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Long-Term Effects of Intrauterine Exposure to Antidepressants on Physical, Neurodevelopmental, and Psychiatric Outcomes: A Systematic Review

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ABSTRACT

Objective: Reviews on child outcomes following in utero antidepressant exposure have focused on short-term outcomes. However, several recent individual studies reported on adverse physical, neurodevelopmental, and psychiatric outcomes beyond infancy and early childhood. The objective of this systematic review was to establish the long-term effects of prenatal antidepressant exposure on physical, neurodevelopmental, and psychiatric outcomes in individuals aged 4 years and older.

Data Sources: Embase, MEDLINE Ovid, Web of Science, Cochrane Central, and Google Scholar were systematically searched for all relevant articles, written in English and published prior to November 8, 2018, using terms describing antidepressants, pregnancy, and developmental outcomes.

Study Selection: All original research articles on long-term outcomes of prenatal antidepressant exposure were eligible for inclusion. After screening and removal of duplicates, a total of 34 studies were identified.

Data Extraction: Included articles were qualitatively analyzed to determine inconsistency, indirectness, imprecision, and study bias.

Results: The identified studies demonstrated statistically significant associations between prenatal antidepressant exposure and a range of physical, neurodevelopmental, and psychiatric outcomes. Yet, the risk of confounding by indication was high. When controlling for confounders, 5 studies investigating physical outcomes (asthma, cancer, body mass index [BMI], epilepsy) found no association except conflicting outcomes for BMI. Eighteen studies examining neurodevelopmental outcomes (cognition, behavior, IQ, motor development, speech, language, and scholastic outcomes) found no consistent associations with antidepressant exposure after taking confounders into account. Eleven studies investigated psychiatric outcomes. After adjusting for confounders, prenatal antidepressant exposure was associated with affective disorders but not with childhood psychiatric outcomes (eg, autism spectrum disorders, attention-deficit/hyperactivity disorder).

Conclusions: Reported associations between in utero exposure to antidepressants and physical, neurodevelopmental, and psychiatric outcomes, in large part, seem to be driven by the underlying maternal disorder. When limiting confounding by indication, prenatal exposure to antidepressants was significantly associated only with offspring BMI and affective disorders.

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Depression and anxiety are highly prevalent mental disorders and the leading cause of disability worldwide.[1] Perinatal depression, defined as depression during pregnancy and after delivery, affects approximately 11.5% of new mothers annually in the United States.[2] If left untreated, perinatal depression puts mothers at increased risk of experiencing negative mental and physical health outcomes.[3,4] Moreover, perinatal depression has been linked to poor child outcomes, including adverse birth outcomes, poorer long-term cognitive and social development, and the risk of future psychopathology.[5] Antidepressants are usually given as first-line treatment for depression and anxiety,[6,7] and many patients continue to take their antidepressants for long periods of time as maintenance treatment to prevent relapse.[8] As a result, antidepressant use during pregnancy is common, with estimated prevalence rates ranging between 2% and 13%.[9–12]

However, since antidepressants cross the placenta, as well as the blood-brain barrier,[13] concern is growing about sequelae of in utero antidepressant exposure in the unborn child. Many antidepressants target the serotonergic system, and modifications of serotonergic signals are thought to influence brain development and subsequent functioning.[14] Moreover, the serotonergic system is involved in mechanisms besides brain functioning, including motor control, food intake, and body weight regulation.[15,16] Consequently, approximately 50% of women decide to discontinue their antidepressants either before or during pregnancy.[17]

A substantial number of observational studies have examined the use of antidepressants during pregnancy, with inconsistent results. Observational studies always carry the risk of confounding, particularly confounding by indication. Some of these studies found associations between in utero exposure to antidepressants and adverse neonatal outcomes, including low birth weight, preterm birth, persistent

Clinical Points

- There are no clear recommendations on antidepressant management during pregnancy because the evidence base, especially on long-term outcomes, is weak and inconsistent. Evidence indicating a causal relationship between in utero exposure to antidepressants and long-term health of the offspring is limited, but concerns remain.
- Treatment decisions regarding pregnant depressed patients must take disorder severity, the course of illness, and patient preferences into account.

pulmonary hypertension of the neonate, and poor neonatal adaptation,[18–25] as well as associations between prenatal antidepressant exposure and poorer neurodevelopmental and neurobehavioral outcomes in early childhood.[26–28] While these short-term outcomes have frequently been investigated and subsequently consolidated in systematic reviews (eg, references [29–32]), very few long-term child outcomes were included in these reviews. Recently, several individual studies have reported on adverse long-term outcomes beyond infancy and early childhood, including studies on intellectual disability at age 8 years,[33] as well as childhood cancer[61] and psychiatric disorders[34] over 15- and 17-year follow-up periods, respectively.

Our aim was to systematically evaluate the literature, examining the long-term effects of in utero exposure to antidepressants on child outcomes including and beyond the age of 4 years and untangling the results from confounding factors, such as confounding by indication, socioeconomic status, untreated mood/anxiety symptoms, and exposures to other substances. We chose to focus on outcomes from age 4 onward because the short-term effects of in utero exposure to antidepressants have been well established in a plethora of reviews focusing on infancy and very early childhood. Yet, it is paramount to also understand the long-term health effects of prenatal antidepressant exposure. Furthermore, many children start preschool at age 4, and measurements of childhood psychiatric disorders, learning disabilities, and cognitive development become more reliable at that age and afterward. Due to the nonspecific action of antidepressants, we included all investigated developmental outcomes, including physical, neurodevelopmental, and psychiatric outcomes.

METHODS

Literature Search and Data Sources

The systematic electronic literature search was performed by a medical information specialist (Wichor Bramer, MSc; Erasmus MC Medical Library; Rotterdam, the Netherlands) on November 8, 2018. All large databases, including Embase, MEDLINE Ovid, Web of Science, Cochrane Central, and Google Scholar, were searched, using search terms describing types of antidepressants (eg, *selective serotonin reuptake inhibitor*, *tricyclic antidepressant*), the target population (eg, *pregnancy*, *pregnant women*, *maternal exposure*), and outcome measurement timing (eg, *childhood*, *child development*, *adolescent*). A complete overview of the search terms used is included in Supplementary Appendix 1. This systematic review was registered in PROSPERO (no. CRD42019116981).

Selection Criteria

The selection procedure was conducted according to the guidelines described in the PRISMA statement.[35] Studies were eligible for inclusion if they were peer-reviewed and written in English and if they described a population of women using any antidepressants, including serotonin reuptake inhibitors (SRIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and other antidepressants during pregnancy. We defined long-term outcomes as any child outcome from the age of 4 years onward, not restricting our search to a maximum follow-up period. All original research articles were eligible for inclusion.

Study Selection and Data Extraction

Duplicate articles were screened and removed with the citation manager EndNote. Two reviewers (N.M.M. and Rachel Cohen, BSc; Icahn School of Medicine at Mount Sinai; New York, New York) independently screened the titles and abstracts and assessed the full text of potentially eligible studies. Disagreements between reviewers' selection were resolved by discussion among the reviewers and authors. When multiple articles reported on the same cohort and the same outcome measurement, the article with the highest level of detail was included. Data were extracted using a standardized data extraction form by two reviewers (N.M.M., A.-S.R.; see Supplementary Appendix 2). Two reviewers (N.M.M., A.-S.R.) independently assessed the quality of the studies using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Institutes of Health). The overall quality of evidence per outcome was summarized according to the GRADE guidelines[36] only for those outcomes reported in 5 or more studies.

Data Synthesis

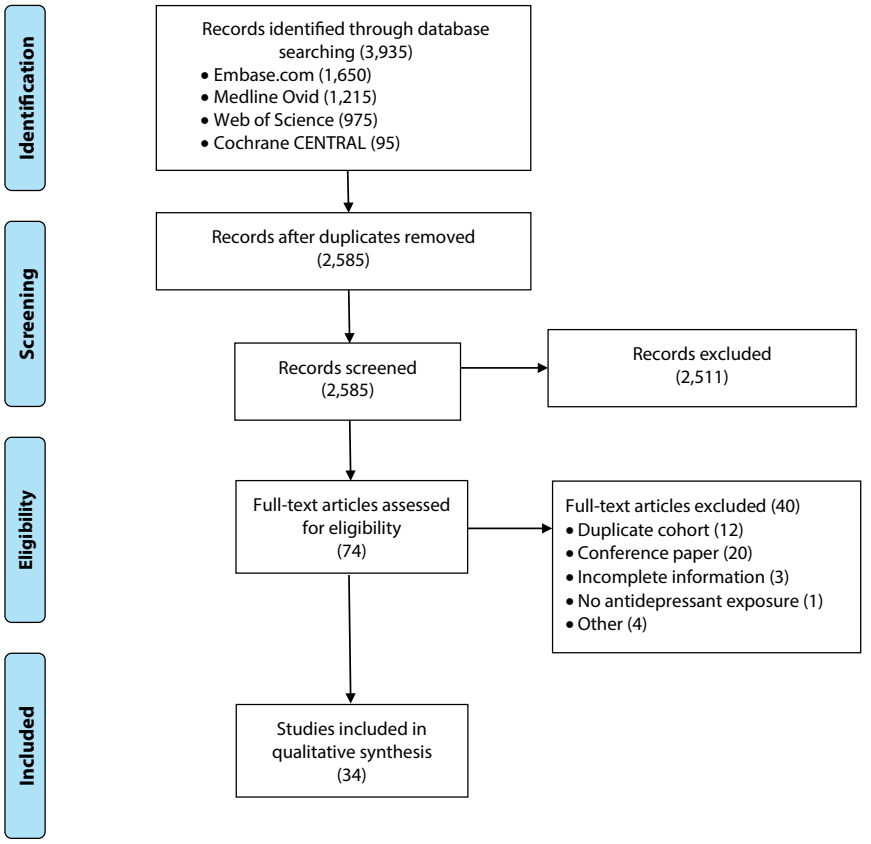
Here, we report a narrative synthesis of the evidence and present extracted adjusted relative risks and 95% confidence intervals (CIs) when possible. We did not perform a meta-analysis of the results because the physical health and neurodevelopment outcomes assessed in the included studies were too varied and biased to be pooled. Moreover, a meta-analysis of the psychiatric outcomes was futile because not enough research has investigated psychiatric disorders manifesting in adolescence and adulthood and childhood psychiatric outcomes have been meta-analyzed extensively.

RESULTS

Identified and Included Articles

Thirty-four studies met the predefined inclusion criteria and were included in this review (Figure 1, Supplementary

Figure 1. PRISMA Flow Chart of Included and Excluded Studies



Appendix 3). Interrater reliability was high (raw interrater agreement = 98.9%). Studies reported on physical health outcomes (5), neurodevelopmental outcomes (18), and psychiatric disorders (11). Fifteen studies (44.1%) were prospectively designed. Sample size per study ranged between 36 and 1,580,629 children. All studies included SSRIs, while some also focused on SNRIs (19), TCAs (13), and MAOIs (10). Detailed characteristics of all studies, including the quality assessment per study, are provided in Table 1.

Physical Health Outcomes

Four retrospective studies reporting on physical health outcomes were identified and their quality rated fair to good (Table 2). Two studies by Grzeskowiak et al[46,47] focused on childhood overweight, classified as a BMI > 85th percentile. In an Australian cohort of 6,560 women,[46] an association between SSRI exposure and childhood overweight at the age of 4 to 5 years was found for female but not male offspring. In contrast, in a Danish cohort of 36,185 pregnancies,[47] an association between SSRIs and childhood overweight was found for male but not female offspring at the age of 7. The authors assign the inconsistent results to the differences in study methods and indicate a higher accuracy in the Danish study.

Liu et al[55] did not find an association between antidepressant use and asthma in a large Danish population-based cohort. Only use of older antidepressants (mainly TCAs) was associated with an increased risk of asthma when treated individuals were compared to an untreated control group. However, this finding could reflect confounding by the severity of maternal depression, which cannot be assessed directly in register-based studies.

Momen et al[61] examined the association between in utero antidepressant exposure and childhood cancer. No association was found between antidepressant use during pregnancy and childhood cancer in general, leukemia, and nervous system tumors.

Mao et al[59] examined the association between antidepressant exposure and epilepsy. Children exposed to antidepressants in utero (n = 12,438) had a higher overall risk of epilepsy compared to unexposed children, but this difference was not significant when compared to children of mothers who discontinued antidepressants shortly before pregnancy, indicating that the underlying maternal disease plays a role in the observed association.

