1. Title Page

Title	Antipsychotics in pregnancy and the risk of adverse pregnancy outcomes - a nationwide study
Research question & Objectives	1) To assess the association of antipsychotic medication use with spontaneous abortions (primary) 2) To assess the association of antipsychotic medication use with other adverse pregnancy outcomes (secondary)
Protocol version	V1
Last update date	30/04/2024
Contributors	**Primary investigator:** Prof Hedvig Marie Egeland Nordeng, PhD. Professor and Head, PharmacoEpidemiology and Drug Safety (PharmaSafe) Research Group, Department of Pharmacy, University of Oslo, Oslo, Norway **Contributor names:** Marleen van Gelder, PhD. PharmacoEpidemiology and Drug Safety (PharmaSafe) Research Group, Department of Pharmacy, University of Oslo, Oslo, Norway Takamasa Sakai, PhD. Assistant Professor, Drug Informatics, Faculty of Pharmacy, Meijo University, Nagoya, Japan Visiting Researcher, University of Oslo, Oslo, Norway
Study registration	**Site:** We plan to register the study in the HMA-EMA Catalogue of real-world data studies. **Identifier:**
Sponsor	**Organization:** iAPOGEE program, Pharmacoepidemiology and Drug Safety Research group, Department of Pharmacy, University of Oslo, Norway **Contact:** Hedvig Nordeng
Conflict of interest	None declared

Table of contents

1. Title Page 1
2. Abstract 3
3. Amendments and updates 4
4. Milestones 5
Table 1. Milestones 5
5. Rationale and background 6
6. Research question and objectives 7
Table 2. Primary and secondary research questions and objective 7
7. Research methods 9
7.1. Study design 9
7.2. Study design diagram 10
7.3. Setting 12
7.3.1 Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population 12
Table 3. Operational Definition of Time 0 (index date) and other primary time anchors 12
7.3.2 Context and rationale for study inclusion criteria: 13
Table 4. Operational Definitions of Inclusion Criteria 13
7.4. Variables 17
7.4.1 Context and rationale for exposure(s) of interest 17
Table 5. Operational Definitions of Exposure 17
7.4.2 Context and rationale for outcome(s) of interest 22
Table 6. Operational Definitions of Outcome 22
7.4.3 Context and rationale for covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications). 24
Table 7. Operational Definitions of Covariates 35
7.5. Data analysis 41
7.5.1 Context and rationale for analysis plan 41
Table 8. Primary, secondary, and subgroup analysis specification 41
Table 9. Sensitivity analyses – rationale, strengths and limitations 42
7.6. Data sources 43
7.6.1 Context and rationale for data sources 45
Table 10. Metadata about data sources and software 45
7.7. Data management 46
7.8. Quality control 46
7.9. Study size and feasibility 47
8. Limitation of the methods 50
9. Protection of human subjects 50
10. Reporting of adverse events 50
11. References 50
12. Appendices 53

2. Abstract

Maternal use of antipsychotics is increasing in recent years, and occurs in 0.28 to 4.64 % of all pregnancies[1]. Prior studies on antipsychotic safety during pregnancy have mainly focused on congenital malformations, indicating no increased risks[2,3]. However, less is known about other pregnancy outcomes, including spontaneous abortions. In a prior Denmark registry study, it was reported that women who used antipsychotic medications during pregnancy had a higher risk of spontaneous abortion compared to unexposed women (adjusted relative risk (aRR) [95% confidence interval(95%CI)]: 1.34[1.22-1.46]), but a similar risk compared to women exposed prior to (but not during) pregnancy (1.04[0.93-1.17]). Higher antipsychotic dosage (>50% of DDD) had a higher risk of spontaneous abortion compared to unexposed women (3.19 [2.65-3.84])[4]. Questions remain as to the risk of spontaneous abortion among women who use antipsychotics in early pregnancy, also due to the methodological challenges of studying spontaneous abortion as an outcome. Therefore, using a novel pregnancy algorithm that captures early non-live births, we aim to assess the association of second-generation antipsychotic use during pregnancy with spontaneous abortions. In addition, we will assess associations with the other maternal and pregnancy outcomes.

We will use Norwegian nationwide registry data, which consist of the Medical Birth Registry of Norway (MBRN), linked to the Norwegian Prescription Database (NorPD) covering all dispensed medications to outpatients, the Norwegian control and payment of health reimbursements (KUHR) covering primary care contacts and the Norwegian Patient Registry (NPR) covering secondary care contacts through the maternal personal identification number. Identification of pregnancy episodes and outcomes will be done using the pregnancy algorithm developed by PharmaSafe research group at UiO[5]. In brief, all pregnancies lasting ≥12 weeks will be identified in the MBRN, whereas primary and secondary care registries will identify pregnancies lasting <12 weeks.

The primary exposure group is defined as second-generation antipsychotics during early pregnancy (23 days prior to gestational week 20 / end of pregnancy). Several comparison groups will be employed: 1. Unexposed, diseased comparison group, 2. First-generation antipsychotics during pregnancy (Active comparator), 3. Exposed to second-generation antipsychotics only prior to pregnancy (Discontinuer). The primary outcome is defined as spontaneous abortions and elective termination is considered a competing outcome. We will estimate the hazard ratio with 95% CI with each comparator group, while controlling for measured confounders identified using Directed Acyclic Graphs.

In the secondary analysis, we will restrict to pregnancies identified in the MBRN. We will assess the secondary outcomes: preterm birth, small-for-gestational age (SGA), low Apgar score, transfer to NICU, congenital malformations, caesarean section, gestational diabetes, and preeclampsia.

3. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason
30/04/2024	**1**	**Final first draft**		

4. Milestones

Table 1. Milestones

Milestone	**Planned date**
Feasibility counts	30/09/2023
Protocol finalized	30/04/2024
Registration of protocol	30/04/2024
Final report of study results	28/02/2025

5. Rationale and background

What is known about the condition: Psychiatric conditions for which antipsychotics are prescribed include schizophrenia, bipolar disorders and depressive disorders. These conditions have all been associated with adverse pregnancy outcomes[6–9]. For example, in a French population-based study, women with schizophrenia experienced more pregnancy complications (aOR[95%CI]: 1.41[1.31–1.51]), delivery complications (1.18[1.09–1.29]), and caesarean sections (1.15[1.05–1.25]) compared with women without severe mental disorders[10]. In the same study, newborns of women with schizophrenia had more neonatal complications (1.38[1.27–1.50]), were more commonly born preterm (1.64[1.42 -1.90]), small-for-gestational-age (1.34[1.19-1.50]) and with a low birth weight (1.75[1.53–2.00])[10]. In an Australian population-based cohort study, women with severe mental illness had higher risks of gestational diabetes (aOR[95%CI]:1.57 [1.34–1.84]), unplanned caesarean section (1.17 [1.02–1.33]), having a newborn with a low Apgar score at 5 minutes (1.50 [1.19–1.90]), preterm birth (1.40 [1.20–1.63]), and low birth weight (1.26 [1.06–1.49]) [11]. Furthermore, in a Norwegian registry study, some psychiatric disorders have been associated with an increased risk of spontaneous abortion after adjustment for co-occurring psychiatric disorders with an aOR of 1.22 [95%CI 1.03–1.44] for schizophrenia spectrum disorders, 1.27 [1.19–1.36] for bipolar disorders, and 1.21 [1.19–1.23] for depressive disorders). This risk was further increased among women with more than one psychiatric diagnosis (aOR[95%CI]: 1.45 [1.40–1.51] for two psychiatric diagnoses, 1.51 [1.31–1.73] for three or more diagnoses)[12].

What is known about the exposure of interest: In many countries, the prevalence of antipsychotic use during pregnancy is increasing, especially for second-generation antipsychotics, ranging typically between 0.17 and 1.53%[1]. In Norway (2005–2015), the prevalence of antipsychotic use during the pregnancy period was 1.16% (second-generation antipsychotics: 0.24%, first-generation antipsychotics: 0.95%)[1].

From Denmark, it is reported that women who used antipsychotic medication during pregnancy had a 34% higher risk of spontaneous abortion (aRR [95%CI]: 1.34[1.22; 1.46]) compared to unexposed women, but a similar risk compared to women exposed prior to (but not during) pregnancy (1.04[0.93; 1.17]). Higher antipsychotic dosage (>50% of DDD) had a higher risk of spontaneous abortion compared to unexposed women (3.19 [2.65; 3.84]) [4]. From the analysis of a Japanese spontaneous reporting database, a potential signal for spontaneous abortion was detected for aripiprazole [reporting OR [95%CI]: 2.76 [1.62-4.69]; n = 18]. In contrast, no potential signal for spontaneous abortion was detected for other second-generation antipsychotics[13]. Post-marketing surveillance studies on olanzapine, quetiapine, and risperidone showed no associations with spontaneous abortion [14–16].

Gaps in knowledge: Questions remain as to the risk of spontaneous abortion among women who use antipsychotics in early pregnancy. More specifically, the risks of different antipsychotics classes (first-generation antipsychotics, second-generation antipsychotics) are unknown.

What is the expected contribution of this study? This study using nation-wide registries from Norway contributes to the safety information of second-generation antipsychotic use during pregnancy on birth outcomes other than congenital malformations.

6. Research question and objectives

Table 2. Primary and secondary research questions and objective

A. Primary research question and objective

Objective:	To evaluate the association of exposure to second-generation antipsychotics during pregnancy with the risk of spontaneous abortion while taking into account competing risks of elective terminations.
Hypothesis:	The risk of spontaneous abortion is elevated with second-generation antipsychotic use during pregnancy.
Population *(mention key inclusion-exclusion criteria):*	All pregnancies identified in the MBRN (Medical Birth Registry of Norway) for pregnancies lasting ≥12 weeks, and primary and secondary care registries for pregnancies lasting <12 weeks. We will use the recently developed pregnancy algorithm by PharmaSafe researchers at UiO including approximately 860,000 pregnancies (2008-2018), including live-births (74.8%), spontaneous abortions (13.1%), elective terminations (11.0%), ectopic pregnancies (0.7%), stillbirths (0.3%), and molar pregnancies (0.1%). Ectopic and molar pregnancies will be excluded.
Exposure:	Second-generation antipsychotics during early pregnancy (23 days prior to gestational week 20 / end of pregnancy), having a mental disease diagnosis up to 6 months prior to pregnancy
Comparator:	1. Unexposed, diseased-comparison group (Unexposed, having a mental disease diagnosis up to 6 months prior to pregnancy, no antipsychotic) 2. Active comparator (First-generation antipsychotics during early pregnancy, having a mental disease diagnosis up to 6 months prior to pregnancy) 3. Discontinuer (Exposed to second-generation antipsychotics only prior to pregnancy, having a mental disease diagnosis up to 6 months prior to pregnancy)
Outcome:	Spontaneous abortion (=miscarriage)
Time *(when follow up begins and ends)*:	From the start of the pregnancy to 20 weeks of gestation
Setting:	Primary and secondary care (Dx), Outpatient (Rx), MBRN information
Main measure of effect:	Hazard Ratio with 95% confidence intervals

B. Secondary research question and objective

Objective:	To evaluate the association of exposure to second-generation antipsychotics during pregnancy with the risk of selected pregnancy outcomes other than spontaneous abortion
Hypothesis:	The risk of other selected pregnancy outcomes is elevated with second-generation antipsychotic use during pregnancy.
Neonatal outcomes	
Population *(mention key inclusion-exclusion criteria):*	All pregnancies identified in the MBRN (Medical Birth Registry of Norway)
Exposure:	Second-generation antipsychotics during pregnancy (congenital malformations: during first trimester, preterm birth: until gestational week 37)
Comparator:	1. Unexposed, diseased-comparison group (Unexposed, having a mental disease diagnosis up to 6 months prior to pregnancy, no antipsychotic) 2. Active comparator (First-generation antipsychotics during pregnancy, having a mental disease diagnosis up to 6 months prior to pregnancy) 3. Discontinuer (Exposed to second-generation antipsychotics only prior to pregnancy, having a mental disease diagnosis up to 6 months prior to pregnancy)
Outcome:	Preterm birth, small-for-gestational-age (SGA), low Apgar score, transfer to NICU, congenital malformations
Time *(when follow up begins and ends):*	From the start of the pregnancy to the delivery date: preterm birth, SGA, low Apgar score From the start of the pregnancy to the discharge: transfer to NICU From the start of the pregnancy to 1 year after birth: congenital malformations
Setting:	Primary and secondary care (Dx), Outpatient (Rx), MBRN information
Main measure of effect:	Relative Risk with 95% confidence intervals: SGA, low Apgar score, congenital malformations, transfer to NICU Hazard Ratio with 95% confidence intervals: preterm birth

Maternal outcomes	
Population ***(mention key inclusion-exclusion criteria):***	All pregnancies identified in the MBRN (Medical Birth Registry of Norway)
Exposure:	Second-generation antipsychotics during pregnancy
Comparator:	1. Unexposed, diseased-comparison group (Unexposed, having a mental disease diagnosis up to 6 months prior to pregnancy, no antipsychotic) 2. Active comparator (First-generation antipsychotics during pregnancy, having a mental disease diagnosis up to 6 months prior to pregnancy) 3. Discontinuer (Exposed to second-generation antipsychotics only prior to pregnancy, having a mental disease diagnosis up to 6 months prior to pregnancy)
Outcome:	Gestational diabetes, preeclampsia, caesarean section
Time ***(when follow up begins and ends):***	From the start of the pregnancy to the delivery date: gestational diabetes, preeclampsia, caesarean section,
Setting:	Primary and secondary care (Dx), Outpatient (Rx), MBRN information
Main measure of effect:	Hazard Ratio with 95% confidence intervals: gestational diabetes, preeclampsia Relative Risk with 95% confidence intervals: caesarean section,

