# Supplementary Online Content

Zhang T, Sidorchuk A, Sevilla-Cermeño L, et al. Association of cesarean delivery with risk of neurodevelopmental and psychiatric disorders in the offspring: a systematic review and meta-analysis. *JAMA Netw Open*. 2019;2(8):e1910236. doi:10.1001/jamanetworkopen.2019.10236



**This supplementary material has been provided by the authors to give readers additional information about their work.**

## **eTable 1.** Full search strategy

Date: 19 December 2018
Topic/research question: Association of obstetric mode of delivery and psychiatric disorders in the offspring
Librarian(s): Magdalena Svanberg & GunBrit Knutssön (Karolinska Institutet University Library)

### **eTable 1a.** Summary data for each database

| **Databases**[a] | **Number of hits** |
|---|---|
| Medline (Ovid) | 1911 |
| Embase (embase.com) | 2649 |
| Web of Science Core Collection | 1714 |
| PsycINFO | 679 |

[a] Full search strategy was presented for Medline database. Search strategy for other databases was similar to eTable 1b.

### **eTable 1b. Search terms for Medline search**

| # | **Searches** | **Results** |
|---|---|---|
| 1 | Delivery, Obstetric/ | 27303 |
| 2 | exp Cesarean Section/ | 42113 |
| 3 | exp Extraction, Obstetrical/ | 3306 |
| 4 | Obstetrical Forceps/ | 1621 |
| 5 | ("c section*" or c-section* or cesar* or caesar* or delivery mode or delivery modes or elective cs or "mode of delivery" or obstetric* forcep* or planned cs* or ventouse*).ti,ab,kf. | 63787 |
| 6 | ((obstetric* or vacuum) adj2 extract*).ti,ab,kf. | 1931 |
| 7 | ((abdominal or assisted or forcep* or instrument* or operative or vacuum) adj2 (birth* or deliver* or vd)).ti,ab,kf. | 7486 |
| 8 | ((birth or delivery or obstetric*) adj3 complication*).ti,ab,kf. | 8687 |
| 9 | (birth histor* or birth information).ti,ab,kf. | 756 |
| 10 | ((obstetric* or peri-natal or perinatal) adj3 (characteristic* or factor* or risk*)).ti,ab,kf. | 11138 |
| 11 | or/1-10 | 112357 |
| 12 | Mental Disorders/ | 153526 |
| 13 | exp Anxiety Disorders/ | 75153 |
| 14 | exp "Bipolar and Related Disorders"/ | 37869 |
| 15 | exp "Disruptive, Impulse Control, and Conduct Disorders"/ | 7998 |
| 16 | exp Dissociative Disorders/ | 4085 |
| 17 | exp Elimination Disorders/ | 5264 |
| 18 | exp "Feeding and Eating Disorders"/ | 28361 |
| 19 | Mood Disorders/ | 13343 |
| 20 | Depressive Disorder, Major/ | 26811 |
| 21 | Depressive Disorder/ | 69223 |
| 22 | Depressive Disorder, Treatment-Resistant/ | 906 |
| 23 | Dysthymic Disorder/ | 1113 |
| 24 | Cyclothymic Disorder/ | 653 |
| 25 | exp Neurodevelopmental Disorders/ | 167979 |
| 26 | Neurotic Disorders/ | 17943 |
| 27 | exp "Schizophrenia Spectrum and Other Psychotic Disorders"/ | 140016 |
| 28 | exp Substance-Related Disorders/ | 262328 |
| 29 | exp "Trauma and Stressor Related Disorders"/ | 36310 |
| # | **Searches** | **Results** |

| | | |
|---|---|---|
| 30 | (adhd or attention deficit or anorexia or asd or autism or autistic or binge eating or bipolar* or bulimia* or compulsive or depress* or dyscalculia* or dyslexia* or neurosis or neuroses or ocd or obsessive or panic or paranoi* or phobia or phobic or psychosis or psychoses or psychological trauma* or psychotic or ptsd or schizophren* or tics).ti,ab,kf. | 747722 |
| 31 | ((acute stress or adjustment or anxiety or conduct or dissociative or disruptive or eating or hyperactivity or learning or mood or neurodevelopmental or neurotic or personality or posttrauma* or tic or traumatic stress) adj3 (disease* or disorder*)).ti,ab,kf. | 145950 |
| 32 | ((development* or intellectual*) adj2 (disorder* or disabilit*)).ti,ab,kf. | 31244 |
| 33 | (mental* adj2 (disease* or disorder* or ill* or problem*)).ti,ab,kf. | 90872 |
| 34 | ((alcohol or drug* or substance*) adj3 (abuse or disorder* or misuse)).ti,ab,kf. | 90017 |
| 35 | or/12-34 | 1361923 |
| 36 | exp Case-Control Studies/ | 960041 |
| 37 | Control Groups/ | 1601 |
| 38 | Matched-Pair Analysis/ | 4661 |
| 39 | exp Cohort studies/ | 1807116 |
| 40 | Cross-Sectional Studies/ | 281284 |
| 41 | observational study.pt. | 55739 |
| 42 | Registries/ | 77457 |
| 43 | Prevalence/ | 261164 |
| 44 | (cohort* or cross sectional or control group* or longitudinal or observational or prevalence or prospective or register stud* or registr* or retrospective or transversal).ti,ab,kf. | 2576728 |
| 45 | (case* adj5 control*).ti,ab,kf. | 171126 |
| 46 | (case adj3 comparison*).ti,ab,kf. | 2894 |
| 47 | or/36-46 | 3768258 |
| 48 | exp Child/ | 1801194 |
| 49 | Adolescent/ | 1901581 |
| 50 | Infant/ | 750175 |
| 51 | Siblings/ | 10077 |
| 52 | Twin study/ | 8005 |
| 53 | Prenatal Exposure Delayed Effects/ | 26420 |
| 54 | (adoles* or adult* or boy* or child* or girl* or infant* or infancy or kid or kids or offspring or school age or schoolchild* or sibling* or teen* or toddler* or twin*).ti,ab,kf. | 2855577 |
| 55 | or/48-54 | 4503500 |
| 56 | 11 and 35 and 47 and 55 | 1911 |

**eTable 2.** Characteristics of the articles excluded due to duplicate data

| Study | Study location Period | Study design | Number of participants | | Outcome(s) | Outcome assessments | Offspring' age range | Variables adjusted for | Matched factors | Newcastle-Ottawa score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Caesarean section | Vaginal delivery | | | | | | |
| Bilder, 2009[1] | United States 2002 | Case-Control | 1331 | 11068 | ASD including Autism, PDD-NOS, and AS | ICD-9 and DSM-IV-TR | 8 years old | Maternal age, gestational length, and parity | Gender and birth year | 7 |
| Brimacombe, 2007[2] | United States 2001-2003 | Cohort | NR | NR | ASD including autism, PDD-NOS, and AS | DSM-IV, Autism Diagnostic Interview-Revised, Autism Diagnostic Observation Schedule-Generic, CARS | 2 to 18 years | None | / | 5 |
| Dalman, 1999[3] | Sweden 1973-1995 | Cohort | NR | NR | Schizophrenia | ICD-9 code 295 | 10-22 years | Psychotic illness in mother, maternal age, marital status, child's birth year, birth hospital and sex. | / | 8 |

| Study | Study location Period | Study design | Number of participants | | Outcome(s) | Outcome assessments | Offspring' age range | Variables adjusted for | Matched factors | Newcastle-Ottawa score |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Caesarean section | Vaginal delivery | | | | | | |
| Gunnel, 2003[4] | Sweden 1973-1997 | Cohort | 20,558 | 226,097 | Non-affective psychosis | ICD-9 codes 295, 297-299 and ICD-10 codes F20, F21-F29 | Mean age at first hospital admission was 21 years | None | / | 6 |
| Nilsen, 2013[5] | Norway 1999-2010 | Cohort | 41,279 | 260,081 | ASD, including childhood autism, atypical autism, AS, other PDD, and PDD, unspecified. | the Autism Diagnostic Interview - Revised, the Autism Diagnostic Observation Schedule, DSM-IV, and ICD-10 codes F84.0, F84.1, F84.5, F84.8, F84.9. | 3-11 years | Year of birth, maternal age, paternal age, marital status, parity, and hospital size. | / | 9 |

*Abbreviations*: ASD, autism spectrum disorders; PDD-NOS, pervasive developmental disorder-not otherwise specified; AS, Asperger's Syndrome; DSM, The Diagnostic and Statistical Manual of Mental Disorders; ICD, the International Statistical Classification of Diseases and Related Health Problems; CARS, Childhood Autism Rating Scale; NR, not reported.

