



Original Investigation | Psychiatry

Association of Cesarean Delivery With Risk of Neurodevelopmental and Psychiatric Disorders in the Offspring

A Systematic Review and Meta-analysis

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Abstract

IMPORTANCE Birth by cesarean delivery is increasing globally, particularly cesarean deliveries without medical indication. Children born via cesarean delivery may have an increased risk of negative health outcomes, but the evidence for psychiatric disorders is incomplete.

OBJECTIVE To evaluate the association between cesarean delivery and risk of neurodevelopmental and psychiatric disorders in the offspring.

DATA SOURCES Ovid MEDLINE, Embase, Web of Science, and PsycINFO were searched from inception to December 19, 2018. Search terms included all main mental disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).

STUDY SELECTION Two researchers independently selected observational studies that examined the association between cesarean delivery and neurodevelopmental and psychiatric disorders in the offspring.

DATA EXTRACTION AND SYNTHESIS Two researchers independently extracted data according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines and assessed study quality using the Newcastle-Ottawa Scale. Random-effects meta-analyses were used to pool odds ratios (ORs) with 95% CIs for each outcome. Sensitivity and influence analyses tested the robustness of the results.

MAIN OUTCOMES AND MEASURES The ORs for the offspring with any neurodevelopmental or psychiatric disorder who were born via cesarean delivery compared with those were born via vaginal delivery.

RESULTS A total of 6953 articles were identified, of which 61 studies comprising 67 independent samples were included, totaling 20 607 935 deliveries. Compared with offspring born by vaginal delivery, offspring born via cesarean delivery had increased odds of autism spectrum disorders (OR, 1.33; 95% CI, 1.25-1.41; $I^2 = 69.5\%$) and attention-deficit/hyperactivity disorder (OR, 1.17; 95% CI, 1.07-1.26; $I^2 = 79.2\%$). Estimates were less precise for intellectual disabilities (OR, 1.83; 95% CI, 0.90-3.70; $I^2 = 88.2\%$), obsessive-compulsive disorder (OR, 1.49; 95% CI, 0.87-2.56; $I^2 = 67.3\%$), tic disorders (OR, 1.31; 95% CI, 0.98-1.76; $I^2 = 75.6\%$), and eating disorders (OR, 1.18; 95% CI, 0.96-1.47; $I^2 = 92.7\%$). No significant associations were found with depression/affective psychoses or nonaffective psychoses. Estimates were comparable for emergency and elective cesarean delivery. Study quality was high for 82% of the cohort studies and 50% of the case-control studies.

(continued)

Key Points

Question Is birth by cesarean delivery associated with an increased risk of neurodevelopmental and psychiatric disorders in the offspring compared with birth by vaginal delivery?

Findings In this systematic review and meta-analysis of 61 studies comprising more than 20 million deliveries, birth by cesarean delivery was significantly associated with autism spectrum disorder and attention-deficit/hyperactivity disorder.

Meaning The findings suggest that understanding the potential mechanisms behind these associations is important, especially given the increase in cesarean delivery rates for nonmedical reasons.

+ Supplemental content

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Abstract (continued)

CONCLUSIONS AND RELEVANCE The findings suggest that cesarean delivery births are associated with an increased risk of autism spectrum disorder and attention-deficit/hyperactivity disorder, irrespective of cesarean delivery modality, compared with vaginal delivery. Future studies on the mechanisms behind these associations appear to be warranted.

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Introduction

Cesarean delivery can effectively reduce maternal and neonatal mortality and morbidity in the presence of complications, such as antepartum hemorrhage, fetal distress, abnormal fetal presentation, and hypertensive disease.¹ During the past 3 decades, worldwide cesarean delivery rates have seen a more than 3-fold increase, from approximately 6% in 1990 to 21% in 2015, with substantial variations among and within countries.¹ There is no precise information on appropriate cesarean delivery rates at the population level, although the international health care community considers 10% to 15% to be an optimal rate.² Public health concerns have been raised because access to medically indicated cesarean delivery may be difficult in low-resource settings and unnecessary cesarean deliveries may be performed in high-resource settings.^{1,3,4}

Despite being a life-saving procedure in the presence of complications, no evidence, to our knowledge, indicates that cesarean delivery, if not indicated, is beneficial for the offspring. On the contrary, previous studies have reported negative health outcomes in offspring born via cesarean delivery, including obesity,^{5,6} allergy,⁶ asthma,^{6,7} type 1 diabetes,⁸ and acute lymphoblastic leukemia.⁹ Cesarean delivery also has a potential association with early brain development. Previous studies have reported worse child cognitive development¹⁰ and higher rates of autism spectrum disorders (ASD) associated with cesarean delivery.¹¹ Whether cesarean delivery is associated with increased risks of other neurodevelopmental and psychiatric disorders is unclear.

Previous studies^{4,10,12} have discussed the hypothesized biological mechanisms that may explain the associations between cesarean delivery and negative health outcomes in the offspring. For example, cesarean delivery might alter immune development through the perturbation of bacterial colonization, disturbing immune and sensory activation through lack of stress response or modifying epigenetic regulation in DNA methylation.^{4,10,12} Moreover, these adverse effects might vary depending on whether a cesarean delivery is performed before the onset of labor (ie, elective cesarean delivery) or after (ie, emergency cesarean delivery).¹³ Elective cesarean delivery can be scheduled by obstetricians in the presence of medical indications¹⁴ (eg, breech presentation, cephalopelvic disproportion) or requested by the mother because of culture preferences, previous negative birth experience, or fear of birth,^{15,16} which may indicate a genetic vulnerability to factors associated with psychological changes, such as stress, and associated in turn with neurodevelopmental or psychiatric illness in the offspring. However, emergency cesarean delivery occurs in more traumatic situations (eg, severe fetal distress, preeclampsia) that are associated with multiple negative birth outcomes.¹³ Elective and emergency cesarean deliveries are characterized by different factors and thus may be differentially associated with neurodevelopmental and psychiatric outcomes.

To address these gaps in the literature, we conducted a systematic review and meta-analysis of observational studies to quantify the extent of the association between cesarean delivery and a range of neurodevelopmental and psychiatric outcomes compared with vaginal delivery. Moreover, we investigated whether type of cesarean delivery (elective or emergency) or assisted vaginal delivery (ie, involving use of vacuum or forceps), compared with unassisted vaginal delivery, were differentially associated with neurodevelopmental and psychiatric outcomes in the offspring.

