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Prenatal exposure to selective serotonin reuptake inhibitors and childhood overweight at 7 years of age

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Title Page

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Short Title: Prenatal SSRI Exposure and Childhood Overweight

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Conflict of Interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Abstract

Purpose: To investigate a possible association between prenatal SSRI exposure and childhood overweight at 7-years of age.

Methods: Information on pregnancy exposures and prevalence of childhood overweight at 7-years of age was obtained from the Danish National Birth Cohort. Overweight was classified as BMI>85th percentile, based on age and sex. Based on an *a priori* hypothesis, we conducted analyses stratified by child sex to examine sex-specific differences.

Results: Of eligible pregnant women, 127 reported using a SSRI, 490 reported having a psychiatric illness but no psychotropic medication use, and 35 568 reported no psychiatric illness and no psychotropic medication use. In comparison to children of mothers with a psychiatric illness but no SSRI use during pregnancy, prenatal SSRI exposure overall was not associated with an increased risk of childhood overweight (aPR 1.12 [95% confidence interval: 0.71, 1.77]). However, when stratified according to child sex, an increased risk was observed among males (aPR 1.78 [1.01, 3.12]) but not females (aPR 0.86 [0.37, 1.99]). In contrast, female children of mothers with a psychiatric illness but no SSRI use during pregnancy were more likely to be overweight than female children of unexposed mothers (aPR 1.45 [1.05, 2.02]). This association was not mirrored among males (aPR 1.06 [0.76, 1.50]).

Conclusions: We observed the potential for opposing sex-specific differences in the long-term effects of prenatal exposure to SSRI use and/or maternal psychiatric illness on childhood overweight. Limitations of the present study suggest further research in this area may be warranted with larger sample sizes and longer follow-up.

Abbreviations

SSRI – selective serotonin reuptake inhibitor

PR – prevalence ratio

CI – confidence interval

5-HT – serotonin

5-HTT – serotonin transporter

Text

Introduction

Antidepressant use during pregnancy has increased dramatically over the last 10-15 years. In Denmark, antidepressant use has increased from 0.8% of pregnancies in 1996 to 4.1% in 2009 [1]. This trend is echoed in other countries such as the United States, where use of selective serotonin reuptake inhibitors (SSRIs) in particular has increased from 1.5% of pregnancies in 1996 to 6.4% in 2005 [2].

Long-term effects of prenatal SSRI exposure is an important area of concern given the key role serotonin (5-HT) plays as a neurotransmitter within the central nervous system, affecting neurogenesis, migration and differentiation of neurons in the fetal brain [3-5]. The importance of the serotonergic system in regulating food intake and body weight places particular interest in the potential long-term effects of prenatal SSRI exposure on child growth [6-8].

Sex-specific alterations in the serotonergic system, as a result of disruption of 5-HT homeostasis during critical periods of fetal development, have been identified in animal studies [9-14]. When serotonergic tone is increased, as a result of SSRI exposure, a resultant increase in negative feedback signalling is possible, which may blunt the maturation of the serotonergic system [15]. This could lead to altered development of the serotonergic system in early fetal life, which impacts on serotonergic regulation of food intake and body weight in later life, ultimately influencing the risk of childhood overweight [16]. Supporting this hypothesis is evidence from animal studies demonstrating that disruption of 5-HT homeostasis *in utero* results in adult-onset obesity in males, but not females [12, 14].

Data from human studies, however, remains scarce. Two studies demonstrated a reduction in weight gain between 1-6 months of age among infants exposed to SSRIs [17, 18], the long-term consequences of which are unknown. In contrast, a recent study involving

174 children with prenatal exposure to either a SSRI (N=46), major depression without SSRI (N=31) or no SSRI and no depression (N=97) observed no differences in infant growth with respect to weight, length, or head circumference from birth through 12 months of age [19]. Limitations of these studies make it difficult to draw accurate conclusions regarding potential long-term risks. Furthermore, an additional challenge in examining evidence generated from animal and human studies lies in understanding the complex interplay between prenatal SSRI exposure and exposure to maternal psychiatric illness or stress during pregnancy [16]. This is an important consideration as exposure to maternal psychiatric illness or stress during pregnancy is associated with long-term adverse effects on the metabolic health of the offspring [16], including increased risk of childhood overweight [20].

Given the paucity of evidence, we sought to clarify whether prenatal SSRI exposure is associated with childhood overweight at 7-years of age, while taking into consideration the sex of the child.