Neurodevelopmental Outcomes

Cognition. None of the 5 studies[43,45,51,52,62] investigating cognitive-neurophysiologic outcomes following in utero antidepressant exposure found a significant association between prenatal exposure to antidepressants and cognitive performance in a total of 166 antidepressant-exposed

Table 1. Characteristics of Included Studies Measuring Child Outcomes Beyond the Age of 4 After in Utero Antidepressant Exposure

Study	Study Design 1	Study Design 2	Antidepressants Studied	Data Source, Country (Period)	Quality Rating
Boukhris et al 2016[37]	R	Cohort	SSRIs, TCAs, MAOIs, SNRIs, other	Quebec Pregnancy Children's cohort, Canada (1998–2009)	Good
Boukhris et al 2017[38]	R	Cohort	SSRIs, TCAs, MAOIs, SNRIs, other	Quebec Pregnancy Children's cohort, Canada (1998–2009)	Good
Brown et al 2016[39]	R	Cohort	SSRIs	National Registers, Finland (1996–2010)	Good
Brown et al 2017[40]	R	Cohort	SSRIs, SNRIs	Administrative databases, Ontario, Canada (2002–2010)	Good
Castro et al 2016[41]	R	Case-control	SSRIs, TCAs, dual-action antidepressants	Electronic Health Records, Massachusetts (1997–2010)	Good
El Marroun et al 2014[42]	P	Cohort	SSRIs	Generation R study, the Netherlands (2002–2006)	Fair
El Marroun et al 2017[43]	P	Cohort	SSRIs	Generation R study, the Netherlands (2002–2006)	Fair
Figueroa 2010[44]	R	Cohort	SSRIs, bupropion	MarketScan data, United States (1997–2002)	Poor
Galbally et al 2015[45]	P	Case-control	SSRIs, SNRIs, TCAs, NaSSA	Victorian Psychotropic Registry, Australia (2004)	Poor
Grzeskowiak et al 2012[46]	R	Cohort	SSRIs	Women's and Children's Health Network, Australia (2000–2005)	Good
Grzeskowiak et al 2013[47]	R	Cohort	SSRIs	Danish National Birth Cohort, Denmark (1996–2002)	Fair
Grzeskowiak et al 2016[48]	R	Cohort	All antidepressants (ATC code N06A)	Danish National Birth Cohort, Denmark (1996–2002)	Fair
Hanley et al 2015[49]	P	Cohort	SSRIs, SNRIs	Primary maternity care providers BC, Vancouver, Canada (unknown)	Poor
Harrington et al 2014[50]	P	Case-control	SSRIs	Childhood Autism Risks from Genetics and the Environment study, United States (2003–2010)	Poor
Hermansen et al 2016[51]	P	Cohort	SSRIs	Mother and Child Cohort Study, Norway (2008–2009)	Poor
Hermansen et al 2017[52]	P	Cohort	SSRIs	Mother and Child Cohort Study, Norway (2008–2009)	Poor
Johnson et al 2016[28]	P	Cohort	SSRIs, SNRIs	Emory Women's Mental Health Program, United States (2010–2012)	Fair
Kragholm et al 2018[53]	R	Cohort	SSRIs	Danish National Birth Cohort, Denmark (2005–2008)	Good
Laugesen et al 2013[54]	R	Cohort	All antidepressants (ATC code N06A)	Danish National Birth Cohort, Denmark (1996–2009)	Good
Liu et al 2015[55]	R	Cohort	SSRIs, TCAs, antidepressants with ATC code N06AX	Danish National Birth Cohort, Denmark (1996–2007)	Good
Liu et al 2017[34]	R	Cohort	All antidepressants (ATC code N06A)	Danish National Birth Cohort, Denmark (1998–2012)	Good
Lupattelli et al 2018[56]	P	Cohort	SSRIs	Mother and Child Cohort Study, Norway (1999–2008)	Good
Malm et al 2016[57]	R	Cohort	SSRIs	National Registers, Finland (1996–2010)	Good
Man et al 2017[58]	R	Cohort	All antidepressants (BNF 4.3)	Clinical Data Analysis & Reporting System, Hong Kong (2001–2009)	Good
Mao et al 2016[59]	R	Cohort	All antidepressants (ATC code N06A)	Danish National Birth Cohort, Denmark (1997–2008)	Good
Misri et al 2006[60]	P	Cohort	SSRIs	British Columbia Women's Hospital, Vancouver, Canada (1997–1999)	Poor
Momen et al 2018[61]	R	Cohort	All antidepressants (ATC code N06A)	Danish National Birth Cohort, Denmark (1998–2012)	Good
Nulman et al 2012[64]	P	Cohort	SSRIs, venlafaxine	Motherisk Program, Toronto, Canada (2001–2006)	Fair
Nulman et al 2015[63]	P	Cohort	SSRIs, SNRIs	Motherisk Program, Toronto, Canada (2005–2008)	Fair
Oberlander et al 2007[65]	P	Cohort	SSRIs	British Columbia Women's Hospital, Vancouver, Canada (1997–1999)	Poor
Partridge et al 2016[66]	P	Cohort	SSRIs	Infants Hospital Rhode Island, United States (unknown)	Poor
Sujan et al 2017[67]	R	Cohort	All antidepressants (ATC code N06A)	National administrative registers, Sweden (1996–2012)	Good
Viktorin et al 2017[33]	R	Cohort	All antidepressants (ATC code N06A)	National administrative registers, Sweden (2006–2007)	Good
Weikum et al 2013[62]	P	Cohort	SRIs	British Columbia Women's Hospital, Vancouver, Canada (unknown)	Poor

Abbreviations: ATC = anatomical therapeutic chemical, BNF = British National Formulary, MAOI = monoamine oxidase inhibitor, NaSSA = noradrenergic and specific serotonergic antidepressant, P = prospective, R = retrospective, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

children, 460 children exposed to untreated maternal depression, and 5,545 unexposed children (Table 3).

Internalizing and externalizing behavior. We identified 7 studies[45,48,49,56,62–64] examining both externalizing and internalizing behavior, 4 studies[28,42,51,65] investigating only externalizing behavior only, and 1 study[60] assessing only internalizing behavior following in utero antidepressant exposure (Table 3). Except for 3 case-control studies,[45,49,60] all studies were longitudinal cohort studies.[28,42,48,51,56,62–65] Two analyses[49,62] used the Health and Behavior Questionnaire to assess externalizing and internalizing behavior, 1 study[48] used the Strength and Difficulties Questionnaire (SDQ),

Table 2. Results for Child Physical Health Outcomes[a]

Study	Child Age at Testing	Outcome	Comparison Groups	Adjusted Outcome	95% CI	Covariates
Grzeskowiak et al 2012[46]	4–5 y	BMI > 85th percentile (females only)	SSRIs (n = 33) vs unexposed (n = 3,072)	**0.27**	**0.07 to 0.99**	Maternal age, BMI, race, socioeconomic status, parity, smoking status, appropriateness of fetal growth (SGA/LGA), breastfeeding at discharge from hospital
			SSRIs (n = 33) vs unmedicated psychiatric illness (n = 106)	**0.23**	**0.05 to 0.98**	
		BMI > 85th percentile (males only)	SSRIs (n = 38) vs unexposed (n = 3,213)	0.93	0.52 to 1.67	
			SSRIs (n = 38) vs unmedicated psychiatric illness (n = 98)	1.17	0.54 to 2.51	
Grzeskowiak et al 2013[47]	7 y	BMI > 85th percentile	SSRIs (n = 127) vs unexposed (n = 35,568)	1.39	0.94 to 2.05	Pre-pregnancy maternal BMI, weight gain during pregnancy, paternal BMI, employment status, smoking status, prenatal distress, maternal postnatal distress score, neonatal birth weight, breastfeeding
			SSRIs (n = 127) vs unmedicated psychiatric illness (n = 490)	1.12	0.71 to 1.77	
		BMI > 85th percentile (females only)	SSRIs (n = 63) vs unexposed (n = 17,320)	0.99	0.43 to 2.26	
			SSRIs (n = 63) vs unmedicated psychiatric illness (n = 239)	0.86	0.37 to 1.99	
		BMI > 85th percentile (males only)	SSRIs (n = 64) vs unexposed (n = 18,248)	**1.54**	**1.01 to 2.37**	
			SSRIs (n = 64) vs unmedicated psychiatric illness (n = 251)	**1.78**	**1.01 to 3.12**	
Liu et al 2015[55]	> 3 y	Asthma (medication and/or hospital contact)	Antidepressants (n = 8,895) vs unexposed (n = 712,314)	**1.25**	**1.18 to 1.33**	Maternal country of origin, parity, age at delivery, maternal social status at birth, smoking during pregnancy, maternal history of asthma, sex of the child, calendar year of birth
			Antidepressants (n = 8,895) vs unmedicated prenatal depression (n = 12,476)	1.00	0.93 to 1.08	
Mao et al 2016[59]	< 13 y	Epilepsy (*ICD-10* code G40–41)	Antidepressants (n = 12,438) vs unexposed (n = 715,319)	**1.27**	**1.05 to 1.54**	Child's sex, family income at birth, maternal age at birth, education, marital status at birth, parity, parental epilepsy diagnosis history before birth, smoking
Momen et al 2018[61]	< 15 y	Childhood cancer (*ICD-10*: C00–C97)	Antidepressants (n = 21,488) vs unexposed (n = 863,033)	1.15	0.78 to 1.72	Maternal age at delivery, primiparity, maternal history of psychiatric disorders at delivery, inpatient psychiatric treatment from 2 years before pregnancy up to delivery, dispensation of other psychotropic prescriptions during pregnancy, smoking during pregnancy, maternal highest education, calendar year of delivery, parental cancer history at time of delivery
			Antidepressants (n = 21,488) vs prior antidepressant users (n = 30,607)	1.03	0.63 to 1.68	

[a]Values in bold are statistically significant. Adjusted outcomes are adjusted relative risks.
Abbreviations: BMI = body mass index, LGA = large for gestational age, SGA = small for gestational age, SSRI = selective serotonin reuptake inhibitor.

Table 3. Results for Neurodevelopmental Outcomes

Study	Child Age at Testing	Outcome	Comparison Groups	Adjusted Outcome[a]	95% CI	Covariates
Brown et al 2016[39]	0–14 y	Specific developmental disorders of speech and language (*ICD-10* code F80)	SSRIs (n = 15,596) vs unexposed (n = 31,207)	**1.53**	**1.26 to 1.86**	Maternal country of birth, parental death, smoking, marital status, socioeconomic status, maternal substance abuse, maternal and paternal age, place of residence, maternal and paternal history of psychiatric diagnosis, parity, child's sex, gestational age, exposure to antiepileptic drugs, anxiolytics/sedatives, entitlement to chronic diseases
			SSRIs (n = 15,596) vs unmedicated psychiatric illness (n = 9,537)	1.20	0.97 to 1.49	
		Specific developmental disorders of scholastic skills (*ICD-10* code F81)	SSRIs vs unexposed	1.09	0.69 to 1.73	
			SSRIs vs unmedicated psychiatric illness	1.00	0.63 to 1.59	
		Specific developmental disorder of motor function (*ICD-10* code F82)	SSRIs vs unexposed	1.26	0.90 to 1.77	
			SSRIs vs unmedicated psychiatric illness	1.18	0.81 to 1.72	
El Marroun et al 2014[42]	4–9 y	Pervasive developmental problems (CBCL score, 1.5–5)	SSRIs (n = 69) vs unexposed (n = 5,531)	**1.91**	**1.13 to 3.47**	Maternal age at intake, child's sex, maternal education, ethnicity, smoking, gestational age, maternal depressive symptoms at 3 y
			SSRIs (n = 69) vs unmedicated depression (n = 376)	1.33	0.68 to 2.57	
		Autistic traits (SRS)	SSRIs vs unexposed	β = **0.15**	**0.08 to 0.22**	
			SSRIs vs unmedicated depression	β = **0.10**	**0.02 to 0.18**	
		Affective problems (CBCL score, 1.5–5)	SSRIs vs unexposed	1.37	0.87 to 2.16	
El Marroun et al 2017[43]	4 y	Executive functioning (BRIEF)	SSRIs (n = 71) vs unexposed (n = 5,427)	**5.58**	**0.98 to 10.25**	Maternal education, cognitive ability, ethnicity, smoking, child's age and sex, birth weight, maternal depressive symptoms at 3 y
			SSRIs vs unexposed (corrected for depressive symptoms during pregnancy)	3.43	−1.29 to 8.16	
	6 y	Nonverbal IQ (SON-R)	SSRIs (n = 71) vs unexposed (n = 5,427)	−0.48	−4.13 to 3.17	
			SSRIs (n = 71) vs unmedicated depression (n = 385)	0.12	−4.11 to 4.36	
	7 y	Attention and executive functioning (NEPSY- II)	SSRIs vs unexposed	−0.06	−0.34 to 021	
			SSRIs vs unexposed (corrected for depressive symptoms during pregnancy)	−0.05	−0.33 to 0.23	
		Language (NEPSY-II)	SSRIs vs unexposed	**−0.40**	**−0.65 to −0.15**	
			SSRIs vs unexposed (corrected for depressive symptoms during pregnancy)	**−0.45**	**−0.70 to −0.19**	
		Memory and learning (NEPSY-II)	SSRIs vs unexposed	0.04	−0.21 to 0.30	
			SSRIs vs unexposed (corrected for depressive symptoms during pregnancy)	0.02	−0.24 to 0.28	
		Visuospatial functioning (NEPSY-II)	SSRIs vs unexposed	0.02	−0.23 to 0.27	
			SSRIs vs unexposed (corrected for depressive symptoms during pregnancy)	0.02	−0.24 to 0.27	
		Sensory motor functioning (NEPSY-II)	SSRIs vs unexposed	0.16	−0.10 to 0.42	
			SSRIs vs unexposed (corrected for depressive symptoms during pregnancy)	0.17	−0.09 to 0.44	
Grzeskowiak et al 2016[48]	7 y	Total difficulties score (SDQ)—abnormal score	Antidepressants (n = 395) vs unexposed (n = 79,238)	0.68	0.34 to 1.36	Child's sex, maternal age at birth, parity, smoking, alcohol use, socioeconomic status, maternal antenatal mood
			Antidepressants (n = 395) vs unmedicated depression (n = 474)	0.84	0.31 to 2.31	

