisson regression, Kaplan-Meier and Cox proportional-hazard regression model	Odds Ratio (OR) and 95%CI, Relative Risks (RR) and 95% CI and Hazard Ratio (HR) and 95% CI

[13] Analysis of time varying confounders uses same statistical techniques as the main analysis

Breastfeeding sub-study

With the exception of the breastfeeding variables, this sub-study will be confined to existing variables.

a. Description of data available, with timeframes, in each country
b. Selection of a common outcome measure, likely 4-8 weeks
c. Investigate selected factors associated with breastfeeding status including specified prescription medications and diagnoses e.g. Associations with breastfeeding at this time point (illness [depression in DP 1.2], prescriptions of SSRI/ SNRI/antidepressants in trimester 1 but not 2 & 3, prescriptions in trimesters 2 or 3, unmedicated depression). Covariates: SES, age, BMI, SGA, gestational age, smoking, parity (primip / multip). Sensitivity analyses: exclude substance misuse/heavy alcohol use, multiples (including twins), congenital anomalies.
d. Breastfeeding as a predictor of neurodevelopmental outcomes. Analyses as above:
    1. with and without breastfeeding variable to test for the possibility of breastfeeding being a mediator variable.
    2. with a breastfeeding * antidepressant interaction variable to test moderation
    3. with prescription of SSRI/ SNRI/ antidepressants during lactation to test confounding
e. mediator analysis if conditions are met i.e. positive results in c & d1 above.
f. collider bias - prevalence of breastfeeding in the included and excluded infants to test for selection and potential collider bias (Wales data only).

Table 10 below gives an overview of the data analysis plan.

Table 10 Overview of breast-feeding data analysis

Objective	Population	Frequencies and proportions	Stratification	Measure of association
Prevalence of breast-feeding	A. women with depression treated i.e. at least 2 records of antidepressant medication prescribed or dispensed)	N (%)	by presence of diagnosis of depression, (before and during the pregnancy of interest), overall and by calendar year, at the time of birth and during the post-natal period	A/C Unadjusted OR (95% CI)
Prevalence of breast-feeding	B. women without any antidepressant medication, with depression (unmedicated depression)	N (%)	during the post-natal period, overall and by calendar year	B/C Unadjusted OR (95% CI)
Prevalence of breast-feeding	C. women without any antidepressant medication, without depression (general population)	N (%)	during the post-natal period, overall and by calendar year	
	D. women with medication but no diagnosis of depression			D/C

Valproic acid

The risk of ASD, ADHD, learning disability or disorders of intellectual development and delayed infant development among pregnancies with **valproic acid exposure** in the three months before pregnancy through to the end of pregnancy will be **compared to** the risk in the **population comparison group**.

Case-control study

Three analytic approaches will be taken:

a) Case-malformed control study with prior hypothesis
b) Case-malformed control study without prior hypothesis
c) Case series review (where less than 20 exposures per medication are recorded in the database).

Case-malformed control study with prior hypothesis.

Cases will be registrations with a congenital anomaly for which a published signal exists in the literature relating to the class of medication investigated. A preliminary list, which will be updated before the analysis, is included in Appendix 14. Controls will be all other registrations divided into non-genetic registrations and genetic syndrome registrations (i.e. two control groups). The non-genetic registrations will be the primary comparison group. If the non-genetic group is small due to a large number of registrations being assigned as cases, the two control groups may be combined.

Odds Ratios (95%CI) will be calculated comparing the proportion of exposures to the medication(s) of interest in the case group to the control group. Results will be shown for subgroups with at least 3 exposed cases.

Case-malformed control study without prior hypothesis

Each EUROCAT subgroup included in the non-genetic control group as described above will be considered a “case” group in turn, compared with all other (non-genetic) controls. Where there are no prior hypotheses, this will be the main analysis. If this analysis reveals a specific association between a EUROCAT subgroup and the medication of interest, a sensitivity analysis will be performed in the prior hypothesis design above, excluding that anomaly from the control group.

Odds ratios will be calculated with 95%CI, with adjustment for multiple testing by controlling the False Discovery Rate using the method proposed by Benjamini and Yekutieli (2001) (Benjamini and Yekutieli, 2001). Results will be shown for subgroups with at least 3 exposed cases across all DAPs and where small number restrictions allow.

Case series review.

When the number of registrations exposed to a medication is very low (below 20), and there is no prior signal to investigate, the series of exposed registrations will be reviewed for evidence of unusual MCA patterns (e.g. multiple MCAs, rare MCAs), and to contribute to the case report literature. It is expected that most such cases may be chance associations with the medication in question.

Case lists will be reviewed by a panel (epidemiologist, medical geneticist, pharmacologist). If a finding of concern is made, registries will be asked to find out more information about exposure (e.g. exact timing, dose) where possible.

Case reviews will be published in such a way that no identifiable information is included. All publications will be reviewed by participating registries before submission to check disclosure risks.

8.8. Quality control

The studies will be conducted in line with the ENCePP Code of Conduct for scientific independence and transparency, and the FAIR (Findable, Accessible, Interoperable, Reusable) principles of the ConcePTION project.

Each DAP will be responsible for the extraction, transformation, and loading (ETL) of their original data to the ConcePTION Common Data Model (CDM). Standardized scripts will be written by the group of statisticians in R for data characterization, and sent, along with instructions, to participating DAPs using the ConcePTION task management system.

The DAPs are responsible for converting their data to the CDM using their preferred software and subsequently running the provided R script against the CDM-converted data. The results of the R-script will be submitted to a computing platform that can be accessed remotely by DAPs and ConcePTION partners using authentication. Access to each DAP's results on the platform will be limited to the DAP, WP1 public partner statisticians, and WP7 public partner statisticians. Results can only be used following approval from each respective DAP.

Data quality will be assessed according to a clear framework based on the ADVANCE database characterization process, the United States FDA Sentinel System data quality indicators the Observational Health Data Sciences and Informatics (OHDSI) data quality dashboard (in development), and EUROCAT indicators for population-based healthcare data sources. The data quality and characterization checks described below will take place in collaboration with partners. All data will remain local and only summary measures described below will be inspected in collaboration with WP7 partners and the task force for data transformation. This process will proceed iteratively in collaboration with each DAP until consensus on fitness for purpose has been reached between WP7 and the DAP. The result of this consensus process and some core results will be made available on the catalogue in a private area for inspection by investigators and DAPs. For all indicators and characterization output resulting in a cell count less than 5, counts will not be reported and will be replaced with "<5" programmatically to meet small number restrictions where applicable.

EUROmediCAT data will also be characterized and sent to each registry for approval and a decision taken, in agreement with the registry, that they are "fit for purpose". Since the exposure-MCA events are rare, data cleaning will consist of sending lists of exposed registrations to each participating registry to confirm the exposure, the outcome (MCA), and the timing of exposure (first trimester). The text information transmitted with exposed registrations regarding exposure, diagnosis, family history and general information will also be examined for relevant information. All cases of teratogenic syndromes should be individually assessed before exclusion, to check for the coding of the medication of interest as an embryopathy.

Level 1 data checks review the completeness and content of each variable in each table of the ConcePTION CDM to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (e.g., data types, variable lengths, formats, acceptable values, etc.).

This is a check conducted in collaboration with DAPs to verify that the ETL procedure to convert from source data to the ConcePTION CDM has been completed as expected. Formats for all values will be assessed and compared to a list of acceptable formats. Frequency tables of variables with finite allowable values will be created to identify unacceptable values.

Level 2 data checks assess the logical relationship and integrity of data values within a variable or between two or more variables within and between tables. Examples of this type of check include: prostate cancer diagnoses in female subjects, observations occurring after a recorded death date, very high birth weight in combination with preterm birth, etc. In this check, we will assess records occurring outside of recorded person time (i.e. before birth, after death, or outside of recorded observation periods).

Level 3 checks will quantify subpopulations of interest. Counts of codes extracted to identify each event and exposure of interest will be calculated overall and by calendar year.

Following completion of level 1, 2 and 3 checks, WP7 will review results with DAPs and assess any detected errors.

8.9. Limitations

A severe limitation will be not having access to case data to test models.

Ascertainment of exposure

Reliance on prescription or dispensing records means that it is not possible to tell if a mother took the medication which was prescribed/dispensed. Also, the assumption of daily dose intake based on the DDD may incorrectly estimate the treatment length associated with a specific prescription/dispensation date. Both limitations may lead to misclassification of exposure status overall and/or by pregnancy trimester because some women may not take the medication or may stockpile the medication and take it later. Women in SSRI/SNRI exposed group who do not adhere to their prescribed medications will have similar outcomes to those in the untreated group with depression, minimising any differences between groups.

Some of the P-gp or BCRP transporter substrates (S) or inhibitors (I) do not require a prescription. The use of these over the counter medications will therefore be underestimated in the administrative prescribing data sources. This would lead to an underestimation of their effect.

Few data sources collect breastfeeding information and those which do often collect limited information such as breastfeeding at birth. Initiation of breastfeeding is however usually regarded as indicating intention, rather than successful breastfeeding (Fiona McAndrew, Jane Thompson, Lydia Fellows, Alice Large, 2012).

Ascertainment of disease and disease severity

The indication for the medication is not comprehensively available in any of the prescribing databases in this study. Administrative databases may lack, or incompletely record, clinical details such as indications for prescriptions and severity of illness. If identification of maternal mental illness, is based on hospital diagnoses only it will be limited to the more severely affected (Morales *et al.*, 2018). In some countries clinicians may be reluctant to record a depression diagnosis, and instead may record depression symptoms, as the diagnosis triggers a minimal required follow-up or because it has implications for the employment or insurance status of the patient. This may mean women with depression are under identified in some data sources. Some pre-pregnancy depression diagnoses may be missed as women may have been diagnosed before the start of the period used here to identify pre-pregnancy depression. This will be less of an issue for pregnancy and post-pregnancy depression as women are monitored much more closely by the healthcare system during and immediately following pregnancy than they are pre-pregnancy. The clinical course of depression such as worsening or improving symptoms and resolution of depression / depressive symptoms, will also be difficult to follow in the limited information available in the administrative datasets. Likewise, the success of antidepressant treatment may not be obvious so when interpreting the results it must be remembered that poorly controlled depression among the SSRI exposed group may further confound results (Fitton *et al.*, 2020).

There will be some degree of under ascertainment in relation to the neurodevelopmental outcomes of interest as children who receive a diagnosis of ASD/ADHD in a private healthcare setting will not necessarily be identified as a case in the administrative healthcare

datasets. Similarly, children whose ASD, ADHD or delayed infant development was undiagnosed at the end of follow-up will not be identified as a case. Children with symptoms of these conditions but who do not quite meet the diagnostic criteria would not be detected in this study. Those who are identified at a younger age are likely to be the more severely affected and this may bias towards non- exposure causes such as genetic diagnoses. Approaches to neurodevelopment diagnosis may vary across included countries and even regions of a specific country. The years of follow up across data sources also varies which may also introduce a source of bias when comparing rates across databases.

The use of medication for ADHD across Europe will vary and this in turn will affect the ability to identify ADHD in those data sources where medication is the only indicator of ADHD. Some medications, such as bupropion or modafinil, may be used off label to treat ADHD. As such we may misclassify such children as not having ADHD if there is no diagnosis information. This will be rare though and is preferable to classifying all children taking these medications as having ADHD.

Limited/missing covariate information

The age of diagnosis of ASD, ADHD, disorders of intellectual development and delayed infant development might be affected by external and extraneous factors. If these factors are differentially distributed in exposed and unexposed groups, the actual associations may be biased. We will adjust for some factors such as maternal SES which may influence age of diagnosis to reduce the bias to some extent. However, we cannot rule out the confounding effects of unmeasured factors. Administrative databases may also lack, or incompletely record, confounding variables such as illicit drug use, alcohol consumption or smoking status. When available such information is often reliant on maternal self-report. Social desirability bias, a bias that tends to be important when the questions deal with socially desirable (or undesirable) attitudes and behaviours (Grimm, 2010), may make women reluctant to admit their true alcohol (Lange *et al.*, 2014), smoking and illicit drug use. Indeed, few studies have been able to adjust for the effect of illegal drug use when examining outcomes following SSRI exposure (Fitton *et al.*, 2020). Illicit/recreational drug use is typically not well captured in administrative data. It may be possible to identify those diagnosed with problems, but not casual users or even regular users with no problems. The definition of 'illegal' drug use may vary across countries and some drugs which may be abused can also be prescribed such as methadone (in drug rehabilitation programmes) and dihydrocodeine, diazepam etc. as part of patient care.

We shall not explore paternal exposure, maternal sibships, family histories or environmental exposures, due to limited resources and limitations of the data.

Covariate information available in the EUROmediCAT database is limited.

Study power

Part 3: Cohort study

The prevalence of maternal depression, SSRI/SNRI use and adverse neurodevelopmental outcomes are shown below, see Table 11.

Table 11 Prevalence of maternal depression, SSRI/SNRI use and adverse neurodevelopmental outcomes used in the sample size calculations

Mother	
Maternal depression	10-20% (Gorman, Kao and Chambers, 2012; Charlton *et al.*, 2015; Zoega *et al.*, 2015; Molenaar *et al.*, 2020)
SSRI/SNRI used at some stage during pregnancy	1-10% (Gorman, Kao and Chambers, 2012; Charlton *et al.*, 2015; Zoega *et al.*, 2015; Molenaar *et al.*, 2020)
Sodium valproate used at some stage during pregnancy	0.02-0.1% (Hurault-Delarue *et al.*, 2019; Julia *et al.*, 2021)
Child	
ADHD	3–5 % (Polanczyk *et al.*, 2014, 2015)
ASD aged 7-9 years	0.4-2.0% (Posada de la Paz, 2018)
ID disorders	1-1.5% (Maulik *et al.*, 2011; McKenzie *et al.*, 2016)
Delayed infant development	Will be identified in **Part 1**.

Using the prevalence of outcomes above and sample size calculations below with 80% power and type I error rate of 0.05:

If 5% of women use SSRI/SNRIs during pregnancy to detect a 50% increased risk: for ASD/ID disorders, we would require a sample size of around 75,000 and for ADHD 14,000 children (see figures below).

If 1% of women use SSRI/SNRIs during pregnancy to detect a 50% increased risk: for ASD/ID disorders, we would require a sample size of around 360,000 and for ADHD 68,000 children (see figures below).

If 0.1% of women use a specific SSRI, SNRI or sodium valproate during pregnancy to detect a 50% increased risk: for ASD/ID disorders, we require a sample size of around 3.5 million and for ADHD 67,500 children (see figures below).

Cohort study sample sizes – 80% study power and type I error rate of 0.05

Study sample size when 5% of the study population are using SSRI/SNRI medications

		Baseline prevalence of Outcome				
		0.01%	**0.1%**	**1%**	**5%**	**10%**
Risk Ratio	**1.1**	170,048,707	17,029,023	1,687,055	323,324	152,857
	1.2	43,888,044	4,384,587	434,241	83,099	39,206
	1.5	7,610,713	760,263	75,218	14,324	6,713
	2	2,133,487	213,082	21,041	3,971	1,836
	5	209,512	20,896	2,035	357	146

Study sample size when 1% of the study population are using SSRI/SNRI medications

		Baseline prevalence of Outcome				
		0.01%	**0.1%**	**1%**	**5%**	**10%**
Risk Ratio	**1.1**	816,484,080	81,572,607	8,081,460	1,548,911	732,340
	1.2	209,883,964	20,968,283	2,076,714	397,462	187,553

	1.5	36,211,891	3,617,363	357,910	68,179	31,960
	2	10,065,884	1,005,338	99,283	18,742	8,672
	5	946,776	94,426	9,191	1,609	655

Study sample size when 0.1% of the study population are using a specific SSRI or SNRI medication or sodium valproate

		Baseline prevalence of Outcome				
		0.01%	**0.1%**	**1%**	**5%**	**10%**
Risk Ratio	**1.1**	8,088,321,488	808,081,490	80,057,486	15,344,223	7,255,043
	1.2	2,078,385,997	207,639,542	20,564,892	3,936,015	1,857,381
	1.5	358,172,230	35,779,422	3,540,137	674,401	316,157
	2	99,366,025	9,924,276	980,096	185,033	85,616
	5	9,246,765	922,213	89,749	15,708	6,378

Part 3: Case-control study

The sample size available will vary with the signal anomalies being examined (case group) and the control group used (non-signal or genetic control groups). Analyses will only be performed for subgroups with at least 3 exposed cases.

9. Other aspects

Ethical considerations

An umbrella protocol covering the five demonstration projects was circulated to the DAPs to enable them to get local ethical approval (where applicable) and to use their data in the demonstration projects.

We will present the protocol to an independent clinical expert with experience in treating pregnant women with depression for input in the SAP and discussion of results.

This project is based on secondary use of data, and will follow the ENCePP Code of Conduct, Revision 4 (http://www.encepp.eu/code_of_conduct/documents/ENCePPCodeofConduct.pdf) to ensure transparency and high scientific standards. If an industry partner's company manufactures antidepressants, he/she will only be involved up to the protocol development stage i.e. they will not be involved in the analysis/ interpretation of results.

10. Protection of human subjects

The project will follow the EU General Data Protection Regulation as well as all ethical and institutional regulations relevant for each data source in the project. Each DAP will ensure that rules and regulations are followed and that required approvals are obtained. Databases may require approval indicating that informed consent is waived and the rationale for this decision will be maintained. The protocol and waiver of informed consent will be reviewed and approved by the appropriate authority (e.g. Research Ethics Board/ Institutional Review Board/Data Protection Officer) before study start. Copies of all approvals will be stored in the ConcePTION secure platform. DAPs will ensure that sensitive data are stored and analysed

at a local secure platform (GDPR compliant). In some instances, this may include a Data Protection Impact Assessment performed by the appropriate Data Protection Officer.

Prior to use of the EUROmediCAT central database, all registries must give approval to use their data in the study. In addition, this study will be submitted to the University of Ulster ethics committee for ethical approval. All registries are responsible for ethics permission in their own areas, but as no additional data than is usually collected by the registry, no problems are foreseen. All data are held anonymously in the EUROCAT Central Registry, within University of Ulster, Newtownabbey. No sensitive data will be taken outside the Central Registry and EUROCAT data handling policies will be adhered to at all times.

Low numbers

Some DAPs such as the SAIL databank (Wales) will only provide data with the requirement that aggregate data on fewer than 5 people are not released. SAIL prohibits the public release of numbers 1-4 in any data category (except 'information missing'). This applies to all documents in the public domain and communications outside secure links (e.g. emails). This not only applies to text and tables, but also to reporting that could lead to the derivation of a low number in any category, for example:

1. Where an unadjusted OR or RR is reported for a contingency table, and the denominators and numerator in the larger category are available, it is easy to calculate the missing value.
2. Where a proportion is reported in a figure or graph or table, and the total number of cases is reported either in the same report or another report or publication, the number can be calculated.
3. Where numbers in categories across Europe are low*, they only have permission to say that 'Wales contributed data'. It is a breach of their conditions of approval to say 'Wales contributed cases'.

*low can only be defined with reference to the number of cases and countries.

In Wales European projects have permission to pass low numbers (1-4) to the centre responsible for analysis, via secure links to authorised colleagues on the above conditions. These numbers are to be aggregated before reporting.
https://www.ncbi.nlm.nih.gov/books/NBK350762/

11. Management and reporting of adverse events/adverse reactions

This study will adhere to the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practice https://www.pharmacoepi.org/resources/policies/guidelines-08027/. Since this is a non-interventional study design which is based on secondary data use, reporting of Adverse Events and Adverse Drug Reactions is not required.

12. Plans for disseminating and communicating study results

The results of this study will be published as scientific papers in peer-reviewed journals. Small numbers will not be published from DAPs in countries where the data protection legislation prohibits this for e.g. if numbers less than 5 or 8 cannot be reported.

Preparation of such manuscripts will be prepared independently by the investigators and in accordance with the current guidelines of STrengthening the Reporting of OBservational

studies in Epidemiology (STROBE), the ENCePP standards (European Medicines Agency, 2018) and EMA guidelines (European Medicines Agency, 2020). The ConcePTION Management Board will review draft manuscripts and provide comments prior to submission of the manuscript for publication.