7. Research methods

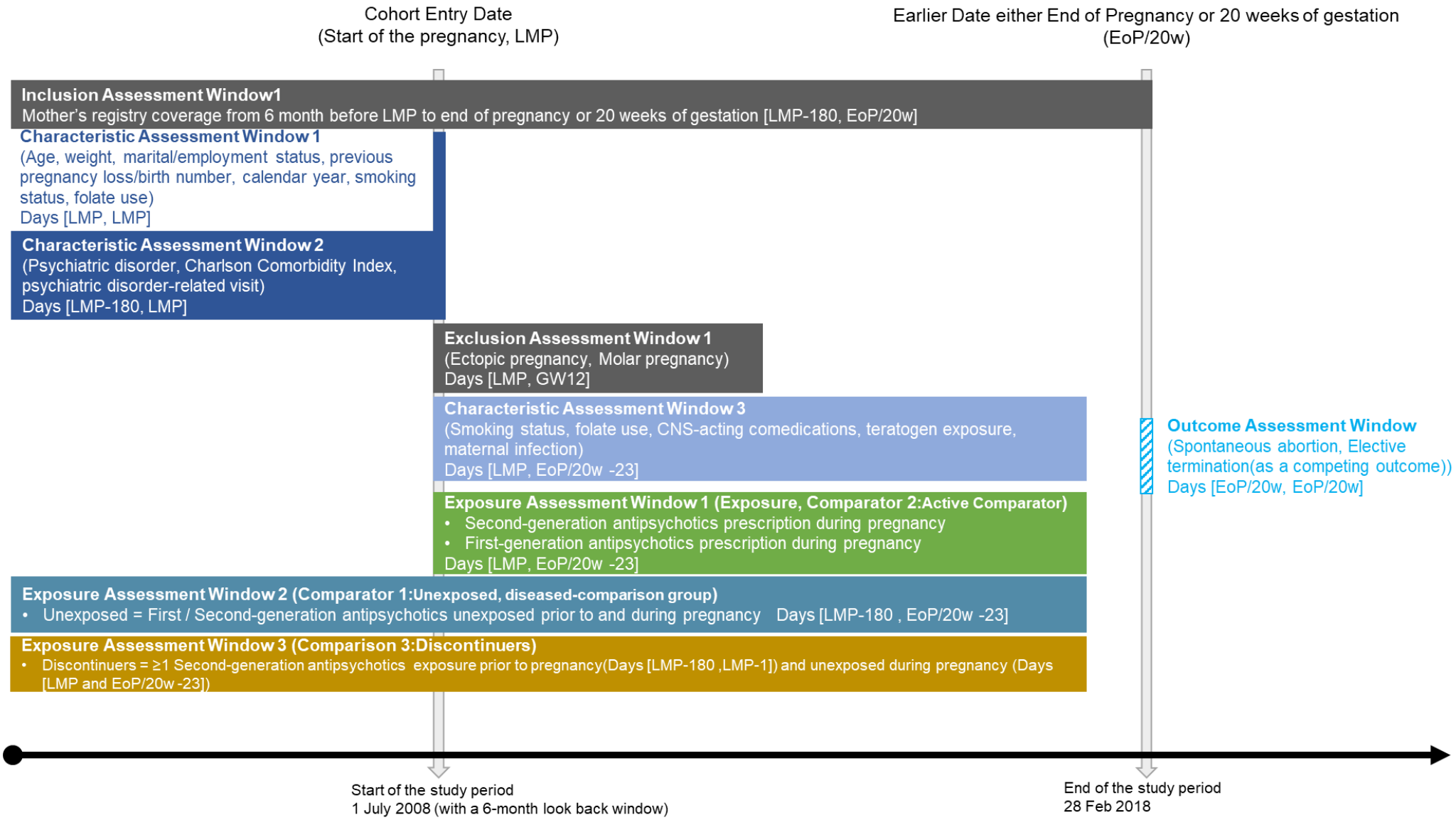
7.1. Study design

Research design: Cohort study

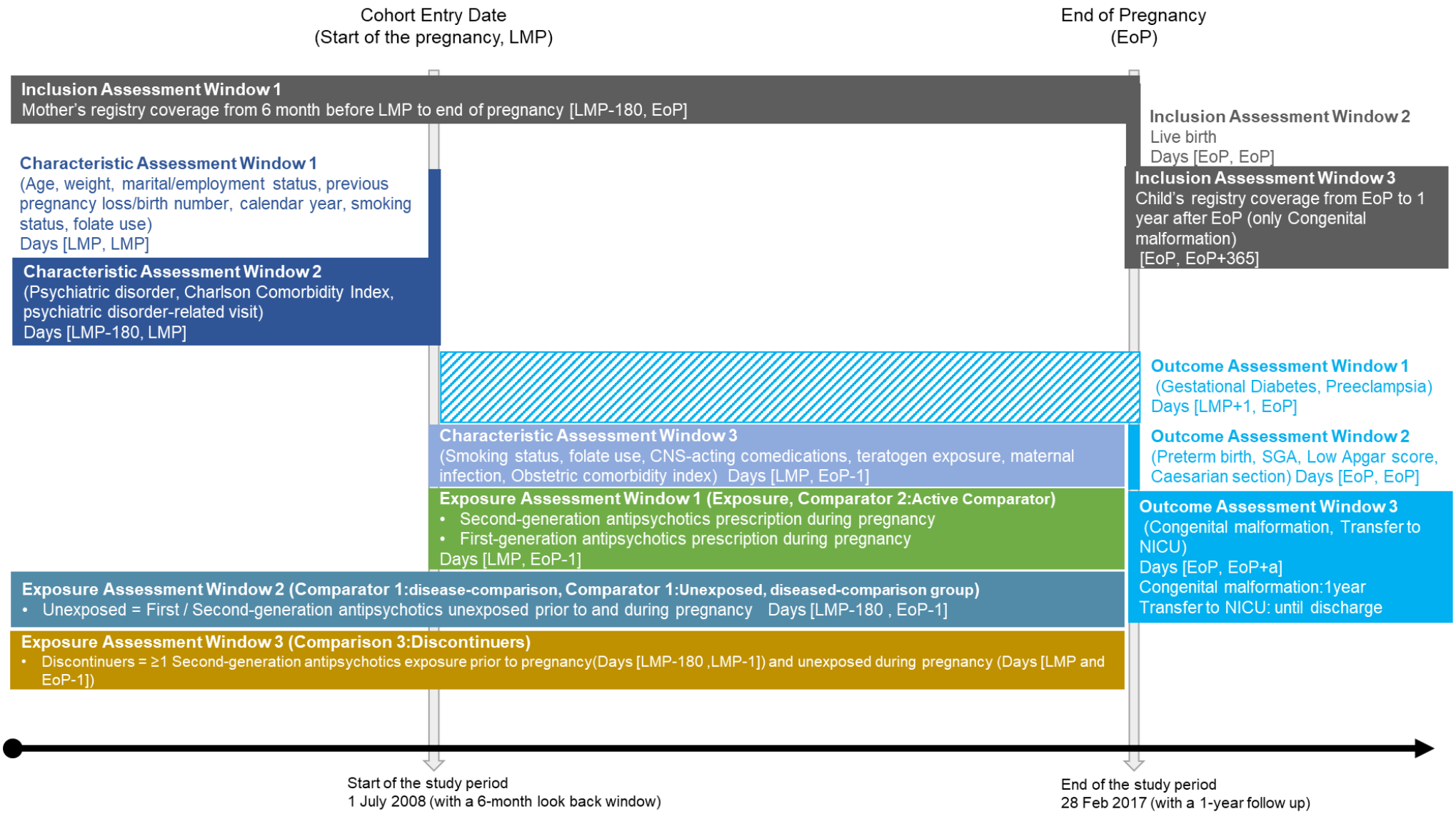
Rationale for study design choice: Since we are planning to study a single exposure in relation to multiple outcomes, we will use a cohort design.

7.2. Study design diagram

Primary outcome



Secondary outcomes



7.3. Setting

7.3.1 Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population

In this study, we will use the date of start of the pregnancy (last menstrual period, LMP) as time 0.
For the primary analysis, follow-up ends at either end of pregnancy or 20 weeks of gestation, whichever comes first.

Table 3. Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Pregnant women	Start of the pregnancy	Multiple (women with multiple pregnancies are allowed to contribute multiple times)	Incident	See pregnancy algorithm	See pregnancy algorithm	ICD-10, ICPC-2, MBRN variables	See pregnancy algorithm	-		MBRN, NPR, KUHR

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2]See appendix for listing of clinical codes for each study parameter

7.3.2 Context and rationale for study inclusion criteria:

Pregnancies identified with the UiO pregnancy algorithm using MBRN for pregnancies lasting ≥12 weeks and primary and secondary care registries for pregnancies lasting <12 weeks will be included. To ensure that there is sufficient observable time, women must haven registry coverage from 6 months before their last menstrual period to end of pregnancy.

Table 4. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/validation	Source for algorithm
Primary outcome									
Pregnancies identified in MBRN, NPR, KUHR		Before selection of study population	See pregnancy algorithm	See pregnancy algorithm	See pregnancy algorithm	See pregnancy algorithm	Pregnant women		pregnancy algorithm[5)]
Observable time	Mother from 6 month before LMP (NPR registers) to end of pregnancy	Before selection of study population	Mother: [LMP-180, EoP/20w]	n/a	n/a	n/a	Pregnant women	n/a	n/a
Secondary outcomes									
Pregnancies identified in MBRN (Congenital malformation, Maternal outcomes other than caesarean section)	Identified from MBRN	After selection of study population by other inclusion criteria	n/a	All	n/a	n/a	Pregnant women		MBRN [17)]
Singleton live birth identified in MBRN (Caesarean section, Neonatal outcomes other than congenital malformation)	Identified from MBRN	After selection of study population by other inclusion criteria	[EoP, EoP]	All	n/a	n/a	Pregnant women		MBRN [17)]
Observable time (Congenital malformations)	Mother from 6 month before LMP (NPR registers) Child to 1 year after delivery	Before selection of study population	Mother: [LMP-180, EoP] Child: [EoP, EoP+1y]	All	n/a	n/a	Pregnant women	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.3.3 Context and rationale for study exclusion criteria

Pregnancies with no possibility of livebirth (e.g. ectopic and molar pregnancies) will be excluded from the primary analysis.

Table 5. Operational Definitions of Exclusion Criteria

Primary outcome

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Ectopic and molar pregnancies	NPR for identification	After selection of study population by inclusion criteria	[LMP, GW12]		ICD-10		Pregnant women	Pregnancy algorithm[5)]	

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Secondary outcomes

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
known teratogen exposure (Neonatal outcomes)		After selection of study population by inclusion criteria	[LMP, EoP-1]		ATC code		Pregnant women		n/a
pre-existing diabetes (Gestational diabetes)	MBRN: DIABETES_MELLITUS Definition: 1: type 1 diabetes diagnosed prior to pregnancy 2: type 2 diabetes diagnosed prior to pregnancy 3: other or unspecified diabetes diagnosed prior to pregnancy	After selection of study population by inclusion criteria		IP, OP	Using variable in MBRN		Pregnant women		MBRN[17)]

7.3.1.1. Appendix A. List of teratogenic medication

Teratogens	**ATC code**	**Data source**
Antiepileptics		NorPD
Carbamazepine	N03AF01	
Phenobarbital	N03AA02	
Primidone	N03AA03	
Valproic acid	N03AG01	
Phenytoin	N03AB02	
	N03AB52	
Fosphenytoin	N03AB05	
Topiramate	N03AX11	
Retinoids		
Acitretin	D05BB02	
Alitretinoin	D11AH04	
Bexarotene	L01XF03	
Isotretinoin	D10BA01	
Tretinoin	L01XF01	
Etretinate	D05BB01	
Anti-thyroids		
Carbimazole	H03BB01	
Thiamazole	H03BB02	
Normothymic		
Lithium	N05AN01	
Anticoagulants		
Warfarin	B01AA03	
Phenindione	B01AA02	
Acenocumarol	B01AA07	
Immunomodulants		
Mycophenolate	L04AA06	
Fingolimod	L04AA27	
Pomalidomide	L04AX06	
Lenalidomide	L04AX04	
Hormonal		
Diethylstilbestrol	L02AA01	
	G03CB02	
	G03CC05	
Misoprostol	A02BB01	
	G02AD06	

7.4. Variables

7.4.1 Context and rationale for exposure(s) of interest

The lack of randomization has to be compensated for by methods that maximize the comparability between the exposed and comparison groups.
Unexposed to any antipsychotics with psychiatric disorder (listed in Appendix B) is a disease-matched control group and unexposed to any antipsychotics without psychiatric disorder is defined as the population comparison group. First-generation antipsychotics are used as active comparators for second-generation antipsychotics which have the overlap of some indication (schizophrenia, mania and bipolar disorder). Past users during 180 days before the pregnancy but unexposed during pregnancy is defines as discontinuers. The selection of the comparison group will not be the only method to increase exchangeability between the exposed and unexposed groups; we will also adjust for measured confounders.

