National Institute for Health and Care Excellence

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Final

Autism spectrum disorder in under 19s: recognition, referral and diagnosis

[A] Evidence review for factors and neurodevelopmental disorders that increase the likelihood of a diagnosis of autism spectrum disorder

NICE guideline CG128

Evidence review

December 2017

This evidence review was developed by the NICE Guideline Updates Team

Disclaimer

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Factors and neurodevelopmental disorders that increase the likelihood of a diagnosis of autism spectrum disorder

Review questions

Do the following risk factors increase the likelihood of a diagnosis of autism spectrum disorders (ASD) and assist in the decision to refer for a formal ASD diagnostic assessment?

- Small for gestational age
- Prenatal use of selective serotonin reuptake inhibitors (SSRIs)
- Fertility treatments

Do neurodevelopmental disorders (such as attention deficit hyperactivity disorder [ADHD] and learning [intellectual] disability) increase the likelihood of a diagnosis of ASD and assist in the decision to refer for a formal ASD diagnostic assessment?

Introduction

The NICE guideline (CG128) on diagnosing autism spectrum disorders (ASD) was reviewed by the surveillance programme in September 2016. The surveillance process identified new evidence indicating that the current recommendations on factors associated with an increased prevalence of ASD should be updated. The following key factors were identified for consideration - being small for gestational age, prenatal use of selective serotonin reuptake inhibitors (SSRIs), use of fertility treatments and the presence of neurodevelopmental disorders. This update reviews the evidence for these factors and considers whether they may alter the likelihood that a person has ASD and whether clinicians should take account of these factors when considering referral for an ASD diagnostic assessment.

Terminology in the NICE guideline on diagnosing ASD (CG128) was also amended throughout to reflect the updated DSM-5 diagnostic criteria. This involved replacing references to the old DSM-IV criteria with references to the new DSM-5 criteria.

PICO table

Population	Children and young people from birth up to their 19th birthday without a diagnosis of ASD
Predictive factors	• Small for gestational age • Prenatal use of SSRIs • Fertility treatments • Neurodevelopmental disorders such as ADHD and learning (intellectual) disability
Outcomes	Clinical diagnosis of ASD
Measures	Adjusted and unadjusted: • Odds ratios • Hazard ratios • Risk ratios

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in Appendix A and Appendix B.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

A systematic search was carried out to identify observational studies and systematic reviews of observational studies, which found 11,223 references (see Appendix C for literature search strategy). Evidence included in the original guideline, evidence identified from the surveillance review and studies referenced in identified systematic reviews were also reviewed, which included a total of 60 references. An additional reference (Rai 2017) which was published after the date of the systematic search was identified by a member of the guideline committee which was considered to be relevant for the update. In total, 11,284 references were identified to be screened at title and abstract level. Using priority screening software, from the first 8,000 references screened, 7,786 were excluded based on their titles and abstracts and 214 references were ordered to be screened based on their full texts. Of these, 23 references were included based on their relevance to the review protocol (Appendix A). The clinical evidence study selection is available in Appendix C.

No relevant papers were identified at title and abstract level in the last 3,000 screened (records 5,000-8,000), and therefore it was agreed to be appropriate to stop screening at this point (based on the priority screening functionality in the EPPI-reviewer systematic reviewing software, see Appendix B for more details). Therefore, the final 3,284 references were not screened on their titles and abstracts, but were automatically excluded.

Studies met the protocol criteria for clinical diagnosis of ASD if they reported that the diagnosis was made by a health professional. In the case of registry-based studies, a clinical diagnosis of ASD was assumed if International Statistical Classification of Diseases and Related Health Problems (ICD) or Diagnostic and Statistical Manual of Mental Disorders (DSM) codes were looked at from the databases. A clinical diagnosis of ASD was not assumed and studies were excluded if the reference reported that diagnoses were made with a questionnaire by researchers, parents or teachers.

No standard definition was found for small for gestation age, and therefore all references were included if they provided the definition of small for gestational age used in their analysis.

Excluded studies

For the full list of excluded studies, with reasons for exclusion, see Appendix H.

Summary of clinical studies included in the evidence review

Author (year)	Title	Study characteristics
Alexander (2016) Country: UK	Morbidity and medication in a large population of individuals with Down syndrome compared to the general population	Study type • Case-control study Predictive factor(s) • Down's syndrome

Author (year)	Title	Study characteristics
		Outcome(s) • Clinical diagnosis of ASD • Odds ratio
Bay (2013) Country: Denmark	Fertility treatment and risk of childhood and adolescent mental disorders: register based cohort study.	Study type • Prospective cohort study Predictive factor(s) • Fertility treatment Fertility treatment was divided into two groups: in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) and hormone treatments for induced ovulation/intrauterine insemination (OI/IUI) Outcome(s) • Clinical diagnosis of ASD • Hazard ratio
Boukhris (2016) Country: Canada	Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children	Study type • Retrospective cohort study Predictive factor(s) • Prenatal use of SSRIs Outcome(s) • Clinical diagnosis of ASD • Hazard ratio
Brown (2017) Country: Canada	Association Between Serotonergic Antidepressant Use During Pregnancy and Autism Spectrum Disorder in Children	Study type • Retrospective cohort study Predictive factor(s) • Prenatal use of SSRIs Outcome(s) • Clinical diagnosis of ASD • Hazard ratio
Durkin (2008) Country: US	Advanced parental age and the risk of autism spectrum disorder.	Study type • Retrospective cohort study Predictive factor(s) • Small for gestational age Birthweight for gestational age >2 SDs below the mean birthweight at a given gestational age for each gender based on all 1994 US births Outcome(s) • Clinical diagnosis of ASD • Odds ratio
Elberling (2016) Country: Denmark	Psychiatric disorders in Danish children aged 5-7 years: A general population study of prevalence	Study type • Cross-sectional study

Author (year)	Title	Study characteristics
	and risk factors from the Copenhagen Child Cohort (CCC 2000)	Predictive factor(s) • ADHD Outcome(s) • Clinical diagnosis of ASD • Odds ratio
Ghirardi (2017) Country: Sweden	The familial co-aggregation of ASD and ADHD: a register-based cohort study	Study type • Cross-sectional study ASD was diagnosed according to International Classification of Diseases, Ninth Revision (ICD-9; 1987–1996) and ICD-10 (1997–2013). Predictive factor(s) • ADHD A recorded diagnosis of ADHD in the National Patient Register (NPR) Outcome(s) • Clinical diagnosis of ASD • Odds ratio
Hvidtjørn (2011) Country: Denmark	Risk of autism spectrum disorders in children born after assisted conception: a population-based follow-up study	Study type • Retrospective cohort study Predictive factor(s) • Fertility treatment Assisted conception was defined as IVF with or without intracytoplasmic sperm injection (ICSI) and ovulation induction (OI) with or without subsequent insemination Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Subgroup analyses • IVF • Ovulation induction
Hviid (2013) Country: Denmark	Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism	Study type • Retrospective cohort study Predictive factor(s) • Prenatal use of SSRIs Prescriptions that were filled during the period from 2 years before the beginning of the pregnancy until delivery. Outcome(s) • Clinical diagnosis of ASD • Risk ratio International Classification of Diseases, 10th Revision (ICD-10) code F84.0.

Author (year)	Title	Study characteristics
Joseph (2017) Country: US	Extremely low gestational age and very low birthweight for gestational age are risk factors for autism spectrum disorder in a large cohort study of 10-year-old children born at 23-27 weeks' gestation.	Study type • Prospective cohort study Predictive factor(s) • Small for gestational age SGA was defined by a birthweight Z-score <-2 SD the median birthweight in reference samples that excluded pregnancies delivered for preeclampsia or foetal indications Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Subgroup analyses • Learning (intellectual) disability Learning (intellectual) disability was defined as an IQ<70
Kissin (2015) Country: US	Association of assisted reproductive technology (ART) treatment and parental infertility diagnosis with autism in ART-conceived children.	Study type • Retrospective cohort study Predictive factor(s) • Fertility treatment Assisted reproductive technology (ART) including: Intracytoplasmic sperm injection (ICSI) Conventional in vitro fertilization (IVF) Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Subgroup analyses • Learning (intellectual) disability
Kuzniewicz (2014) Country: US	Prevalence and neonatal factors associated with autism spectrum disorders in preterm infants.	Study type • Retrospective cohort study Predictive factor(s) • Small for gestational age Small for gestational age was determined by plotting the infant's weight and gestational age on the Fenton curves, using <5th percentile as a cut-off Outcome(s) • Clinical diagnosis of ASD • Hazard ratio
Malm (2016) Country: Finland	Gestational Exposure to Selective Serotonin Reuptake Inhibitors and Offspring Psychiatric Disorders: A National Register-Based Study	Study type • Retrospective cohort study Predictive factor(s) • Prenatal use of SSRIs SSRI exposed (n= 15,729): mothers had one or more purchases of SSRIs (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram)

Author (year)	Title	Study characteristics
		during the period from 30 days before pregnancy until the end of pregnancy. Outcome(s) • Clinical diagnosis of ASD • Hazard ratio
McCoy (2014) Country: Sweden	Mediators of the association between parental severe mental illness and offspring neurodevelopmental problems	Study type • Retrospective cohort study Predictive factor(s) • Small for gestational age Definition was not provided Outcome(s) • Clinical diagnosis of ASD • Hazard ratio
Miodovnik (2015) Country: US	Timing of the Diagnosis of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder.	Study type • Cross-sectional study Predictive factor(s) • ADHD Outcome(s) • Clinical diagnosis of ASD • Odds ratio
Moore (2012) Country: US	Autism risk in small- and large-for-gestational-age infants	Study type • Retrospective cohort study Predictive factor(s) • Small for gestational age Outcome(s) • Clinical diagnosis of ASD • Odds ratio
Pinborg (2004) Country: Denmark	Neurological sequelae in twins born after assisted conception: controlled national cohort study.	Study type • Retrospective cohort study Predictive factor(s) • Fertility treatment Outcome(s) • Clinical diagnosis of ASD • Risk ratio
Rai (2017) Country: Stockholm	Antidepressants during pregnancy and autism in offspring: population based cohort study.	Study type • Retrospective cohort study Predictive factor(s) • Prenatal use of SSRIs

Author (year)	Title	Study characteristics
		Outcome(s) • Clinical diagnosis of ASD Codes: ICD-9:299, ICD-10:F84, or DSM-IV: 299 • Odds ratio
Russell (2014) Country: UK	Prevalence of Parent-Reported ASD and ADHD in the UK: Findings from the Millennium Cohort Study	Study type • Cross-sectional study Predictive factor(s) • ADHD Outcome(s) • Clinical diagnosis of ASD • Odds ratio
Sandin (2013) Country: Sweden	Autism and mental retardation among offspring born after in vitro fertilization.	Study type • Retrospective cohort study Predictive factor(s) • Fertility treatment In vitro fertilization (IVF) classified as: (1) IVF without intracytoplasmic sperm injection (ICSI) with fresh embryo transfer (2) IVF without ICSI with frozen embryo transfer (3) ICSI using ejaculated sperm with fresh embryos (4) ICSI with ejaculated sperm and frozen embryos (5) ICSI with surgically extracted sperm and fresh embryos (6) ICSI with surgically extracted sperm and frozen embryos (risk ratio was not estimable because there were too few cases) Outcome(s) • Clinical diagnosis of ASD • Hazard ratio
Sorensen (2013) Country: Denmark	Antidepressant exposure in pregnancy and risk of autism spectrum disorders	Study type • Retrospective cohort study Predictive factor(s) • Prenatal use of SSRIs Exposure defined as 30 days before conception to the day of birth and included all antidepressant prescriptions filled from January 1, 1996 to December 31, 2006. Outcome(s) • Clinical diagnosis of ASD • Hazard ratio
Sujan (2017) Country: Sweden	Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum	Study type • Retrospective cohort study Predictive factor(s) • Prenatal use of SSRIs Outcome(s) • Clinical diagnosis of ASD

Author (year)	Title	Study characteristics
	Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring	• Hazard ratio
Viktorin (2017) Country: Sweden	Autism risk following antidepressant medication during pregnancy	Study type • Retrospective cohort study Predictive factor(s) • Prenatal use of SSRIs Outcome(s) • Clinical diagnosis of ASD • Risk ratio

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables and appendix G for Forest plots.

Economic evidence

No health economics work was planned for this guideline update, as it was agreed that any recommendations made were highly unlikely to result in a substantial resource impact.

Evidence statements

Small for gestational age

Birth weight for gestational age >2 SDs below the mean

- Very low-quality evidence from 1 retrospective cohort containing 185,164 children (8 years old) could not detect a difference in numbers of clinical diagnoses of ASD between children with a birth weight for gestational age >2 SDs below the mean compared to children with a birth weight for gestational age within 1 SD of the mean.
- Moderate-quality evidence from 1 retrospective cohort containing 866,272 children (younger than 18 years old) found that more children with a birth weight for a given gestational age >2 SDs below the average had a clinical diagnosis of ASD compared to children not being born small for gestational age.

Birth weight for gestational age Z-score <-2

- Moderate-quality evidence from 1 prospective cohort containing 737 children (10 years old) found that more children with a birth weight for gestational age Z-score <-2 had a clinical diagnosis of ASD (reference category was not reported).

Birth weight for gestational age <5th percentile

- Moderate-quality of evidence from 1 retrospective cohort containing 185,506 children (age was not reported) could not detect a difference in numbers of clinical diagnoses of ASD in children with birth weight for gestational age <5th percentile (reference category was not reported).
- Moderate-quality of evidence from 1 retrospective cohort containing 4,692,129 children (4 years and older) could not detect a difference in numbers of clinical diagnoses of ASD in

children with birth weight for gestational age <5th percentile compared to children with birth weight percentile >10 to <90.

Birth weight for gestational age 5 to 10th percentile

- Moderate-quality of evidence from 1 retrospective cohort containing 4,711,838 children (4 years and older) could not detect a difference in numbers of clinical diagnoses of ASD in children with birth weight for gestational age 5 to 10th percentile compared to children with birth weight percentile >10 to <90.

