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Risk of Attention-Deficit Hyperactivity Disorder in Children Following Prenatal Exposure to Antidepressants

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Background

- Gestational use of antidepressants in Norway is about 1.5-2%, mainly SSRIs
- It is estimated that 7-15% of women with depression and/or anxiety during pregnancy are medicated

- SSRIs and also SNRIs can alter the serotonin signaling system during fetal brain maturation

Zoega H, et al. Use of SSRI and SNRI Antidepressants during Pregnancy: A Population-Based Study from Denmark, Iceland, Norway and Sweden.
Lupattelli A, et al. Effect of Time-Dependent Selective Serotonin Reuptake Inhibitor Antidepressants During Pregnancy on Behavioral, Emotional, and Social Development in Preschool-Aged Children.

Background

Research attention on risk of Attention Deficit Hyperactivity Disorder (ADHD) in offspring following in-utero exposure to antidepressants

-> **2 meta-analysis in 2018**

Jiang et al., BJOG

6 cohort studies

- Exposed versus population comparison
  HR: 1.34, 95% CI: 1.14-1.57
- Exposed versus disease comparison
  HR: 0.96, 95% CI: 0.76-1.2

Man et al. Neurosci Biobehav Rev

6 cohort + 1 case-control studies

- Exposed versus population comparison
  RR: 1.39, 95% CI: 1.21-1.61
- Psychiatric disease versus population
  RR: 1.90, 95% CI: 1.47-2.45
- Sibling-matched
  RR: 0.94, 95% CI: 0.75-1.16

Study aims

- To quantify the association between timing and duration of prenatal exposure to **SSRI/SNRI antidepressants** on child risk for **ADHD**, as **clinical diagnosis** and parent-reported **symptoms**

- With quantification of bias due to exposure misclassification

Methods

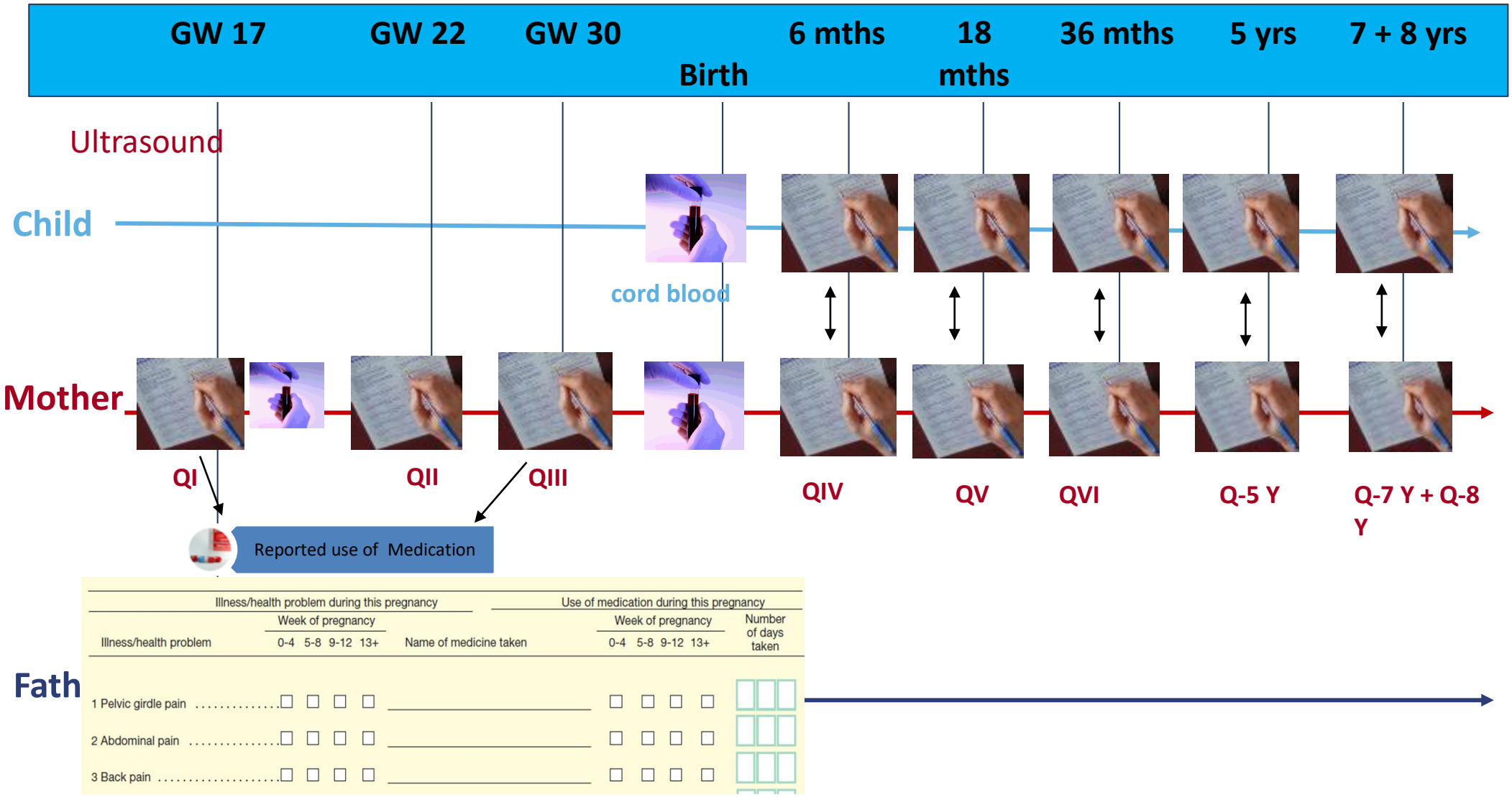
Norwegian **Mother and Child** Cohort Study