Methods

Search Strategy

We reported this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines. The study was preregistered with International Prospective Register of Systematic Reviews (PROSPERO identifier [CRD42018108298](#)) before data extraction and analyses. We searched Ovid MEDLINE, Embase, Web of Science, and PsycINFO from inception to December 19, 2018, without language, date, or location restrictions. The search strategy was developed in association with information specialists at the Karolinska Institutet Library. Search terms included all main mental disorders in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (DSM-5). The search strategy for each database is detailed in eTable 1 in the [Supplement](#). We checked reference lists of relevant reviews for additional studies.

Study Selection

We included observational studies that allowed estimation of the associations between obstetric mode of delivery (cesarean vs vaginal delivery) and neurodevelopmental and psychiatric disorders in the offspring. Studies were included regardless of the method of exposure ascertainment (ie, self-report or birth records). To maximize the quality of the included work, we only included studies if the outcome diagnoses were assessed through structured interviews or using standardized diagnostic criteria (eg, *International Classification of Diseases*, DSM, or equivalent). Self-reported or caregiver-reported outcomes were excluded. We further excluded review articles, book chapters, conference abstracts, and dissertations. Articles in languages other than English were translated by a native speaker or using Google Translate. Two researchers (T.Z. and L.S.-C. or A.V.-P.) independently screened and selected the articles first on the basis of titles and abstracts and then by examining the full texts; discrepancies were resolved through discussion with a senior researcher (A.S.).

Data Extraction and Quality Assessment

Two researchers (T.Z. and L.S.-C. or A.V.-P.) independently extracted the data using predesigned Excel spreadsheets (Microsoft Corp). Disagreements were resolved through discussion. Extracted variables included country; data source; study design; age of the offspring; exposure; method of exposure ascertainment; diagnosis; diagnostic instruments; covariates controlled for by adjustment or matching; sample size; whether the study reported elective and emergency cesarean delivery or assisted and unassisted vaginal delivery separately and study participants in each group; and risk estimates (eg, odds ratios [ORs], hazard ratios). If the original study reported data on several outcomes, information on each outcome was retrieved separately. If studies reported no effect size for association of interest, we calculated ORs from raw data. When duplicate data were identified, we extracted data from the largest sample size for relevant outcomes (characteristics of the articles excluded because of duplicate data are presented in eTable 2 in the [Supplement](#)).

We assessed the methodologic quality of each study using the Newcastle-Ottawa Scale.¹⁷ Two researchers (T.Z. and L.S.-C. or A.V.-P.) independently assessed and scored each study according to the preestablished criteria. We judged the study quality to be high if the score was at least 7 points (of a possible 9) or otherwise to be low.

Statistical Analysis

First, we examined the association between birth by cesarean delivery vs vaginal delivery and each outcome in the offspring separately using random effects models.¹⁸ We reported the results obtained after pooling each individual study's most-adjusted estimate as ORs with 95% CIs. Second, we used the same approach to explore the associations of elective cesarean delivery, emergency cesarean delivery, and assisted vaginal delivery compared with unassisted vaginal delivery with the risk of neurodevelopmental and psychiatric disorders in the offspring. If the original studies reported

the results from the analyses of both population data and sibling comparisons,¹⁹⁻²⁴ we retrieved the former to reduce heterogeneity related to potential differences in study populations. For 8 studies¹⁹⁻²⁶ that did not report ORs but reported hazard ratios, we calculated crude ORs from the data reported in the article using a 2 × 2 table.

Statistical heterogeneity among studies was assessed using Q and I^2 statistics. For the Q statistic, a 2-sided $P < .10$ was considered as representative of statistically significant heterogeneity, and I^2 values of 25%, 50%, and 75% were regarded as low, moderate, and high heterogeneity, respectively.²⁷ If 10 or more original studies were included in the meta-analysis for an outcome, univariate meta-regressions on publication year, cesarean delivery use proportion, study design, country income status, and exposure ascertainment were applied to assess whether they were responsible for the heterogeneity. We assessed the presence of potential publication bias for each outcome using Egger tests and visualized by funnel plots.²⁸ If the Egger tests revealed a potential publication bias, we used the contour-enhanced funnel plot and Duval and Tweedie nonparametric trim and fill method to further test the data.²⁹

Furthermore, we undertook subgroup analyses for any differences in the association between birth by cesarean delivery vs vaginal delivery and each outcome for the following 6 moderators: country status (high- vs middle-income countries, according to the World Bank),³⁰ proportion of cesarean deliveries in the study (lower vs higher than 15% as a proxy indicator for unnecessary cesarean delivery),² exposure ascertainment (medical records vs self-report), offspring sex, whether risk measures were adjusted for parental psychiatry history, and study quality (high vs low). The results of the subgroup analyses were reported if at least 3 original studies were present in each stratum. We also performed influence analyses (so-called leave-1-out analysis) by iteratively removing 1 study at a time to confirm that the findings were not influenced by any single study. Finally, we performed sensitivity analyses using the least-adjusted or crude estimates from each study to assess whether the pooled effect size was sensitive to adjustment strategy.

All analyses were performed in Stata, version 15.1 (StataCorp). A 2-sided $P < .05$ was considered to be statistically significant.

Results

We identified 6953 articles, of which 549 abstracts were selected for detailed assessment (**Figure 1**). A total of 61 studies comprising 67 independent samples and 20 607 935 deliveries met our inclusion criteria. The main characteristics of the included studies are presented in **Table 1**, and the variables adjusted and/or matched in each study are presented in eTable 3 in the **Supplement**. Of the 61 included studies, 27 studies^{20,23,31-54,83} reported on the association of cesarean delivery with a diagnosis of ASD (59 795 cases), 13 studies^{19,24,42,52,55-63} with attention-deficit/hyperactivity disorder (ADHD) (92 718 cases), 3 studies^{42,64,65} with intellectual disabilities (485 cases), 3 studies^{22,66,67} with tic disorders (6181 cases), 4 studies^{25,26,68,69} with eating disorders (4550 cases), 3 studies^{21,70,71} with obsessive-compulsive disorder (OCD; 7295 cases), 5 studies⁷²⁻⁷⁶ with major depression or affective psychoses (8561 cases), and 7 studies^{73,77-82} with nonaffective psychoses (7195 cases). Study quality was defined as high for 18 of 22 cohorts (82%) and 20 of 40 case-control studies (50%). Quality assessment summary scores are reported in Table 1.