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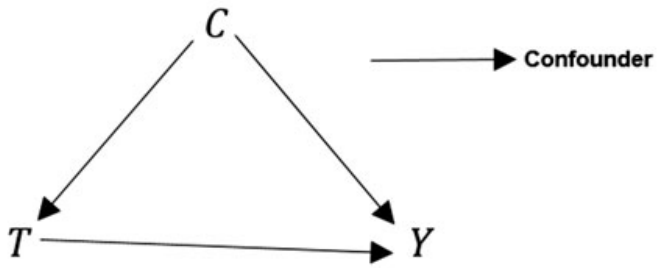
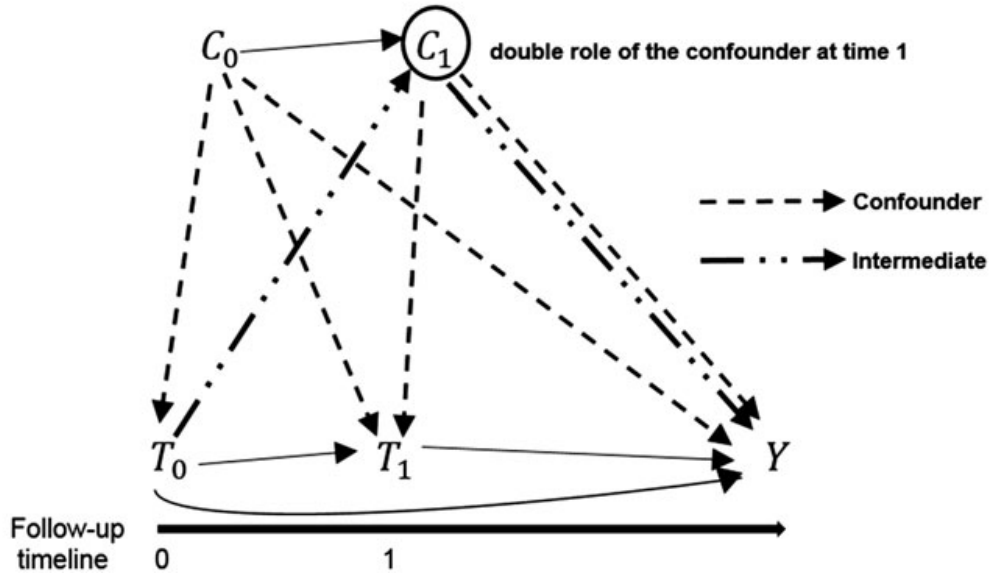
Appendix 1 Directed acyclic graphs showing confounding and time varying confounding

DAG A: Confounder at a single time point (cross-sectional studies)



DAG B: Time-varying confounder (longitudinal studies)



DAG A: Relationship between a confounder variable C, a treatment variable T, and an outcome variable Y in a time point study. DAG B: Relationships between a time - varying exposure, a time varying confounder (which also acts as an intermediate factor), and an outcome variable in a longitudinal study. The double role of the confounder level C1 is indicated by drawing a double arrow. The observations at each time point of the time-varying exposure and the time - varying confounder are indicated, respectively, with T0, T1, C0, and C1 since they are measured at time 0 and at time 1. The variable Y indicates the outcome. For simplicity of the graphical representations, in DAG A and in DAG B a variable representing the set of potential unmeasured confounders has been omitted (Pazzagli et al., 2018).

Appendix 2 Identification of maternal depression

Identification of maternal depression and mental illness

Underlying maternal mental illness in pregnancy and/or the postpartum period has been shown to be associated with suboptimal behavioural, cognitive, and socio-emotional development (Field, 2011; Kingston, Tough and Whitfield, 2012; Kingston and Tough, 2014; Kobayashi *et al.*, 2016; Kaplan *et al.*, 2017; Wood *et al.*, 2018; Halvorsen *et al.*, 2019) raising the potential for confounding by indication. Both maternal depression, and antidepressant use, may change over time. Maternal depression therefore has the potential to be a time-varying confounder when estimating the risk of adverse neurodevelopmental outcomes following antidepressant exposure during pregnancy (Mansournia *et al.*, 2017b). There are two distinct types of time-varying confounders: (1) time-varying confounding not affected by prior treatment, and (2) time-varyinag confounding affected by prior treatment (Burcu and Oehrlein, 2016). Conventional statistical methods can introduce bias in the presence of time varying confounding (Mansournia *et al.*, 2017b) particularly time-varying confounding affected by prior treatment (Burcu and Oehrlein, 2016). As maternal depression is a time varying confounder affected by prior SSRI/SNRI treatment appropriate statistical methods should be used to adjust for the confounding effect of depression, but not for the effect of SSRI/SNRI exposure on depression. In order to do this however it must be possible to identify maternal depression, over time, in the administrative datasets used.

A range of algorithms have been published and validated to identify depression in primary care (Spettell *et al.*, 2003; John *et al.*, 2016; Doktorchik *et al.*, 2019), hospital discharge diagnosis records (Fiest *et al.*, 2014) and claims data (Solberg *et al.*, 2006). These tend to be database specific and there no definitive gold standard algorithm. A systematic review by Townsend et al. found that including pharmacy records indicating an antidepressant prescription tends to increase sensitivity by capturing more patients with depression. As antidepressants are not just prescribed for depression it comes at the expense of false positive cases that diminish the positive predictive value (PPV)(Townsend *et al.*, 2012). Spettell et al. recommended the use of at least two diagnoses, two prescriptions for an antidepressant or one prescription and a diagnosis (Spettell *et al.*, 2003). The use of 1 inpatient or two outpatient codes within a year has also been shown to improve the PPV (Spettell *et al.*, 2003; Solberg *et al.*, 2006). There is evidence of decreasing use of diagnostic codes in favour of symptom codes in the UK (Rait *et al.*, 2009; John *et al.*, 2016). The most suitable algorithms for detecting depression in administrative data will vary depending on the nature of the data (primary care, hospital, claims etc.) and on the context. For surveillance purposes, the most inclusive algorithms will ensure that as few affected individuals are missed as possible. In contrast where diagnostic certainty is required more restrictive algorithms are preferable (Townsend *et al.*, 2012; Fiest *et al.*, 2014). The impact of different algorithms to determine depression, and depression timing, will be explored. It is important to note that IMI ConcePTION does not have access to patients or their medical charts, although some DAPs may review a sub-sample of charts as a validation check. Therefore, validation activities cannot compare algorithm-identified cases to a gold standard. Standard accuracy measures such as positive-predictive value cannot be produced. Instead, changes in prevalence across various dimensions (calendar time, maternal age etc), consistency with published estimates obtained from traditionally validated work, and expert opinion will be used to determine face validity.

Across the data sources contributing to this project maternal depression may be recorded in a number of ways, see Table 1 below. The estimated sample available across the DAPs is included in Appendix 2.

Table 1 Depression information across DAPs

Data Access Provider (Births with medication exposure available)	Years with medication exposure in pregnancy	Primary care diagnoses	Inpatient diagnoses	Outpatient diagnoses	Prescriber speciality	Other information to identify depression
EFEMERIS & POMME	2004-2009 2010 and 2015	None	ICD-10 if hospitalised in the public University Hospital of Toulouse ONLY DURING PREGNANCY 2004-2019	None	Yes	Special reimbursement for “depression as a long term disability”
Finland	1996-2019	ICPC2 from 2012	ICD-10 1996-2019	ICD-10 1996-2019	Only available in Finnish. Variable changed, uncertain availability of this information 2015 onwards.	
GePaRD	2006-2019	Primary care does not exist in health system.	ICD-10-GM 2004-2019	ICD-10-GM 2004-2019	Yes	
Italy - Emilia Romagna	2004-2019	None	ICD-9-CM 2004-2019	ICD-10 2013-2019	No	
Italy – Tuscany	2003-2019	None	ICD-9-CM 2003-2019	None	No	

Norway	2004-2019	None	ICD-10 2008-2019	ICD-10 2008-2019	Yes	
Wales	1998-2019	Read codes 2000- ~ 79% of population covered	ICD-10 2000-	ICD-10 2000-	No	

NOTE: maternal depression information does not necessarily cover the same period as that with medication exposure available.

When validating maternal depression the aims are to:

1. To compare a range of algorithms to identify depression
2. To determine how the prevalence of depression varies in the pre-pregnancy, pregnancy and post-natal periods based on the algorithms used to identify depression

Depression diagnosis codes

In Finland and Wales medication use, primary care and hospital inpatient and outpatient diagnoses will be available. In GePaRD and Norway medication use and hospital inpatient and outpatient diagnoses will be available. In Tuscany medication and hospital inpatient diagnosis only will be available. In Emilia Romagna only medication use and outpatient mental health service diagnoses are available. In EFEMERIS/POMME medication use and hospital inpatient diagnoses from three months before and during pregnancy will be available as well as special reimbursement for “depression as a long term disability”. In all other data sources information should be available pre, during and post pregnancy.

Three categories of maternal depression will be examined based on the below codes:

Depression

- ICD-9: Major Depressive Disorder, single episode (296.2), Major Depressive Disorder, recurrent episode (296.3), Dysthymic Disorder/neurotic depression (300.4) Depressive Disorder not elsewhere Classified (311), Mental disorders complicating pregnancy childbirth or the puerperium (648.4).
- ICD-10: depressive episode (F32), Recurrent depressive disorder (F33), dysthymia (F34.1), mixed anxiety and depressive disorder (F41.2), postnatal/postpartum depression (F53.0).
- ICPC2: It is therefore not possible to distinguish those who had just depression in ICPC2. Depressive disorder code includes depressive neurosis/psychosis; mixed anxiety and depression; puerperal/postnatal depression; reactive depression) (P76).
- Read codes: depression diagnosis, symptom and review codes, see Appendix 1 (to be updated).

Data characterisation by WP7 will reveal if the level of detail recorded provides information on severity and/or type of depression. This will be indicated by the number of digits available in ICD or Read codes. ICPC2 does not indicate severity of depression and it does not have different codes for depression and anxiety – P76 includes depression but also mixed anxiety and depression. In Finland, while ICPC2 is the official system used physicians still use ICD10. Some regions only use ICPC2 but ICD10 will still capture a lot of diagnoses.

The number of depression diagnosis codes and median age at time of first diagnosis will be examined, see Table 2. This will be done for each data set/table which records diagnoses within a DAP. This will facilitate a comparison between primary care, outpatient and inpatient diagnoses. In Finland where both ICD10 and ICPC2 diagnoses may be recorded in primary care there should be a) a table for ICPC2, b) a table for ICD10 and c) a table for ICPC2 and ICD10). Tables to be produced for women of childbearing age with the cohort entry date the latest of the date when they joined the database, the date of their 15th birthday or 1st of Jan of the earliest year of data available in the data source. The cohort exit date will be the earliest of the date they left the database, date of death, the date of their 49th birthday or 31st of December of the last full year of data available in the data source. For Finland who only have women who had a pregnancy the table will be produced for this sample only. In EFEMERIS/POMME and the medical birth registries (such as in Finland or Norway) where a

woman is in the dataset during her pregnancy this table is not applicable. Instead, the median, and IQR, number of depression diagnoses will be requested.

Table 2 Number of depression diagnosis codes among women of childbearing age (to be completed for each data source which records diagnoses within a DAP).

Data source/table name		**Origin of diagnosis (Primary care, Inpatient, Outpatient)**	
Number of depression diagnostic codes	**Total number of women N**	**Median time in study population and Inter Quartile Range (Years)**	**Median age of women at time of first diagnostic code and Inter-Quartile Range (Years)**
0			
1			
2+			
Total			

For each data source within a DAP the median time between first and second depression diagnosis and Inter-Quartile Range (Years) will be calculated, see Table 3.

Table 3 Median time between first and second depression diagnosis, and Inter-Quartile Range, for women of childbearing age

Number of depression diagnostic codes	**Median time between first and second depression diagnosis and Inter-Quartile Range (Years)**
Depression	

Antidepressant medication use

All data sources record maternal medication exposure based on prescriptions issued or dispensed. Antidepressants will be identified by ATC codes starting N06A. The number of diagnosis codes, and how this relates to medication, and special reimbursement for "depression as a long term disability" in EFEMERIS/POMME, will be examined among women of childbearing age, or the pregnant population in Finland and EFEMERIS/POMME, as per Table 4 below.

Table 4 Number of depression diagnosis codes by medication and special reimbursement for "depression as a long term disability" (EFEMERIS/POMME only)across linked datasets within each DAP.

Number of Depression diagnostic codes	Number of women with					Total number of women
	No antidepressant medication	≥ 1 Antidepressant medication	>1 Antidepressant medication	Special reimbursement for "depression as a long term disability"	>1 Antidepressant and special reimbursement for "depression as a long term disability"	
0						
1						
2+						
Total						

Within each DAP the medication use, diagnosis will be combined as below, see Table 5. Special reimbursement for “depression as a long term disability” is specific to EFEMERIS/POMME and will only be used in this DAP. At least two prescriptions/dispensations for an antidepressant are required before a woman is considered to have depression based on medication use.

Table 5 Algorithms to identify depression

Algorithm	Medication	Diagnosis codes	Other measure
Depression only			
D1	>1 antidepressant medication		
D2		≥1 Diagnosis code	
D3			Special reimbursement
D4	>1 antidepressant medication or ≥1 diagnosis code or Special reimbursement		

Each of the tables below will be completed for the four groups below (where available):

- Women of childbearing age
- Women with a pregnancy
    - Pre-pregnancy depression – one year before pregnancy up to three months before the date of conception
    - Pregnancy depression – from three months before or during pregnancy
    - Depression in the post-natal period (depression or post-natal depression) – depression during the first years after delivery

This will be done for each algorithm to determine if the prevalence is internally stable and consistent over calendar year and woman’s age in each DAP. The prevalence seen will be also be compared to that in the published literature. In EFEMERIS only the estimate of pregnancy depression will be possible.

Table 6 Prevalence over time per 1,000 women for each algorithm separately

	Algorithm Number	Number of women with diagnoses according to algorithm	Number of women in study population	Prevalence per 1,000 women	95% Confidence Interval of Prevalence per 1,000 women [14]
1996	D1				
1997					
	….				
	….				
2018					
2019					
1996	D2				
1997					

[14] *Confidence intervals to be calculated using the Wilson score method*

	….				
	….				
2018					
2019					
	Etc.				

Table 7 Prevalence stratified by age and calendar period per 1,000 women for each algorithm separately

Year in study	**Age of women**	**Algorithm Number**	**Number of women in study population**	**Number of women with diagnoses according to algorithm**	**Prevalence per 1,000 women**	**95% Confidence Interval of Prevalence per 1,000 women[17]**
1996-2000	15-19	D1				
1996-2000	20-24	D1				
1996-2000	25-29	D1				
1996-2000	30-34	D1				
1996-2000	35-39	D1				
1996-2000	40-44	D1				
1996-2000	45-49	D1				
2001-2004	15-19	D1				
2001-2004	20-24	D1				
2001-2004	25-29	D1				
2001-2004	30-34	D1				

2001-2004	35-39	D1				
2001-2004	40-44	D1				
2001-2004	45-49	D1				
2005-2009	15-19	D1				
2005-2009	20-24	D1				
2005-2009	25-29	D1				
2005-2009	30-34	D1				
2005-2009	35-39	D1				
2005-2009	40-44	D1				
2005-2009	45-49	D1				
2010-2014	15-19	D1				
2010-2014	20-24	D1				
2010-2014	25-29	D1				
2010-2014	30-34	D1				
2010-2014	35-39	D1				
2010-2014	40-44	D1				
2010-2014	45-49	D1				

2015-2019	15-19	D1				
2015-2019	20-24	D1				
2015-2019	25-29	D1				
2015-2019	30-34	D1				
2015-2019	35-39	D1				
2015-2019	40-44	D1				
2015-2019	45-49	D1				
2005-2009	15-19	D1				
		……				
2015-2019	45-49	###				

Cells will be collapsed if small numbers are an issue.

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Appendix 1 Read Codes for Depression

Eu32.	[X]Depressive episode	
	Eu320	[X]Mild depressive episode
	Eu321	[X]Moderate depressive episode
	Eu322	[X]Severe depressive episode without psychotic symptoms
	Eu323	[X]Severe depressive episode with psychotic symptoms
	Eu324	[X]Mild depression
	Eu325	[X]Major depression, mild
	Eu326	[X]Major depression, moderately severe
	Eu327	[X]Major depression, severe without psychotic symptoms
	Eu328	[X]Major depression, severe with psychotic symptoms
	Eu329	[X]Single major depressive episode, severe, with psychosis, psychosis in remission
	Eu32A	[X]Recurrent major depressive episodes, severe, with psychosis, psychosis in remission
	Eu32B	[X]Antenatal depression
	Eu32y	[X]Other depressive episodes
	Eu32z	[X]Depressive episode, unspecified
E2B..	Depressive disorder NEC	
	E2B0.	Postviral depression
	E2B1.	Chronic depression
1B17.	Depressed	
	(no sub levels)	
1B1U.	Symptoms of depression	
	(no sub levels)	
	Depressed	
1BT..	mood	
	(no sub levels)	
9H9..	Mental health annual physical examination done	
	9H90.	Depression annual review
	9H91.	Depression medication review
	9H92.	Depression interim review

Appendix 2 Sample size across DAPs

DAP	Medication exposure in pregnancy		Primary care diagnoses		Inpatient diagnoses		Outpatient diag	
	Years available	Total births (1,000)	Years available	Total births (1,000)	Years available	Total births (1,000)	Years available	Tot bir (1,(
Finland	1996-2019	1,575	2012-2019	424	1996-2019	1,575	1996-2019	1,5
EFEMERIS database	2004-2019	156			2004-2019	156		
POMME database	2010 and 2015	18			2010 and 2015	18		
Italy – Emilia Romagna	2004-2019	573			2004-2019	573	2013-2019	266
Italy - Tuscany	2003-2019	480			2003-2019	480		
Norway	2004-2019	890			2008-2019	720	2008-2019	720
Wales	1998-2020	726	2000-2020[15]	521.4	2000-2020	660	2000-2020	660
Germany	2006-2019	1,335	Primary care does not exist in health system		2004-2019	1,335	2004-2019	1,3
Total sample		5,735		945		5,499		4,5

[15] Assuming 79% of population of Wales have GP data

Appendix 3 Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is characterized by a persistent pattern (at least 6 months) of inattention and/or hyperactivity-impulsivity, with onset during the developmental period, typically early to mid-childhood(Fayyad *et al.*, 2017). The degree of inattention and hyperactivity-impulsivity is outside the limits of typical variation expected for age and level of intellectual functioning and significantly interferes with academic or social functioning. Inattention refers to significant difficulties in sustaining attention to tasks that do not provide a high level of stimulation or frequent rewards, distractibility and problems with organization. Hyperactivity refers to excessive motor activity and difficulties with remaining still, most evident in structured situations that require behavioural self-control. Impulsivity is a tendency to act in response to immediate stimuli, without deliberation or consideration of the risks and consequences. The relative balance and the specific manifestations of inattentive and hyperactive-impulsive characteristics varies across individuals and may change over the course of development. To be diagnosed, the behaviour pattern must be clearly observable in more than two settings and impact on everyday functioning.

1. Synonyms / lay terms used
    - ADHD
    - Attention deficits disorder with hyperactivity
    - Attention deficit hyperactivity disorder
    - Attention deficit syndrome with hyperactivity
- Hyperkinetic disorder

2. Laboratory tests done specific for event
None. Genetic testing may be undertaken to rule out other conditions.

3. Diagnostic tests done specific for event
Diagnostic practices are variable across countries. Diagnosis may be made as part of a multidisciplinary team or by an individual clinician. Information collected to inform the diagnostic process also varies by what information is collected and who this information comes from. At a minimum there is a direct observation of the child by the diagnosing clinician/ team and information on early development and daily functioning collected from parents and educators. Psychometric questionnaires may also be utilized and include the Child Behaviour Checklist (CBCL), Conner's Rating Scales or the Vanderbilt ADHD Rating Scale. Cognitive attention, IQ and other cognitive skills such as language functioning may also be assessed to determine any comorbid difficulties.
Diagnosis maybe based on the guidance in the Diagnostic and Statistical Manual of Mental Disorders,
which is now on its 5th edition, rather than on ICD-11 categories.

4. Medications used to treat
Attention Deficit Hyperactivity Disorder can be treated with stimulant medications which include: Methylphenidate (N06BA04), dexmethylphenidate (N06BA11), lisdexamfetamine N06BA12), atomoxetine (N06BA09) and guanfacine (C02AC02).

Stimulant medication is not always used and instead environmental or behavioural management techniques are
utilised.

5. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed
Specialist outpatient appointments. There is often an observation of the child in the home and/or school environment.