Methods

Study Setting

This study involves data obtained from mother-child dyads participating in the Danish National Birth Cohort, an ongoing nationwide, follow-up study of pregnant women and their children [21]. Recruitment took place from 1996 to 2002, with 60% of invited pregnant women agreeing to participate in initial studies. A total of 101 042 pregnancies were included. At the time of providing consent, women were asked to report on medication use during early pregnancy in a self-administered questionnaire (at approx. 6-10 weeks of gestation). After providing consent, women were interviewed by telephone twice during pregnancy, at 17 and 32 weeks gestation, and twice after pregnancy, when their children were 6 and 18 months old. The cohort has been described elsewhere [21]. As part of the overall

study objectives of the DNBC, a self-administered questionnaire completed by parents was used to follow-up children at age 7.

Study population

Women included in this study were those who signed the original consent form and completed both prenatal interviews (N=80,669). We excluded women who took psychotropic medications other than SSRIs during pregnancy (i.e. anxiolytics (N=492), antipsychotics (N=45), antiepileptics (N=271)) or other antidepressants (N=64). Of the remaining women (N=79,797), we restricted the analysis to those who participated in postnatal interviews when their child was 6 months and 7-years of age (N=38,693). We further excluded dyads where child height and weight measurements were not recorded (N=2 370) or were outside of biologically plausible values (N=82), based on predefined criteria. In addition, we excluded dyads in which the child's age at follow-up was less than 5 years (N=56), leaving a final study population of 36,185 mother-child dyads. This represented a loss to follow-up of 55%.

Exposure variables

SSRI use was defined as self-reported use of any drugs in World Health Organization-defined Anatomic Therapeutic Chemical Classification System group N06AB during pregnancy [22]. Information on drug use was obtained from the initial consent form and both prenatal interviews and was coded either using predefined names or in a text string recorded by the interviewer and later coded for analysis by the investigators. Women were classified as exposed if they reported taking a SSRI at any stage during pregnancy.

Presence of a psychiatric illness during pregnancy was identified based on maternal self-report, according to questions asked at the 2 prenatal interviews. In the first interview women were asked: (1) Have you ever suffered from a mental disorder or neurosis?; (2) Did

you see a medical doctor or psychologist for the disorder?; (3) What was the name of the disorder?; and (4) Have you experienced symptoms of the disorder during pregnancy? In the second interview women were asked whether they had experienced a mental disorder during pregnancy.

Outcome variable

The primary outcome was childhood overweight at 7 years of age. The secondary outcome was Body Mass Index (BMI)-for-age z-scores. BMI (weight/(height(m)^2) was calculated based on self-reported information from the parents on weight and height of the child. Women were asked to indicate who took the measurements (either the parents [67%] or the general practitioner/school nurse [33%]), with no difference in the source of the measurements according to exposure status (P=0.974). International cut-off scores were utilized to define overweight, *i.e.*, a BMI at or exceeding the age- and sex-specific 85th percentile [23].

Covariates

Information on maternal age, parity, prenatal exposure to alcohol and smoking, and pre-pregnancy weight and height were obtained from the first prenatal interview. Parity was categorised as either primiparous (0) or multiparous (1-8 previous births). Smoking was categorised according to number of cigarettes smoked on average each day (none, 1-10 cigarettes and >10 cigarettes per day). Maternal pre-pregnancy BMI was coded into three categories (<25; ≥25 to <30, and ≥30). The socioeconomic status score was defined as described by Bech et al. [24] by using data from the first prenatal interview. The score was based on the highest self-reported occupation of either the woman or her partner. Information on gestational weight gain and maternal postpartum distress was obtained from the first

postnatal interview. Gestational weight gain was categorised as low, normal, or high based on the U.S. Institute of Medicine (2009) recommendations for gestational weight gain for singleton pregnancies [25]. Information on breastfeeding was obtained from the second postnatal interview. Breastfeeding was categorised as breastfed <1 month (including no breastfeeding), 1-4 months and ≥4 months. Paternal BMI was coded in the same manner as maternal BMI. Maternal pre- and post- natal distress was assessed using 9 questions, which asked mothers about feelings of anxiety, depression and stress. Each question presented an item and was taken from two earlier validated questionnaires i.e., the Symptom Distress Checklist (SCL-90)[26] and the General Health Questionnaire (GHQ 60)[27]. Possible responses included; "no" = 0, "a little" =1 or "a lot" 2 (forming a 3-point Likert scale). The scores from the nine questions were summed together and treated as a continuous variable, the use of which has been previously validated [28].