Table 6. Operational Definitions of Exposure

Primary Outcome

The lag time between arrest of development and spontaneous abortion (median 23 days) [18)] is considered in the assessment windows.

Exposure group name(s)	**Detail**	**Washout window**	**Assessment Window**	**Care Setting[1]**	**Code Type[2]**	**Diagnosis position[3]**	**Applied to study populations**	**Incident with respect to…**	**Measurement characteristics/validation**	**Source of algorithm**
Exposure: Second-generation antipsychotics	Second-generation antipsychotics exposure as listed in Appendix C		[LMP, EoP/20w-23]** Disease: [LMP-180,LMP]	n/a	ATC code	n/a	Pregnant women with psychiatric disorder*		No validation study	Investigator defined
Comparator 1: **Unexposed, diseased-comparison group**	With mental illness but no antipsychotic up to 6 months prior to pregnancy and during pregnancy.	[LMP-180, LMP]	[LMP-180, EoP/20w-23]** Disease: [LMP-180,LMP]	n/a	ATC code	n/a	Pregnant women with psychiatric disorder*		No validation study	Investigator defined

Comparator 2: **Active comparator**	First-generation antipsychotics exposure as listed in Appendix C (Active comparator)		[LMP, EoP/20w-23]** Disease: [LMP-180,LMP]	n/a	ATC code	n/a	Pregnant women with psychiatric disorder*		No validation study	Investigator defined
Comparator 3: **Discontinuer**	Non-use of antipsychotics during pregnancy but past users during 6 months before the start of the pregnancy (Discontinuer)		[LMP-180, EoP/20w-23]** Disease: [LMP-180,LMP]	n/a	ATC code	n/a	Pregnant women with psychiatric disorder*		No validation study	Investigator defined

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)
* Definition of psychiatric disorder will be listed in appendix B
** Earlier date either 23 days prior to end of pregnancy or 20 weeks of gestation.

7.4.1.1. Appendix B. Codes for the psychiatric disorder

Covariates		**Data source**	**Code (ICD-10 code/ICPC-2 code)**
Psychiatric disorder	Schizophrenia	NPR/KUHR	ICD-10 code: F20-F29 ICPC-2 code: P72, P73, P98
	Bipolar disorder		ICD-10 code: F31
	Mania		ICD-10 code: F30
	Depressive disorder with psychotic symptoms		ICD-10 code: F323, F333

7.4.1.2. Appendix C. ATC codes for the drug exposure

Group of antipsychotics (Investigator defined)		Data source	ATC code
Second-generation antipsychotics	Sertindole	NorPD	N05AE03
	Ziprasidone		N05AE04
	Lurasidone		N05AE05
	Clozapine		N05AH02
	Olanzapine		N05AH03
	Quetiapine		N05AH04
	Asenapine		N05AH05
	Sulpiride		N05AL01
	Sultopride		N05AL02
	Remoxipride		N05AL04
	Amisulpride		N05AL05
	Levosulpiride		N05AL07
	Risperidone		N05AX08
	Mosapramine		N05AX10
	Zotepine		N05AX11
	Aripiprazole		N05AX12
	Paliperidone		N05AX13
	Iloperidone		N05AX14
	Cariprazine		N05AX15
	Brexpiprazole		N05AX16
First-generation antipsychotics	Chlorpromazine		N05AA01
	Levomepromazine		N05AA02
	Promazine		N05AA03
	Acepromazine		N05AA04
	Triflupromazine		N05AA05
	Cyamemazine		N05AA06
	Chlorproethazine		N05AA07
	Dixyrazine		N05AB01
	Fluphenazine		N05AB02
	Perphenazine		N05AB03
	Prochlorperazine		N05AB04
	Thiopropazate		N05AB05
	Trifluoperazine		N05AB06
	Acetophenazine		N05AB07
	Thioproperazine		N05AB08
	Butaperazine		N05AB09
	Perazine		N05AB10
	Periciazine		N05AC01
	Thioridazine		N05AC02
	Mesoridazine		N05AC03
	Pipotiazine		N05AC04
	Haloperidol		N05AD01

	Trifluperidol		N05AD02
	Melperone		N05AD03
	Moperone		N05AD04
	Pipamperone		N05AD05
	Bromperidol		N05AD06
	Benperidol		N05AD07
	Droperidol		N05AD08
	Fluanisone		N05AD09
	Oxypertine		N05AE01
	Molindone		N05AE02
	Flupentixol		N05AF01
	Clopenthixol		N05AF02
	Chlorprothixene		N05AF03
	Tiotixene		N05AF04
	Zuclopenthixol		N05AF05
	Fluspirilene		N05AG01
	Pimozide		N05AG02
	Penfluridol		N05AG03
	Loxapine		N05AH01
	Clotiapine		N05AH06
	Tiapride		N05AL03
	Veralipride		N05AL06
	Prothipendyl		N05AX07

***Note**

The ATC codes are cited from previous drug utilization study:

Reutfors J, Cesta CE, Cohen JM, et al. Antipsychotic drug use in pregnancy: A multinational study from ten countries. Schizophr Res. 2020 Jun;220:106-115. PMID: 32295750.

Secondary Outcome

Exposure group name(s)	Detail	Washout window	Assessment Window †	Care Setting[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations	Incident with respect to…	Measurement characteristics/validation	Source of algorithm
Exposure: Second-generation antipsychotics	Second-generation antipsychotics exposure as listed in Appendix C		[LMP, EoP-1] Disease: [LMP-180, LMP]	n/a	ATC code	n/a	Pregnant women with psychiatric disorder*		No validation study	Investigator defined
Comparator 1: **Unexposed, diseased-comparison group**	With mental illness but no antipsychotic up to 6 months prior to pregnancy and during pregnancy.	[LMP-180, LMP]	[LMP-180, EoP-1] Disease: [LMP-180, LMP]	n/a	ATC code ICPC-2 code ICD-10	n/a	Pregnant women with psychiatric disorder*		No validation study	Investigator defined
Comparator 2: **Active comparator**	First-generation antipsychotics exposure as listed in Appendix C (Active comparator)		[LMP, EoP-1] Disease: [LMP-180, LMP]	n/a	ATC code	n/a	Pregnant women with psychiatric disorder*		No validation study	Investigator defined
Comparator 3: **Discontinuer**	Non-use of antipsychotics during pregnancy but past users during 6 months before the start of the pregnancy (Discontinuer)		[LMP-180, EoP-1] Disease: [LMP-180, LMP]	n/a	ATC code	n/a	Pregnant women with psychiatric disorder*		No validation study	Investigator defined

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2] See appendix for listing of clinical codes for each study parameter

[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

* Definition of psychiatric disorder will be listed in Appendix B

† Exposure assessment window: congenital malformations: during first trimester, preterm birth: until 37 week

Appendix B. Codes for the psychiatric disorder

Appendix C. ATC codes for the drug exposure

7.4.2 Context and rationale for outcome(s) of interest

Little is known about the risk of spontaneous abortion following the use of second-generation antipsychotics in early pregnancy.

Table 7. Operational Definitions of Outcome

Primary analysis

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Outcome measurement characteristics/ validation	Source of algorithm
Spontaneous abortion	Days from cohort entry date, numerical	Yes	time-varying (binary)	n/a	IP, OP	Using variables in MBRN, NPR, KUHR	Primary	Pregnant women		Pregnancy algorithm[5)]
Elective termination	As a competing outcome of spontaneous abortion. Days from cohort entry date, numerical	No	time-varying (binary)	n/a	IP, OP	Using variables in MBRN, NPR	Primary	Pregnant women		Pregnancy algorithm[5)]

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Secondary analysis

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Outcome measurement characteristics/ validation	Source of algorithm
Preterm birth	Length of gestation in whole weeks, numerical (SVLEN) <37	Yes	binary	n/a	IP, OP	Using variables in MBRN		Neonate	Acta Obstet Gynecol Scand. 2016;95(5):519-527.	MBRN[17)]
Small-for-gestational-age	Defined as the 10% of children with the lowest birth weight given gestational age. Deviations from the expected birth weight for the child given gestational age and child sex,	Yes	binary	n/a	IP, OP	Using variables in MBRN		Neonate		MBRN[17)]

	numerical (ZSCORE_BW_GA) <-1.28 (lower 10 percentile value)									
Low Apgar score	Apgar score at 5 minutes after birth (APGAR5) < 7	Yes	binary	n/a	IP, OP	Using variables in MBRN		Neonate		MBRN[17)]
Transfer to NICU	Child transferred to neonatal intensive care unit (OVERFLYTTET) Definition: 1: yes	Yes	binary	n/a	IP, OP	Using variables in MBRN		Neonate		MBRN[17)]
Congenital malformations	Child congenital malformation, any (MISD) Definition: 1: yes	Yes	binary	n/a	IP, OP	Using variables in MBRN		Infant		MBRN[17)] EUROCAT Guide 1.4: Instruction for the registration of congenital anomalies: EUROCAT Central registry, University of Ulster, 2013
Caesarean section	we will utilize following variable to code the unplanned caesarean section binary; Caesarean section (KSNITT) Definition: KSNITT != Null 1: planned caesarean 2: emergency caesarean 3: unspecified caesarean	Yes	binary	n/a	IP, OP	Using variables in MBRN		Pregnant women	Acta Obstet Gynecol Scand. 2017;96(7):892-897.	MBRN[17)]
Gestational diabetes	Maternal diabetes (DIABETES_MELLITUS) Definition: 4: gestational diabetes	Yes	binary	n/a	IP, OP	Using variables in MBRN		Pregnant women		MBRN[17)]
Preeclampsia	Early onset preeclampsia (PREEKLTIDL) 1: yes Preeclampsia – a hypertensive disorder of pregnancy (PREEKL) 1: mild, 2: severe, 3: unspecified Definition: PREEKL != Null or PREEKLTIDL == 1	Yes	binary	n/a	IP, OP	Using variables in MBRN		Pregnant women	Acta Obstet Gynecol Scand 2013;92(8):943-950.	MBRN[17)]

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4.3 Context and rationale for follow up

Table 8. Operational Definitions of Follow Up

A. Primary analysis

Follow up start	Start of the pregnancy (LMP)	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	Including competing outcomes
Date of death	No	
End of observation in data	No	
Day X following index date *(specify day)*	Yes	20 weeks of gestation
End of study period (specify date)	No	
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	No	
Date of add to/switch from exposure *(specify algorithm)*	No	
Other date *(specify)*	No	

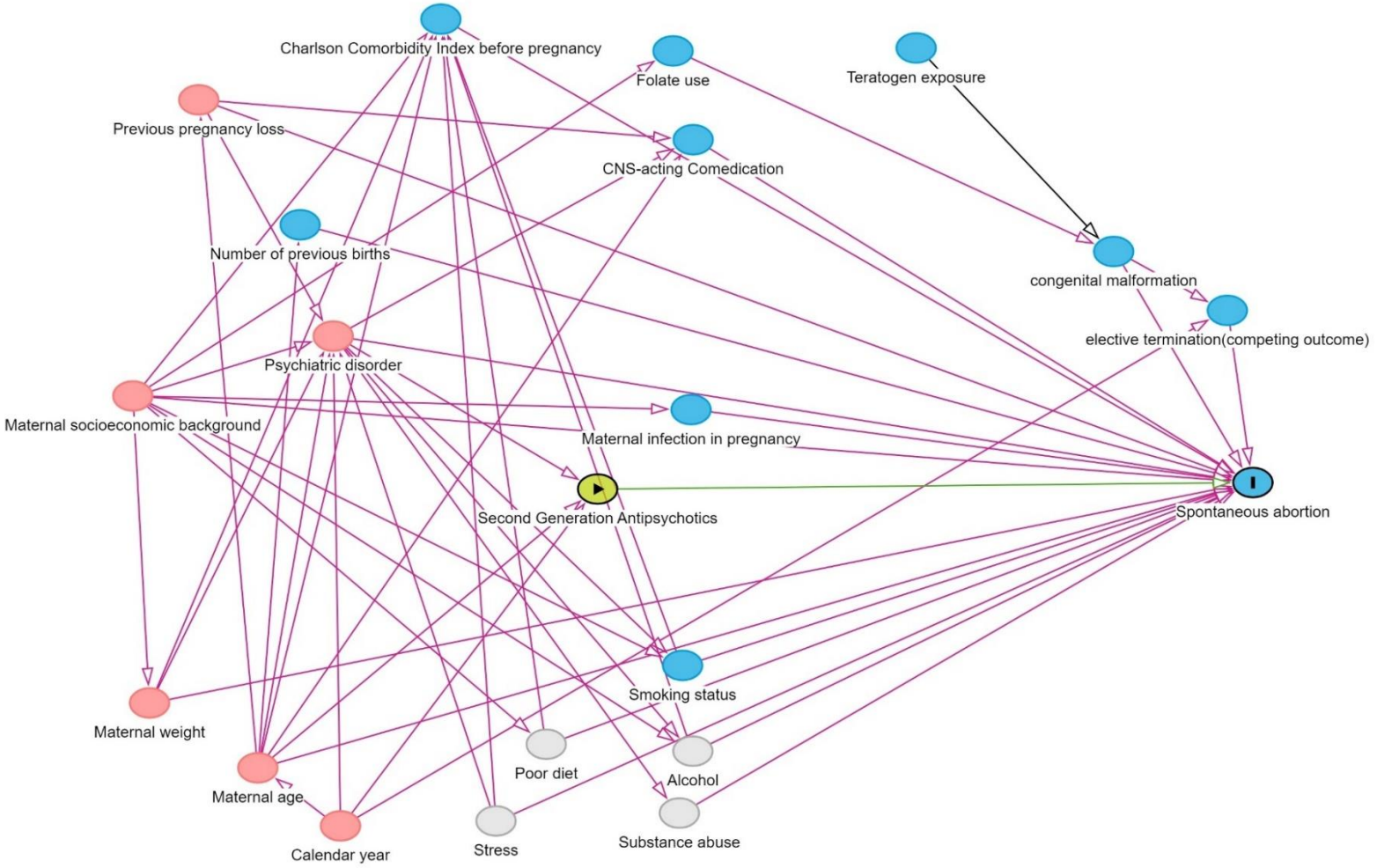
[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