ADHD ICD-10, ICD-9, ICPC2 and Read codes

ICD-10	Description	Comments
F90 Hyperkinetic disorders	A group of disorders characterized by an early onset (usually in the first five years of life), lack of persistence in activities that require cognitive involvement, and a tendency to move from one activity to another without completing any one, together with disorganized, ill-regulated, and excessive activity. Several other abnormalities may be associated. Hyperkinetic children are often reckless and impulsive, prone to accidents, and find themselves in disciplinary trouble because of unthinking breaches of rules rather than deliberate defiance.	Using this parent code will not allow for the differentiation between inattentive and hyperactive types
F90.0	Disturbance of activity and attention. Attention deficit disorder with hyperactivity, hyperactivity disorder, syndrome with hyperactivity	
F90.1	Hyperkinetic conduct disorder. Hyperkinetic disorder associated with conduct disorder	
F90.8	Other hyperkinetic disorder	
F90.9	Hyperkinetic disorder, unspecified. Hyperkinetic syndrome not otherwise specified	
ICD-9		
314 Attention deficit disorder	A disorder characterized by a marked pattern of inattention and/or hyperactivity-impulsivity that is inconsistent with developmental level and clearly interferes with functioning in at least two settings (e.g. At home and at school). At least some of the symptoms must be present before the age of 7 years	Using this parent code will not allow for the differentiation between inattentive and hyperactive types
314	Attention deficit disorder without mention of hyperactivity	
314.1	Attention deficit disorder with hyperactivity	
314.8	Other specified manifestations of hyperkinetic syndrome	
ICPC-2(The Directorate of eHealth, 2021)		
P81	Hyperkinetic disorder - attention deficit disorder (ADD); hyperactivity. Early onset of a lack of persistence in activities requiring cognitive involvement, with a tendency to move from one activity to another without completing any one, with disorganised and ill-regulated behaviour, and excessive activity	Excludes hyperkinetic disorder with adolescent onset P23; learning disorder P24. ICD-10 equivalent F90.0; F90.1; F90.8; F90.9.

Read codes			
		To be defined in **Part 1** with input from DAP.	

Appendix 4 Autistic Spectrum Disorders

ASD is characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behaviour and interests (Ousley and Cermak, 2014; Masi et al., 2017). The onset of the disorder occurs during the developmental period, typically in early childhood, but symptoms may not become fully manifest until later, when social demands exceed limited capacities. Deficits are sufficiently severe to cause impairment in personal, family, social, educational, occupational or other important areas of functioning and are usually a pervasive feature of the individual's functioning observable in all settings, although they may vary according to social, educational, or other context. Individuals along the spectrum exhibit a full range of intellectual functioning and language abilities.

1. Synonyms / lay terms used
    - Autism
    - Autism syndrome
    - Infantile autism
    - 'ASD'
    - Asperger's syndrome
    - Pervasive developmental disorder
    - Autistic disorder
2. Laboratory tests done specific for event

None. Genetic testing may be undertaken to rule out other conditions.

3. Diagnostic tests done specific for event

Diagnostic practices are variable across countries. Diagnosis may be made as part of a multidisciplinary team or by an individual clinician. Information collected to inform the diagnostic process also varies by what information is collected and who this information comes from. At a minimum there is a direct observation of the child by the diagnosing clinician/ team and information on early development and daily functioning collected from parents and educators. Psychometric measurements may also be utilized and include the Modified Checklist for Autism in Toddlers (MCAT), Screening Tool for Autism in Toddlers and Young Children (STAT), Autism Diagnostic Observation Schedule (ADOS), Autism Diagnostic Interview-Revised (ADI-R) or the Childhood Autism Rating Scale (CARS). IQ and other cognitive skills such as language may also be assessed to determine any comorbid difficulties. Diagnosis maybe based on the guidance in the Diagnostic and Statistical Manual of Mental Disorders, which is now on its 5th edition, rather than on ICD-11 categories.

4. Medications used to treat event

None. Certain medications may be used in the treatment of comorbid symptoms (e.g. melatonin for sleep difficulties), but none are specific enough to autism to be utilised as a proxy marker for this condition.

5. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

Specialist outpatient appointments. There may also be some observation of the child in the home and/or school environment.

ASD ICD-10, ICD-9, ICPC-2 and Read codes

ICD-10	Description	Comments
F84 Pervasive developmental disorders	A group of disorders characterized by qualitative abnormalities in reciprocal social interactions and in patterns of communication, and by a restricted, stereotyped, repetitive repertoire of interests and activities. These qualitative abnormalities are a pervasive feature of the individual's functioning in all situations.	Using the parent code F84 will be unreliable due to the wide variability of conditions included here, some of which are genetic in origin and therefore not linked to disease or medication teratogenicity. F84.3 includes a wide range of heterogeneous conditions including those arising from acquired brain injuries.
F84.0 Childhood autism	A type of pervasive developmental disorder that is defined by: (a) the presence of abnormal or impaired development that is manifest before the age of three years, and (b) the characteristic type of abnormal functioning in all the three areas of psychopathology: reciprocal social interaction, communication, and restricted, stereotyped, repetitive behaviour. In addition to these specific diagnostic features, a range of other nonspecific problems are common, such as phobias, sleeping and eating disturbances, temper tantrums, and (self-directed) aggression.	
F84.1 Atypical Autism	A type of pervasive developmental disorder that differs from childhood autism either in age of onset or in failing to fulfil all three sets of diagnostic criteria. This subcategory should be used when there is abnormal and impaired development that is present only after age three years, and a lack of sufficient demonstrable abnormalities in one or two of the three areas of psychopathology required for the diagnosis of autism (namely, reciprocal social interactions, communication, and restricted, stereotyped, repetitive behaviour) in spite of characteristic abnormalities in the other area(s). Atypical autism arises most often in profoundly retarded individuals and in individuals with a severe specific developmental disorder of receptive language. Includes typical childhood psychosis and mental retardation with autistic features.	
F84.3 Other childhood disintegrative disorder	A type of pervasive developmental disorder that is defined by a period of entirely normal development before the onset of the disorder, followed by a definite loss of previously acquired skills in several areas of development over the course of a few months. Typically, this is accompanied by a general loss of interest in the environment,	

		by stereotyped, repetitive motor mannerisms, and by autistic-like abnormalities in social interaction and communication. In some cases the disorder can be shown to be due to some associated encephalopathy but the diagnosis should be made on the behavioural features. Includes dementia infantilis, disintegrative psychosis and Heller syndrome (childhood disintegrative disorder).	
	F84.4 Overactive disorder associated with mental retardation and stereotyped movements	An ill-defined disorder of uncertain nosological validity. The category is designed to include a group of children with severe mental retardation (IQ below 35) who show major problems in hyperactivity and in attention, as well as stereotyped behaviours.	
	F84.5 Asperger's Syndrome	A disorder of uncertain nosological validity, characterized by the same type of qualitative abnormalities of reciprocal social interaction that typify autism, together with a restricted, stereotyped, repetitive repertoire of interests and activities. It differs from autism primarily in the fact that there is no general delay or retardation in language or in cognitive development. This disorder is often associated with marked clumsiness. There is a strong tendency for the abnormalities to persist into adolescence and adult life. Psychotic episodes occasionally occur in early adult life.	
	F84.8 Other pervasive developmental disorders		
	F84.9 Pervasive developmental disorder, unspecified		
ICD- 9			
		Description	Comments
299 Autistic Disorder		Disorder beginning in childhood marked by the presence of markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interest; manifestations of the disorder vary greatly depending on the developmental level and chronological age of the individual.	Note infantile psychosis would not be grouped with autism in recent times
	299.0 Autistic disorder	Applies to, Childhood autism, Infantile psychosis, Kanner's syndrome	Other specific codes under 299 code

			for non-autism conditions such as Heller's syndrome
	299.8 Other specified pervasive developmental disorders	Neuropsychiatric disorder whose major manifestation is an inability to interact socially; other features include poor verbal and motor skills, singlemindedness, and social withdrawal. Syndrome or disorder usually first diagnosed in childhood, characterized by severe and sustained impairment in social interactions and restricted, repetitive patterns of behaviours, interests, and activities. Syndrome or disorder usually first diagnosed in childhood, characterized by severe and sustained impairment in social interactions and restricted, repetitive patterns of behaviours, interests, and activities.	
	299.80 Other specified pervasive developmental disorders, current or active state		
	299.81 Other specified pervasive developmental disorders, residual state		
	299.90 Unspecified pervasive developmental disorder	A category of developmental disorders characterized by impaired communication and socialization skills. The impairments are incongruent with the individual's developmental level or mental age. Group of disorders characterized by delays in the development of socialization and communication skills; typical age of onset is before 3 years of age; symptoms may include problems with using and understanding language; difficulty relating to people, objects, and events; unusual play with toys and other objects; difficulty with changes in routine or familiar surroundings, and repetitive body movements or behaviour patterns; autism is the most characteristic and best studied pdd; other types of pdd include Asperger syndrome, childhood disintegrative disorder, and Rett syndrome; prefer nts where possible Broad term for disorders, usually first diagnosed in children prior to age 4, characterized by severe and profound impairment in social interaction, communication, and the presence of	Note genetic conditions will also be included in this code

		stereotyped behaviours, interests, and activities. Compare developmental disabilities. These disorders can be associated with general medical or genetic conditions	
ICPC-2(The Directorate of eHealth, 2021)			
	P99	Psychological disorders other - autism; neurosis NOS.	ICD10 equivalent - F48.1; F48.8; F48.9; F53.8; F53.9; F54; F59; F84.0; F84.1; F84.2; F84.3; F84.4; F84.5; F84.8; F84.9; F88; F89; F99
Read codes			
		To be defined in **Part 1** with input from DAP.	

Appendix 5 Learning disability or disorders of intellectual development

1. Synonyms / lay terms used
    - Mental retardation (or 'retarded')
    - Intellectual impairment
    - Low IQ
    - Incomplete development of the mind
    - Feeble-mindedness
    - Mental sub normality

2. Laboratory tests done specific for event
None. Genetic testing may be undertaken to rule out this as being part of a wider syndrome such as a genetic syndrome.

3. Diagnostic tests done specific for event
Diagnostic practices are variable across countries. Diagnosis may be made as part of a multidisciplinary team or by an individual clinician. Information collected to inform the diagnostic process also varies by what information is collected and who this information comes from. At a minimum there is a direct observation of the child by the diagnosing clinician/ team and information on early development and daily functioning collected from parents and educators. If the level of impairment is very obvious no psychometric assessments are utilized however other cases may require an assessment of intellectual functioning. The score from this assessment is called the intelligence quotient (IQ). Other cognitive skills are also likely to be assessed to inform on the extent of the difficulty across cognitive functioning. Learning disability is heterogenous in terms of presentation and aetiologies. Whilst ICD codes are available for 'mild', 'moderate', 'severe' and 'profound' learning disability, these collectively only represent the most severe of cases (despite the utilization of the term 'mild') and a substantial impact on daily functioning can be found with IQ levels slightly above these cut offs.

4. Drugs used to treat event
None. Medications may be used to treat comorbidities but not this condition directly.

5. Procedures used specific for event treatment
Treatment will be non-medicinal in nature and will vary substantially between countries.

6. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

Specialist outpatient appointments. There is often an observation of the child in the home and/or school environment.

7. ICD-9, ICD-10, ICPC2 and Read codes

ICD-10		
F70-F79 Mental retardation	**Description**	**Comments**
F70 Mild mental retardation	Approximate IQ range of 50 to 69 (in adults, mental age from 9 to under 12 years). Likely to result in some learning difficulties in school. Many adults will be	

		able to work and maintain good social relationships and contribute to society.	
	F70.0 Mild mental retardation with the statement of no, or minimal, impairment of behaviour	Mild mental retardation with no or very minimal impairment to behaviour	
	F70.1 Mild mental retardation : significant impairment of behaviour requiring attention or treatment	Mild mental retardation plus a significant impairment of behaviour requiring attention or treatment	
	F70.8 Mild mental retardation : other impairments of behaviour	Mild mental retardation with other impairments of behaviour	
	F70.9 Mild mental retardation without mention of impairment of behaviour	Mild mental retardation without mention of impairment of behaviour	
	F71 Moderate mental retardation	Approximate IQ range of 35 to 49 (in adults, mental age from 6 to under 9 years). Likely to result in marked developmental delays in childhood but most can learn to develop some degree of independence in self-care and acquire adequate communication and academic skills. Adults will need varying degrees of support to live and work in the community.	
	F71.0 Moderate mental retardation with the statement of no, or minimal, impairment of behaviour	Moderate mental retardation with the statement of no, or minimal, impairment of behaviour	
	F71.1 Moderate mental retardation : significant impairment of behaviour requiring attention or treatment	Moderate mental retardation with a significant impairment of behaviour requiring attention or treatment	
	F71.8 Moderate mental retardation : other impairments of behaviour	Moderate mental retardation with other impairments of behaviour	
	F71.9 Moderate mental retardation	Moderate mental retardation without mention of impairment of behaviour	

	without mention of impairment of behaviour		
	F72 Severe mental retardation	Approximate IQ range of 20 to 34 (in adults, mental age from 3 to under 6 years). Likely to result in continuous need of support.	
	F72.0 Severe mental retardation with the statement of no, or minimal, impairment of behaviour	Severe mental retardation with no or minimal impairment of behaviour	
	F72.1 Severe mental retardation : significant impairment of behaviour requiring attention or treatment	Severe mental retardation with significant impairment of behaviour requiring attention or treatment	
	F72.8 Severe mental retardation : other impairments of behaviour	Severe mental retardation with other impairments	
	F72.9 Severe mental retardation without mention of impairment of behaviour	Severe mental retardation without mention of impairment of behaviour	
	73.0 Profound mental retardation	IQ under 20 (in adults, mental age below 3 years). Results in severe limitation in self-care, continence, communication and mobility.	
	F73.0 Profound mental retardation with the statement of no, or minimal, impairment of behaviour	Profound mental retardation with no or minimal impairment of behaviour	
	F73.1 Profound mental retardation : significant impairment of behaviour requiring attention or treatment	Profound mental retardation with significant impairment of behaviour requiring attention or treatment	
	F73.8 Profound mental retardation : other impairments of behaviour	Profound mental retardation with other impairments of behaviour	
	F73.9 Profound mental retardation without mention of	Profound mental retardation without mention of impairment of behaviour	

	impairment of behaviour		
	F78 Other mental retardation	Other mental retardation; no further specification given	
	F78.0 Other mental retardation with the statement of no, or minimal, impairment of behaviour	Other mental retardation with no or minimal impairment of behaviour	
	F78.1 Other mental retardation : significant impairment of behaviour requiring attention or treatment	Other mental retardation with significant impairment of behaviour requiring attention or treatment	
	F78.8 Other mental retardation : other impairments of behaviour	Other mental retardation: other impairments of behaviour	
	F78.9 Other mental retardation without mention of impairment of behaviour	Other mental retardation without mention of impairment of behaviour	
	F79 Unspecified mental retardation	Including 'sub normality' and deficiency not otherwise specified	
	F79.0 Unspecified mental retardation with the statement of no, or minimal, impairment of behaviour	Unspecified mental retardation with the statement of no, or minimal, impairment of behaviour	
	F79.1 Unspecified mental retardation : significant impairment of behaviour requiring attention or treatment	Unspecified mental retardation : significant impairment of behaviour requiring attention or treatment	
	F79.8 Unspecified mental retardation : other impairments of behaviour	Unspecified mental retardation with other impairments of behaviour	
	F79.9 Unspecified mental retardation without mention of impairment of behaviour	Unspecified mental retardation without mention of impairment of behaviour	
ICD-09			
317-319 Intellectual Disabilities		**Description**	**Comments**

	317 Mild intellectual disabilities	Intellectual disability with IQ 50-70	US versions use the term mental retardation
	318 Other specified intellectual disabilities	None specified intellectual disabilities	
	318.0 Moderate intellectual disabilities	Intellectual disability with IQ 35-49	
	318.1 Severe intellectual disabilities	Severe intellectual disabilities IQ 20-34	
	318.3 Profound intellectual disabilities	Profound intellectual disability IQ less than 20	
	319 Unspecified intellectual disabilities	Subnormal intellectual functioning which originates during the developmental period; multiple potential aetiologies, including genetic defects and perinatal insults; intelligence quotient (iq) scores are commonly used to determine whether an individual is mentally retarded; iq scores between 70 and 79 are in the borderline mentally retarded range and scores below 67 are in the retarded range	
ICPC-2(The Directorate of eHealth, 2021)			
P85		Mental retardation. Arrested/incomplete development of the mind with impairment of skills during the developmental period, and a low overall level of intelligence, with/without impairment of behaviour. Excludes mental retardation due to CA.	ICD10 equivalent: F70.0; F70.1; F70.8; F70.9; F71.0; F71.1; F71.8; F71.9; F72.0; F72.1; F72.8; F72.9; F73.0; F73.1; F73.8; F73.9; F78.0; F78.1; F78.8; F78.9; F79.0; F79.1; F79.8; F79.9
Read codes			
		To be defined in **Part 1** with input from DAP.	

Appendix 6 EFEMERIS/POMME developmental assessments

Original name	Meaning	Data dictionary in English (if useful)	Percentage of completeness (2004-2018)	Comment
M9_JOUE_COUCOU	able to play 'peek-a-boo'	0 = no 1 = yes	82%	
M9_MOTRICITE_MEMBRES	Limb motor skill	0 = no 1 = yes	83%	Measures the symmetric motor function, two by two, of the limbs. It assesses the global motor function and coordination of the child.
M9_POINTE_DOIGT	able to point the finger	0 = no 1 = yes	81%	
M9_REAGIT_PRENOM	reaction to own name	0 = no 1 = yes	98%	
M9_SE_DEPLACE	Able to move around	0 = no 1 = yes	98%	
M9_SAISIE_OBJET	Able to grab an object	0 = no 1 = yes	89%	
M9_REPETE_SYLLABE	able to repeat a syllable	0 = no 1 = yes	98%	
M9_TIENT_ASSIS	Able to stay seated	0 = no 1 = yes	98%	
M24_OBEIT_ORDRE	able to understand a simple instruction	0=no 1=yes	98%	
M24_NOMME_IMAGE	able to name a picture	0=no 1=yes	98%	
M24_SUPERPOSE_OBJET	Able to place something on top of something else	0=no 1=yes	98%	
M24_ASSOCIE_2_MOTS	able to associate two words	0=no 1=yes	81%	
M24_MOTRICITE_MEMBRES	Limb motor skill	0=no 1=yes	81%	
M24_MARCHE_ACQUISE	Able to walk	0=no 1=yes	98%	
M24_AGE_MARCHE_ACQUISE	Age at first step		86%	In month

Appendix 7: List of teratogenic medications

A detailed list of teratogenic exposures and diseases is currently under development by the University of Swansea. When finalised, the list of teratogenic exposures relevant to neurodevelopmental outcomes and congenital anomalies will be included in the SSRI study SAP and reported in the analysis.

Table 1. WP2 List of medications with an association with disruption of structural organ development or growth.

Medication	**Physical affects**
Oral retinoid	
Acitretin	Multiple malformations including central nervous system abnormalities, orofacial clefts, cardiovascular, skeletal, limb and ear. Facial dysmorphia.
Alitretinoin	
Bexarotene	
Isotretinoin	
Tretinoin	
Antiepileptic/ anticonvulsants	
Carbamazepine	Variable by individual medication type but include cardiovascular (phenobarbital, primidone, valproate), neural tube (valproate, carbamazepine), skeletal (valproate), orofacial cleft (topiramate, valproate) and limb (valproate). Facial dysmorphia (phenytoin, carbamazepine, valproate). Growth disruption (topiramte).
Phenytoin	
Fosphenytoin	
Primidone	
Topiramate	
Valproate	
Phenobarbital	
Antithyroid	
Carbimazole	Multiple malformation including skin defects including aplasia cutis, choanal atresia, esophageal atresia, other malformations of the gastrointestinal tract. Facial dysmorphia.
Methimazole	
Anticoagulant	
Coumarin	Multiple malformations including nasal hypoplasia, stippled epiphyses, skeletal and digital. Growth disruption. Facial dysmorphia.
Phenindione	
Warfarin	
Acenocoumarol	
Immunosuppressive	
Mycophenolate	Multiple malformations including orofacial cleft, microtia, external auditory canal atresia, micrognathia, cardiovascular, oesophageal atresia.
Methotrexate and Aminopterin	Multiple malformations including skeletal, cardiovascular, urogenital, holoprosencephaly. Growth disruption.