Meta-analytic Association Between Cesarean Delivery and Neurodevelopmental and Psychiatric Disorders

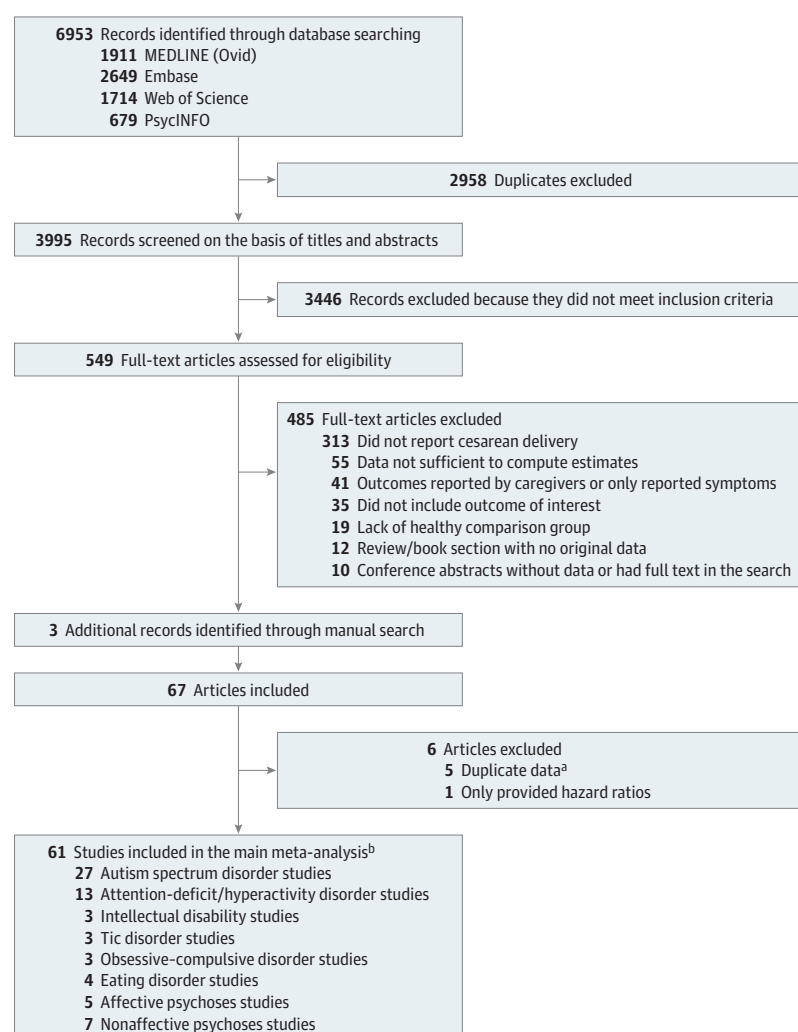
Results of the meta-analysis for the first aim revealed that birth by cesarean delivery was significantly associated with increased odds of the offspring being diagnosed with ASD (OR, 1.33; 95% CI, 1.25-1.41) and ADHD (OR, 1.17; 95% CI, 1.07-1.26) compared with birth by vaginal delivery (**Figure 2**). The magnitude of the estimates was similar or higher for other neurodevelopmental and psychiatric outcomes, but the associations were not statistically significant (possibly because of the limited number of studies): intellectual disabilities (OR, 1.83; 95% CI, 0.90-3.70), OCD (OR, 1.49; 95% CI,

0.87-2.56), tic disorders (OR, 1.31; 95% CI, 0.98-1.76), and eating disorders (OR, 1.18; 95% CI, 0.96-1.47). The OR for depression/affective psychoses was 1.06 (95% CI, 0.98-1.14) and for nonaffective psychoses was 0.97 (95% CI, 0.78-1.21) (**Figure 3**).

For intellectual disabilities, OCD, tic disorders, and eating disorders, leave-1-out analysis revealed statistically significant associations with cesarean delivery births after omitting the following studies: Chen and colleagues⁴² (for intellectual disabilities; OR after exclusion, 2.61; 95% CI, 1.51-4.53), Vasconcelos and colleagues⁷¹ (for OCD; OR, 1.13; 95% CI, 1.08-1.19), and Cubo and colleagues⁶⁷ (for tic disorders; OR, 1.24; 95% CI, 1.02-1.50) (eTable 4 in the [Supplement](#)). For the rest of the disorders, no individual studies influenced the results seen in the main analyses.

Study heterogeneity was high for ADHD ($I^2 = 79.2\%$), intellectual disabilities ($I^2 = 88.2\%$), tic disorders ($I^2 = 75.6\%$), and eating disorders ($I^2 = 92.7\%$); medium for ASD ($I^2 = 69.5\%$), OCD ($I^2 = 67.3\%$), and nonaffective psychosis ($I^2 = 82.6\%$); and low for depression and affective psychoses ($I^2 = 0.0\%$). Egger tests and funnel plots suggested a potential publication bias for ASD (eFigure 1 in the [Supplement](#)). In addition, a contour-enhanced funnel plot for ASD supported the Egger test, suggesting that the asymmetry was likely caused by publication bias (eFigure 2 in the [Supplement](#)). Furthermore, the Duval and Tweedie nonparametric trim and fill method for ASD led to a result similar to that obtained in the main analysis (OR, 1.32; 95% CI, 1.24-1.40).

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Diagram



^a Characteristics of these studies are presented in eTable 2 in the [Supplement](#).

^b Some studies address associations with more than 1 outcome.