B. Secondary analysis

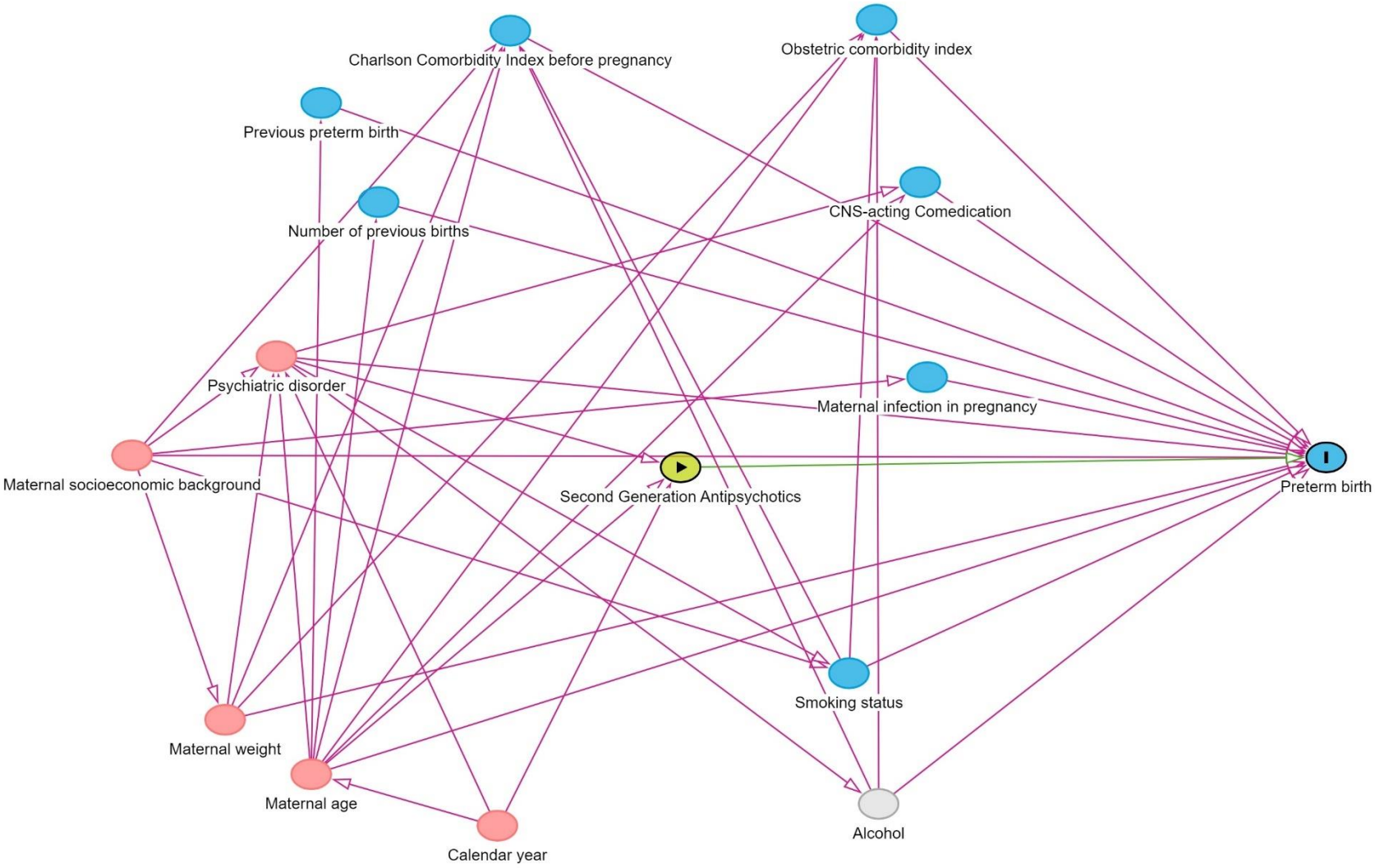
Follow up start	Start of the pregnancy (LMP)	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	
Date of death	No	
End of observation in data	No	
Day X following index date *(specify day)*	Yes	transfer to NICU: until the discharge congenital malformations: 1 year after birth
End of study period (specify date)	No	
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	No	
Date of add to/switch from exposure *(specify algorithm)*	No	
Other date *(specify)*	No	

7.4.4 Context and rationale for covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications).

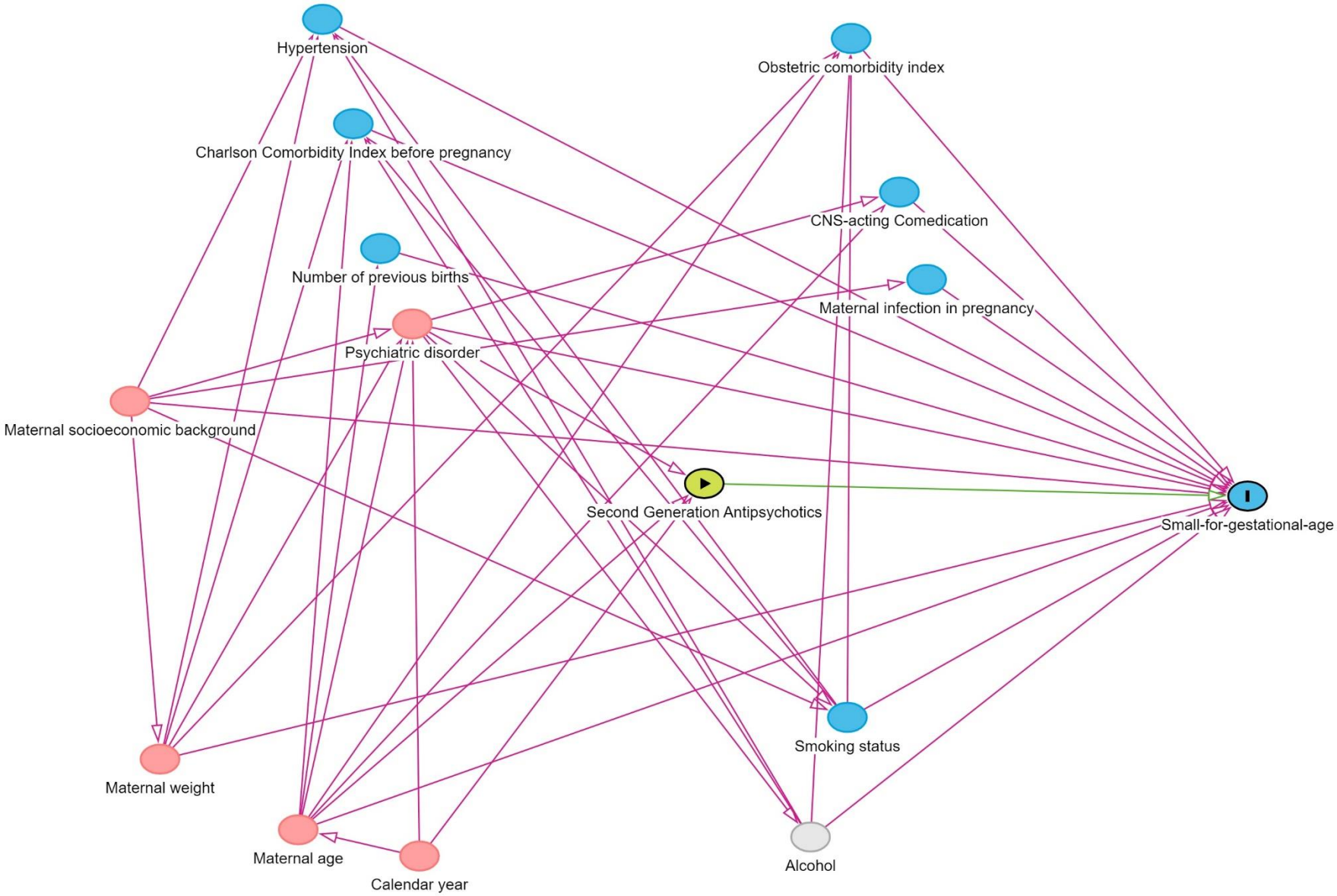
We will measure maternal characteristics including baseline sociodemographic characteristics, maternal comorbidities, and concomitant medications, and pregnancy characteristics. These were selected due to their potential to act as confounders or effect modifiers based on following the directed acyclic graph (DAG) below.
Primary outcome:
Spontaneous abortion