- Data from the Norwegian Mother, Father and Child Cohort study (MoBa) linked to the Norwegian Medical Birth Registry, Prescription Database, and Patient Registry

- MoBa is a prospective cohort study including 114,000 mother-child pairs recruited between 1999-2008 all over Norway

Magnus P, Birke C, Vejrup K, et al. Cohort Profile Update: The Norwegian Mother and Child Cohort Study (MoBa). Int J Epidemiol 2016;45(2):382-388.

Data collection in Mo



GW=gestational week

Data collection in MoBa

GW=gestational week

Covariates

GW 17

GW 30

BIRTH

5 years

QI

Depression and anxiety SSRI/SNRI exposure (by 4-week intervals)
SSRI/SNRI filled prescriptions records)

Depressive and anxiety symptoms
via the SCL-5 (Hopkins symptoms check-list, 5 items)

QIII

Depression SSRI/SNRI exposure (by 4-week intervals)
SSRI/SNRI filled prescriptions records

Depressive and anxiety symptoms
via the SCL-5 (Hopkins symptoms check-list, 5 items)

Q5-y

ADHD symptoms
via Conners Parent Rating Scale-Revised (**CPRS-R**) 12-items

ADHD diagnosis (ICD-10 F90) or filled ADHD prescription (2004-2016)

Strand, B.H., et al. (2003) Measuring the mental health status of the Norwegian population: A comparison of the instrument SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36).
Conners CK, et al. (1998) The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity

Definition study sample

- Pregnancies within women reporting depression/anxiety during pregnancy and taking SSRI/SNRI in pregnancy
  -> Medicated to SSRI/SNRI, n=818

- Pregnancies within women reporting depression/anxiety during pregnancy but unexposed to antidepressants in pregnancy **-> Non-medicated, n=5228**

- Pregnancies within women taking antidepressants 6 months prior to pregnancy but with no depression/anxiety during pregnancy **-> Discontinuers, n=349**

