

## **Appendix: Prenatal antidepressant exposure and the risk of attention-deficit hyperactivity disorder: A population based cohort study**

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**Supplementary material 1: Treatment utilisation of antidepressants and antipsychotics in the cohort**

<b>Period</b>	<b>SSRI<sup>a</sup> only</b>	<b>Other antidepressant only</b>	<b>Antipsychotic only</b>	<b>SSRI and other antidepressant</b>	<b>SSRI and antipsychotic</b>	<b>Other antidepressant and antipsychotic</b>	<b>All<sup>b</sup></b>	<b>Non- exposed</b>
Before Pregnancy	553	849	475	360	171	155	187	187,868
During Pregnancy	425	470	364	129	101	91	36	189,002
1st Trimester	324	294	298	58	86	69	14	189,475
2nd Trimester	235	273	280	49	55	59	13	189,654
3rd Trimester	250	320	298	38	56	56	8	189,592

<sup>a</sup>SSRI= Selective serotonin re-uptake inhibitor.

<sup>b</sup>Patients exposed to SSRI, other antidepressants and antipsychotics in that period.

**Supplementary material 2: Treatment continuation and switching pattern in the cohort**

<b>During pregnancy</b>	<b>SSRI only</b>	<b>Other antidepressant only</b>	<b>Antipsychotic only</b>	<b>SSRI and other antidepressant</b>	<b>SSRI and antipsychotic</b>	<b>Other antidepressant and antipsychotic</b>	<b>All</b>
Discontinued <sup>a</sup>	367	667	234	185	77	76	58
Continued <sup>b</sup>	144	156	231	42	42	32	13
New user	155	217	77	38	19	17	7
Switched to other regimen	42	26	10	133	52	47	116
Switched from other regimen	126	97	56	49	40	42	16

<sup>a</sup>Patients who were on that treatment regimen before pregnancy and stopped before pregnancy started.

<sup>b</sup>Patients who were on that treatment regimen before pregnancy and continued when pregnancy started.

### Supplementary material 3: Sensitivity analysis of including children born after 2009

<b>Exposure</b>	<b>Crude estimate</b>			<b>Model 1<sup>a</sup></b>			<b>Model 2<sup>b</sup></b>			<b>Model 3<sup>c</sup></b>						
	HR	95%CI	p-value	HR <sup>d</sup>	95%CI <sup>e</sup>	p-value	HR	95%CI	p-value	HR	95%CI	p-value				
<b><i>Antidepressants (Included children born after 2009)</i></b>																
During Pregnancy	2.21	1.76	2.78	<0.01	2.33	1.85	2.94	<0.01	1.33	1.03	1.73	0.03	1.32	1.01	1.72	0.04
1st Trimester	2.37	1.70	2.95	<0.01	2.39	1.81	3.15	<0.01	1.41	1.04	1.91	0.03	1.36	1.00	1.86	0.05
2nd Trimester	2.35	1.74	3.18	<0.01	2.58	1.91	3.50	<0.01	1.44	1.04	1.99	0.03	1.42	1.02	1.98	0.04
3rd Trimester	2.31	1.72	3.09	<0.01	2.47	1.84	3.32	<0.01	1.32	0.96	1.82	0.09	1.35	0.97	1.87	0.07
<b><i>SSRIs (Included children born after 2009)</i></b>																
During Pregnancy	2.10	1.51	2.93	<0.01	2.16	1.55	3.03	<0.01	1.16	0.81	1.67	0.41	1.06	0.74	1.53	0.75
1st Trimester	2.14	1.45	3.17	<0.01	2.26	1.52	3.35	<0.01	1.24	0.82	1.88	0.31	1.13	0.75	1.72	0.71
2nd Trimester	2.04	1.26	3.29	<0.01	2.15	1.32	3.48	<0.01	1.13	0.69	1.87	0.63	1.04	0.63	1.73	0.87
3rd Trimester	2.13	1.34	3.40	<0.01	2.18	1.36	3.49	<0.01	1.12	0.69	1.82	0.65	1.09	0.67	1.78	0.72
<b><i>Non-SSRIs (Included children born after 2009)</i></b>																
During Pregnancy	2.51	1.92	3.29	<0.01	2.70	2.05	3.55	<0.01	1.56	1.16	2.09	<0.01	1.53	1.14	2.06	<0.01
1st Trimester	2.52	1.78	3.67	<0.01	2.74	1.92	3.91	<0.01	1.66	1.15	2.39	<0.01	1.58	1.09	2.29	<0.01
2nd Trimester	2.64	1.85	3.79	<0.01	2.98	2.07	4.28	<0.01	1.67	1.14	2.44	<0.01	1.65	1.12	2.42	0.01
3rd Trimester	2.65	1.87	3.75	<0.01	2.89	2.04	4.09	<0.01	1.54	1.07	2.24	0.02	1.57	1.08	2.29	0.01