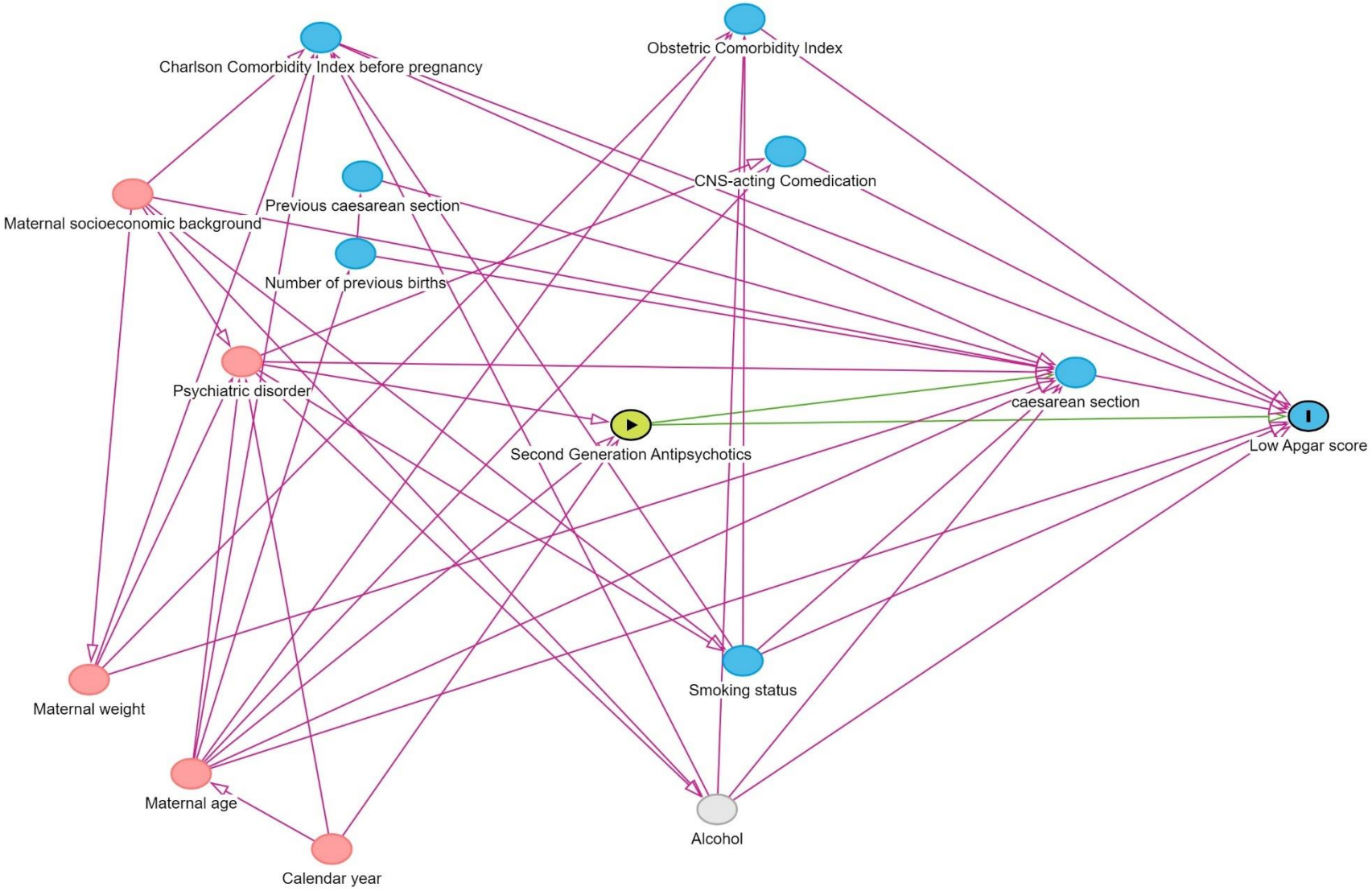
Secondary outcomes:
Preterm birth



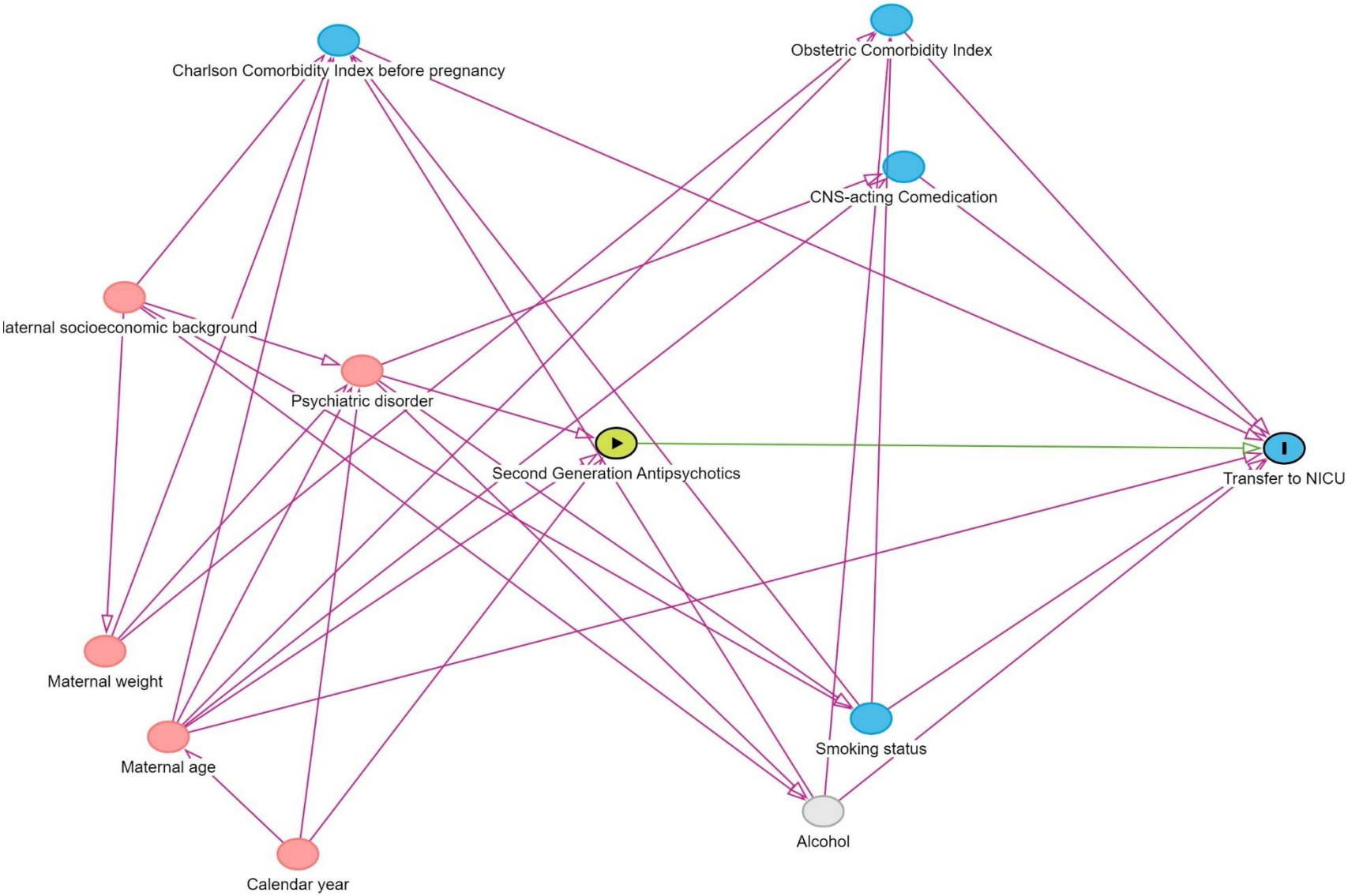
Small-for-gestational-age



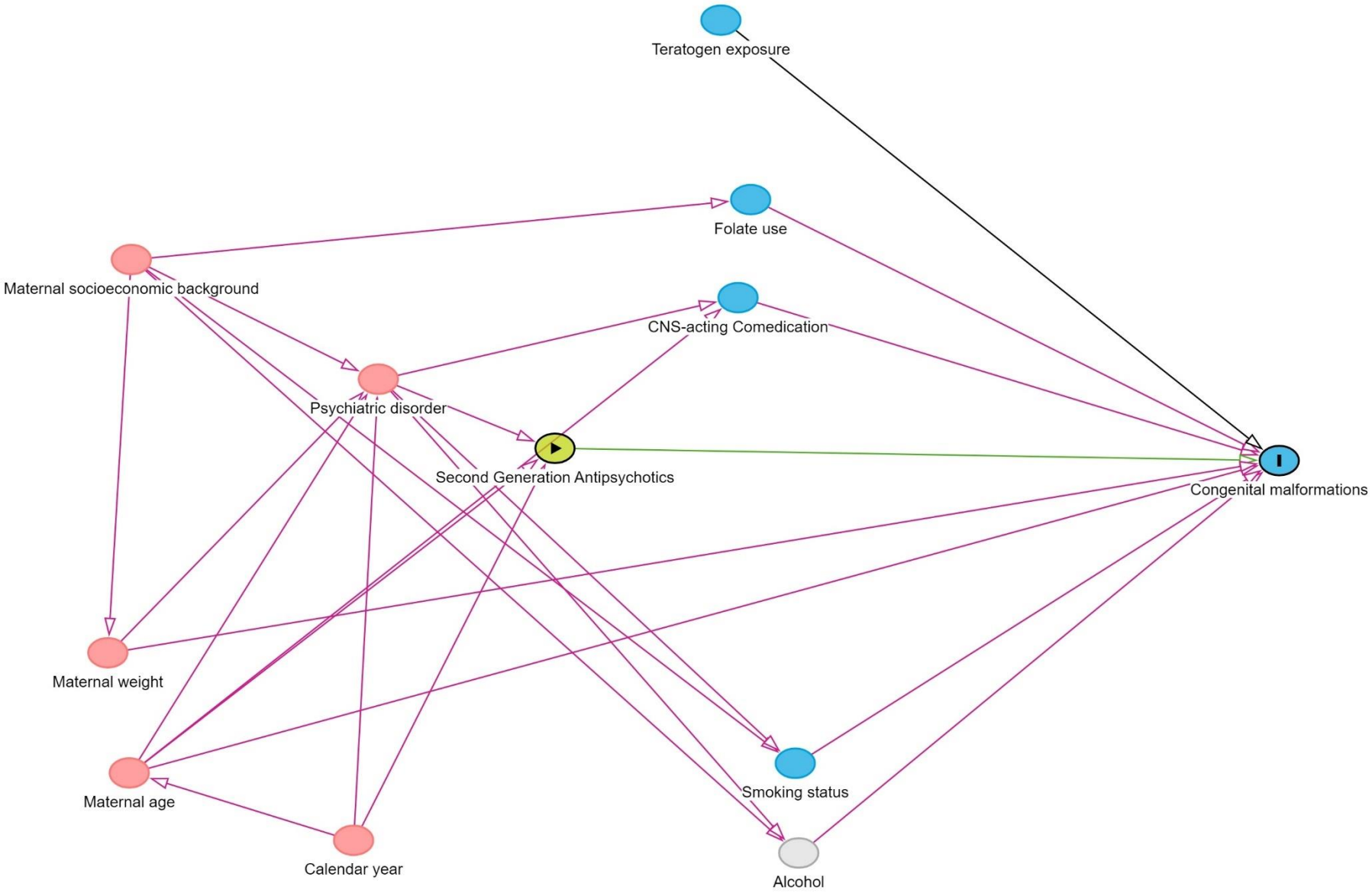
Low Apgar score



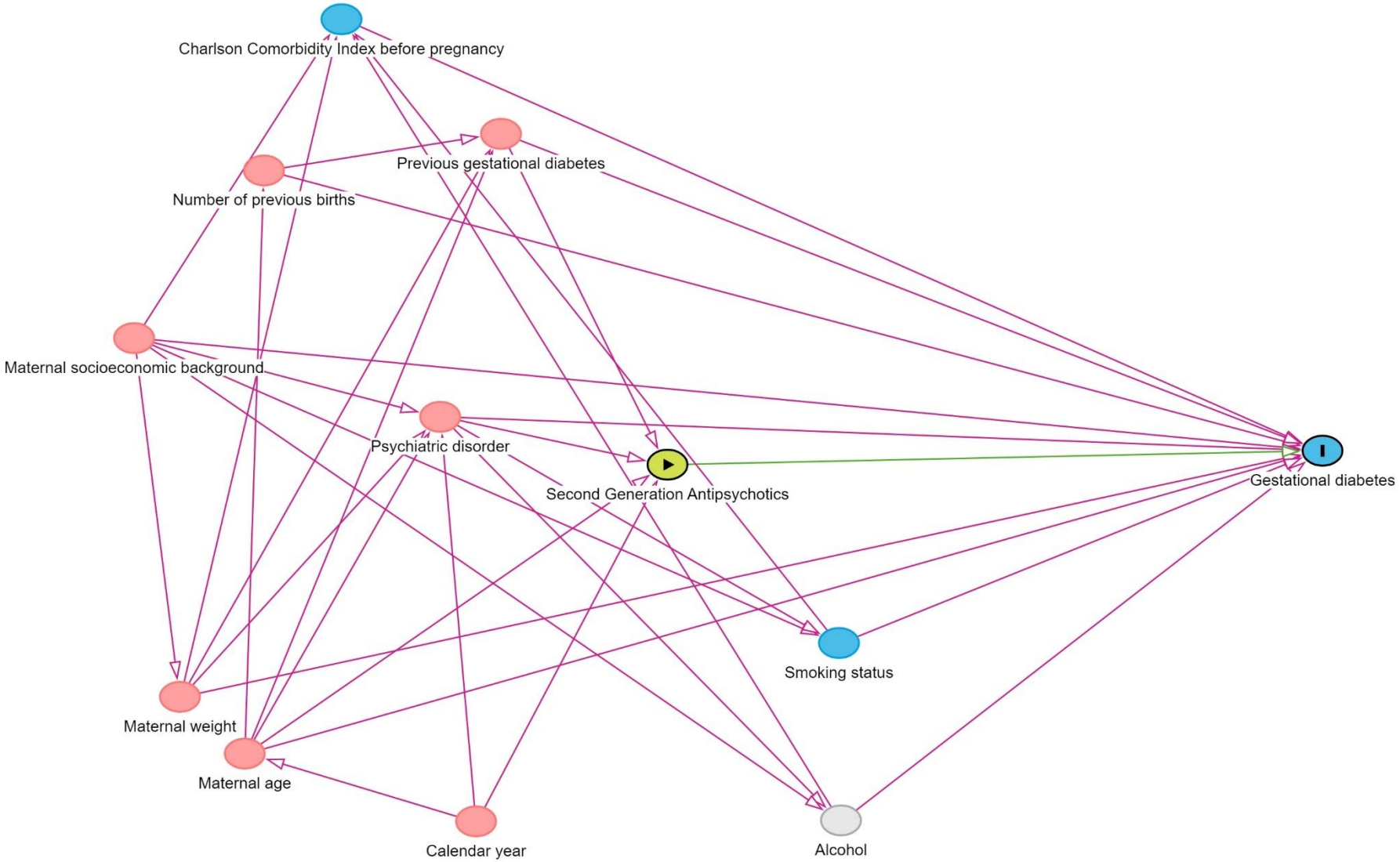
Transfer to NICU



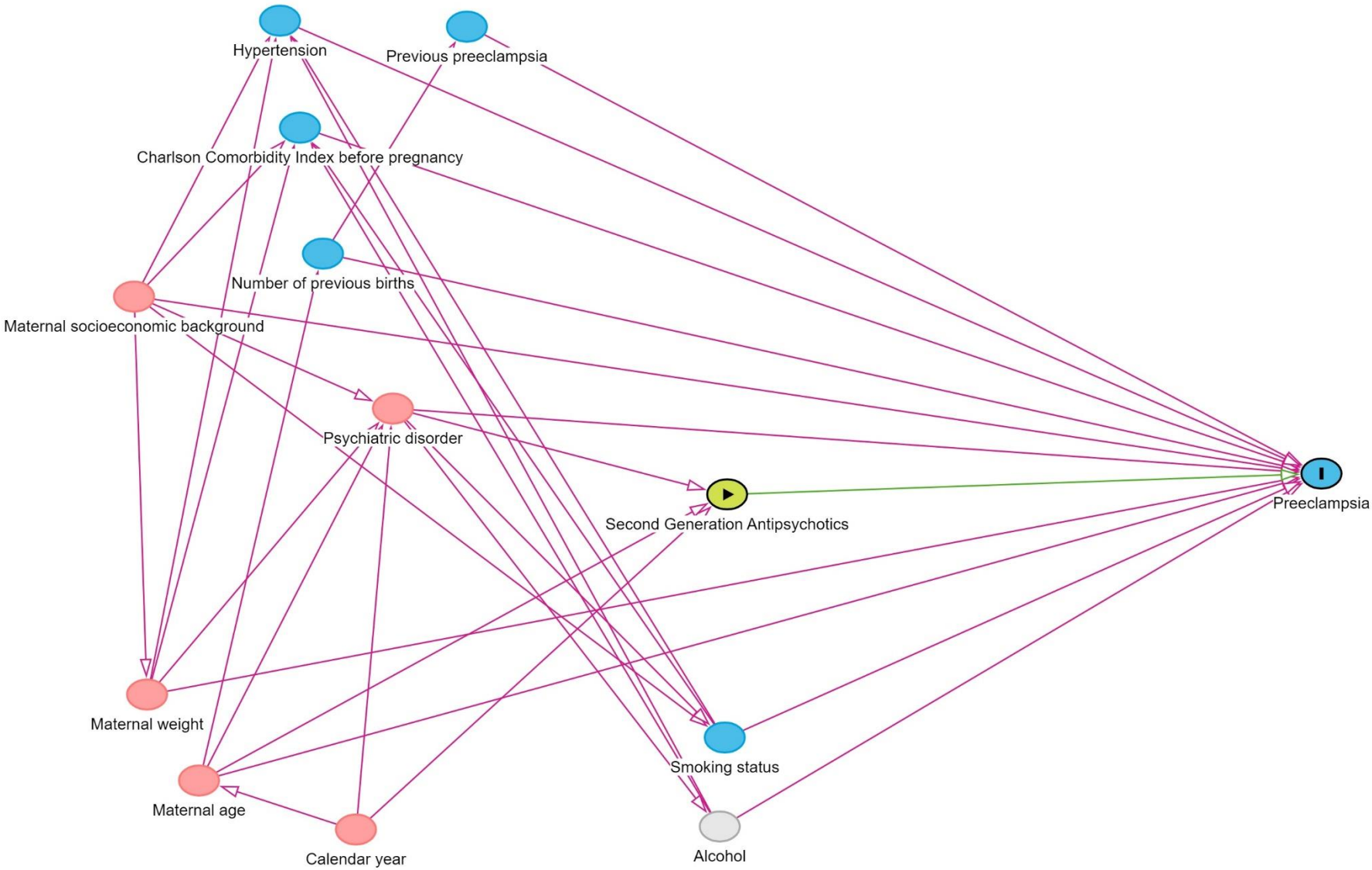
Congenital malformations



Gestational diabetes



Preeclampsia



Caesaren section

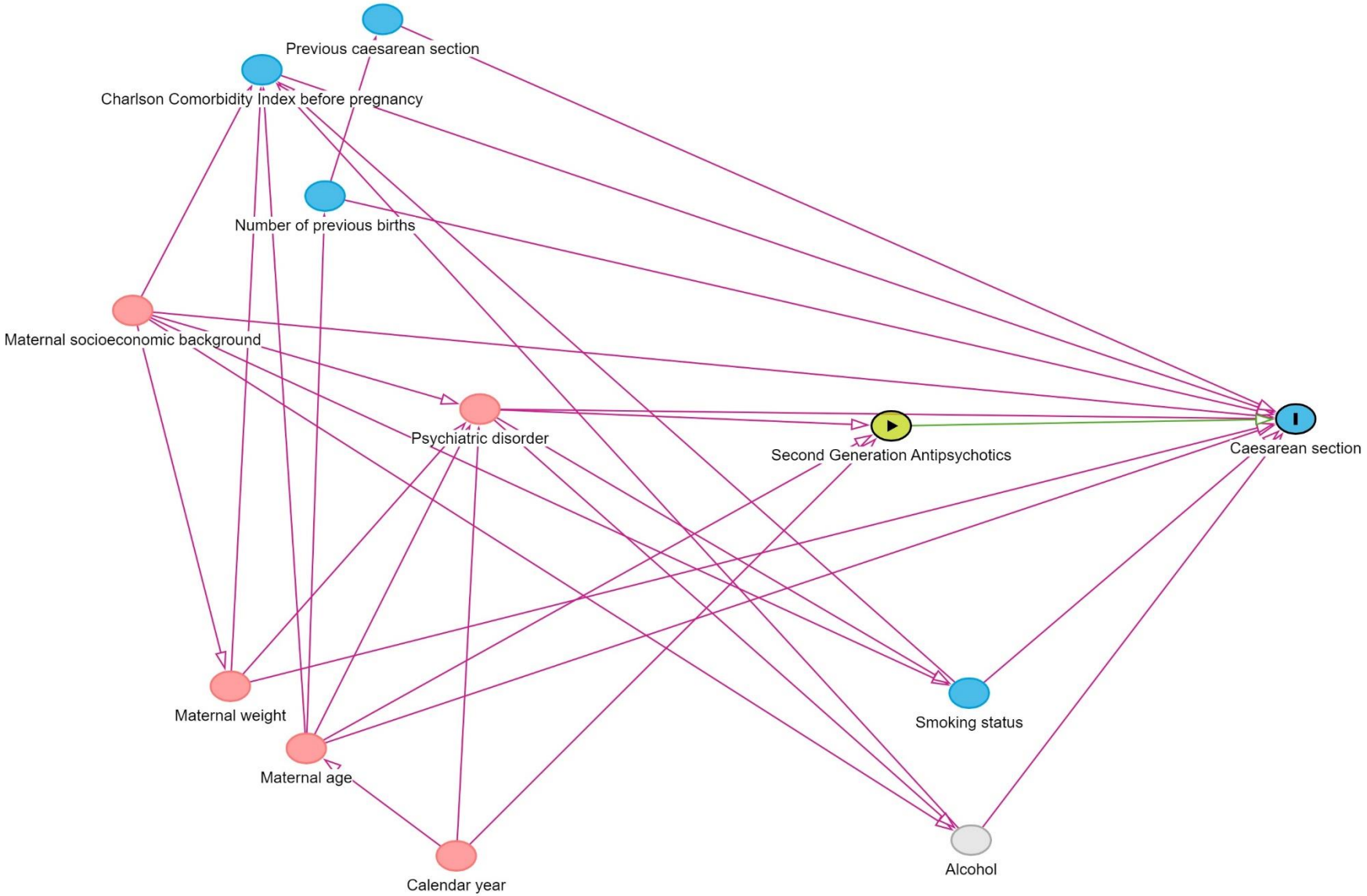


Table 9. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/validation	Source for algorithm
Maternal characteristics									
Maternal age	MORS_ALDER	Continuous	[LMP, LMP]	n/a	MBRN (numerical)	n/a	Pregnant women	n/a	MBRN[17)]
Marital status	SIVST Married or not Yes/No As socioeconomic background	Binary	[LMP, LMP]	n/a	MBRN (categorical)	n/a	Pregnant women	n/a	MBRN[17)]
Maternal employment status	YRKE_KODE Yes/No 1: not employed 2: full time employed 3: part time employed As socioeconomic background	Binary	[LMP, LMP]	n/a	MBRN (categorical)	n/a	Pregnant women	n/a	MBRN[17)]
Smoking status	ROYK_FOER, ROYK_BEG, ROYK_AVSL Prior/at the beginning/at the end 1: no 2: yes, sometimes 3: yes, daily	Primary Binary Secondary Binary	Primary ROYK_FOER, ROYK_BEG Secondary ROYK_FOER, ROYK_BEG, ROYK_AVSL	n/a	MBRN (categorical)	n/a	Pregnant women	n/a	MBRN[17)]
Maternal weight	Mother's weight before pregnancy (MORS_VEKT_FOER)	Continuous	[LMP, LMP]	n/a	MBRN (numerical)	n/a	Pregnant women	n/a	MBRN[17)]
Calendar year	Year of start of the pregnancy	Continuous	[LMP, LMP]	n/a	MBRN (numerical)	n/a	Pregnant women	n/a	MBRN[17)]
Hypertension	Maternal hypertension diagnosed before pregnancy (HYPERTENSJON_KRONISK)	Binary	[LMP, LMP]	n/a	MBRN (categorical)	n/a	Pregnant women	n/a	MBRN[17)]

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/validation	Source for algorithm
Charlson Comorbidity Index before pregnancy	Refer to Appendix D	Continuous	[LMP-180, LMP]	Any	NPR KUHR	n/a	Pregnant women	n/a	Clin Epidemiol. 2013;5:39-46. JAMA Psychiatry. 2023;80:441-450.
Central Nervous System (CNS)-acting comedications	CNS-acting comedications which may be associated with spontaneous abortions. Anticonvulsants, benzodiazepines, SSRI, SNRI	Binary	Primary [LMP, EoP/20w-23] Secondary [LMP, EoP-1]	Any	NorPD(ATC code)	n/a	Pregnant women	n/a	Investigator defined
Teratogen exposure	Refer to Appendix A (Not for neonatal outcomes)	Binary	Primary [LMP, EoP/20w-23] Secondary [LMP, EoP-1]	Any	NorPD(ATC code)	n/a	Pregnant women	n/a	n/a
Pregnancy characteristics									
Folate use	FOLATF (Use of folate before pregnancy) FOLATU (Use of folate during pregnancy) Yes/No/Missing	Categorical	PrimaryFOLATF FOLATU Secondary FOLATF, FOLATU	n/a	MBRN (binary)	n/a	Pregnant women	n/a	MBRN[17)]
Previous pregnancy loss	SPABORT_12_5 (Number of previous spontaneous abortions before week 12) SPABORT_23_5 (Number of previous spontaneous abortions/stillbirths week 12-23)	Categorical	[LMP, LMP]	n/a	MBRN (Categorical) And pregnancy algorithm[5)] using variables in MBRN, NPR, KUHR	n/a	Pregnant women	n/a	MBRN[17)] pregnancy algorithm[5)]

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/validation	Source for algorithm
	DODFODTE_5 (Number of previous stillbirths after week 24) Combine the above variables, or if MBRN information is not available, we will count the number based on the UiO pregnancy algorithm. 0, 1, 2, 3, 4+								