Data analysis

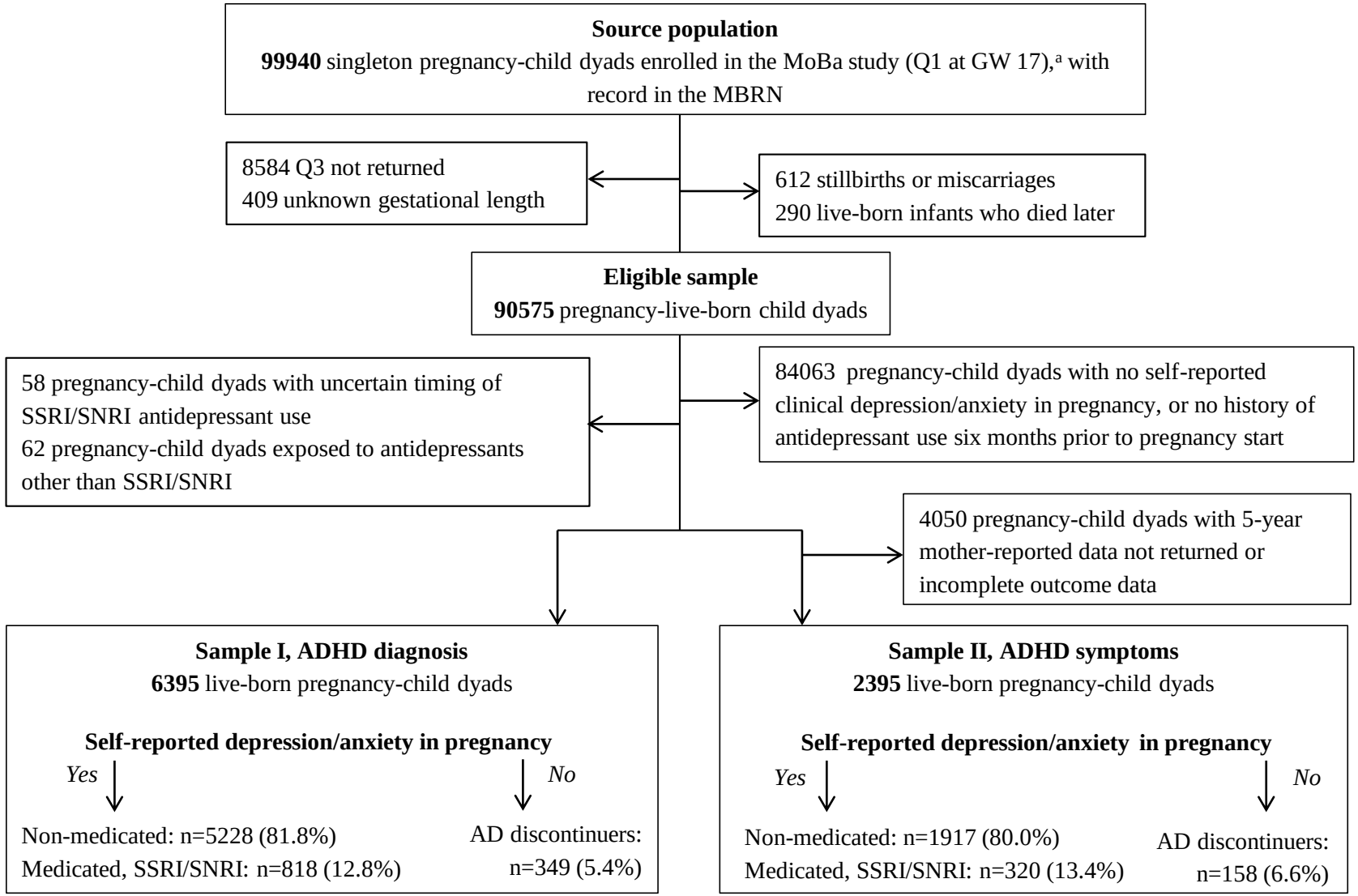
Marginal Structural Models (MSM)

- Stabilized inverse probability of treatment weights **(IPTW)** at time points t1 (week 17) and t2 (week 30)

Main model: Baseline maternal factors (e.g., BMI, marital status, education, age of mother and father, folate use, obstetric index)
Time-varying covariates (i.e., depressive/anxiety symptoms, co-medication with analgesics, anxiolytics and sedatives, acetaminophen)
Time-fixed covariates (e.g., smoking in early pregnancy, alcohol use, ADHD medication filled by mothers and fathers)
+ 8 additional, alternative model specifications