Prenatal use of selective serotonin reuptake inhibitors (SSRIs)

SSRIs used during pregnancy

- Low-quality evidence from 1 retrospective cohort containing 35,618 children (4 to 10 years old) could not detect a difference in numbers of clinical diagnoses of ASD between children born to mothers using SSRIs during pregnancy compared to children born to mothers without a prescription of serotonergic antidepressants during pregnancy.
- High-quality evidence from 1 retrospective cohort containing 16,997 children (10 years or younger) found that, in a sub-analysis of a cohort restricted to women with a documented diagnosis of a mood or anxiety disorder within 2 years previous to conception, more children born to mothers using SSRIs or selective norepinephrine reuptake inhibitors during pregnancy had a diagnosis of ASD compared to children born to mothers without a prescription of serotonergic antidepressants during pregnancy.
- Low-quality evidence from 1 retrospective cohort containing 626,875 children (10 years or younger) could not detect a difference in numbers of clinical diagnoses of ASD between children born to mothers using SSRIs during pregnancy compared to children born to mothers not using SSRIs during pregnancy.
- Low-quality evidence from 1 retrospective cohort containing 27,842 children (10 years or younger) could not detect a difference in numbers of clinical diagnoses of ASD between children born to mothers using SSRIs during pregnancy compared to children born to mothers not using SSRIs during pregnancy in both subgroup analyses: mothers with previous psychiatric diagnoses (n=24,360) or mothers with previous diagnosis of depression (n=3,482).
- Moderate-quality evidence from 1 retrospective cohort containing 15,035 children (4 to 7 years old) found that more children born to mothers using SSRIs during pregnancy had a diagnosis of ASD compared to children born to mothers with a psychiatric disorder not using antidepressants during pregnancy.
- Moderate-quality evidence from 1 retrospective cohort containing 15,035 children (4 to 7 years old) found that more children born to mothers using SSRIs during pregnancy had a diagnosis of ASD without learning (intellectual) disability compared to children born to mothers with a psychiatric disorder not using antidepressants during pregnancy.
- High-quality evidence from 3 retrospective cohorts containing 877,235 children (younger than 14 years old) found that more children born to mothers using SSRIs during pregnancy had a diagnosis of ASD compared to children born to mothers not using antidepressants during pregnancy.
- Low-quality evidence from 1 retrospective cohort containing 5,799 children (younger than 14 years old) could not detect a difference in numbers of clinical diagnoses of ASD between children born to mothers using SSRIs during pregnancy compared to children born to mothers not using SSRIs during pregnancy in an analysis restricted to mothers with a hospital-diagnosed affective disorder.
- Low-quality evidence from 1 retrospective cohort containing 25,380 children (younger than 14 years old) could not detect a difference in numbers of clinical diagnoses of ASD

between children born to mothers using SSRIs during pregnancy compared to children born to mothers with psychiatric disorder but no antidepressant use.

SSRIs used during first trimester

- Low-quality evidence from 1 retrospective cohort containing 626,875 children (10 years or younger) could not detect a difference in numbers of clinical diagnoses of ASD between children born to mothers using SSRIs during first trimester of pregnancy compared to children born to mothers not using SSRIs during pregnancy.
- High-quality evidence from 2 retrospective cohorts containing 1,580,210 children (younger than 14 years old) found that more children born to mothers using SSRIs during first trimester of pregnancy had a diagnosis of ASD compared to children born to mothers not using antidepressants during pregnancy.
- Low-quality evidence from 1 retrospective cohort containing 654,288 children (10 years or younger) could not detect a difference in numbers of clinical diagnoses of ASD between children born to mothers using SSRIs during first trimester of pregnancy compared to children born to mothers not using SSRIs during pregnancy in an analysis restricted to mothers with a hospital-diagnosed affective disorder.

SSRIs used during second and/or third trimester

- Low-quality evidence from 3 retrospective cohorts containing 852,957 children (younger than 14 years old) could not detect a difference in numbers of clinical diagnoses of ASD between children born to mothers using SSRIs during second and/or third trimester of pregnancy compared to children born to mothers not using antidepressants during pregnancy.

Fertility treatment

Assisted conception including in vitro fertilisation (IVF) and ovulation induction (OI)

- Moderate-quality evidence from 1 retrospective cohort containing 588,967 children (age was not reported) could not detect a difference in numbers of clinical diagnoses of ASD between children born after assisted conception including IVF and OI compared to children born after natural conception.

IVF with or without intracytoplasmic sperm injection (ICSI)

- Low-quality evidence from 2 retrospective cohorts containing 3,111,944 children (age was not reported) could not detect a difference in numbers of clinical diagnoses of ASD between children born after IVF with or without ICSI compared to children born after natural conception.

IVF and ICSI

- Moderate-quality evidence from 1 retrospective cohort containing 570,819 children (age was not reported) could not detect a difference in numbers of clinical diagnoses of ASD between children born after IVF and ICSI compared to children born after natural conception.
- Very low-quality evidence from 1 retrospective cohort containing 13,632 twin children (2 to 7 years old) could not detect a difference in numbers of clinical diagnoses of ASD between children born after IVF and ICSI compared to children born after natural conception.

Different procedures of fertility treatments

- Low-quality evidence from 1 retrospective cohort containing 2,541,125 children (age was not reported) could not detect a difference in numbers of clinical diagnoses of ASD between children born after natural conception compared to children born after the following procedures:

- IVF without ICSI, fresh embryo transfer
- IVF without ICSI, frozen embryo transfer
- ICSI using ejaculated sperm with fresh embryos
- ICSI with ejaculated sperm and frozen embryos
- Spontaneously conception with hormone treatment as the only fertility treatment

ICSI with surgical extracted sperm and fresh embryos

- Moderate-quality evidence from 1 retrospective cohort containing 2,510,794 children (age was not reported) found that more children born after ICSI with surgical extracted sperm and fresh embryos had a diagnosis of ASD compared to children born after natural conception.

OI or intrauterine insemination (IUI)

- Moderate-quality evidence from 1 retrospective cohort containing 573,976 children (age was not reported) could not detect a difference in numbers of clinical diagnoses of ASD between children born after OI/IUI compared to children born after natural conception.
- Moderate-quality evidence from 1 retrospective cohort containing 573,976 children (age was not reported) could not detect a difference in numbers of clinical diagnoses of ASD between children born after OI compared to children born after natural conception.

ICSI

- Moderate-quality evidence from 1 retrospective cohort containing 35,481 children (5 years and younger) could not detect a difference in numbers of clinical diagnoses of ASD between children born after ICSI compared to children born after IVF without ICSI.

Neurodevelopmental disorders

Attention deficit hyperactivity disorder (ADHD)

- Moderate-quality evidence from 3 cross-sectional studies containing 1,914,808 children (9 years and younger) found that more children with ADHD had a diagnosis of ASD compared to children without ADHD.

Down's syndrome

- Very low-quality evidence from 1 case-control study containing 25,606 children and adults found that more people with Down's syndrome had a clinical diagnosis of ASD compared to people without Down's syndrome.

Learning (intellectual) disability

- Moderate-quality evidence from 1 prospective cohort containing 737 children (10 years old) found that more children with learning (intellectual) disability had a clinical diagnosis of ASD compared to children without learning (intellectual) disability.

ADHD before ASD

- Low-quality evidence from 1 cross-sectional study containing 1,059 children (2 to 17 years old) found that more children had a clinical diagnosis of ASD delayed until after 6 years of age if they were diagnosed with ADHD before ASD compared to children who were only diagnosed with ASD.

ADHD same/after ASD

- Very low-quality evidence from cross-sectional study containing 1,138 children (2 to 17 years old) could not detect a difference in numbers of clinical diagnoses of ASD delayed until after 6 years of age between children diagnosed with ADHD and ASD at the same time compared to children who were diagnosed with only ASD.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that for all the factors included in the review, the critical outcome was whether the presence of those factors increased the likelihood of a diagnosis of ASD. For small for gestational age, maternal use of SSRIs during pregnancy and use of fertility treatments the committee agreed cohort studies would be the most appropriate study design, as the focus is on the impact of these maternal and neonatal factors on long-term rates of ASD diagnosis. For neurodevelopmental disorders, they agreed that cross-sectional studies would also be an appropriate study design, as the focus here is less on the time course of which diagnoses comes first, and simply on how often the two diagnosis co-exist.

The quality of the evidence

There was considerable variety in the quality of the evidence available, with ratings ranging from very low to high. The main reasons for downgrading were imprecision in effect estimates and risk of bias, in particular resulting from not appropriately adjusting for relevant confounding variables. The committee agreed that unadjusted odds ratios were an acceptable outcome measure for ADHD as a factor that increased the likelihood of a clinical diagnosis of ASD, because this update was not about causation and it was expected that studies would provide evidence of diagnosis of ADHD and ASD at the same point in time. Therefore, studies on ADHD were not downgraded if they reported unadjusted odds ratios. The committee agreed the effect sizes from the different studies on the association between ADHD and ASD were not clinically meaningfully different from each other (and all demonstrated a substantial increase in ASD rates in people with ADHD) and therefore the evidence was not downgraded for inconsistency as a result of this unexplained heterogeneity.

The committee also highlighted that indirectness was not a problem in the evidence from the meta-analysis of ADHD. One of the studies (Elberling 2016) reported on hyperkinetic disorders according to ICD-10 codes which includes a list of disorders apart from ADHD. However, the committee agreed that the most common hyperkinetic disorder is ADHD and they were confident that this was the case in Elberling 2016. Another study in the meta-analysis (Ghirardi 2017) reported that diagnosis of ASD was recorded with ICD-9 or ICD-10 codes which included Rett's syndrome. However, the committee agreed that Rett's syndrome is a rare disorder and they did not expect the numbers of such cases to make a meaningful difference to the results.

Benefits and harms

The committee agreed that ADHD was the most important factor identified that increased the likelihood of a clinical diagnosis of ASD, with the included studies showing a clear association between ADHD and ASD. The committee also highlighted that in clinical practice, ADHD is often already considered when diagnosing ASD (and vice versa). Therefore, the committee agreed to include ADHD to the list of factors that could assist in the decision to refer for a formal ASD diagnostic assessment and in the decision to carry out an ASD diagnostic assessment. The committee suggested that ADHD be added to the current list of factors after learning (intellectual) disability as both were considered neurodevelopmental disorders.

The committee noted that this recommendation change also interacted with the decision made to refer to the new DSM-5 criteria for ASD diagnosis. Comorbid diagnosis of ADHD and ASD was not allowed in the previous DSM-IV version, but is allowed in the DSM-5. The committee discussed a list of benefits from adding ADHD as a factor associated with an

increased prevalence of ASD, such as the consideration of a joint assessment of both ADHD and ASD in children who show signs and symptoms that may be attributable to either diagnosis. Another benefit could be the early diagnosis of ASD in children with signs and symptoms of ADHD. Otherwise, having only an ADHD diagnosis without assessing for ASD might lead to diagnostic overshadowing of ADHD over ASD. Having an early diagnosis of ASD allows families to access educational and financial support, to adjust their life and coping mechanisms; to seek support groups for children and their family.

The committee agreed that there was insufficient evidence on the rest of the factors reviewed in this update for them to be added to the list of factors associated with an increased prevalence of autism. The committee agreed that the evidence for small for gestational age was mixed with some studies finding that more children identified as small for gestational age were diagnosed with ASD compared to other studies which were unable to detect a difference. Results from Joseph (2017) showed a large effect for the association between small for gestational age and ASD diagnosis but this was a small study and the population was limited to very preterm children (children born between 23 and 27 weeks gestation), which was considered to be an unusual cohort of children. The committee also agreed that gestational age less than 35 weeks was a considerably more important association than being small for gestational age, and this was already a factor associated with an increased prevalence of ASD in the recommendation.

The committee highlighted that whilst there appeared to be an association between SSRI use and an the increased number of clinical diagnoses of ASD when mothers taking SSRIs were compared to all mothers not taking SSRIs, this weakened substantially when studies compared mothers with psychiatric or mood disorders using SSRI treatment to mothers with such disorders not using SSRI treatment, which was agreed to be the most relevant comparison. Therefore, the committee agreed there was no robust evidence that SSRI use increased rates of ASD, above the effects known from 'parental schizophrenia-like psychosis or affective disorder', a factor already included in the recommendation.

The evidence for fertility treatments only showed an effect on clinical diagnosis of ASD for the least common fertility treatment procedure (ICSI with surgical extracted sperm and fresh embryos). The evidence for this procedure was from a smaller sample size compared to the rest of procedures (n=628), with only 8 cases of ASD. The committee also agreed that this procedure is considered to be the least common fertility treatment, and agreed there was insufficient evidence to add it to the list of factors.

Cost effectiveness and resource use

The committee agreed that the addition of ADHD as a relevant factor to consider was unlikely to lead to a substantial resource impact, as it reflects current clinical practice which is already changing to reflect the known interaction between ASD and ADHD.

Other factors the committee took into account

The committee agreed there was no evidence identified to suggest that Down's syndrome and learning (intellectual) disability should be removed from the list of factors, and therefore these were retained in the list of factors that increased the likelihood of a clinical diagnosis of ASD.

The rest of the factors included in the existing recommendations were not reviewed as part of this update and therefore no further changes were made to the list.

Sex, language and cultural background were discussed by the committee as part of the equality impact assessment. The committee agreed that ASD and ADHD are both often underdiagnosed in females. The addition of ADHD to the list was not expected to either improve or worsen the potential for under-diagnosis of ASD in females. The committee also

agreed that language and familiarity with the health system might have an effect on the time of ASD diagnosis and that there might be an ASD diagnosis stigma from some cultural backgrounds but the addition of ADHD to the recommendation was not expected to modify these effects.

The committee discussed that registry-based studies from the UK were not available for most of the factors except for Down's syndrome. However, the committee agreed that they did not expect to find differences between studies from the UK and other European or American countries. Therefore, additional UK registry-based studies would not add more evidence to that currently available and a research recommendation was not considered necessary.

Appendices

Appendix A – Review protocols

Review protocol for factors and neurodevelopmental disorders with an increased likelihood of a diagnosis of ASD

Field	Content
Review questions	Do the following risk factors increase the likelihood of a diagnosis of ASD and assist in the decision to refer for a formal ASD diagnostic assessment? • Small for gestational age • Prenatal use of SSRIs • Fertility treatments Do neurodevelopmental disorders (such as ADHD and learning [intellectual] disability) increase the likelihood of a diagnosis of ASD and assist in the decision to refer for a formal ASD diagnostic assessment?
Type of review questions	Association
Objective of the review	To update the list of factors for ASD referred to in the current NICE diagnosis of ASD guideline.

Eligibility criteria – population	Children and young people from birth up to their 19th birthday without a diagnosis of ASD at the time of factors evaluation.
Eligibility criteria – factors	• Small for gestational age • Prenatal use of SSRIs • Fertility treatments • Diagnosis of ADHD • Learning (intellectual) disability
Measures	• Risk ratios • Odds ratios • Hazard ratios
Outcomes	Clinical diagnosis of ASD
Eligibility criteria – study design	• Prospective and retrospective cohort studies • Systematic reviews of observational studies • Case-control studies (if <5 cohort studies are found per factor) • Cross-sectional studies
Other inclusion/exclusion criteria	Other inclusion criteria: • English language

	• Published studies only Other exclusion criteria • Studies without extractable data • Studies only reporting on Rett disorder
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups • Children with a learning (intellectual) disability • Duration of ADHD, age, and use of medications for ADHD • Looked-after children and young people
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	*See Appendix B*

Information sources – databases and dates	See Appendix C **Sources searched** Clinical searches: • Cochrane Central Register of Controlled Trials (Wiley) • Cochrane Database of Systematic Reviews (Wiley) • Database of Abstracts of Reviews of Effects (Wiley) *(legacy records)* • EMBASE (Ovid) • Health Technology Assessment Database (Wiley) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) • PsycINFO (Ovid) • PubMed (NLM) Economic searches – • EconLit (Ovid) • EMBASE (Ovid) • Health Technology Assessment Database (Wiley) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) • NHS Economic Evaluation Database (Wiley) *(legacy records)* Economic evaluations and quality of life filters were appended to the population search terms in EMBASE, MEDLINE and MEDLINE In-Process to identify relevant evidence.

