

Title	Prenatal maternal stress and risk of neurodevelopmental disorders in the offspring: a systematic review and meta-analysis
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Table S1: study characteristics for ASD. n= number of subject exposed; N= total outcome number

<i>1st author (year)</i>	<i>Sample size and exposed (n)</i>	<i>Study design</i>	<i>Measurement of stress</i>	<i>Type of exposure</i>	<i>Time of exposure</i>	<i>Gender effect</i>	<i>Covariates accounted for</i>	<i>Outcome (n/N)</i>	<i>Measurement of the outcome</i>	<i>Main effect size (Crude)</i>	<i>Main effect size (adjusted)</i>
Beverdoff, 2005 (USA)	400 (101)	Case-control (mean age 7.9±4.0)	Survey distribution	Severe life events (events matching the SRRS)	During pregnancy with peak at 21-32 weeks gestation	No	-	ASD (61/188)	Diagnosis according to DSM-IV	2.07 (1.30-3.28) calculated	
Class, 2014 (Sweden)	738,144 (6625)	Cohort (follow-up up to 17 years)	Nationwide register	Maternal bereavement	At any time and 3rd trimester	Yes (no difference)	Sex, birth weight, gestational age, parental age, birth country, education, criminal conviction, mental illness, death by suicide	ASD (79/6,430)	Inpatient and outpatient diagnoses of Autism and Asperger's syndrome	Across pregnancy: 1.36 (1.09-1.70); 3 rd trimester: 1.67 (1.22-2.28)	Across pregnancy: 1.30 (1.04-1.62); 3 rd trimester: 1.58 (1.15-2.17)
George, 2014 (India)	343 (100)	Case-control (child age 2-6y)	Questionnaire	Excessive mental stress	At any time during pregnancy	No	Gender, place of residence, family size, type of family education of mother and father, occupation of father, SES	ASD (54/143)	CARS score >30	2.03 (1.27-3.26)	1.74 (0.98-3.08)
Grossi, 2016 (Italy)	113 (Death or disease 5; Conjugal problems 6; job difficulties 10)	Case-control (mean age 12.88±3.49)	Structured interview	Stressful life events	At any time during pregnancy	No	-	ASD (Death or disease 2 Conjugal problems 5; job difficulties 7/ 45)	Diagnosis according to DSM-V	Death or disease of a relative: 1.01 p>0.05; conjugal problems: 8.4 p=0.056; Job difficulties: 4.0 p=0.054	-
Hamade, 2013 (Lebanon)	258 (72)	Case-control (child age 3 to 27y)	Self-administered Questionnaire	Depressive symptoms	At any time during pregnancy	No	Living close to an industry; age and sex of the child; Previous childhood infection	ASD (40/86)	Diagnosis according to DSM-IV	3.80 (2.15-6.73) [calculated]	5.77 (2.11-15.80)
Kinney (2008) (USA)	320.686 (high: 9,003: medium: 95651)	Case-control	NCHS census data	Natural disaster (storm)	During pregnancy and 5 gestational periods;	Yes (no difference)	-	ASD (12 high-58 moderate exposed/ 167)	Children with DSM-III o IV diagnosis	High: 2.98 (1.63-5.42); Medium: 1.35 (0.97-1.87);)	-