Outcome modelling: Cox regression and Generalized Linear Models

Data flow


Source population
99940 singleton pregnancy-child dyads enrolled in the MoBa study (Q1 at GW 17),[a] with record in the MBRN
8584 Q3 not returned
409 unknown gestational length
612 stillbirths or miscarriages
290 live-born infants who died later
Eligible sample
90575 pregnancy-live-born child dyads
58 pregnancy-child dyads with uncertain timing of SSRI/SNRI antidepressant use
62 pregnancy-child dyads exposed to antidepressants other than SSRI/SNRI
84063 pregnancy-child dyads with no self-reported clinical depression/anxiety in pregnancy, or no history of antidepressant use six months prior to pregnancy start
4050 pregnancy-child dyads with 5-year mother-reported data not returned or incomplete outcome data
Sample I, ADHD diagnosis
6395 live-born pregnancy-child dyads
Self-reported depression/anxiety in pregnancy
Yes
No
Non-medicated: n=5228 (81.8%)
Medicated, SSRI/SNRI: n=818 (12.8%)
AD discontinuers: n=349 (5.4%)
Sample II, ADHD symptoms
2395 live-born pregnancy-child dyads
Self-reported depression/anxiety in pregnancy
Yes
No
Non-medicated: n=1917 (80.0%)
Medicated, SSRI/SNRI: n=320 (13.4%)
AD discontinuers: n=158 (6.6%)

Results

Some characteristics of study sample I (N=6395)

	Self-reported depression/anxiety during pregnancy		
	Yes		No
	Non-medicated	Medicated SSRI/SNRI	AD discontinuers
Characteristics	**n=5228**	**n=818**	**n=349**
Age (years); mean ± sd	29.6 ± 5.1	30.1 ± 5.1	29.7 ± 4.7
BMI at conception; mean ± sd	24.2 ± 4.5	24.5 ± 4.9	24.8 ± 4.9
Primiparity; n (%)	2892 (55.3)	384 (49.9)	167 (47.9)
Married/Cohabiting; n (%)	4775 (91.3)	716 (87.5)	318 (91.1)
Educational level;[a] n (%)			
University/College	2653 (50.8)	418 (51.1)	184 (52.7)
Lower than University/College	2541 (48.6)	399 (48.8)	163 (46.7)
Gross yearly income;[b] n (%)			
Average	3212 (61.4)	502 (61.4)	213 (61.0)
Low	1412 (27.0)	237 (29.0)	97 (27.8)
High	402 (7.7)	56 (6.9)	32 (9.2)
Depressive/anxiety symptoms; mean score ± sd			
SCL-5 at GW 17	1.8 (0.6)	1.9 (0.7)	1.5 (0.5)
SCL-5 at GW 30	1.8 (0.6)	1.8 (0.7)	1.5 (0.5)
ADHD maternal prescriptions; n (%)	149 (2.9)	53 (6.5)	15 (4.3)