	Supplementary search techniques • None identified **Limits** • Studies reported in English • Observational study design filters applied • Animal studies excluded from the search results • Conference abstracts excluded from the search results • Date limit from October 2010

Identify if an update	Update of 2011 ASD in under 19s: recognition, referral and diagnosis guideline question:
	
	In children with suspected autism (based on signs and symptoms) what information assists in the decision to refer for a formal autism diagnostic assessment?
	
	• What information about the child and family increases the likelihood of a diagnosis of autism and would assist in the decision to refer for a formal autism diagnostic assessment?
	  ○ risk factors (part 1)
	  ○ conditions with an increased risk of autism (part 2)

Author contacts	Guideline update

Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B
Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B

Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Tessa Lewis in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	N/A

Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstracts of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstracts can be stopped, assuming a defined threshold for the proportion of relevant papers which it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstracts (or 1,000 records, if that is a greater number) were always screened.
- After this point, the number of included studies was recorded after every 1,000 records were screened. If, assuming studies were to be found in the remainder of the dataset at the same rate as in that 1,000 records (for example, if 5 includes were found, every subsequent 1,000 records would contain 5 includes), it was estimated that at least 95% of the includable studies in the database had been identified, then the screening was stopped.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search. If a meaningful number of studies were found that had been eliminated by the priority screening feature, the full original database was then screened.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from surveillance review or early in the database search), they were used as the main source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 1. When systematic reviews were used as a source of primary data, any unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 1: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis and evaluation of risk of bias. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

Association studies

In this guideline, association studies are defined those reporting data showing an association of a predictor (either a single variable or a group of variables) and an outcome variable, where the data are not reported in terms of outcome classification (i.e. diagnostic/prognostic accuracy). Data were reported as hazard ratios (if measured over time), or odds ratios or risk

ratios (if measured at a specific time-point). Data reported in terms of model fit or predictive accuracy were not assessed using this method. Odds ratios were calculated when studies did not report any of the measures of interest (hazard ratios, risk ratios or odds ratios) but reported extractable data for the calculation of odds ratios.

Quality assessment

Individual cohort and case-control studies were quality assessed using the CASP cohort study and case-control checklists, respectively. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Individual cross sectional studies were quality assessed using the Joanna Briggs Institute critical appraisal checklist for analytical cross sectional studies (2016), which contains 8 questions covering: inclusion criteria, description of the sample, measures of exposure, measures of outcomes, confounding factors, and statistical analysis. Each individual study was classified into one of the following groups:

- Low risk of bias – Evidence of non-serious bias in zero or one domain.
- Moderate risk of bias – Evidence of non-serious bias in two domains only, or serious bias in one domain only.
- High risk of bias – Evidence of bias in at least three domains, or of serious bias in at least two domains.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, predictors and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, predictors and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, predictors and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the population, predictors and/or outcomes.

Methods for combining predictive modelling evidence

Where appropriate and from univariate analyses, hazard ratios were pooled using the inverse-variance method, and odds ratios or risk ratios were pooled using the Mantel-Haenszel method. Adjusted odds ratios from multivariate models were only pooled if the same set of predictor variables were used across multiple studies and if the same thresholds to measure predictors were used across studies.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are

presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, predictors or outcomes was identified by the reviewer in advance of data analysis. This decision would need to be made and recorded before any data analysis is undertaken.
- The presence of significant statistical heterogeneity, defined as $I^2 \geq 50\%$.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences

The Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience.

The Guideline Committee agreed to use a MID of 10% as a starting point for discussion of association between predictors and outcomes. The same parameter was used as a starting point to assess imprecision.

Modified GRADE for predictive evidence

GRADE has not been developed for use with predictive studies; therefore a modified approach was applied using the GRADE framework. Data from cohort studies was initially rated as high quality, data from case-control studies as low quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. Cross-sectional studies were only included for evidence on neurodevelopmental disorders, and were initially rated as high quality because it was expected that studies reporting on ASD and neurodevelopmental disorders were likely to diagnose both conditions at the same time, and this study design was felt to be appropriate to address the review question, as it focuses only on association rather than causation.

Table 2: Rationale for downgrading quality of evidence for predictive modelling questions

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias. In addition, unadjusted odds ratio outcomes from univariate analyses were downgraded one level, in addition to any downgrading for risk of bias in individual studies. Adjusted odds ratios from multivariate analyses were not similarly downgraded.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the association strength demonstrated across studies (heterogeneity). This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts or protocols without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Appendix C – Literature search strategies

Search summary

The search strategies were based on the population strategy used in CG128, *(appendix F, page 34).* The final cut-off date for searches in the original guideline was 11 *October 2010 (page 41).* A date limit was added to the new strategies to reflect this.

The clinical searches were conducted in July 2017.

Sources searched for this guideline are shown below.

Databases	Date searched	Version/files
Cochrane Central Register of Controlled Trials (CENTRAL)	06/07/17	Issue 6 of 12, June 2017
Cochrane Database of Systematic Reviews (CDSR)	06/07/17	Issue 7 of 12, July 2017
Database of Abstracts of Reviews of Effect (DARE)	06/07/17	Issue 2 of 4, April 2015
Embase (Ovid)	06/07/17	1980 to 2017 Week 27
Health Technology Assessment Database (HTA)	06/07/17	Issue 4 of 4, October 2016
MEDLINE (Ovid)	06/07/17	1946 to June Week 5 2017
MEDLINE In-Process (Ovid)	06/07/17	June 29, 2017
PsycINFO (Ovid)	06/07/17	2002 to June Week 4 2017
PubMed	06/07/17	n/a

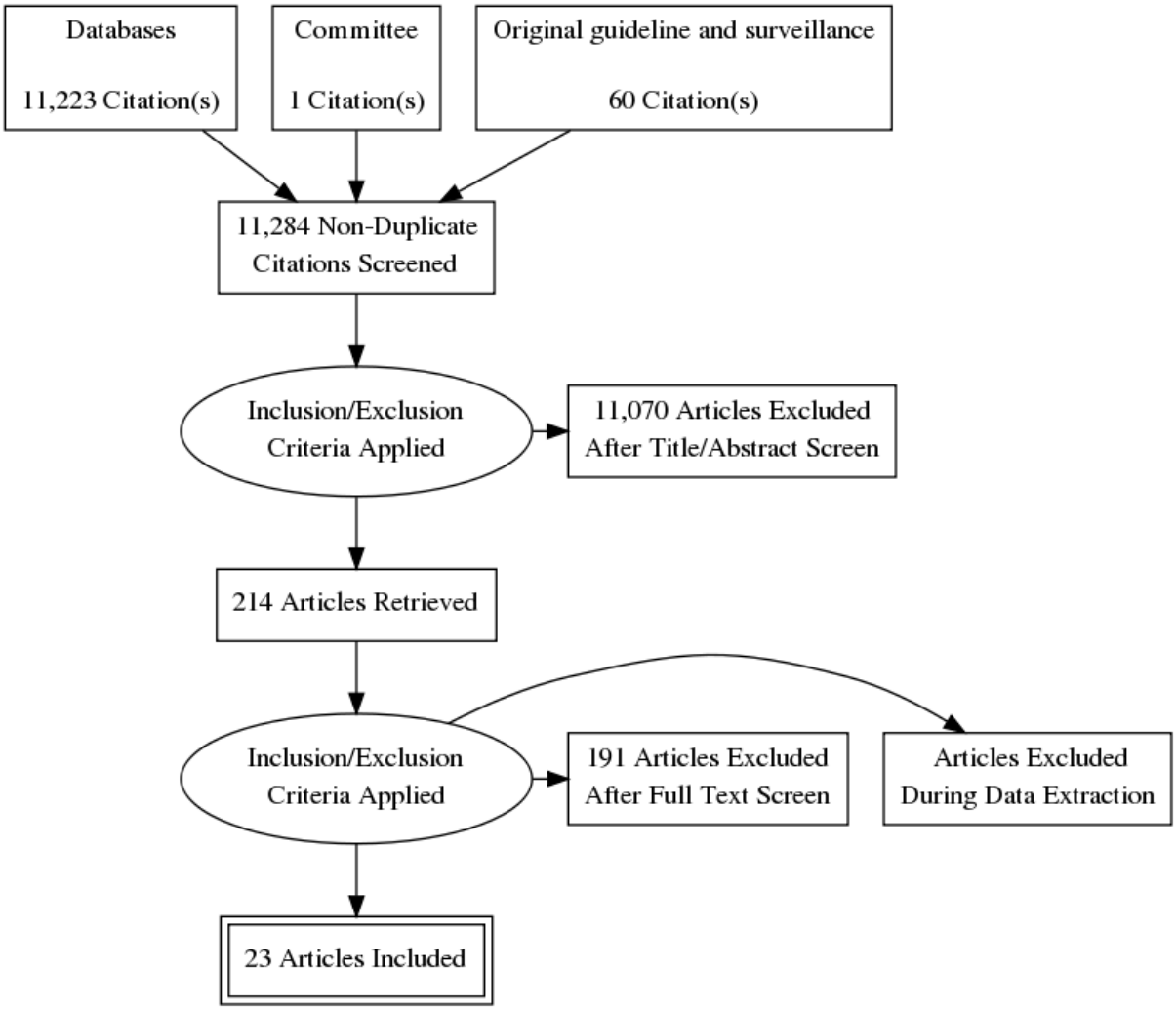
Clinical search strategy (Medline)

The MEDLINE search strategy is presented below. It was translated for use in all other databases.

Database: Medline
1 Autistic Disorder/
2 Autism Spectrum Disorder/
3 asperger syndrome/
4 (autistic or autism or kanner* or asperger*).tw.
5 child development disorders, pervasive/
6 ((pervasive* or child* or young* or youth*) adj2 (development* or neurodevelopmental*) adj2 disorder*).tw.
7 (ASD or PDD or PDD-NOS).tw.
8 or/1-7
9 (2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).ed. (6224514)
10 8 and 9
11 Observational Studies as Topic/
12 Observational Study/
13 Epidemiologic Studies/
14 exp Case-Control Studies/
15 exp Cohort Studies/
16 Cross-Sectional Studies/
17 Interrupted Time Series Analysis/
18 case control$.tw.
19 (cohort adj (study or studies)).tw.
20 cohort analy$.tw.

Database: Medline	
21	(follow up adj (study or studies)).tw.
22	(observational adj (study or studies)).tw.
23	longitudinal.tw.
24	prospective.tw.
25	retrospective.tw.
26	cross sectional.tw.
27	or/11-26
28	exp Risk/
29	(Risk* adj1 (factor* or assess*)).tw.
30	Logistic* model*.tw.
31	Protective* factor*.tw.
32	(association* or regression*).tw.
33	or/28-32
34	27 or 33
35	10 and 34
36	Comment/ or Letter/ or Editorial/ or Historical article/ or (conference abstract or conference paper or "conference review" or letter or editorial or case report).pt.
37	35 not 36
38	Animals/ not Humans/
39	37 not 38
40	limit 39 to english language

Appendix D – Clinical evidence study selection



Appendix E – Clinical evidence tables

Author (year)	Title	Study details	Quality assessment
Alexander (2016)	Morbidity and medication in a large population of individuals with Down syndrome compared to the general population	Study type • Case-control study Study details • Study location UK • Study setting Clinical Practice Research Datalink (CPRD) • Study dates January 2004 to December 2013 • Duration of follow-up Down's syndrome: 29,920 person-years Controls (3 matched controls per case): 89,739 person-years • Sources of funding Roche Products Limited Inclusion criteria • At least one record for Down's syndrome from date of patient's registration until 31 December 2013 Exclusion criteria • Females with a first record of Down's syndrome after pregnancy code Sample characteristics • Sample size Down's syndrome N=6,430 Controls N=19,176 • %female Down's syndrome 46.8% Controls 46.8%	Did the study address a clearly focused issue? • Yes Did the authors use an appropriate method to answer their question? • Yes Were the cases recruited in an acceptable way? • Yes Were the controls selected in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Unclear ICD codes for autism were not reported. Those might have included Rett's syndrome. Have the authors taken account of potential confounding factors in the design and/or in their analysis? • No Overall risk of bias • High

Author (year)	Title	Study details	Quality assessment
		Predictive factor(s) • Down's syndrome Outcome(s) • Clinical diagnosis of ASD	Directness • Partially directly applicable ICD codes for autism were not reported. Those might have included Rett's syndrome. The sample included children and adults.
Bay (2013)	Fertility treatment and risk of childhood and adolescent mental disorders: register based cohort study.	Study type • Prospective cohort study Study details • Study location Denmark • Study setting Nationwide register • Study dates January 1995 to December 2003 • Duration of follow-up From day of birth to the earliest of either diagnosis, death, emigration, or end of follow-up on February 2012 • Sources of funding This study was funded by a fellowship granted by Aarhus University and partially funded by the Augustinus Foundation, Denmark Inclusion criteria • Children of mothers above 20 years Exclusion criteria • None reported Sample characteristics • Sample size IVF/ICSI: n=14,991 OI/IUI: n=18,148 Spontaneous conception: n=555,828	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough?

Author (year)	Title	Study details	Quality assessment
		• %female IVF/ICSI: 47.4% OI/IUI: 48.3% Spontaneous conception: 48.7% • Mean age (SD) Age at the end of follow-up 8 to 12 years old IVF/ICSI: 61.5% OI/IUI: 59.9% Spontaneous conception: 50.2% 13 to 18 years old IVF/ICSI: 34.1% OI/IUI: 35.9% Spontaneous conception: 44.4% Predictive factor(s) • Fertility treatment Fertility treatment was divided into two groups: in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) and hormone treatments for induced ovulation/intrauterine insemination (OI/IUI). Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Confounding factors - multivariate analysis • Maternal age • Parity • Educational level • Smoking in pregnancy • Maternal psychiatric history • Birth year • Child's sex • Multiplicity	• Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable
Boukhris (2016)	Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children	Study type • Retrospective cohort study Study details • Study location Canada	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way?