**eTable 3.** Variables adjusted for or matched by in each study included in the main analysis

| Study | Adjusted for | Matched for |
|---|---|---|
| Al-Jammas, 2012[6] | / | / |
| Amiri, 2012[7] | / | / |
| Axelsson, 2018[8] [a] | / | / |
| Axelsson, 2019[9] [a] | / | / |
| Bain, 2000[10] | / | The obstetric unit of birth, gender, data of birth, maternal age, maternal parity and father's occupation. |
| Bilder, 2013[11] | / | / |
| Brander, 2016[12] [a] | / | / |
| Brander, 2018[13] [a] | / | / |
| Burstyn, 2010[14] | / | / |
| Byrne, 2000[15] | / | Gender, maternal age, parity, social class and home/hospital birth |
| Cak, 2013[16] | / | / |
| Chen, 2017[17] [a] | / | / |
| Chien, 2015[18] | / | / |
| Chudal, 2014[19] | Maternal age, psychiatric history, education level, birth place, maternal smoking during pregnancy and number of pervious birth | Sex, date of birth and residence in Finland on the first date of diagnosis of the case |
| Cnattingius, 1999[20] | / | Year and hospital of birth |
| Cubo, 2014[21] | Family history of tics, BMI, and presence of any coexistent comorbid neuropsychiatric disturbances | Age and gender |
| Curran, 2015[22] [a] | / | / |
| Curran, 2016[23] [a] | / | / |
| Dodds, 2011[24] | / | |
| Duan, 2014[25] | Parental age, parents' level of education, parents' character, family history of psychiatric disorder, stress, passive smoking, pregnancy complications, premature delivery, jaundice, threatened abortion, infections | age and gender |
| Durkin, 2015[26] | / | / |
| El-Baz, 2011[27] | / | Age, gender, environment and habit |

| Study | Adjusted for | Matched for |
|---|---|---|
| Eriksson, 2012[28] | / | / |
| Geller, 2008[29] | / | Age, gender, socioeconomic status, and family intact status. |
| Glasson, 2004[30] | / | Sex |
| Gourion, 2008[31] | Sex, perinatal condition, obstetrical complications, family adversity, maternal diagnostic of lifetime of major depressive disorder | / |
| Guisso, 2018[32] | Gender, age, delivery complications, and feeding difficulty, gestation variables, socioeconomic variables (including family history of psychiatric disease). | / |
| Gustafsson, 2011[33] | / | / |
| Haglund, 2011[34] | / | / |
| Halmoy, 2012[35] | Year of birth, maternal age, parity, marital status of mother, educational level of mother | / |
| Hamadé, 2013[36] | / | Age, region |
| Harrison, 2003[37] | / | / |
| Hultman, 1999[38] | / | Sex, year of birth, and hospital of birth |
| Hultman, 2002[39] | Maternal age, parity, smoking habits during pregnancy, mothers' country of birth, hypertensive diseases, diabetes, pregnancy bleeding, season of birth, gestational age, birth weight for gestational age, Apgar score at 5 minutes, congenital malformations | Sex, year, and hospital of birth |
| Hvelplund, 2016[40 a] | / | / |
| Ji, 2018[41] | / | / |
| Jones, 1998[42] | Sex, socioeconomic status at birth, maternal Depression, and maternal smoking | / |
| Karlsson, 2012[43] | / | Sex, date of birth, birth hospital, and municipality. |
| Kendell, 2000[44] | / | the obstetric unit of birth, gender, date of birth (+2 months), maternal age (+2 years), maternal parity (first baby v. second or subsequent baby) and father's occupation (manual v. non-manual) |
| Ketzer, 2012[45] | IQ, maternal ADHD and cigarettes/day during pregnancy. | Gender and age |
| Kim, 2015[46] | Age, gender and socioeconomic status | / |

| | | |
|---|---|---|
| Kissin, 2014[47] | / | / |
| **Study** | **Adjusted for** | **Matched for** |
| Leivonen, 2016[48] | Maternal age, maternal SES, maternal psychiatric history, paternal age, and paternal psychiatric history. | Sex, date of birth, and place of birth |
| Maimburg, 2006[49] | Paternal age, mothers citizenship, birthweight and gestational age, Apgar, birth defect and irregular foetal position | Sex, year and country of birth |
| Maramara, 2014[50] | / | / |
| Matsuishi, 1999[51] | / | / |
| Micali, 2015[52] | Parental social class | / |
| Mrozek-Budzyn, 2013[53] | / | Year of birth, gender, and general practitioners |
| Murray, 2016[54] | / | / |
| O'Neill, 2016[55] | Gestational age, small for gestational age, Apgar score at 5min, maternal age, and maternal psychiatric history | / |
| Ordonez, 2005[56] | / | / |
| Polo-Kantola, 2014[57] | Maternal age, smoking during pregnancy, parity, and maternal psychiatric history. | Sex, date of birth, and place of birth |
| Razaz, 2018[58] [a] | / | / |
| Schieve, 2014[59] | / | Birth year, sex, maternal country of residence, race-ethnicity, age and education. |
| Silva, 2014[60] | Maternal age, Apgar at 5 min, year of birth, and socio-economic indexes for areas | Year of birth, gender, and socioeconomic status |
| Sucksdorff, 2018[61] [a] | / | Data of birth, sex and place of birth |
| Sussmann, 2009[62] | / | Age |
| Vasconcelos, 2007[63] | / | Gender and age |
| Winkler-Schwartz, 2014[64] | / | / |
| Yip, 2017[65] | Gestational age and paternal age | / |
| Zhang, 2010[66] | Paternal age at delivery, gender and birth year | Gender and birth year |

[a] Studies originally adjusted for confounders but were re-calculated with 2 by 2 table in our main meta-analysis. Confounders that they originally adjusted for are:

Axelsson, 2018: Childhood antibiotic use, parental age, parental education, maternal marital status, maternal smoking, infant sex, 5-min Apgar score, use of CPAP or a ventilator, asphyxia, parental epilepsy, preeclampsia or hypertension, gestational diabetes, parity, maternal antibiotic use during the pregnancy, maternal infection during the pregnancy, parental psychiatric history
Axelsson, 2019: Childhood antibiotic use, parental age, parental education, maternal marital status, maternal smoking, infant sex, 5-min Apgar score, use of CPAP or a ventilator, asphyxia, parental epilepsy, preeclampsia or hypertension, gestational diabetes, parity, maternal antibiotic use during the pregnancy, maternal infection during the pregnancy, parental psychiatric history
Brander, 2016: Sex, year of birth, age of mother and father, and parity.
Brander, 2018: Sex, year of birth, age of mother and father, and parity.
Chen, 2017: Gestational age, children's and parental characteristics
Curran, 2015: Year of birth, infant sex, maternal age, gestational age, 5-minute Apgar score, maternal and paternal country of birth, small for gestational age, large for gestational age, first born, family income, and maternal and paternal depression, bipolar disorder, and non-affective disorder.
Curran, 2016: Year of birth, infant gender, maternal age, maternal smoking during pregnancy, gestational age, 5-min Apgar score, maternal and paternal country of birth, small for gestational age, large for gestational age, firstborn, family income, maternal and paternal depression, bipolar disorder and non-affective disorder.
Hvelplund, 2016: Gender, gestational age, parents' ethnicity, parity, SGA, cesarean delivery, Apgar score <7 at 5 minutes, and congenital malformations.
Razaz, 2018: Maternal age, country of birth, education, mother cohabits with partner, parity, maternal height, smoking, year of delivery, gestational age at delivery, birth weight for gestational age
Sucksdorff, 2018: Gestational age and weight for gestational age, maternal age, psychiatric history, substance abuse, smoking, socioeconomic status and parity.

**eTable 4.** Leave-one-study-out analyses

| Outcome | Study omitted | Pooled OR | 95% CI |
|---|---|---|---|
| Attention-deficit/hyperactivity disorder | Cak, 2013 | 1.17 | (1.08, 1.27) |
| | Murray, 2016 (Pelotas) | 1.18 | (1.09, 1.28) |
| | Kim, 2015 | 1.17 | (1.08, 1.27) |
| | Gustafsson, 2011 | 1.17 | (1.08, 1.27) |
| | Axelsson, 2018 | 1.2 | (1.10, 1.32) |
| | Silva, 2014 | 1.17 | (1.08, 1.28) |
| | Curran, 2016 | 1.2 | (1.07, 1.36) |
| | Sucksdorff, 2018 | 1.17 | (1.06, 1.28) |
| | Chen, 2017 | 1.16 | (1.07, 1.26) |
| | Halmoy, 2012 | 1.15 | (1.05, 1.25) |
| | Ketzer, 2012 | 1.16 | (1.07, 1.26) |
| | Ji, 2018 | 1.15 | (1.06, 1.25) |
| | Murray, 2016 (ALSPAC) | 1.16 | (1.09, 1.28) |
| | Amiri, 2012 | 1.13 | (1.08, 1.27) |
| | **Pooled estimate** | **1.17** | **(1.08, 1.27)** |
| Autism spectrum disorders | Ji, 2018 | 1.32 | (1.25 , 1.40) |
| | Chien, 2015 | 1.34 | (1.26 , 1.43) |
| | Curran, 2015 | 1.34 | (1.25 , 1.44) |
| | Glasson, 2004 | 1.31 | (1.24 , 1.39) |
| | Yip, 2017 (Norway) | 1.32 | (1.25 , 1.41) |
| | Matsuishi, 1999 | 1.33 | (1.25 , 1.41) |
| | Haglund, 2011 | 1.33 | (1.25 , 1.41) |
| | Winkler-Schwartz, 2014 | 1.33 | (1.25 , 1.41) |
| | Axelsson, 2019 | 1.35 | (1.28 , 1.42) |
| | Al-Jammas, 2012 | 1.32 | (1.25 , 1.40) |
| | Burstyn, 2010 | 1.35 | (1.27 , 1.43) |
| | Eriksson, 2012 | 1.32 | (1.25 , 1.40) |
| | Chen, 2017 | 1.33 | (1.25 , 1.41) |
| | Polo-Kantola, 2014 | 1.32 | (1.24 , 1.40) |
| | Schieve, 2014 | 1.33 | (1.25 , 1.41) |
| | Dodds, 2011 | 1.34 | (1.26 , 1.42) |
| | Yip, 2017 (Finland) | 1.33 | (1.25 , 1.42) |
| | Hultman, 2002 | 1.32 | (1.25 , 1.40) |
| | Duan, 2014 | 1.33 | (1.25 , 1.41) |
| | Durkin, 2015 | 1.33 | (1.25 , 1.41) |
| | Mrozek-Budzyn, 2013 | 1.33 | (1.26 , 1.42) |
| | Maramara, 2014 | 1.34 | (1.26 , 1.42) |
| | Zhang, 2010 | 1.33 | (1.25 , 1.41) |
| | Yip, 2017 (WA) | 1.31 | (1.24 , 1.40) |
| | Kissin, 2014 | 1.31 | (1.24 , 1.39) |
| | Hamadé, 2013 | 1.33 | (1.26 , 1.41) |
| | Maimburg, 2006 | 1.33 | (1.26 , 1.41) |
| | El-Baz, 2011 | 1.32 | (1.25 , 1.40) |
| | Guisso, 2018 | 1.33 | (1.25 , 1.41) |