<sup>a</sup>Model 1 adjusted maternal age at delivery, infant's gender, birth year, birth hospital, parity, maternal underlying illness before delivery (pre-existing diabetes, epilepsy, gestational diabetes, hypertension; yes/no) and socioeconomic status.

<sup>b</sup>Model 2 adjusted all the factors in model 1 and maternal psychiatric conditions.

<sup>c</sup>Model 3 adjusted all the factors in model 2 and other psychiatric medication use.

<sup>d</sup>HR=Hazard ratio

<sup>e</sup>CI=Confidence interval

#### Supplementary material 4: Sensitivity analysis of extending exposure period

<b>Exposure</b>	<b>Crude estimate</b>			<b>Model 1<sup>a</sup></b>			<b>Model 2<sup>b</sup></b>			<b>Model 3<sup>c</sup></b>						
	<b>HR<sup>d</sup></b>	<b>95%CI<sup>e</sup></b>		<b>p-value</b>	<b>HR</b>	<b>95%CI</b>		<b>p-value</b>	<b>HR</b>	<b>95%CI</b>		<b>p-value</b>				
<b><i>Antidepressants (exposure extended by 30 days)</i></b>																
During Pregnancy	2.36	1.90	2.94	<0.01	2.51	2.01	3.13	<0.01	1.51	1.18	1.95	<0.01	1.50	1.16	1.94	<0.01
1st Trimester	2.41	1.86	3.13	<0.01	2.60	1.99	3.38	<0.01	1.60	1.20	2.14	<0.01	1.57	1.16	2.11	<0.01
2nd Trimester	2.52	1.93	3.28	<0.01	2.73	2.09	3.57	<0.01	1.61	1.20	2.15	<0.01	1.60	1.19	2.15	<0.01
3rd Trimester	2.32	1.74	3.08	<0.01	2.46	1.85	3.28	<0.01	1.37	1.00	1.86	0.05	1.39	1.01	1.90	0.04
<b><i>Antidepressants (exposure extended by 60 days)</i></b>																
During Pregnancy	2.38	1.93	2.93	<0.01	2.52	2.03	3.11	<0.01	1.55	1.21	1.99	<0.01	1.53	1.19	1.97	<0.01
1st Trimester	2.41	1.88	3.08	<0.01	2.58	2.01	3.31	<0.01	1.63	1.24	2.14	<0.01	1.57	1.18	2.09	<0.01
2nd Trimester	2.36	1.83	3.04	<0.01	2.53	1.96	3.27	<0.01	1.52	1.14	2.01	<0.01	1.47	1.10	1.96	<0.01
3rd Trimester	2.23	1.72	2.89	<0.01	2.38	1.84	3.10	<0.01	1.34	1.01	1.80	0.05	1.35	1.01	1.81	0.04

<sup>a</sup>Model 1 adjusted maternal age at delivery, infant's gender, birth year, birth hospital, parity, maternal underlying illness before delivery (pre-existing diabetes, epilepsy, gestational diabetes, hypertension; yes/no) and socioeconomic status.