Author (year)	Title	Study details	Quality assessment
		• Study setting Register-based study • Study dates Data analysis was conducted from October 2014 to June 2015 • Duration of follow-up 1 year before the first day of gestation, during pregnancy, and until December 31, 2009, for mothers and their children. • Sources of funding The study was supported by the Canadian Institutes of Health Research and the Quebec Training Network in Perinatal Research Inclusion criteria • Full-term (≥37 weeks' gestation) singleton infants Exclusion criteria • None reported Sample characteristics • Sample size N=145,456 • %female 49% • Mean age (SD) Mean (SD) age at first ASD diagnosis: 4.6 years (2.2; median 4.0 years) Mean (SD) age of children at the end of follow-up: 6.2 years (3.2; median 7.0 years) Predictive factor(s) • Prenatal use of SSRIs Outcome(s) • Clinical diagnosis of ASD • Hazard ratio	• Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Confounding factors - multivariate analysis • Maternal age • High school completed (≥12 years) • Recipient of social assistance • Living alone • Chronic or gestational hypertension • Chronic or gestational diabetes • Maternal psychiatric history • Birth year • Child's sex • SSRIs 1 year before the first day of gestation • Use of SSRIs in the first trimester	
Brown (2017)	Association Between Serotonergic Antidepressant Use During Pregnancy and Autism Spectrum Disorder in Children	Study type • Retrospective cohort study Study details • Study location Canada • Study setting Health administrative data • Study dates April 2002 to March 2010 • Sources of funding Institute for Clinical Evaluative Sciences Inclusion criteria • Singleton children born in Ontario hospitals between April 1, 2002, and March 31, 2010, whose mothers were between the ages of 16 and 50 years and eligible for public drug benefits during pregnancy Exclusion criteria • Children born to non-Ontario residents • Children without a valid health card number	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or

Author (year)	Title	Study details	Quality assessment
		• Children who died before the age 2 years Sample characteristics • Sample size N=35,906 • %female 50% Predictive factor(s) • Prenatal use of SSRIs Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Confounding factors - multivariate analysis • Maternal age • Parity • Child's sex • Gestational age • Neighbourhood income • Rural residence • Medical and psychiatric diagnoses • Health service use before and during pregnancy • Use of other prescribed medications • Prenatal care	analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable
Durkin (2008)	Advanced parental age and the risk of autism spectrum disorder.	Study type • Retrospective cohort study Study details • Study location US • Study setting Centers for Disease Control and Prevention's Autism and	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes

Author (year)	Title	Study details	Quality assessment
		Developmental Disabilities Monitoring Network • Study dates 2002 • Duration of follow-up From birth to 8 years • Sources of funding Centers for Disease Control and Prevention University of Wisconsin Inclusion criteria • None reported Exclusion criteria • None reported Sample characteristics • Sample size N=254,598 • %female ASD cases: 18.2% Comparison group: 48.6% Predictive factor(s) • Small for gestational age Birthweight for gestational age >2 SDs below the mean birthweight at a given gestational age for each gender based on all 1994 US births Outcome(s) • Clinical diagnosis of ASD • Odds ratio Confounding factors - multivariate analysis • Maternal age • Paternal age • Educational level	Was the exposure accurately measured to minimise bias? • Unclear Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • No Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • High Directness • Directly applicable Participants were 8 years old

Author (year)	Title	Study details	Quality assessment
		• Birth order • Child's sex • Child's race/ethnicity • Gestational age	
Elberling (2016)	Psychiatric disorders in Danish children aged 5-7 years: A general population study of prevalence and risk factors from the Copenhagen Child Cohort (CCC 2000)	Study type • Cross-sectional study Study details • Study location Denmark • Study setting Substudy of a cohort of children 5 to 7 years old (Copenhagen child cohort 2000) • Study dates Not reported • Sources of funding Capital Region of Denmark, Health Insurance Foundation, Mrs C. Hermansens Memorial Fund, the Foundation of Butcher Max Wørzner and wife, the Psychiatric Foundation of 1967, the Tryg Foundation, the Augustinus Foundation, the Danish Association for Mental Health. Inclusion criteria • None reported Exclusion criteria • None reported Sample characteristics • Sample size N=1,585 • %female 48.4% • Mean age (SD)	Were the criteria for inclusion in the sample clearly defined? • Yes Were the study subjects and the setting described in detail? • Yes Was the exposure measured in a valid and reliable way? • Yes Were objective, standard criteria used for measurement of the condition? • Yes Were confounding factors identified? • No Were strategies to deal with confounding factors stated? • No Were the outcomes measured in a valid and reliable way? • Yes Was appropriate statistical analysis used?

Author (year)	Title	Study details	Quality assessment
		6.1 years (0.45) Predictive factor(s) • ADHD Outcome(s) • Clinical diagnosis of ASD • Odds ratio	• Unclear Overall risk of bias • High Directness • Partially directly applicable ICD-10 was used to investigate hyperkinetic disorders which includes ADHD as well as other disorders. Therefore, it is not possible to know how many children were diagnosed as having ADHD specifically
Ghirardi (2017)	The familial co-aggregation of ASD and ADHD: a register-based cohort study	Study type • Cross-sectional study ASD was diagnosed according to International Classification of Diseases, Ninth Revision (ICD-9; 1987–1996) and ICD-10 (1997–2013). Study details • Study location Sweden • Study setting Register based • Study dates Not reported • Sources of funding Swedish Research Council and European Union's Horizon 2020 research and innovation programme. Inclusion criteria • Individuals born between 1987 and 2006	Were the criteria for inclusion in the sample clearly defined? • Yes Were the study subjects and the setting described in detail? • No Was the exposure measured in a valid and reliable way? • Yes Were objective, standard criteria used for measurement of the condition? • Not applicable Were confounding factors identified? • No

Author (year)	Title	Study details	Quality assessment
		Exclusion criteria • Children who have died. • Still births • Serious congenital malformations • migrated before their seventh birthday • Biological parents unidentifiable • Adopted away Sample characteristics • Sample size 1,899,654, of which 28,468 (1.5%) had ASD. • %female 0.94% (8734) were female and had ASD. • Mean age (SD) Not reported. Predictive factor(s) • ADHD A recorded diagnosis of ADHD in the National Patient Register (NPR) Outcome(s) • Clinical diagnosis of ASD • Odds ratio	Were strategies to deal with confounding factors stated? • No Were the outcomes measured in a valid and reliable way? • Yes Was appropriate statistical analysis used? • No Overall risk of bias • High Directness • Partially directly applicable ICD code for ASD included Rett's syndrome.
Hvidtjørn (2011)	Risk of autism spectrum disorders in children born after assisted conception: a population-based follow-up study	Study type • Retrospective cohort study Study details • Study location Denmark • Study setting Register based • Study dates Jan 1995 - May 2008	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		• Duration of follow-up 4 - 13 years (median 9 years) • Loss to follow-up Not reported. • Sources of funding The Danish Agency for Science, Technology and Innovation, University of Aarhus and The Elsass Foundation. Further funding was supplied by Sofiefonden, The Health Insurance Foundation, The Augustinus Foundation, Julie von Mullens Foundation, Direktør Jacob Madsen and Hustru Olga Madsens Fond and Aase and Ejnar Danielsen Foundation. Inclusion criteria • Children exposed to IVF Children exposed to IVF were identified through the IVF Register which holds data from all private and public fertility clinics including underlying causes of infertility. Children exposed to OI were identified through the Danish Drug Prescription Register (DDPR) which holds information on all prescription drugs sold at pharmacies in Denmark. Exclusion criteria • Women from ovulation induction group who were in the IVF Register with the same last menstrual period date. Sample characteristics • Sample size 588,967 children to 399,598 mothers aged 20 years or over. • %female Not reported. • Mean age (SD) Mean age of children not reported. Predictive factor(s) • Fertility treatment	• Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • No From section of discussion: "As a number of children were followed for <6 years, some children with ASD may not have been diagnosed before the end of follow-up." Overall risk of bias • Moderate Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		Assisted conception was defined as IVF with or without intracytoplasmic sperm injection (ICSI) and ovulation induction (OI) with or without subsequent insemination. Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Confounding factors - multivariate analysis • Maternal age • Parity • Educational level • Smoking • Multiplicity • Body weight Subgroup analyses • IVF • Ovulation induction	
Hviid (2013)	Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism	Study type • Retrospective cohort study Study details • Study location Denmark • Study setting Register based • Study dates January 1996 - December 2005. • Duration of follow-up Birth until 2010 or until child reached 10 years of age. • Loss to follow-up 387 children were lost to follow-up. • Sources of funding	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		Danish Health and Medicines Authority Inclusion criteria • Live singleton births • Known gestational age. Exclusion criteria • Fragile X syndrome, tuberous X syndrome, tuberous sclerosis, Angelman's syndrome, Down's syndrome, DiGeorge's syndrome, neurofibromatosis, and Prader–Willi syndrome. Sample characteristics • Sample size 626,875 • %female 48.7% • Mean age (SD) Median age at ASD diagnosis was 5.6 years (IQR = 4.1 - 7.5) Predictive factor(s) • Prenatal use of SSRIs Prescriptions that were filled during the period from 2 years before the beginning of the pregnancy until delivery. Outcome(s) • Clinical diagnosis of ASD • Risk ratio International Classification of Diseases, 10th Revision (ICD-10) code F84.0. Confounding factors - multivariate analysis • Maternal age At onset of pregnancy. • Parity • Smoking in pregnancy	• Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Maternal country of origin • Place of residence at the start of pregnancy • Maternal psychiatric history Does not include diagnoses made by a medical specialist in the primary care setting. • Birth year	
Joseph (2017)	Extremely low gestational age and very low birthweight for gestational age are risk factors for autism spectrum disorder in a large cohort study of 10-year-old children born at 23-27 weeks' gestation.	Study type • Prospective cohort study Study details • Study location US • Study dates 2002 to 2004 • Duration of follow-up 10 years • Loss to follow-up 13% lost to follow up 966 children were recruited 840 were assessed for both ASD and learning (intellectual) disability • Sources of funding The study was supported by the National Institute of Neurological Disorders and Stroke, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the Wayne State University Perinatal Initiative. Inclusion criteria • Extremely preterm infants <28 weeks' gestation Exclusion criteria • Children with significant visual and/or motor impairment accompanied by severe learning (intellectual) disability Sample characteristics • Sample size	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough?

Author (year)	Title	Study details	Quality assessment
		N=840 • %female 49% • Mean age (SD) All participants were 10 years old Predictive factor(s) • Small for gestational age SGA was defined by a birthweight Z-score <-2 SD the median birthweight in reference samples that excluded pregnancies delivered for preeclampsia or foetal indications Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Subgroup analyses • Learning (intellectual) disability Learning (intellectual) disability was defined as an IQ<70	• Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable
Kissin (2015)	Association of assisted reproductive technology (ART) treatment and parental infertility diagnosis with autism in ART-conceived children.	Study type • Retrospective cohort study Study details • Study location US • Study setting The study is based on linkages between National ART (assisted reproductive technology) Surveillance System (NASS) data for 1996–2006, California Birth Certificate data for 1997–2006 and California Department of Developmental Services (DDS) Autism Caseload data for 1997–2011. • Study dates All live born ART conceived infants born in 1997–2006 • Duration of follow-up	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		5 years • Sources of funding This research is partially supported by the NIH Director's Pioneer Award program, part of the NIH Roadmap for Medical Research, through grant and the National Institutes of Mental Health award. Inclusion criteria • All live born ART conceived infants born in 1997–2006 in the state of California Exclusion criteria • None reported Sample characteristics • Sample size N=42,383 • %female 49.2% Predictive factor(s) • Fertility treatment Assisted reproductive technology (ART) including: Intracytoplasmic sperm injection (ICSI) Conventional in vitro fertilization (IVF) Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Confounding factors - multivariate analysis • Maternal age • Paternal age • Parity • Birth year	• Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes From methods section: "Since the majority of autism cases are typically diagnosed by age 5 (85.3% in our sample), we allowed 5 years of follow-up for each child in the study." Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Child's sex • Gestational age • Birthweight • Mode of delivery Subgroup analyses • Learning (intellectual) disability	
Kuzniewicz (2014)	Prevalence and neonatal factors associated with autism spectrum disorders in preterm infants.	Study type • Retrospective cohort study Study details • Study location US • Study setting Kaiser Permanente Northern California • Study dates January 2000 to December 2007 • Sources of funding Supported by a grant from the Kaiser Permanente Northern California Community Benefit Program. Inclusion criteria • Infants born alive at a gestational age of ≥24 weeks who survived to discharge Exclusion criteria • Infants with missing data on gestational age • Infants with missing data on sex • Missing maternal age • Infants who transferred out of Keiser Permanente Northern California during their hospitalisation • Children who did not remain in the health plan at 2 years of age	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size N=195,021 • %female With ASD = 0.5% Without ASD = 99.4% Ruled out ASD = 0.1% Predictive factor(s) • Small for gestational age Small for gestational age was determined by plotting the infant's weight and gestational age on the Fenton curves, using <5th percentile as a cut-off. Outcome(s) • Clinical diagnosis of ASD • Hazard ratio	Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable
Malm (2016)	Gestational Exposure to Selective Serotonin Reuptake Inhibitors and Offspring Psychiatric Disorders: A National Register-Based Study	Study type • Retrospective cohort study Study details • Study location Finland • Study setting Register based. • Study dates January 1996 - December 2010. • Duration of follow-up 4 years • Loss to follow-up Not reported. • Sources of funding NIH grant, Sackler Institute for Developmental Psychobiology of Columbia University, Sigrid Juselius Foundation, the Foundation for Pediatric Research in Finland and the Finnish Medical	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors?

Author (year)	Title	Study details	Quality assessment
		Foundation. Inclusion criteria • Live singleton births Exclusion criteria • Diagnosis of depression during the first two years of life if the diagnosis was not recorded at later stages. Sample characteristics • Sample size 845,345 live singleton births • %female • Mean age (SD) Not reported. Children were between 0 to 14 years. Predictive factor(s) • Prenatal use of SSRIs SSRI exposed (n= 15,729): mothers had one or more purchases of SSRIs (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, escitalopram) during the period from 30 days before pregnancy until the end of pregnancy. Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Confounding factors - multivariate analysis • Maternal age • Maternal history of psychiatric diagnoses (excluding depression-related disorders, which were used in defining one comparison group, and substance abuse) • Sex • Preterm birth • Neonatal care unit	• Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Socioeconomic status • entitlement to special reimbursement for chronic disease	
McCoy (2014)	Mediators of the association between parental severe mental illness and offspring neurodevelopmental problems	Study type • Retrospective cohort study Study details • Study location Sweden • Study setting Register based, includes Multi-Generation Register, Medical Birth Registry and National Patient Register. • Study dates Birth between 1992 and 2001. • Duration of follow-up Not reported. • Sources of funding National Institute of Child Health and Development, National Institute of Mental Health, Swedish Council for Working Life and Social Research, the Swedish Research Council (Medicine), and the Swedish Society of Medicine. Inclusion criteria • Individuals diagnosed before the age of 10. Exclusion criteria • Children who have died. • Congenital malformations • Gestational age under 23 weeks or over 42 weeks 6 days • Multiple births • Individuals with missing maternal or paternal identification numbers. Sample characteristics • Sample size	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough?

Author (year)	Title	Study details	Quality assessment
		870,017 • %female 48.9% • Mean age (SD) Not reported. Predictive factor(s) • Small for gestational age Definition was not provided Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Confounding factors - multivariate analysis • Maternal age • Paternal age • Parity • Parental education • Parental country of origin • Child's sex • Parental cohabitation status • Parental criminality • Maternal, paternal, and average parental income at childbirth	• Unclear Overall risk of bias • Moderate Directness • Directly applicable
Miodovnik (2015)	Timing of the Diagnosis of Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder.	Study type • Cross-sectional study Study details • Study location US • Study setting 2011–2012 National Survey of Children's Health • Study dates February 2011 to June 2012	Were the criteria for inclusion in the sample clearly defined? • No Were the study subjects and the setting described in detail? • Yes Was the exposure measured in a valid and reliable way?