| | | | |
|---|---|---|---|
| | **Pooled estimate** | **1.33** | **(1.25. 1.41)** |
| **Outcome** | **Study omitted** | **Pooled OR** | **95% CI** |
| Intellectual disability | **Chen, 2017** | **2.61** | **(1.51, 4.53)** |
| | Sussmann, 2009 | 1.93 | (0.82, 4.54) |
| | Bilder, 2013 | 1.26 | (1.00, 1.60) |
| | **Pooled estimate** | **1.83** | **(0.90, 3.70)** |
| Tic disorder | Leivonen, 2016 | 2.4 | (0.59, 9.81) |
| | Brander, 2017 | 2.21 | (0.44, 11.16) |
| | **Cubo, 2014** | **1.24** | **(1.02, 1.50)** |
| | **Pooled estimate** | **1.31** | **(0.98, 1.76)** |
| Obsessive-compulsive disorder | Brander, 2016 | 1.95 | (0.93, 4.11) |
| | Geller, 2008 | 1.66 | (0.68, 4.02) |
| | **Vasconcelos, 2007** | **1.13** | **(1.08, 1.19)** |
| | **Pooled estimate** | **1.49** | **(0.87, 2.56)** |
| Eating disorder | Cnattingius, 1999 | 1.23 | (0.96, 1.58) |
| | Razaz, 2018 | 1.25 | (0.93, 1.68) |
| | Micali, 2015 | 1.20 | (0.82, 1.74) |
| | Hvelplund, 2016 | 1.08 | (0.98, 1.18) |
| | **Pooled estimate** | **1.18** | **(0.96, 1.47)** |
| Major depression and affective psychoses | Hultman, 1999 | 1.06 | (0.99, 1.14) |
| | O'Neill, 2016 | 1.2 | (0.97, 1.48) |
| | Bain, 2000 | 1.06 | (0.98, 1.14) |
| | Chudal, 2014 | 1.04 | (0.97, 1.13) |
| | Gourion, 2008 | 1.06 | (0.98, 1.14) |
| | **Pooled estimate** | **1.06** | **(0.98, 1.14)** |
| Non-affective psychoses | Karlsson, 2012 | 1.02 | (0.82, 1.27) |
| | Harrison, 2003 | 1.06 | (0.86, 1.31) |
| | O'Neill, 2016 | 0.88 | (0.60, 1.28) |
| | Ordonez, 2005 | 1 | (0.81, 1.24) |
| | Jones, 1998 | 0.98 | (0.79, 1.22) |
| | Kendell, 2000 | 0.96 | (0.76, 1.21) |
| | Byrne, 2000 | 0.87 | (0.69, 1.11) |
| | **Pooled estimate** | **0.97** | **(0.78, 1.21)** |

**eTable 5.** Subgroup analyses according to country's income level and exposure ascertainment for neurodevelopmental and psychiatric disorders in caesarean-born offspring compared to vaginal-born offspring

| Outcome | Country's income level | | | Exposure ascertainment | | |
|---|---|---|---|---|---|---|
| | High income | Middle income | P-value | Medical records | Self-report | P-value |
| | OR (95% CI) | OR (95% CI) | | OR (95% CI) | OR (95% CI) | |
| ADHD | 1.14 (1.06-1.22)** | 1.27 (0.62-2.59)** | 0.93 | 1.13 (1.05-1.21)** | 1.71 (0.84-3.49)** | 0.51 |
| ASD | 1.33 (1.24-1.42)* | 1.37 (1.14-1.64) | 0.60 | 1.34 (1.26-1.42)** | 1.17 (0.89-1.53) | 0.56 |
| Psychosis | 1.05 (0.92-1.20)* | .. | NA | 1.02 (0.91-1.14) | .. | NA |

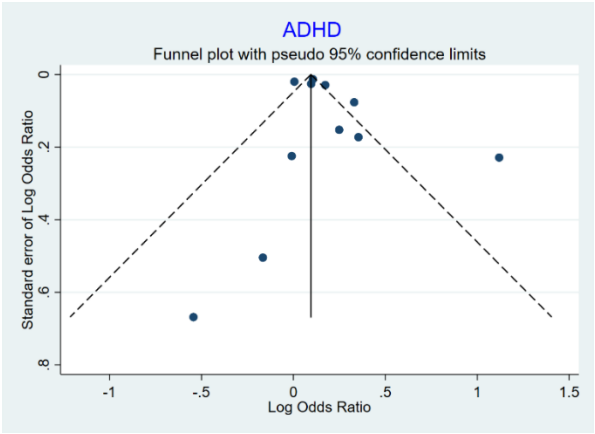
*Note:* Results shown are odds ratios with 95% confidence intervals. P-values presented in the table are for group differences. Significant results are highlighted in bold.
*Abbreviations:* ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorders; OR, odds ratio; CI, confidence interval
NA: calculation of the p value is not applicable.
* Study heterogeneity medium ($50\% < I^2 < 75\%$), p-value<0.05
** Study heterogeneity high ($I^2 > 75\%$), p-value<0.05

**eTable 6.** Meta-regression analyses

| | Test of moderators | | | | Variance accounted for | Test for residual heterogeneity | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of studies | Regression coefficient | 95% CI | p value | | $Q_{res}$ statistic | $I^2_{res}$ | DF | p value |
| *For ADHD* | | | | | | | | | |
| Publication year | 11 | -0.03 | -0.11 - 0.05 | 0.4 | 4.81% | 53.09 | 83.05 % | 9 | <0.001 |
| CS use proportion | 11 | 0.69 | -0.75 - 2.14 | 0.31 | 30.14% | 62.62 | 85.63 % | 9 | <0.001 |
| Study design | 11 | -0.19 | -0.59 – 0.21 | 0.31 | 0.7% | 51.05 | 82.37 % | 9 | <0.001 |
| Country income | 11 | -0.78 | -1.41 – (-0.16) | **0.02** | **77.3%** | 47.24 | 80.95 % | 9 | <0.001 |
| Exposure ascertainment | 11 | 0.74 | 0.12- 1.35 | **0.02** | **76.48%** | 47.72 | 81.14 % | 9 | <0.001 |
| *For ASD* | | | | | | | | | |
| Publication year | 28 | -0.01 | -0.03 - 0.003 | 0.11 | 23.49% | 68.94 | 62.29 % | 26 | <0.001 |
| CS use proportion | 28 | 0.26 | -0.33 - 0.85 | 0.38 | -1.39% | 87.81 | 70.39 % | 26 | <0.001 |
| Study design | 28 | -0.11 | -0.25 – 0.03 | 0.12 | 23.32% | 71.63 | 63.70 % | 26 | <0.001 |
| Country income | 28 | -0.11 | -0.38 – 0.15 | 0.39 | -0.03% | 87.57 | 70.31 % | 26 | <0.001 |
| Exposure ascertainment | 27 | -0.17 | -0.35 – 0.10 | 0.26 | -1.67% | 86.81 | 71.2% | 25 | <0.001 |

*Abbreviations:* ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorders; CI, confidence interval; DF: degree of freedom

**eFigure 1.** Publication bias: Funnel plots and Egger's tests for the main analyses

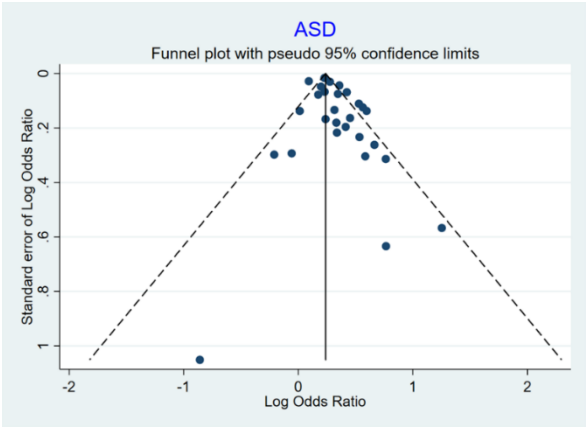



Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies = 11 Root MSE = 2.455

| Std_Eff | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| slope | .0707799 | .0308947 | 2.29 | 0.048 | .0008913 | .1406685 |
| bias | 1.180413 | .9986772 | 1.18 | 0.268 | -1.078752 | 3.439577 |