Results – ADHD diagnosis

323 (5.1%) children with ADHD, 84.8% filled ADHD medication

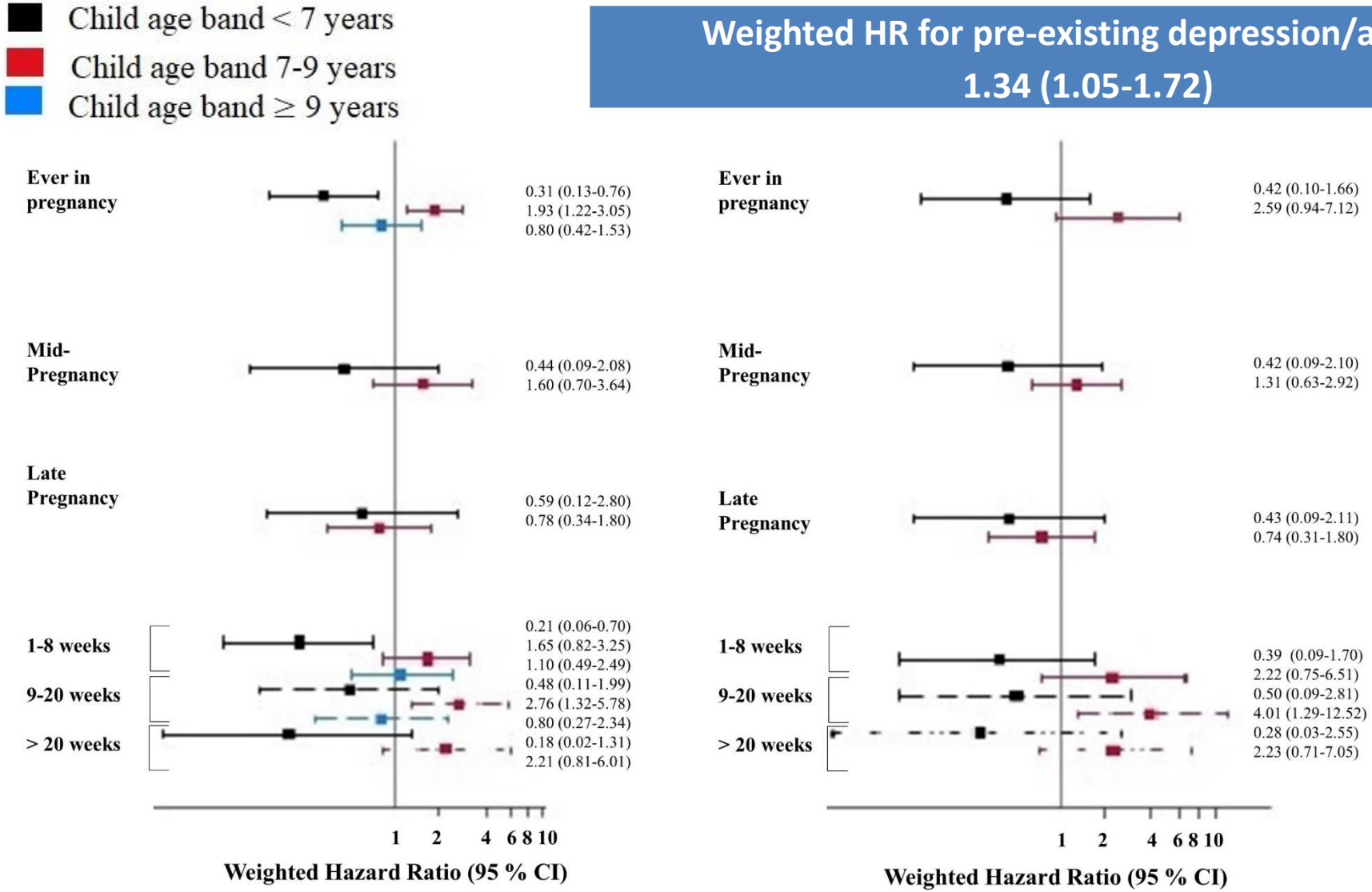
Exposure definition	No. events	Crude HR (95% CI)	Weighted HR (95% CI)	Crude HR (95% CI)	Weighted HR (95% CI)
Any time in pregnancy*					
Non-medicated (n=5228)	250	1	1	-	-
Discontinuers of AD (n=349)	14	-	-	1	1
SSRI/SNRI (n=818)	54	1.42 (1.06-1.91)	1.07 (0.76-1.51)	1.64 (0.91-2.96)	1.53 (0.77-3.07)
By timing of exposure**					
Non-medicated (n=5228)	250	1	1	-	-
Discontinuers of AD (n=349)	14	-	-	1	1
SSRI/SNRI week 17-28 (n=302)	18	1.25 (0.77-2.01)	0.98 (0.55-1.71)	1.05 (0.61-1.80)	0.82 (0.45-1.52)
SSRI/SNRI week 29-34 (n=252)	15	1.24 (0.74-2.09)	1.08 (0.47-2.47)	1.04 (0.59-1.85)	0.97 (0.43-2.19)
By duration of exposure*					
SSRI/SNRI, 1-8 weeks	27	1.32 (0.89-1.95)	1.07 (0.64-1.77)	1.53 (0.81-2.90)	1.50 (0.74-3.05)
SSRI/SNRI, 9-20 weeks	18	2.05 (1.26-3.31)	1.40 (0.79-2.50)	2.37 (1.19-4.74)	2.13 (0.97-4.68)
SSRI/SNRI, >20 weeks	9	1.04 (0.53-2.03)	0.85 (0.33-2.18)	1.16 (0.50-2.67)	0.89 (0.38-2.12)