Appendix 8 Information items of interest to this project

Information item	
Pregnancy timing	
Pregnancy timing	☒
Medication exposure	
Source of medication information	
Primary care/General practitioner	☒
Inpatient	☐
Outpatient specialist	☐
Prescription records (prescribed or dispensed)	☒
Private prescriptions – private healthcare	☐
Maternal self-report	☐
Details of medication	
Name/ATC code of medication of interest	☒
Date of issued/dispensed prescription, administration or used	☒
Strength	☐
Dosage – amount taken per day	☐
Frequency – per day	☐
Formulation (oral, injection, cream etc).	☐
DDD dispensed	☐
Quantity prescribed or dispensed (tablets)	☐
Prescriber specialty	☐
Co-medications	☒
Maternal disease/medication indication	
Diagnosis	
Diagnosis in healthcare database e.g. ICD10	☒
Diagnosis in disease registry	☐
Type of ward where the diagnosis was given	☐
Intervention in healthcare database as surrogate for disease	☐
Healthcare admission as surrogate for disease/disease severity	☐
Severity of disease	
Health care visit pattern	☐
Co-morbid diagnosis/diagnoses	☒
Co-morbidity – Infection – COVID-19	☐
Outcomes	
Maternal pregnancy outcomes	
Spontaneous abortions	☒
Termination of pregnancy - elective	☒
Termination of pregnancy - for fetal anomaly	☒
Pregnancy related conditions e.g. GD, preeclampsia, hypertension	☒
Mode of delivery	☐
Maternal death	☒
Maternal diagnoses postpartum (e.g. stroke, infection, psychosis, death)	☒
Perinatal outcomes	

Live birth: normal	☒
Stillbirth	☒
Neonatal death	☒
Major congenital anomalies	☒
Gestational age at delivery/preterm birth	☒
Small for gestational age/ IUGR	☐
Birth weight	☒
Head circumference	☐
Length at birth	☐
Apgar score (5, 10 minutes)	☐
Admission to Neonatal Intensive Care Unit	☐
Childhood outcomes	
Death - infant or childhood	☒
Health visitor/public health nurse records	☐
Growth in childhood	☐
Diagnosis in a specialist disease registry	☐
Healthcare diagnosis records – ADHD, ASD	☒
Referrals to specialists	☐
Hospital admissions during childhood	☐
Childhood prescriptions	☐
Registered disability in child	☐
Academic results and school performance	☐
Special educational needs/educational support	☒
Psychometric measurements	☒
Confounders/covariates	
Folic acid - pre-conception, first trimester, none	☐
Assisted conception	☐
Maternal age at delivery	☒
Maternal socioeconomic status –or occupation, employment, income, education etc.	☐
Smoking status – prior to/ during pregnancy	☐
Alcohol consumption – during pregnancy	☐
Substance misuse - during pregnancy	☐
Body mass index	☐
Parity	☐
Plurality	☒
Breast feeding	☒
Paternal medication	☐
Family structure (linkage to siblings)	☐

☒ required
☐ desirable

Appendix 9 Subtask 1.3.3 – Neurodevelopment

ADHD Tables

Table naming convention

- Table Number_*Country*_*Data base name*_Table description
  - The person creating the tables will need to provide information about the country, database, and dates, indicated by *red, italicized text*.
  - Information on birth cohort years in the table will need to be provided by the person working with the data. This information is indicated by *red, italicized text* in the table.

Source Cohort definition (Cohort that gives rise to the identification of patients with ADHD)

- All children (< 18 years) born to mothers with pregnancy medication exposure data available (to be defined by the Work Package 7 Common Data Model and the DP1.2. protocol, "Study Population")
  - Children should be captured in the database for at least 28 days

Algorithm information

Algorithms adopted from Lindemann et al 2017

- Algorithm 1: One **specialist code** for ADHD provided
  - Index date: Date of specialist diagnosis (may occur during hospital admission or specialist outpatient clinic visit, for example); any diagnosis with an explicit qualifier of "ruled out" or "suspected" should not be considered.
- Algorithm 2: Two **non-specialist codes** for ADHD that are at least 28 days apart, but within 1.5 years
  - Index date: Date of second non-specialist diagnosis. Where available and applicable, any diagnosis with an explicit qualifier of "ruled out" or "suspected" should not be considered.
- Algorithm 3: One **non-specialist code** and 1 at least dispensing/prescription for ADHD medication within a year of diagnosis
  - Index date: The later of either the non-specialist code or medication dispensing; any diagnosis with an explicit qualifier of "ruled out" or "suspected" should not be considered.
- Algorithm 4: For countries where an ADHD medication must be 1st prescribed by specialist (5 of the 6 countries in this study. In GePaRD stimulants and non-stimulants prescribed by a specialist) only one medication is required.
  - In this case the index date is the first medication dispensing.

  In GePaRD for non-stimulants prescribed by a non-specialist, at least two dispensings/prescriptions within 120 days
  - Index date: Date of the second qualifying dispensing/medication

The identification of disease classification and medication codes will depend on the database being used and will need to be agreed upon prior to programming. The mock tables provide ICD-10 diagnosis codes and ATC medication codes. The table footnotes will need to be updated based on what is available for the database.

Calculation of prevalence

- *Numerator*: The child will be considered to have ADHD upon completion of the algorithm requirements. For example, Algorithm 2 requires two outpatient diagnoses. For Algorithm 2, the child will be considered to have ADHD on the second outpatient diagnosis. Because ADHD is a chronic disease, the child will be assumed to have ADHD for the remainder of their time in the study population.
- *Denominator*: The denominator should include all children present at least 28 days in the defined period. For example, Table 4 examines the prevalence of ADHD. In the prevalence calculation for Birth Cohort 1, the denominator should include all children born in within the defined birth years. In Table 5, the denominator should include all children in the birth cohort during a given calendar year.

Source of ND diagnosis and confidence in this

Data access providers (DAP) were contacted to gather information on how neurodevelopmental disorders are diagnosed in their countries/health care systems. The below table summarises the responses.

Table 12 Source of ND diagnosis and confidence

DAP	Specialist diagnosis/Rx (CONFIDENT in Dx)	Non-specialist diagnosis	Note
Finland	Hospital inpatient or outpatient diagnoses. No medication use available for children in this study but ADHD medication would be started by specialists (if available).		VISIT_OCCURRENCE and EVENTS record diagnoses in secondary/tertiary and primary care. meaning_of_visit can be used to determine the setting where a diagnosis was recorded.
EFEMERIS/POMME database	ADHD diagnosis is made by a child psychiatrist, paediatrician or a neurologist. The FIRST prescription must come from one of these specialists working in an hospital (or from a hospital sleep centre). The prescription can be renewed by GPs or private paediatricians or psychiatrists. Methylphenydate is the only medication marketed for ADHD in France and is prescribed for a maximum of 28 days on a special form.	GPs recommended to refer to a child psychiatrist, paediatrician or a neurologist for diagnosis.	
Emilia Romagna and Tuscany	Mental Health Databank -Only child neuropsychiatrists (NPI) can confirm the diagnosis. A qualified phycologist can do it, but a NPI visit is strongly recommended. Medications always started by a specialist in specific centers "Centri Prescrittori" dedicated to the prescription of medications. Methylphenidate and atomoxetine are recommended, both prescribed by a specialist. Other medications are not really considered. Patients receive the first dose of methylphenidate in a day hospital which will be recorded in the day hospital system.	No primary care available.	
Norway	Outpatient diagnoses in Norwegian Patient Registry (NPR) Prescription (both stimulant and non-stimulant) indicates specialist diagnosis.	Primary care diagnoses in Norway Control and Payment of Primary Health Care Refunds (KUHR)	

SAIL	Prescription indicates specialist diagnosis – including non-stimulant prescriptions (atomoxetine, guanfacine). Originate in outpatient data but recorded in primary care following letters to GP from specialist. No way to tell if diagnosis in primary care has originated from a specialist or GP suspicion.	Primary care	Could exclude read codes for 'referral' and potentially those with 'suspected'
GePaRD	Hospital diagnosis Outpatient diagnosis – specialist (e.g. child and adolescent psychiatrist) Prescription of a stimulant indicates specialist diagnosis. Non-stimulant medications (atomoxetine, guanfacine) started by a specialist.	Outpatient diagnosis - GP, paediatrician, psychotherapists and all other specialties Non-stimulant medications (atomoxetine, guanfacine) started by a non-specialist.	Can exclude diagnoses "ruled out" or "suspected" – the variables to do this are included in the CDM. Specialist is recorded and can be used to distinguish between specialist and non-specialist outpatient diagnoses. Prescribers speciality available in the data to distinguish between non-stimulant medications started by a specialist or non-specialist.

Algorithm Tables

Table 1_*Germany*_*GePaRd*_ADHD Diagnoses the in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

	Total number of children N=#			**Time in study population[a] (months)** Median (IQR) Mean (SD)			**Age at first diagnostic code (years)** Median (IQR) Mean (SD)			**Time between diagnosis codes (months)** Median (IQR) Mean (SD)		
Number of ADHD diagnostic codes[b]	F	M	Total	F	M	Total	F	M	Total	F	M	Total
0	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA	NA	NA	NA
1	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA
2	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)
3+	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)

F= Female; IQR= Inter-quartile range; M=Male; Med= Median; NA= Not applicable; SD= Standard deviation

[a] Time in source cohort calculated from first diagnosis

[b] ICD-10 diagnosis codes for ADHD: F90.0, F90.1, F90.8, F90.9

Table 2_*Germany*_*GePaRd*_ADHD Medication (treatment) by Diagnoses in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

	Total number of children with no ADHD Medication[b] N=#			**Total number of children with ≥ 1 ADHD Medication**[b] N=#			**Time between 1st ADHD dx and 1st ADHD medication (months)** Median (IQR) Mean (SD)		
Number of ADHD diagnostic codes[a]	Females	Males	Total	Females	Males	Total	Females	Males	Total
0	n	n	n	n	n	n	Not applicable	Not applicable	Not applicable
1	n	n	n	n	n	n	Median (IQR) Mean (SD)	Median (IQR) Mean (SD)	Median (IQR) Mean (SD)
2	n	n	n	n	n	n	Median (IQR) Mean (SD)	Median (IQR) Mean (SD)	Median (IQR) Mean (SD)
3+	n	n	n	n	n	n	Median (IQR) Mean (SD)	Median (IQR) Mean (SD)	Median (IQR) Mean (SD)
Overall	n	n	n	n	n	n	Median (IQR) Mean (SD)	Median (IQR) Mean (SD)	Median (IQR) Mean (SD)

IQR= Inter-quartile range

[a] ICD-10 diagnosis codes for ADHD: F90.0, F90.1, F90.8, F90.9

[b] ATC codes for ADHD medication: Amfetamine (N06BA01); Atomoxetine (N06BA09); Dexamfetamine Sulfate (N06BA02); Dexmethylphenidate (N06BA11); Guanfacine (C02AC02); Lisdexamfetamine (N06BA12); Methylphenidate (N06BA04); Modafinil (N06BA07); Racemic amphetamine sulfate (N06BA01)

Table 3_*Germany*_*GePaRd*_ADHD Diagnosis Setting in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

			1st ADHD Diagnosis n (%)		**2nd ADHD Diagnosis** n (%)		**3rd ADHD Diagnosis** n (%)	
			Specialist	*Non-Specialist*	*Specialist*	*Non-Specialist*	*Specialist*	*Non-Specialist*
Number of ADHD Diagnostic Codes[a]	1	Female	n (%)	n (%)				
		Male	n (%)	n (%)				
		Total	n (%)	n (%)				
	2	Female	n (%)	n (%)	n (%)	n (%)		
		Male	n (%)	n (%)	n (%)	n (%)		
		Total	n (%)	n (%)	n (%)	n (%)		
	3+	Female	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Male	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Total	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[a]ICD-10 diagnosis codes for ADHD: F90.0, F90.1, F90.8, F90.9

Table 4_*Germany*_*GePaRd*_Prevalence of ADHD per 1,000 Children (< 18 years) by birth cohort for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

		Algorithm #1		***Algorithm #2***		***Algorithm #3***		***Algorithm #4***	
Birth Cohort	**Children in Source Cohort by birth years** (n)	**Children identified with ADHD** (n)	**Prevalence per 1,000 Children** (95% CI)	**Children identified with ADHD** (n)	**Prevalence per 1,000 Children** (95% CI)	**Children identified with ADHD** (n)	**Prevalence per 1,000 Children** (95% CI)	**Children identified with ADHD** (n)	**Prevalence per 1,000 Children** (95% CI)
1 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
2 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
3 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
4 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
5 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
. . .		. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .

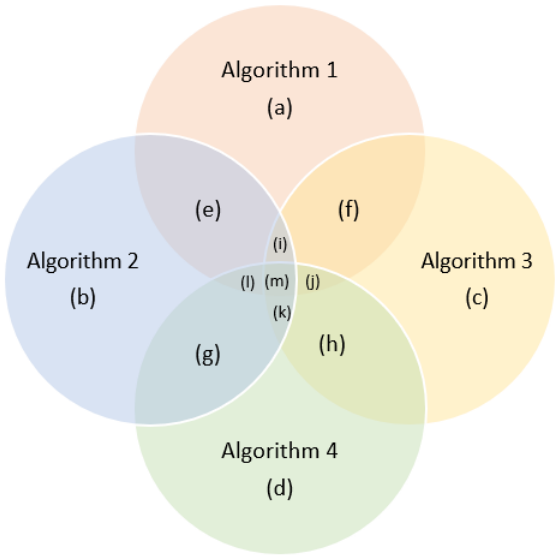
Table 5_*Germany*_*GePaRd*_Prevalence of ADHD per 1,000 Children (< 18 years) by age for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

		Algorithm #1		***Algorithm #2***		***Algorithm #3***		***Algorithm #4***	
Age	**Children in Source Cohort by age** (n)	**Children identified with ADHD** (n)	**Prevalence per 1,000 Children** (95% CI)	**Children identified with ADHD** (n)	**Prevalence per 1,000 Children** (95% CI)	**Children identified with ADHD** (n)	**Prevalence per 1,000 Children** (95% CI)	**Children identified with ADHD** (n)	**Prevalence per 1,000 Children** (95% CI)
<5	n	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
<7	n	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
<13	n	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)
<18	n	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)

Total	n	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)	n	Prev (95% CI)

Figure 1B_ *Germany*_*GePaRd*_Venn diagram displaying the number of children (<18 years) identified as having ADHD, by algorithm, data available from *DD-MON-YYYY* through *DD-MON-YYYY*

Section of Venn Diagram	Definition	n
a	The number of children identified by algorithm 1 but not by algorithms 2, 3, or 4	n
b	The number of children identified by algorithm 2 but not by algorithms 1, 3, or 4	n
c	The number of children identified by algorithm 3 but not by algorithms 1, 2, or 4	n
d	The number of children identified by algorithm 4 but not by algorithms 1, 2, or 3	n
e	The number of children identified by algorithms 1 and 2 but not algorithms 3 or 4	n
f	The number of children identified by algorithms 1 and 3 but not algorithms 2 or 4	n
g	The number of children identified by algorithms 2 and 4 but not algorithms 1 or 3	n
h	The number of children identified by algorithms 3 and 4 but not algorithms 1 or 2	n
i	The number of children identified by algorithms 1, 2, and 3, but not algorithm 4	n
j	The number of children identified by algorithms 1, 3, and 4, but not algorithm 2	n



k	The number of children identified by algorithms 2, 3, and 4, but not algorithm 1	n
l	The number of children identified by algorithms 1, 2, and 4, but not algorithm 3	n
m	The number of children identified by algorithms 1, 2, 3, and 4	n

ASD Tables

Table naming convention

- Table Number_*Country*_*Data base name*_Table description
    - The person creating the tables will need to provide information about the country, database, and dates, indicated by *red, italicized text*.
    - Information on birth cohort years in the table will need to be provided by the person working with the data. This information is indicated by *red, italicized text* in the table.

Source Cohort definition (Cohort that gives rise to the identification of patients with ASD)

- All children (< 18 years) born to mothers with pregnancy medication exposure data available (the Work Package 7 Common Data Model and the DP1.2. protocol, "Study Population")
    - Children should be captured in the database for at least 28 days

Algorithm information

- Algorithm 1: One **specialist code** for ASD provided
    - Index date: Date of specialist diagnosis (may occur during hospital admission or specialist outpatient clinic visit, for example); any diagnosis with an explicit qualifier of "ruled out" or "suspected" should not be considered.
- Algorithm 2: Two **non-specialist codes** for ASD that are at least 28 days apart, but within 1.5 years
    - Index date: Date of second non-specialist diagnosis; any diagnosis with an explicit qualifier of "ruled out" or "suspected" should not be considered.

The identification of disease classification and medication codes will depend on the database being used and will need to be agreed upon prior to programming. The mock tables provide ICD-10 diagnosis codes and ATC medication codes. The table footnotes will need to be updated based on what is available for the database.

Calculation of prevalence

- *Numerator*: The child will be considered to have ASD upon completion of the algorithm requirements. For example, Algorithm 2 requires two outpatient diagnoses. For Algorithm 2, the child will be considered to have ASD on the second outpatient diagnosis. Because ASD is a chronic disease, the child will be assumed to have ASD for the remainder of their time in the study population.
- *Denominator*: The denominator should include all children present at least one day in the defined period. For example, Table 4 examines the prevalence of ASD. In the prevalence calculation for Birth Cohort 1, the denominator should include all children born in within the defined birth years. In Table 5, the denominator should include all children in the birth cohort during a given calendar year.

Source of ND diagnosis and confidence in this

Data access providers (DAP) were contacted to gather information on how neurodevelopmental disorders are diagnosed in their countries/health care systems. See ***Table 12 Source of ND diagnosis and confidence*** in ADHD tables for more information.

Algorithm Tables

Table 1_*Germany*_*GePaRd*_ASD Diagnoses the in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

	Total number of children N=#			**Time in study population[a] (months)** Median (IQR) Mean (SD)			**Age at first diagnostic code (years)** Median (IQR) Mean (SD)			**Time between diagnosis codes (months)** Median (IQR) Mean (SD)		
Number of ASD diagnostic codes[b]	F	M	Total	F	M	Total	F	M	Total	F	M	Total
0	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA	NA	NA	NA
1	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA
2	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)
3+	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)

F= Female; IQR= Inter-quartile range; M=Male; Med= Median; NA= Not applicable; SD= Standard deviation

[a] Time in source cohort calculated from first diagnosis

[b] ICD-10 diagnosis codes for ASD: F84.0, F84.1, F84.4, F84.5, F84.8, F84.9

Table 2_*Germany*_*GePaRd*_ASD Diagnosis Setting in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

			1st ASD Diagnosis n (%)		**2nd ASD Diagnosis** n (%)		**3rd ASD Diagnosis** n (%)	
			Specialist	*Non-Specialist*	*Specialist*	*Non-Specialist*	*Specialist*	*Non-Specialist*
Number of ASD Diagnostic Codes[a]	1	Female	n (%)	n (%)				
		Male	n (%)	n (%)				
		Total	n (%)	n (%)				
	2	Female	n (%)	n (%)	n (%)	n (%)		
		Male	n (%)	n (%)	n (%)	n (%)		
		Total	n (%)	n (%)	n (%)	n (%)		
	3+	Female	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Male	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Total	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[a] ICD-10 diagnosis codes for ASD: F84.0, F84.1, F84.4, F84.5, F84.8, F84.9

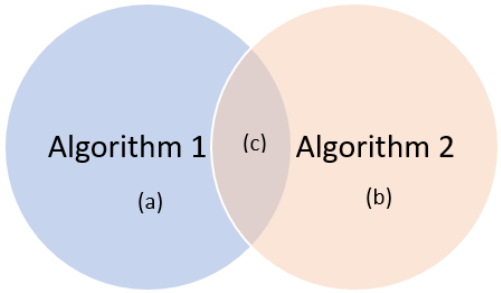
Table 3_*Germany*_*GePaRd*_Prevalence of ASD per 1,000 Children (< 18 years) by birth cohort for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

		Algorithm #1		***Algorithm #2***	
Birth Cohort	**Children in Source Cohort by birth years** (n)	**Children identified with ASD** (n)	**Prevalence per 1,000 Children** (95% CI)	**Children identified with ASD** (n)	**Prevalence per 1,000 Children** (95% CI)
1 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)
2 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)
3 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)
4 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)
5 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)
. . .		. . .	. . .	. . .	. . .

Table 5_*Germany*_*GePaRd*_Prevalence of ASD per 1,000 Children (< 18 years) by age for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

		Algorithm #1		***Algorithm #2***	
Age	**Children in Source Cohort by age** (n)	**Children identified with ASD** (n)	**Prevalence per 1,000 Children** (95% CI)	**Children identified with ASD** (n)	**Prevalence per 1,000 Children** (95% CI)
<5	n	n	Prev (95% CI)	n	Prev (95% CI)
<7	n	n	Prev (95% CI)	n	Prev (95% CI)
<13	n	n	Prev (95% CI)	n	Prev (95% CI)
<18	n	n	Prev (95% CI)	n	Prev (95% CI)
Total	n	n	Prev (95% CI)	n	Prev (95% CI)

Figure 1B_ *Germany*_*GePaRd*_Venn diagram displaying the number of children (<18 years) identified as having ASD, by algorithm, data available from *DD-MON-YYYY* through *DD-MON-YYYY*



Section of Venn Diagram	Definition	n
a	The number of children identified by algorithm 1 but not by algorithm 2	n
b	The number of children identified by algorithm 2 but not by algorithm 1	n
c	The number of children identified by algorithms 1 and 2	n

ID Tables

Table naming convention

- Table Number_*Country_Data base name*_Table description
    - The person creating the tables will need to provide information about the country, database, and dates, indicated by *red, italicized text*.
    - Information on birth cohort years in the table will need to be provided by the person working with the data. This information is indicated by *red, italicized text* in the table.