Table 1. Characteristics of the Studies Included in the Main Meta-analysis

Source	Study Location	Period	Design	No. of Participants		Outcome(s)	Outcome Ascertainment	Age of Offspring	Newcastle -Ottawa Score
				Cesarean Delivery	Vaginal Delivery				
ASD									
Matsuishi et al, ³¹ 1999	Japan	1983-1987	Case-control	18	205	Autistic disorder	DSM-III-R	2-5 y	4
Mrozek-Budzyn et al, ³² 2013	Poland	2007	Case-control	74	204	Childhood or atypical autism	ICD-10 codes F84.0 and F84.1	2-15 y	5
Hamadé et al, ⁸³ 2013	Lebanon	2012	Case-control	31872	84023	Autistic disorder	DSM-IV-TR	3-27 y	4
Maramara et al, ³³ 2014	United States	2000-2006	Case-control	31872	84023	Autistic disorder, PDD-NOS, or Asperger syndrome	DSM-IV-TR	NR	2
Burstyn et al, ³⁴ 2010	Canada	1998-2008	Cohort	49456	170572	ASD	ICD-9 codes 299.0 and 299.8	4-10 y	8
Axelsson et al, ²⁰ 2019	Denmark	1997-2014	Cohort	119433	560440	ASD	ICD-10 codes F84.0, F84.1, F84.5, F84.8	4-17 y	9
Maimburg and Vaeth, ³⁵ 2006	Denmark	1990-1999	Case-control	633	4099	Infantile autism	ICD-8 code 299.0 and ICD-10 code F84.0	Mean age at diagnosis, 4.6 y	8
Dodds et al, ³⁶ 2011	Canada	1990-2002	Cohort	26754	102948	ASD	ICD-9 code 299 and ICD-10 code F84	2-15 y	7
Chien et al, ³⁷ 2015	Taiwan	2004-2007	Cohort	174376	362297	Infantile autism	ICD-9 code 299.0	2-6 y	9
Curran et al, ²³ 2015	Sweden	1982-2011	Cohort	340108	2357206	ASD	ICD-9 code 299 and ICD-10 code F84	4-29 y	9
Guisso et al, ³⁸ 2018	Lebanon	NR	Case-control	125	189	ASD	DSM-IV and DSM-5	2-18 y	7
Yip et al, ³⁹ 2017	Norway Finland WA	1984-2004 1987-2004 1984-1999	Cohort	Norway: 127922; Finland: 156863; WA: 65953	Norway: 924475; Finland: 891684; WA: 279228	ASD	ICD-8, ICD-9, ICD-10, and DSM-IV	5-25 y	9
Schieve et al, ⁴⁰ 2014	United States	1994-2002 2000-2008	Case-control	NR	NR	ASD	DSM-IV-TR	8 y	6
Haglund and Källén, ⁴¹ 2011	Sweden	1980-2005	Case-control	7434	61530	Autistic disorder, childhood autism, Asperger syndrome	DSM-III/IV codes 299.00, 299.80; ICD-10 codes F84.0, F98.5. Gillberg criteria	2.5-20 y	7
Chen et al, ⁴² 2017	Taiwan	2005-2010	Cohort	6285	12698	Autism	DSM-5	5.5 y	9
Polo-Kantola et al, ⁴³ 2014	Finland	1990-2007	Case-control	3349	17117	Childhood autism, PDD, and Asperger syndrome	ICD-9 code 299.x, ICD-10 code F84.x	2-17 y	8
Duan et al, ⁴⁴ 2014	China	2011-2013	Case-control	287	285	Childhood autism	DSM-IV and Childhood Autism Rating Scale	3-6 y	5
Durkin et al, ⁴⁵ 2015	United States	1994-2008	Case-control	4624	26843	ASD including autistic disorder, PDD-NOS, and Asperger syndrome	DSM-IV-TR and ICD-9 codes	8 y	7
Eriksson et al, ⁴⁶ 2012	Sweden	2002-2008	Case-control	23286	94242	ASD	Clinical diagnosis	20-54 mo	5
Hultman et al, ⁴⁷ 2002	Sweden	1974-1993	Case-control	352	2096	Infantile autism	ICD-9 code 299A	<10 y (mean age, 4.4 y for boys and 4.6 y for girls)	8
Kissin et al, ⁴⁸ 2015	United States	1996-2011	Cohort	27152	15231	Autistic disorder	DSM-IV code 299.0	5 y	6

(continued)

Table 1. Characteristics of the Studies Included in the Main Meta-analysis (continued)

Source	Study Location	Period	Design	No. of Participants		Outcome(s)	Outcome Ascertainment	Age of Offspring	Newcastle-Ottawa Score
				Cesarean Delivery	Vaginal Delivery				
Glisson et al, ⁴⁹ 2004	Australia	1980-1999	Case-control	380	1398	ASD including autism, PDD-NOS, and Asperger syndrome	DSM-III and DSM-IV	4-19 y	8
Zhang et al, ⁵⁰ 2010	China	2007	Case-control	77	104	Autism	ICD-10 and Childhood Autism Rating Scale	3-21 y	5
El-Baz et al, ⁵¹ 2011	Egypt	2008-2010	Case-control	89	213	Autism	DSM-IV-TR	2-13 y	4
Ji et al, ⁵² 2018	United States	1998-2016	Case-control	214	434	ASD	ICD-9 codes 299.0, 299.00, 299.01, 299.8, 299.80, 299.81, 299.9, 299.90, 299.91 and ICD-10 codes F84.0, F84.8, F84.9	Median age at first ADHD diagnosis, 7 y	6
Winkler-Schwartz et al, ⁵³ 2014	Canada	1991-2013	Cohort	35	48	ASD	DSM-IV	3-17 y	5
Al-Jammas and Al-Dobooni, ⁵⁴ 2012	Iraq	2011-2012	Case-control	19	81	Autism, Asperger disorder, Rett syndrome	DSM-IV-TR	1.5-7 y	3
ADHD									
Cak and Gökler, ⁵⁵ 2013	Turkey	2003-2008	Cohort	80	12	ADHD	K-SADS-PL and DSM-IV	5 y	5
Murray et al, ⁵⁶ 2016	United Kingdom, Brazil	ALSPAC: 1991 to NR; Pelotas: 2004 to NR	Cohort	NR	NR	Any ADHD diagnosis including hyperactive-impulsive ADHD, inattentive ADHD, and combined ADHD	Development and well-being assessment based on DSM-IV criteria	7 y	7
Yeo et al, ⁵⁷ 2015	South Korea	2012-2013	Case-control	34	46	ADHD	DSM-IV and K-SADS-PL	6-12 y	5
Gustafsson and Källén, ⁵⁸ 2011	Sweden	1986-1996	Case-control	2996	29016	ADHD	DSM-III-R and DSM-IV	Age at diagnosis, 5 to 17 y	6
Axelsson et al, ¹⁹ 2019	Denmark	1997-2014	Cohort	117 863	553 727	ADHD or attention-deficit disorder	ICD-8 code 308.01 or ICD-10 codes F90 and F98 or ≥2 redeemed prescriptions for ADHD medication	4-17 y	8
Silva et al, ⁵⁹ 2014	Australia	1981-2003	Case-control	8863	34 829	ADHD	DSM-IV or ICD-10	4-25 y	8
Curran et al, ²⁴ 2016	Sweden	1990-2011	Cohort	238 687	1483 861	ADHD	ICD-10 codes F90 and F98.8 or prescription of the psychostimulants methylphenidate (ATC code: N06BA04), amphetamine (N06BA01), dexamphetamine (N06BA02), or the noradrenergic reuptake inhibitor atomoxetine (N06BA09)	3-21 y	9
Sucksdorff et al, ⁶⁰ 2018	Finland	1991-2011	Case-control	8034	40 963	ADHD	ICD-9 code 314 and ICD-10 code F90	2-20 y	8
Chen et al, ⁴² 2017	Taiwan	2005-2010	Cohort	6320	12 758	ADHD	DSM-5	5.5 y	9
Ketzer et al, ⁶¹ 2012	Brazil	2001-2007	Case-control	NR	NR	ADHD-inattentive type	K-SADS-PL and DSM-IV	6-17 y	8
Halmøy et al, ⁶² 2012	Norway	1967-2005	Case-control	69051	1 103 345	ADHD	DSM-IV or ICD-10	18-38 y	8
Ji et al, ⁵² 2018	United States	1998-2016	Case-control	267	525	ADHD	ICD-9 codes 314.00, 314.01, 314.1, 314.2, 314.8, or 314.9 or ICD-10 codes F90.0, F90.1, F90.2, F90.8, or F90.9	Median age at first ADHD diagnosis, 7 y	6