<sup>b</sup>Model 2 adjusted all the factors in model 1 and maternal psychiatric conditions.

<sup>c</sup>Model 3 adjusted all the factors in model 2 and other psychiatric medication use.

<sup>d</sup>HR=Hazard ratio

<sup>e</sup>CI=Confidence interval

**Supplementary material 5: Sensitivity analysis of excluding children with ADHD medication but without ADHD diagnosis**

<b>Exposure</b>	<b>Crude estimate</b>			<b>Model 1<sup>a</sup></b>			<b>Model 2<sup>b</sup></b>			<b>Model 3<sup>c</sup></b>						
	<b>HR<sup>d</sup></b>	<b>95%CI<sup>e</sup></b>		<b>HR</b>	<b>95%CI</b>		<b>HR</b>	<b>95%CI</b>		<b>HR</b>	<b>95%CI</b>					
<b><i>Antidepressants (excluded children with ADHD medication but no ADHD diagnosis)</i></b>																
During Pregnancy	2.01	1.52	2.66	<0.01	2.14	1.62	2.85	<0.01	1.28	0.93	1.76	0.13	1.27	0.92	1.75	0.14
1st Trimester	2.09	1.49	2.92	<0.01	2.27	1.62	3.18	<0.01	1.40	0.98	2.02	0.07	1.37	0.95	1.99	0.09
2nd Trimester	1.96	1.33	2.89	<0.01	2.19	1.48	3.24	<0.01	1.27	0.84	1.91	0.26	1.27	0.84	1.91	0.26
3rd Trimester	2.19	1.54	3.12	<0.01	2.36	1.65	3.37	<0.01	1.33	0.91	1.96	0.14	1.37	0.93	2.03	0.11
<b><i>SSRIs (excluded children with ADHD medication but no ADHD diagnosis)</i></b>																
During Pregnancy	1.58	1.00	2.48	0.05	1.66	1.06	2.61	0.03	0.92	0.57	1.49	0.74	0.83	0.51	1.34	0.45
1st Trimester	1.65	0.98	2.79	0.06	1.79	1.06	3.02	0.03	1.03	0.59	1.78	0.93	0.93	0.54	1.62	0.80
2nd Trimester	1.66	0.89	3.09	0.11	1.80	0.96	3.37	0.07	0.99	0.52	1.89	0.98	0.93	0.49	1.77	0.83
3rd Trimester	1.49	0.77	2.87	0.24	1.55	0.80	3.01	0.19	0.83	0.42	1.64	0.60	0.80	0.41	1.57	0.51
<b><i>Non-SSRIs (excluded children with ADHD medication but no ADHD diagnosis)</i></b>																
During Pregnancy	2.47	1.80	3.40	<0.01	2.65	1.92	3.66	<0.01	1.62	1.15	2.30	<0.01	1.66	1.17	2.34	<0.01
1st Trimester	2.49	1.65	3.75	<0.01	2.72	1.79	4.12	<0.01	1.73	1.13	2.66	0.01	1.71	1.11	2.65	0.02
2nd Trimester	2.32	1.48	3.64	<0.01	2.62	1.66	4.16	<0.01	1.55	0.96	2.49	0.07	1.56	0.97	2.51	0.07
3rd Trimester	2.83	1.91	4.20	<0.01	3.07	2.06	4.56	<0.01	1.76	1.15	2.68	<0.01	1.84	1.20	2.81	<0.01

<sup>a</sup>Model 1 adjusted maternal age at delivery, infant's gender, birth year, birth hospital, parity, maternal underlying illness before delivery (pre-existing diabetes, epilepsy, gestational diabetes, hypertension; yes/no) and socioeconomic status.