Source Cohort definition (Cohort that gives rise to the identification of patients with ID)

- All children (< 18 years) born to mothers with pregnancy medication exposure data available (the Work Package 7 Common Data Model and the DP1.2. protocol, "Study Population")
    - Children should be captured in the database for at least 28 days

Algorithm information

- Algorithm 1: One **specialist code** for ID provided
    - Index date: Date of specialist diagnosis (may occur during hospital admission or specialist outpatient clinic visit, for example); any diagnosis with an explicit qualifier of "ruled out" or "suspected" should not be considered.
- Algorithm 2: Two **non-specialist codes** for ID that are at least 28 days apart, but within 1.5 years
    - Index date: Date of second non-specialist diagnosis; any diagnosis with an explicit qualifier of "ruled out" or "suspected" should not be considered.

The identification of disease classification and medication codes will depend on the database being used and will need to be agreed upon prior to programming. The mock tables provide ICD-10 diagnosis codes and ATC medication codes. The table footnotes will need to be updated based on what is available for the database.

Calculation of prevalence

- *Numerator*: The child will be considered to have ID upon completion of the algorithm requirements. For example, Algorithm 2 requires two outpatient diagnoses. For Algorithm 2, the child will be considered to have ID on the second outpatient diagnosis. Because ID is a chronic disease, the child will be assumed to have ID for the remainder of their time in the study population.
- *Denominator*: The denominator should include all children present at least one day in the defined period. For example, Table 4 examines the prevalence of ID. In the prevalence calculation for Birth Cohort 1, the denominator should include all children born in within the defined birth years. In Table 5, the denominator should include all children in the birth cohort during a given calendar year.

Source of ND diagnosis and confidence in this

Data access providers (DAP) were contacted to gather information on how neurodevelopmental disorders are diagnosed in their countries/health care systems. See ***Table 12 Source of ND diagnosis and confidence*** in ADHD tables for more information.

Algorithm Tables

Table 1_*Germany*_*GePaRd*_ID Diagnoses the in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

	Total number of children N=#			**Time in study population[a] (months)** Median (IQR) Mean (SD)			**Age at first diagnostic code (years)** Median (IQR) Mean (SD)			**Time between diagnosis codes (months)** Median (IQR) Mean (SD)		
Number of ID diagnostic codes[b]	F	M	Total	F	M	Total	F	M	Total	F	M	Total
0	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA	NA	NA	NA
1	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	NA	NA	NA
2	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)
3+	n	n	n	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)	Med (IQR) Mean (SD)

F= Female; IQR= Inter-quartile range; M=Male; Med= Median; NA= Not applicable; SD= Standard deviation

[a] Time in source cohort calculated from first diagnosis

[b] ICD-10 diagnosis codes for ID: F70, F70.0, F70.1, F70.8, F70.9, F71, F71.0, F71.1, F71.8, F71.9, F72, F72.0, F72.1, F72.8, F72.9, F73.0, F73.1, F73.8, F73.9, F78, F78.1, F78.8, F78.9, F79, F79.0, F79.1, F79.8, F79.9

Table 2_*Germany*_*GePaRd*_ID Diagnosis Setting in the Source Cohort during *DD-MON-YYYY* through *DD-MON-YYYY*

			1st ID Diagnosis n (%)		**2nd ID Diagnosis** n (%)		**3rd ID Diagnosis** n (%)	
			Specialist	*Non-Specialist*	*Specialist*	*Non-Specialist*	*Specialist*	*Non-Specialist*
Number of ID Diagnostic Codes[a]	1	Female	n (%)	n (%)				
		Male	n (%)	n (%)				
		Total	n (%)	n (%)				
	2	Female	n (%)	n (%)	n (%)	n (%)		
		Male	n (%)	n (%)	n (%)	n (%)		
		Total	n (%)	n (%)	n (%)	n (%)		
	3+	Female	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Male	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
		Total	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

[a] ICD-10 diagnosis codes for ID: F70, F70.0, F70.1, F70.8, F70.9, F71, F71.0, F71.1, F71.8, F71.9, F72, F72.0, F72.1, F72.8, F72.9, F73.0, F73.1, F73.8, F73.9, F78, F78.1, F78.8, F78.9, F79, F79.0, F79.1, F79.8, F79.9

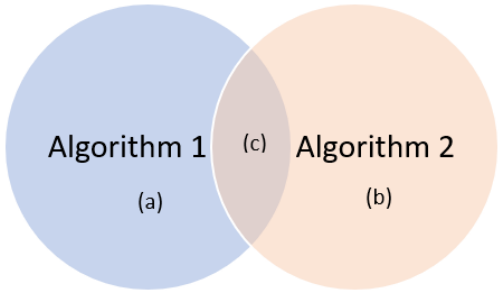
Table 3_*Germany*_*GePaRd*_Prevalence of ID per 1,000 Children (< 18 years) by birth cohort for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

		Algorithm #1		***Algorithm #2***	
Birth Cohort	**Children in Source Cohort by birth years** (n)	**Children identified with ID** (n)	**Prevalence per 1,000 Children** (95% CI)	**Children identified with ID** (n)	**Prevalence per 1,000 Children** (95% CI)
1 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)
2 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)
3 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)
4 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)
5 (*YYYY-YYYY*)		n	Prev (95% CI)	n	Prev (95% CI)
. . .		. . .	. . .	. . .	. . .

Table 5_*Germany*_*GePaRd*_Prevalence of ID per 1,000 Children (< 18 years) by age for data available from *DD-MON-YYYY* through *DD-MON-YYYY*

		Algorithm #1		***Algorithm #2***	
Age	**Children in Source Cohort by age** (n)	**Children identified with ID** (n)	**Prevalence per 1,000 Children** (95% CI)	**Children identified with ID** (n)	**Prevalence per 1,000 Children** (95% CI)
<5	n	n	Prev (95% CI)	n	Prev (95% CI)
<7	n	n	Prev (95% CI)	n	Prev (95% CI)
<13	n	n	Prev (95% CI)	n	Prev (95% CI)
<18	n	n	Prev (95% CI)	n	Prev (95% CI)
Total	n	n	Prev (95% CI)	n	Prev (95% CI)

Figure 1B_ *Germany*_*GePaRd*_Venn diagram displaying the number of children (<18 years) identified as having ID, by algorithm, data available from *DD-MON-YYYY* through *DD-MON-YYYY*



Section of Venn Diagram	Definition	n
a	The number of children identified by algorithm 1 but not by algorithm 2	n
b	The number of children identified by algorithm 2 but not by algorithm 1	n
c	The number of children identified by algorithms 1 and 2	n

Supplementary information on ND diagnosis
Finland

1) In your health care system, are ADHD diagnoses in children confirmed by a specialist?

My understanding is that ADHD diagnoses are only made by specialists i.e. children with symptoms suggestive for ADHD are referred to secondary/tertiary health care for confirmation.

2) If a specialist recorded the diagnosis which data set would this be recorded in?

In the ConcePTION CDM, we have mapped diagnoses from secondary/tertiary care 1996 onwards and diagnoses form primary health care 2011 onwards. These are both in VISIT_OCCURRENCE and EVENTS data. You can distinguish between hospitalization/outpatient visit/primary care by my meaning_of_visit variable. However, we only have information during which visit diagnoses of interest was recorded. We do not have information when exactly the diagnoses was made and by whom.

3) If a non-specialist recorded the diagnosis which data set would this be recorded in?

Kindly see my response above.

4) If a data set contains both specialist and non-specialist diagnoses, is there a variable to identify who had made the diagnosis?

No. As I told previously, we do not know who exactly made the diagnoses. However, we have mapped variable specialty of visit in VISIT OCCURRENCE where you can e.g. find an admission to child or youth psychiatry.

5) Would it be possible to exclude any diagnoses with an explicit qualifier “ruled out” or “suspected” in your data? If so, could you give an example of how we would do this (variables etc).

No. This is the biggest problem in administrative data as it records everything. If, for instance, a clinician in the primary care considers ADHD and refers a child to secondary care, it is possible that a referral includes ADHD diagnosis code and then written text “suspected/suspicion” but the administrative database will only capture the diagnosis code. We know from previous validation studies that administrative health care data includes false positive diagnoses. Only possibility to clean these false-positives is to use algorithms which, for instance, require two diagnoses codes or one code and a drug or similar.

6) Some countries will have specialist care/consultation only at hospital, others may have specialist’s consultation at the specialist’s practice (outside hospital). Could you give us some details on the setting where these disorders are typically identified and followed-up in your country?

In Finland, hospital districts can organize the health care service the way they find it most meaningful. I would assume that the most common practice is that specialist consultation occurs at hospital/outpatient visit when the diagnoses is made. However, follow-up can also be in primary care. Even changes for drug dose can occur in primary care based on written instructions from a specialist.

7) Would a non-specialist start ADHD medication, or would this always be done by a specialist?

There is no medication use available for children in this study in Finland but ADHD medication would be started by specialists (if available).

Emilia Romagna and Tuscany (response below from Emilia Romagna).

1. In your health care system, are ADHD diagnoses in children confirmed by a specialist?
Yes, in the Emilia Romagna Region (I think also in Italy) only the child neuropsychiatrist (NPI) can confirm the diagnosis. Also a qualified phycologist can do it, but a NPI visit is strongly recommended.

2. If a specialist recorded the diagnosis which data set would this be recorded in?
NPI code ADHD using ICD-10, in a specific national register dedicated only to patients requiring pharmacological treatment. All the NPI visits (not only ADHD) and treatment are collected in a specific digitalized medical record system. NPI records all diagnoses in ICD10 (ADHD or autism and others) and this flow is available with specific permission from 2010.

3. If a non-specialist recorded the diagnosis which data set would this be recorded in?
NA

4. If a data set contains both specialist and non-specialist diagnoses, is there a variable to identify who had made the diagnosis?
NA

5. Would it be possible to exclude any diagnoses with an explicit qualifier “ruled out” or “suspected” in your data? If so, could you give an example of how we would do this (variables etc).
NA

6. Some countries will have specialist care/consultation only at hospital, others may have specialist’s consultation at the specialist’s practice (outside hospital). Could you give us some details on the setting where these disorders are typically identified and followed-up in your country?
Only outside hospital; admission only for first administration of Methylphenidate (day hospital system)

7. Would a non-specialist start ADHD medication, or would this always be done by a specialist? *Always a specialist*

8. Is there any distinction made depending on the type of ADHD medication? For example, in Germany the stimulant ADHD medications need to be started by a specialist, but non-stimulant medications (atomoxetine, guanfacine) can be started by a non-specialist.
There are specific centers "Centri Prescrittori" dedicated to the prescription of medications. Methylphenidate and atomoxetine are recommended, both prescribed by a specialist. Other medications are not really considered. Patients receive the first dose of methylphenidate in hospital.

Norway

1. In your health care system, are ADHD diagnoses in children confirmed by a specialist?

Yes, we rely on diagnosis as given by specialists in child development. The national guidelines for the diagnostic and treatment of ADHD in children and other developmental

disorders state that if the GP suspects / observes possible symptoms of ADHD/other disorders, the child has to be referred to the specialist clinic.

2. If a specialist recorded the diagnosis which data set would this be recorded in?

Norwegian Patient Registry.

3. If a non-specialist recorded the diagnosis which data set would this be recorded in?

Norway Control and Payment of Health Reimbursement (KUHR) Database.

4. If a data set contains both specialist and non-specialist diagnoses, is there a variable to identify who had made the diagnosis?

Yes, the diagnoses given in primary vs secondary care stem from different registries, so we can distinguish between them. We may contain information on the specialty of the physician giving the diagnosis.

5. Would it be possible to exclude any diagnoses with an explicit qualifier "ruled out" or "suspected" in your data? If so, could you give an example of how we would do this (variables etc).

We cannot directly distinguish between "suspected" diagnoses and "verified" ones. National reports have however shown that for ADHD for example, 80% of the children with a specialist diagnosis in Norway also receive psychostimulant medication, supporting the fact that ADHD was most likely verified. Since children with suspected ADHD or other developmental issues by the GP are referred to a specialist (see my first reply), specialist diagnosis are most likely verified.

6. Some countries will have specialist care/consultation only at hospital, others may have specialist's consultation at the specialist's practice (outside hospital). Could you give us some details on the setting where these disorders are typically identified and followed-up in your country?

In Norway, children receive specialist care/consultations at district outpatient clinics, within the public healthcare system.

7. Would a non-specialist start ADHD medication, or would this always be done by a specialist?
For ADHD, GPs may still prescribe ADHD medications to children, but only after the first prescription has been issued by a specialist doctor.

8. Is there any distinction made depending on the type of ADHD medication? For example, in Germany the stimulant ADHD medications need to be started by a specialist, but non-stimulant medications (atomoxetine, guanfacine) can be started by a non-specialist.
In Norway all medications for ADHD in children (i.e., both stimulants and non-stimulants) have to be initiated by a specialist.

SAIL

1. In your health care system, are ADHD diagnoses in children confirmed by a specialist?
Prescriptions must be under specialist supervision ie. Diagnosis made by specialist. Dexamfetamine, lisdexamfetamine, atomoxetine & guanfacine must be initiated by specialists. In children, they are only licensed for ADHD. Therefore all these rxes will be associated with specialist diagnosis. This applies to methylphenidate in general, but some brands only carry this warning in EMC, not BNF. Only licensed from 6 years.

2. If a specialist recorded the diagnosis which data set would this be recorded in?

A letter would be written to the GP, but finding the record of this would be difficult. There is a Read code.

3. If a non-specialist recorded the diagnosis which data set would this be recorded in?

GP – primary care. It would likely be as given by the specialist.

4. If a data set contains both specialist and non-specialist diagnoses, is there a variable to identify who had made the diagnosis?

The presence of the prescriptions indicates a specialist diagnosis. Only specialists can give this diagnosis.

5. Would it be possible to exclude any diagnoses with an explicit qualifier "ruled out" or "suspected" in your data? If so, could you give an example of how we would do this (variables etc).

There are Read codes, but not sure how well this would be recorded.
There are Read codes for referrals. However, not all referrals give a diagnosis. ADHD is difficult to rule out, but it is often too mild to be worth medicating. There is usually a trial without medication, often with referrals to groups (online these days). Not all of these are reimbursed, so may not be well recorded.

6. Some countries will have specialist care/consultation only at hospital, others may have specialist's consultation at the specialist's practice (outside hospital). Could you give us some details on the setting where these disorders are typically identified and followed-up in your country?

Out-patients. Admissions v rare. Psychiatrist, paediatrician or specialist social worker or OT. Follow up rxes are from the GP.
https://www.nhs.uk/conditions/attention-deficit-hyperactivity-disorder-adhd/diagnosis/
There is some private practice, which is outside SAIL.

7. If you have any additional comments that will explain how children are diagnosed with ADHD/ ASD or intellectual disability in your country, please let us know.

Autism is harder – not medicated. There are Read codes. Intellectual disability would be best as SEN in the education data. There is also the HV data: this was changed in 2015.

GePaRD

1. In your health care system, are ADHD diagnoses in children confirmed by a specialist?

A confirmation by a specialist is not required. We also don't see in our data if a pediatrician has a special qualification for ADHS diagnosis and therapy.

2. If a specialist recorded the diagnosis which data set would this be recorded in?

Both in outpatient and hospital data.

3. If a non-specialist recorded the diagnosis which data set would this be recorded in?

Outpatient data. Pediatricians are the first point of contact and should be counted as non-specialists.

4. If a data set contains both specialist and non-specialist diagnoses, is there a variable to identify who had made the diagnosis?

Yes, the specialty of the physician is available.

5. Would it be possible to exclude any diagnoses with an explicit qualifier “ruled out” or “suspected” in your data? If so, could you give an example of how we would do this (variables etc).

Yes. The variables are included in the CDM.

6. Some countries will have specialist care/consultation only at hospital, others may have specialist’s consultation at the specialist’s practice (outside hospital). Could you give us some details on the setting where these disorders are typically identified and *followed-up in your country?*

ADHD is usually identified and followed-up in the outpatient setting by a pediatrician. Some patients will also see specialists or be even treated/diagnosed in the hospital setting.

Prescribing ADHD medication:
Non-stimulant ADHD medication (atomoxetine, guanfacine) can be prescribed by any physician to children without any further restrictions.
For stimulant medication (methylphenidate—about 94% of incident ADHD drugs [1]—, lisdexamfetamine, dexamfetamine), the following applies (according to the regulations of the Federal Joint Committee):
“The medicines must be prescribed only by a specialist in behavioral disorders in children and/or adolescents”
In this case, the “specialist” may also be a pediatrician, especially if they have undergone appropriate further training—which we cannot see in our data.
“In exceptional cases, primary care physicians may also provide follow-up prescriptions if it is ensured that supervision is provided by a behavioral health specialist.”
So, even GPs may prescribe stimulants, however, only when a specialist (see above) started medication—that sounds like what you heard from the other countries.
Percentage of incident diagnoses and incident ADHD meds by specialty:
Importantly—as in other countries—the child and adolescent psychiatrist is generally best qualified to diagnose and treat children with ND including ADHD.
In children aged 5–12 years, about 55% and 23% of incident diagnoses *were made by pediatricians and child and adolescent psychiatrist, respectively [2]. However, among children aged 0–17 years, about 24% and 50% of* incident ADHD medications *were prescribed by pediatricians and child and adolescent psychiatrist, respectively [1].*
My recommendation regarding assignment of German “specialists”:
When the incident diagnosis *would be the outcome, I think the diagnosis from a child and adolescent psychiatrist is most reliable; then pediatricians and psychotherapists (which however, are only accounting for 2% of diagnoses [2]); then all other specialties—so, three categories would make sense, if possible; or “child and adolescent psychiatrist” as specialist and all others as non-specialists.*
When the incident ADHD medication *would be the outcome (which I would prefer if sample size allows), I think all specialties are to some extent reliable (as prescribing stimulants is generally already quite restricted). However, if assignment to “specialist” is necessary, I would include child and adolescent psychiatrist and pediatricians (as we do not know about how well they are trained).*
By the way, the different requirements for starting ADHD medication—even within Europe—lead to extreme differences in the prevalence of ADHD medication use among children. For example, 0.5% of children in UK and almost 4% of children in the Netherlands had at least one prescription of ADHD medication (Germany: about 2%) [3].
[1] Scholle, O., Kollhorst, B., Riedel, O., & Bachmann, C. J. (2021). First-Time Users of ADHD Medication Among Children and Adolescents in Germany: An Evaluation of Adherence to Prescribing Guidelines Based on Claims Data. Frontiers in Psychiatry*, 12, 653093. Retrieved from https://doi.org/10.3389/fpsyt.2021.653093*

[2] Scholle, O., Fegert, J. M., Kollhorst, B., Öztürk, E. E., Riedel, O., & Kölch, M. (2020). Predictors for Receiving Medication and/or Psychotherapy in Children Newly Diagnosed With ADHD: A Longitudinal Population-Based Cohort Study. Journal of Attention Disorders*, 24(2), 255–264. Retrieved from https://doi.org/10.1177/1087054718816172*
[3] Bachmann, C. J., Wijlaars, L. P., Kalverdijk, L. J., Burcu, M., Glaeske, G., Schuiling-Veninga, C. C. M., … Zito, J. M. (2017). Trends in ADHD medication use in children and adolescents in five western countries, 2005–2012. European Neuropsychopharmacology*, 27(5), 484–493. Retrieved from https://doi.org/10.1016/j.euroneuro.2017.03.002*

EFEMERIS/POMME (France)

*In France it is recommended that general practitioner's who think that a child is suffering from ADHD send it to a **child psychiatrist, a pediatrician or a neurologist**.*
*The **FIRST prescription** must come from one of these specialist working in an **hospital** (or from a hospital sleep center). The prescription can be renewed by GPs or private pediatricians or psychiatrists. **Methylphenydate** is the only medication marketed for ADHD in France. It can be prescribed for a maximum of 28 days on a special form.*

Appendix 10 Subtask 1.3.7 - Breastfeeding

Task 1.3 Subtask 1.3.7 Breastfeeding
Version: 5

1. Overview of ConcePTION WP1 Task 1.3 and Task 1.3.7

Task 1.3 has been set up to "To develop definitions and validate proposed algorithms to identify outcomes of interest, exposure and confounders and produce background and disease-specific prevalence rates of pregnancy outcomes".
In Work Package 1, Task 1.2, a "pre-protocol" document was agreed which describes methodological approaches to medication safety studies in pregnancy, including the definitions of outcome, exposure and confounders. Task 1.3 will operationalise Task 1.2 in the databanks selected for Demonstration Projects. The 7 subtasks in Task 1.3 will aim to validate (e.g. from literature reviews, direct applications to DAPS or expert consultations etc.) the identification of specific outcomes in different health care databases.
This task is developed in conjunction with work designed to meet the aims of the Demonstration study: Exposure to SSRI/SNRI and depression in pregnancy and long-term childhood outcomes: the effect of modifying factors (copied below for reference):
A medication utilisation and disease prevalence study will assess the prevalence of depression and the pattern of SSRI and SNRI (Serotonin and norepinephrine reuptake inhibitors) use in women before, during, and after pregnancy. Patterns of co-medication and breastfeeding will also be described plus variation by country, age, parity, socioeconomic, and educational status. A medication safety study will assess the risk of long-term neurodevelopmental outcomes in children, taking into account the mental health of the mother [over time,] breastfeeding, and other confounders. The impact of this study will be to help create evidence-based clinical guidelines on risks and benefits of antidepressant treatment in pregnancy and to establish appropriate methodology for post-marketing surveillance in relation to long term neurodevelopmental outcomes..
Note to DAPs. To meet the stated aims of task 1.3.7, the only additional data collection for this task is prevalence of breastfeeding (any) at time points to be agreed (likely birth, 4-6 weeks, ?6 months) and use of medication of interest in weeks 1-6 of infant's life. Data will be described and used to explore existing outcomes and statistical techniques.