Test of H0: no small-study effects P = 0.268

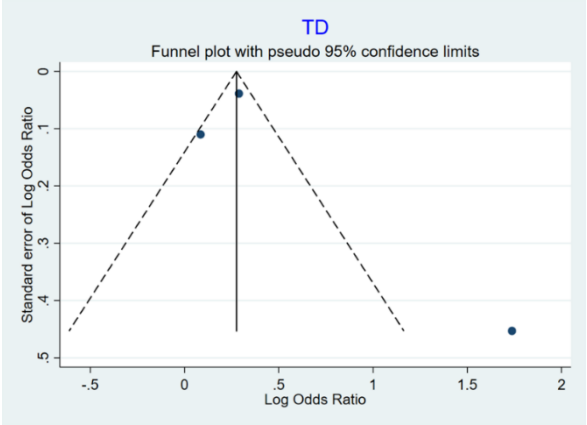



Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies = 28 Root MSE = 1.699

| Std_Eff | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| slope | .2000437 | .0251453 | 7.96 | 0.000 | .1483567 | .2517307 |
| bias | .9799376 | .4305486 | 2.28 | 0.031 | .0949322 | 1.864943 |

Test of H0: no small-study effects P = 0.031

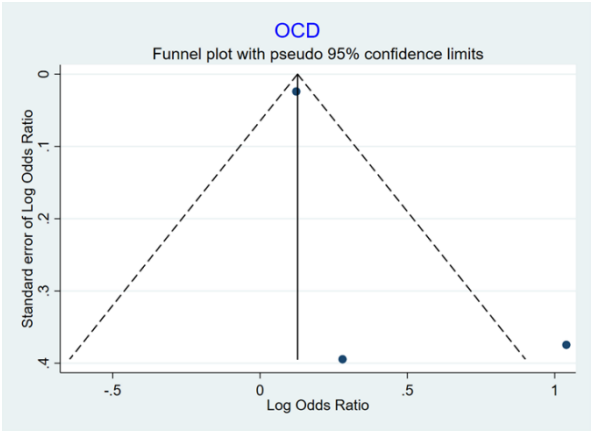



Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies = 3 Root MSE = 3.268

| Std_Eff | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| slope | .1994783 | .1895517 | 1.05 | 0.484 | -2.209005 | 2.607961 |
| bias | 1.55448 | 3.014338 | 0.52 | 0.697 | -36.74632 | 39.85527 |

Test of H0: no small-study effects P = 0.697

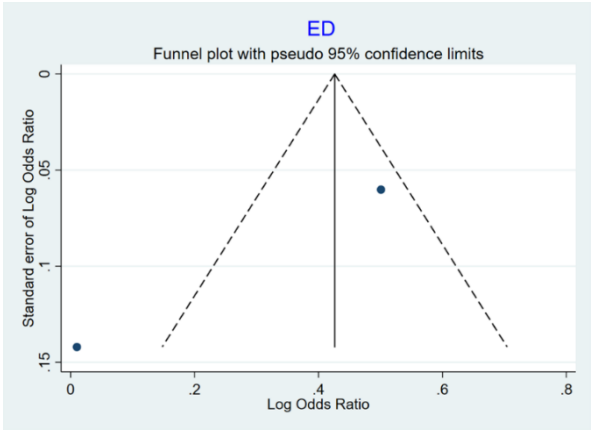



Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

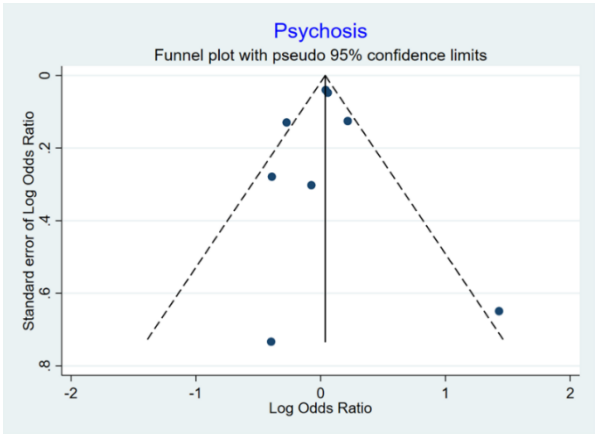
Number of studies = 3 Root MSE = 1.452

| Std_Eff | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| slope | .08673 | .0454468 | 1.91 | 0.307 | -.4907261 | .6641861 |
| bias | 1.514836 | 1.099458 | 1.38 | 0.400 | -12.45511 | 15.48478 |

Test of H0: no small-study effects P = 0.400




Egger's test was not performed since there were less than three studies were included.



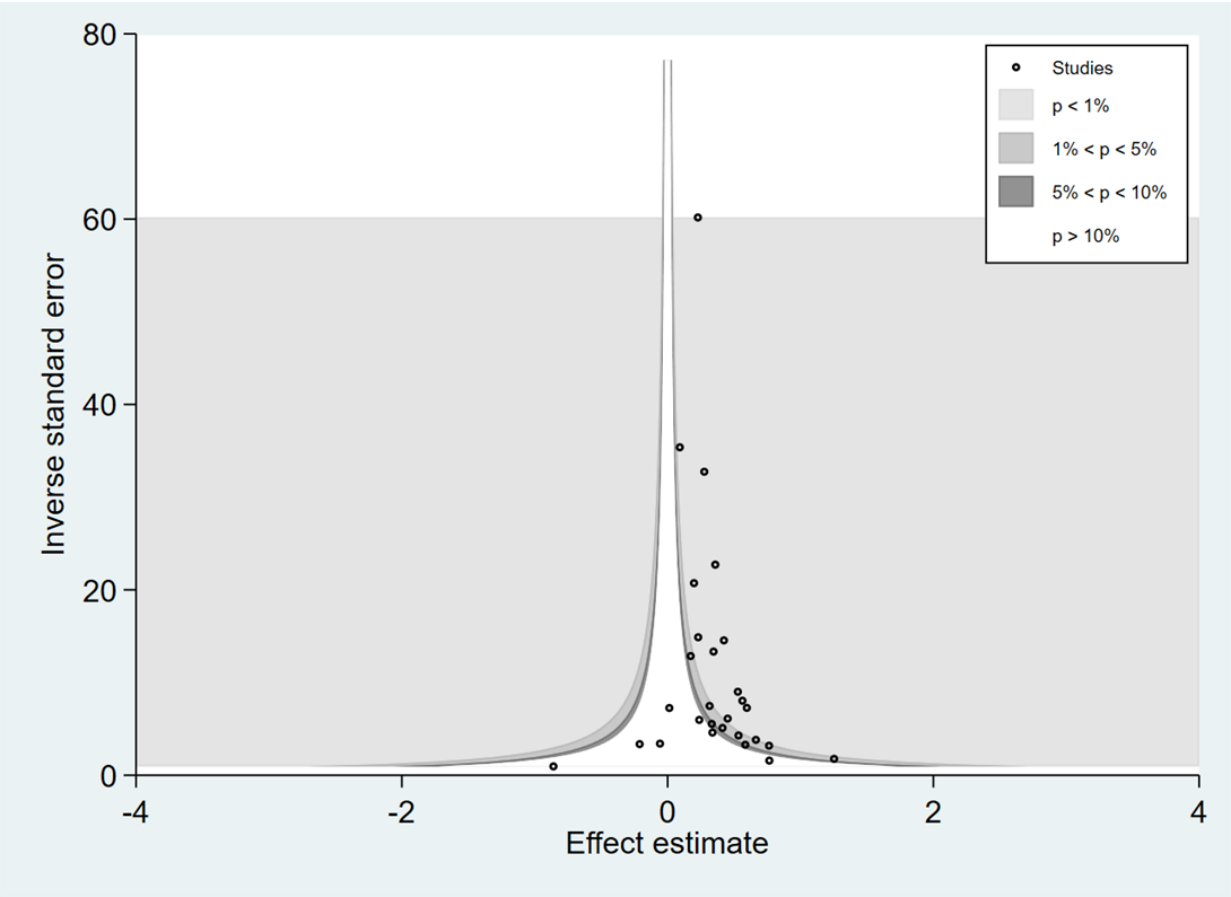

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies = 8 Root MSE = 1.594

| Std_Eff | Coef. | Std. Err. | t | P>\|t\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| slope | .0489981 | .0661743 | 0.74 | 0.487 | -.1129245 | .2109208 |
| bias | -.206496 | .817432 | -0.25 | 0.809 | -2.20668 | 1.793688 |

Test of H0: no small-study effects P = 0.809

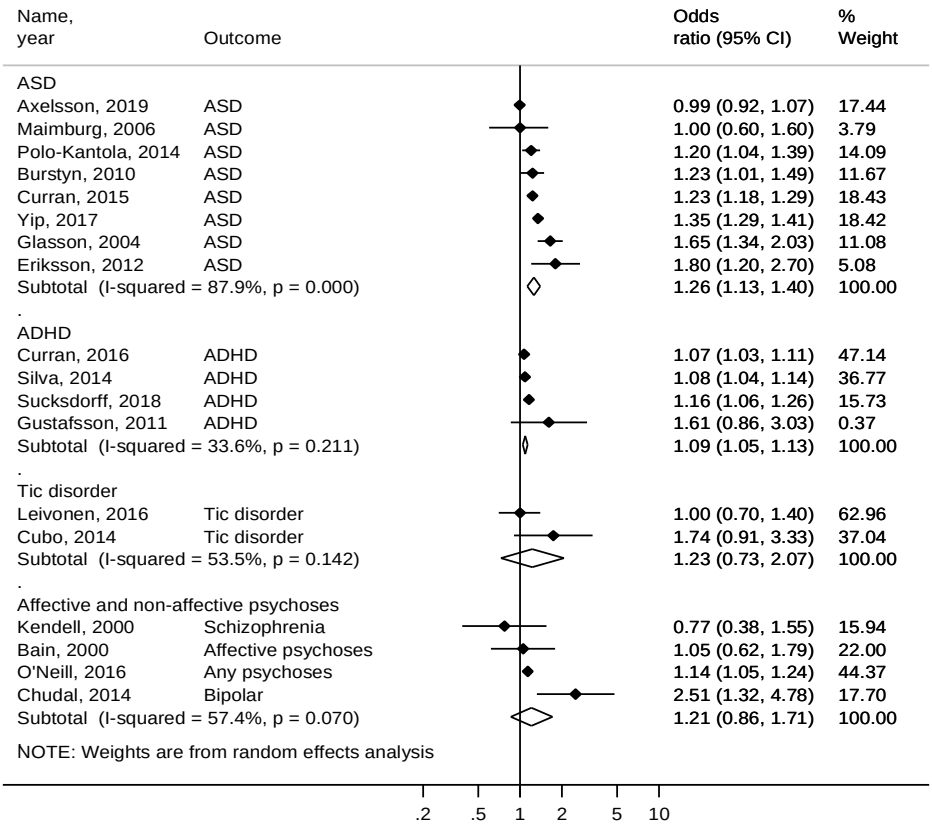
**eFigure 2.** Contour-enhanced funnel plot for ASD **for potential publication bias**