(continued)

Table 1. Characteristics of the Studies Included in the Main Meta-analysis (continued)

Source	Study Location	Period	Design	No. of Participants		Outcome(s)	Outcome Ascertainment	Age of Offspring	Newcastle-Ottawa Score
				Cesarean Delivery	Vaginal Delivery				
Amiri et al, ⁶³ 2012	Iran	2009	Case-control	162	168	ADHD	K-SADS-PL	Mean age, 9.2 y for cases and 9.02 y for controls	5
Intellectual Disabilities									
Chen et al, ⁴² 2017	Taiwan	2005-2010	Cohort	6360	12 825	Learning disabilities	DSM-V	5.5 y	9
Sussmann et al, ⁶⁴ 2009	United Kingdom	NR	Case-control	16	74	Intellectual disability	Wechsler Intelligence Scale and ICD-10	13-22 y	6
Bilder et al, ⁶⁵ 2013	United States	1994-2002	Case-control	2679	14 387	Learning disabilities	ICD-9	8 y	7
Tic Disorders									
Leivonen et al, ⁶⁶ 2016	Finland	1991-2010	Case-control	581	2961	Tourette syndrome	ICD-9 code 307.2D, ICD-10 code F95.2	NR	8
Brander et al, ²² 2018	Sweden	1973-2013	Cohort	336 063	2 611 439	Tourette syndrome and chronic tic disorders	ICD-8 code 306.2, ICD-9 code 307C, and ICD-10 codes F95.0, F95.1, F95.2, F95.8, F95.9	10-40 y	9
Cubo et al, ⁶⁷ 2014	Spain	2007-2009	Case-control	31	122	Tic disorder	DSM-IV-TR	6-16 y	7
Eating Disorders									
Razaz et al and Cnattingius, ⁶⁸ 2018	Sweden	1992-2012	Cohort	53 807	428 768	Anorexia nervosa	ICD-9 code 307B or ICD-10 codes F500 and F501	10-20 y	8
Cnattingius et al, ⁶⁸ 1999	Sweden	1973-1984	Case-control	387	4299	Anorexia nervosa	ICD-9 code 307B	10-21 y	7
Micali et al, ⁶⁹ 2015	United Kingdom	NR	Cohort	NR	NR	Eating disorders	Eating Disorders Examination Questionnaire	Mean age at assessment, 20.8 y	7
Hvelplund et al, ²⁵ 2016	Denmark	1997-2010	Cohort	173 937	727 290	Feeding and Eating disorder	ICD-10 codes F98.2 and F50.8	0-48 mo	9
OCD									
Brander et al, ²¹ 2016	Sweden	1973-2013	Cohort	248 840	2 137 846	OCD	ICD-10 code F42	17-40 y	9
Geller et al, ⁷⁰ 2008	United States	NR	Case-control	47	132	OCD	K-SADS-PL, Children's Yale-Brown Obsessive Compulsive Scale, and DSM-IV	Mean age, 11.6 y	5
Vasconcelos et al, ⁷¹ 2007	Brazil	NR	Case-control	47	91	OCD	SCID-I/P and K-SADS	11-44 y	3
Affective Psychoses and Major Depressive Disorder									
Hultman et al, ⁷² 1999	Sweden	1973-1994	Case-control	89	1099	Affective psychoses	ICD-9 code 296	15-21 y	7
O'Neill et al, ⁷³ 2016	Sweden	1982-2011	Cohort	125 356	1 215 881	Bipolar affective disorder, mania with psychotic symptoms, severe depressive episode with psychotic symptoms, and recurrent depressive disorder; current episode severe with psychotic symptoms	ICD-10 codes F31, F30.2, F32.3, F33.3	16-29 y	9
Bain et al, ⁷⁴ 2000	United Kingdom	1971-2000	Case-control	NR	NR	Affective psychosis	ICD-9 codes 296.0-296.9 and ICD-10 codes F30, F31, F32.2, F32.3, F33.2, F33.3	18-26	5

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Table 1. Characteristics of the Studies Included in the Main Meta-analysis (continued)