(continued)

Table 3 (continued).

Study	Child Age at Testing	Outcome	Comparison Groups	Adjusted Outcome	95% CI	Covariates
Johnson et al 2016[28]	2.5–5.5 y	Expressive language skills (TELD)	SRIs (n = 102) vs unexposed (n = 76)	β = **−0.15**[a]	**−0.19 to −0.02**	Maternal education, prenatal depressive symptoms, prenatal mood episodes, prenatal caffeine, alcohol, smoking, gestational age, Apgar score, child age, cognitive ability
		Cognitive functioning (DAS)	SRIs vs unexposed	…	NS[b]	NA
		Pervasive Developmental Disorder Subscale (alternate caregiver-rated CBCL)	SRIs vs unexposed	β = **0.17**[a]	**<0.01 to <0.01**[c]	Maternal epilepsy, no. of children in the home
		Pervasive Developmental Disorder Subscale (mother-rated CBCL)	SRIs vs unexposed	β = **0.16**[a]	**<0.01 to <0.01**[c]	Preschool maternal depressive symptoms, postpartum antidepressants, prenatal tobacco
Kragholm et al 2018[53]	< 7 y	Special education needs in elementary school	SSRIs (n = 3,214) vs unexposed (history of SSRI use) (n = 3,536)	1.12	0.82 to 1.55	Maternal age at birth, maternal education, birth year, diabetes prior to pregnancy, gestational diabetes, maternal hypertension, preeclampsia, smoking, Apgar score, birth weight relative to gestational length/age, preterm birth
		Delayed entry in elementary school	SSRIs vs unexposed (history of SSRI use)	1.17	0.99 to 1.38	
Lupattelli et al 2018[56]	5 y	Internalizing behavior (CBCL)	SSRIs late pregnancy (n = 290) vs unexposed with a history of SSRI use (n = 3,775)	0.39	−0.25 to 1.02	Maternal BMI, parity, maternal education, gross yearly income, marital status, folic acid use, smoking, alcohol use, illicit substance use, paternal education, analgesics, anxiolytics and sedatives, antipsychotics, non-SSRI antidepressants, severity of maternal depressive and anxiety symptoms in pregnancy, lifetime history of major depression
		Emotionally reactive (CBCL)	SSRIs late pregnancy vs unexposed with a history of SSRI use	0.05	−0.50 to 0.61	
		Anxious/depressed (CBCL)	SSRIs late pregnancy vs unexposed with a history of SSRI use	**0.50**	**0.04 to 0.95**	
		Somatic complaints (CBCL)	SSRIs late pregnancy vs unexposed with a history of SSRI use	0.27	−0.30 to 0.84	
		Externalizing behavior (CBCL)	SSRIs late pregnancy vs unexposed with a history of SSRI use	0.21	−0.40 to 0.82	
		Attention problems (CBCL)	SSRIs late pregnancy vs unexposed with a history of SSRI use	0.26	−0.64 to 1.17	
		Aggressive behavior (CBCL)	SSRIs late pregnancy vs unexposed with a history of SSRI use	0.07	−0.30 to 0.45	
		Activity (EAS)	SSRIs late pregnancy vs unexposed with a history of SSRI use	0.13	−0.31 to 0.57	
		Emotionality (EAS)	SSRIs late pregnancy vs unexposed with a history of SSRI use	0.12	−0.60 to 0.85	
		Shyness (EAS)	SSRIs late pregnancy vs unexposed with a history of SSRI use	−0.08	−0.79 to 0.63	
		Sociability (EAS)	SSRIs late pregnancy vs unexposed with a history of SSRI use	0.25	−0.42 to 0.92	

(continued)

Table 3 (continued).

Study	Child Age at Testing	Outcome	Comparison Groups	Adjusted Outcome	95% CI	Covariates
Misri et al 2006[60]	4–5 y	Internalizing behavior (parent-rated CBCL)	SSRIs (n = 22) vs unexposed (n = 14)	0.99	0.13 to 7.88	Maternal depression
		Internalizing behavior (alternate caregiver–rated CBCL)	SSRIs vs unexposed	2.85	0.26 to 31.20	
		Child's irritability (Crowell)	SSRIs vs unexposed	0.65	0.07 to 5.69	
		Child's withdrawal (Crowell)	SSRIs vs unexposed	2.45	0.60 to 10.00	
		Child's positivity (Crowell)	SSRIs vs unexposed	0.46	0.10 to 1.98	
Viktorin et al 2017[33]	0–8 y	Intellectual disability (*ICD-10* codes F70–F79)	Antidepressant (n = 3,982) vs unexposed (n = 172,646)	1.33	0.90 to 1.98	Maternal diagnosis of depression before childbirth, maternal and paternal psychiatric diagnoses before childbirth, paternal psychotropic medication use during pregnancy, child's birth date, maternal and paternal age and education levels at delivery

Study	Child Age at Testing	Outcome	Comparison Groups	Mean AD[d]	Mean Unmedicated	Mean Unexposed	*P* Value	Covariates
Galbally et al 2015[45]	4 y	Full scale IQ (WPPSI)	Antidepressants (n = 20) vs unexposed (n = 21)	115.40	…	115.76	.92	None. Authors report that results do not change when controlling for maternal depression in pregnancy and gestational age[b]
		Behavior (BRIEF-P)	Antidepressants vs unexposed	88.15	…	84.95	.53	
		Movement ABC	Antidepressants vs unexposed	80.40	…	83.43	.45	
		Internalizing behavior (CBCL)	Antidepressants vs unexposed	6.05	…	6.45	.81	
		Externalizing behavior (CBCL)	Antidepressants vs unexposed	9.30	…	9.25	.98	
Hanley et al 2015[49]	6 y	Externalizing behaviors (HBQ)	SRIs (n = 44) vs unexposed (n = 66)	0.26	…	0.29	.53	Concurrent maternal depression during the second and third trimester and 6 mo postpartum, cesarean section, child's sex, other psychometric medications during pregnancy, alcohol use during pregnancy, education
		Internalizing behaviors (HBQ)	SRIs vs unexposed	**0.39**	…	**0.29**	**.04**	
		Overanxious (HBQ)	SRIs vs unexposed	0.46	…	0.38	.13	
		Inattention (HBQ)	SRIs vs unexposed	0.53	…	0.61	.31	
Hermansen et al 2016[51]	5–6 y	Reasoning (WPPSI-R)	SSRIs (n = 28) vs unmedicated depression (n = 42) vs unexposed (n = 33)	10.92	11.55	11.06	.35	None
		Similarities (WPPSI-R)	SSRIs vs unmedicated depression vs unexposed	11.36	11.48	10.94	.70	
		Vocabulary (WPPSI-R)	SSRIs vs unmedicated depression vs unexposed	12.19	12.62	12.78	.66	
		Block design (WPPSI-R)	SSRIs vs unmedicated depression vs unexposed	9.14	9.79	9.82	.66	
		Visual attention (NEPSY-II)	SSRIs vs unmedicated depression vs unexposed	4.52	4.44	4.58	.55	
		Statue (NEPSY-II)	SSRIs vs unmedicated depression vs unexposed	3.68	3.69	3.58	.90	
		Behavior (CBCL)	SSRIs vs unmedicated depression vs unexposed	50.93	49.46	43.63	.06	

(continued)

Table 3 (continued).

Study	Child Age at Testing	Outcome	Comparison Groups	Mean AD[d]	Mean Unmedicated	Mean Unexposed	*P* Value	Covariates
Hermansen et al 2017[52]	4–7 y	Interference suppression (reaction time on a flanker task)	SSRIs (n = 21) vs unmedicated depression (n = 33) vs unexposed (n = 26)	1,271	1,230	1,295	NS[b]	None
		Interference suppression (LSW amplitude and latency—flanker task)	SSRIs vs unmedicated depression vs unexposed	…	…	…	NS[b]	
		Conflict monitoring (N2 latency and amplitude—flanker task)	SSRIs vs unmedicated vs unexposed	…	…	…	NS[b]	
Nulman et al 2012[64]	3–7 y	Full scale IQ (WPPSI)	SSRIs (n = 62) vs unexposed (n = 62)	**105**	…	**112**	**<.05**	Antidepressant dose, duration of antidepressant treatment during pregnancy, severity of depression during depression and at the time of testing, maternal IQ, child's age and sex
			SSRIs (n = 62) vs unmedicated (n = 54)	105	108	…	NS[b]	
			Venlafaxine (n = 62) vs unexposed (n = 62)	**105**	…	**112**	**<.01**	
		Verbal IQ (WPPSI)	SSRIs vs unexposed	**107**	…	**113**	**<.05**	
			SSRIs vs unmedicated	107	109	…	NS[b]	
			Venlafaxine vs unexposed	**106**	…	**113**	**<.01**	
		Performance IQ (WPPSI)	SSRIs vs unexposed	**102**	…	**108**	**<.05**	
			SSRIs vs unmedicated	102	105	…	NS[b]	
			Venlafaxine vs unexposed	103	…	108	NS[b]	
		Behavior (CBCL)	Antidepressants vs unexposed	…	…	…	NS[b]	
Nulman et al 2015[63]	3–7 y	Full scale IQ (WPPSI)	SRIs (n = 45) vs unexposed siblings (n = 45)	103	…	106	.30	Child's age, birth order, severity of depression during pregnancy
		Verbal IQ (WWPPSI)	SRIs vs unexposed siblings	104	…	107	.25	
		Performance IQ (WPPSI)	SRIs vs unexposed siblings	101	…	103	.28	
		Internalizing problems (CBCL)	SRIs vs unexposed siblings	5	…	3	.46	
		Externalizing problems (CBCL)	SRIs vs unexposed siblings	5	…	5	1.00	
		Total problems (CBCL)	SRIs vs unexposed siblings	6	…	4	.48	
Oberlander et al 2007[65]	4–5 y	Externalizing problems (CBCL)	SSRIs (n = 22) vs unexposed (n = 14)	49.8	…	48.4	NS[b]	None
		ADHD problems (CBCL)	SSRIs vs unexposed	52.3	…	53.1	NS[b]	
		Oppositional defiant problems (CBCL)	SSRIs vs unexposed	56.1	…	50.8	NS[b]	
		Attention problems (CBCL)	SSRIs vs unexposed	51.5	…	53.8	NS[b]	
		Aggressive behavior (CBCL)	SSRIs vs unexposed	55.6	…	53.7	NS[b]	
		Externalizing problems (TRF)	SSRIs vs unexposed	49.6	…	48.2	NS[b]	
		ADHD problems (TRF)	SSRIs vs unexposed	52.9	…	53.1	NS[b]	
		Oppositional defiant problems (TRF)	SSRIs vs unexposed	54.0	…	54.5	NS[b]	
		Attention problems (TRF)	SSRIs vs unexposed	52.8	…	52.3	NS[b]	
		Aggressive behavior (TRF)	SSRIs vs unexposed	53.2	…	54.2	NS[b]	
		Movement (Crowell)	SSRIs vs unexposed	110.8	…	103.2	NS[b]	
		Aggressiveness (Crowell)	SSRIs vs unexposed	8.1	…	7.6	NS[b]	
		Attention (Crowell)	SSRIs vs unexposed	11.9	…	12.4	NS[b]	
		Emotion (Crowell)	SSRIs vs unexposed	6.0	…	5.9	NS[b]	

(continued)

Table 3 (continued).