<sup>b</sup>Model 2 adjusted all the factors in model 1 and maternal psychiatric conditions.

<sup>c</sup>Model 3 adjusted all the factors in model 2 and other psychiatric medication use.

<sup>d</sup>HR=Hazard ratio

<sup>e</sup>CI=Confidence interval

Supplementary material 6: Sensitivity analysis of including the first pregnancy only

<b>Exposure</b>	<b>Crude estimate</b>				<b>Model 1<sup>a</sup></b>			<b>Model 2<sup>b</sup></b>			<b>Model 3<sup>c</sup></b>					
	<b>HR<sup>d</sup></b>	<b>95%CI<sup>e</sup></b>		<b>p-value</b>	<b>HR</b>	<b>95%CI</b>		<b>p-value</b>	<b>HR</b>	<b>95%CI</b>		<b>p-value</b>	<b>HR</b>	<b>95%CI</b>		<b>p-value</b>
<b><i>Antidepressants (first pregnancy only)</i></b>																
During Pregnancy	2.92	2.12	4.02	<0.01	2.68	1.95	3.70	<0.01	1.82	1.27	2.60	<0.01	1.82	1.27	2.62	<0.01
1st Trimester	2.94	1.97	4.39	<0.01	2.79	1.87	4.18	<0.01	1.88	1.23	2.88	<0.01	1.84	1.18	2.86	<0.01
2nd Trimester	3.16	2.04	4.91	<0.01	3.10	2.00	4.82	<0.01	1.98	1.24	3.16	<0.01	1.95	1.21	3.14	<0.01
3rd Trimester	3.17	2.12	4.73	<0.01	3.00	2.01	4.49	<0.01	1.92	1.25	2.97	<0.01	1.95	1.26	3.01	<0.01
<b><i>SSRIs (first pregnancy only)</i></b>																
During Pregnancy	2.87	1.81	4.57	<0.01	2.58	1.63	4.11	<0.01	1.59	0.98	2.60	0.06	1.37	0.83	2.27	0.22
1st Trimester	3.07	1.78	5.29	<0.01	2.87	1.66	4.95	<0.01	1.77	1.00	3.12	0.05	1.60	0.90	2.84	0.11
2nd Trimester	2.71	1.35	5.41	<0.01	2.53	1.27	5.07	<0.01	1.53	0.75	3.11	0.25	1.33	0.64	2.74	0.44
3rd Trimester	3.43	1.90	6.19	<0.01	3.22	1.78	5.82	<0.01	1.94	1.05	3.59	0.03	1.77	0.95	3.30	0.07
<b><i>Non-SSRIs (first pregnancy only)</i></b>																
During Pregnancy	3.42	2.36	4.96	<0.01	3.17	2.19	4.61	<0.01	2.16	1.45	3.22	<0.01	2.06	1.36	3.11	<0.01
1st Trimester	3.12	1.84	5.27	<0.01	2.98	1.76	5.03	<0.01	2.08	1.21	3.57	<0.01	1.91	1.10	3.33	0.02
2nd Trimester	3.47	2.02	5.97	<0.01	3.42	1.98	5.89	<0.01	2.16	1.23	3.80	<0.01	2.05	1.15	3.66	0.02
3rd Trimester	3.50	2.17	5.63	<0.01	3.34	2.07	5.38	<0.01	2.12	1.28	3.50	<0.01	2.04	1.23	3.40	<0.01

<sup>a</sup>Model 1 adjusted maternal age at delivery, infant's gender, birth year, birth hospital, parity, maternal underlying illness before delivery (pre-existing diabetes, epilepsy, gestational diabetes, hypertension; yes/no) and socioeconomic status.

<sup>b</sup>Model 2 adjusted all the factors in model 1 and maternal psychiatric conditions.

<sup>c</sup>Model 3 adjusted all the factors in model 2 and other psychiatric medication use.