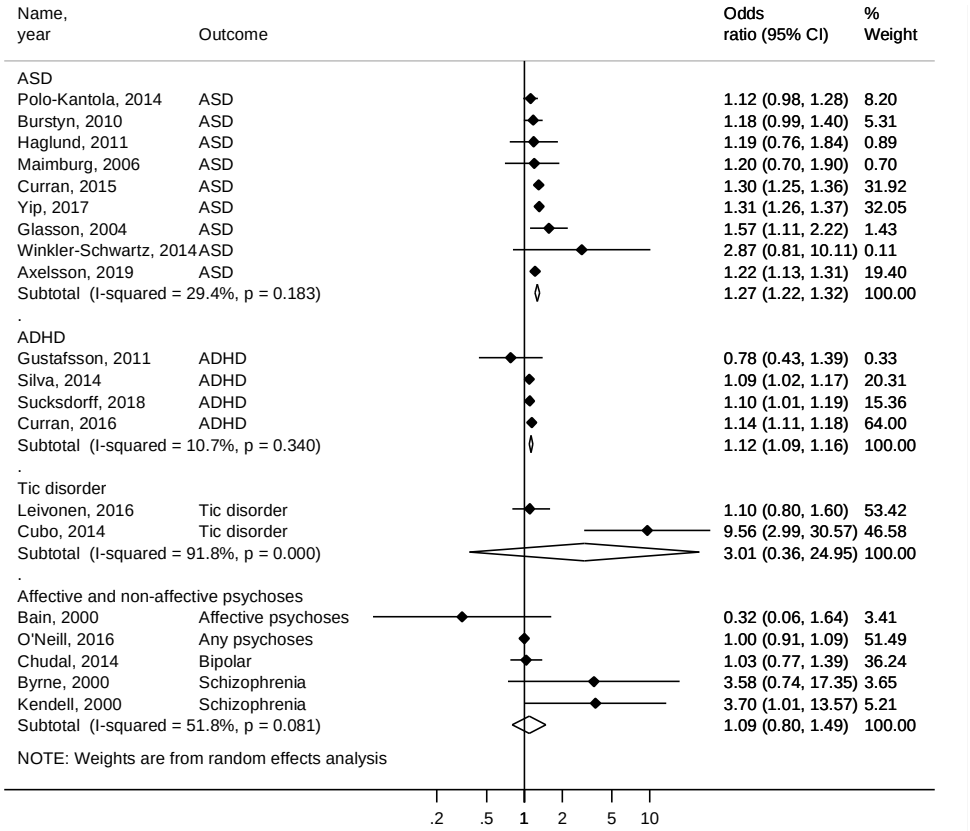

There is a suggestion of missing studies on the darker area (i.e. indicating high statistical significance) of left-hand-side of the plot, for which publication bias is a plausible explanation.

**eFigure 3.** Forest Plots of the Results of Random Effects Meta-analyses Stratified by Type of Cesarean Delivery (Elective or Emergency) and the Disorders

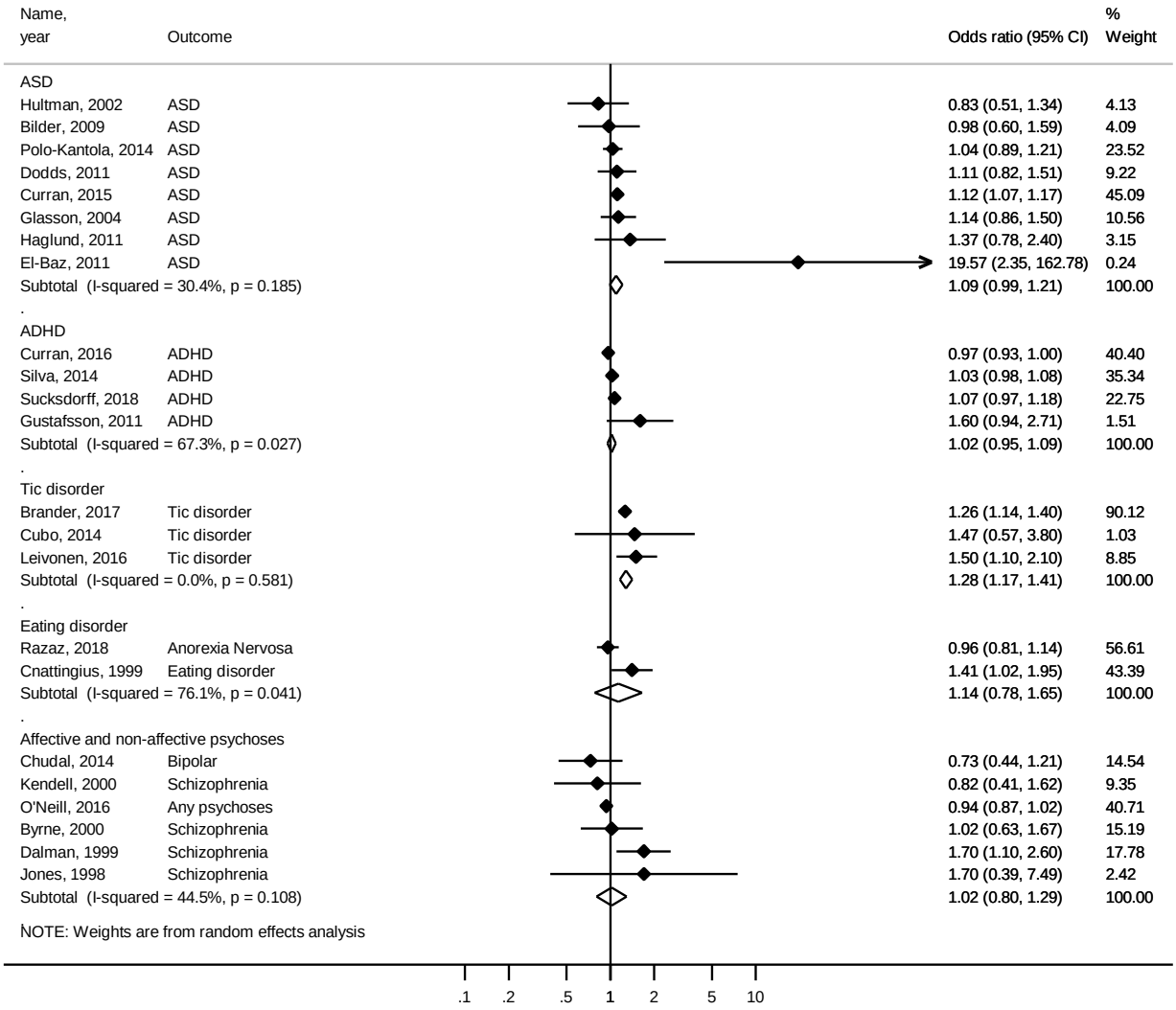
A. *Elective* caesarean section compared to *unassisted* vaginal delivery