Previous preterm birth, gestational diabetes, preeclampsia, caesarean section	Count up the each outcomes in the previous pregnancies using the same difinicion of each outcomes.	Continuous	Same as the outcome section	Same as the outcome section	Same as the outcome section	Same as the outcome section	Same as the outcome section	Same as the outcome section	MBRN[17)]
Parity	PARITET_5 (Number of previous births) 0, 1, 2, 3, 4+	Categorical	[LMP, LMP]	n/a	MBRN (Categorical)	n/a	Pregnant women	n/a	MBRN[17)]
Maternal infection in pregnancy	Refer to Appendix D	Binary	Primary [LMP, EoP/20w-23]	n/a	NPR KUHR	n/a	Pregnant women	n/a	Investigator defined
Obstetric comorbidity index	Secondary analysis only Refer to Appendix D	Continuous	[LMP, EoP]	n/a	MBRN	n/a	Pregnant women	n/a	Clin Epidemiol. 2021 Feb 26;13:161-174.
Psychiatric disorder-related characteristics									
Psychiatric disorder-related outpatient visit	As a proxy of psychiatric disorder severity	Continuous	[LMP-180, LMP]	OP	NPR(ICD-10) KUHR (ICD-10, ICPC-2) Refer to appendix B	Primary or secondary	Pregnant women	n/a	n/a
Psychiatric disorder-related hospitalization	As a proxy of psychiatric disorder severity	Binary	[LMP-180, LMP]	IP	NPR(ICD-10) KUHR (ICD-10, ICPC-2) Refer to appendix B	Primary or secondary	Pregnant women	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

*7.4.1.3. **Appendix D. Data source and codes for defining the covariates***

Covariates		**Data source**	**Code (ATC code/ICD-10 code/ICPC-2 code)**
Obstetric comorbidity index		MBRN	Refer to Appendix D-1
Charlson Comorbidity Index before pregnancy		NPR KUHR	Refer to Appendix D-2
Maternal infection in pregnancy		NPR KUHR	ICD-10: O23.5 Infections of genitourinary tract in pregnancy O98 Maternal infectious and parasitic diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerperium ICPC-2: W71 Infection complicating pregnancy
		KUHR	Respiratory infection ICPC-2: R71, R72, R74, R75, R76, R77, R78, R80, R81, R83 Urinary infection ICPC-2: U70, U71, U72 Other infection ICD-10: E06.0, I30.x except I30.0, I32.0, I32.1, I33.x, I38, I39.x, I40.0, I41.0, I41.1, I41.2, I43.0, I52.0 ICPC-2: K70, L87, T70, W70, W71, W94
Teratogen exposure (from list in data booklet)		NorPD	Refer to Appendix A
Psychiatric comedications	Anticonvulsants	NorPD	N03A
	Benzodiazepines		N05BA, N05CD
	SSRI		N06AB
	SNRI		N06AX16, N06AX17, N06AX21, N06AX23, N06AX28

*7.4.1.4. **Appendix D-1 Obstetric Comorbidity Index***

Co-morbidity	**ICD10 code**
Alcohol abuse	F10
Asthma	J44, J45

Cardiac Valvular Disease	I05-I09, I34-I39
Chronic Congestive Heart Failure	I50.0
Chronic Ischemic Heart Disease	I20, I25
Chronic Renal Disease	N02.2, N03-N05, N08, N17.1, N17.2, N18, N25, O26.8
Congenital Heart Disease	Q20-Q26
Drug Abuse	F11-F16, F18, F19
Gestational Hypertension	O13, O16 (without pre-eclampsia/eclampsia or pre-existing hypertension)
Human Immunodeficiency Virus	B20, B24, O98.7, Z21
Mild/Unspecified Pre-Eclampsia	O11, O140, O14.9 (without severe pre-eclampsia/eclampsia)
Multiple Gestation	O30, O31, Z37.2-Z37.7, Z37.9
Placenta Previa	O44
Pre-Existing Diabetes Mellitus	E10, E11, O24.5-O24.7
Pre-Existing Hypertension	I10-I13, I15, O10, O11
Previous Caesarean Delivery	O34.20 or registered in the previous pregnancy outcome in the The Medical Birth Registry of Norway
Pulmonary Hypertension	I27.0, I27.2, I27.8, I27.9
Severe Pre-Eclampsia	O14.1, O14.2, O15
Sickle Cell Disease	D56, D57
Systemic Lupus Erythematosus	M32