Study	Child Age at Testing	Outcome	Comparison Groups	Mean AD[d]	Mean Unmedicated	Mean Unexposed	*P* Value	Covariates
Partridge et al 2016[66]	4–5 y	Visual-motor coordination (no. of MUs)	SRIs (n = 15) vs unmedicated (n = 10) vs unexposed (n = 15)	2.63	2.54	2.40	.66	Maternal level of depression at study visit, child's mean age at study visit, gestational age
		Visual-motor coordination (Proportion of time to the end of first MU)	SRIs vs unmedicated vs unexposed	0.22	0.23	0.25	.13	
		Visual-motor coordination (peak velocity in cm/s)	SRIs vs unmedicated vs unexposed	64.2	61.0	66.3	.38	
		Visual-motor coordination (proportion of maximum aperture)	SRIs vs unmedicated vs unexposed	0.65	0.60	0.63	.20	
		Visual-motor coordination (phase duration in ms)	SRIs vs unmedicated vs unexposed	449	382	428	.29	
		Visual-motor coordination (no. of minor MUs)	SRIs vs unmedicated vs unexposed	2.71	2.72	2.75	1.00	
		Visual-motor coordination (straightness)	SRIs vs unmedicated vs unexposed	1.57	1.47	1.48	.24	
		Fine motor control (no. of MUs)	SRIs vs unmedicated vs unexposed	3.16	2.90	2.91	.59	
		Fine motor control (proportion of time to the end of first MUs)	SRIs vs unmedicated vs unexposed	0.19	0.17	0.18	.67	
		Fine motor control (peak velocity in cm/s)	SRIs vs unmedicated vs unexposed	56.9	58.2	61.8	.39	
		Fine motor control (proportion of maximum aperture)	SRIs vs unmedicated vs unexposed	**0.66**[e]	**0.58**[e]	**0.64**	**.003**	
		Fine motor control (phase duration in ms)	SRIs vs unmedicated vs unexposed	**655**[e]	**441**[e,f]	**581**	**<.001**	
		Fine motor control (no. of minor MUs)	SRIs vs unmedicated vs unexposed	3.85	2.98	3.75	.19	
		Fine motor control (straightness)	SRIs vs unmedicated vs unexposed	**1.68**[e]	**1.53**[e,f]	**1.66**	**.004**	
Weikum et al 2013[62]	6 y	Internalizing symptoms (HBQ)	SRIs (n = 26) vs unexposed (n = 38)	0.33	…	0.33	.62	Child's age, prenatal (third trimester) and postnatal (6 y) maternal mood
		Externalizing symptoms (HBQ)	SRIs vs unexposed	**0.23**	…	**0.29**	**.02**	
		ADHD symptoms (HBQ)	SRIs vs unexposed	**0.47**	…	**0.67**	**.03**	
		Executive functioning—reaction time and accuracy (H&F)	SRIs vs unexposed	…	…	…	NS[b]	

[a]Values for Johnson et al[28] are standardized. Other adjusted outcomes are relative risks unless otherwise noted.
[b]Exact numbers not reported.
[c]Unstandardized.
[d]AD = antidepressant group.
[e]SRI vs unmedicated group, $P < .05$.
[f]Unmedicated vs control group, $P < .05$.

Abbreviations: ADHD = attention-deficit/hyperactivity disorder; BMI = body mass index; BRIEF = Behavior Rating Inventory of Executive Functioning–Preschool Version; CBCL = Child Behavior Checklist; Crowell = Crowell procedure; DAS = Differential Ability Scales; EAS = Emotionality, Activity and Sociability Temperament Questionnaire; HBQ = MacArthur Health and Behavior Questionnaire; H&F = Hearts & Flowers flanker task; LSW = late slow wave; Movement ABC = Movement Assessment Battery for Children; MU = movement unit; NA = not applicable; NEPSY-II = Developmental NEuroPSYchological Assessment; NS = not specified; SDQ = Strengths and Difficulties Questionnaire; SON-R = Snijders-Oomen Niet-verbale intelligentie Test-Revisie; SRI = serotonin reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TELD = Test of Early Language Development; TRF = Child Behavior Checklist-Teacher Report Form; WPPSI = Wechsler Preschool and Primary Scale of Intelligence.

and 9 studies[28,42,45,51,56,60,63–65] assessed externalizing and internalizing behavior using the Child Behavior Checklist (CBCL).

A positive association between antidepressant exposure and externalizing behavior was reported in 3 studies,[28,42,62] including a total of 197 individuals prenatally exposed to SRIs and 5,645 unexposed individuals. One study,[49] including 44 individuals exposed to SRIs in utero and 66 unexposed individuals, showed a positive association between antidepressant exposure and internalizing behavior as assessed by the CBCL. Eight other studies,[45,48,51,56,60,63–65] including a total of 946 children exposed to antidepressants, 570 children exposed to untreated depression, and 83,202 unexposed children, did not show a relationship between in utero antidepressant exposure and internalizing and/or externalizing behavior.

Intelligence quotient. Of the 5 prospective studies that examined IQ scores,[43,45,51,63,64] only 1 study showed a small significant difference in IQ scores in children exposed to antidepressants in utero[64] (Table 3). Nulman et al[64] compared children of depressed women taking venlafaxine during pregnancy (n = 62) and children of depressed women taking SSRIs during pregnancy (n = 62) to children of untreated depressed pregnant women (n = 54) and children of nondepressed, healthy pregnant women (n = 62). Children of nondepressed mothers had significantly higher full-scale and verbal IQs than those in the venlafaxine and SSRI groups. However, after correcting for covariates, dose and duration of antidepressant use during pregnancy did not predict child IQ score. This finding suggests that factors other than antidepressant exposure during pregnancy predict children's intellect, including maternal IQ and sex of the child. The other 4 studies,[43,45,51,63] together reporting on 164 children exposed to antidepressants in utero, observed no association between antidepressant exposure and IQ scores in children between 3 and 7 years of age.

Viktorin et al[33] examined the association between antidepressant exposure in utero and intellectual disability (*ICD-10* codes F70–F79). No significant association was observed after adjustment for potential confounding factors.

Motor development. Five studies examined motor development in the offspring; 4 prospective studies[43,45,65,66] and 1 retrospective study[39] (Table 3). Brown et al[39] used an *ICD-10* diagnosis of specific developmental disorders of motor development as outcome, while the prospective studies used a kinematic task of visual motor and fine motor function, the Movement Assessment Battery for Children, the sensorimotor function of the Developmental NEuroPSYchological Assessment, and the movement subscale of the Crowell procedure.[43,45,65,66] Of the 4 prospective studies, together reporting on 128 antidepressant-exposed children between the ages of 4 and 7 years, only 1 study[66] reported significant findings. Partridge et al[66] performed a kinematic task of visual motor and fine motor functions at ages 4–5 years in SRI-exposed children (n = 15), children of untreated depressed pregnant women (n = 10), and a control group (n = 15). Children with prenatal SRI exposure had poorer fine motor control compared with children who were not exposed to SRIs.

Speech, language, and scholastic outcomes. One prospective[28] and 2 retrospective studies[39,53] reported on speech, language, and scholastic outcomes (Table 3). Johnson et al[28] examined 178 mother-child dyads, including 102 dyads with in utero SRI exposure, with the Expressive Language subtest of the Test of Early Language Development, 3rd edition (TELD-3). There was a modest mean difference of approximately 5 points in Expressive Language scores in favor of non-SRI exposure. Brown et al[39] examined specific developmental disorders of speech and language and specific developmental disorders of scholastic skills according to *ICD-10* diagnosis. Children exposed to SSRIs in utero had a significant increase in the risk of speech-language disorders compared to unexposed children. No overall association was found between in utero SSRI exposure and special education needs or delayed school start.[53]

Psychiatric Disorders

Autism spectrum disorders. We identified 7 studies—1 case-control study,[50] 2 health record analyses,[40,41] and 4 register-based cohort studies[34,37,57,67]—that reported on the association between in utero antidepressant exposure and autism spectrum disorders (ASDs) (Table 4). All 4 register-based cohort studies[34,37,57,67] reported a significant association between in-utero antidepressant exposure and risk for ASDs, with relative risks (RRs) ranging from 1.23 to 4.39. Three studies[39,41,50] did not find a significant association. All, except 1 study,[50] based their outcome definition on the *ICD* diagnoses of ASD. Harrington et al[50] employed the Autism Diagnostic Interview–Revised and the Autism Diagnostic Observation Schedule.

The case-control study[50] compared children with ASD (n = 492) to typically developing controls (n = 320) on self-reported maternal SSRI use during pregnancy. Children with ASDs were not more likely to have been exposed to SSRIs during pregnancy (5.9%) than typically developing children (3.4%). Restricting the analysis to boys produced a significant association (OR = 2.92; 95% CI, 1.07–7.93), but further reduced the already small number of children exposed to SSRIs in utero (n = 40; for boys, n = 32).

The 2 health record analyses[40,41] employed diverging methods. One study[41] identified individuals with an ASD diagnosis (n = 1,245) and compared them to typically developing controls (n = 3,405). The other study[40] compared individuals prenatally exposed to SSRIs (n = 2,837) both to unexposed controls (n = 33,069) and to an unexposed sibling (n = 620). Neither of these studies reported a significant association between in utero antidepressant exposure and risk for ASDs.

The 4 register-based cohort studies[34,37,57,67] reporting a significant association included a total of 58,365 individuals prenatally exposed to antidepressants and compared them to a total of 2,586,644 unexposed individuals. To control for confounding by indication, Liu et al[34] and Malm et al[57] further compared the antidepressant-exposed individuals to a total

Table 4. Results for Neurodevelopmental Disorders[a]