B. *Emergency* caesarean section compared to *unassisted* vaginal delivery

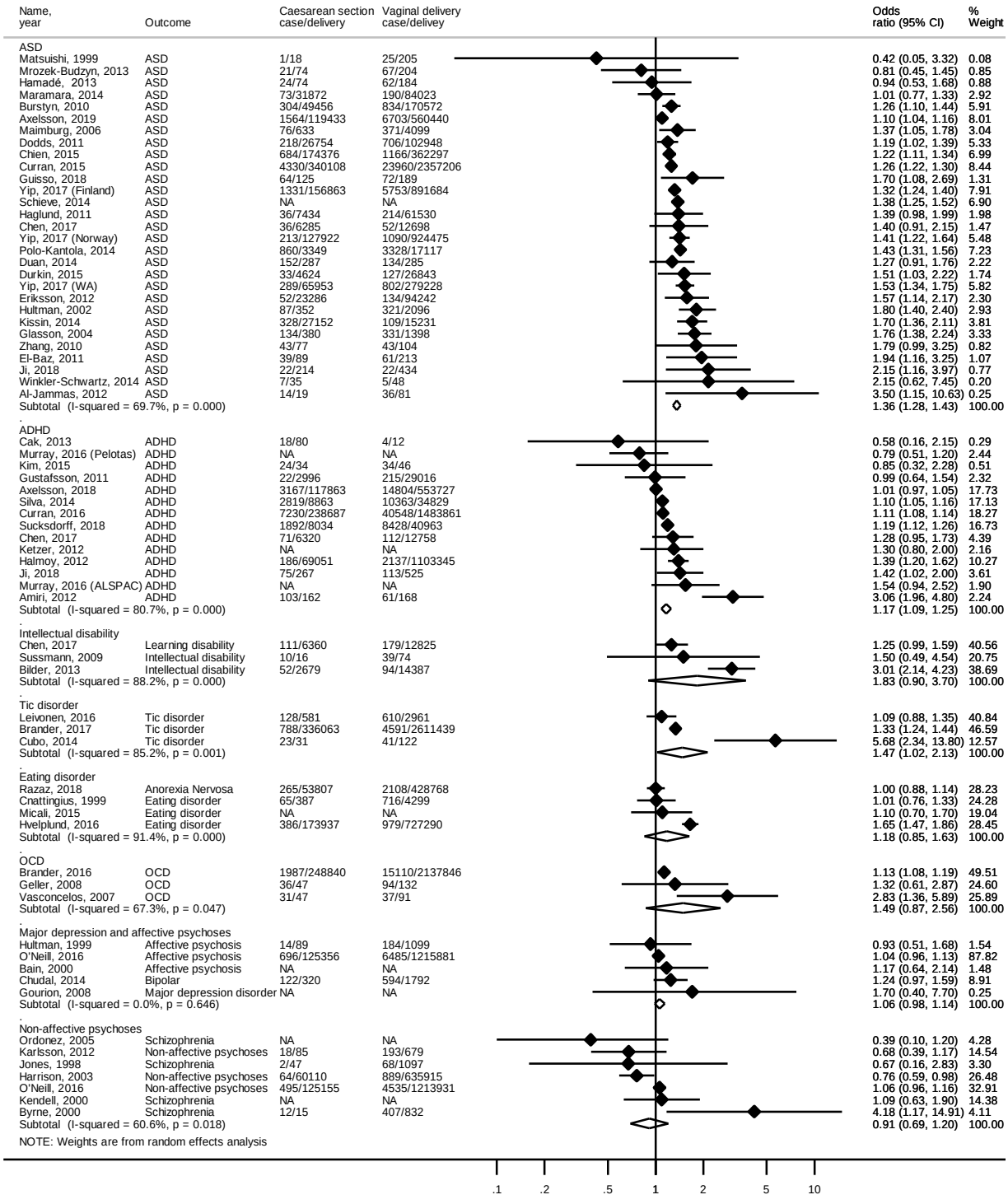


**eFigure 4.** Results of the association between birth by *assisted* vaginal delivery (compared to *unassisted* vaginal delivery) and neurodevelopmental and psychiatric disorders in the offspring



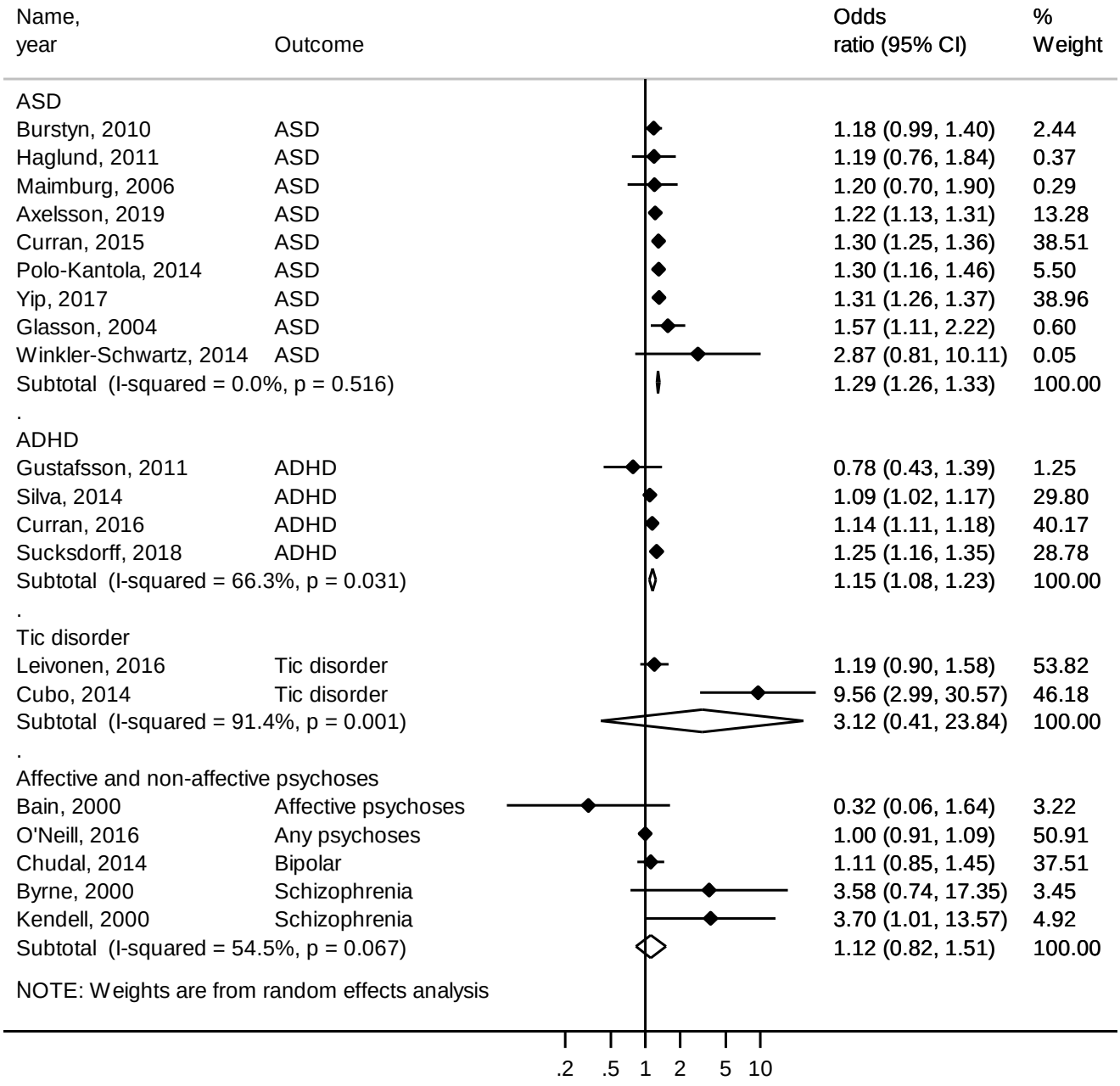

*Abbreviations:* ADHD: attention-deficit hyperactivity disorder; ASD: autism spectrum disorder

**eFigure 5.** Sensitivity analysis**:** Crude or least adjusted models
**eFigure 5a.** Forest plot of crude or least adjusted estimates of the association between birth by *caesarean section* and neurodevelopmental and psychiatric disorders in the offspring



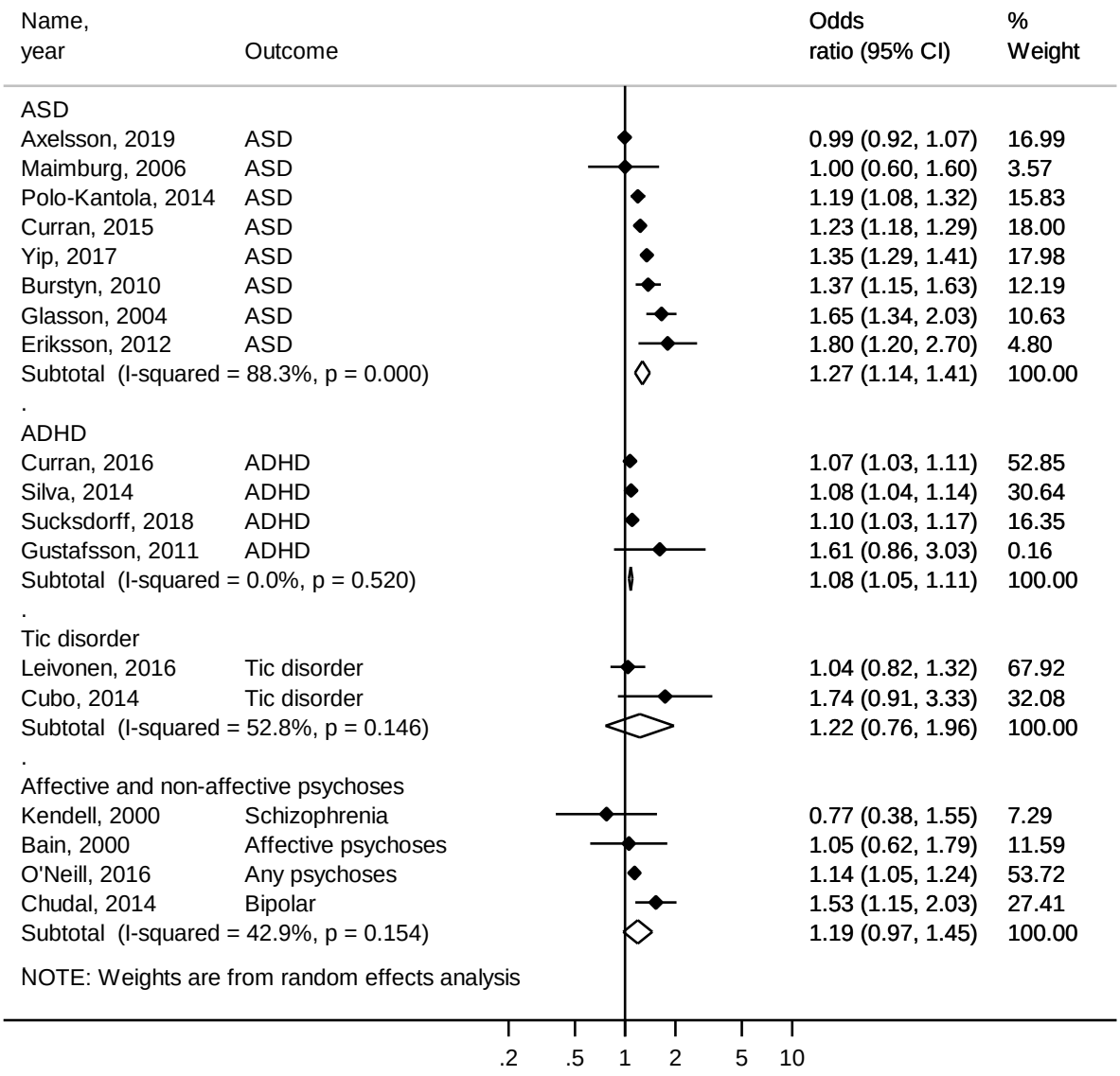

*Abbreviations:* NA: not available; ADHD: attention-deficit hyperactivity disorder; ASD: autism spectrum disorder; OCD: obsessive-compulsive disorder;