Lei, 2015 (China)	926 (69)	Case-control (mean age 9.90±4.39)	Survey questionnaire (yes/no)	Unhappy emotional state	At any time during pregnancy	No	Socioeconomic factors	ASD (20/193)	Children diagnosed by pediatrician according to DSM-IV and to CARS score >30	1.61 (0.93-2.79)	4.82 (3.05-7.63)
Li (2009) (Denmark)	1.492.709 (37,275)	Cohort (follow-up up to 28y)	Nationwide register	Maternal bereavement	1 year before & during pregnancy	Yes (no difference)	Gender, birth weight, gestational age, sibling order, paternal age, maternal age, maternal psychiatric history, maternal education, maternal income, maternal residence, and maternal cohabitation status.	ASD (31/2367)	Children in psychiatric hospital or in receipt of outpatient care because of autism	1.70 (1.19-2.42);	1.15 (0.80-1.65)
Oerlemans (2016 (the Netherlands))	405 (65)	Case-control (mean age 12.0±3.7)	Questionnaire (1=yes; 0=no)	Maternal stress (severe tensions)	During pregnancy	No	-	ASD (31/152)	ASQ and ADI-R	1.31 (0.77-2.27)	
Rai et al, 2012a (Sweden)	47706 (181 exp. during pregnancy)	Cohort	Nationwide register	Severe life events (death, serious accident or illnesses)	During pregnancy and 1-2-3 years after birth	No	Age of parents, parity, family income, education, occupational class, migration status of parents; for life events at other time points	ASD (17/4429)	Diagnosis by parental report, direct observation and a structured neuropsychiatric assessment	1 year before: 1.28 (0.92-1.79); during pregnancy: 1.00 (0.60–1.65);	1 year before 1.28(0.91-1.78); during pregnancy: 0.88 (0.53–1.46);
Rai et al, 2012b (England)	11154	Cohort	Questionnaire	Exposure to rare and common life events	Early and mid-late pregnancy; at 8, 21, 33mts postnatal; and at 3 yr 11 mts postnatal	No	Parent age, highest occupational class of either parent; tenure of accommodation; parity sex of child and for weighted life event scores at all other time points under study.	ASD (86)	Diagnosis identified through National Health Records and the Pupil Level Annual Schools Census (PLASC)	Early pregnancy 0.98(0.95-1.01; late pregnancy: 0.99(0.95-1.02);	Early pregnancy 1.00 (0.95-1.06); late pregnancy: 1.01(0.95-1.07);
Roberts, 2016 (USA)	54,770 (1,343)	Cohort	Question “were you physically hurt by your spouse during this pregnancy?”	Sexual, emotional or physical abuse	1 and 2 yrs before birth; during birth yr and during pregnancy	No	birth weight, gestational age, smoking or alcohol, gestational diabetes, preeclampsia, or induced abortion. maternal age, birth year., child’s sex, mother’s childhood SES and mother’s abuse in childhood	ASD (451)	Administration of the ADI-R in subsample of 50 randomly selected cases	Birth year: 0.68 (0.44, 1.03); 1yr before: 1.92 (1.28-2.88)	<i>During pregnancy: 0.62 (0.24, 1.67)</i> Birth year: 0.64(0.41-1.00); 1yr before: 1.58 (1.04-2.40);
Say et al, 2016 (Turkey)	180 (52)	Case Control (mean age 8.80±1.98)	Standardized questionnaire	Depressive mood	At any time during pregnancy	No	-	ASD (38/100)	Diagnosis according to DSM-IV	2.88 (1.43-5.84) [calculated]	-

Visser et al, 2012 (Netherlands)	507 (60)	Case control (age [months] 32.6±6.6)	Questionnaire	Questions about severe stress and depression	At any time during pregnancy	No	-	ASD (40/196)	Diagnostic protocol with medical history, observation, psychiatric evaluation, ADOS, ADI-R	3.06 (1.72-5.44)	-
Ward, 1990 (USA)	118 (93)	Case-control (child age 7to12y)	Questionnaire	Family problems	At any time during pregnancy	No	-	ASD (46/59)	Children hospitalized	t-test p<0.05 0.90 (0.38-2.19) [calculated]	-
Zhang, 2010 (China)	190 (95)	Case Control (child age 3to21y)	Questionnaire	Unhappy emotional state	At any time during pregnancy	No	advanced paternal age, sex and birth year	ASD (29/38)	Autism diagnosis according to the World Health Organization's International Classification of Diseases, Tenth Revision (ICD-10).	4.20 (1.86-9.47)	4.08 (1.77-9.41)

Table S2: study characteristics for ADHD. n= number of subject exposed; N= total outcome number