Study	Child Age at Testing	Outcome	Comparison Groups	Adjusted Outcome	95% CI	Covariates
Boukhris et al 2016[37]	0–11 y	ASD (*ICD-9* code 299 and *ICD-10* code F84)	ADs in second and/or third trimester (n = 2,532) vs unexposed (n = 142,924)	**1.87**	**1.15 to 3.04**	AD use 1 y before the first day of gestation, antidepressant use in 1st trimester, chronic/gestational hypertension, chronic/gestational diabetes, other psychiatric disorders, year of birth, child's sex, maternal age at first day of gestation, level of education recipient of social assistance, living alone
			Combined use of ADs (≥ 2 classes) in second and/or third trimester (n = 167) vs unexposed (n = 142,924)	**4.39**	**1.44 to 13.32**	
Boukhris et al 2017[38]	0–11 y	ADHD (*ICD-9* code 314 and *ICD-10* code F90; or ≥ 1 prescription for ADHD medications [ATC codes: N06BA02, N06BA04, N06BA01, N06BA09])	SSRIs in second and/or third trimester (n = 1,561) vs. unexposed (n = 141,905)	1.2	0.9 to 1.6	AD use in first trimester, chronic/gestational hypertension, chronic/gestational diabetes, other psychiatric disorders, maternal history of depression/anxiety, maternal history of ADHD, year of birth, child's sex, maternal age at first day of gestation, level of education, recipient of social assistance, living alone, area of residence on first day of gestation
			Combined use of ADs (≥ 2 classes) in second and/or third trimester (n = 162) vs unexposed (n = 141,905)	1.5	0.8 to 2.8	
Brown et al 2017[40]	2–12 y	ASD (≥ 2 outpatient diagnoses by pediatrician/psychiatrist, ≥ 1 diagnosis in hospital databases after age 2 years, or both, using *ICD-9* codes 299 and *ICD-10* codes F84)	SSRIs (n = 16,906.1)[a] vs unexposed (n = 18,999.9)[b]	1.61	0.997 to 2.59	Inverse probability of treatment weighting based on a high-dimensional propensity score to balance exposure group differences, measuring a battery of surrogate variables (diagnoses, procedures, drug claims) to control for relevant unobserved confounders
			SSRIs (n = 620) vs unexposed siblings (n = 620)	1.60	0.69 to 3.74	
Castro et al 2016[41]	2–19 y	ASD (*ICD-9* code 299 and *ICD-10* code F84)	ASD (n = 1,245) vs healthy controls (n = 3,405)	0.90	0.50 to 1.54	Past history of maternal depression, year of birth, child's sex, race/ethnicity, insurance type, median income tertile
		ADHD (*ICD-9* code 314)	ADHD (n = 1,701) vs healthy controls (n = 3,405)	0.97	0.53 to 1.69	
Figueroa 2010[44]	> 5 y	ADHD (insurance claims with a primary or secondary diagnosis of ADHD and prescription claims for stimulants)	SSRIs (n = 916) vs unexposed (n = 29,329)	0.91	0.51 to 1.60	Year of birth, child's sex, maternal age, urbanicity, age at last claim, age at end of eligibility
Harrington et al 2014[50]	2–5 y	ASD (ADI-R and ADOS)	ASD (n = 492) vs typically developing controls (n = 320)	1.55	0.59 to 4.08	Inverse probability weights, child's birth year, regional center, and mother's birthplace
		Developmental delays other than ASD (Vineland Adaptive Behavior Scales and Mullen Scales of Early Learning)	Developmental delays (n = 154) vs typically developing controls (n = 320)	1.62	0.59 to 4.42	
Laugesen et al 2013[54]	0–14 y	ADHD (*ICD-8*, *ICD-9* and *ICD-10*; or prescription for ADHD medication)	Any AD (n = 15,008) vs unexposed (n = 816,792)	**1.2**	**1.1 to 1.4**	Maternal and paternal psychiatric diagnoses, maternal diseases during pregnancy (infections, epilepsy), maternal anxiolytics, hypnotics, sedatives use, maternal smoking, calendar time at birth, birth order, child's sex, maternal age at delivery
			SSRIs (n = 11,721) vs unexposed (n = 816,792)	**1.2**	**1.0 to 1.5**	
			AD (n = 330) vs unexposed siblings (n = 330)	0.7	0.4 to 1.4	

(continued)

Table 4 (continued).

Study	Child Age at Testing	Outcome	Comparison Groups	Adjusted Outcome	95% CI	Covariates
Liu et al 2017[34]	0–16.5 y	First diagnosis of psychiatric disorders (*ICD-10* codes F00–F99)	AD continuation† (n = 17,560) vs unexposed (n = 854,241)	**1.64**	**1.53 to 1.76**	Inverse probability weights, maternal and paternal psychiatric history at delivery, maternal age at delivery, inpatient and outpatient psychiatric treatment from 2 y before pregnancy until delivery, prescriptions for other psychotropic and antiepileptic drugs during pregnancy, no. of nonpsychiatric hospital visits during pregnancy, smoking during pregnancy, primiparity, calendar year of delivery, place of residence, marital status, highest education, income status
			AD continuation† (n = 17,560) vs AD discontinuation‡ (n = 30,079)	**1.27**	**1.17 to 1.38**	
		ASD (*ICD-10* code F84)	AD continuation† vs unexposed	**1.82**	**1.54 to 2.15**	
			AD continuation† vs AD discontinuation‡	**1.23**	**1.01 to 1.51**	
		Mood disorder (F30–F39)	AD continuation† vs unexposed	**3.20**	**2.12 to 4.81**	
			AD continuation† vs AD discontinuation‡	**2.76**	**1.59 to 4.78**	
		Neurotic, stress-related and somatoform disorder (F40–F48)	AD continuation† vs unexposed	**2.40**	**2.08 to 2.76**	
			AD continuation† vs AD discontinuation‡	**1.62**	**1.36 to 1.94**	
		Behavioral and emotional disorder (F90–F98)	AD continuation† vs unexposed	**1.49**	**1.35 to 1.65**	
			AD continuation† vs AD discontinuation‡	**1.13**	**1.01 to 1.27**	
		Mental retardation (F70–F79)	AD continuation† vs unexposed	1.21	0.83 to 1.74	
			AD continuation† vs AD discontinuation‡	1.21	0.78 to 1.90	
Malm et al 2016[57]	0–14 y	Depression (*ICD-10* codes F32–39)	SSRI continuation† (n = 15,729) vs unexposed (n = 31,394)	**2.61**	**1.59 to 4.28**	Maternal and paternal psychiatric history, maternal history of substance abuse, smoking during pregnancy, child's sex, socioeconomic status
			SSRI continuation† (n = 15,729) vs SSRI discontinuation‡ (n = 7,980)	**1.84**	**1.14 to 2.97**	
			SSRI continuation† (n = 15,729) vs untreated mental illness (n = 9,651)	**1.78**	**1.12 to 2.82**	
		Anxiety (*ICD-10* codes F40–41)	SSRI continuation† vs unexposed	**1.74**	**1.16 to 2.61**	Maternal psychiatric history, maternal use of antiepileptic drugs, smoking during pregnancy, parental death, preterm birth, low birth weight, child's sex, marital status at delivery
			SSRI continuation† vs SSRI discontinuation‡	1.53	0.94 to 2.50	
			SSRI continuation† vs untreated mental illness	1.30	0.84 to 2.01	
		ASD (*ICD-10* code F84)	SSRI continuation† vs unexposed	**1.40**	**1.02 to 1.92**	Maternal chronic disease, preterm birth, neonatal care unit, child's sex, maternal age
			SSRI continuation† vs SSRI discontinuation‡	1.30	0.88 to 1.92	
			SSRI continuation† vs untreated mental illness	0.88	0.65 to 1.20	
		ADHD (*ICD-10* code F90)	SSRI continuation† vs unexposed	**1.66**	**1.27 to 2.16**	Maternal and paternal history of psychiatric disorder, maternal substance abuse, smoking during pregnancy, parental death, neonatal care unit, child's sex, socioeconomic status
			SSRI continuation† vs SSRI discontinuation‡	0.98	0.75 to 1.27	
			SSRI continuation† vs untreated mental illness	0.98	0.77 to 1.24	
Man et al 2017[58]	6–14 y	ADHD (*ICD-9-CM* code 314, or a prescription for methylphenidate or atomoxetine)	AD (n = 1,252) vs unexposed (n = 189,002)	**1.39**	**1.07 to 1.82**	Maternal preexisting diabetes, epilepsy, gestational diabetes, psychiatric conditions, hypertension, use of antipsychotics, birth year, birth hospital, parity, child's sex, socioeconomic status, maternal age at delivery
			SSRI (n = 425) vs unexposed (n = 189,002)	1.11	0.77 to 1.60	
			AD (n = 1,252) vs AD discontinuation‡ (n = 1,486)	0.75	0.51 to 1.10	
			AD (n = 26,808) vs unexposed sibling (n = 26,808)	0.54	0.17 to 1.74	

(continued)

Table 4 (continued).

Study	Child Age at Testing	Outcome	Comparison Groups	Adjusted Outcome	95% CI	Covariates
Sujan et al 2017[67]	0–15 y	ASD (*ICD-9* codes 299 and *ICD-10* codes F84)	First trimester AD (n = 22,544) vs unexposed (n = 1,558,085)	**1.64**	**1.46 to 1.83**	Maternal preexisting diabetes, epilepsy, gestational diabetes, psychiatric conditions, hypertension, use of antipsychotics, birth year, birth hospital, parity, child's sex, socioeconomic status, maternal age at delivery
			First trimester SSRI (18,470) vs unexposed (n = 1,558,085)	**1.66**	**1.46 to 1.89**	
			First trimester AD (n = 10,976) vs unexposed sibling (n = 13,994)	0.83	0.62 to 1.13	
		ADHD (*ICD-9* codes 314 and *ICD-10* codes F90)	First trimester AD vs unexposed	**1.58**	**1.46 to 1.71**	
			First trimester SSRI vs unexposed	**1.60**	**1.47 to 1.75**	
			First trimester AD vs unexposed sibling	0.99	0.79 to 1.25	

[a]Estimates in bold are statistically significant. Adjusted outcomes are adjusted relative risks.
[b]Pseudopopulation based on a high-dimensional propensity score (observed population: AD users n = 2,837 and nonusers n = 33,069).
†Children whose mothers used antidepressant medication both before and during pregnancy.
‡Children whose mothers used antidepressant medication before but not during pregnancy.
Abbreviations: AD = antidepressant, ADHD = attention-deficit/hyperactivity disorder, ADI-R = Autism Diagnostic Interview–Revised, ADOS = Autism Diagnostic Observation Schedule, ASD = autism spectrum disorder.

of 38,059 individuals whose mothers had taken antidepressant medication before, but not during, pregnancy (discontinuation group). Malm et al[57] added an additional comparison group of 9,651 individuals who were exposed to untreated mental illness in utero. Sujan et al[67] carried out a discordant sibling analysis. These attempts at controlling for confounding by indication yielded mixed results. While Liu et al[34] reported a small significant association between antidepressant exposure and ASDs, Malm et al[57] and Sujan et al[67] did not find significant associations.

Attention-deficit/hyperactivity disorder. We identified 7 studies, 1 insurance data analysis,[44] 2 health record analyses,[41,58] and 4 register-based cohort studies,[38,54,57,67] that examined the association between attention-deficit/hyperactivity disorder (ADHD) and in utero antidepressant exposure (Table 4). Three[54,57,67] of the 4 register-based cohort studies and 1 health record analysis[58] reported a significant association between in utero antidepressant exposure and risk for ADHD, with RRs ranging from 1.2 to 1.66. Three studies did not report a significant association.[38,41,44] All except 1 study[44] based their outcome definition on the *ICD* diagnoses of ADHD. Figueroa et al[44] based ADHD diagnoses on insurance and prescription claims.

Figueroa et al[44] investigated the association between in utero SSRI exposures and the presence of ADHD in the child by the age of 5 years (N = 30,245) and found that, while maternal ADHD, depressive disorders, and prenatal bupropion exposure increased the risk for ADHD, in utero SSRI exposure did not.

The 2 health record analyses[41,58] employed diverging methods. One study[41] identified individuals with an ADHD diagnosis (n = 1,701) and compared them to typically developing controls (n = 3,405). The other study[58] compared individuals prenatally exposed to antidepressants (n = 1,252) to unexposed controls (n = 189,002) and a discontinuation group (n = 1,486). In addition, the researchers in each study conducted a post hoc sibling-matched analysis to control for shared genetic and social confounding, including 53,616 children of 26,049 mothers. Castro et al[41] did not find a significant association between risk for ADHD and prenatal antidepressant exposure. Man et al[58] found a significant association only when comparing the exposed children to unexposed controls, but not when comparing the exposed children to the discontinuation group or in the sibling-matched analyses, which aimed to control for confounding by indication.

The 3 register-based cohort studies[54,57,67] reporting a significant association compared a total of 53,281 individuals prenatally exposed to antidepressants to 2,407,290 unexposed individuals. One register-based cohort study[38] not showing a significant association included 1,561 individuals exposed to SSRIs in the second and/or third trimester and 141,905 unexposed individuals. To control for confounding by indication, Malm et al[57] further compared the antidepressant-exposed individuals to a total of 7,980 individuals whose mothers had used antidepressant medication before, but not during, pregnancy and 9,651 individuals who were exposed to untreated mental illness in utero. In addition, Sujan et al[67] and Laugesen et al[54] carried out discordant sibling analyses. These attempts at controlling for confounding by indication resulted in the loss of the significant associations between antidepressant exposure and increased risk for ADHD in all 3 studies.

Affective disorders. Two studies[34,57] report on affective disorders diagnosed in adolescence, taking advantage of the long-term follow-up of the Scandinavian national registers (Table 4). Malm et al[57] assessed depression and anxiety (*ICD* diagnoses) in SSRI-exposed offspring compared to unexposed offspring, offspring exposed to untreated

mental illness in utero, and offspring whose mothers had used antidepressants before, but not during, pregnancy. Children exposed to SSRIs during gestation (n = 15,729) were at increased risk of developing depression compared to the other exposure groups. There was no association between SSRI exposure and a diagnosis of anxiety disorders.