**eFigure 5b.** Forest plot of crude or least adjusted estimates of the association between birth by *emergency CS* and neurodevelopmental and psychiatric disorders in the offspring



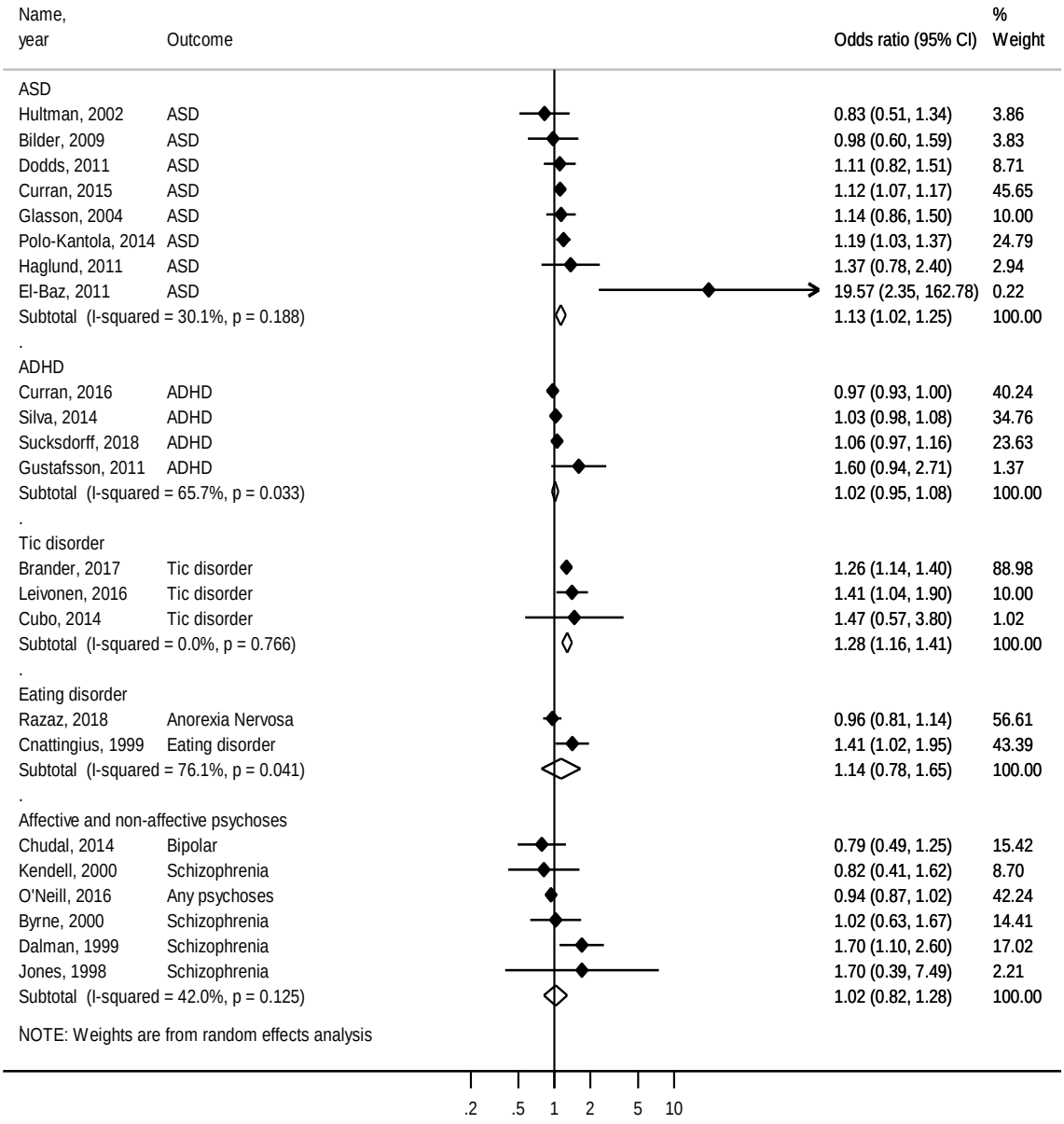

*Abbreviations:* NA: not available; ADHD: attention-deficit hyperactivity disorder; ASD: autism spectrum disorder

**eFigure 5c.** Forest plot of crude or least adjusted estimates of the association between birth by elective CS and psychiatric disorders in the offspring




*Abbreviations:* NA: not available; ADHD: attention-deficit hyperactivity disorder; ASD: autism spectrum disorder

**eFigure 5d.** Forest plot of crude or least adjusted estimates of the association between birth by *assisted* VD and psychiatric disorders in the offspring




*Abbreviations:* NA: not available; ADHD: attention-deficit hyperactivity disorder; ASD: autism spectrum disorder

**eReferences**


1. Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics. 2009;123(5):1293-1300.
2. Brimacombe M, Ming X, Lamendola M. Prenatal and birth complications in autism. Matern Child Health J. 2007;11(1):73-79.
3. Dalman C, Allebeck P, Cullberg J, Grunewald C, Koster M. Obstetric complications and the risk of schizophrenia: a longitudinal study of a national birth cohort. Arch Gen Psychiatry. 1999;56(3):234-240.
4. Gunnell D, Rasmussen F, Fouskakis D, Tynelius P, Harrison G. Patterns of fetal and childhood growth and the development of psychosis in young males: A cohort study. Am J Epidemiol. 2003;158(4):291-300.
5. Nilsen RM, Suren P, Gunnes N, et al. Analysis of self-selection bias in a population-based cohort study of autism spectrum disorders. Paediatr Perinat Epidemiol. 2013;27(6):553-563.
6. Al-Jammas IK, Al-Dobooni RM. Prenatal and perinatal risk factors in autistic disorders. Arab Journal of Psychiatry. 2012;23(2):108-114.
7. Amiri S, Malek A, Sadegfard M, Abdi S. Pregnancy-related maternal risk factors of attention-deficit hyperactivity disorder: a case-control study. ISRN pediatr. 2012;2012:458064.
8. Axelsson PB, Clausen TD, Petersen AH, et al. Investigating the effects of cesarean delivery and antibiotic use in early childhood on risk of later attention deficit hyperactivity disorder. J Child Psychol Psychiatry. 2018;23:23.
9. Axelsson PB, Clausen TD, Petersen AH, et al. Relation Between Infant Microbiota and Autism?: Results from a National Cohort Sibling Design Study. Epidemiology. 2019;30(1):52-60.
10. Bain M, Juszczak E, McInneny K, Kendell RE. Obstetric complications and affective psychoses. Two case-control studies based on structured obstetric records. Br J Psychiatry. 2000;176:523-526.
11. Bilder DA, Pinborough-Zimmerman J, Bakian AV, et al. Prenatal and perinatal factors associated with intellectual disability. Am J Intellect Dev Disabil. 2013;118(2):156-176.
12. Brander G, Rydell M, Kuja-Halkola R, et al. Association of Perinatal Risk Factors With Obsessive-Compulsive Disorder A Population-Based Birth Cohort, Sibling Control Study. JAMA Psychiatry. 2016;73(11):1135-1144.
13. Brander G, Rydell M, Kuja-Halkola R, et al. Perinatal risk factors in Tourette's and chronic tic disorders: a total population sibling comparison study. Mol Psychiatry. 2018;23(5):1189-1197.
14. Burstyn I, Sithole F, Zwaigenbaum L. Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada. Chronic Dis Can. 2010;30(4):125-134.
15. Byrne M, Browne R, Mulryan N, et al. Labour and delivery complications and schizophrenia. Case-control study using contemporaneous labour ward records. Br J Psychiatry. 2000;176:531-536.
16. Çak HT, Gökler B. Attention deficit hyperactivity disorder and associated perinatal risk factors in preterm children. Turk Pediatri Arsivi. 2013;48(4):315-322.
17. Chen G, Chiang WL, Shu BC, et al. Associations of caesarean delivery and the occurrence of neurodevelopmental disorders, asthma or obesity in childhood based on Taiwan birth cohort study. BMJ Open. 2017;7(9):e017086.
18. Chien L-N, Lin H-C, Shao Y-HJ, Chiou S-T, Chiou H-Y. Risk of autism associated with general anesthesia during Cesarean delivery: A population-based birth-cohort analysis. J Autism Dev Disord. 2015;45(4):932-942.
19. Chudal R, Sourander A, Polo-Kantola P, et al. Perinatal factors and the risk of bipolar disorder in Finland. J Affect Disord. 2014;155:75-80.
20. Cnattingius S, Hultman CM, Dahl M, Sparen P. Very preterm birth, birth trauma, and the risk of anorexia nervosa among girls. Arch Gen Psychiatry. 1999;56(7):634-638.
21. Cubo E, Hortiguela M, Jorge-Roldan S, et al. Prenatal and Perinatal Morbidity in Children with Tic Disorders: A Mainstream School-based Population Study in Central Spain. Tremor Other Hyperkinet Mov (N Y). 2014;4:272.
22. Curran EA, Dalman C, Kearney PM, et al. Association Between Obstetric Mode of Delivery and Autism Spectrum Disorder: A Population-Based Sibling Design Study. JAMA Psychiatry. 2015;72(9):935-942.
23. Curran EA, Khashan AS, Dalman C, et al. Obstetric mode of delivery and attention-deficit/hyperactivity disorder: a sibling-matched study. Int J Epidemiol. 2016;45(2):532-542.
24. Dodds L, Fell DB, Shea S, et al. The role of prenatal, obstetric and neonatal factors in the development of autism. J Autism Dev Disord. 2011;41(7):891-902.
25. Duan G, Yao M, Ma Y, Zhang W. Perinatal and background risk factors for childhood autism in central China. Psychiatry Res. 2014;220(1-2):410-417.