<sup>d</sup>HR=Hazard ratio

<sup>e</sup>CI=Confidence interval

Supplementary material 7: Sensitivity analysis: start of follow-up at 5 years old

<b>Exposure</b>	<b>Crude estimate</b>			<b>Model 1<sup>a</sup></b>			<b>Model 2<sup>b</sup></b>			<b>Model 3<sup>c</sup></b>						
	<b>HR<sup>d</sup></b>	<b>95%CI<sup>e</sup></b>		<b>p-value</b>	<b>HR</b>	<b>95%CI</b>		<b>p-value</b>	<b>HR</b>	<b>95%CI</b>		<b>p-value</b>				
<b><i>Antidepressants (Follow-up started at 5 years old)</i></b>																
During Pregnancy	2.30	1.83	2.90	<0.01	2.24	1.78	2.83	<0.01	1.35	1.04	1.76	0.03	1.33	1.02	1.74	0.03
1st Trimester	2.36	1.79	3.12	<0.01	2.29	1.73	3.04	<0.01	1.41	1.04	1.91	0.03	1.36	0.99	1.80	0.05
2nd Trimester	2.49	1.84	3.36	<0.01	2.45	1.80	3.31	<0.01	1.43	1.03	1.98	0.03	1.42	1.02	1.97	0.04
3rd Trimester	2.39	1.77	3.22	<0.01	2.36	1.75	3.18	<0.01	1.32	0.95	1.83	0.09	1.36	0.98	1.89	0.07
<b><i>SSRIs (Follow-up started at 5 years old)</i></b>																
During Pregnancy	2.19	1.56	3.06	<0.01	2.04	1.45	2.86	<0.01	1.15	0.80	1.66	0.45	1.05	0.72	1.51	0.81
1st Trimester	2.29	1.55	3.39	<0.01	2.16	1.45	3.20	<0.01	1.25	0.82	1.89	0.30	1.13	0.74	1.72	0.57
2nd Trimester	2.19	1.36	3.54	<0.01	2.06	1.27	3.35	<0.01	1.14	0.69	1.89	0.61	1.06	0.64	1.76	0.81
3rd Trimester	2.16	1.34	3.49	<0.01	1.99	1.23	3.24	<0.01	1.07	0.65	1.77	0.78	1.05	0.64	1.74	0.84
<b><i>Non-SSRIs (Follow-up started at 5 years old)</i></b>																
During Pregnancy	2.59	1.97	3.40	<0.01	2.58	1.96	3.40	<0.01	1.56	1.16	2.10	<0.01	1.53	1.14	2.07	<0.01
1st Trimester	2.65	1.87	3.75	<0.01	2.62	1.84	3.73	<0.01	1.64	1.14	2.37	<0.01	1.56	1.07	2.26	0.02
2nd Trimester	2.78	1.94	3.99	<0.01	2.81	1.95	4.05	<0.01	1.66	1.13	2.42	<0.01	1.64	1.11	2.41	0.01
3rd Trimester	2.70	1.90	3.84	<0.01	2.75	1.93	3.93	<0.01	1.54	1.06	2.25	0.02	1.58	1.08	2.32	0.02

<sup>a</sup>Model 1 adjusted maternal age at delivery, infant's gender, birth year, birth hospital, parity, maternal underlying illness before delivery (pre-existing diabetes, epilepsy, gestational diabetes, hypertension; yes/no) and socioeconomic status.

<sup>b</sup>Model 2 adjusted all the factors in model 1 and maternal psychiatric conditions.

<sup>c</sup>Model 3 adjusted all the factors in model 2 and other psychiatric medication use.