*7.4.1.5. **Appendix D-2 Charlson Comorbidity Index***

Co-morbidity	**ICD10 code**	**Weight**
Myocardial infarction	I21, I22, I23	1
Congestive heart failure	I50, I11.0, I13.0, I13.2	1
Peripheral vascular disease	I70, I71, I72, I73, I74, I77	1
Cerebrovascular disease	I60–I69, G45, G46	1
Dementia	F00–F03, F05.1, G30	1
Chronic pulmonary disease	J40–J47, J60–J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2, J98.3	1
Connective tissue disease	M05, M06, M08, M09, M30, M31, M32, M33, M34, M35, M36, D86	1
Ulcer disease	K22.1, K25–K28	1
Mild liver disease	B18, K70.0-K70.3, K70.9, K71, K73, K74, K76.0	1
Diabetes type 1	E10.0, E10.1, E10.9	1
Diabetes type 2	E11.0, E11.1, E11.9	1
Hemiplegia	G81, G82	2
Moderate-to-severe renal disease	I12, I13, N00–N05, N07, N11, N14, N17–N19, Q61	2
Diabetes with end organ damage		2

Type 1 Type 2	E10.2–E10.8 E11.2–E11.8	
Any tumor	C00–C75	2
Leukemia	C91–C95	2
Lymphoma	C81–C85, C88, C90, C96	2
Moderate-to-severe liver disease	B15.0, B16.0, B16.2, B19.0, K70.4, K72, K76.6, I85	3
Metastatic solid tumor	C76–C80	6
AIDS	B21–B24	6

Cite from: Ording AG, Cronin-Fenton DP, Jacobsen JB, Nørgaard M, Thomsen RW, Christiansen P, Søgaard M. Comorbidity and survival of Danish breast cancer patients from 2000-2011: a population-based cohort study. Clin Epidemiol. 2013 Nov 1;5(Suppl 1):39-46. PMID: 24227922

Trinh NTH, Munk-Olsen T, Wray NR, et al. Timing of Antidepressant Discontinuation During Pregnancy and Postpartum Psychiatric Outcomes in Denmark and Norway. JAMA Psychiatry. 2023 May 1;80(5):441-450. PMID: 36884236.

7.5. Data analysis

7.5.1 Context and rationale for analysis plan

Table 10. Primary, secondary, and subgroup analysis specification

A. Primary analysis

Hypothesis:	Maternal use of second-generation antipsychotics during pregnancy increases the risk of spontaneous abortion
Exposure contrast:	Second-generation antipsychotics vs Comparator 1: Unexposed, diseased-comparison group Second-generation antipsychotics vs Comparator 2: Active comparator Second-generation antipsychotics vs Comparator 3: Discontinuer
Outcome:	Spontaneous abortion
Analytic software:	R
Model(s):	Outcome model: HRs will be estimated with Cox proportional hazards regression models. We will use robust standard errors to account for correlation within women who participated with >1 pregnancy in this study. An elective termination could potentially have ended in a spontaneous abortion, if the pregnancy had not already been terminated. This case should be censored, thereby taking competing risks into account. If mother filled a prescription before pregnancy that overlaps LMP, Exposed person-time starts on the index date. Otherwise, exposed person-time will be defined to start on the date of the first prescription fill during pregnancy; thereafter, women were considered exposed throughout follow-up[19]. Propensity score model: Cox regression model, Exposure = covariates **Covariates:** Maternal age, Marital status, Maternal employment status, Smoking status, Maternal weight, Calendar year, Charlson Comorbidity Index before pregnancy, CNS-acting comedications, Folate use, Previous pregnancy loss, Parity, Maternal infection in pregnancy, Psychiatric disorder-related outpatient visit, Psychiatric disorder-related hospitalization
Confounding adjustment method	Propensity scores will be estimated using Cox regression with the time to exposure as a dependent variable and potential confounders and risk factors for the outcome as independent variables. Including all potential confounders and risk factors for the outcome in the propensity score estimation has demonstrated increased precision without increased bias. After checking the propensity score distribution, we will decide how to deal with the extreme scores. Based on the predicted time-dependent propensity scores, a patient exposed to second-generation antipsychotics during pregnancy at any given time from LMP to EoP will be sequentially matched with a patient who was at risk of being exposed to second-generation antipsychotics and had the nearest propensity score within the same time. In the matched cohort, we will estimate HRs with Cox proportional hazards regression models. Depending on the results of the exploratory data analyses, we may apply other confounding adjustment methods (e.g. pooled logistic regression) of deemed more appropriate with regard to exposure patterns.
Missing data methods	If information derived from the MBRN on covariates is missing, obtain the information from other registries as long as possible. If the information is still missing, imputation by chained equations with the R mice package will be used to address the missing values of aforementioned factors. Datasets will be imputed and results will be summarized over the imputed datasets using Rubin's rules. Number of datasets will be determined on % of pregnancies with missing values.
Subgroup Analyses	Subgroup analysis according to subclass or ingredients of second-generation antipsychotics exposure

Table 11. Sensitivity analyses – rationale, strengths and limitations

	What is being varied? How?	**Why? (What do you expect to learn?)**	**Strengths of the sensitivity analysis compared to the primary**	**Limitations of the sensitivity analysis compared to the primary**
Sensitivity analysis 1	Redefined exposure as having at least 2 pharmacy dispensing records for antipsychotics during pregnancy (but exposure start date will not change). Pregnant women who have only one pharmacy dispensing record for antipsychotics during pregnancy will be considered as unexposed.	To evaluate the effect of exposure misclassification. Non-differential misclassification generally tends to bias results towards the null.	The assumption is that women with at least 2 prescriptions filled are more likely to have adhered to at least the first one	Reduces sample size of exposed patients
Sensitivity analysis 2	Restricting the maternal psychiatric disorder to schizophrenia only.	To reduce the confounding by indication. First generation antipsychotics are not so often prescribed for mania, bipolar disorder.	Potentially improve exchangeability between the exposure group and comparator.	Reduces sample size of exposed patients, unexposed diseased-comparison group, active comparator group.
Sensitivity analysis 3	Change the lag time between exposure and spontaneous abortion 14days	To evaluate the effect of lag time between exposure and spontaneous abortion. While it is known that there is the lag time between the arrest of development and spontaneous abortion, the lag time between exposure and spontaneous abortion is not completely clear.	Potentially add the knowledge about induction time.	Slightly reduces sample size of unexposed patients.

B. Secondary analysis

Hypothesis:	The risk of other selected pregnancy outcomes is elevated with second-generation antipsychotic use during pregnancy.
Exposure contrast:	Second-generation antipsychotics vs Comparator 1: Unexposed, diseased-comparison group Second-generation antipsychotics vs Comparator 2: Active comparator Second-generation antipsychotics vs Comparator 3: Discontinuer
Outcome:	Neonatal outcomes: preterm birth, small for gestational age (SGA), low Apgar score, transfer to NICU, congenital malformations, Maternal outcomes: caesarean section, gestational diabetes, preeclampsia
Analytic software:	R
Model(s):	**- Neonatal outcome: preterm birth,** **- Maternal outcomes: gestational diabetes, preeclampsia** Outcome model: Weighted HRs will be estimated with Cox proportional hazards regression models. We will use robust standard errors to account for correlation within women who participated with >1 pregnancy in this study. If mother was filled a prescription before pregnancy that overlaps LMP, Exposed person-time starts on the index date. Otherwise, exposed person-time will be defined to start on the date when the first prescription during pregnancy was filled; thereafter, women were considered exposed throughout follow-up[19)]. Propensity score model: Cox regression model, Exposure = covariates **- Neonatal outcomes : SGA, low Apgar score, transfer to NICU, congenital malformations** **- Maternal outcome : caesarean section** Outcome model: Adjusted RRs will be estimated with modified Poisson regression or binomial regression models in which the second-generation antipsychotics unexposed pregnancies were weighted by the PS distribution of the second-generation antipsychotics exposed pregnancies. We will use robust standard errors to account for correlation within women who participated with >1 pregnancy in this study. Propensity score model: logistic regression model, Exposure = covariates
Confounding adjustment method	Propensity scores will be estimated when using Cox regression with the time to exposure as a dependent variable and potential confounders and risk factors for the outcome as independent variables, when using logistic regression with the exposure as a dependent variable. Including all potential confounders and risk factors for the outcome in the propensity score estimation has demonstrated increased precision without increased bias. Based on the predicted time-dependent propensity scores, a patient exposed to second-generation antipsychotics during pregnancy at any given time from LMP to EoP will be sequentially matched with a patient who was at risk of being exposed to second-generation antipsychotics and had the nearest propensity score within the same time. In the matched cohort, we will estimate with the above models. Depending on the results of the exploratory data analyses, we may apply other confounding adjustment methods (e.g. pooled logistic regression) of deemed more appropriate with regard to exposure patterns.
Missing data methods	If information derived from the MBRN is missing, obtain the information from other registries as long as possible. If the information is still missing, imputation by chained equations with the R mice package will be used to address the missing values of aforementioned factors. Datasets will be imputed and results will be summarized over the imputed datasets using Rubin's rules. Number of datasets will be determined on % of pregnancies with missing values.
Subgroup Analyses	Subgroup analysis according to subclass or ingredients of second-generation antipsychotics exposure

B. Sensitivity analyses in secondary analysis

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Sensitivity analysis 1	Redefined exposure as having at least 2 pharmacy dispensing records for antipsychotics during pregnancy (but exposure start date will not change). Pregnant women who have only one pharmacy dispensing record for antipsychotics during pregnancy will be considered as unexposed.	To evaluate the effect of exposure misclassification. Non-differential misclassification generally tends to bias results towards the null.	The assumption is that women with at least 2 prescriptions filled are more likely to have adhered to at least the first one	Reduces sample size of exposed patients
Sensitivity analysis 2	Restricting the maternal psychiatric disorder to schizophrenia only.	To reduce the confounding by indication. First generation antipsychotics are not so often prescribed for mania, bipolar disorder.	Potentially improve exchangeability between the exposure group and comparator.	Reduces sample size of exposed patients, unexposed diseased-comparison group, active comparator group.

Other analyses

We will also calculate the estimated excess number of spontaneous abortions by subtracting rates of spontaneous abortion among women with second-generation antipsychotics treated/ first-generation antipsychotics treated /non-treated psychiatric disorders in pregnancy from the rates of spontaneous abortion in the general birth population (per 1000 pregnancies) in Norway. The general pregnancy population will consist of all pregnancies in our linked data file used as the initial population, excluding pregnancies with psychiatric disorders or use of second-generation antipsychotics / first-generation antipsychotics.

7.6. Data sources

7.6.1 Context and rationale for data sources

Reason for selection:

Strengths of data source(s): Our study is based on national health registries with nationwide coverage covering a time period over ten years. The population size allows for analysis on several individual antipsychotics. Important information on maternal characteristics, lifestyle factors and maternal medical complications enables us to control for several important confounding factors. Another important strength with our study is being a prospectively registered nationwide study, which eliminates recall and selection bias. The newly developed pregnancy algorithm to identify early spontaneous abortions and elective terminations (< GW 12) is also one of the strengths[5)]. Validity of information on several pregnancy outcomes (preterm birth, birth weight (this relates to SGA), caesarean section, preeclampsia) in MBRN has shown to be very high, which is required to produce robust results[21–23)].

Limitations of data source(s):

-Factors leads to less precision: Some potential relevant confounders are unmeasured. These may be substance abuse, poor diet, stress, alcohol use are unmeasured. These may be risk factors for adverse outcomes such as spontaneous abortion[20)].

Adherence: The exposure measurement is based on dispensed antipsychotic medications in pregnancy. No information about the validity of antipsychotic dispensation is available. However, we expect it to be similar to that of other psychotropics. In particular, antidepressant exposure validity was reported to have a sensitivity of 66.9% and specificity of 99.7% [24)]. Benzodiazepines as anxiolytics and hypnotics exposure validity were reported as a sensitivity of 44.8%, 27.8% and specificity of 99.7%, 100% respectively[24)].

Data source provenance/curation: The Norwegian data sources are widely used for research and the data holders provide thorough documentation of data contents, assumptions and limitations.

Table 12. Metadata about data sources and software

	Data 1	**Data 2**	**Data 3**	**Data 4**
Data Source(s):	The Medical Birth Registry of Norway (MBRN)	The Norwegian Prescription Registry (NorPD)	The Norwegian Patient Registry (NPR)	Norwegian control and payment of health reimbursements (KUHR)
Study Period:	2004-2018	2004-2019	2008-2019	2006-2019
Eligible Cohort Entry Period:	2008-2018	2008-2018	2008-2018	2008-2018
Data Version (or date of last update):				
Data sampling/extraction criteria:	Personal identification number given to all residents in Norway	Personal identification number given to all residents in Norway	Personal identification number given to all residents in Norway	Personal identification number given to all residents in Norway
Type(s) of data:	Registry	Registry	Registry	Administrative database

Data linkage:	All data			
Conversion to CDM*:	Not reported	Not reported	Not reported	Not reported
Software for data management:				

7.7. Data management

Data files are provided by the Health registries of Norway and labeled according to the project number, version, and date of access. The provided data from these health registries to researchers at UiO are stored in secure servers operated by the University of Oslo called Tjenester for Sensitive Data (TSD). An isolated virtual machine (VM) with a proper operation system and dedicated encrypted storage and CPU resources will be allocated by TSD for each project upon application which stores the received data from registries. The VMs are isolated and only accessible within the UiO network and through secure authentication protocols. Only researchers registered within the specific project number can access TSD and the VM. The project meets the new GDPR requirements as required. Health registries in Norway anonymize data before sending them to TSD by replacing the original IDs with the project-specific generated IDs while preserving the ability to link different data sources. Exporting the results from TSD is strictly limited and needs to be coordinated by the project's admin in a sign-off meeting. Exporting results that can be linked to individual identifications is not permitted. Back-up of the data is automatically and routinely performed multiple times per week within the TSD infrastructure at the University of Oslo.