Author (year)	Title	Study details	Quality assessment
		• Sources of funding No external funding Inclusion criteria • ASD diagnosis at least 2 years of age • ADHD diagnosis at least 3 years of age Exclusion criteria • None reported Sample characteristics • Sample size N=1,496 • %female ADHD Before ASD: 12.4% ADHD Same/After ASD: 11.2% ASD Only: 19% • Mean age (SD) Age at survey completion: ADHD Before ASD mean (SD) 11.8 years (0.4) ADHD Same/After ASD mean (SD) 10.8 years (0.4) ASD Only mean (SD) 10.0 years (0.3) Predictive factor(s) • ADHD Outcome(s) • Clinical diagnosis of ASD • Odds ratio Confounding factors - multivariate analysis • Mother's education • Child's age • Child's sex • Child's race/ethnicity • Speech problem • Learning (intellectual) disability	• No Were objective, standard criteria used for measurement of the condition? • No Were confounding factors identified? • Yes Were strategies to deal with confounding factors stated? • Yes Were the outcomes measured in a valid and reliable way? • No Was appropriate statistical analysis used? • Yes Overall risk of bias • High Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Household income • ASD severity	
Moore (2012)	Autism risk in small- and large-for-gestational-age infants	Study type • Retrospective cohort study Study details • Study location US • Study setting Register based. • Study dates January 1991 - Dec 2001 • Duration of follow-up 11 years Inclusion criteria • Infants who survived to 1 year of age. Exclusion criteria • None reported Sample characteristics • Sample size 5,979,605 of which 21,717 had autism • %female 49% • Mean age (SD) Not reported. Predictive factor(s) • Small for gestational age Outcome(s) • Clinical diagnosis of ASD	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough?

Author (year)	Title	Study details	Quality assessment
		• Odds ratio	• Yes From materials and methods section: "While autism is typically diagnosed by age 3 years, the analysis included cases identified by DDS through Nov. 30, 2006, at which time the youngest member of our cohort was 4 years and 11 months old, leaving time for most of the children with a delayed diagnosis to be included in the analysis." Overall risk of bias • Low Directness • Directly applicable
Pinborg (2004)	Neurological sequelae in twins born after assisted conception: controlled national cohort study.	Study type • Retrospective cohort study Study details • Study location Denmark • Study setting Danish medical birth registry Danish registry for in vitro fertilisation Danish patients' registry Denmark's psychiatric central registry • Study dates January 1995 to December 2002 • Sources of funding Danish Medical Research Council; Danish Hospital Foundation for Medical Research; Region of Copenhagen, the Faroe Islands and Greenland; and the Research Foundation of Queen Louise's Paediatric Hospital.	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors?

Author (year)	Title	Study details	Quality assessment
		Inclusion criteria • Children aged between 2 to 7 years at time of follow-up Exclusion criteria • Still births Sample characteristics • Sample size N=13,632 • %female IVF-ICSI twins: 47.9% Control twins: 48.7% • Mean age (SD) Mean children's age at follow-up: IVF-ICSI mean (SD) 4.2 years (1.7) Control mean (SD) 4.4 (1.7) Predictive factor(s) • Fertility treatment Outcome(s) • Clinical diagnosis of ASD • Risk ratio	• Unclear Have they taken account of the confounding factors in the design and/or analysis? • No Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Unclear Overall risk of bias • High Directness • Directly applicable
Rai (2017)	Antidepressants during pregnancy and autism in offspring: population based cohort study.	Study type • Retrospective cohort study Study details • Study location Stockholm • Study setting Register-based • Study dates 1996 to 2007 • Sources of funding Swedish Research Council NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes

Author (year)	Title	Study details	Quality assessment
		University of Bristol Inclusion criteria • None reported Exclusion criteria • Cohort members born before 1996 • Children not linked to the medical birth register • Children who could not be linked to their biological mothers • Adopted children • Children living in Stockholm County for less than 4 years Sample characteristics • Sample size N=254,610 • %female Exposed to antidepressants during pregnancy 48.3% Maternal psychiatric disorder and unexposed to antidepressants 47.7% No maternal psychiatric disorder and unexposed to antidepressants 48.8% Predictive factor(s) • Prenatal use of SSRIs Outcome(s) • Clinical diagnosis of ASD Codes: ICD-9:299, ICD-10:F84, or DSM-IV: 299 • Odds ratio Confounding factors - multivariate analysis • Birth year • Maternal depression • Antidepressant polypharmacy (2 or more antidepressants)	Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Unclear Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Unclear Overall risk of bias • Moderate Directness • Partially directly applicable Diagnoses included codes for Rett's syndrome/disorder: ICD-9: F84.2, ICD-10: 299, DSM-IV: 299

Author (year)	Title	Study details	Quality assessment
Russell (2014)	Prevalence of Parent-Reported ASD and ADHD in the UK: Findings from the Millennium Cohort Study	Study type • Cross-sectional study Study details • Study location UK • Study setting Millennium Cohort Study • Sources of funding National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) for the South West Peninsula Inclusion criteria • Wave 4 ASD/ADHD status data (mean age of child 7 years old) Exclusion criteria • Families with twins or triplets where all siblings participated Sample characteristics • Sample size N=13,586 • %female ASD 16.1% ADHD 17.8% ASD and ADHD 7.0% No diagnosis of ASD or ADHD 50.1% • Mean age (SD) 7 years (0.2; range 6.3 to 8.2) Predictive factor(s) • ADHD Outcome(s) • Clinical diagnosis of ASD	Were the criteria for inclusion in the sample clearly defined? • Yes Were the study subjects and the setting described in detail? • Yes Was the exposure measured in a valid and reliable way? • No Were objective, standard criteria used for measurement of the condition? • No Were confounding factors identified? • No Were strategies to deal with confounding factors stated? • No Were the outcomes measured in a valid and reliable way? • No Was appropriate statistical analysis used? • No Overall risk of bias • High

Author (year)	Title	Study details	Quality assessment
			Directness • Directly applicable
Sandin (2013)	Autism and mental retardation among offspring born after in vitro fertilization.	Study type • Retrospective cohort study Study details • Study location Sweden • Study setting Data from Swedish national registers • Study dates 1982 to 2009 • Duration of follow-up Each child was followed up from age 1.5 years to death, emigration from Sweden, onset of disease, the age of 28 years, or December 31, 2009, whichever came first. • Sources of funding The study was funded by Autism Speaks and the Swedish Research Council. Inclusion criteria • None reported Exclusion criteria • None reported Sample characteristics • Sample size N=2,541,125 • %female From 49.3% to 55.4% depending on type of conception (spontaneous or IVF)	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough?

Author (year)	Title	Study details	Quality assessment
		Predictive factor(s) • Fertility treatment In vitro fertilization (IVF) classified as: (1) IVF without intracytoplasmic sperm injection (ICSI) with fresh embryo transfer (2) IVF without ICSI with frozen embryo transfer (3) ICSI using ejaculated sperm with fresh embryos (4) ICSI with ejaculated sperm and frozen embryos (5) ICSI with surgically extracted sperm and fresh embryos (6) ICSI with surgically extracted sperm and frozen embryos (risk ratio was not estimable because there were too few cases) Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Confounding factors - multivariate analysis • Maternal age • Paternal age • Maternal psychiatric history • Paternal psychiatric history • Child's age • Birth year • Child's sex	• Yes Overall risk of bias • Low Directness • Directly applicable
Sorensen (2013)	Antidepressant exposure in pregnancy and risk of autism spectrum disorders	Study type • Retrospective cohort study Study details • Study location Denmark • Study setting Register based. • Study dates Children born alive between January 1996 and December 2006. • Duration of follow-up	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		• Loss to follow-up Up to 13 years. • Sources of funding No funding received for the study. Inclusion criteria • Children with an estimated time of conception after February 1996. Exclusion criteria • Infants with missing data on gestational age • Children who have died. During first year of life and later than one year after birth. • Children who emigrated. • Adopted away • Children with missing information about the mother • Children with extreme values of gestational age (less than or = 23 weeks of more than or equal to 45 weeks) Sample characteristics • Sample size 655,615 • %female 48.1% • Mean age (SD) 8.8 years (range 0 - 14, median 8.9) Predictive factor(s) • Prenatal use of SSRIs Exposure defined as 30 days before conception to the day of birth and included all antidepressant prescriptions filled from January 1, 1996 to December 31, 2006. Outcome(s) • Clinical diagnosis of ASD	• Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Author (year)	Title	Study details	Quality assessment
		• Hazard ratio Confounding factors - multivariate analysis • Maternal age At conception. • Paternal age At conception. • Parity • Maternal psychiatric history Except maternal affective disorder. • Paternal psychiatric history • Sex • Gestational age • Birthweight	
Sujan (2017)	Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring	Study type • Retrospective cohort study Study details • Study location Sweden • Study setting Population-based data from Swedish registries • Duration of follow-up Children born between 1996 and 2012 were followed up through 2013 • Sources of funding Inclusion criteria • None reported Exclusion criteria • None reported	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes

Author (year)	Title	Study details	Quality assessment
		Sample characteristics • Sample size N=1,580,629 Predictive factor(s) • Prenatal use of SSRIs Outcome(s) • Clinical diagnosis of ASD • Hazard ratio Confounding factors - multivariate analysis • Maternal age • Parity • Educational level • Maternal country of birth • Paternal country of birth • Maternal history of any criminal convictions • Paternal history of any criminal convictions • Maternal history of any suicide attempts • Paternal history of any suicide attempts • Maternal psychiatric history • Paternal psychiatric history • Birth year	Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Unclear Overall risk of bias • Low Directness • Directly applicable
Viktorin (2017)	Autism risk following antidepressant medication during pregnancy	Study type • Retrospective cohort study Study details • Study location Sweden • Study setting Register based: Swedish National registers. • Study dates All live-born children conceived from July 1, 2005 and born in	Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias?

Author (year)	Title	Study details	Quality assessment
		2006 and 2007 • Duration of follow-up From birth through 2014 when aged 7 or 8. • Loss to follow-up Not reported. • Sources of funding National Institutes of Health; the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute of Environmental Health Sciences, and National Institute of Neurological Disorders and Stroke; the National Institute of Mental Health; by the Beatrice and Samuel A. Seaver Foundation; Fredrik and Ingrid Thuring Foundation; and by the Swedish Society of Medicine. Inclusion criteria • None reported Exclusion criteria • Children who had incomplete data. Sample characteristics • Sample size 179,007 • %female 49.7% • Mean age (SD) Not reported. Predictive factor(s) • Prenatal use of SSRIs Outcome(s) • Clinical diagnosis of ASD • Risk ratio	• Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Unclear Overall risk of bias • Low Directness • Partially directly applicable ICD-10 code for Rett's syndrome (F84.2) was included under ASD diagnosis

Author (year)	Title	Study details	Quality assessment
		Confounding factors - multivariate analysis • Maternal age • Paternal age • Maternal psychiatric history • Paternal psychiatric history • Child's age • Father’s medication with any psychotropic drugs overlapping • Mother’s dispensations of other psychotropic medication	

Appendix F – GRADE tables

Small for gestational age

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Birth weight for gestational age >2 SDs below the mean (reference category: birth weight for gestational age within 1 SD of the mean)										
1 (Durkin 2008)	Retrospective cohort	185,164	aOR 1.1 (0.7, 1.6)	4.8 per 1,000	5.2 per 1,000 (3.3, 7.6)	Very serious[2]	N/A[3]	Not serious	Very serious[4]	VERY LOW
Birth weight for gestational age >2 SDs below the mean (reference category: not small for gestational age)										
1 (McCoy 2014)	Retrospective cohort	866,272	aHR 1.50 (1.32, 1.71)	N/E	N/E	Serious[5]	N/A[3]	Not serious	Not serious	MODERATE
Birth weight Z-score <-2 (reference category: not reported) in very preterm children (<28 weeks gestational age)										
1 (Joseph 2017)	Prospective cohort	737	aOR 9.9 (3.3, 30)	N/E	N/E	Not serious	N/A[3]	Serious[6]	Not serious	MODERATE
Birth weight for gestational age <5th percentile on the Fenton curves (reference category: not reported)										
1 (Kuzniewicz 2014)	Retrospective cohort	185,506[7]	aHR 1.5 (1.1, 1.9)	12.5 per 1,000	18.7 per 1,000 (13.7, 23.7)	Not serious	N/A[3]	Not serious	Serious[8]	MODERATE
Birth weight for gestational age <5th percentile (reference category: birth weight percentile >10 to <90)										
1 (Moore 2012)	Retrospective cohort	4,692,129	aOR 1.10 (1.04, 1.18)	3.5 per 1,000	3.8 per 1,000 (3.6, 4.0)	Not serious	N/A[3]	Not serious	Serious[8]	MODERATE
Birth weight for gestational age 5 to 10th percentile (reference category: birth weight percentile >10 to <90)										
1 (Moore 2012)	Retrospective cohort	4,711,838	aOR 1.04 (0.98, 1.11)	3.5 per 1,000	3.6 per 1,000 (3.4, 3.8)	Not serious	N/A[3]	Not serious	Serious[8]	MODERATE

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

[1]Absolute risk for exposed and its 95% CI were calculated using the effect size and its 95% CI. For odds ratios, these were first converted to risk ratios using the prevalence from the unexposed arm of the study before calculating absolute risks.

[2]Study rated as being at high risk of bias.

[3]Inconsistency not applicable as outcome is from one study.

[4]95% confidence interval crosses both ends of a defined MID interval.

[5]Study rated as being at moderate risk of bias.

[6]Study was downgraded because the reference category to estimate the effect size was not reported.

[7]Sample size was assumed to have 'appropriate for gestational age' as the reference category and that 'rule out ASD' was not used in the calculation of hazard ratio.

[8]95% confidence interval crosses one end of a defined MID interval.

SDs: standard deviations; aOR: adjusted odds ratio; aHR: adjusted hazard ratio; N/E: not extractable (data was not reported in an extractable format).