Statistical methods

Statistical analyses were performed using Stata 11.1 (Stata, College Station, TX, USA). Characteristics between groups were compared using an unpaired t test, Wilcoxon rank-sum test, or Fisher's exact test where appropriate. Rates of overweight were compared using a generalised linear model (Poisson distribution) with cluster-robust standard errors, yielding prevalence ratios (PRs) for the effect estimate and 95% confidence intervals (CIs). In a secondary analysis we examined differences in BMI-z scores between the groups using multiple linear regression analysis. Statistical significance was defined as a 2-sided *P* value of 0.05.

We included two adjusted models. The first included smoking status, pre-pregnancy maternal BMI, employment status, prenatal distress and paternal BMI, while the second included covariates in the first model and neonatal birth weight, weight gain during

pregnancy, breastfeeding and maternal postnatal distress score. In accordance with previous evidence highlighting the potential for sex-specific differences [17], based on an *a priori* hypothesis analyses were further stratified according to child sex. An interaction term between child sex and prenatal SSRI exposure was included in the linear and logistic regression analyses, but no statistical interactions were observed. The sample size did not allow for stratification according to individual SSRI type or timing of exposure.

To evaluate bias due to loss to follow-up, we used logistic regression (complete data vs. lost to follow-up as outcome) to determine weights for each individual using the inverse probability of response [29]. Complete follow-up data was predicted based on exposure to SSRIs or psychiatric illness during pregnancy, maternal age, parity, neonatal birth weight, maternal BMI, prenatal distress, smoking status and socioeconomic status. The individual weighting factor for these covariates (their inverse probability) was used as a sample weighting adjustment in subsequent analyses.

Ethics Statement

The Danish National Committee on Biomedical Research Ethics approves the establishment and the data collection of the DNBC. Written informed consent was obtained from each of the participants at the time of enrolment and mothers are able to withdraw at any time. This study was approved by the Danish Data Protection Agency, the Institutional Board Committee of the DNBC and the University of South Australia Human Research Ethics Committee.

Results

Of the mother-child-dyads with follow-up data on weight and height (N=36 185), 127 (0.4%) mothers reported taking a SSRI during pregnancy, 490 (1.4%) mothers reported having a psychiatric illness but no use of psychotropic medication and 35 568 (98.3%)

mothers did not report taking psychotropic medications or having a psychiatric illness during pregnancy (**Table 1**).

A number of significant differences were apparent between women taking SSRIs and unexposed women (**Table 1**), with women taking SSRIs more likely to be of lower socioeconomic status, smoke during pregnancy and have higher prenatal and postnatal distress scores. In contrast, women taking SSRIs and women with a psychiatric illness but no SSRI use were comparable, except for the presence of a lower prenatal distress scores in those taking SSRIs. Sex and age of the children at follow-up did not differ significantly between groups (**Table 1**).

After adjustment for confounders, no significant associations were observed between prenatal SSRI exposure and risk of overweight at 7-years of age (**Table 2** and **Table 3**). When stratified according to child sex, however, male children with prenatal SSRI exposure were more likely to be overweight than male children of mothers with a psychiatric illness but no SSRI use (aPR 1.78 [1.01, 3.12]) and male children of unexposed mothers (aPR 1.54 [1.01, 2.37]). In secondary analyses, no difference was observed in relation to BMI-z scores of male children with prenatal SSRI exposure compared to male children of mothers with a psychiatric illness but no SSRI use (0.30 [-0.06, 0.66]) or male children of unexposed mothers (0.11 [-0.17, 0.39]).

While no increased risk of childhood overweight was observed amongst female children with prenatal SSRI exposure, female children of mothers with a psychiatric illness but no SSRI use during pregnancy were more likely to be overweight than female children of unexposed mothers (aPR 1.45 [1.05, 2.02]), and were more likely to have an elevated BMI-z score (0.21 [0.06, 0.36]).

Discussion

We observed the potential for opposing sex-specific differences in the long-term effects of prenatal exposure to SSRI use and/or maternal psychiatric illness on childhood overweight. An increased risk of childhood overweight was observed among male, but not female, children following prenatal exposure to SSRIs. In contrast, an increased risk of childhood overweight was observed among female, but not male, children following prenatal exposure to maternal psychiatric illness without SSRI use.