<i>1st author, year and (country)</i>	<i>Sample size and exposed (n)</i>	<i>Study design</i>	<i>Measurement of stress</i>	<i>Type of exposure</i>	<i>Time of exposure</i>	<i>Analysis of gender effect</i>	<i>Covariates accounted for</i>	<i>Outcome exposed (n/N)</i>	<i>Measurement of the outcome</i>	<i>Main effect size (Crude)</i>	<i>Main effect size (adjusted)</i>
Class, 2014 (Sweden)	738,144 (6625)	Cohort (follow-up: 17 years)	Nationwide register	Maternal bereavement	At any time during pregnancy and 3 rd trimester	Yes (no difference)	Child sex, birth order, birth weight, gestational age, parental age, country of birth, education, criminal history, severe mental illness, death by suicide	ADHD (79/14,313)	Inpatient and outpatient diagnosis of hyperkinetic disorder	Across pregnancy: 1.15 (0.98-1.35); 3 rd trimester: 1.34 (1.06-1.70)	Across pregnancy: 1.12 (0.95-1.32); 3 rd trimester 1.31 (1.04-1.66)
Grizenko 2012 (Canada)	142 (43)	Case control (child age 9 to 10)	5 point likert scale (KMGQ)	Stressful life events (separation, repeated physical or sexual abuse, imprisonment of a spouse or death of a very close relative)	At any time during pregnancy	No	-	ADHD (29/71)	(CBCL) and the Conners' Global Index for Parents (CGI-P)	6.29 (1.45-27.26)	
Kim, 2009 (Korea)	2,673	Retrospective cohort (child mean age; 9)	Structured questionnaire	Maternal stress and depression	At any time during pregnancy	No	Age, gender, SES	Full and subthreshold ADHD (119/354)	DISC-IV	3.61 (1.48-8-80)	3.23 (1.27-8.22)
Lee, 2006 (Taiwan)	120	Case-control (child mean age 8)	Questionnaires (MAS, MSS and SRSS)	Marital adaptation, marital satisfaction and life events perception	At any time during pregnancy	No	Child age and sex	ADHD (60)	patient of the hospital that fulfilled the DSM-IV criteria.	-	Marital adaptation: 0.96 (0.94-0.99)
Li 2010 (Denmark)	1,015,912 (20,094)	Cohort (follow-up: 16 years)	Nationwide register	Maternal bereavement (unexpected death)	At any time during pregnancy and 3 rd	Yes (only in boys)	Sex, birth year maternal age, residence, education, income, psychiatric diseases, smoking; gestational age, Apgar, SGA	ADHD (51/10,278)	Hospital diagnosis (ICD-10) and ADHD medication	1.67 (1.09-2.56) Boys: 1.77; 3rd trimester: 3.04 (1.26-7.31)	1.62 (1.04–2.52); boys 1.72 (1.09–2.73); 3rd trimester 2.98 (1.24–7.16)