Liu et al[34] investigated the overall risk of psychiatric disorders, as well as affective disorders more specifically (*ICD-10* diagnoses), during a maximum follow-up of 16.5 years. Increased risks for affective disorders were seen in children exposed to antidepressants in utero compared to children whose mother discontinued antidepressants before pregnancy.

Quality of Evidence (GRADE Assessment)

The quality of evidence was summarized for all outcomes reported in 5 or more studies. According to GRADE criteria, the overall quality of evidence was considered low for ASD and ADHD and very low for cognition, behavior, IQ, and motor development.

DISCUSSION

On the basis of our comprehensive systematic review of the literature, we found statistically significant associations between in utero exposure to antidepressants and a wide range of physical, neurodevelopmental, and psychiatric outcomes. Yet, the evidence is inconsistent, and the risk of residual confounding, particularly confounding by indication, is high. Across all identified and included studies, the quality of evidence of the examined outcomes was rated low to very low (GRADE[36]).

In studying the effects of prenatal antidepressant exposure, it is crucial to consider that the indication for antidepressant use, namely maternal psychopathology, has also been shown to increase the risk of adverse outcomes in the child.[68] This issue is known as confounding by indication. Maternal psychopathology may assert its effect on the offspring via shared genetic susceptibility, environmental stress, and/or parenting practices.[69–71] All but 9 studies[44–46,51–53,55,59,65] statistically controlled for some form of maternal psychopathology. Because these statistical adjustments are unlikely to fully control for the source of confounding, some studies have used additional strategies to disentangle the effects of antidepressant use from the effects of the underlying maternal illness. These strategies include comparing antidepressant-exposed individuals to individuals born to mothers who discontinued antidepressants or to individuals born to mothers with untreated mental illness. In addition, discordant sibling designs, which compare exposed individuals to an unexposed sibling, aim to address this issue by controlling for all genetic and environmental factors shared between siblings. In general, attempts to control for confounding by indication led to a decrease in the magnitude of the association between in utero antidepressant exposure and adverse child outcomes. We discuss studies in which the association persisted as follows.

Physical Health Outcomes

Two small studies[46,47] found sex-related decreases and increases in the risk of childhood overweight following in utero antidepressant exposure. Prenatal SSRI exposure can alter postnatal components of central serotonergic signaling, a pathway that plays a critical role in regulating mammalian energy homeostasis.[72] In animals, fetal and neonatal SSRI exposure has been shown to result in changes consistent with type 2 diabetes and its comorbidities.[73] Previous studies on short-term outcomes in humans have also repeatedly found associations of in utero exposure to antidepressants and decreased birth weight.[18] Decreased birth weight, in turn, may reflect altered programming of organ structures and associated functions, which can lead to changes that carry into adulthood, including increased risk of diabetes and heart disease.[74,75]

Interestingly, both animal and human studies indicate a sex difference. In theory, this sex difference could be related to sex hormones, because estrogen is known to influence the serotonergic system[76,77] and regulates serotonin transporter expression, enhancing serotonergic signaling pathways.[78,79] Indeed, a study in rats[80] demonstrated that genes that regulate serotonin signaling and action in the ovary are altered in prenatally SSRI-exposed offspring. These rats had impaired reproductive cycling and an increased number of follicles in the ovary. In humans, menstrual cycling and fecundity have not yet been investigated.

Psychiatric Disorders

Childhood psychiatric disorders, particularly ADHD and ASDs, have received the majority of attention from researchers. At least a dozen systematic reviews and meta-analyses have attempted to examine a causal link between exposure to antidepressants in utero and ADHD and/or ASDs in the offspring, often with inconclusive results (eg, references [81 and 82]). This popularity very likely results from methodological considerations since ADHD and ASDs usually manifest early in life and may thus be assessed after a relatively short follow-up period.[83] An increased risk for ADHD following prenatal exposure to antidepressants was found in 4 large cohort studies[38,54,57,67] when comparing exposed to unexposed individuals. This significant association disappeared when these studies attempted to address confounding by indication in their study designs. Moreover, 4 large register-based cohort studies[34,37,57,67] reported a significant association between in utero antidepressant exposure and risk for ASDs. Only 1 of these studies[34] found that a small but significantly increased risk for ASDs remained in individuals exposed to antidepressants in utero when comparing them to individuals born to mothers who discontinued antidepressants before pregnancy. For all other studies, the significant association between prenatal antidepressant exposure and ASDs disappeared when exposed individuals were compared to individuals born to mothers who discontinued antidepressants, to individuals born to mothers with untreated mental illness, or to unexposed siblings. Moreover, none of these studies was able to take the severity of the underlying maternal illness into account.

These results, therefore, suggest that the underlying maternal disorder, rather than in utero antidepressant exposure, may be driving the association between in utero exposure to antidepressants and childhood psychiatric disorders. This association is conceivable, given that psychiatric disorders are highly heritable[84] and maternal psychopathology may assert its effects via environmental stress and suboptimal parenting practices.[69–71]

The average age at onset of most psychiatric disorders, including depression, anxiety, psychosis, and mania, is around late adolescence or early adulthood. This makes it harder to assess these disorders, because longitudinal and register-based studies in existence today have limited follow-up durations. Consequently, only 2 studies[34,57] thus far have reported on affective disorders. Interestingly, both studies found that the risk for depression was increased in individuals prenatally exposed to antidepressants, even compared to individuals born to mothers who discontinued antidepressants before pregnancy or individuals born to mothers with untreated mental illness. These findings point to a putative causal relationship between in utero antidepressant exposure and depressive disorder in the offspring. However, comparing antidepressant-exposed individuals to individuals born to mothers who discontinued antidepressants before pregnancy or individuals born to mothers with untreated mental illness may still not be sufficiently addressing confounding by indication, because women who continue antidepressants throughout pregnancy may be fundamentally different from women who discontinue or women who have never used antidepressants. In particular, mothers with severe symptoms are more likely to continue treatment during pregnancy,[85] and the severity of symptoms may differ between pregnancies. To address residual confounding by indication, randomized controlled trials, in which women are randomly assigned to an antidepressant continuation or discontinuation (plus cognitive therapy) group, are needed. This approach will ensure that all potential confounding factors are distributed equally among the groups to be compared.

Strengths and Limitations

The literature search was performed by an experienced medical information specialist. Study selection, data extraction, and risk of bias assessments were conducted by two reviewers, ensuring validity and accuracy. However, due to resource limitations, we were unable to include articles published in languages other than English. Moreover, the clinical implications of our findings are limited by the quality of the reviewed studies, including their selection of confounding factors, and the heterogeneity of the investigated outcome measures.

Implications

Approximately 50% of women who take antidepressants before pregnancy decide to discontinue their antidepressants, either before or during pregnancy, due to concerns about the negative consequences for the child. However, evidence indicating a causal relationship between in utero exposure to antidepressants and long-term health of the offspring is limited. Concerns remain given the significant associations of prenatal antidepressant exposure with BMI and affective disorders, the heterogeneity of the literature, and the scarcity of findings on long-term outcomes. As potential negative consequences of psychiatric illness during pregnancy may transcend potential negative consequences of in utero exposure to antidepressants, women and their health care providers must carefully weigh the risks and benefits of antidepressant (dis)continuation during pregnancy. Treatment decisions will need to be tailored to the individual patient, taking her disorder severity, course of illness and psychiatric history, previous experiences with antidepressant discontinuation, and treatment preferences into account. Substantial evidence points to the efficacy of alternative non-pharmacologic interventions, such as cognitive-behavioral therapy and interpersonal therapy, in preventing perinatal depression in at-risk women.[86] Women may, therefore, capitalize on these treatment options to minimize risks of exposure to antidepressants and untreated illness and maximize treatment of the disorder. However, judicious use of pharmacotherapy is recommended for women with severe mental illness or a high risk of relapse based on psychiatric history to avoid undertreatment and the resulting exposure to untreated illness.

To date, most clinical guidelines do not give any clear recommendations on antidepressant management during pregnancy.[87] It is challenging to formulate such guidelines when the evidence base is weak and inconsistent, and confounding by indication is difficult to avoid. Consequently, future research may use randomization to not only limit confounding by indication but also identify women who may discontinue antidepressant use during pregnancy with a low risk of relapse and women for whom antidepressant treatment is indicated to remain euthymic.[88]

CONCLUSION

Our comprehensive systematic review of the literature revealed statistically significant associations between in utero exposure to antidepressants and a wide range of physical, neurodevelopmental, and psychiatric outcomes. However, rather than reflecting a causal relationship, most of these associations seem to be driven by the underlying maternal disorder. After limiting confounding by indication, in utero exposure to antidepressants remained significantly associated only with BMI and increased risk for affective disorders.

The literature is heterogeneous, and findings on long-term outcomes are scarce. As time goes on, more data will become available on the long-term effects of prenatal antidepressant exposure, including on physical and mental health outcomes. These data will help to clarify the relationship between prenatal antidepressant exposure and BMI. Future research must also substantiate the association between in utero antidepressant exposure and affective disorders in adolescence and adulthood and investigate the associations between prenatal antidepressant exposure and other psychopathologies arising later in life.

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Supplementary Material

Article Title: Long-Term Effects of Intra-Uterine Exposure to Antidepressants on Physical, Neurodevelopmental and Psychiatric Outcomes: A Systematic Review

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List of Supplementary Material for the article

1. **Appendix 1** Search Terms
2. **Appendix 2** Data extraction sheet
3. **Appendix 3** Reference list of included papers

