

Table 1: Characteristics of sample I by prenatal SSRI/SNRI antidepressant exposure (N=6395)

Characteristics	Self-reported clinical depression/anxiety during pregnancy		
	Yes		No
	Non-medicated n=5228	Medicated SSRI/SNRI n=818	AD discontinuers n=349
Maternal sociodemographics			
Age (years); mean \pm sd	29.6 \pm 5.1	30.1 \pm 5.1	29.7 \pm 4.7
BMI at conception; mean \pm sd	24.2 \pm 4.5	24.5 \pm 4.9	24.8 \pm 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)
Smoking at week 17; n (%)			
No	3338 (63.9)	455 (55.6)	231 (66.2)
Yes	738 (14.1)	180 (22.0)	59 (16.9)
Stopped in pregnancy	1085 (20.8)	176 (21.5)	59 (16.9)
Alcohol use at week 17; n (%)			
No/very limited	4352 (83.2)	692 (84.6)	294 (84.2)
Medium/weekly use	154 (3.0)	24 (2.9)	9 (2.6)
Periconceptional folate use (yes); n (%)	4049 (77.5)	655 (80.1)	293 (84.0)
Maternal health			
LTH of MD (yes); ^c n (%)	999 (19.1)	375 (45.8)	102 (29.2)
Depression/anxiety before pregnancy (yes); n (%)	1905 (36.4)	766 (93.6)	286 (82.0)
Number of psychiatric disorders in pregnancy; n (%)			
One	4479 (85.7)	551 (67.4)	-
Two	649 (12.4)	195 (23.8)	-
Three	100 (1.9)	72 (8.8)	-
Depressive/anxiety symptoms; mean score \pm 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)
Comorbidity index; mean \pm sd	0.6 (1.0)	0.6 (1.1)	0.6 (1.1)
Number of infections in pregnancy; mean \pm sd	0.5 (0.8)	0.5 (0.8)	0.5 (0.7)
Co-medication in pregnancy (yes); n (%)			
Benzodiazepines/z-hypnotics	135 (2.6)	87 (10.6)	11 (3.2)
NSAIDs	400 (7.7)	85 (10.4)	30 (8.6)
Paracetamol	2675 (51.2)	431 (52.7)	191 (54.7)
Opioid analgesics	161 (3.1)	39 (4.8)	15 (4.3)
Antipsychotics	82 (1.6)	33 (4.0)	8 (2.3)

	Self-reported clinical depression/anxiety during pregnancy		
	Yes		No
	Non-medicated	Medicated SSRI/SNRI	AD discontinuers
Antiepileptics	36 (0.7)	19 (2.3)	1 (0.3)
Illicit substance (yes);^d n (%)	118 (2.3)	31 (3.8)	8 (2.3)
ADHD prescriptions;^e n (%)	149 (2.9)	53 (6.5)	15 (4.3)
<i>Child characteristics</i>			
Infant sex (male); n (%)	2561 (49.0)	425 (52.0)	159 (45.6)
Any malformation (yes); n (%)	252 (4.8)	35 (4.3)	22 (6.3)
Premature birth (yes); n (%)	228 (4.4)	46 (5.6)	20 (5.7)
Breastfeeding months from age 0 to 7 months; mean \pm sd	4.7 \pm 2.9	4.5 \pm 3.0	4.8 \pm 2.8
<i>Paternal sociodemographics and health-related factors</i>			
Age (years); n (%)			
< 25	438 (8.4)	64 (7.8)	22 (6.3)
25-39	4177 (79.9)	632 (77.3)	277 (79.4)
40-49	552 (10.6)	109 (13.3)	45 (12.9)
> 49	42 (0.8)	4 (0.5)	4 (1.2)
Educational level;^a n (%)			
University/College	1554 (29.7)	239 (29.2)	110 (31.5)
Lower than University/College	2227 (42.6)	357 (43.6)	145 (41.6)
Receipt of social security benefits (yes); n (%)	34 (0.7)	10 (1.2)	1 (0.3)
ADHD prescriptions;^e n (%)	68 (1.3)	10 (1.2)	8 (2.3)
Depressive/anxiety symptoms; mean score \pm sd			
SCL-8 at woman's GW 17	1.2 \pm 0.4	1.2 \pm 0.4	1.2 \pm 0.3

Abbreviations: AD=Antidepressant; ADHD=Attention Deficit Hyperactivity Disorder; BMI=body mass index; GW=Gestational week; LTHMD=Life Time History of Major Depression; NSAID=non-steroidal anti-inflammatory drugs; SCL-5=short version (5-item) of The Hopkins Symptom Checklist; SNRI=Serotonin–norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitor.

Numbers may not add up to total due to missing values on maternal correlates: education (0.6%), smoking (1.2%), BMI at conception (3.2%), LTH of MD (3.0%), income (3.6%) and alcohol use (13.6%), as well as on paternal factors: age (0.5%), and education (27.6%). For maternal SCL, missing values were 5.6% and 3.7% in early and late pregnancy, respectively, while for the paternal it was 28.7%.

^aIncludes ongoing or completed educational level. ^bAverage indicates income approximately between 17501 and 46800 USD; Low indicates income \leq 17500 USD; High indicates income \geq 46801USD. ^cDefined as Kendlers Life time major depression scale score of 3 or more simultaneous depressive symptoms of duration of more than 2 weeks. ^dIndicates use before and/or during pregnancy. ^eIndicates prescription for any ADHD medication filled by fathers or mothers at any time.