Prenatal use of SSRIs

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
SSRIs used during pregnancy (reference category: no serotonergic antidepressants prescribed during pregnancy)										
1 (Brown 2017)	Retrospective cohort	35,618	aHR 1.40 (0.80, 2.46)	10.0 per 1,000	14.0 per 1,000 (8.0, 24.6)	Not serious	N/A[2]	Not serious	Very serious[3]	LOW
SSRIs used during pregnancy (reference category: no SSRIs use during pregnancy)										
1 (Hviid 2013)	Retrospective cohort	626,875	aRR 1.20 (0.90, 1.61)	6.0 per 1,000	7.2 per 1,000 (5.4, 9.6)	Not serious	N/A[2]	Not serious	Very serious[3]	LOW
Subgroup of mothers with previous psychiatric diagnoses **SSRIs used during pregnancy (reference category: no SSRIs use during pregnancy)**										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Hviid 2013)	Retrospective cohort	24,360	aRR 0.86 (0.53, 1.40)	6.0[4] per 1,000	5.1 per 1,000 (3.1, 8.4)	Not serious	N/A[2]	Not serious	Very serious[3]	LOW
Subgroup of mothers with previous diagnosis of depression **SSRIs used during pregnancy (reference category: no SSRIs use during pregnancy)**										
1 (Hviid 2013)	Retrospective cohort	3,482	aRR 0.57 (0.24, 1.33)	6.0[4] per 1,000	3.4 per 1,000 (1.4, 7.9)	Not serious	N/A[2]	Not serious	Very serious[3]	LOW
SSRIs used during pregnancy (reference category: no antidepressants during pregnancy in women with a psychiatric disorder)										
1 (Rai 2017)	Retrospective cohort	15,035	aOR 1.45 (1.14, 1.83)	28.6 per 1,000	40.8 per 1,000 (32.3, 51.1)	Serious[5]	N/A[2]	Not serious[6]	Not serious	MODERATE
ASD without learning (intellectual) disability **SSRIs used during pregnancy (reference category: no antidepressants during pregnancy in women with a psychiatric disorder)**										
1 (Rai 2017)	Retrospective cohort	15,035[7]	aOR 1.54 (1.20, 1.97)	23.6 per 1,000	35.8 per 1,000 (28.0, 45.3)	Serious[5]	N/A[2]	Not serious[6]	Not serious	MODERATE
SSRIs used during pregnancy (reference category: no antidepressants during pregnancy)										
1 (Malm 2016)	Retrospective cohort	47,123	aHR 1.40 (1.02, 1.92)	3.1 per 1,000	4.3 per 1,000 (3.1, 5.9)	Not serious	Not serious[8]	Not serious[8]	Not serious[10]	HIGH
1 (Sorensen 2013)	Retrospective cohort	654,288	aHR 1.6 (1.3, 2.0)	8.2 per 1,000	13.1 per 1,000 (10.6, 16.4)					

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Viktorin 2017)	Retrospective cohort	175,824	aRR 1.30 (0.99, 1.69)	8.8 per 1,000	11.4 per 1,000 (8.7, 14.8)					
Analysis restricted to mothers with a hospital-diagnosed affective disorder SSRIs used during pregnancy (reference category: no antidepressants during pregnancy)										
1 (Sorensen 2013)	Retrospective cohort	5,799	aHR 1.4 (0.8, 2.4)	11.1 per 1,000	15.5 per 1,000 (8.8, 26.6)	Not serious	N/A[2]	Not serious	Very serious[3]	LOW
SSRIs used during pregnancy (reference category: mothers with psychiatric disorder but no antidepressant use)										
1 (Malm 2016)	Retrospective cohort	25,380	aHR 0.88 (0.65, 1.20)	8.1 per 1,000	7.1 per 1,000 (5.2, 9.7)	Not serious	N/A[2]	Not serious	Very serious[3]	LOW
SSRIs used during first trimester (reference category: no SSRIs use during pregnancy)										
1 (Hviid 2013)	Retrospective cohort	626,875[11]	aRR 1.35 (0.90, 1.61)	6.0 per 1,000	8.1 per 1,000 (5.4, 9.6)	Not serious	N/A[2]	Not serious	Very serious[3]	LOW
SSRIs used during first trimester (reference category: no antidepressants during pregnancy)										
1 (Sorensen 2013)	Retrospective cohort	654,288[11]	aHR 1.6 (1.3, 2.0)	8.2 per 1,000	13.1 per 1,000 (10.6, 16.4)	Not serious	Not serious	Not serious	Not serious	HIGH
1 (Sujan 2017)	Retrospective cohort	1,580,210	aHR 1.66 (1.46, 1.89)	9.1 per 1,000	15.1 per 1,000 (13.2, 17.1)					
Analysis restricted to mothers with a hospital-diagnosed affective disorder SSRIs used during first trimester (reference category: no antidepressants during pregnancy)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Sorensen 2013)	Retrospective cohort	N/R	aHR 1.4 (0.8, 2.6)	N/E	N/E	Not serious	N/A[2]	Not serious	Very serious[3]	LOW
SSRIs used during second and/or third trimester (reference category: no antidepressants during pregnancy)										
1 (Sorensen 2013)	Retrospective cohort	654,288[11]	aHR 1.4 (0.7, 2.7)	8.2 per 1,000	11.4 per 1,000 (5.7, 22.1)	Not serious	Not serious[8]	Not serious	Very serious[12]	LOW
1 (Boukhris 2016)	Retrospective cohort	144,507	aHR 2.17 (1.20, 3.93)	7.1 per 1,000	15.4 per 1,000 (8.5, 27.9)					
1 (Sujan 2017)	Retrospective cohort	708,450	aHR 2.13 (0.96, 4.76)	N/E	N/E					

[1]Absolute risk for exposed and its 95% CI were calculated using the effect size and its 95% CI. For odds ratios, these were first converted to risk ratios using the prevalence from the unexposed arm of the study before calculating absolute risks.

[2]Inconsistency not applicable as outcome is from one study.

[3]95% confidence interval crosses both ends of a defined MID interval.

[4]Absolute risk for unexposed was calculated for the whole population of unexposed (no SSRIs used during pregnancy; n=620,807) because number of children with ASD diagnosis was not reported for the unexposed group in the subgroup analysis.

[5]Study rated as being at moderate risk of bias.

[6]Diagnoses included codes for Rett's syndrome/disorder: ICD-9: F84.2, ICD-10: 299, DSM-IV: 299. However, indirectness was considered to be not serious because Rett's syndrome is considered to be rare which means that few cases are expected in general.

[7]Sample size was not reported specifically for children without learning (intellectual) disability. Therefore, we are reporting the sample size which included exposed to SSRIs and unexposed to antidepressants in mother with psychiatric disorder.

[8]Inconsistency was not assessed using the I^2 statistic. However, inconsistency was considered not to be serious because effect size was not meaningfully different between studies with the smallest and largest effect sizes.

[9]Viktorin 2017 included ICD-10 code for Rett's syndrome (F84.2) under ASD diagnosis. However, overall indirectness was considered not to be serious because the other 2 studies did not include Rett's syndrome. Furthermore, Rett's syndrome is considered to be rare which means that few cases are expected in general.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
[10]Imprecision was considered not to be serious because all 3 mean estimates are above a defined MID interval and the largest study also reported 95% CI above a defined MID. [11]Sample size for analysis during first trimester was not reported. Therefore, it was assumed that the sample size was used as for the entire pregnancy duration. [12]For 2 of the 3 studies (Sorensen 2013; Sujan 2017), 95% confidence interval crosses both ends of a defined MID interval. aHR: adjusted hazard ratio; aRR: adjusted risk ratio; aOR: adjusted odds ratio; N/R: not reported; N/E: not extractable (data was not reported in an extractable format).										

Fertility treatments

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Assisted conception including IVF and OI (reference category: natural conception)										
1 (Hvidtjørn 2011)	Retrospective cohort	588,967	aHR 1.13 (0.97, 1.31)	6.1 per 1,000	6.8 per 1,000 (5.9, 7.9)	Serious[2]	N/A[3]	Not serious	Serious[4]	MODERATE
IVF with or without ICSI (reference category: natural conception)										
1 (Hvidtjørn 2011)	Retrospective cohort	570,819	aHR 1.04 (0.83, 1.31)	6.1 per 1,000	6.3 per 1,000 (5.0, 7.9)	Not serious	Not serious	Not serious	Very serious[5]	LOW
1 (Sandin 2013)	Retrospective cohort	2,541,125	aRR 1.14 (0.94, 1.39)	2.7 per 1,000	3.0 per 1,000 (2.5, 3.7)					
IVF and ICSI (reference category: natural conception)										
1 (Bay 2013)	Retrospective cohort	570,819	aHR 1.02 (0.87, 1.20)	12.7 per 1,000	12.9 per 1,000 (11.0, 15.2)	Not serious	N/A[3]	Not serious	Serious[4]	MODERATE

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Pinborg 2004)	Retrospective cohort	13,632 twins	RR 0.82 (0.23, 2.95)	1.0 per 1,000	0.82 per 1,000 (0.23, 2.95)	Very serious[6]	N/A[3]	Not serious	Very serious[7]	VERY LOW
IVF without ICSI, fresh embryo transfer (reference category: natural conception)										
1 (Sandin 2013)	Retrospective cohort	2,526,834	RR 1.01 (0.77, 1.32)	2.7 per 1,000	2.7 per 1,000 (2.0, 3.5)	Not serious	N/A[3]	Not serious	Very serious[7]	LOW
IVF without ICSI, frozen embryo transfer (reference category: natural conception)										
1 (Sandin 2013)	Retrospective cohort	2,512,943	RR 1.43 (0.77, 2.66)	2.7 per 1,000	3.8 per 1,000 (2.0, 7.1)	Not serious	N/A[3]	Not serious	Very serious[7]	LOW
ICSI using ejaculated sperm with fresh embryos (reference category: natural conception)										
1 (Sandin 2013)	Retrospective cohort	2,519,407	RR 1.23 (0.86, 1.75)	2.7 per 1,000	3.3 per 1,000 (2.3, 4.7)	Not serious	N/A[3]	Not serious	Very serious[7]	LOW
ICSI with ejaculated sperm and frozen embryos (reference category: natural conception)										
1 (Sandin 2013)	Retrospective cohort	2,511,643	RR 0.32 (0.04, 2.24)	2.7 per 1,000	0.8 per 1,000 (0.1, 6.0)	Not serious	N/A[3]	Not serious	Very serious[7]	LOW
ICSI with surgical extracted sperm and fresh embryos (reference category: natural conception)										
1 (Sandin 2013)	Retrospective cohort	2,510,794	RR 4.56 (2.28, 9.13)	2.7 per 1,000	12.3 per 1,000 (6.1, 24.6)	Not serious	N/A[3]	Not serious	Serious[8]	MODERATE
Spontaneously conceived with hormone treatment as the only fertility treatment (reference category: spontaneously conceived without hormone treatment)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Sandin 2013)	Retrospective cohort	2,510,166	aRR 0.91 (0.62, 1.34)	2.7 per 1,000	2.4 per 1,000 (1.6, 3.6)	Not serious	N/A[3]	Not serious	Very serious[7]	LOW
OI or IUI (reference category: natural conception)										
1 (Bay 2013)	Retrospective cohort	573,976	aHR 1.20 (1.05, 1.37)	12.7 per 1,000	15.2 per 1,000 (13.3, 17.3)	Not serious	N/A[3]	Not serious	Serious[4]	MODERATE
OI (reference category: natural conception)										
1 (Hvidtjørn 2011)	Retrospective cohort	573,976	aHR 1.20 (0.99, 1.44)	6.1 per 1,000	7.3 per 1,000 (6.0, 8.7)	Not serious	N/A[3]	Not serious	Serious[4]	MODERATE
ICSI (reference category: IVF without ICSI)										
1 (Kissin 2015)	Retrospective cohort	35,481	aHR 1.65 (1.08, 2.52)	8.5 per 1,000	14.0 per 1,000 (9.1, 21.4)	Not serious	N/A[3]	Not serious	Serious[4]	MODERATE

[1]Absolute risk for exposed and its 95% CI were calculated using the effect size and its 95% CI.

[2]Study rated as being at moderate risk of bias.

[3]Inconsistency not applicable as outcome is from one study.

[4]95% confidence interval crosses one end of a defined MID interval.

[5]Imprecision was considered to be very serious because 95% confidence interval of the adjusted hazard ratio crosses both ends of a defined MID interval. aHR was considered to be a more accurate estimate which takes follow-up time into consideration.

[6]Study rated as being at high risk of bias.

[7]95% confidence interval crosses both ends of a defined MID interval.

[8]Study rated a serious because the number of events (children with ASD diagnosis) was small (n=8).

aHR: adjusted hazard ratio; aRR: adjusted risk ratio; RR: unadjusted risk ratio.

Neurodevelopmental disorders

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
ADHD (reference category: no ADHD)										
3 (Elberling 2016; Ghirardi 2017; Russell 2014)	Cross-sectional	1,914,808	OR 22.91 (9.31, 56.38)	15.7 per 1,000	267.5 per 1,000 (129.2, 473.3)	Serious[2]	Not serious[3]	Not serious[4]	Not serious	MODERATE
Down's syndrome (reference category: control participants without Down's syndrome)										
1 (Alexander 2016)	Case-control	25,606	OR 4.41 (3.04, 6.40)	2.4 per 1,000	10.4 per 1,000 (7.2, 15.1)	Very serious[2]	N/A[5]	Serious[6]	Not serious	VERY LOW
Learning (intellectual) disability in very preterm children (<28 weeks gestational age)										
1 (Joseph 2017)	Prospective cohort	737	OR 11.85 (6.72, 20.90)	36.6 per 1,000	256.5 per 1,000 (180.0, 337.4)	Not serious	N/A	Not serious	Not serious	HIGH

[1]Absolute risk for exposed and its 95% CI were calculated using the effect size and its 95% CI. For odds ratios, these were first converted to risk ratios using the prevalence from the unexposed arm of the study before calculating absolute risks.

[2]Studies were rated as being at high risk of bias. However, the effect size was sufficiently large as to highly unlikely to be attributable to bias alone, and therefore the outcome was only downgraded 1 level for risk of bias rather than 2.

[3]Inconsistency was considered not to be serious because effect size was not meaningfully different between studies with the smallest and largest effect sizes, despite the i^2 value being above the defined level for downgrading.

[4]Indirectness was considered not to be serious. Although ICD code for ASD included Rett's syndrome (Ghirardi 2017), Rett's syndrome was considered to be rare which means that few cases were expected. ICD-10 was used to investigate hyperkinetic disorders which includes other disorders apart from ADHD but it was considered that ADHD is most frequent disorder.

[5]Inconsistency not applicable as outcome is from one study.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed[1] (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
[6]ICD codes for autism were not reported. The sample included children and adults. ADHD: attention deficit hyperactivity disorder; OR: unadjusted odds ratio.										

Outcome: ASD diagnosis >6 years of age

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: unexposed	Absolute risk: exposed (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
ADHD before ASD (reference category: ASD only)										
1 (Miodovnik 2015)	Cross-sectional	1,059	aOR 16.7 (7.03, 39.7)	N/E	N/E	Very serious[1]	N/A	Not serious	Not serious	LOW
ADHD same/after ASD (reference category: ASD only)										
1 (Miodovnik 2015)	Cross-sectional	1,138	aOR 0.57 (0.28, 1.15)	N/E	N/E	Very serious[1]	N/A	Not serious	Very serious[2]	VERY LOW
[1]Study rated as being at high risk of bias. [2]95% confidence interval crosses both ends of a defined MID interval. aOR: adjusted odds ratio; N/E: not extractable (data was not reported in an extractable format).										