There is a convincing biologically plausible argument to expect different effect sizes according to child sex. Known sex variations in human brain development and function exist, including differences in the serotonergic system [30, 31]. For example, male 5-HTT knock-out mice develop late-onset obesity [12, 14], while females are protected from this effect. While the mechanism underlying sex-specific differences is poorly understood, it has been hypothesised that observed differences could be related to sex hormones (i.e. oestrogen) [14], as there is evidence that oestrogen can influence serotonin system function [9, 32]. Furthermore, female mice exposed to prenatal maternal stress display significantly higher basal and stress-induced plasma corticosterone concentrations as well as reductions in the density of hippocampal glucocorticoid receptors, compared to non-stressed controls [33-35]. These sex-specific differences may be associated with reductions in placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) activity, which has been associated with reduced fetal growth and higher cortisol concentrations in the umbilical vein of female, but not male, infants of mothers with untreated asthma [36]. It is important to note that the risks associated with exposures during fetal life may be modulated by the postnatal environment. This effect may also be sex-specific, with quality of maternal care in the early postnatal period shown to influence hippocampal volume in adulthood in females, but not males [37].

Few studies have investigated long-term growth outcomes amongst children exposed to SSRIs or antidepressants *in utero* [17-19], especially beyond 12 months of age. This study

has a number of strengths compared to our previous study involving just 71 exposed children [38], which identified an association between prenatal SSRI exposure and a decreased risk of overweight among female (aPR 0.23 [0.05, 0.98]), but not male (aPR 1.17 [0.54, 2.51]), children at 4- to 5-years of age. The current study included more detailed data on the use of SSRIs and other psychotropic medications during pregnancy and more detailed assessment of potentially confounding maternal and infant covariates including prenatal stress score, weight gain during pregnancy, paternal BMI and duration of breastfeeding.

While male children with prenatal SSRI exposure were at increased risk of being overweight at 7- years of age, this was not supported by a corresponding increase in BMI-z score (0.3 [-0.06, 0.66]). This apparent incongruence reflects challenges associated with utilising standardised cut-points as opposed to continuous measures to evaluate outcomes and may reflect an alteration in the distribution of BMI-z scores among the male children with prenatal SSRI exposure.

A major strength of this study is inclusion of women with untreated psychiatric illness. In addition to the effects on the serotonergic system, exposure to maternal stress during gestation has been demonstrated to adversely affect development and regulation of the HPA axis [39, 40]. Maternal stress during pregnancy increases circulating concentrations of glucocorticoids, which can enter the fetal circulation and down-regulate central glucocorticoid receptors in the hippocampus. This leads to reduced feedback inhibition and an overactive HPA axis, resulting in increased cortisol secretion in the basal state and in conditions of stress [41, 42]. This has a number of important implications for metabolic function in later life, as overactivity of the HPA axis has been associated with a range of cardio-metabolic outcomes in later life, including hypertension, insulin resistance and obesity [43, 44].

Notably, a recent study demonstrated an association between prenatal stress (related to maternal bereavement immediately prior to pregnancy) and increased risk of childhood overweight [20]. Importantly, the increased risk of overweight was only observed in children beyond 10 years of age. That study did not include stratification of data by sex, and it was not clear how many women, if any, were taking SSRIs during pregnancy.

In light of this, we observed an association between psychiatric illness during pregnancy and increased risk of overweight in female children at 7-years of age (aPR 1.45 [1.05, 2.02]). While this finding was in accordance with evidence obtained from animal studies [16], it contrasts the recent finding of Ingstrup *et al.*[45] who, also using data from the DNBC, observed a small tendency of overweight in males (aOR 1.15 [0.99, 1.33]) but not females (aOR 0.98 [0.85, 1.13]) at 7-years of age who were exposed to maternal distress during pregnancy. The contrasting results could be explained by a number of key methodological differences in that we included a separate group of women who were taking a SSRI during pregnancy and excluded women exposed to psychotropic medication other than SSRIs. Furthermore, we classified childhood overweight as a BMI at or exceeding the age- and sex-specific 85^{th} percentile, compared to a cut-off of $>95^{th}$ percentile [45].