Table 2: Associations of SSRI/SNRI windows of exposure with child ADHD (Sample I) and symptoms at age 5 years (Sample II)

SSRI/SNRI vs Non-medicated				SSRI/SNRI vs AD discontinuers			
Sample I, ADHD diagnosis							
Exposure window	No.	No. events	IR per 1000 py	Crude HR (95% CI)	Weighted* HR (95% CI)	Crude HR (95% CI)	Weighted* HR (95% CI)
Non-medicated	5228	250	4.4	Reference	Reference		
AD discontinuers	349	14	3.8	-	-	Reference	Reference
SSRI/SNRI, ever	818	54	6.2	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 duration in pregnancy [§]							
SSRI/SNRI, 1-8 weeks	432	27	5.8	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	193	18	8.8	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	193	9	4.4	1.04 (0.53-2.03)	0.85 (0.33-2.18)	1.16 (0.50-2.67)	0.89 (0.38-2.12)
By timing in pregnancy [¶]							
SSRI/SNRI, mid-pregnancy	302	18	5.6	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, late pregnancy	252	15	5.6	1.24 (0.74-2.09)	1.08 (0.47-2.47)	1.04 (0.59-1.85)	0.97 (0.43-2.19)
Sample II, ADHD symptoms							
	No	Mean	sd	Crude β (95% CI)	Weighted* β (95% CI)	Crude β (95% CI)	Weighted* β (95% CI)
Non-medicated	1917	1.50	0.49	Reference	Reference	-	-
AD discontinuers	158	1.45	0.42	-	-	Reference	Reference
SSRI/SNRI, ever	320	1.47	0.43	-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 duration in pregnancy [§]							
SSRI/SNRI, 1-8 weeks	158	1.45	0.41	-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	75	1.47	0.47	-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	87	1.50	0.43	-0.01 (-0.25, 0.23)	-0.07 (-0.44, 0.29)	0.12 (-0.17, 0.40)	-0.02 (-0.36, 0.32)
By timing in pregnancy [¶]							
SSRI/SNRI, mid-pregnancy	119	1.52	0.46	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, late pregnancy	100	1.52	0.46	0.06 (-0.18, 0.30)	-0.11 (-0.42, 0.21)	0.19 (-0.07, 0.45)	0.03 (-0.28, 0.35)

Abbreviations: AD=Antidepressant; ADHD=Attention-Deficit/Hyperactivity Disorder; SNRI=Serotonin–norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors.

β : indicates standardized mean difference in symptoms of ADHD, as parent reported via the Conners Parent Rating Scale revised version.

*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 history treatment) in the timing analysis, and stabilized inverse probability of treatment weighting using same set of covariates by duration and by any time/any duration.

[§]The week intervals do not imply that women took the medication continuously in all the weeks; women could check in the questionnaire exposure in 4-weeks intervals, eg week 0-4, 5-8, and so on.

^aThe reference is unexposed women within the exposure window.

Table 3: Associations with ADHD diagnosis and symptoms at age 5 years in children born to women who were truly exposed to SSRI/SNRI in pregnancy compared to truly unexposed, based on two data sources of exposure

Exposure window	No.	No. events	IR per 1000 py	SSRI/SNRI vs Non-medicated		SSRI/SNRI vs AD discontinuers	
				Crude HR (95% CI)	Weighted* HR (95% CI)	Crude HR (95% CI)	Weighted* HR (95% CI)
Non-medicated	5155	247	4.4	Reference	Reference	-	-
AD discontinuers	308	13	3.9	-	-	Reference	Reference
SSRI/SNRI, ever	466	29	6.4	1.46 (0.96-2.15)	1.18 (0.73-1.92)	1.66 (0.77-3.57)	1.38 (0.57-3.35)
Child age band < 7 years				1.47 (0.83-2.59)	0.89 (0.46-1.73)	1.19 (0.45-3.17)	0.82 (0.27-2.45)
Child age band 7-9 years				2.96 (1.78-4.87)	1.98 (1.06-3.68)	3.61 (1.06-12.31)	3.04 (0.85-10.90)
Child age band ≥ 9 years				1.31 (0.60-2.86)	1.11 (0.45-2.72)	1.33 (0.31-5.74)	-
	No.	Mean score (sd)		Crude β (95% CI)	Weighted* β (95% CI)	Crude β (95% CI)	Weighted* β (95% CI)
Non-medicated	1886	1.50 (0.49)		Reference	Reference	-	-
AD discontinuers	136	1.46 (0.42)		-	-	Reference	Reference
SSRI/SNRI, ever	241	1.47 (0.43)		-0.08 (-0.23, 0.07)	-0.22 (-0.39, -0.06)	0.04 (-0.19, 0.27)	-0.23 (-0.53, 0.07)

Abbreviations: AD=Antidepressant; ADHD=Attention Deficit Hyperactivity Disorder; SNRI=Serotonin–norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors.

*Weighted with stabilized inverse probability of treatment weighting the sufficient set of covariates.

In the age band ≥ 9 years no period-specific HR could be computed for the ever exposure versus discontinuers because of few ADHD cases.