2. Task 1.3 Aims

The aim of Task 1.3 is to make recommendations for future analyses in the Demonstration Projects. Specifically, this subtask should:

- Develop definitions and validate proposed algorithms to identify outcomes of interest, exposure and confounders;
- Produce background and disease-specific prevalence rates
- Develop the criteria for determining which DAPS have data suitable for analysis for the specified outcomes
- Provide recommendations on any specific analyses relating to the specified outcomes (if appropriate).

Aims of Task 1.3.7

1.3.7 will address the above aims for infant feeding by:

- Examining the availability, status, provenance and validity of breastfeeding data at any postnatal age in the databanks used in the demonstration projects and

- Investigating selected factors associated with breastfeeding status including specified prescription medications and diagnoses.

3. Rationale and background to 1.3.7

Suboptimal breastfeeding is one of the main threats to global health (Lawn et al 2014). The impact of breastfeeding on infants and mothers is well documented in epidemiological studies (Victora et al 2016). These include reductions in: infant mortality from infectious diseases, diarrhoea, respiratory infections, acute otitis media, asthma/ wheezing, malocclusion, obesity and type 2 diabetes; maternal breast and ovarian cancer, type 2 diabetes, necrotising enterocolitis and sudden infant death syndrome (Victora et al 2016). Accordingly, epidemiologists concerned with maternal, infant and child health need to consider the effect of breastfeeding. One of the few randomized control trials in breastfeeding, conducted in Belarus, indicated a positive impact on children's cognitive enhancement (Kramer, 2008), indicating that all studies of childhood 'cognitive performance' should consider how breastfeeding may influence these outcomes. Associations between infection in infancy and breastfeeding are also too large to be overlooked with one study observing reduced risks of admission for diarrhoea RR 0.28, 0.16-0.50 and for respiratory infections RR 0.43, 0.35-0.55 (Horta et al 2013).

Women using prescription medications are less likely to breastfeed, particularly if there is little information about the transfer of the medication to breastfed infants (Saha, 2015). Therefore, when evaluating infant and childhood outcomes, it is important to separate the effect of the exposure to medications *in utero* from the effect of 'not breastfeeding'. In Wales, antidepressant prescriptions in late pregnancy are associated with reduced breastfeeding prevalence at 6-8 weeks (aOR 0.81, 95%CI 0.67-0.98) (Jordan, 2019). In any subsequent follow up of this population, we shall need to account for this association. When applying this research, it will be important to define target behaviours: for example, should the emphasis be on prescription reduction or breastfeeding support? Linear relationships between economic deprivation and breastfeeding (Jordan, 2005; Jordan, 2009) and antidepressant prescribing (Jordan, 2019) are compounding socio-economic disadvantage, and introducing complexity into statistical models.

The physiology of lactation initiation is complex, and vulnerable to disruption by prescribed medications (Jordan et al 2005, 2009, 2019). Breastfeeding at 6, 12 or 26 weeks indicates a healthy dyad, and warrants consideration as an outcome measure. Initiation of breastfeeding is usually regarded as indicating intention, rather than successful breastfeeding (McAndrew, 2012).

Outcomes of interest (WHO 2018)

The outcomes of interest considered critical for decision-making included the following:
■ early initiation of breastfeeding within one hour after birth
■ any breastfeeding at 4–6 weeks
■ exclusive breastfeeding at 4–6 weeks
■ any breastfeeding at 6 months
■ exclusive breastfeeding at 6 months
■ giving any additional foods or fluids in the first 2 days after birth
■ use of artificial teats and bottles in the first 6 months.

4. Research questions and objectives

The key objectives of Subtask 1.3.7 Breastfeeding are to:

1. Examine the availability, status, provenance and validity of breastfeeding data at any postnatal age in the databanks used by the databanks in the demonstration projects (DP)s.
2. Report on the definitions and terminology used when recording infant feeding in each data source (see Appendix 3: Breastfeeding glossary).
3. Investigate the extent to which selected prescription medications and recorded diagnoses are associated with breastfeeding status (initiation, at 6 weeks, and duration).
4. Explore the impact of factors associated with breastfeeding status (including maternal age at childbirth, SES, maternal and infant ill-health) to validate future analyses concerning breastfeeding and outcomes.
5. Compare breastfeeding rates and other data with external sources (section 7 below).

5. Study population

All pregnancies with a known live birth outcome and survival of mother and infant to time point of breastfeeding recorded in populations defined by each DP. Timing of pregnancy will be as in the DP/ umbrella standardization protocols.

6. Study variables

a. Table 1. Study variables

Breastfeeding definition / outcome (no ICD10 codes)		
		Comments
Terms	"Breastfeeding OR Lactation OR Breastfe* OR Breast-fe* OR "Breast fe*" OR Lactat* OR "Infant feed*" OR "Infant Nutrition"	These terms are used in literature searches. They may be useful to search databanks.
Time points	Birth/ day 1,4- 6 weeks, 12 weeks, 26 weeks, 1 year As in database	Assume no initiation as infant ages. Feeding at all time points will be described as percentages / proportions. Feeding at 4-6 weeks will be subjected to inferential analyses.
Completeness	Exclusive, partial, any (see glossary for definitions)	We shall use 'any' breastfeeding in inferential analyses.

b. 6.2 Factors affecting breastfeeding (Table 2 and 3 in excel file)

Maternal Factors

A small number of women are advised against breastfeeding (see limitations). We shall explore, descriptively, these exposures:
Clozapine (ATC N05AH02) in pregnancy
Lithium (ATC N05AN / N05AN01) in pregnancy)
Breast cancer (Wales only)
Breastfeeding is affected by demographics and lifestyle. The following factors will be as recorded in the DP and the breastfeeding rates will be described:

- Year of birth

- Maternal age
- SES (at birth)
- Parity (primip/ multip)
- Smoking (y/n)
- BMI
- Heavy alcohol use ever (y/no record)
- Substance misuse ever (y/no record) (Available in Wales only)
- Community mental health team referral ever (y/no record) (Available in Wales only)
- Mode of delivery (Available in Wales only)

Other factors are discussed under 'limitations'. We believe it will be outside the scope of the project to collect data on variables such as mastitis.

Infant Factors We shall describe breastfeeding rates for infants at risk of 'not breastfeeding'.

- Infants with galactosaemia (ICD10=74.2) will be described but excluded from further analysis.
- Infants with congenital anomalies will be defined in all DPs. These infants will be excluded from the main analysis. The proportion of infants with congenital anomalies (any) and cleft palate who are breastfeeding will be described. The categories of anomalies to be described can be expanded where numbers permit e.g. Down syndrome.
- Preterm birth <32 and <37 weeks
- SGA <10th and <3rd centile (or equivalent in DAP)
- Twin or higher multiple
- Variables being defined in DP 2 (antidepressants)

c. 6.3 Exposures

Exposures will be as defined by DPs (Table 2 and in excel file). Table 2, below will be repeated for each medication group or medication of interest.

Table 2 : Exposures affecting breastfeeding

Exposures affecting breastfeeding		
Variable	*Definition in words*	*Categorization*
Prescribed medications in pregnancy		Details as in rest of study
High dose	Maximum tablet strength	If in the DP
Other dose		
Co-prescriptions		If in the DP
Indication for prescription		
Medicated depression		
Unmedicated depression		
Co-morbidities		As in the DP
Discontinuation of prescription in T1		
Discontinuation of prescription pre-pregnancy		
Prescriptions in T2 or T3		

Prescriptions during breastfeeding weeks 1-6		

* Note. This may not be possible for all conditions, and is for discussion. We have previously published using 'depression medicated' and 'depression unmedicated'. This is confounded by severity of indication, and is predicated on the depression diathesis hypothesis; however, it represents one strategy to explore the contributions of both the medications and the condition.

7. Data Sources

a. External Data

External databanks for comparisons: WHO 2019, UNICEF 2018, Theurich et al 2019, Bagci Bosi et al 2016, national statistics (e.g. NHS England 2020, Stats Wales 2019, Infant feeding survey). These surveys and NHS data records report breastfeeding rates at specified infant ages. The provenance of the data and data entry methods and any information on incentivisation (Bagci Bosi et al 2016) will be described.
Earlier work has explored the impact of: medications (any), antidepressants, AEDs and asthma medications on breastfeeding rates (Jordan et al in preparation has a review). There are also suggestions that infants exposed to AEDs *in utero* are protected from transgenerational ADRs; however, the only data identified to date are based on a volunteer cohort (Veiby et al 2013). We shall compare findings with the database studies identified in our literature search (in progress) (e.g. Ito et al 1995, Gorman & Chambers 2012, Kronenfeld et al 2018).

b. Participating registries

The ConcePTION databanks working on this subtask of DP 1.2 will be France, Tuscany and Wales.

Table 2 Collaborators providing breastfeeding data in Task 1.3.7

REGISTER
France
EFEMERIS : Evaluation chez la Femme Enceinte des MEdicaments et de leurs RISques (Evaluation in Pregnant Women of MEdications and their RISK) Toulouse
Italy
Tuscany birth path for pregnancy Anna
UK
Wales, SAIL

8. Methods

a. Information to be collected from databanks

Study variables are listed in section 6, above.
Issues such as timing of medication exposures will use the methods determined/specified by the DPs
We have surveyed the DPs with breastfeeding data, asking them to complete the table below.

Table 3. DAP survey

Specify how you plan to identify breastfeeding in your data source Search terms from the literature include:	

"Breastfeeding OR Lactation OR Breastfe* OR Breast-fe* OR "Breast fe*" OR Lactat* OR "Infant feed*" OR "Infant Nutrition"	
Specify the infant ages for data collection for breastfeeding	Initiation / birth 6, 12, 26 weeks, 1 year As in database
Specify the years of data collection	
Specify the extent of breasting e.g. exclusive, any	
Information from existing DP for rest of subtask.	

b. Analytic methods

Tables are drafted in the attached excel file.

Cases to be excluded from analyses: infant not surviving to 6 weeks. Inferential analyses will exclude dyads with contra-indications to breastfeeding (maternal lithium, clozapine, infant galactosaemia). , Multiple pregnancies Will be treated as in rest of DP. See above and limitations, below.

i. Descriptive aggregate results for all live births, breastfeeding:

a) At time points of birth or 1 day, 4-6 weeks and 6 months (if available), numbers of live and surviving births with any record of whether the mother breastfed at all.
b) At time points of birth or 1 day, 4-6 weeks and 6 months (if available), numbers of live births who were breastfed exclusively or not. (if we have >1 country?)
c) Distribution of all variables listed in 2 and in attached excel table 2

ii. Descriptive aggregate results for those with breastfeeding information (inferential unadjusted) (Section 6, above):

d) Proportions not breastfeeding, breastfeeding any at 4-6 weeks are to be reported as in excel table 2:

- Age of mother
- Year of birth of baby
- Mother's SES at birth
- Maternal smoking in pregnancy
- Maternal heavy alcohol use ever
- Community mental health team referral ever
- Parity
- BMI
- Twins / multiples
- Maternal depression. If possible medicated and unmedicated.
- Congenital anomalies
- Preterm births <32 and <37 weeks
- SGA < 3rd and 10th centile.
- Medications listed according to DP. If possible, high dose and low dose.
- Mode of delivery (Wales only)
- Maternal substance misuse, ever (Wales only)

The categorisations and explicit definitions are provided for each maternal/child factor are outlined in task 1.2 Section 6, and in the umbrella protocol, the DP protocol and the standardisation protocol.

The above data will be presented separately for each DAP and, if appropriate, summary measures will be obtained across all DAPS. Numbers 1-4 will not be disclosed.

iii. Comparison of breastfeeding rates with country-specific rates.

We shall describe breastfeeding rates in participating DAPs (Table 1 in excel file). We shall also tabulate comparisons with data collected by other sources for participating countries and all high-income countries (examples in table 4). (These comparisons will be illustrative, and not subjected to inferential analyses.

Table 4 Examples of comparator data

	UNICEF 2018				WHO 2019*	
Country	Year	Ever breastfed %	Year	Any breastfeeding 4-8 weeks %	Year	Infants exclusively breastfed for the first six months of life (%)
France	calculated 2016	63			-	-
Italy	calculated 2016	86			1999	5
UK	calculated 2016	81			2010	1
High income	Calculated 2016	79**			2016	~1
Wales (Stats Wales 2020)	2020	64.5	2020	39	2020	32
Scotland (2019)	2019	65	2019	43		-

* From: GHO | By category | Exclusive breastfeeding under 6 months - Data by country (who.int)
** 74% in USA, 54% in Ireland

We shall also describe the proportion of women initiating breastfeeding (recorded as breastfeeding at birth/ day 0/ day 1) who are not breastfeeding at 4-6 weeks. This will identify the women who tried to breastfeed, but with limited success. Women not intending to breastfeed rarely initiate breastfeeding (Jordan et al 2005). As described in Table 1 in excel file, this will be calculated from existing data, without additional variables.

iv. Breastfeeding at 4-6 weeks (Inferential adjusted)

Outcome: Breastfeeding rates for specified time point (4-6 weeks). Excel sheet, tables 2a & 2b, lists possible covariates. Covariates to be entered as above.
Logistic regression models will be built, using covariates in section 6. Outcome variable will be 'any breastfeeding at 4-6 weeks'.
If there are sufficient data, we shall also explore an outcome variable 'change in breastfeeding status between birth an 4-6 weeks'. Dyads that did not initiate breastfeeding will be described and excluded from this analysis.

v. Sensitivity analyses of cases excluded from analyses:

- Exposed to medication or disease posing greater risk than exposure under consideration, to be defined from above cross tabulations. These are likely to include: substance misuse, heavy alcohol use, insulin (as marker for type 1 diabetes), AEDs, antispychotics.
- Infants at increased (but not 100%) risk of not breastfeeding: congenital anomalies, birth <32, <37 weeks, SGA <3rd centile.

Selection of exposures and conditions will be informed by earlier analyses. Data for Wales 2004-2010 are appended. These are copied from Jordan et al 2019, supplementary material.

vi. A priori Subgroup analyses

We shall examine the impact of antidepressants on breastfeeding rates in: 'At risk' women: substance misuse/ heavy alcohol use, insulin use, AED use, community mental health team clients, cancer, MS, lowest socio-economic status (5th Townsend quintile). Examples from Jordan et al 2016 indicate the impact of SSRI exposure on the rates of congenital anomalies in these vulnerable groups.

'At risk' infants: preterm <32, <37 weeks, SGA <3rd centile, congenital anomalies., twins, birth by section.

Some medications of interest in Conception (e.g. chemotherapies, monoclonal antibodies) are not recommended during breastfeeding. We anticipate undertaking an exploratory analysis in one database (Wales).

vii. 7. Breastfeeding as a mediator or confounder

For some outcomes e.g. neurodevelopment, breastfeeding may be a mediator, rather than a confounder. This will be explored by testing the impact of

a) medication of interest (e.g. antidepressant, baclofen) on breastfeeding (as above)
b) breastfeeding on outcome of interest (neurodevelopment, infections) (Jordan et al in preparation) DP 1.2 is planning to include breastfeeding as a covariate in the neurodevelopmental outcomes.

Should these conditions be met, we shall seek further funding to explore causal models.

9. Dissemination plan

The results will also be used to identify the characteristics of women who do not breastfeed at 4-6 weeks despite initiation of breastfeeding. This behaviour pattern often indicates a willingness to breastfeed, but a difficulty in sustaining feeding. Characterisation of women most at risk will inform healthcare professionals as to which women need additional support.

Paper 1
Breastfeeding in 3 European countries: the impact of prescribed medications

Paper 2
Breastfeeding as a mediator or confounder in pharmacovigilance (section 7 above)

10. Limitations of task 1.3.7

Information on infant feeding is rarely reported in pharmaco-epidemiological studies (Jordan et al in preparation). Breastfeeding is basically recommended for all mothers with few exceptions. This study will not be able to exclude all mothers with contraindications to

breastfeeding, but numbers will be low. We shall not be able to identify women diagnosed with open TB or HIV infections. Some medications of interest in Conception (e.g. chemotherapies, monoclonal antibodies) are not recommended during breastfeeding. We anticipate undertaking an exploratory analysis in just one database (Wales).

Breastfeeding is complicated by serious illness in infant or mother. It will not be possible to identify all dyads affected by serious illness, for example, we are unable to identify admissions to NICU. However, despite infant admission to intensive care, mothers are encouraged to breastfeed, and the rates of 'any breastfeeding' at 4 weeks of life in NICU (~60%) or discharge from NICU (~43%) are comparable with national rates (Akuma et al 2018). We are unable to identify use of milk banks (there are none in Wales), donor milk or wet nursing, which is often informal.

We acknowledge that discontinuation of breastfeeding is sometimes associated with mastitis (ICD10 codes: JB45 Infections of breast associated with childbirth, GB21 Inflammatory disorders of breast, GB21.Y Other specified inflammatory disorders of breast), particularly as breastfeeding progresses, but we may not have resources to explore this. Return to work is a further consideration, but this is relatively unusual before 6 weeks in Europe. It is very difficult to explore this and other social factors in electronic data.

Breastfeeding data is as reported by mothers or carers to or observed by health visitors, nurses, midwives or data collected. No reimbursement is associated with these data. As with many variables in Conception (smoking, alcohol use) we are unable to explore any social desirability response.