While the small number of infants exposed to SSRIs during pregnancy represents a study limitation, this is reflective of the low prevalence of SSRI use in Denmark in the study period [46]. Further limitations include the potential for selection bias as a result of incomplete data or loss to follow-up. However, when we compared incomplete data from partial responders with estimates from the main analysis based on complete data we observed no differences in the prevalence of childhood overweight. Furthermore, to assess the impact of loss to follow-up, we attached inverse probability weighting to subjects included in the analyses to restore the representation of those lost to follow-up. This aims to construct a pseudo-population of the same size as the original study population, but in which nobody is

lost to follow-up [29]. We found no difference between the weighted and non-weighted results (data not presented).

It is possible that some women did not accurately report taking a SSRI during pregnancy or having a psychiatric illness. However, since data on medication use and the presence of a psychiatric illness were collected prospectively, any exposure misclassification would most likely lead to a bias towards the null. Similarly, a degree of measurement error in relation to child heights and weights is expected, but unlikely related to maternal exposure. This is supported by a validation study in 1200 children participating in the 7-year follow-up, which found no systematic errors in maternal self-reported child heights and weights [47].

Although the inclusion of a control group of women with untreated psychiatric illness accounted for confounding by the indication for treatment to some extent, residual confounding due to the type or severity of the underlying maternal psychiatric illness might still prevail. Differences in outcomes according to types of psychiatric illnesses reported by women (e.g. depression, anxiety) were not evaluated. The presence of maternal psychiatric illness during early phases of childhood development may result in suboptimal nutritional intake among these children. This may occur through negative effects on mother–child interactions or differences in feeding practices [48]. Conversely, women with psychiatric illness may have more obesogenic behaviours (i.e. abnormal eating behaviours or physical activity levels), which are passed on to their children. We had no data on paternal psychiatric illness which could also play an important role in influencing childhood outcomes.

The lack of inclusion of data on postnatal factors such as the child's diet, energy intake and physical activity may constitute a study limitation. However, these factors lie in the predicted pathway between prenatal SSRI exposure and childhood overweight, given the involvement of the serotonergic system in the regulation of appetite (influencing energy intake[6-8]) as well as motor control (influencing physical activity in later life[49]).

We observed the potential for opposing sex-specific differences in the long-term effects of prenatal exposure to SSRI use and/or maternal psychiatric illness on childhood overweight. Limitations of the present study, including the small number of children exposed to SSRIs and maternal psychiatric illness, suggest further research in this area may be warranted with larger sample sizes and longer follow-up. It is also important for future research to examine other potential long-term effects associated with prenatal exposure to SSRI use and/or maternal psychiatric illness and the role of child sex on those outcomes.

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Table 1. Demographic and Clinical Measures for Women and Children Exposed to a SSRI Antidepressant, Psychiatric Illness Without SSRIs, or Neither During Pregnancy.

Characteristic[‡]	Exposure During Pregnancy				
	SSRI N=127	**Psychiatric Illness N=490**	***P* for SSRI vs Psychiatric Illness**	**Unexposed N=35 568**	***P* for SSRI vs Unexposed**
Maternal Age, mean (SD), years	30.7 (4.3)	29.9 (4.7)	0.096	30.2 (4.2)	0.203
Maternal BMI, n (%)[†]					
<25 kg/m^2	91 (71.7)	332 (68.5)	0.333	26 016 (73.6)	0.300
≥25 & <30 kg/m^2	22 (17.3)	111 (22.9)		6 719 (19.0)	
≥30 kg/m^2	14 (11.0)	42 (8.7)		2 636 (7.5)	
Paternal BMI, n (%)[†]					
<25 kg/m^2	73 (60.3)	239 (52.8)	0.091	18 410 (53.3)	0.255
≥25 & <30 kg/m^2	39 (32.2)	169 (37.3)		13 643 (39.5)	
≥30 kg/m^2	9 (7.4)	45 (9.9)		2 522 (7.3)	
Weight Gain During Pregnancy, n (%)[†]					
Low	25 (19.8)	88 (18.5)	0.517	5 788 (16.5)	0.117
Normal	37 (29.4)	166 (34.8)		13 416 (38.2)	
High	64 (50.8)	223 (46.8)		15 880 (45.3)	
Parity					
≥1, n (%)[†]	68 (53.5)	284 (58.0)	0.669	19 121 (53.8)	0.951
Socioeconomic Status, n (%)[†]					
High	84 (66.7)	270 (55.6)	0.033	24 822 (70.0)	0.001
Middle	31 (24.6)	180 (37.0)		9 617 (27.1)	
Low	11 (8.7)	36 (7.4)		1 034 (2.9)	
Smoking Status, n (%)[†]					