<sup>d</sup>HR=Hazard ratio

<sup>e</sup>CI=Confidence interval



Supplementary material 8: Sensitivity analysis: adjust maternal depression, anxiety and substance abuse only

<b>Exposure</b>	<b>Crude estimate</b>			<b>Model 1<sup>a</sup></b>			<b>Model 2<sup>b</sup></b>			<b>Model 3<sup>c</sup></b>						
	<b>HR<sup>d</sup></b>	<b>95%CI<sup>e</sup></b>		<b>p-value</b>	<b>HR</b>	<b>95%CI</b>		<b>p-value</b>	<b>HR</b>	<b>95%CI</b>		<b>p-value</b>				
<b><i>Antidepressants (Follow-up started at 5 years old)</i></b>																
During Pregnancy	2.26	1.80	2.84	<0.01	2.39	1.90	3.02	<0.01	1.75	1.36	2.26	<0.01	1.61	1.23	2.11	<0.01
1st Trimester	2.29	1.74	3.03	<0.01	2.45	1.85	3.25	<0.01	1.91	1.43	2.56	<0.01	1.68	1.22	2.31	<0.01
2nd Trimester	2.41	1.78	3.26	<0.01	2.65	1.96	3.59	<0.01	1.92	1.40	2.64	<0.01	1.76	1.26	2.46	<0.01
3rd Trimester	2.37	1.76	3.17	<0.01	2.55	1.90	3.42	<0.01	1.72	1.25	2.37	<0.01	1.69	1.21	2.36	<0.01
<b><i>SSRIs (Follow-up started at 5 years old)</i></b>																
During Pregnancy	2.17	1.56	3.03	<0.01	2.23	1.60	3.12	<0.01	1.58	1.11	2.25	0.01	1.28	0.89	1.84	0.19
1st Trimester	2.21	1.49	3.27	<0.01	2.32	1.57	3.45	<0.01	1.74	1.16	2.62	<0.01	1.39	0.91	2.11	0.13
2nd Trimester	2.11	1.31	3.41	<0.01	2.22	1.37	3.60	<0.01	1.58	0.96	2.60	0.07	1.31	0.80	2.17	0.29
3rd Trimester	2.21	1.38	3.52	<0.01	2.26	1.41	3.63	<0.01	1.46	0.90	2.38	0.13	1.33	0.82	2.18	0.25
<b><i>Non-SSRIs (Follow-up started at 5 years old)</i></b>																
During Pregnancy	2.56	1.95	3.35	<0.01	2.76	2.10	3.62	<0.01	1.98	1.48	2.65	<0.01	1.76	1.30	2.38	<0.01
1st Trimester	2.57	1.82	3.64	<0.01	2.80	1.96	3.99	<0.01	2.19	1.52	3.14	<0.01	1.82	1.24	2.68	<0.01
2nd Trimester	2.70	1.88	3.86	<0.01	3.04	2.12	4.38	<0.01	2.18	1.49	3.17	<0.01	1.93	1.30	2.87	<0.01
3rd Trimester	2.70	1.91	3.83	<0.01	2.96	2.08	4.20	<0.01	1.98	1.37	2.56	<0.01	1.90	1.29	2.80	<0.01

<sup>a</sup>Model 1 adjusted maternal age at delivery, infant's gender, birth year, birth hospital, parity, maternal underlying illness before delivery (pre-existing diabetes, epilepsy, gestational diabetes, hypertension; yes/no) and socioeconomic status.

<sup>b</sup>Model 2 adjusted all the factors in model 1 and maternal psychiatric conditions.

<sup>c</sup>Model 3 adjusted all the factors in model 2 and other psychiatric medication use.

<sup>d</sup>HR=Hazard ratio

<sup>e</sup>CI=Confidence interval

Supplementary material 9: Comparisons of antidepressant exposure rate

<b>Study</b>	<b>Percentage of exposed children</b>	<b>Standardised difference</b>
Our current study	0.7%	--
Castro 2016	1.5%	-0.086
Clements 2015	1.6%	-0.093
Figueroa 2010	2.7%	-0.16
Laugesen 2013	1.7%	-0.078
Malm 2016	0.6%	0.0072
Sujan 2017	1.4%	-0.069

Reference:

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