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12. Appendices

Appendix 1 Infants at increased risk of not breastfeeding. (from Jordan et al 2019, S2 file)

Table B1. Infants exposed to Insulin or Anti-epileptic drugs [AEDs]

	exclusions = anomalies + TOPFAs [n=113316]					exclusions = anomalies + TOPFAs [n=113316]				
	insulin in trimester 1					AEDs in trimester 1				
	Exposed n [%]	% without unknown outcome	Unexposed n [%]	% without unknown outcome	unadjusted OR [95% CI	Exposed n [%]	% without unknown outcome	Unexposed n [%]	% without unknown outcome	unadjusted OR [95% CI
Breastfeeding 2004-2010										
at birth										
Yes	165 [23.98]	45.83	25,930 [23.02]	52.3	0.77 [0.63, 0.95]	226 [19.42]	40.5	25,869 [23.07]	52.38	0.62 [0.52, 0.73]
No	195 [28.34]	54.17	23654 [21]	47.7		332 [28.52]	59.5	23,517 [20.97]	47.62	
Total without unknowns	360 [52.33]	100	49,584 [44.02]	100		558 [47.94]	100	49,386 [44.03]	100	
Unknown	328 [47.67]		63,044 [55.98]			606 [52.06]		62,766 [55.97]		
Total	688 [100]		112,628 [100]			1164 [100]		112,152 [100]		
at 6-8 weeks										
Yes	75 [10.9]	25	13,,102 [11.63]	32.59	0.69 [0.53, 0.90]	84 [7.22]	19.31	13,093 [11.67]	32.68	0.49 [0.39, 0.63]
No	225 [32.7]	75	27100 [24.06]	67.41		351 [30.15]	80.69	26,974 [24.05]	67.32	
Total without unknowns	300 [43.6]	100	40,202 [35.69]	100		435 [37.37]	100	40,067 [35.73]	100	
Unknown	388 [56.4]		72,426 [64.31]			729 [62.63]		72,085 [64.27]		
Total	688 [100]		112,628 [100]			1164 [100]		112,152 [100]		

Table B2. Infants exposed to coumarins or heavy drinking or substance misuse (exclusions = anomalies + TOPFAs [n=113316])

	coumarins [anticoagulants] in trimester 1					heavy drinking/ substance misuse				
	Exposed n [%]	% without unknown outcomes	Unexposed n [%]	% without unknown outcomes	unadjusted OR [95% CI	Exposed n [%]	% without unknown outcomes	Unexposed n [%]	% without unknown outcomes	unadjusted OR [95% CI
Breastfeeding 2004-2010										
at birth										
Yes	57 [14.92]	39.58	26,038 [23.06]	52.29	0.60 [0.43, 0.84]	294 [16.38]	35.94	25,801 [23.14]	52.52	0.51 [0.44, 0.59]
No	87 [22.77]	60.42	23762 [21.04]	47.71		524 [29.19]	64.06	23,325 [20.92]	47.48	
Total without unknowns	144 [37.7]	100	49,800 [44.1]	100		818 [45.57]	100	49,126 [44.05]	100	
Unknown	238 [62.3]		63,134 [55.9]			977 [54.43]		62,395 [55.95]		
Total	382 [100]		112,934 [100]			1795 [100]		111,521 [100]		
at 6-8 weeks										
Yes	16 [4.19]	14.68	13161 [11.65]	32.58	0.36 [0.21, 0.61]	117 [6.52]	17.94	13,060 [11.71]	32.77	0.45 [0.37, 0.55]
No	93 [24.35]	85.32	27,232 [24.11]	67.42		535 [29.81]	82.06	26,790 [24.02]	67.23	
Total without unknowns	109 [28.53]	100	40,393 [35.77]	100		652 [36.32]	100	39,850 [35.73]	100	
Unknown	273 [71.47]		72,541 [64.23]			1143 [63.68]		71,671 [64.27]		
Total	382 [100]		112,934 [100]			1795 [100]		111,521 [100]		

Table B3. Infants excluded from the analysis: those with congenital anomalies or multiples

	exclusions = anomalies + TOPFAs [n=113316]					no exclusions [n=117717]				
	Multiples					anomalies including TOPFAs				
	Exposed n [%]	% without unknown outcomes	Unexposed n [%]	% without unknown outcomes	unadjusted OR [95% CI	Exposed n [%]	% without unknown outcomes	Unexposed n [%]	% without unknown outcomes	unadjusted OR [95% CI
Breastfeeding 2004-2010										
at birth										
Yes	487 [18.81]	52.14	25,608 [23.13]	52.25	1.00 [0.88, 1.13]	700 [15.91]	47.78	26,095 [23.03]	52.25	1.00 [0.88, 1.13]
No	447 [17.27]	47.86	23,402 [21.13]	47.75		765 [17.38]	52.22	23,849 [21.05]	47.75	
Total without unknowns	934 [36.08]	100	49,010 [44.26]	100		1465 [33.29]	100	49,944 [44.07]	100	
Unknown	1655 [63.92]		61,717 [55.74]			2936 [66.71]		63,372 [55.93]		
Total	2589 [100]		110,727 [100]			4401 [100]		113,316 [100]		
at 6-8 weeks										
Yes	196 [7.57]	25.42	12,981 [11.72]	32.67	0.70 [0.60, 0.83]	315 [7.16]	26.72	13,177 [11.63]	32.53	0.70 [0.60, 0.83]
No	575 [22.21]	74.58	26,750 [24.16]	67.33		864 [19.63]	73.28	27,325 [24.11]	67.47	
Total without unknowns	771 [29.78]	100	39,731 [35.88]	100		1179 [26.79]	100	40,502 [35.74]	100	
Unknown	1818 [70.22]		70,996 [64.12]			3222 [73.21]		72,814 [64.26]		
Total	2589 [100]		11,0727 [100]			4401 [100]		113,316 [100]		

Appendix 2. Breastfeeding information From DP 1.2

Table 1 Region, time period and pregnancies covered for data sources used in this study (pending data characterisation results)

Region	Data sources (bold provide ND outcomes, italic breast feeding)	Time period	Pregnancies in period covered (1,000)
France			
Haute-Garonne	***EFEMERIS database***	2004-2017	137
Haute-Garonne	***POMME database***	Two birth cohorts (2010, 2015), both followed until end of 2017 (soon data on 2018 will be added)	18
Italy			
Tuscany	**SALM – mental health services,** CAP and *CAP2 – birth registry*, SPF – dispensation of medications in community pharmacies, FED – dispensations of medications from hospital pharmacies for outpatient use	2003- (2010 with ND outcomes)	480
United Kingdom			
Wales	**In-patient and out-patient PEDW records, Primary Care GP dataset, *National Community Child Health Database (NCCHD),*** CARIS congenital anomaly registry	1998, breastfeeding 2005-	945

Appendix 3: Breastfeeding Glossary

Breastfeeding as an outcome measure or confounder is not straightforward in terms of timing of recording and reporting. The infant feeding literature offers little consistency regarding the timing of data collection. Consequently, to compare data sets commonalities will need to be determined. Definitions of full and partial breastfeeding will need to be considered.

It is recognised that the WHO categories of breastfeeding do not allow finer distinctions; for example, they would classify as complementary feeding the mother giving an occasional formula feed, and therefore almost fully breastfeeding, and the mother giving an occasional breastfeed, and therefore almost exclusively formula feeding. In addition, the WHO definition of complementary feeding does not allow distinguishing between feeding with and without the use of formula. Monitoring systems, or more often operational research, willing to gain a better understanding of different patterns of infant feeding, may add categories to the WHO definitions, provided they use them anyway for international comparisons (EC 2008 p.11). Therefore, some databanks ask those entering data to estimate % breastmilk e.g. NHS Wales 2017.

Term	Definition	Reference	Notes
Breastfeeding	Breastmilk, including wet nurse or expressed milk via tube or cup or syringe	WHO 1991, 2008	
Completeness			
Exclusive / total	Infant receives only breast milk from his/her mother or a wet nurse, or expressed breast milk via tube, cup or syringe, and no other liquids or solids with the exception of drops or syrups consisting of vitamins, mineral supplements or medication.	EC 2008, based on WHO 1991, 2008	
	Only breastmilk or essential medications. *It is intended that milk feeding should be recorded as exclusive breast milk feeding even if solid food has been introduced if breast milk is the only source of fluids. As other drinks are introduced milk feeding should be recorded as combined milk feeding (predominant or partial as appropriate).*	NHS Wales 2017	
Predominant	Predominant breastfeeding: the infant's predominant source of nourishment is breast milk. However, the infant may also receive water and water-based drinks; Oral Rehydration Solution (ORS); drop and syrup forms of vitamins, minerals and medications; and ritual fluids (in limited quantities).With the exception of fruit juice and	EC 2008, based on WHO 1991, 2008	

	sugar-water, no food-based fluid is allowed under this definition.		
Full	Predominant or exclusive	EC 2008	Use this portmanteau term will avoid differences in data collection
Partial or mixed	Currently receiving breast milk (this may be expressed breast milk) at 6 weeks of age and who are also receiving formula milk or any other liquids or food.	NHS England 2014	
Complementary	Breastmilk plus solid or semi-solid foods or liquids, including non-human milk	WHO 1991, 2008	
Combined milk feeding – predominantly breast	>75% of the feeds in the previous 24 hours were breastfeeds	NHS Wales 2017	
Combined milk feeding – partially breast	75% or less of the feeds in previous 24 hours were breastfeeds	NHS Wales 2017	
Any	Full or complementary or combined	NHS Wales 2017	
Bottle feeding	Liquid or solid from a bottle with a teet, including breastmilk fed this way.	WHO 1991, 2008	Finland would not include bottle-fed breastmilk in this category
Artificial milk feeding	Formula milk and any other drink but no breast milk	NHS Wales 2017	
Other terms			
Continued breastfeeding	Breastfeeding (any) after 12 months	WHO 1991	
Galactagogue	A galactagogue is a material or action that stimulates milk production.	Lawrence 2011	
Infant formula	The Federal Food, Drug, and Cosmetic Act (FFDCA) defines infant formula as "a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk" (FFDCA 201(z)). FDA regulations define infants as persons not more than 12 months old (Title 21, Code of	Source: Excerpted from Guidance for Industry: Frequently Asked Questions about FDA's Regulation of Infant Formula March 1, 2006. Cited in FDA 2018	

	Federal Regulations 21 CFR 105.3(e)). 3 main types: modified bovine (or goat/ hircine) whey, soy (phyto-oestrogens may be problematic), hydrolysed "hypo-allergenic". Not to be confused with 'follow on' milk, which is not regulated.		
Ritual fluids	Typically herbal preparations or teas. These may include water (boiled or otherwise) from the family source. They may be the 1st intake, as colostrum is not always offered (considered unclean).	Davies-Aetugbo 1997	
Support	From the first feed, women should be offered skilled breastfeeding support (from a healthcare professional, mother-to-mother or peer support) to enable comfortable positioning of the mother and baby and to ensure that the baby attaches correctly to the breast to establish effective feeding and prevent concerns such as sore nipples. Extra support should be given following narcotics, general anaesthetics, sections, delayed skin-to-skin contact.	NICE 2014, 1.3.15	
Timely complementary feeding	Complementary feeding over 6 months	WHO 1991	
Weaning	Introducing solid foods or complementary feeding	NHS 2019	

Outcomes of interest (WHO 2018)

The outcomes of interest considered critical for decision-making included the following:
- early initiation of breastfeeding within one hour after birth
- any breastfeeding at 4–6 weeks
- exclusive breastfeeding at 4–6 weeks
- any breastfeeding at 6 months
- exclusive breastfeeding at 6 months
- giving any additional foods or fluids in the first 2 days after birth
- use of artificial teats and bottles in the first 6 months.

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NHS 2019 Your Baby's first solid foods. https://www.nhs.uk/conditions/pregnancy-and-baby/solid-foods-weaning/

NHS England 2014 Data flows for direct commissioning: <12 week *Maternal Assessment, Breastfeeding Initiation & 6 to 8 weeks breastfeeding UNIFY Collections: Guidance & Frequently Asked Questions* NHS England, Quarry House, Quarry Hill, Leeds, LS2 7UE https://webcache.googleusercontent.com/search?q=cache:1TxqojqrkC8J:https://www.england.nhs.uk/statistics/wp-content/uploads/sites/2/2014/03/BFI-12-WRA-Guidance-Document.doc+&cd=13&hl=en&ct=clnk&gl=uk

NHS Wales Data Dictionary 2017 http://www.datadictionary.wales.nhs.uk/#!WordDocuments/infantfeedingdatarequirements.htm

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Appendix 11 Medication, ATC code and P-gp or BCRP substrates (S) or inhibitors (I) status

Medication	ATC code	P-gp transporter substrate/ Inhibitor	BCRP transporter substrate/ Inhibitor
Ranitidine	A02BA02	S	
Famotidine	A02BA03	S	
Nizatidine	A02BA04	S	
Omeprazole	A02BC01	S,I	I
Pantoprazole	A02BC02	S,I	S,I
Lansoprazole	A02BC03	S,I	I
Rabeprazole	A02BC04	I	I
Loperamide	A07DA03	S,I	I
Sulfasalazine	A07EC01	S	S,I
Olsalazine	A07EC03	S	
Metformin	A10BA02	S	S
Pioglitazone	A10BG03		I
Sitagliptin	A10BH01	S,I	
Repaglinide	A10BX02	S,I	
Dipyridamole	B01AC07	S,I	S,I
Digoxin	C01AA05	S,I	
Flecainide	C01BC04	S,I	
Prazosin	C02CA01	S,I	S,I
Hydrochlortiazide	C03AA03	S	
Furosemide	C03CA01		S,I
Spironolactone	C03DA01	I	
Propranolol	C07AA05	I	
Acebutolol	C07AB04	S	
Celiprolol	C07AB08	S,I	
Labetalol	C07AG01	S	
Carvedilol	C07AG02	S,I	
Amlodipine	C08CA01	S,I	I
Felodipine	C08CA02	I	
Isradipine	C08CA03	I	
Nifedipine	C08CA05	I	I
Verapamil	C08DA01	S,I	I
Diltiazem	C08DB01	S,I	
Simvastatin acid	C10AA01	S,I	I
Simvastatin	C10AA01	S,I	I
Lovastatin	C10AA02	S,I	
Fluvastatin	C10AA04	S	S,I
Atorvastatin	C10AA05	S,I	S,I
Rosuvastatin	C10AA07	S,I	S,I
Miconazole	G01AF04	I	

Bromocriptine	G02CB01	S	
Estradiol (17-beta)	G03CA03		I
Estriol	G03CA04	S	
Progesterone	G03DA04	I	
Dexamethasone	H02AB02	S	I
Methylprednisolone	H02AB04	S	I
Prednisolone	H02AB06	S	
Prednisone	H02AB07	S	
Hydrocortisone	H02AB09	S	
Dicloxacillin	J01CF01	S	
Trimethoprim	J01EA01	S	
Erythromycin	J01FA01	S,I	S
Roxithromycin	J01FA06	S,I	
Clarithromycin	J01FA09	S,I	
Azithromycin	J01FA10	S,I	
Telithromycin	J01FA15	S,I	
Ofloxacin	J01MA01		S
Ciprofloxacin	J01MA02	S	S
Norfloxacin	J01MA06		S
Levofloxacin	J01MA12	S, I	
Moxifloxacin	J01MA14	S	
Nitrofurantoin	J01XE01		S
Tedizolid	J01XX11		I
Ketokonazole	J02AB02	S,I	I
Ketoconazole	J02AB02	S,I	I
Itraconazole	J02AC02	I	
Famciclovir	J05AB09	S	
Oseltamivir	J05AH02	S,I	
Tamoxifen	L02BA01	S,I	
Anastrozole	L02BG03	S	
Letrozole	L02BG04	S	
Cyclosporine	L04AD01	S,I	I
Tacrolimus	L04AD02	S,I	I
Indomethacin	M01AB01	S,I	
Diclofenac	M01AB05		S,I
Meloxicam	M01AC06	I	
Naproxen	M01AE02	I	
Celecoxib	M01AH01	S,I	I
Rofecoxib	M01AH02	I	
Etoricoxib	M01AH05	I	
Diclofenac (topical)	M02AA15		S
Allopurinol	M04AA01		S
Oxycodone	N02AA05	S	

Buprenorphine	N02AE01	S	
Zolmitriptan	N02CC03	S	
Eletriptan	N02CC06	S	
Chlorpromazine	N05AA01	I	
Methotrimeprazine (levomepromazine)	N05AA02	I	
Fluphenazine	N05AB02	S,I	
Perphenazine	N05AB03	I	
Prochlorperazine	N05AB04		I
Thioridazine	N05AC02	I	I
Haloperidol	N05AD01	I	
Ziprasidone	N05AE04	I	
Chlorprothixene	N05AF03	I	I
Clozapine	N05AH02	I	
Quetiapine	N05AH04	I	
Risperidone	N05AX08	S,I	
Aripiprazole	N05AX12	I	I
Lorazepam	N05BA06	S	
Hydroxyzine	N05BB01	S	
Midazolam	N05CD08	I	
Amitriptyline	N06AA09	I	
Citalopram	N06AB04	S,I	
Paroxetine	N06AB05		S
Sertraline	N06AB06	I	
Fluvoxamine	N06AB06	I	
Bupropion	N06AX12	S	S
Tinidazole	P01AB02	I	
Fluticasone	R01AD08	S	
Lidocaine	R02AD02	I	
Budesonide	R03BA02	S	
Montelukast	R03DC03	I	
Cetirizine	R06AE07	S, I	
Levocetirizine	R06AE09	S	
Levocetirizine (R-cetirizine)	R06AE09	S	
Astemizole	R06AX11	S,I	
Terfenadine	R06AX12	S,I	
Loratadine	R06AX13	S	
Acrivastine	R06AX18	S	
Ebastine	R06AX22	I	
Fexofenadine (terfenadine carboxylate)	R06AX26	S	
Fexofenadine	R06AX26	S	
Desloratadine	R06AX27	S	
Desloratadine	R06AX27	S	

Prednisolone (local)	S01BA04	S	
Diclofenac (local)	S01BC03		S
Diclofenac	S01BC03		S

Appendix 12 Covariates available across data sources

	Socioeconomic status (SES), maternal education	Ethnicity	Smoking / alcohol use	BMI	Parity
Finland registers	Mother's occupation (25% missing)	NA	smoking yes/no (recorded at the first antenatal visit)	available only 2004/2005 onwards with 2-5.1% missing	Available
France: EFEMERIS / POMME	Maternal occupation (employed Y/N, 16% missing), level of education (45% missing)	NA	yes/no during pregnancy (60% missing) alcohol use collected but difficult to interpret	NA	Available
Italy – Emilia Romagna	Maternal and paternal employment - maternal education and paternal education. Paternal data could have missing data. To check depending on year. In 2018 we had 4.1% (n=13239 missed values for pat edu, and 3.1% (1004) missed values for pat employment.	Available	Yes/no during pregnancy. if Yes: discontinued before pregnancy, when pregnancy discovered, continued during pregnancy	BMI to be derived	Available
Italy - Tuscany	Among cases with congenital anomalies 2005-2017: maternal employment (40% missing), maternal education (23% missing, among LB with CA 12% missing)	For cases with congenital anomalies: maternal country of birth (28% missing)	Among cases with congenital anomalies: smoking during pregnancy yes/no (26% missing), if yes, n° cigarettes/day (12% missing) alcohol yes/no (44% missing)	For cases with congenital anomalies (26% missing)	Available
Norwegian Registries	Maternal employment status	Maternal country of birth	Yes/no (86% complete)	50% missing	Available
Wales / SAIL linked datasets	SES at birth (100% complete). Based on Welsh Index of Multiple Deprivation (IMD) or Townsend	No data earlier years. Withheld later years, as sensitive.	Categories Codes for SUD or referral for heavy alcohol consumption / substance misuse Smoking >90% complete, but	BMI at start and end of pregnancy/ 1st midwifery appointment ~90% complete from 2015.	~100% complete for primip / multip. After 3rd child data unreliable and low numbers.

			has 'ex-smoker' category	60-70% complete earlier	
Germany / GePaRD	Deprivation index of place of living (complete 100%). Highest educational attainment based on occupational codes available for employees – missing for children, students and retired people	NA	Codes for alcohol abuse / P codes recording harm to child due to alcohol and smoking	Codes for obesity / underweight	To derive based on previous records of pregnancies

Appendix 13 Meta Analytic Techniques for use in ConcePTION

Version: 4 :16/11/2020
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Purpose
The purpose of this document is to suggest possible methods for use by the different demonstration projects for pooling analytic results and aggregate date from the different databases in ConcePTION.
All DPs consist of
Medication Utilisation and Event/Outcome Definition Study:
The aim of the medical utilisation study is to describe the frequency / quantity of prescriptions of specified medications in the database and in particular in pregnant women within the database. The aim of the event outcome definition study is to define specific algorithms to identify outcomes / events. This is likely to involve analysing prevalence of events/outcomes over time and possibly by pre-specified subgroups of interest, in particular pregnant women. But there may be additional information on, for example, groups defined according to socio-economic status
Medication Safety Study:
The aim is to assess the safety in pregnancy of specified medications. Safety will be assessed using a range of outcomes and confounders and mediators are likely to be included in analyses.
It is expected that both study types will use similar meta-analytic techniques to analyse their results when appropriate. However, many of the results from these studies are expected to be database specific and therefore meta-analytic techniques will not be required.

Appropriateness of Conducting a Meta-Analysis
Before combining results between countries, it is key that the effect estimates to be combined are logically comparable. The following questions should be considered before conducting any meta-analysis of effect estimates across countries:

- Are the outcome definitions being analysed by each country the same?
- Are the methods used to obtain exposure definitions comparable between countries?
- Do the countries have comparable medication utilisation profiles?
- Do the data sources being compared have any other underlying differences?

When extreme heterogeneity is present between countries, it would not be advisable to produce a combined effect estimate as its interpretable value is low and may be misinterpreted by readers.

Use of Controls
When combining results from different data sources (especially if they are from different countries) it is highly recommended that all analyses include controls in order to reduce country specific differences. For example in table 1, when IQ scores in children born to women taking a specific medication the IQ score of children of women not exposed to the medication should be also analysed as it will vary by data source.

Table 1: Example of using control data in analysis

Database	**Mean Score Exposed**	**Mean Score Controls**	**Difference in mean score (E-C)**	**Ratio of mean scores (E/C)**
A	100	110	10	1.1
B	100	105	5	1.05
C	80	88	8	1.1
Meta-analysis all studies	Exposed	Control	Diff	Ratio

The ideal measure to summarize across data sources may either be the difference in scores compared to unexposed babies or the ratio of scores . This depends on which you believe to be most relevant. In general it is not advised to combine all the exposed mean scores and then to combine all the control mean scores. This will introduce more variation in the models. with a confidence interval for this difference or the ratio of scores – the difference could be on an arithmetic (the actual difference) or log scale (the proportional difference). Similarly, when analysing the occurrence of SGA, the ideal comparison would be the increased odds of SGA compared to unexposed pregnancies.