trimester											
Martini 2010 (Germany)	935 (102)	Cohort (follow-up 10 years)	Question “During pregnancy, how much did you feel strained?”	Self-perceived distress	At any time during pregnancy	No	Anxiety before birth	ADHD (11/N)	Composite International Diagnostic Interview (CIDI)	4.7 (2.2–10.0)	4.5 (2.0–10.12)
Motlagh 2010 (USA)	222 (18)	Case control (mean age 11.8 ±2.7)	MSRPFED interview	Psychosocial stressors about home environment, parental relationship, emotional supports, employment, financial status, physical health, and legal issues	At any time during pregnancy	No	Gender	ADHD (13/52)	SADS-PLV	4.23 (1.38-12.97)	6.8 (2.0–23.12)
Oerlemans, 2016 Netherlands	476 (84)	Case-control (mean age 11.8 ±2.4)	Interview (1=yes; 0=no)	Maternal stress (tensions and concerns about the child)	At any time during pregnancy	No	-	ADHD (50/162)	CTRS and PACS	ADHD vs NC: 2.61 (1.52-4.48);	-
Park, 2014 (Korea)	900 (313)	Case-control (mean age 8.63 ±2.21)	Question (had you been stressed during pregnancy: yes/no)	Stressful life events	At any time during pregnancy	No	(e.g., low birth weight, preterm delivery, or intensive care)	ADHD-I (32/65) ADHD-C (38/82)	ADHD diagnosis made by an expert psychiatrist	ADHD-I: 2.11 (1.17-3.79); ADHD-C: 1.81 (1.07-3.05)	ADHD-I: 2.21(1.06-4.61); ADHD-C: 1.89 (1.00-3.56)
Rodriguez & Bohlin, 2005 (Sweden)	290	Cohort (follow-up: 7 year)	Perceived Stress Scale (PSS)	Global perceived stress	At any time during pregnancy (Stronger week 10)	Yes (only in boys)	-	ADHD (n/7)	Fulfilment of ADHD criteria based on those listed in DSM.	9.30 (1.65–52.38)	
Sasaluxnanon, 2005 (Turkey)	241	Case-control (child age 6 to 12)	Self-report questionnaire	Emotional distress (anxiety, depression, stressed)	At any time during pregnancy	No	-	ADHD (n/122)	Clinical diagnosis based DSM-IV TR criteria	4.49 (2.37-8.45)	-
Say, 2016 (Turkey)	180 (40)	Case Control (mean age 8.80±1.98)	Standardized questionnaire	Depressive mood-anhedonia	At any time during pregnancy	No	-	ADHD (26/100)	Diagnosis by expert psychiatrist using the DSM-IV	2.76 (1.35-5.64;	-

Figure S1: Forest plot of ASD studies which reported both crude and adjusted estimates

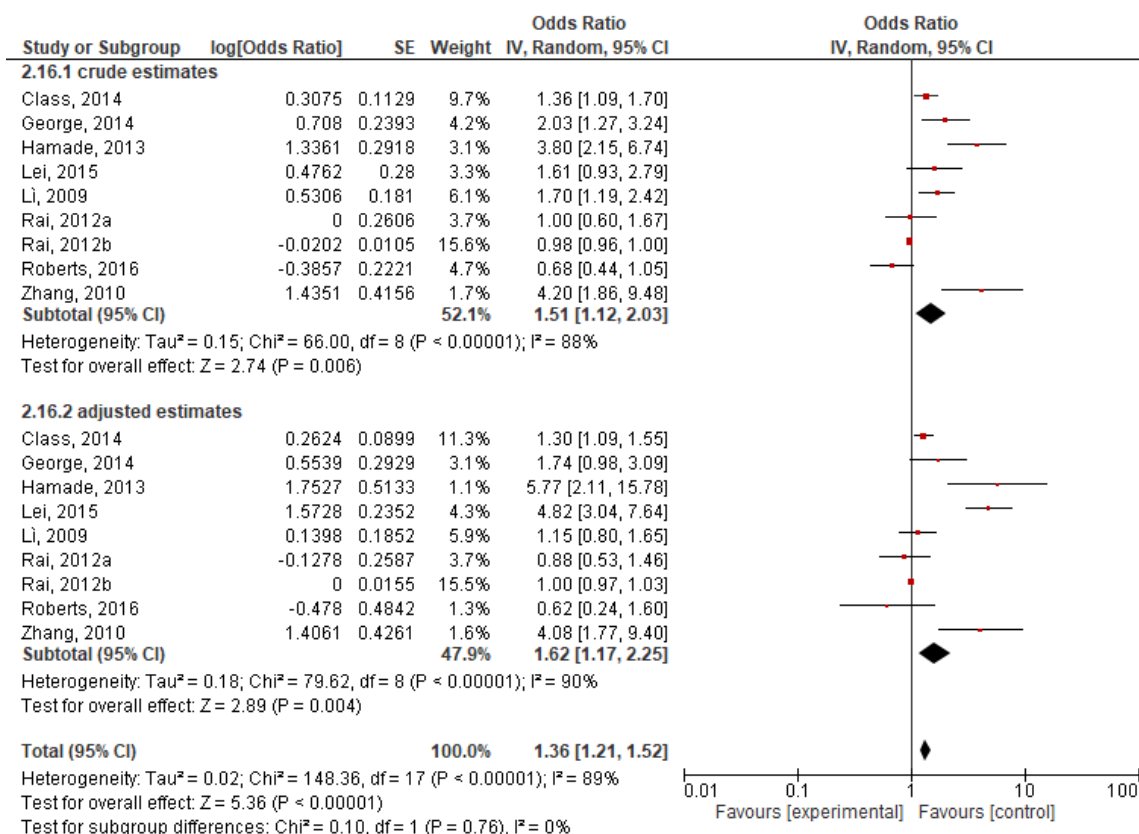


Figure S2: Forest plot of ADHD studies which reported both crude and adjusted estimates