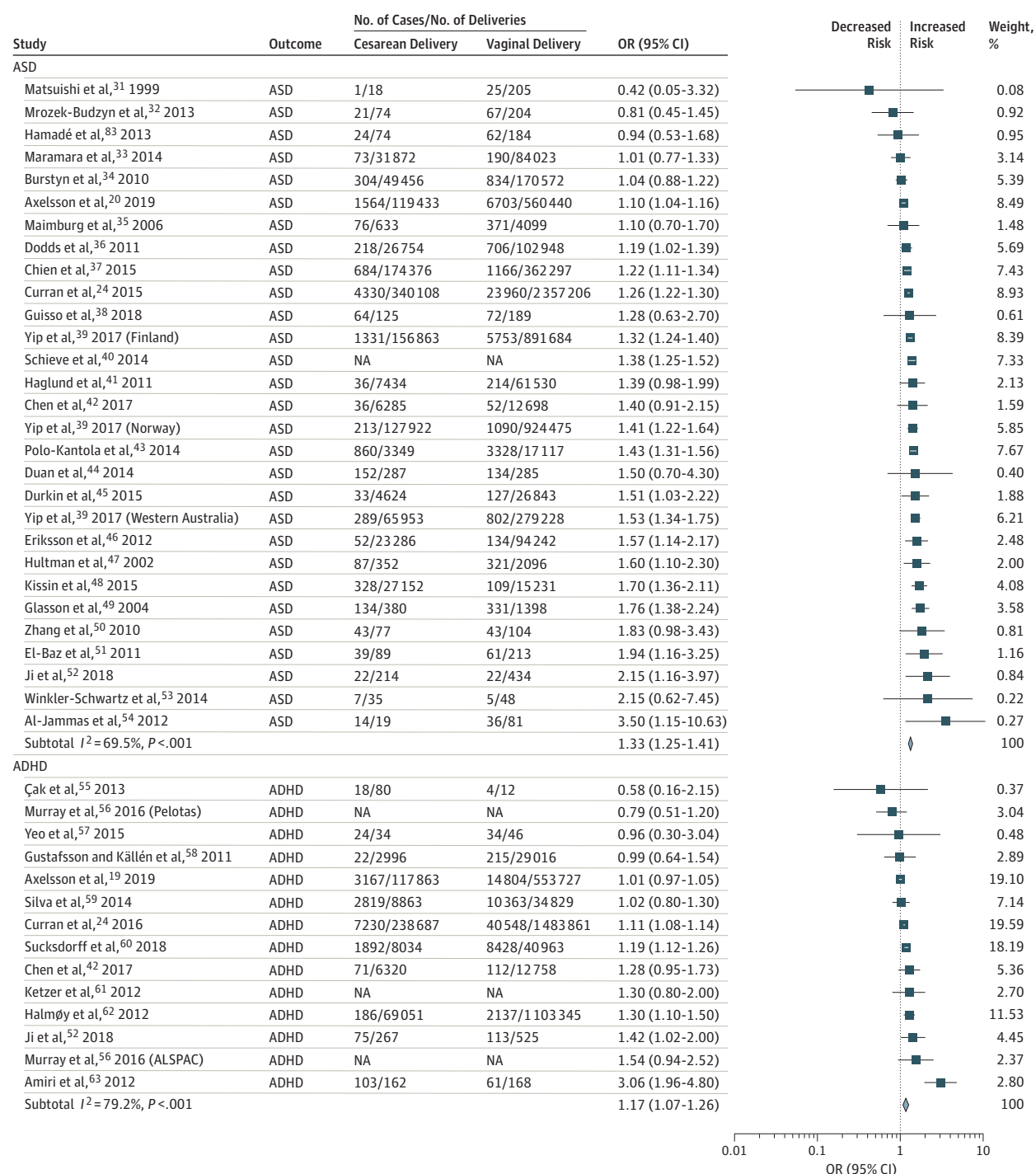
Source	Study		No. of Participants		Design	Outcome(s)	Outcome Ascertainment	Age of Offspring	Newcastle-Ottawa Score
	Location	Period	Cesarean Delivery	Vaginal Delivery					
Chudal et al, ⁷⁵ 2014	Finland	1983-2008	320	1792	Case-control	Bipolar disorder	ICD-9 codes 296.2, 296.3, 296.4, 296.7 and ICD-10 code F31.X	10-21 y	8
Gourion et al, ⁷⁶ 2008	Canada	1986-2005	NR	NR	Cohort	Major depressive disorder	DSM-III-R and DSM-IV	21 y	8
Nonaffective Psychoses									
Ordóñez et al, ⁷⁷ 2005	United States	NR	NR	NR	Cohort	Childhood-onset schizophrenia	K-SADS-PL and DSM-IV	12 y	3
Karlsson et al, ⁷⁸ 2012	Sweden	1975-2003	85	679	Case-control	Schizophrenia, schizoaffective disorders, persistent delusional disorders, induced delusional disorder, acute and transient psychotic disorders, unspecified nonorganic psychosis, schizotypal disorder	DSM-IV codes 295.x, 297.1, 297.3, 298.8, 298.9, 301.22; ICD-9 codes 295.x, 297, 298 excluding A and B and ICD-10 code F20-25, F28-29	<28 y	7
Jones et al, ⁷⁹ 1998	Finland	1966-1993	47	1097	Case-control	Schizophrenia	DSM-III-R codes 295.1, 295.2, 295.3, 295.6, or 295.9	16-28 y	8
Harrison et al, ⁸⁰ 2003	Sweden	1973-1997	60 110	635 915	Cohort	Nonaffective psychosis	ICD-9 code 295, 297-298, ICD-10 code F20-29	16-26 y	7
O'Neill et al, ⁷³ 2016	Sweden	1982-2011	125 155	1 213 931	Cohort	Schizophrenia, schizotypal disorder, persistent delusional disorders, acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorders, other nonorganic psychotic disorders, and unspecified nonorganic psychosis	ICD-10 codes F20-29	16-29 y	9
Kendell et al, ⁸¹ 2000	United Kingdom	1971-1996	NR	NR	Case-control	Schizophrenia	ICD-9 codes 295.0-259.9, ICD-10 codes F20.0-20.3 and F20.5-20.9	18-25 y	7
Byrne et al, ⁸² 2000	Ireland	1972-1992	15	832	Case-control	Schizophrenia	ICD-9 codes 295.0-295.9	NR	5

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, autism spectrum disorders; ATC, Anatomic Therapeutic Chemical; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; ICD, *International Statistical Classification of Diseases and Related Health Problems*; K-SADS, Kiddie Schedule for Affective Disorders and Schizophrenia; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Versions; NR, not reported; OCD, obsessive-compulsive disorder; PDD-NOS, pervasive developmental disorder—not otherwise specified; SCID-I/P, Structured Clinical Interview for DSM-IV, Axis I disorders—patient edition; WA, Western Australia.

Meta-analytic Association Between Elective and Emergency Cesarean Delivery and Neurodevelopmental and Psychiatric Disorders

For the second aim, 20 studies^{20,23,24,34,35,39,41,43,49,53,58-60,66,67,73-75,81,82} (10 620 715 deliveries) and 18 studies^{20,23,24,34,35,39,43,46,49,58-60,66,67,73-75,81} (10 597 234 deliveries) assessed the risk of ASD,