26. Durkin MS, DuBois LA, Maenner MJ. Inter-Pregnancy Intervals and the Risk of Autism Spectrum Disorder: Results of a Population-Based Study. J Autism Dev Disord. 2015;45(7):2056-2066.
27. El-Baz F, Ismael NA, El-Din SMN. Risk factors for autism: An Egyptian study. Egypt J Med Hum Genet. 2011;12(1):31-38.
28. Eriksson MA, Westerlund J, Anderlid BM, Gillberg C, Fernell E. First-degree relatives of young children with autism spectrum disorders: some gender aspects. Res Dev Disabil. 2012;33(5):1642-1648.
29. Geller DA, Wieland N, Carey K, et al. Perinatal factors affecting expression of obsessive compulsive disorder in children and adolescents. J Child Adolesc Psychopharmacol. 2008;18(4):373-379.
30. Glasson EJ, Bower C, Petterson B, et al. Perinatal factors and the development of autism: a population study. Arch Gen Psychiatry. 2004;61(6):618-627.
31. Gourion D, Arseneault L, Vitaro F, et al. Early environment and major depression in young adults: a longitudinal study. Psychiatry Res. 2008;161(2):170-176.
32. Guisso DR, Saadeh FS, Saab D, et al. Association of Autism with Maternal Infections, Perinatal and Other Risk Factors: A Case-Control Study. J Autism Dev Disord. 2018;48(6):2010-2021.
33. Gustafsson P, Källén K. Perinatal, maternal, and fetal characteristics of children diagnosed with attention-deficit-hyperactivity disorder: Results from a population-based study utilizing the Swedish Medical Birth Register. Dev Med Child Neurol. 2011;53(3):263-268.
34. Haglund NG, Kallen KB. Risk factors for autism and Asperger syndrome. Perinatal factors and migration. Autism. 2011;15(2):163-183.
35. Halmoy A, Klungsoyr K, Skjaerven R, Haavik J. Pre- and perinatal risk factors in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2012;71(5):474-481.
36. Hamade A, Salameh P, Medlej-Hashim M, et al. Autism in children and correlates in Lebanon: a pilot case-control study. J. 2013;13(2):119-124.
37. Harrison G, Fouskakis D, Rasmussen F, et al. Association between psychotic disorder and urban place of birth is not mediated by obstetric complications or childhood socio-economic position: a cohort study. Psychol Med. 2003;33(4):723-731.
38. Hultman CM, Sparen P, Takei N, Murray RM, Cnattingius S. Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study. BMJ. 1999;318(7181):421-426.
39. Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology. 2002;13(4):417-423.
40. Hvelplund C, Hansen BM, Koch SV, Andersson M, Skovgaard AM. Perinatal Risk Factors for Feeding and Eating Disorders in Children Aged 0 to 3 Years. Pediatrics. 2016;137(2):e20152575.
41. Ji Y, Riley AW, Lee LC, et al. Maternal biomarkers of acetaminophen use and offspring attention deficit hyperactivity disorder. Brain Sci. 2018;8(7):E127.
42. Jones PB, Rantakallio P, Hartikainen AL, Isohanni M, Sipila P. Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 north Finland general population birth cohort. Am J Psychiatry. 1998;155(3):355-364.
43. Karlsson H, Blomstrom A, Wicks S, et al. Maternal antibodies to dietary antigens and risk for nonaffective psychosis in offspring. Am J Psychiatry. 2012;169(6):625-632.
44. Kendell RE, McInneny K, Juszczak E, Bain M. Obstetric complications and schizophrenia. Two case-control studies based on structured obstetric records. Br J Psychiatry. 2000;176:516-522.
45. Ketzer CR, Gallois C, Martinez AL, Rohde LA, Schmitz M. Is there an association between perinatal complications and attention-deficit/hyperactivity disorder-inattentive type in children and adolescents? Braz J Psychiatry. 2012;34(3):321-328.
46. Yeo J, Choi S, Joo Y, Kim H. Prenatal, perinatal and developmental risk factors of attention-deficit hyperactivity disorder. J Korean Acad Child Adolesc Psychiatry. 2015;26(2):112-119.
47. Kissin DM, Zhang Y, Boulet SL, et al. Association of assisted reproductive technology (ART) treatment and parental infertility diagnosis with autism in ART-conceived children. Hum Reprod. 2015;30(2):454-465.
48. Leivonen S, Voutilainen A, Chudal R, et al. Obstetric and Neonatal Adversities, Parity, and Tourette Syndrome: A Nationwide Registry. J Pediatr. 2016;171:213-219.
49. Maimburg RD, Vaeth M. Perinatal risk factors and infantile autism. Acta Psychiatr Scand. 2006;114(4):257-264.
50. Maramara LA, He W, Ming X. Pre- and perinatal risk factors for autism spectrum disorder in a New Jersey cohort. J Child Neurol. 2014;29(12):1645-1651.

51. Matsuishi T, Yamashita Y, Ohtani Y, et al. Brief report: incidence of and risk factors for autistic disorder in neonatal intensive care unit survivors. J Autism Dev Disord. 1999;29(2):161-166.
52. Micali N, Kothari R, Nam KW, et al. Eating disorder psychopathology, brain structure, neuropsychological correlates and risk mechanisms in very preterm young adults. Eur Eat Disord Rev. 2015;23(2):147-155.
53. Mrozek-Budzyn D, Majewska R, Kieltyka A. Prenatal, perinatal and neonatal risk factors for autism - Study in Poland. Cent Eur J Med. 2013;8(4):424-430.
54. Murray E, Pearson R, Fernandes M, et al. Are fetal growth impairment and preterm birth causally related to child attention problems and ADHD? Evidence from a comparison between high-income and middle-income cohorts. J Epidemiol Community Health. 2016;70(7):704-709.
55. O'Neill SM, Curran EA, Dalman C, et al. Birth by Caesarean Section and the Risk of Adult Psychosis: A Population-Based Cohort Study. Schizophr Bull. 2016;42(3):633-641.
56. Ordonez AE, Bobb A, Greenstein D, et al. Lack of evidence for elevated obstetric complications in childhood onset schizophrenia. Biol Psychiatry. 2005;58(1):10-15.
57. Polo-Kantola P, Lampi KM, Hinkka-Yli-Salomaki S, et al. Obstetric risk factors and autism spectrum disorders in Finland. J Pediatr. 2014;164(2):358-365.
58. Razaz N, Cnattingius S. Association between maternal body mass index in early pregnancy and anorexia nervosa in daughters. Int J Eat Disord. 2018;51(8):906-913.
59. Schieve LA, Tian LH, Baio J, et al. Population attributable fractions for three perinatal risk factors for autism spectrum disorders, 2002 and 2008 autism and developmental disabilities monitoring network. Ann Epidemiol. 2014;24(4):260-266.
60. Silva D, Colvin L, Hagemann E, Bower C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. Pediatrics. 2014;133(1):e14-22.
61. Sucksdorff M, Lehtonen L, Chudal R, et al. Lower Apgar scores and Caesarean sections are related to attention-deficit/hyperactivity disorder. Acta Paediatr. 2018;107(10):1750-1758.
62. Sussmann JE, McIntosh AM, Lawrie SM, Johnstone EC. Obstetric complications and mild to moderate intellectual disability. Br J Psychiatry. 2009;194(3):224-228.
63. Vasconcelos MS, Sampaio AS, Hounie AG, et al. Prenatal, perinatal, and postnatal risk factors in obsessive-compulsive disorder. Biol Psychiatry. 2007;61(3):301-307.
64. Winkler-Schwartz A, Garfinkle J, Shevell MI. Autism spectrum disorder in a term birth neonatal intensive care unit population. Pediatr Neurol. 2014;51(6):776-780.
65. Yip BHK, Leonard H, Stock S, et al. Caesarean section and risk of autism across gestational age: a multi-national cohort study of 5 million births. Int J Epidemiol. 2017;46(2):429-439.
66. Zhang X, Lv CC, Tian J, et al. Prenatal and perinatal risk factors for autism in China. J Autism Dev Disord. 2010;40(11):1311-1321.