Non Smoker	76 (59.8)	340 (69.4)	0.068	28 690 (80.7)	<0.001
1-10 cigarettes per day	37 (29.1)	97 (19.8)		5 146 (14.5)	
>11 cigarettes per day	14 (11.0)	53 (10.8)		1 730 (4.9)	
Breastfeeding, n (%)[†]			0.884		0.085
< 1 month	10 (7.9)	46 (9.4)		1 890 (5.3)	
1-4 months	26 (20.5)	91 (18.6)		4 245 (11.9)	
≥4 months	91 (71.7)	353 (72.0)		29 403 (82.7)	
Prenatal Distress Score, mean (SD)	5.1 (3.7)	7.0 (4.0)	<0.001	2.6 (2.4)	<0.001
Postnatal Distress Score, mean (SD)	4.5 (3.9)	5.1 (4.0)	0.129	2.1 (2.6)	<0.001
Child Sex					
Male, n (%)[†]	64 (50.4)	251 (51.2)	0.867	18 248 (51.3)	0.838
Birth Weight, mean (SD), years					
Male	3 697 (557)	3 640 (612)	0.595	3 683 (547)	0.877
Female	3 462 (656)	3 465 (569)	0.588	3 557 (526)	0.527
Gestational Age, mean (SD), weeks					
Male	39.7 (1.5)	39.9 (1.6)	0.359	40.0 (1.6)	0.060
Female	39.9 (1.7)	39.9 (1.6)	0.935	40.1 (1.5)	0.215
Age of Child at Measurement, mean (SD), months	84.5 (3.2)	84.5 (3.4)	0.979	84.5 (3.4)	0.847
Childhood Overweight (BMI>85th Percentile), n (%)[†]					
Male	16 (25.0)	39 (15.5)	0.075	2 305 (12.6)	0.003
Female	8 (12.7)	38 (15.9)	0.750	1 978 (11.4)	0.750
Childhood BMI-z Score, mean (SD)					
Male	0.16 (1.0)	-0.05 (1.2)	0.192	-0.08 (1.0)	0.065
Female	-0.13 (1.1)	0.06 (1.0)	0.181	-0.09 (1.2)	0.794

[†] Percentages are calculated from available (non-missing) data.

Table 2. Risk of overweight at 7-years of age for children of women exposed to SSRI Antidepressants, Psychiatric Illness Without SSRIs, or Neither During Pregnancy

		Maternal SSRI Use vs. Psychiatric Illness	Maternal SSRI Use vs. Unexposed	Maternal Psychiatric Illness vs. Unexposed
			PR [95% CI]	
All	**Unadjusted**	1.13	1.54	1.36
	N=36 185			
	Model 1	1.15 [0.73, 1.82]	1.39 [0.93, 2.08]	1.20 [0.95, 1.52]
	N=34 825			
	Model 2	1.12 [0.71, 1.77]	1.39 [0.94, 2.05]	1.24 [0.98, 1.56]
	N=34 410			
Stratified According to Sex				
Males	**Unadjusted**	1.49	2.00	1.34
	N=18 563			
	Model 1	1.77 [0.99, 3.19]	1.56 [0.99, 2.45]	1.04 [0.74, 1.45]
	N=17 893			
	Model 2	**1.78 [1.01, 3.12]**	**1.54 [1.01, 2.37]**	1.06 [0.76, 1.50]
	N=17 680			
Females	**Unadjusted**	0.71	0.98	1.38
	N=17 622			
	Model 1	0.74 [0.33, 1.65]	0.99 [0.43, 2.24]	**1.41 [1.01, 1.97]**
	N=16 932			
	Model 2	0.86 [0.37, 1.99]	0.99 [0.43, 2.26]	**1.45 [1.05, 2.02]**
	N=16 730			

Model 1. PR adjusted for maternal age, smoking status, pre-existing diabetes, gestational diabetes, pre-pregnancy maternal BMI, socioeconomic status, prenatal distress and paternal BMI
Model 2. PR adjusted as in Model 1 and also for neonatal birth weight, weight gain during pregnancy, breastfeeding and postnatal distress

Table 3. Linear regression coefficients for BMI-z score at 7-years of age for children of women exposed to SSRI Antidepressants, Psychiatric Illness Without SSRIs, or Neither During Pregnancy