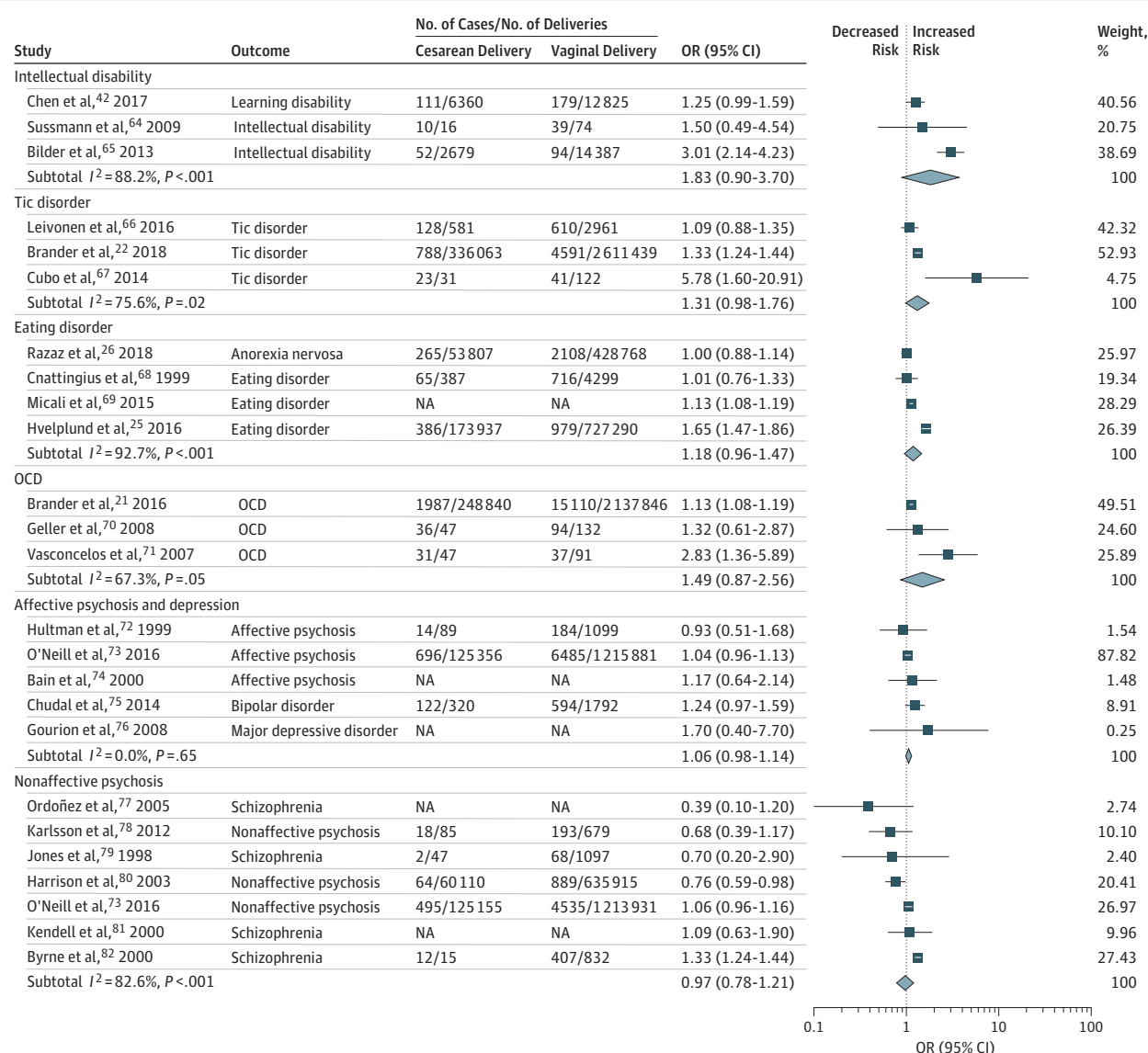
Figure 2. Forest Plot of the Results of Random-Effects Meta-analyses Stratified by Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD)



Forest plot of odds ratios (ORs) in studies investigating the associations between cesarean delivery and each outcome. Diamonds show overall pooled estimate for each outcome. ALSPAC indicates Avon Longitudinal Study of Parents and Children; NA, not available.

ADHD, tic disorders, and affective and nonaffective psychoses in offspring born via elective and emergency cesarean delivery, each compared with offspring born via unassisted vaginal delivery. Similar to the results of the main analyses, both elective and emergency cesarean deliveries were associated with increased odds of ADHD and ASD; for these analyses, heterogeneity was low (I^2 range, 10.7%-33.6%) except for ASD when assessing the association with elective cesarean delivery ($I^2 = 87.9\%$) (eFigure 3 in the Supplement). Elective and emergency cesarean deliveries were not associated with tic disorders or affective and nonaffective psychoses. In the 23 studies^{22-24,26,36,41,43,45,47,49,51,58-60,66-68,73,75,79,81,82,84,85} (8 415 429 deliveries) that assessed the associations with assisted vs unassisted vaginal delivery, we did not observe any association with any of the outcomes of interest except for tic disorders (OR, 1.28; 95% CI, 1.17-1.41; $I^2 = 0.0\%$) (eFigure 4 in the Supplement).

Figure 3. Forest Plot of the Results of Random-Effects Meta-analyses Stratified by Intellectual Disability, Tic Disorder, Eating Disorder, Obsessive-Compulsive Disorder (OCD), Affective Psychosis/Depression, and Nonaffective Psychosis



Forest plot of odds ratios (ORs) in studies investigating the associations between cesarean delivery and each outcome. Diamonds show overall pooled estimate for each outcome. NA indicates not available.

Subgroup and Meta-regression Analyses

Results of our subgroup analyses for study design revealed that, compared with offspring born via vaginal delivery, the odds of offspring born via cesarean delivery being diagnosed with ASD or ADHD were significantly higher when pooling the results of case-control studies than when pooling those of cohort studies (**Table 2**). In studies that indicated unnecessary use of cesarean delivery (proportions $\geq 15\%$), we observed higher odds of ASD compared with studies with cesarean delivery proportions less than 15% (Table 2). Study quality scores and exposure assessment did not significantly affect the results (Table 2 and eTable 5 in the [Supplement](#)). Subgroup analyses on offspring sex and parental psychiatric history were not performed because of too few (<3) studies on each outcome with data available. Owing to data availability, we only performed meta-regression analyses for ASD and ADHD. Country income level and exposure ascertainment were associated with between-study variance for ADHD, but residual heterogeneity still remained significant (eTable 6 in the [Supplement](#)). None of the 5 factors examined (ie, publication year, proportion of cesarean deliveries, study design, country income status, and exposure ascertainment) were associated with heterogeneity or reduced residual heterogeneity. For our sensitivity analyses, we replicated all the analyses using crude or least-adjusted estimates from the same studies (eFigure 5 in the [Supplement](#)). No significant differences between the models were detected, although heterogeneity increased in the model including the least-adjusted estimates.

Discussion

This systematic review and meta-analysis explored the association of cesarean delivery with a wide range of neurodevelopmental and psychiatric outcomes. Compared with vaginal delivery, cesarean delivery was associated with increased risk of several neurodevelopmental and psychiatric disorders. The estimates for ASD (33% increased odds) and ADHD (17% increased odds) were statistically significant, but other disorders, such as learning disabilities, tic disorders, OCD, and eating disorders, presented with similar or higher odds, although these were not statistically significant, possibly because of the modest number of studies. In the leave-1-out analysis, associations with intellectual disabilities, OCD, and tic disorders became statistically significant after the exclusion of single outlier studies. By contrast, the associations were close to the null and nonsignificant for depression and affective and nonaffective psychotic disorders, indicating some specificity. The association between cesarean delivery and offspring psychopathologic disorders contrasts with findings for assisted vaginal delivery (eg, forceps delivery), which was associated only with increased odds of tic disorders, whereas the association was close to the null with the remaining outcomes.