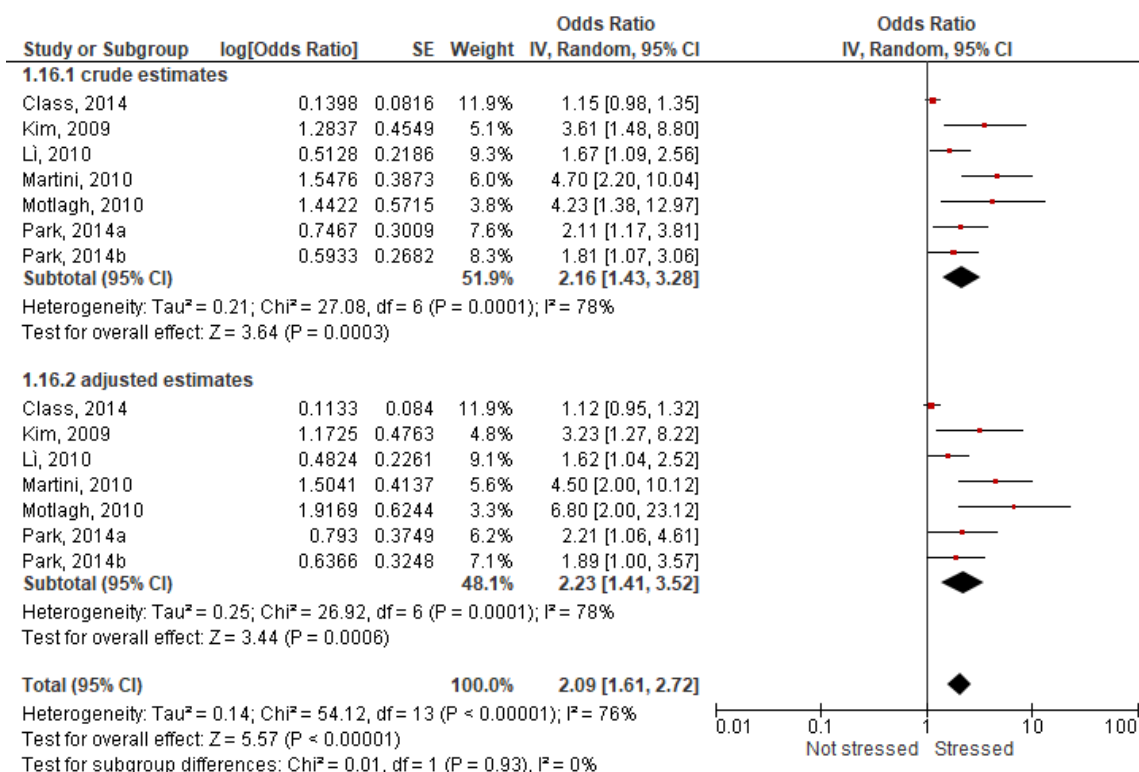


Figure S3: funnel plot with observed values for adjusted estimates for ASD (figure S3A) and ADHD (figure S3B)

