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	