Random Effects vs Fixed Effects
When conducting meta-analyses, most methods fall into one of two categories, fixed effect models or random effect models. Fixed effects models assume that the true effect being estimated in each country is the same. However, random effect models assume that the true effect being estimated varies between countries and so the estimates will also vary. The model accounts for this by assuming these estimates will follow a distribution around the true effect (usually a normal distribution). Which models are used should be decided prior to analysing the data.

Bias
When performing meta-analysis, it is recommended that the STATA programs metabias and metafunnel are run to examine potential bias in estimates. This may not be applicable in this situation when you are analysing data from different data sources rather than from published studies. So it is not essential to run these.

Effects of Covariates
The biggest challenge in this analysis is that it is not likely to be possible to fit individual models to the data in each data source, to examine the fit of the data and to adapt the models for each data source. As the data will vary between data sources this means that many may not have the same complete set of covariates. It will need to be decided if multivariate models can be fitted or whether adjusting for each covariate separately may provide sufficient information. If you have access to at least one data base the whole range of models can be fitted and then inferences can be made about the model fitting to other data sets.

Summary of Meta-Analysis Techniques and Procedures in STATA

1. METAN – Meta-analysis of binary or continuous data with fixed or random effects and by subgroups

metan tdeath tnodeath cdeath cnodeath

metan tsample tmean tsd csample cmean csd,

metan logor selogor

metan mean semean

metan mean lowerci upperci

metan percent lowerci upperci (see metaprop below)

2. METAAN - Similar to metan, but a greater range of estimation methods and different inputs :

metaan eff SEeff,

metaan eff effvar, varc

3. METAPROP– Meta-analysis of proportions with fixed or random effects and by subgroups[1]

4. (ftt Calculate the pooled estimate after Freeman-Tukey Double Arcsine Transformation)

metaprop num denom, ftt
But this has been identified as prone to errors[2] so see also GLMM procedure in STATA

5. METAREG : Meta-analysis of binary or continuous data with fixed or random effects relating value(s) of each study to the observed relative riskor mean

metareg logrr latitude, wsse(selogrr)
metareg smd abstract duration itt, wsse(sesmd) permute(10000)

6. MVMETA : Meta-analysis of several variables simultaneously and can include regression[3]

mvmeta b V
b : set of variables all starting with b for example if looking at related factors such as diagnosis other maternal diseases : diabetes , epilepsy, other all as binary variables you would code them b1 , b2 and b3 and do a meta-analysis of the 3 beta's simultaneously.

Additional programs in STATA

7. XTPOiSSON : Analysing counts with random effects / mixed effects models[4]
    a. Can use small time intervals and then model risk(an event occurring within time interval) against potential confounders etc. Gives greater flexibility to use of multilevel models
    b. Stsplit in STATA will create a data set of small time intervals

8. GLST : Generalized Least Squares for trend estimation of summarized dose-response data[5, 6]

glst depvar dose [indepvars] , se(varname) cov(n cases)
Can use to model changes in log(rr) according to dose. So could have potential when looking at SES categories for instance.

9. MEGLM : Multilevel mixed-effects generalized linear model

These can be used to overcome the issues in METAPROP for count data and can also be specified using MELOGIT or MEPOISSON

Meta-analysis of survival curves
The analysis of survival curves is a different situation as there will be estimated probabilities of survival for a set of different time points. These probabilities are all highly correlated and hence should not ideally be analysed without including information about these correlations.

1. Use of MVMETA
The survival probabilities can be combined if there are only 2 or 3 time points. You may need to use the Freeman-Tukey double arcsine transformation to stabilize the variances first.

2. Multivariate meta-analysis on conditional probabilities [7]
MetaSurv in R does this:

i. Calculate probability survival up to fixed time points conditional on survival up to that time point as the conditioning means that the estimates are not correlated
ii. Combine these probabilities
iii. Multiply these together to get overall estimate

However, MetaSurv includes a continuity correction of 0.5, which creates bias for combining small samples sizes. SGUL are writing a program that will include a smaller continuity correction that will reduce the bias.

3. Bayesian multivariate meta-analysis on conditional probabilities
A Bayesian version of the method proposed by Combescure has been developed by SGUL but is currently being assessed in comparison with Frequentist methods.

Potential Issues: Mainly Small Numbers

1. Continuous Measures
Generally OK particularly if analysing means as you can always estimate a mean and its se if you have at least two data points – the lack of data will usually be reflected in the variance. However, if you only have two data points and they are extremely close then the variance may be very low. You do need to examine all your data carefully.

2. Proportions and Odds Ratios
This can be very problematic as you may have no events and hence 0 in specific cells. Many programs either drop all data from that database or else automatically insert a 0.5 and carry on. You need to check what is happening with this. If there are several databases with this issue it may have a large effect on your overall estimates. There is a difference between medication not being prescribed in a country and hence no events with exposure for that medication in the country with no events occurring when the medication is being prescribed. The FTT transformation in METAPROP may introduce bias especially if your databases vary greatly in size.

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Appendix 14 SSRI/SNRI signal anomalies identified in the literature

Evidence for increased risk following SSRI exposure is conflicting with some studies finding no increased risk. A number of signals have been identified:

SSRIs

- all major malformations combined, aOR 1.13, 95% CI 1.06-1.20 (Furu et al., 2015)
- Anencephaly aOR 2.4, 95% CI 1.1-5.1 (Alwan et al., 2007)
- Hydrocephalus RR 2.7, 95% CI 1.5-4.6 (Munch et al., 2014)
- congenital heart defects aOR 1.15, 95% CI 1.05-1.26 (Furu et al., 2015); use throughout first trimester aOR 2.01, 95% CI 1.60 to 2.53; paused SSRI use aOR 1.85, 95% CI 1.07 to 3.20 (Jimenez-Solem et al., 2012).
    - septal heart defects, aOR 2.04 (95% CI 1.53 to 2.72), paused exposure, aOR 2.56 (95% CI 1.41 to 4.64)(Jimenez-Solem et al., 2012)
    - right ventricular outflow tract obstructions, aOR 1.48, 95% CI 1.15-1.89 (Furu et al., 2015)
    - atrial and ventricular septal defects, aOR 1.17, 95% CI 1.05-1.31 (Furu et al., 2015)
- Cystic kidney disease (OR 2.83, 95% CI 1.14–7.04(Colvin et al., 2011); OR 2.39, 95% CI 1.09-4.54 (M Reis and Källén, 2010)
- omphalocele, aOR 2.11, 95% CI 1.01-4.39 (Furu et al., 2015)
- Lower limb reduction (OR 4.20, 95% CI 1.27-13.93) (Colvin et al., 2011)
- Club foot aOR 1.8, 95% CI 1.1-2.8 (Yazdy et al., 2014); aOR 1.34, 95% CI 1.05-1.71 (Furu et al., 2015); aOR 2.2, 95% CI 1.4-3.6 (Louik et al., 2007)
- Craniosynostosis aOR 2.5, 95% CI 1.5-4.0 (Alwan et al., 2007)

Citalopram

- All major congenital malformations aOR 1.36, 95% CI 1.08-1.73; aOR 1.19, 95% CI 1.07-1.31) (Furu et al., 2015)
- craniosynostosis aOR 3.95, 95% CI 2.08-7.52 (Bérard et al., 2017)
- neural tube defects aOR 2.46, 95% CI 1.20-5.07 (Malm et al., 2011)
- congenital heart defects, odds ratio 2.09, 95% CI 1.25-3.51) (Jordan et al., 2016)
    - Septal defects OR 2.52, 95% CI 1.04-6.10 (Pedersen et al., 2009); OR 1.68, 95% CI 1.15-3.0 (Jimenez-Solem et al., 2012)
    - patent ductus arteriosus (OR 5.5, 95% CI, 2.3-13.6 based on 5 exposed cases) (Colvin et al., 2011)
    - and right ventricular outflow tract obstruction (aOR 1.65, 95% CI 1.10-2.48). (Furu et al., 2015)
    - tetralogy of Fallot (N=2, aOR 4.41, 95% CI 1.02-19.15) (Wemakor et al., 2015)
    - Ebstein anomaly (N=1, aOR 12.36, 95% CI 1.61-95.15) (Wemakor et al., 2015)
- abdominal wall defects OR 3.52, 95% CI 1.56-7.91(Jordan et al., 2016)
    - gastroschisis (aOR 5.10, 95% CI 1.46-17.75) (Wemakor et al., 2015)
- omphalocele aOR 2.8, 95% CI 1.3-5.7 (Alwan et al., 2007)
- Congenital urinary tract when pregnancies in non-depressed women were used as the control aOR 2.07, 95% CI 1.10-3.92 for urinary (Ban et al., 2014).
    - hypospadias aOR 3.21, 95% CI 1.56-6.60 (Wemakor et al., 2015); OR 1.69, 95% CI 1.04-2.73 (Jordan et al., 2016)
- digestive system defects when pregnancies in non-depressed women were used as the control aOR 2.60, 95% CI 1.07-6.32 (Ban et al., 2014).
- musculoskeletal defects aOR 1.92, 95% CI 1.40-2.61 (Bérard et al., 2017)

- lower limb abnormalities (OR 9.8, 95% CI 2.3-41.4 (Colvin et al., 2011)

Escitalopram
Escitalopram is the active enantiomer of citalopram – Reprotox authors argue that this should produce the same results as citalopram

- Ebstein anomaly (N=1, aOR 34.19, 95% CI 4.09-286.04) (Jimenez-Solem et al., 2012)
- atrial septal defects (aOR 3.31, 95% CI 1.11-9.90) (Jimenez-Solem et al., 2012)
  - atrial septal defects without severe congenital heart malformations (N=5, aOR 3.62, 95% CI 1.21-10.83) (Jimenez-Solem et al., 2012)
- atrioventricular septal defects (OR 8.71, 95% CI 1.21-62.64) (Jimenez-Solem et al., 2012)
- club foot aOR 2.9, 95% CI 1.1-7.2 (Yazdy et al., 2014) ; (aOR 3.88, 95% CI 1.19-12.69) (Wemakor et al., 2015); OR 2.18, 95% CI 1.16-4.07) (Jordan et al., 2016)

Fluoxetine

- all major malformations combined (aOR 1.25, 95% CI 1.10-1.42) (Furu et al., 2015)
- neural tube defects, odds ratio 2.57, 95% CI 1.21-5.46 (Jordan et al., 2016)
- Ear/face and neck (OR 4.39, 95% CI 1.40-13.79) (Colvin et al., 2011)
- cardiovascular malformations aOR 4.47; 95% CI 1.31-15.27 (Diav-Citrin et al., 2008); (aOR 1.34, 95% CI 1.10-1.63) (Furu et al., 2015)
  - tetralogy of Fallot (aOR 5.03, 95% CI 1.73-14.58) (Wemakor et al., 2015)
  - atrial and ventricular septal defects (aOR 1.45, 95% CI 1.15-1.84) (Furu et al., 2015)
  - atrial septal defects OR 2.53, 95% CI 1.2-5.32 (Jimenez-Solem et al., 2012)
  - right ventricular outflow tract obstructions (aOR 1.95, 95% CI 1.17-3.25) (Furu et al., 2015); (posterior odds ratio 2.0, 95% CI 1.4-3.1) (Wemakor et al., 2015)
  - patent ductus arteriosus OR, 5.9; 95% CI, 1.5–24.0 (Colvin et al., 2011)
  - Isolated ventricular septal defect (aOR 2.03, 95% CI 1.28-3.21) (Malm et al., 2011)
- Digestive (OR 3.08, 95% CI 1.27-7.48) (Colvin et al., 2011)
- pyloric stenosis OR 8.7, 95% CI 2.3–33.2 (Bakker, De Walle, et al., 2010)
- protective for genital defects when pregnancies in non-depressed women were used as the control aOR 0.38, 95% CI 0.16-0.93 (Ban et al., 2014)
- renal dysplasia (aOR 5.76, 95% CI 2.54-13.08) (Wemakor et al., 2015)
- craniosynostosis (aOR 2.8, 95% CI 1.3-6.1) (Alwan et al., 2007); posterior odds ratio 1.9, 95% CI 1.1-3.0 (Wemakor et al., 2015)

Sertraline

- anencephaly (aOR 3.2, 95% CI 1.1-9.3) (Wemakor et al., 2015)

- cardiac malformations (OR 3.0, 95% CI 1.4-6.4) (Kornum et al., 2010); aOR 2.01, 95% CI 1.60-2.53 (Jimenez-Solem et al., 2012)
    - severe congenital heart defects aOR 2.88, 95% CI 1.09-7.61 (Wemakor et al., 2015)
    - Ebstein's anomaly (1 exposed case) aOR 16.42, 95% CI 2.10-128.38 (Wemakor et al., 2015)
    - septal defects aOR 1.34, 95% CI 1.02-1.76 (Bérard et al., 2015); OR 3.25, 95% CI 1.21-8.75 (Pedersen et al., 2009); OR 3.3, 95% CI 1.5-7.5 (Kornum et al., 2010)
    - ventricular septal defects OR 3.6, 95% CI 1.86-6.96 (Jimenez-Solem et al., 2012)
    - atrial septal defects OR 2.85, 95% CI 1.35-5.99 (Jimenez-Solem et al., 2012)
- respiratory system defects when pregnancies in non-depressed women were used as controls (aOR 4.04, 95% CI 1.00-16.27, P=0.049)(Ban et al., 2014); unspecified respiratory system defects (aOR 3.73, 95% CI 1.18-11.82)(Colvin et al., 2011)
- Omphalocele aOR 5.7 , 95% CI 1.6-20.7 (Louik et al., 2007)
- anal atresia aOR 2.47, 95% CI 1.09-5.57(Furu et al., 2015); aOR 4.4, 95% CI 1.2-16.4 (Louik et al., 2007)
- limb reduction defects aOR 3.9, 95% CI 1.1-13.5 (Louik et al., 2007)
- craniosynostosis (aOR 2.03, 95% CI 1.09-3.75, N=3) (Bérard et al., 2015)
- clubfoot aOR 1.76, 95% CI 1.10-2.81(Furu et al., 2015); aOR 3.05, 95% CI 1.09-8.52 (Wemakor et al., 2015)

Paroxetine

- All congenital malformation aOR 1.89, 95% CI 1.20-2.98 (Cole et al., 2007)
- neural tube defects OR 3.3, 95% CI 1.1-10.4 (Yazdy et al., 2014); aOR 3.3, 95% CI 1.1-10.4 (Louik et al., 2007)
    - anencephaly OR 3.2, 95% CI 1.1-9.3 (Werler et al., 2018); posterior odds ratio 3.2, 95% CI 1.6-6.2(Reefhuis et al., 2015), aOR 5.1, 95% CI 1.7-15.3 (Alwan et al., 2007)
- Eye (RR 2.36, 95% CI 1.20-4.66) (Davis et al., 2007)
- congenital heart defects, odds ratio 1.76, 95% CI 1.09-2.85 (Jordan et al., 2016); aOR 1.45, 95% CI 1.12-1.88 (Bérard et al., 2017); OR 1.63, 95% CI 1.17-2.27(Källén et al., 2013); OR 1.66, 95% CI 1.09-2.53 (M. Reis and Källén, 2010); OR 2.22, 95% CI 1.39-3.55(Källén and Otterblad Olausson, 2006); OR 1.63, 95% CI 1.05-2.53 (Källén et al., 2007); OR 2.93, 95% CI 1.52-5.13 (Källén et al., 2007); congenital heart defects when pregnancies in non-depressed women were used as the control (aOR 1.78, 95% CI 1.09-2.88)(Ban et al., 2014)
    - septal defects aOR 1.92, 95% CI 1.09-3.37 (Bérard et al., 2016); atrial or ventricular septal defect was 3.23, 95% CI 1.30-6.65 (Källén et al., 2007)
    - atrial septal defects OR 3.51, 95% CI 1.57-7.87 (Jimenez-Solem et al., 2012); aOR 5.7; 95% CI, 1.4-23.7(Bakker, Kerstjens-Frederikse, et al., 2010); posterior odds ratio 1.8, 95% CI 1.1-3.0 (Reefhuis et al., 2015)
    - ventricular septal defect OR 2.61, 95% CI 1.47-4.62 (Jordan et al., 2016); aOR 1.91, 95% CI 1.03-3.98 (Bérard et al., 2016)
    - ventricular septal defects without severe congenital heart defects aOR 2.12, 95% CI 1.15-3.92(Bérard et al., 2016)
    - right ventricular outflow tract obstruction aOR 2.54, 95% CI 1.31-4.90 (Furu et al., 2015); aOR 4.68, 95% CI 1.48-14.74 (Malm et al., 2011); OR 3.3, 95% CI 1.3-8.8 (Yazdy et al., 2014); posterior odds ratio 2.4, 95% CI 1.4-3.9(Reefhuis et al., 2015); OR 2.5, 95% CI 1.0-6.0 (Werler et al., 2018)
    - conotruncal and major arch anomalies aOR 2.27, 95% CI 1.01-5.07 (Furu et al., 2015)

    - anomalies of pulmonary artery OR 19.94, 95% CI 6.00-66.22 (Colvin et al., 2010, 2011)
- clubfoot OR 5.8, 95% CI 2.6-12.8 (Yazdy et al., 2014); aOR 5.8, 95% CI 2.6-12.8 (Louik et al., 2007)
- gastroschisis posterior odds ratio 2.5, 95% CI 1.2-4.8 (Reefhuis et al., 2015); OR 2.9, 95% CI 1.0-8.4 (Werler et al., 2018), aOR 2.9, 95% CI 1.0-8.4 8 (Alwan et al., 2007)
- omphalocele OR 8.1, 95% CI 3.1-20.8 (Werler et al., 2018); posterior odds ratio 3.5, 95% CI 1.3-8.0 (Reefhuis et al., 2015), aOR 8.1, 95% CI 3.1-20.8 (Alwan et al., 2007)
- hypospadias OR 2.45, 95% CI 1.12-4.64 (M. Reis and Källén, 2010)
- undescended testes OR 2.8, 95% CI 1.0-7.8 (Yazdy et al., 2014)

SNRIs

Venlafaxine
- anencephaly, aOR 6.3, 95% CI 1.5-20.2 (Polen et al., 2013)
- cleft palate, aOR 3.3, 95% CI 1.1-8.8 (Polen et al., 2013)
- atrial septal defect, aOR 3.1, 95% CI 1.3-7.4 (11 exposed cases) (Polen et al., 2013)
- left ventricular outflow tract defects, aOR 3.3, 95% CI 1.2-8.2 (9 exposed cases, 6 of which were coarctation of the aorta) (Polen et al., 2013)
- respiratory system defects aOR 2.17, 95% CI 1.07-4.38 (Bérard et al., 2017)
- gastroschisis aOR 5.7, 95% CI 1.8-15.9 (Polen et al., 2013); aOR 3.5, 95% CI 1.4-8.4 (Werler et al., 2018)

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Appendix 15 ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Exposure to SSRI/SNRI and depression in pregnancy and long-term childhood outcomes: the effect of modifying factors.

EU PAS Register® number: **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[16]	☒	☐	☐	8.2
1.1.2 End of data collection[17]	☒	☐	☐	8.2
1.1.3 Progress report(s)	☒	☐	☐	5
1.1.4 Interim report(s)	☐	☒	☐	5
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

[16] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[17] Date from which the analytical dataset is completely available.

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
	2.1.2 The objective(s) of the study?	☒	☐	☐	7
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.3
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	10

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2 and 8.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.2
	4.2.2 Age and sex	☒	☐	☐	8.2
	4.2.3 Country of origin	☒	☐	☐	8.2 and 8.4
	4.2.4 Disease/indication	☒	☐	☐	7, 8.3

Section 4: Source and study populations	**Yes**	**No**	**N/ A**	**Section Number**
4.2.5 Duration of follow-up	☒	☐	☐	8.2 and 8.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/ A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	8.3
5.3 Is exposure categorised according to time windows?	☒	☐	☐	8.3
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	Duration 8.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	8.3
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.7

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/ A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3, appendix 3-6 and 11.
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.3 and appendix 3-6 and 11
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.7
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	8.7

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.3 and 8.7

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3, 8.4, Appendix 14
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3 and appendix 14
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.3 and appendix 13

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.3, appendices 3-6
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.3 and appendices 10, 12
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.6

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.5 and 8.9
10.3 Are descriptive analyses included?	☒	☐	☐	8.7 and appendix 10-12
10.4 Are stratified analyses included?	☒	☐	☐	8.7
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	8.7
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9

Comments:

We have an independent clinical expert on the team to comment on the results and papers arising from this study

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	8.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.9, appendices 10-12

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

Ethical review not yet completed.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

Name of the main author of the protocol: Maria Loane, Joanne Given

Date: 01/10/2021

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