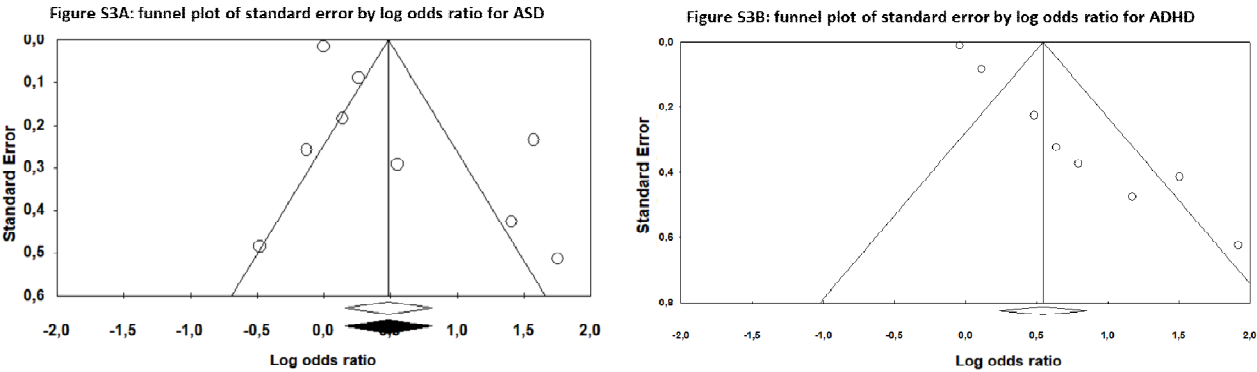
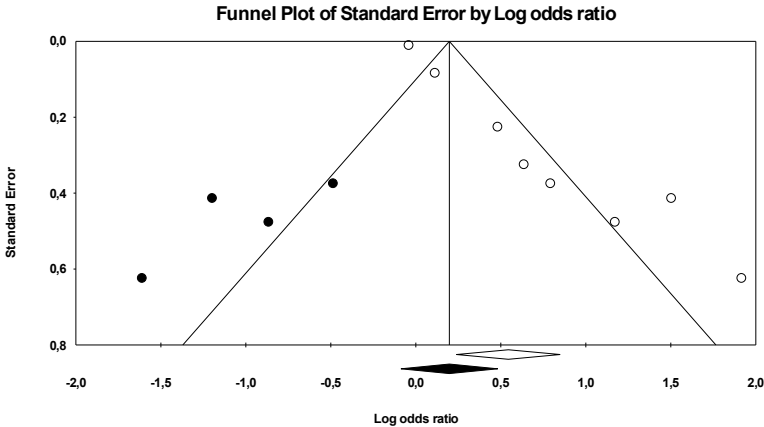


Figure S4: funnel plot with observed and imputed values for adjusted estimates of ADHD



APPENDIX 1

Strategies to search PUBMED, PsycINFO, Web of Science, EMBASE to identify cohort, cross-sectional and case-control studies to determine the association prenatal maternal stress and offspring neurodevelopmental disorders

Search terms
<i>For PubMed (1966- March 2018)</i>
1. ADHD
2. ASD
3. attention deficit hyperactivity disorder
4. Autism
5. autism spectrum disorder
6. Autism spectrum disorders
7. Autistic
8. Autistic spectrum
9. Autistic spectrum disorder
10. Autistic spectrum disorders
11. Case control study
12. Child
13. Cohort study
14. Cross sectional study
15. Development
16. Distress
17. Emotional Stress
18. hyperactivity disorder
19. impulsivity
20. Inattent*
21. Infant
22. Life Stress
23. Life Stresses
24. Maternal
25. Maternal Exposure
26. Maternal Exposures
27. neurodevelopment
28. Offspring
29. Outcomes
30. perinatal
31. Pregnancy
32. Pregnancy outcome
33. prenatal
34. prenatal maternal stress
35. Prospective study
36. Psychologic Stress
37. Psychological Stress
38. Psychological Stresses
39. Retrospective study
40. Trauma
41. trimester

We used a very similar approach for searching in the other databases.