7.8. Quality control

The data sources have been through extensive quality control procedures by the registry custodian. When new data is received from a registry custodian, the research group has an internal quality check process which includes assessment of reliability and conformance to expected plausible values. Issues are flagged for review by the data quality team and resolved with documentation of decisions made to clean the data before it is released to the research team to conduct studies.

7.9. Study size and feasibility

The source population will include data from the entire Norwegian birthing population between 2008 and 2018, comprising of approximately 860,000 pregnancies, depending on the in- and exclusion criteria that will differ for each objective the study cohorts. Overall antipsychotic exposure prevalence is expected to be 1.16%. Second-generation antipsychotic exposure prevalence is expected to be 0.24%.

Based on an early data extraction (p704), we identified the following approximate numbers of exposed pregnancies:

Analysis	Any antipsychotic	First generation antipsychotic	Second generation antipsychotic
Primary: UiO pregnancy algorithm (2008-2018), exposure in GW0-19	7,000	4,500	2,500
Secondary: MBRN (2008-2018), exposure in pregnancy	6,000	4,500	1,500
Secondary: MBRN (2008-2018), exposure in trimester 1	5,000	3,500	1,500

At a substance level, the following exposures were identified:

ATC code	Antipsychotic	Type	Primary: GW0-19	Secondary: Pregnancy, any time	Secondary: Trimester 1
N05AA01	Chlorpromazine	First generation	600	600	500
N05AA02	Levomepromazine	First generation	500	600	300
N05AB04	Prochlorperazine	First generation	28,00	2,800	2,400
N05AH04	Quetiapine	Second generation	1,700	1,100	900
N05AH03	Olanzapine	Second generation	400	300	300
N05AX12	Aripiprazole	Second generation	300	200	200
N05AX08	Risperidone	Second generation	100	50	50

Table 13. Sample size calculations -cohort study: second-generation antipsychotic exposed vs all unexposed pregnancies (in the whole cohort)

Sample size required to detect associations given 80% study power and type I error rate of 0.05

	RR					RR				
Prevalence of exposure	**1.25**	**1.5**	**2**	**3**	**5**	**1.25**	**1.5**	**2**	**3**	**5**
	BASELINE RISK of outcome: 10% SPONTANEOUS ABORTIONS**					**BASELINE RISK of outcome: 8%** PREMATURITY**				
0.3%	**852000**	**233333**	**68000**	**21333**	**7000**	1092000	**300000**	**88000**	**28000**	**9500**
1%	255600	70000	20400	6400	2100	327600	90000	26400	8400	2850
2%	127800	35000	10200	3200	1050	163800	45000	13200	4200	1425
5%	51120	14000	4080	1280	420	65520	18000	5280	1680	570
10%	25560	7000	2040	640	210	32760	9000	2640	840	285
	BASELINE RISK of outcome: 5% LOW BIRTH WEIGHT**					**BASELINE RISK of outcome: 3%** GESTATIONAL DIABETES/ PRECLAMPSIA**				
0.3%	1812000	**500000**	**148000**	**48000**	**17000**	3092000	855556	**254667**	**83556**	**30333**
1%	543600	150000	44400	14400	5100	927600	256667	76400	25067	9100
2%	271800	75000	22200	7200	2550	463800	128333	38200	12533	4550
5%	108720	30000	8880	2880	1020	185520	51333	15280	5013	1820
10%	54360	15000	4440	1440	510	92760	25667	7640	2507	910
	BASELINE RISK of outcome: 2% ANY MAJOR CONGENITAL ANOMALY**									
0.3%	4692000	1300000	**388000**	**128000**	**47000**					
1%	1407600	390000	116400	38400	14100					
2%	703800	195000	58200	19200	7050					
5%	281520	78000	23280	7680	2820					
10%	140760	39000	11640	3840	1410					

For the primary analysis, 860,000 pregnancies are expected to provide 80% study power to detect a nearly 1.25-fold elevation in spontaneous abortion risk for second-generation antipsychotics compared to other pregnancies in the dataset with 95% confidence intervals excluding the null.

Table 14. Sample size calculations -cohort study: second-generation antipsychotic exposed vs first-generation antipsychotic exposed (in the antipsychotics exposed cohort)

In the feasibility count, there were approximately 7,000 pregnancies with any antipsychotic exposure. The number of second-generation antipsychotic exposure was 2,500 (35%). The number of first-generation antipsychotic exposure was 4,500(65%).

Sample size required to detect associations given 80% study power and type I error rate of 0.05.

	RR					RR				
Prevalence of exposure	**1.25**	**1.5**	**2**	**3**	**5**	**1.25**	**1.5**	**2**	**3**	**5**
	BASELINE RISK of outcome: 10% SPONTANEOUS ABORTIONS**					**BASELINE RISK of outcome: 8%** PREMATURITY**				
1%	255600	70000	20400	6400	2100	327600	90000	26400	8400	2850
5%	51120	14000	4080	1280	420	65520	18000	5280	1680	570
10%	25560	7000	**2040**	**640**	**210**	32760	9000	**2640**	**840**	**285**
30%	8520	**2333**	**680**	**213**	**70**	10920	**3000**	**880**	**280**	**95**
50%	**5112**	**1400**	**408**	**128**	**42**	6552	**1800**	**528**	**168**	**57**
	BASELINE RISK of outcome: 5% LOW BIRTH WEIGHT**					**BASELINE RISK of outcome:3%** GESTATIONAL DIABETES/ PRECLAMPSIA**				
1%	543600	150000	44400	14400	5100	927600	256667	76400	25067	9100
5%	108720	30000	8880	2880	1020	185520	51333	15280	5013	1820
10%	54360	15000	**4440**	**1440**	**510**	92760	25667	7640	**2507**	**910**
30%	18120	**5000**	**1480**	**480**	**170**	30920	8555	**2546**	**835**	**303**
50%	10872	**3000**	**888**	**288**	**102**	18552	**5133**	**1528**	**501**	**182**
	BASELINE RISK of outcome:2% ANY MAJOR CONGENITAL ANOMALY**									
1%	1407600	390000	116400	38400	14100					
5%	281520	78000	23280	7680	2820					
10%	140760	39000	11640	**3840**	**1410**					
30%	46920	13000	**3880**	**1280**	**470**					
50%	28152	7800	**2328**	**768**	**282**					

For the primary analysis, 7,000 pregnancies provide 80% study power to detect a nearly 1.5 to 2-fold elevation in spontaneous abortion risk for second-generation antipsychotics compared to first-generation antipsychotics with 95% confidence intervals excluding the null.

8. Limitation of the methods

There are several potential limitations with the methods specified in this protocol.

1. The data were not collected for research and some important variables may not be collected or will be measured imperfectly
    a. We have selected validated algorithms when possible
    b. We have created proxies for important variables that are not directly captured in the data to reduce confounding by unmeasured factors
2. There will not be randomization
    a. We will balance exposure groups on important risk factors for the exposure and outcome(s)

9. Protection of human subjects

The proposed study is observational research that makes secondary use of data collected as part of routine care and does not involve any intervention, alteration in standard clinical care or use of any procedure in patients. Therefore, there will be no adverse events related to the study itself. No patients will be contacted for any of the proposed studies. Prior to our acquisition of the data, all personal identifiers will be encrypted. This encryption minimizes the risk of patient reidentification in the unlikely event of a breach in data security.

10. Reporting of adverse events

The proposed study is observational research that makes secondary use of data collected as part of routine care and does not involve any intervention or alteration in clinical care. Therefore, reporting of adverse events related to this study is not applicable. Safety evaluations for this study are limited to the specified safety outcomes stated in section 4.4.2.

11. References

1) Reutfors J, Cesta CE, Cohen JM, et al. Antipsychotic drug use in pregnancy: A multinational study from ten countries. Schizophr Res. 2020 Jun;220:106-115. PMID: 32295750.

2) Huybrechts KF, Straub L, Karlsson P, et al. Association of In Utero Antipsychotic Medication Exposure With Risk of Congenital Malformations in Nordic Countries and the US. JAMA Psychiatry. 2023 Feb 1;80(2):156-166. PMID: 36477338.

3) Liu X, Kolding L, Momen N, et al. Maternal antipsychotic use during pregnancy and congenital malformations. Am J Obstet Gynecol MFM. 2023 Jun;5(6):100950. PMID: 37015311.

4) Sørensen MJ, Kjaersgaard MI, Pedersen HS, et al. Risk of Fetal Death after Treatment with Antipsychotic Medications during Pregnancy. PLoS One. 2015 Jul 10;10(7):e0132280. PMID: 26162087.

5) Nordeng HME, Lupattelli A, Engjom HM, et al. Detecting and dating early non-live pregnancies: generation of a novel pregnancy algorithm from Norwegian linked health registries.[preprint] doi: 10.22541/au.171344385.51209752/v1

6) Tang W, Zhou LJ, Zhang WQ, et al. Adverse perinatal pregnancy outcomes in women with schizophrenia: A systematic review and meta-analysis. Schizophr Res. 2023 Dec;262:156-167. PMID: 37979419.

7) Jarde A, Morais M, Kingston D, et al. Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2016 Aug 1;73(8):826-37. PMID: 27276520.

8) Grigoriadis S, VonderPorten EH, Mamisashvili L, et al. The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis. J Clin Psychiatry. 2013 Apr;74(4):e321-41. PMID: 23656857.

9) Rusner M, Berg M, Begley C. Bipolar disorder in pregnancy and childbirth: a systematic review of outcomes. BMC Pregnancy Childbirth. 2016 Oct 28;16(1):331. PMID: 27793111.

10) Fabre C, Pauly V, Baumstarck K, et al. Pregnancy, delivery and neonatal complications in women with schizophrenia: a national population-based cohort study. Lancet Reg Health Eur. 2021 Sep 7;10:100209. PMID: 34806069.

11) Edvardsson K, Hughes E, Copnell B, et al. Severe mental illness and pregnancy outcomes in Australia. A population-based study of 595 792 singleton births 2009-2016. PLoS One. 2022 Feb 28;17(2):e0264512. PMID: 35226688.

12) Magnus MC, Havdahl A, Morken NH, et al. Risk of miscarriage in women with psychiatric disorders. Br J Psychiatry. 2021 Sep;219(3):501-506. PMID: 33448259

13) Sakai T, Ohtsu F, Mori C, et al. Signal of Miscarriage with Aripiprazole: A Disproportionality Analysis of the Japanese Adverse Drug Event Report Database. Drug Saf. 2017 Nov;40(11):1141-1146. PMID: 28664356.

14) Twaites BR, Wilton LV, Shakir SA. The safety of quetiapine: results of a post-marketing surveillance study on 1728 patients in England. J Psychopharmacol. 2007 Jun;21(4):392-9. PMID: 17656426.

15) Goldstein DJ, Corbin LA, Fung MC. Olanzapine-exposed pregnancies and lactation: early experience. J Clin Psychopharmacol. 2000 Aug;20(4):399-403. PMID: 10917399.

16) Coppola D, Russo LJ, Kwarta RF Jr, et al. Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. Drug Saf. 2007;30(3):247-64. PMID: 17343431.

17) Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. Acta Obstet Gynecol Scand. 2000 Jun;79(6):435-9. PMID: 10857866.

18) Sundermann AC, Mukherjee S, Wu P, et al. Gestational Age at Arrest of Development: An Alternative Approach for Assigning Time at Risk in Studies of Time-Varying Exposures and Miscarriage. Am J Epidemiol. 2019 Mar 1;188(3):570-578. PMID: 30521025.

19) Harris GM, Wood M, Ystrom E, et al. Association of Maternal Use of Triptans During Pregnancy With Risk of Attention-Deficit/Hyperactivity Disorder in Offspring. JAMA Netw Open. 2022 Jun 1;5(6):e2215333. PMID: 35657626.

20) Quenby S, Gallos ID, Dhillon-Smith RK, et al. Coomarasamy A. Miscarriage matters: the epidemiological, physical, psychological, and economic costs of early pregnancy loss. Lancet. 2021 May 1;397(10285):1658-1667. PMID: 33915094.

21) Lehmann S, Baghestan E, Børdahl P, et al. Validation of data in the Medical Birth Registry of Norway on delivery after a previous cesarean section. Acta Obstet Gynecol Scand. 2017;96(7):892-897. PMID: 28196281.

22) Moth FN, Sebastian TR, Horn J, et al. Validity of a selection of pregnancy complications in the Medical Birth Registry of Norway. Acta Obstet Gynecol Scand. 2016;95(5):519-527. PMID: 26867143.

23) Thomsen LC, Klungsøyr K, Roten LT, et al. Validity of the diagnosis of preeclampsia in the Medical Birth Registry of Norway. Acta Obstet Gynecol Scand 2013;92(8):943-950. PMID: 23621424.

24) Skurtveit S, Selmer, R, Odsbu I, et al. Self-reported data on medicine use in the Norwegian Mother and Child cohort study compared to data from the Norwegian Prescription Database. Norsk Epidemiologi, 2014, 24(1-2).

12. Appendices

12.1.1. Appendix E. Tentative flow chart