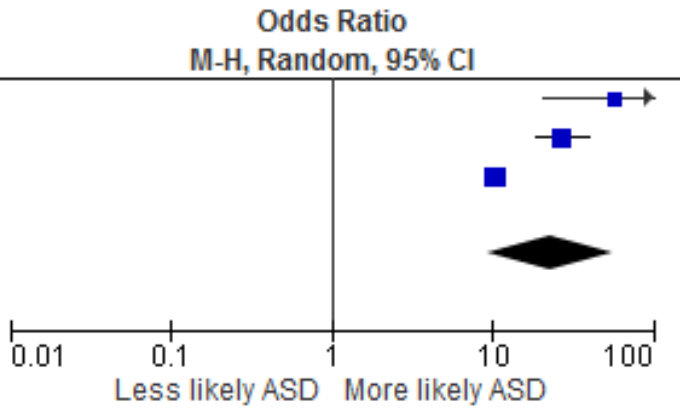
Appendix G – Forest plots

Outcome: Clinical diagnosis of ASD; Predictor: ADHD

	ADHD		No ADHD			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Elberling 2016	8	20	18	1565	25.9%	57.30 [20.91, 157.01]
Russell 2014	44	173	165	13396	35.9%	27.35 [18.80, 39.80]
Ghirardi 2017	13793	96191	28468	1803463	38.3%	10.44 [10.22, 10.66]
Total (95% CI)		**96384**		**1818424**	**100.0%**	**22.91 [9.31, 56.38]**
Total events	13845		28651			

Heterogeneity: Tau² = 0.55; Chi² = 36.20, df = 2 (P < 0.00001); I² = 94%

Test for overall effect: Z = 6.82 (P < 0.00001)



Appendix H – Excluded studies

Author (year)	Title	Reason for exclusion
Abel (2013)	Deviance in fetal growth and risk of autism spectrum disorder.	• Case-control study
Alkandari (2015)	Fetal ultrasound measurements and associations with postnatal outcomes in infancy and childhood: a systematic review of an emerging literature	• Systematic review - relevant studies already included
Arvidsson (1997)	Autism in 3-6-Year-Old Children in a Suburb of Goteborg, Sweden	• Study does not contain any of the outcomes of interest
Atladottir (2016)	Gestational Age and Autism Spectrum Disorder: Trends in Risk Over Time	• Study does not contain any relevant predictive variables
Bagal (2016)	To study the age of recognition of symptoms and their correlates in children diagnosed with autism spectrum disorders: A retrospective study	• Study does not contain any of the outcomes of interest
Bakare (2012)	Prevalence of autism spectrum disorder among Nigerian children with intellectual disability: A stopgap assessment	• ASD diagnosis with questionnaire
Bay (2013)	Assisted reproduction and child neurodevelopmental outcomes: A systematic review	• Systematic review - relevant studies already included
Bay (2014)	Fertility treatment: long-term growth and mental development of the children	• Study does not contain any of the outcomes of interest • Systematic review - relevant studies already included
Ben (2011)	Advanced parental ages and low birth weight in autism spectrum disorders--rates and effect on functioning	• Full text paper not available
Boulet (2011)	Birth Weight and Health and Developmental Outcomes in US Children, 1997-2005	• Study does not contain any relevant predictive variables
Bowers (2015)	Phenotypic differences in individuals with autism spectrum disorder born preterm and at term gestation	• Study does not contain any of the outcomes of interest
Brock (2010)	Distinguishing features of autism in boys with fragile X syndrome	• Study does not contain any of the outcomes of interest
Brown (2017)	The association between antenatal exposure to selective serotonin reuptake inhibitors and autism: A systematic review and meta-analysis	• Systematic review - relevant studies already included
Bryson (2008)	Prevalence of autism among adolescents with intellectual disabilities.	• Study does not contain any of the outcomes of interest

Author (year)	Title	Reason for exclusion
Canals (2016)	ADHD Prevalence in Spanish Preschoolers: Comorbidity, Socio-Demographic Factors, and Functional Consequences	• ASD diagnosis with questionnaire
Caravella (2017)	Adaptive skill trajectories in infants with fragile X syndrome contrasted to typical controls and infants at high risk for autism	• Full text paper not available
Cassimos (2016)	Perinatal and parental risk factors in an epidemiological study of children with autism spectrum disorder	• Study does not contain any relevant predictive variables
Castro (2016)	Absence of evidence for increase in risk for autism or attention-deficit hyperactivity disorder following antidepressant exposure during pregnancy: a replication study	• Study does not contain any relevant predictive variables
Catford (2017)	Long-term follow-up of intra-cytoplasmic sperm injection-conceived offspring compared with in vitro fertilization-conceived offspring: a systematic review of health outcomes beyond the neonatal period	• Systematic review - relevant studies already included
Class (2014)	Fetal growth and psychiatric and socioeconomic problems: population-based sibling comparison	• Study does not contain any of the outcomes of interest
Clements (2015)	Prenatal antidepressant exposure is associated with risk for attention-deficit hyperactivity disorder but not autism spectrum disorder in a large health system	• Study does not contain any relevant predictive variables
Close (2012)	Co-occurring conditions and change in diagnosis in autism spectrum disorders	• ASD diagnosis with questionnaire
Cochran (2015)	Contrasting age related changes in autism spectrum disorder phenomenology in Cornelia de Lange, Fragile X, and Cri du Chat syndromes: Results from a 2.5 year follow-up	• Study does not contain any of the outcomes of interest
Conti (2013)	Are children born after assisted reproductive technology at increased risk of autism spectrum disorders? A systematic review	• Systematic review - relevant studies already included
Cooper (2014)	Autistic traits in children with ADHD index clinical and cognitive problems	• Study does not contain any of the outcomes of interest
Cornish (2013)	Do behavioural inattention and hyperactivity exacerbate cognitive difficulties associated with autistic symptoms? Longitudinal profiles in fragile X syndrome	• Study does not contain any of the outcomes of interest

Author (year)	Title	Reason for exclusion
Corsello (2007)	Between a ROC and a hard place: decision making and making decisions about using the SCQ.	• Not a relevant study design
Croen (2002)	Descriptive Epidemiology of Autism in a California Population: Who Is at Risk?	• Study does not contain any relevant predictive variables
Croen (2011)	Antidepressant use during pregnancy and childhood autism spectrum disorders	• Case-control study
Darcy-Mahoney (2016)	Probability of an Autism Diagnosis by Gestational Age	• Study does not contain any relevant predictive variables
Darcy-Mahoney (2016)	Maternal and Neonatal Birth Factors Affecting the Age of ASD Diagnosis	• Study does not contain any relevant predictive variables
David (2014)	Prevalence and characteristics of children with mild intellectual disability in a French county	• Study does not contain any of the outcomes of interest
Davidovitch (2015)	Late diagnosis of autism spectrum disorder after initial negative assessment by a multidisciplinary team	• Not a relevant study design
de Bildt (2005)	Prevalence of pervasive developmental disorders in children and adolescents with mental retardation.	• Study does not contain any of the outcomes of interest
de Bruin (2007)	High rates of psychiatric co-morbidity in PDD-NOS.	• Study does not contain any of the outcomes of interest
Dietz (2006)	Screening for autistic spectrum disorder in children aged 14-15 months. II: population screening with the Early Screening of Autistic Traits Questionnaire (ESAT). Design and general findings.	• Not a relevant study design
DiGuiseppi (2010)	Screening for autism spectrum disorders in children with Down syndrome: population prevalence and screening test characteristics	• Not a relevant study design
D'Onofrio (2013)	Preterm birth and mortality and morbidity: a population-based quasi-experimental study.	• Study does not contain any relevant predictive variables
Duan (2014)	Perinatal and background risk factors for childhood autism in central China	• ASD diagnosis with questionnaire
Dudova (2014)	Comparison of three screening tests for autism in preterm children with birth weights less than 1,500 grams	• Study does not contain any relevant predictive variables
Dudova (2014)	Screening for autism in preterm children with extremely low and very low birth weight	• Study does not contain any relevant predictive variables
Ehlers (1999)	A screening questionnaire for Asperger syndrome and other high-	• Not a relevant study design

Author (year)	Title	Reason for exclusion
	functioning autism spectrum disorders in school age children.	
El Marroun (2014)	Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness symptoms of autism: population-based study of young children.	• ASD diagnosis with questionnaire
El-Baz (2011)	Risk factors for autism: An Egyptian study	• Study does not contain any relevant predictive variables
Emerson (2003)	Prevalence of psychiatric disorders in children and adolescents with and without intellectual disability	• Not a relevant study design
Emerson (2007)	Mental health of children and adolescents with intellectual disabilities in Britain.	• Not a relevant study design
Fevang (2016)	Mental health in children born extremely preterm without severe neurodevelopmental disabilities	• Study does not contain any of the outcomes of interest
Fountain (2015)	Association between assisted reproductive technology conception and autism in California, 1997-2007	• Case-control study
Frenette (2013)	Factors affecting the age at diagnosis of autism spectrum disorders in Nova Scotia, Canada	• Study does not contain any of the outcomes of interest
Frolli (2015)	Developmental changes in cognitive and behavioural functioning of adolescents with fragile-X syndrome	• No diagnosis of ASD.
Gadow (2005)	Clinical significance of tics and attention-deficit hyperactivity disorder (ADHD) in children with pervasive developmental disorder.	• Study does not contain any of the outcomes of interest
Gadow (2016)	Clinical Correlates of Co-occurring Psychiatric and Autism Spectrum Disorder (ASD) Symptom-Induced Impairment in Children with ASD	• Data not reported in an extractable format
Gardener (2011)	Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis	• Data not reported in an extractable format
Geier (2015)	A Prospective Longitudinal Assessment of Medical Records for Diagnostic Substitution among Subjects Diagnosed with a Pervasive Developmental Disorder in the United States	• No diagnosis of ASD.
Geier (2017)	Neonatal factors among subjects diagnosed with a pervasive developmental disorder in the US	• Study does not contain any relevant predictive variables
Gellec (2011)	Neurologic outcomes at school age in very preterm infants born with severe or mild growth restriction	• Study does not contain any of the outcomes of interest

Author (year)	Title	Reason for exclusion
Gentile (2015)	Prenatal antidepressant exposure and the risk of autism spectrum disorders in children. Are we looking at the fall of Gods?	• Systematic review - relevant studies already included
Gidaya (2014)	In Utero Exposure to Selective Serotonin Reuptake Inhibitors and Risk for Autism Spectrum Disorder	• Case-control study
Giltaij (2015)	Psychiatric diagnostic screening of social maladaptive behaviour in children with mild intellectual disability: differentiating disordered attachment and pervasive developmental disorder behaviour.	• Not a relevant study design
Goldin (2016)	Premature birth as a risk factor for autism spectrum disorder	• Study does not contain any relevant predictive variables
Goldstein (2004)	The comorbidity of Pervasive Developmental Disorder and Attention Deficit Hyperactivity Disorder: results of a retrospective chart review.	• Study does not contain any of the outcomes of interest
Grandgeorge (2013)	Autism spectrum disorders: head circumference and body length at birth are both relative	• Study does not contain any of the outcomes of interest
Gray (2015)	Screening for autism spectrum disorder in very preterm infants during early childhood	• Full text paper not available
Green (2015)	Autism spectrum disorder symptoms in children with ADHD: A community-based study.	• ASD diagnosis with questionnaire
Green (2016)	Association between autism symptoms and functioning in children with ADHD	• ASD diagnosis with questionnaire
Grefer (2016)	The emergence and stability of attention deficit hyperactivity disorder in boys with fragile X syndrome	• Study does not contain any of the outcomes of interest
Grether (2013)	Is Infertility Associated with Childhood Autism?	• Case-control study
Guinchat (2012)	Pre-, peri- and neonatal risk factors for autism	• Systematic review - relevant studies already included
Guy (2015)	Infants born late/moderately preterm are at increased risk for a positive autism screen at 2 years of age.	• ASD diagnosis with questionnaire
Hack (2009)	Behavioral outcomes of extremely low birth weight children at age 8 years.	• Study does not contain any relevant predictive variables
Haglund (2011)	Risk factors for autism and Asperger syndrome	• Duplicate reference
Haglund (2011)	Risk factors for autism and Asperger syndrome. Perinatal factors and migration	• Case-control study

Author (year)	Title	Reason for exclusion
Harrington (2013)	Association of autism with maternal SSRi use during pregnancy	• Case-control study
Harrington (2014)	Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay	• Case-control study
Hart (2013)	The longer-term health outcomes for children born as a result of IVF treatment. Part II--Mental health and development outcomes	• Study does not contain any of the outcomes of interest
Hassiotis (2012)	Mental health needs in adolescents with intellectual disabilities: cross-sectional survey of a service sample	• Study does not contain any of the outcomes of interest
Healy (2016)	Links between serotonin reuptake inhibition during pregnancy and neurodevelopmental delay/spectrum disorders: A systematic review of epidemiological and physiological evidence	• Systematic review - relevant studies already included
Hoffmire (2014)	High prevalence of sleep disorders and associated comorbidities in a community sample of children with Down syndrome	• Study does not contain any of the outcomes of interest
Honda (2009)	Extraction and Refinement Strategy for detection of autism in 18-month-olds: a guarantee of higher sensitivity and specificity in the process of mass screening.	• Not a relevant study design
Hultman (2002)	Perinatal risk factors for infantile autism.	• Case-control study
Hwang (2013)	Higher prevalence of autism in Taiwanese children born prematurely: a nationwide population-based study.	• Study does not contain any relevant predictive variables
Imran (2012)	Children's mental health: Pattern of referral, distribution of disorders and service use in child psychiatry outpatient setting	• Study does not contain any relevant predictive variables
Indredavik (2010)	Perinatal risk and psychiatric outcome in adolescents born preterm with very low birth weight or term small for gestational age	• Study does not contain any of the outcomes of interest
Jacob (2016)	Co-morbidity in Attention-Deficit Hyperactivity Disorder: A Clinical Study from India	• Study does not contain any of the outcomes of interest
Jaspers (2013)	Early childhood assessments of community pediatric professionals predict autism spectrum and attention deficit hyperactivity problems	• ASD diagnosis with questionnaire
Jauhari (2012)	Comorbidities associated with intellectual disability among pediatric outpatients seen at a teaching hospital in Northern India	• Study does not contain any of the outcomes of interest