APPENDIX 2

Bias classification - ADHD

Study	Selection	Exposure	Outcome	Confounding	Analytical	Attrition	Total
Class, 2014	Minimal	Low (Assessment of exposure from a dataset)	Minimal	Minimal (Assessed for common confounders)	Minimal	Minimal	LOW
Grizenko, 2012	Minimal (Rational for case and control selection explained)	Moderate (Recall >5 years after birt, but additional steps taken)	Minimal	Moderate (Not assessed for confounders)	Minimal	NR	MODERATE
Kim, 2009	Low (Sample selected from large population but selection criteria not defined)	High	Minimal	Low (Only certain confounders assessed)	Minimal	NR	MODERATE
LI, 2010	Minimal	Low (Assessment of exposure from a dataset)	Minimal	Minimal (Assessed for common confounders)	Minimal	Minimal	LOW
Lee, 2006	Moderate (Rationale for cases and controls not explained)	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for correct confounders)	Minimal	NR	MODERATE
Martini, 2010	Minimal	Moderate (Extrapolating data from population)	Minimal	Moderate (Not assessed for correct confounders)	Minimal	NR	MODERATE
Motlagh, 2010	Minimal	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for correct confounders)	Low	NR	HIGH
Oerlemans, 2016	Minimal (Rational for case and control)	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for correct	Low	NR	HIGH

	selection explained)			confounders)			
Park, 2014	Minimal (Rational for case and control selection explained)	High (Recall >5 years after birt)	Minimal	Low (Only certain confounders assessed)	Low	NR	MODERATE
Rodriguez, 2005	Minimal	Minimal	Minimal	Moderate (Not assessed for confounders)	Low	High (>20% attrition),	MODERATE
Sasaluxanon, 2005	Low	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for confounders)	Low	NR	MODERATE
Say, 2016	Minimal	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for confounders)	Moderate	NR	HIGH

Bias classification - ASD

Study	Selection	Exposure	Outcome	Confounding	Analytical	Attrition	Total
Beverdorf, 2005	Minimal (Rational for case and control selection explained)	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for confounders)	Low	NR	MODERATE
Class, 2014	Minimal	Low (Assessment of exposure from a dataset)	Minimal	Minimal	Minimal	Low	LOW
Lei, 2015	Low	High (Recall >5 years after birt)	Low	Moderate (Not assessed for correct confounders)	Low	NR	MODERATE
George, 2014	Moderate (Sample selection ambiguous)	Moderate (Recall 1-5 years after birth)	Low	Moderate (Not assessed for correct confounders)	NR	NR	MODERATE
Grossi, 2016	Moderate (Sample selection ambiguous)	High (Recall >5 years after birt)	Minimal	Moderate (Not assessed for confounders)	Minimal	NR	MODERATE
Hamade, 2013	High (A very select population studied)	High (Recall >5 years after birt)	Minimal	Low (Only certain confounders assessed)	Low	NR	HIGH
Kinney, 2008	Minimal	Low (Assessment	Minimal	Moderate (Not	Low	NR	LOW

		of exposure from a dataset)		assessed for confounders)			
Li, 2010	Minimal	Low (Assessment of exposure from a dataset)	Minimal	Minimal	Minimal	Minimal	LOW
Oerlemans, 2016	Minimal (Rational for case and control selection explained)	High (Recall >5 years after birth)	Minimal	Moderate (Not assessed for correct confounders)	Low	NR	HIGH
Rai, 2012a	Minimal	Low (Assessment of exposure from a dataset)	Minimal	Minimal	Minimal	Minimal	LOW
Rai, 2012b	Minimal	Minimal	Minimal	Minimal	Minimal	Low	LOW
Roberts, 2016	Minimal	Minimal (direct questioning)	Low (administration of the ADI-R)	Low (Only certain confounders assessed)	Minimal	Low	LOW
Say, 2016	Minimal	High (Recall >5 years after birth)	Minimal	Moderate (Not assessed for confounders)	Moderate	NR	HIGH
Visser, 2012	Minimal (Rational for case and control selection explained)	Moderate	Minimal	Moderate (Not assessed for confounders)	Minimal	NR	MODERATE
Ward, 1990	Moderate (Sample selection ambiguous)	Moderate	Low (Hospitalized children)	Moderate (Not assessed for confounders)	High	NR	HIGH
Zhang, 2010	Minimal (Rational for case and control selection explained)	Moderate	Minimal	Low (Only certain confounders assessed)	Minimal	NR	LOW