Our findings are consistent with previous meta-analyses conducted with a limited range of psychiatric outcomes, such as ASD¹¹ or schizophrenia,⁸⁶ and considerably expand the evidence by

Table 2. Subgroup Analyses According to Proportion of Cesarean Deliveries, Study Quality Assessment, and Study Design for Neurodevelopmental and Psychiatric Disorders in Offspring Born via Cesarean Delivery Compared With Vaginal Delivery^a

Outcome	Cesarean Delivery Use Proportion			Study Quality			Study Design		
	<15%		P Value ^b	High (NOS Score ≥ 7)		P Value ^b	Cohort		P Value
	No. of Studies	OR (95% CI)		No. of Studies	OR (95% CI)		No. of Studies	OR (95% CI)	
ADHD	3	1.16 (1.03-1.31)		8	1.22 (1.05-1.42) ^c	.52	9	1.12 (1.05-1.21) ^c	
				5	1.37 (0.82-2.29) ^d	.68	6	1.07 (0.98-1.18) ^c	
ASD	8	1.29 (1.24-1.34)	.02	16	1.30 (1.22-1.39) ^c		11	1.28 (1.19-1.37) ^c	
Psychoses	9	1.00 (0.89-1.12)	>.99	9	1.02 (0.93-1.12)		5	0.99 (0.88-1.12)	
				3	1.14 (0.74-1.74)	.89	7	1.18 (1.00-1.39)	.02

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; NOS, Newcastle-Ottawa Scale; OR, odds ratio.

^a Results of subgroup analyses on country income level and exposure ascertainment are reported in eTable 5 in the Supplement.

^b P values presented in the table are for group differences.

^c Study heterogeneity high ($I^2 > 75\%$; $P < .05$).

^d Study heterogeneity medium ($I^2 = 50\%$ - 75% ; $P < .05$).

including all available data on a broad range of neurodevelopmental and psychiatric disorders. This inclusion was in part possible because of increased power afforded by the publication of large, nationwide registry-based studies on psychiatric disorders. For example, Curran and colleagues¹¹ could not confirm an association between cesarean delivery and ADHD because of the availability of only 2 suitable studies at the time. We were able to include 13 studies on ADHD, of which 7 used data from population-based registries^{19,24,58-60,62} or national birth cohorts.⁴²

For the first time, to our knowledge, we were able to examine elective cesarean delivery separately from emergency cesarean delivery in association with neurodevelopmental and psychiatric disorders. This distinction is theoretically important because it may hint at potentially different implicated mechanisms in the association between cesarean delivery and neurodevelopmental and psychiatric disorders. Of interest, the odds of ASD and ADHD in offspring born via elective and emergency cesarean delivery were nearly identical compared with unassisted vaginal delivery. The results for tic disorders and affective and nonaffective psychoses were less conclusive because of the few studies with small sample sizes. Of note, there have been no clear definitions of elective and emergency cesarean delivery in the literature, which may have influenced our results toward the null because of potential nondifferential exposure misclassification. Future studies should carefully define elective and emergency cesarean delivery, for example, using the Robson classification system.⁸⁷

Subgroup analyses and meta-regressions (only performed for ADHD and ASD) suggested a potential association between higher rates of cesarean delivery and the presence of disorders in the offspring. Although it seems reasonable to assume that cesarean delivery is overused when exceeding a 15% rate of the total deliveries, additional studies are needed to investigate the reasons behind potentially unnecessary cesarean delivery to properly evaluate costs and benefits. Our subgroup analyses by type of study design found that the odds for ASD and ADHD were significantly weaker in cohort studies compared with case-control studies, indicating a potential bias in the main meta-analysis, in which studies of both designs were pooled together. This finding is also reflected in our quality assessment, in which cohort studies were more likely to be classified as high quality; however, subgroup analyses did not detect significant group differences between high- and low-quality studies. Future research should examine how potential bias, such as confounders, in particular indications for cesarean delivery, contribute to the observed associations.

Strengths and Limitations

A strength of our review is the comprehensive scope of the literature search across multiple neurodevelopmental and psychiatric disorders, across 19 countries, in all languages, and with low publication bias. We used 4 different bibliographic databases and conducted the screening, data extraction, and quality assessment in duplicate. The main limitation of our study is the high level of heterogeneity in all outcomes except for depression and affective psychoses. Heterogeneity was decreased when we separated elective and emergency cesarean deliveries. Nevertheless, neither the subgroup nor meta-regression analyses could fully explain the high level of heterogeneity. Several other factors might have contributed to it. First, indication for cesarean delivery likely contributes to the heterogeneity among studies, but we were unable to explore the role of indications because of a lack of data in the original studies. The medical indications in the mothers may play an important role in the observed associations between cesarean delivery and the outcomes. Second, baseline age, age at diagnosis, and follow-up time substantially varied among studies and were not reported in some studies, which precluded us from exploring the role of these factors as contributors to heterogeneity. Third, methodologic differences in adjustment for parental, perinatal, and fetal factors in each study might account for the variance among studies. Studies with both population and sibling analyses suggest that the observed associations are likely attributable to familial confounding because the significant findings from the population-level analyses were attenuated in sibling comparisons.^{20,21,23,36,59} We therefore acknowledge the existence of unadjusted confounders

and that the observed associations cannot be explained by only a single factor but are likely to be multifactorial.

Conclusions

Our study findings suggest that birth by cesarean delivery is associated with certain neurodevelopmental and psychiatric disorders. The results appear to further add to the known adverse health outcomes associated with cesarean delivery and suggest judicious use of cesarean delivery.^{1,3,4} Statistical heterogeneity was high in the meta-analysis of some specific outcomes despite the use of strict inclusion criteria and our attempts to address the source of heterogeneity in subgroup analyses and meta-regression. This finding might suggest that other confounders, such as indication for cesarean delivery, could contribute to explaining some of the variation across studies. Future research should include further adjustment for potential confounders and consider genetically sensitive designs, such as sibling comparisons or twin and adoption studies. The mechanisms underlying the observed associations remain unknown and require empirical investigation to examine whether cesarean delivery plays a causal role in the development of neurodevelopmental and psychiatric disorders.

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SUPPLEMENT.**eTable 1.** Full search strategy**eTable 2.** Characteristics of the articles excluded due to duplicate data**eTable 3.** Variables adjusted for or matched by in each included study in the main analysis**eTable 4.** Leave-one-study-out analyses**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**eTable 6.** Meta-regression analyses**eFigure 1.** Publication bias: Funnel plots and Egger's tests for the main analyses**eFigure 2.** Contour-enhanced funnel plot for ASD for potential publication bias**eFigure 3.** Forest Plots of the Results of Random Effects Meta-analyses Stratified by Type of Cesarean Delivery (*Elective* or *Emergency*) and the Disorders**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**eFigure 5.** Sensitivity analyses: crude or least adjusted models**eReferences**