Author (year)	Title	Reason for exclusion
Jensen (2015)	Comorbid mental disorders in children and adolescents with attention-deficit/hyperactivity disorder in a large nationwide study	• ASD diagnosis before predictor evaluation
Johnson (2010)	Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study.	• Study does not contain any relevant predictive variables
Johnson (2010)	Autism spectrum disorders in extremely preterm children.	• Study does not contain any relevant predictive variables
Johnson (2011)	Screening for autism in preterm children: diagnostic utility of the Social Communication Questionnaire	• Study does not contain any relevant predictive variables
Johnson (2016)	Preschool outcomes following prenatal serotonin reuptake inhibitor exposure: differences in language and behavior, but not cognitive function	• Study does not contain any of the outcomes of interest
Joseph (2017)	Prevalence and associated features of autism spectrum disorder in extremely low gestational age newborns at age 10 years	• Study does not contain any relevant predictive variables
Kamowski-Shakibai (2015)	Parent-reported use of assisted reproduction technology, infertility, and incidence of autism spectrum disorders	• Full text paper not available
Kamp-Becker (2009)	Dimensional structure of the autism phenotype: relations between early development and current presentation.	• Study does not contain any relevant predictive variables
Kantzer (2013)	Autism in community pre-schoolers: developmental profiles.	• Study does not contain any relevant predictive variables
Kaplan (2016)	Prenatal selective serotonin reuptake inhibitor use and the risk of autism spectrum disorder in children: A systematic review and meta-analysis	• Systematic review - relevant studies already included
Karmel (2010)	Early medical and behavioral characteristics of NICU infants later classified with ASD	• Study does not contain any relevant predictive variables
Kato (2016)	Extremely preterm infants small for gestational age are at risk for motor impairment at 3 years corrected age	• Study does not contain any of the outcomes of interest
Kaufmann (2017)	Autism spectrum disorder in fragile X syndrome: Cooccurring conditions and current treatment	• Study does not contain any relevant predictive variables
Khandake (2014)	A population-based longitudinal study of childhood neurodevelopmental disorders, IQ and subsequent risk of psychotic experiences in adolescence	• Study does not contain any relevant predictive variables

Author (year)	Title	Reason for exclusion
Kim (2000)	The Prevalence of Anxiety and Mood Problems among Children with Autism and Asperger Syndrome	• ASD diagnosis before predictor evaluation
Kim (2016)	Predictive Validity of the Modified Checklist for Autism in Toddlers (M-CHAT) Born Very Preterm.	• Not a relevant study design
Kobayashi (2016)	Autism spectrum disorder and prenatal exposure to selective serotonin reuptake inhibitors: A systematic review and meta-analysis	• Systematic review - relevant studies already included
Kochhar (2011)	Autistic spectrum disorder traits in children with attention deficit hyperactivity disorder	• Study does not contain any of the outcomes of interest
Kommu (2017)	Profile of two hundred children with Autism Spectrum Disorder from a tertiary child and adolescent psychiatry centre	• Study does not contain any of the outcomes of interest
Kotte (2013)	Autistic traits in children with and without ADHD	• No diagnosis of ASD.
Kuban (2009)	Positive Screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in Extremely Low Gestational Age Newborns	• Study does not contain any relevant predictive variables
Kuban (2016)	Girls and Boys Born before 28 Weeks Gestation: Risks of Cognitive, Behavioral, and Neurologic Outcomes at Age 10 Years	• Study does not contain any of the outcomes of interest
Kumar (2017)	Prevalence of autism spectrum disorders and its association with Epileptiform activity among children with intellectual disability in a tertiary centre	• Study does not contain any of the outcomes of interest
Lampi (2012)	Risk of autism spectrum disorders in low birth weight and small for gestational age infants.	• Case-control study
Langridge (2013)	Maternal conditions and perinatal characteristics associated with autism spectrum disorder and intellectual disability	• Study does not contain any relevant predictive variables
Larsson (2005)	Risk factors for autism: perinatal factors, parental psychiatric history, and socioeconomic status.	• Case-control study
Leavey (2013)	Gestational age at birth and risk of autism spectrum disorders in Alberta, Canada	• Study does not contain any relevant predictive variables
Lehti (2013)	Autism spectrum disorders in IVF children: a national case-control study in Finland	• Case-control study
Levy (2010)	Autism spectrum disorder and co-occurring developmental, psychiatric, and medical conditions among children in multiple populations of the United States.	• ASD diagnosis before predictor evaluation

Author (year)	Title	Reason for exclusion
Leyfer (2006)	Comorbid psychiatric disorders in children with autism: interview development and rates of disorders.	• Not a relevant study design
Linsell (2016)	Prognostic Factors for Behavioral Problems and Psychiatric Disorders in Children Born Very Preterm or Very Low Birth Weight: A Systematic Review	• Study does not contain any of the outcomes of interest
Losh (2012)	Lower birth weight indicates higher risk of autistic traits in discordant twin pairs	• Study does not contain any relevant predictive variables
Lyall (2012)	Fertility therapies, infertility and autism spectrum disorders in the Nurses' Health Study II	• Case-control study
Lyall (2013)	Infertility and its treatments in association with autism spectrum disorders: a review and results from the CHARGE study	• Case-control study
Mackay (2013)	Obstetric factors and different causes of special educational need: retrospective cohort study of 407,503 schoolchildren	• Study does not contain any relevant predictive variables
Magnúsdóttir (2016)	The impact of attention deficit/hyperactivity disorder on adaptive functioning in children diagnosed late with autism spectrum disorder—A comparative analysis	• Study does not contain any of the outcomes of interest
Maimburg (2006)	Perinatal risk factors and infantile autism	• Case-control study
Malm (2012)	Prenatal exposure to selective serotonin reuptake inhibitors and infant outcome	• Review article but not a systematic review
Mamidala (2013)	Prenatal, perinatal and neonatal risk factors of Autism Spectrum Disorder: a comprehensive epidemiological assessment from India	• Full text paper not available
Mamidala (2013)	Maternal hormonal interventions as a risk factor for Autism Spectrum Disorder: An epidemiological assessment from India	• Case-control study
Man (2015)	Exposure to selective serotonin reuptake inhibitors during pregnancy and risk of autism spectrum disorder in children: a systematic review and meta-analysis of observational studies.	• Systematic review - relevant studies already included
Mann (2010)	Pre-eclampsia, birth weight, and autism spectrum disorders	• Case-control study
Mannion (2013)	An investigation of comorbid psychological disorders, sleep problems, gastrointestinal symptoms and epilepsy in children and	• ASD diagnosis before predictor evaluation

Author (year)	Title	Reason for exclusion
	adolescents with Autism Spectrum Disorder	
Maramara (2014)	Pre- and perinatal risk factors for autism spectrum disorder in a New Jersey cohort	• Study does not contain any relevant predictive variables
Mathewson (2017)	Mental health of extremely low birth weight survivors: A systematic review and meta-analysis	• Study does not contain any relevant predictive variables
Mattila (2010)	Comorbid psychiatric disorders associated with Asperger syndrome/high-functioning autism: a community- and clinic-based study.	• ASD diagnosis before predictor evaluation
Meijerink (2016)	Behavioral, cognitive, and motor performance and physical development of five-year-old children who were born after intracytoplasmic sperm injection with the use of testicular sperm	• Study does not contain any of the outcomes of interest
Mezzacappa (2017)	Risk for autism spectrum disorders according to period of prenatal antidepressant exposure: A systematic review and meta-analysis	• Systematic review - relevant studies already included
Mohammed (2016)	Incidence of autism in high risk neonatal follow up	• Study does not contain any relevant predictive variables
Moore (2012)	Screening for autism in extremely preterm infants: problems in interpretation.	• Study does not contain any relevant predictive variables
Moster (2008)	Long-term medical and social consequences of preterm birth.	• Study does not contain any relevant predictive variables
Movsas (2012)	The Effect of Gestational Age on Symptom Severity in Children with Autism Spectrum Disorder	• Study does not contain any relevant predictive variables
Mpaka (2016)	Prevalence and comorbidities of autism among children referred to the outpatient clinics for neurodevelopmental disorders	• Study does not contain any of the outcomes of interest
Nærland (2017)	Age and gender-related differences in emotional and behavioural problems and autistic features in children and adolescents with Down syndrome: a survey-based study of 674 individuals	• ASD diagnosis with questionnaire
Nilsen (2013)	Analysis of self-selection bias in a population-based cohort study of autism spectrum disorders	• Study does not contain any relevant predictive variables
Nomura (2014)	A clinical study of attention-deficit/hyperactivity disorder in preschool children--prevalence and differential diagnoses	• Study does not contain any of the outcomes of interest
Oberman (2015)	Autism spectrum disorder in Phelan-McDermid syndrome: initial	• Study does not contain any of the outcomes of interest

Author (year)	Title	Reason for exclusion
	characterization and genotype-phenotype correlations	
Oeseburg (2010)	Pervasive developmental disorder behavior in adolescents with intellectual disability and co-occurring somatic chronic diseases	• Study does not contain any of the outcomes of interest
Oeseburg (2010)	Prevalence of chronic diseases in adolescents with intellectual disability	• Study does not contain any of the outcomes of interest
Oeseburg (2011)	Prevalence of chronic health conditions in children with intellectual disability: a systematic literature review	• Review article but not a systematic review
Ortiz (2017)	Early warning signs of autism spectrum disorder in people with Down syndrome	• Data not reported in an extractable format
Oshodi (2016)	Autism spectrum disorder in a community-based sample with neurodevelopmental problems in Lagos, Nigeria	• Study does not contain any of the outcomes of interest
Padilla (2016)	Intrinsic Functional Connectivity in Preterm Infants with Fetal Growth Restriction Evaluated at 12 Months Corrected Age	• Study does not contain any relevant predictive variables
Pinto-Martin (2011)	Prevalence of autism spectrum disorder in adolescents born weighing <2000 grams.	• Study does not contain any of the outcomes of interest
Polyak (2015)	Comorbidity of intellectual disability confounds ascertainment of autism: implications for genetic diagnosis	• Full text paper not available
Pondé (2010)	Frequency of symptoms of attention deficit and hyperactivity disorder in autistic children	• ASD diagnosis before predictor evaluation
Pringsheim (2013)	Social behavior and comorbidity in children with tics	• Study does not contain any of the outcomes of interest
Pritchard (2016)	Autism in Toddlers Born Very Preterm	• Study does not contain any relevant predictive variables
Rais (2014)	Association Between Antidepressants Use During Pregnancy and Autistic Spectrum Disorders: A Meta-analysis	• Systematic review - relevant studies already included
Rellini (2004)	Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC) correspondence and conflicts with DSM-IV criteria in diagnosis of autism.	• Not a relevant study design
Rimal (2016)	Prevalence of attention deficit hyperactivity disorder among school children and associated co-morbidities - a hospital based descriptive study	• Study does not contain any of the outcomes of interest

Author (year)	Title	Reason for exclusion
Roberts (2012)	Heart activity and autistic behavior in infants and toddlers with fragile X syndrome	• No diagnosis of ASD.
Roberts (2012)	Visual Attention and Autistic Behavior in Infants with Fragile X Syndrome	• No diagnosis of ASD.
Roberts (2016)	Infant Development in Fragile X Syndrome: Cross-Syndrome Comparisons	• Study does not contain any of the outcomes of interest
Ryland (2012)	Autism spectrum symptoms in children with neurological disorders	• No diagnosis of ASD.
Saemundsen (2013)	Prevalence of autism spectrum disorders in an Icelandic birth cohort	• Study does not contain any of the outcomes of interest
Saltik (2012)	Neurological disorders combined with autism in children	• Study does not contain any relevant predictive variables
Sanmaneechai (2013)	Treatment outcomes of West syndrome in infants with Down syndrome	• Study does not contain any of the outcomes of interest
Scheirs (2009)	Differentiating among children with PDD-NOS, ADHD, and those with a combined diagnosis on the basis of WISC-III profiles.	• Study does not contain any of the outcomes of interest
Schieve (2014)	Population attributable fractions for three perinatal risk factors for autism spectrum disorders, 2002 and 2008 autism and developmental disabilities monitoring network	• Case-control study
Schieve (2015)	Comparison of Perinatal Risk Factors Associated with Autism Spectrum Disorder (ASD), Intellectual Disability (ID), and Co-occurring ASD and ID	• Case-control study
Schieve (2016)	Population impact of preterm birth and low birth weight on developmental disabilities in US children	• Study does not contain any of the outcomes of interest
Schrieken (2013)	Head circumference and height abnormalities in autism revisited: the role of pre- and perinatal risk factors	• Study does not contain any relevant predictive variables
Shimada (2012)	Parental age and assisted reproductive technology in autism spectrum disorders, attention deficit hyperactivity disorder, and Tourette syndrome in a Japanese population	• Study does not contain any of the outcomes of interest
Simonoff (2008)	Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample	• ASD diagnosis before predictor evaluation
Singh (2013)	Mental Health Outcomes in US Children and Adolescents Born Prematurely or with Low Birthweight	• Study does not contain any of the outcomes of interest

Author (year)	Title	Reason for exclusion
Skotko (2013)	Contributions of a specialty clinic for children and adolescents with Down syndrome	• Study does not contain any of the outcomes of interest
Srebnicki (2013)	Adolescent outcome of child ADHD in primary care setting: stability of diagnosis	• Study does not contain any of the outcomes of interest
Stahlberg (2010)	Mental health problems in youths committed to juvenile institutions: Prevalences and treatment needs	• Study does not contain any of the outcomes of interest
Stephens (2012)	Screening for autism spectrum disorders in extremely preterm infants.	• Study does not contain any relevant predictive variables
Tonnsen (2016)	Prevalence of autism spectrum disorders among children with intellectual disability	• Study does not contain any of the outcomes of interest
Treyvaud (2013)	Psychiatric outcomes at age seven for very preterm children: rates and predictors.	• Not a relevant study design
Unenge (2012)	Is autism spectrum disorder common in schizophrenia?	• Study does not contain any relevant predictive variables
Ververi (2012)	Clinical and laboratory data in a sample of Greek children with autism spectrum disorders	• Study does not contain any of the outcomes of interest
Wang (2017)	Prenatal, perinatal, and postnatal factors associated with autism: A meta-analysis	• Study does not contain any relevant predictive variables
Webb (2003)	Prevalence of autistic spectrum disorder in children attending mainstream schools in a Welsh education authority.	• Study does not contain any relevant predictive variables
Weisbrot (2005)	The presentation of anxiety in children with pervasive developmental disorders.	• ASD diagnosis before predictor evaluation
Williams (2008)	Perinatal and maternal risk factors for autism spectrum disorders in New South Wales, Australia.	• Case-control study
Wong (2014)	Evaluation of early childhood social-communication difficulties in children born preterm using the Quantitative Checklist for Autism in Toddlers.	• Study does not contain any relevant predictive variables
Worley (2011)	Prevalence of autism spectrum disorders in toddlers receiving early intervention services	• Study does not contain any relevant predictive variables
Wu (2016)	Risk of Autism Associated With Hyperbilirubinemia and Phototherapy	• Study does not contain any relevant predictive variables
Zachor (2011)	Assisted reproductive technology and risk for autism spectrum disorder	• Full text paper not available
Zachor (2013)	Do risk factors for autism spectrum disorders affect gender representation?	• Study does not contain any of the outcomes of interest

Author (year)	Title	Reason for exclusion
Zhang (2010)	Prenatal and perinatal risk factors for autism in China	• Study does not contain any relevant predictive variables
Zuckerman (2015)	Parental concerns, provider response, and timeliness of autism spectrum disorder diagnosis.	• Study does not contain any relevant predictive variables

Appendix I – References

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