*Weighted with stabilized inverse probability of treatment weighting using the propensity score

**MSM weighted with stabilized inverse probability of treatment weighting (constructed at each time point using baseline covariates, time-varying and time-fixed confounding factors, and SSRI/SNRI history treatment)

Results – ADHD diagnosis, temporal associations

Weighted HR for pre-existing depression/anxiety: 1.34 (1.05-1.72)



Point estimates < 1: Favors SSRI/SNRI exposure. Point estimates > 1 favors reference exposure. For duration of exposure: the continuous line indicates duration of 1-8 weeks; the dashed line 9-20 weeks; and the dot-dot-dash line > 20 weeks.

Results – ADHD symptoms at 5 years

Exposure definition	Mean	Crude HR (95% CI)	Weighted HR (95% CI)	CrudeHR (95% CI)	Weighted HR (95% CI)
Any time in pregnancy*					
Non-medicated	1.50	Reference	Reference	-	-
Discontinuers of AD	1.45	-	-	Reference	Reference
SSRI/SNRI	1.47	-0.09 (-0.22, 0.04)	-0.23 (-0.39, -0.08)	0.03 (-0.18, 0.24)	-0.18 (-0.45, 0.09)
By timing of exposure**					
SSRI/SNRI week 17-28	1.52	0.05 (-0.17, 0.27)	-0.09 (-0.37, 0.19)	0.19 (-0.06, 0.43)	0.06 (-0.22, 0.34)
SSRI/SNRI week 29-34	1.52	0.06 (-0.18, 0.30)	-0.11 (-0.42, 0.21)	0.19 (-0.07, 0.45)	0.03 (-0.28, 0.35)
By duration of exposure*					
SSRI/SNRI, 1-8 weeks	1.45	-0.14 (-0.31, 0.04)	-0.27 (-0.46, -0.08)	-0.02 (-0.26, 0.22)	-0.17 (-0.43, 0.10)
SSRI/SNRI, 9-20 weeks	1.47	-0.09 (-0.37, 0.19)	-0.29 (-0.56, -0.02)	0.03 (-0.29, 0.36)	-0.31 (-0.67, 0.05)
SSRI/SNRI, >20 weeks	1.50	-0.01 (-0.25, 0.23)	-0.07 (-0.44, 0.29)	0.12 (-0.17, 0.40)	-0.02 (-0.36, 0.32)

*Weighted with stabilized inverse probability of treatment weighting using the propensity score

**MSM weighted with stabilized inverse probability of treatment weighting (constructed at each time point using baseline covariates, time-varying and time-fixed confounding factors, and SSRI/SNRI history treatment)

Underestimation of effects due to exposure misclassification was modest for both ADHD diagnosis and symptoms: about 10%

Main strengths

- Population based, prospective
- ADHD as diagnosis and symptoms
- Account for time-varying confounders affected by previous treatment
- Multiple imputation for missing data on confounders
- Several sensitivity analyses and misclassification

Main limitations

- Low response rate in MoBa (41%)
- Time-varying confounders at two time points only
- Limited power to examine individual medications
- No information on dose, but available proxy for duration (four-week intervals) and cumulative daily doses dispensed

When the ADHD hazard was averaged over the follow-up, there was no association between prenatal SSRI/SNRI exposure and ADHD in offspring. The risk for child ADHD following prenatal SSRI/SNRI exposure was elevated only at age 7-9 years.

The lack of a clear duration-related relationship, and the observed confounding by maternal depression/anxiety in this study, does not support a causal link between SSRI/SNRI and child ADHD

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Thank you for your attention