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Appendix 1 – Search Terms

embase.com

(('antidepressant agent'/exp/mj NOT (cotinine/mj OR cocaine/mj OR methamphetamine/mj)) OR (antidepress* OR anti-depress* OR (serotonin* NEAR/3 (uptake* OR reuptake*) NEAR/3 inhibitor*) OR SSRI* OR sertralin* OR paroxetin* OR fluvoxamin* OR fluoxetin* OR citalopram* OR escitalopram* OR ((depress* OR Mood-disorder*) NEAR/3 (drug OR agent*)) OR (monoamin* NEAR/3 oxidas* NEAR/3 inhibitor*) OR ((serotonin* OR noradrenalin* OR triple) NEAR/3 (reuptake OR uptake) NEAR/3 inhibitor*) OR aaptamin* OR abio-0801* OR adatanserin* OR adinazolam-mesilat* OR afalanin* OR agomelatin* OR alaproclat* OR almoxaton* OR amezinium* OR amfebutamon* OR amibegron* OR amiflamin* OR amineptin* OR amitifadin* OR amitriptylin* OR amitriptylin* OR amitriptylinoxid* OR amoxapin* OR amoxapin* OR anpirtolin* OR apimostinel* OR aprepitant* OR atibepron* OR atomoxetin* OR basimglurant* OR bazinaprin* OR befetupitant* OR befloxaton* OR befuralin* OR beloxepin* OR beloxepin* OR benmoxin* OR bicifadin* OR bifemelan* OR binedalin* OR brasofensin* OR brexanolon* OR brofaromin* OR butriptylin* OR centanafadin* OR cericlamin* OR chlorphentermin* OR cianopramin* OR ciclazindol* OR cilobamin* OR cimoxaton* OR citalopram* OR clemeprol* OR clomipramin* OR clomipramin* OR clorgylin* OR clorotepin* OR clovoxamin* OR danitracen* OR dapoxetin* OR deanol-acetamidobenzoat* OR decoglurant* OR delfaprazin* OR demexiptilin* OR desipramin* OR desipramin* OR desvenlafaxin* OR deudextromethorphan* OR dexmecamylamin* OR dibenzepin* OR diclofensin* OR dilopetin* OR dimetacrin* OR dopexamin* OR dosulepin* OR doxepin* OR doxepin* OR duloxetin* OR eclanamin* OR edivoxetin* OR elzasonan* OR emicerfont* OR eprobemid* OR escitalopram* OR etizolam* OR etoperidon* OR etrabamin* OR etryptamin* OR farampator* OR femoxetin* OR fenfluramin* OR fengabin* OR fezolamin* OR flerobuterol* OR flibanserin* OR fluoxetin* OR fluparoxan* OR fluvoxamin* OR gamfexin* OR gepiron* OR harmalin* OR hydroxynefazodon* OR hyperforin* OR ifoxetin* OR imipramin* OR imipramin* OR imipraminoxid* OR indalpin* OR indantadol* OR indatralin* OR iprindol* OR iproclozid* OR iproniazid* OR ipsapiron* OR isocarboxazid* OR l-759274* OR ladostigil* OR lazabemid* OR lensiprazin* OR levoprotilin* OR liafensin* OR lithium-acetat* OR lithium-carbonat* OR lithium-chlorid* OR lithium-citrat* OR lithium-gluconat* OR lithium-hydroxybutyrat* OR lithium-salt* OR lithium-sulfat* OR litoxetin* OR lofepramin* OR lortalamin* OR lubazodon* OR lusaperidon* OR manifaxin* OR maprotilin* OR maprotilin* OR mazindol* OR medifoxamin* OR melitracen* OR metapramin* OR methylphenidat* OR metralindol* OR mianserin* OR mifepriston* OR milacemid* OR milnacipran* OR minaprin* OR mirtazapin* OR moclobemid* OR mofegilin* OR moxifetin* OR moxiraprin* OR nafenodon* OR naluzotan* OR nefazodon* OR nefopam* OR nelivaptan* OR netamiftid* OR netarsudil* OR nialamid* OR nisoxetin* OR nitroxazepin* OR nomelidin* OR nomifensin* OR norcitalopram* OR norclomipramin* OR nordoxepin* OR norfenfluramin* OR norfluoxetin* OR norselegilin* OR norsertralin* OR nortrimipramin* OR nortriptylin* OR nortriptylin* OR noxiptilin* OR omiloxetin* OR opipramol* OR optimax* OR orvepitant* OR osemozotan* OR oxaflozan* OR oxaprotilin* OR panuramin* OR pargylin* OR paroxetin* OR pexacerfont* OR phenelzin* OR pheniprazin* OR piberalin* OR pirandamin* OR pirlindol* OR progabid* OR propizepin* OR prosulprid* OR protriptylin* OR protriptylin* OR quinupramin* OR radafaxin* OR rapastinel* OR rasagilin* OR reboxetin* OR rislenemdaz* OR rolipram* OR s-3344* OR safinamid* OR safrazin* OR selegilin* OR sembragilin* OR sercloremin* OR sertralin* OR sibutramin* OR sifaprazin* OR siramesin* OR solriamfetol* OR sunepitron* OR talsupram* OR tametralin* OR tampramin* OR tandamin* OR tapentadol* OR teciptilin* OR teniloxazin* OR tesofensin* OR tetrindol* OR thionisoxetin* OR tianeptin* OR tiflucarbin* OR timirdin* OR tofisopam* OR toloxaton* OR tranylcypromin* OR trazium-esilat* OR tribulin* OR trimipramin* OR venlafaxin* OR verucerfont* OR vestipitant* OR viloxazin* OR viqualin* OR vixotrigin* OR zometapin*):ab,ti) AND ('pregnancy'/exp OR 'pregnant woman'/exp OR 'prenatal exposure'/exp OR 'maternal exposure'/de OR 'prenatal drug exposure'/exp OR 'prenatal period'/de OR 'perinatal period'/de OR parity/exp OR 'named groups by

pregnancy'/exp OR 'perinatal depression'/exp OR 'antenatal depression'/de OR 'gestational age'/de OR 'puerperium'/exp OR (pregnan* OR prenatal* OR parit* OR nullipar* OR primipar* OR multipar* OR primigravid* OR multigravid* OR perinatal* OR antenatal* OR peri-natal* OR ante-natal* OR gestation* OR maternal* OR puerper* OR postpart* OR post-part* OR postnatal* OR post-natal*):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND ('preschool child'/exp OR 'school child'/exp OR 'child'/de OR 'kindergarten'/exp OR adolescent/de OR adolescence/de OR childhood/de OR 'child behavior'/de OR 'Child Behavior Checklist'/de OR 'child development'/de OR (preschool* OR schoolage OR schoolchild* OR school-age* OR pre-school* OR children* OR (child* NEAR/3 (outcome* OR effect*)) OR kindergart* OR ((age OR ages OR aged) NEAR/3 (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17)) OR ((after) NEXT/1 (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17) NEXT/1 (year OR years OR yr OR yrs)) OR adolescen* OR teenage* OR puber*):ab,ti)

Medline Ovid

((exp * Antidepressive Agents/ NOT (Cotinine/ OR Cocaine/ OR Methamphetamine/)) OR (antidepress* OR anti-depress* OR (serotonin* ADJ3 (uptake* OR reuptake*) ADJ3 inhibitor*) OR SSRI* OR sertralin* OR paroxetin* OR fluvoxamin* OR fluoxetin* OR citalopram* OR escitalopram* OR ((depress* OR Mood-disorder*) ADJ3 (drug OR agent*)) OR (monoamin* ADJ3 oxidas* ADJ3 inhibitor*) OR ((serotonin* OR noradrenalin* OR triple) ADJ3 (reuptake OR uptake) ADJ3 inhibitor*) OR aaptamin* OR abio-0801* OR adatanserin* OR adinazolam-mesilat* OR afalanin* OR agomelatin* OR alaproclat* OR almoxaton* OR amezinium* OR amfebutamon* OR amibegron* OR amiflamin* OR amineptin* OR amitifadin* OR amitriptylin* OR amitriptylin* OR amitriptylinoxid* OR amoxapin* OR amoxapin* OR anpirtolin* OR apimostinel* OR aprepitant* OR atibepron* OR atomoxetin* OR basimglurant* OR bazinaprin* OR befetupitant* OR befloxaton* OR befuralin* OR beloxepin* OR beloxepin* OR benmoxin* OR bicifadin* OR bifemelan* OR binedalin* OR brasofensin* OR brexanolon* OR brofaromin* OR butriptylin* OR centanafadin* OR cericlamin* OR chlorphentermin* OR cianopramin* OR ciclazindol* OR cilobamin* OR cimoxaton* OR citalopram* OR clemeprol* OR clomipramin* OR clomipramin* OR clorgylin* OR clorotepin* OR clovoxamin* OR danitracen* OR dapoxetin* OR deanol-acetamidobenzoat* OR decoglurant* OR delfaprazin* OR demexiptilin* OR desipramin* OR desipramin* OR desvenlafaxin* OR deudextromethorphan* OR dexmecamylamin* OR dibenzepin* OR diclofensin* OR dilopetin* OR dimetacrin* OR dopexamin* OR dosulepin* OR doxepin* OR doxepin* OR duloxetin* OR eclanamin* OR edivoxetin* OR elzasonan* OR emicerfont* OR eprobemid* OR escitalopram* OR etizolam* OR etoperidon* OR etrabamin* OR etryptamin* OR farampator* OR femoxetin* OR fenfluramin* OR fengabin* OR fezolamin* OR flerobuterol* OR flibanserin* OR fluoxetin* OR fluparoxan* OR fluvoxamin* OR gamfexin* OR gepiron* OR harmalin* OR hydroxynefazodon* OR hyperforin* OR ifoxetin* OR imipramin* OR imipramin* OR imipraminoxid* OR indalpin* OR indantadol* OR indatralin* OR iprindol* OR iproclozid* OR iproniazid* OR ipsapiron* OR isocarboxazid* OR l-759274* OR ladostigil* OR lazabemid* OR lensiprazin* OR levoprotilin* OR liafensin* OR lithium-acetat* OR lithium-carbonat* OR lithium-chlorid* OR lithium-citrat* OR lithium-gluconat* OR lithium-hydroxybutyrat* OR lithium-salt* OR lithium-sulfat* OR litoxetin* OR lofepramin* OR lortalamin* OR lubazodon* OR lusaperidon* OR manifaxin* OR maprotilin* OR maprotilin* OR mazindol* OR medifoxamin* OR melitracen* OR metapramin* OR methylphenidat* OR metralindol* OR mianserin* OR mifepriston* OR milacemid* OR milnacipran* OR minaprin* OR mirtazapin* OR moclobemid* OR mofegilin* OR moxifetin* OR moxiraprin* OR nafenodon* OR naluzotan* OR nefazodon* OR nefopam* OR nelivaptan* OR netamiftid* OR netarsudil* OR nialamid* OR nisoxetin* OR nitroxazepin* OR nomelidin* OR nomifensin* OR norcitalopram* OR norclomipramin* OR nordoxepin* OR norfenfluramin* OR norfluoxetin* OR norselegilin* OR norsertralin* OR nortrimipramin* OR nortriptylin* OR nortriptylin* OR noxiptilin* OR omiloxetin* OR opipramol* OR optimax* OR orvepitant* OR osemozotan* OR oxaflozan* OR oxaprotilin* OR panuramin* OR pargylin* OR paroxetin* OR pexacerfont* OR phenelzin* OR

pheniprazin* OR piberalin* OR pirandamin* OR pirlindol* OR progabid* OR propizepin* OR prosulprid* OR protriptylin* OR protriptylin* OR quinupramin* OR radafaxin* OR rapastinel* OR rasagilin* OR reboxetin* OR rislenemdaz* OR rolipram* OR s-3344* OR safinamid* OR safrazin* OR selegilin* OR sembragilin* OR sercloremin* OR sertralin* OR sibutramin* OR sifaprazin* OR siramesin* OR solriamfetol* OR sunepitron* OR talsupram* OR tametralin* OR tampramin* OR tandamin* OR tapentadol* OR teciptilin* OR teniloxazin* OR tesofensin* OR tetrindol* OR thionisoxetin* OR tianeptin* OR tiflucarbin* OR timirdin* OR tofisopam* OR toloxaton* OR tranylcypromin* OR trazium-esilat* OR tribulin* OR trimipramin* OR venlafaxin* OR verucerfont* OR vestipitant* OR viloxazin* OR viqualin* OR vixotrigin* OR zometapin*).ab,ti.) AND (exp Pregnancy/ OR Pregnant Women/ OR Maternal Exposure/ OR Prenatal Exposure Delayed Effects/ OR exp Prenatal Injuries/ OR exp Parity/ OR Gestational Age/ OR Postpartum Period/ OR (pregnan* OR prenatal* OR parit* OR nullipar* OR primipar* OR multipar* OR primigravid* OR multigravid* OR perinatal* OR antenatal* OR peri-natal* OR ante-natal* OR gestation* OR maternal* OR puerper* OR postpart* OR post-part* OR postnatal* OR post-natal*).ab,ti.) NOT (exp animals/ NOT humans/) AND (exp Child/ OR Adolescent/ OR exp Child Behavior/ OR Child Behavior Disorders/ OR exp Child Development/ OR (preschool* OR schoolage OR schoolchild* OR school-age* OR pre-school* OR children* OR (child* ADJ3 (outcome* OR effect*)) OR kindergart* OR ((age OR ages OR aged) ADJ3 ("4 OR 5" OR "6" OR "7" OR "8" OR "9" OR "10" OR "11" OR "12" OR "13" OR "14" OR "15" OR "16" OR "17")) OR ((after) ADJ ("4" OR "5" OR "6" OR "7" OR "8" OR "9" OR "10" OR "11" OR "12" OR "13" OR "14" OR "15" OR "16" OR "17") ADJ (year OR years OR yr OR yrs)) OR adolescen* OR teenage* OR puber*).ab,ti.