		Maternal SSRI Use vs. Psychiatric Illness	Maternal SSRI Use vs. Unexposed	Maternal Psychiatric Illness Vs. Unexposed
		Regression estimate [95% CI]		
All	**Unadjusted N=36 185**	0.01	0.10	0.10
	Model 1 N=34 825	0.04 [-0.19, 0.27]	0.09 (-0.10, 0.28]	0.05 [-0.07, 0.16]
	Model 2 N=34 410	0.04 [-0.19, 0.26]	0.10 (-0.09, 0.29]	0.06 [-0.05, 0.18]
Stratified According to Sex				
Males	**Unadjusted N=18 563**	0.19	0.23	0.05
	Model 1 N=17 893	0.29 [-0.06, 0.63]	0.11 [-0.18, 0.40]	-0.09 [-0.26, 0.09]
	Model 2 N=17 680	0.30 [-0.06, 0.66]	0.11 [-0.17, 0.39]	-0.07 [-0.24, 0.11]
Females	**Unadjusted N=17 622**	-0.20	-0.04	0.16
	Model 1 N=16 932	-0.13 [-0.43, 0.17]	0.05 [-0.19, 0.29]	**0.19 [0.04, 0.35]**
	Model 2 N=16 730	-0.10 [-0.39, 0.20]	0.07 [-0.18, 0.31]	**0.21 [0.06, 0.36]**

Model 1. PR adjusted for maternal age, smoking status, pre-existing diabetes, gestational diabetes, pre-pregnancy maternal BMI, socioeconomic status, prenatal distress and paternal BMI
Model 2. PR adjusted as in Model 1 and also for neonatal birth weight, weight gain during pregnancy, breastfeeding and postnatal distress

Supplementary Table 1. Demographic and Clinical Measures for Women and Children Who Were Lost and Not Lost to Follow-Up

Characteristic‡	**Lost to Follow-Up N=43 612**	**Completed Follow-Up N=36 185**	**P-value**
Maternal Age, mean (SD), years	29.8 (4.3)	30.2 (4.2)	0.000
Maternal BMI, n (%)†			
<25 kg/m^2	29 088 (70.4)	26 439 (73.4)	0.000
≥25 & <30 kg/m^2	8 410 (20.3)	6 852 (19.0)	
≥30 kg/m^2	3 848 (9.3)	2 692 (7.5)	
Paternal BMI, n (%)†			
<25 kg/m^2	18 684 (52.8)	18 722 (53.3)	0.410
≥25 & <30 kg/m^2	14 113 (39.9)	13 851 (39.4)	
≥30 kg/m^2	2 612 (7.4)	2 576 (7.3)	
Weight Gain During Pregnancy, n (%)†			
Low	5 067 (16.8)	5 901 (16.5)	0.000
Normal	10 599 (35.2)	13 619 (38.2)	
High	14 434 (48.0)	16 167 (45.3)	
Parity			
≥1, n (%)†	24 597 (56.4)	19 473 (53.8)	0.000
Socioeconomic Status, n (%)†			
High	27 139 (65.4)	25 176 (69.8)	0.000
Middle	12 577 (30.3)	9 828 (27.2)	
Low	1 758 (4.2)	1 081 (3.0)	
Smoking Status, n (%)†			
Non Smoker	31 461 (75.5)	29 106 (80.4)	0.000
1-10 cigarettes per day	7 464 (17.9)	5 280 (14.6)	
>11 cigarettes per day	2 733 (6.6)	1 797 (5.0)	
Breastfeeding, n (%)†			

< 1 month	2 390 (7.2)	1 946 (5.4)	0.000
1-4 months	5 192 (15.6)	4 362 (12.1)	
≥4 months	25 815 (77.3)	29 847 (82.6)	
Prenatal Distress Score, mean (SD)	2.9 (2.7)	2.6 (2.5)	0.000
Postnatal Distress Score, mean (SD)	2.3 (2.9)	2.2 (2.7)	0.000
Exposure Status			
Unexposed	42 585 (97.6)	35 568 (98.3)	0.000
Psychiatric Illness	781 (1.8)	490 (1.4)	
SSRI Use	249 (0.6)	127 (0.4)	
Child Sex			
Male, n (%)[†]	22 242 (51.0)	18 563 (51.3)	0.393
Birth Weight, mean (SD), years	3 569 (584)	3 621 (541)	0.000
Gestational Age, mean (SD), weeks	39.9 (2.3)	40.1 (2.1)	0.000

[†] Percentages are calculated from available (non-missing) data.