Web of science

TS=(((antidepress* OR anti-depress* OR (serotonin* NEAR/2 (uptake* OR reuptake*) NEAR/2 inhibitor*) OR SSRI* OR sertralin* OR paroxetin* OR fluvoxamin* OR fluoxetin* OR citalopram* OR escitalopram* OR ((depress* OR Mood-disorder*) NEAR/2 (drug OR agent*)) OR (monoamin* NEAR/2 oxidas* NEAR/2 inhibitor*) OR ((serotonin* OR noradrenalin* OR triple) NEAR/2 (reuptake OR uptake) NEAR/2 inhibitor*) OR aaptamin* OR abio-0801* OR adatanserin* OR adinazolam-mesilat* OR afalanin* OR agomelatin* OR alaproclat* OR almoxaton* OR amezinium* OR amfebutamon* OR amibegron* OR amiflamin* OR amineptin* OR amitifadin* OR amitriptylin* OR amitriptylin* OR amitriptylinoxid* OR amoxapin* OR amoxapin* OR anpirtolin* OR apimostinel* OR aprepitant* OR atibepron* OR atomoxetin* OR basimglurant* OR bazinaprin* OR befetupitant* OR befloxaton* OR befuralin* OR beloxepin* OR beloxepin* OR benmoxin* OR bicifadin* OR bifemelan* OR binedalin* OR brasofensin* OR brexanolon* OR brofaromin* OR butriptylin* OR centanafadin* OR cericlamin* OR chlorphentermin* OR cianopramin* OR ciclazindol* OR cilobamin* OR cimoxaton* OR citalopram* OR clemeprol* OR clomipramin* OR clomipramin* OR clorgylin* OR clorotepin* OR clovoxamin* OR danitracen* OR dapoxetin* OR deanol-acetamidobenzoat* OR decoglurant* OR delfaprazin* OR demexiptilin* OR desipramin* OR desipramin* OR desvenlafaxin* OR deudextromethorphan* OR dexmecamylamin* OR dibenzepin* OR diclofensin* OR dilopetin* OR dimetacrin* OR dopexamin* OR dosulepin* OR doxepin* OR doxepin* OR duloxetin* OR eclanamin* OR edivoxetin* OR elzasonan* OR emicerfont* OR eprobemid* OR escitalopram* OR etizolam* OR etoperidon* OR etrabamin* OR etryptamin* OR farampator* OR femoxetin* OR fenfluramin* OR fengabin* OR fezolamin* OR flerobuterol* OR flibanserin* OR fluoxetin* OR fluparoxan* OR fluvoxamin* OR gamfexin* OR gepiron* OR harmalin* OR hydroxynefazodon* OR hyperforin* OR ifoxetin* OR imipramin* OR imipramin* OR imipraminoxid* OR indalpin* OR indantadol* OR indatralin* OR iprindol* OR iproclozid* OR iproniazid* OR ipsapiron* OR isocarboxazid* OR l-759274* OR ladostigil* OR lazabemid* OR lensiprazin* OR levoprotilin* OR liafensin* OR lithium-acetat* OR lithium-carbonat* OR lithium-chlorid* OR lithium-citrat* OR lithium-gluconat* OR lithium-hydroxybutyrat* OR lithium-salt* OR lithium-sulfat* OR litoxetin* OR lofepramin* OR lortalamin* OR lubazodon* OR lusaperidon* OR manifaxin* OR maprotilin* OR maprotilin* OR mazindol* OR medifoxamin* OR melitracen* OR metapramin* OR methylphenidat* OR

metralindol* OR mianserin* OR mifepriston* OR milacemid* OR milnacipran* OR minaprin* OR mirtazapin* OR moclobemid* OR mofegilin* OR moxifetin* OR moxiraprin* OR nafenodon* OR naluzotan* OR nefazodon* OR nefopam* OR nelivaptan* OR netamiftid* OR netarsudil* OR nialamid* OR nisoxetin* OR nitroxazepin* OR nomelidin* OR nomifensin* OR norcitalopram* OR norclomipramin* OR nordoxepin* OR norfenfluramin* OR norfluoxetin* OR norselegilin* OR norsertralin* OR nortrimipramin* OR nortriptylin* OR nortriptylin* OR noxiptilin* OR omiloxetin* OR opipramol* OR optimax* OR orvepitant* OR osemozotan* OR oxaflozan* OR oxaprotilin* OR panuramin* OR pargylin* OR paroxetin* OR pexacerfont* OR phenelzin* OR pheniprazin* OR piberalin* OR pirandamin* OR pirlindol* OR progabid* OR propizepin* OR prosulprid* OR protriptylin* OR protriptylin* OR quinupramin* OR radafaxin* OR rapastinel* OR rasagilin* OR reboxetin* OR rislenemdaz* OR rolipram* OR s-3344* OR safinamid* OR safrazin* OR selegilin* OR sembragilin* OR sercloremin* OR sertralin* OR sibutramin* OR sifaprazin* OR siramesin* OR solriamfetol* OR sunepitron* OR talsupram* OR tametralin* OR tampramin* OR tandamin* OR tapentadol* OR teciptilin* OR teniloxazin* OR tesofensin* OR tetrindol* OR thionisoxetin* OR tianeptin* OR tiflucarbin* OR timirdin* OR tofisopam* OR toloxaton* OR tranylcypromin* OR trazium-esilat* OR tribulin* OR trimipramin* OR venlafaxin* OR verucerfont* OR vestipitant* OR viloxazin* OR viqualin* OR vixotrigin* OR zometapin*)) AND ((pregnan* OR prenatal* OR parit* OR nullipar* OR primipar* OR multipar* OR primigravid* OR multigravid* OR perinatal* OR antenatal* OR peri-natal* OR ante-natal* OR gestation* OR maternal* OR puerper* OR postpart* OR post-part* OR postnatal* OR post-natal*)) AND ((preschool* OR schoolage OR schoolchild* OR school-age* OR pre-school* OR children* OR (child* NEAR/2 (outcome* OR effect*)) OR kindergart* OR ((age OR ages OR aged) NEAR/2 (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17)) OR ((after) NEAR/1 (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17) NEAR/1 (year OR years OR yr OR yrs)) OR adolescen* OR teenage* OR puber*)) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man)))

Cochrane CENTRAL

((antidepress* OR anti-depress* OR (serotonin* NEAR/3 (uptake* OR reuptake*) NEAR/3 inhibitor*) OR SSRI* OR sertralin* OR paroxetin* OR fluvoxamin* OR fluoxetin* OR citalopram* OR escitalopram* OR ((depress* OR Mood-disorder*) NEAR/3 (drug OR agent*)) OR (monoamin* NEAR/3 oxidas* NEAR/3 inhibitor*) OR ((serotonin* OR noradrenalin* OR triple) NEAR/3 (reuptake OR uptake) NEAR/3 inhibitor*) OR aaptamin* OR abio-0801* OR adatanserin* OR adinazolam-mesilat* OR afalanin* OR agomelatin* OR alaproclat* OR almoxaton* OR amezinium* OR amfebutamon* OR amibegron* OR amiflamin* OR amineptin* OR amitifadin* OR amitriptylin* OR amitriptylin* OR amitriptylinoxid* OR amoxapin* OR amoxapin* OR anpirtolin* OR apimostinel* OR aprepitant* OR atibepron* OR atomoxetin* OR basimglurant* OR bazinaprin* OR befetupitant* OR befloxaton* OR befuralin* OR beloxepin* OR beloxepin* OR benmoxin* OR bicifadin* OR bifemelan* OR binedalin* OR brasofensin* OR brexanolon* OR brofaromin* OR butriptylin* OR centanafadin* OR cericlamin* OR chlorphentermin* OR cianopramin* OR ciclazindol* OR cilobamin* OR cimoxaton* OR citalopram* OR clemeprol* OR clomipramin* OR clomipramin* OR clorgylin* OR clorotepin* OR clovoxamin* OR danitracen* OR dapoxetin* OR deanol-acetamidobenzoat* OR decoglurant* OR delfaprazin* OR demexiptilin* OR desipramin* OR desipramin* OR desvenlafaxin* OR deudextromethorphan* OR dexmecamylamin* OR dibenzepin* OR diclofensin* OR dilopetin* OR dimetacrin* OR dopexamin* OR dosulepin* OR doxepin* OR doxepin* OR duloxetin* OR eclanamin* OR edivoxetin* OR elzasonan* OR emicerfont* OR eprobemid* OR escitalopram* OR etizolam* OR etoperidon* OR etrabamin* OR etryptamin* OR farampator* OR femoxetin* OR fenfluramin* OR fengabin* OR fezolamin* OR flerobuterol*

OR flibanserin* OR fluoxetin* OR fluparoxan* OR fluvoxamin* OR gamfexin* OR gepiron* OR harmalin* OR hydroxynefazodon* OR hyperforin* OR ifoxetin* OR imipramin* OR imipramin* OR imipraminoxid* OR indalpin* OR indantadol* OR indatralin* OR iprindol* OR iproclozid* OR iproniazid* OR ipsapiron* OR isocarboxazid* OR l-759274* OR ladostigil* OR lazabemid* OR lensiprazin* OR levoprotilin* OR liafensin* OR lithium-acetat* OR lithium-carbonat* OR lithium-chlorid* OR lithium-citrat* OR lithium-gluconat* OR lithium-hydroxybutyrat* OR lithium-salt* OR lithium-sulfat* OR litoxetin* OR lofepramin* OR lortalamin* OR lubazodon* OR lusaperidon* OR manifaxin* OR maprotilin* OR maprotilin* OR mazindol* OR medifoxamin* OR melitracen* OR metapramin* OR methylphenidat* OR metralindol* OR mianserin* OR mifepriston* OR milacemid* OR milnacipran* OR minaprin* OR mirtazapin* OR moclobemid* OR mofegilin* OR moxifetin* OR moxiraprin* OR nafenodon* OR naluzotan* OR nefazodon* OR nefopam* OR nelivaptan* OR netamiftid* OR netarsudil* OR nialamid* OR nisoxetin* OR nitroxazepin* OR nomelidin* OR nomifensin* OR norcitalopram* OR norclomipramin* OR nordoxepin* OR norfenfluramin* OR norfluoxetin* OR norselegilin* OR norsertralin* OR nortrimipramin* OR nortriptylin* OR nortriptylin* OR noxiptilin* OR omiloxetin* OR opipramol* OR optimax* OR orvepitant* OR osemozotan* OR oxaflozan* OR oxaprotilin* OR panuramin* OR pargylin* OR paroxetin* OR pexacerfont* OR phenelzin* OR pheniprazin* OR piberalin* OR pirandamin* OR pirlindol* OR progabid* OR propizepin* OR prosulprid* OR protriptylin* OR protriptylin* OR quinupramin* OR radafaxin* OR rapastinel* OR rasagilin* OR reboxetin* OR rislenemdaz* OR rolipram* OR s-3344* OR safinamid* OR safrazin* OR selegilin* OR sembragilin* OR sercloremin* OR sertralin* OR sibutramin* OR sifaprazin* OR siramesin* OR solriamfetol* OR sunepitron* OR talsupram* OR tametralin* OR tampramin* OR tandamin* OR tapentadol* OR teciptilin* OR teniloxazin* OR tesofensin* OR tetrindol* OR thionisoxetin* OR tianeptin* OR tiflucarbin* OR timirdin* OR tofisopam* OR toloxaton* OR tranylcypromin* OR trazium-esilat* OR tribulin* OR trimipramin* OR venlafaxin* OR verucerfont* OR vestipitant* OR viloxazin* OR viqualin* OR vixotrigin* OR zometapin*):ab,ti) AND ((pregnan* OR prenatal* OR parit* OR nullipar* OR primipar* OR multipar* OR primigravid* OR multigravid* OR perinatal* OR antenatal* OR peri-natal* OR ante-natal* OR gestation* OR maternal* OR puerper* OR postpart* OR post-part* OR postnatal* OR post-natal*):ab,ti) AND ((preschool* OR schoolage OR schoolchild* OR school-age* OR pre-school* OR children* OR (child* NEAR/3 (outcome* OR effect*)) OR kindergart* OR ((age OR ages OR aged) NEAR/3 (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17)) OR ((after) NEXT/1 (4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17) NEXT/1 (year OR years OR yr OR yrs)) OR adolescen* OR teenage* OR puber*):ab,ti)

Appendix 2 – Data extraction sheet

Name extractor:
Date extraction:

Title manuscript	
Authors	
Journal	
Year of publication	

Country	
Data source(s)	

Design of study 1 (retrospective/prospective)	
Design of study 2 (cohort/case-control/RCT)	
Study start date	
Study end date	

Outcome measurement	
Child age at testing	
Exposure group definition (n=..)	
Control group definition (n=..)	
Adjusted RR	
95% CI	
Mean 1 / mean 2	
p-value	
Covariates	

Outcome measurement	
Child age at testing	
Exposure group definition (n=..)	
Control group definition (n=..)	
Adjusted RR	

95% CI	
Mean 1 / mean 2	
p-value	
Covariates	

Outcome measurement	
Child age at testing	
Exposure group definition (n=..)	
Control group definition (n=..)	
Adjusted RR	
95% CI	
Mean 1 / mean 2	
p-value	
Covariates	

Outcome measurement	
Child age at testing	
Exposure group definition (n=..)	
Control group definition (n=..)	
Adjusted RR	
95% CI	
Mean 1 / mean 2	
p-value	
Covariates	

Outcome measurement	
Child age at testing	
Exposure group definition (n=..)	
Control group definition (n=..)	
Adjusted RR	
95% CI	
Mean 1 / mean 2	
p-value	
Covariates	

Appendix 3 – Reference list of included papers

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