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**Date:** 16 January 2020

**Sources Searched:** Medline, Embase.

## Autism/ADHD in Children Delivered by Caesarean Section

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[See full search strategy](#)

### 1. Association of Cesarean Delivery With Risk of Neurodevelopmental and Psychiatric Disorders in the Offspring: A Systematic Review and Meta-analysis.

**Author(s):** Zhang, Tianyang; Sidorchuk, Anna; Sevilla-Cermeño, Laura; Vilaplana-Pérez, Alba; Chang, Zheng; Larsson, Henrik; Mataix-Cols, David; Fernández de la Cruz, Lorena

**Source:** JAMA network open; Aug 2019; vol. 2 (no. 8); p. e1910236

**Publication Date:** Aug 2019

**Publication Type(s):** Journal Article

**PubMedID:** 31461150

Available at [JAMA network open](#) - from Unpaywall

**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 who 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<sup>2</sup> = 69.5%) and attention-deficit/hyperactivity disorder (OR, 1.17; 95% CI, 1.07-1.26; I<sup>2</sup> = 79.2%). Estimates were less precise for intellectual disabilities (OR, 1.83; 95% CI, 0.90-3.70; I<sup>2</sup> = 88.2%), obsessive-compulsive disorder (OR, 1.49; 95% CI, 0.87-2.56; I<sup>2</sup> = 67.3%), tic disorders

(OR, 1.31; 95% CI, 0.98-1.76; I2 = 75.6%), and eating disorders (OR, 1.18; 95% CI, 0.96-1.47; I2 = 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. 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.

**Database:** Medline

## **2. Underlying factors of the association between cesarean section and autism spectrum disorder**

**Author(s):** Menashe I.; Huberman M.; Bashiri A.; Dinstein I.; Meiri G.

**Source:** European Neuropsychopharmacology; 2019; vol. 29

**Publication Date:** 2019

**Publication Type(s):** Conference Abstract

**Abstract:**Background: Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition characterized by impairment in social communication, and restricted, repetitive patterns of behavior, interests, or activities. A wide variety of prenatal and perinatal factors have proposed as risk factors of ASD in the last couple of years. Among these, the association of Cesarean section with ASD is particularly interesting given the continuous increase in the implementation of this procedure worldwide. Thus, understanding the underlying factors of this association is a public health priority. Objective(s): The goal of this study was to explore the contribution of various prenatal, perinatal and neonatal variables to the association between CS and ASD. Method(s): We studied a wide range of prenatal, perinatal and neonatal characteristics in 347 children diagnosed with ASD, 117 children diagnosed with other forms of developmental delay (DD), and 2226 matched controls (matched by sex, birth date, and ethnicity at a 1:5 case-control ratio). Both cases and controls were ascertained from all single-live-born children at the Soroka University Medical Center (SUMC) between the years 2009 - 2016. Diagnosis of ASD and DD was determined according to DSM-V criteria by a child psychiatrist or child neurologist. Prenatal, perinatal and neonatal variables were obtained for both cases and controls from the electronic database of the obstetrics and gynecology department (OGD) of SUMC. The associations between each of these variables and ASD or DD were examined using appropriate univariate analyses. Significantly associated variables were further included in conditional logistic regression models that tested the adjusted effect of CS on the risk of either ASD or DD. Result(s): Delivery by CS was significantly associated with ASD but not with DD (P-values = 0.019 and 0.540 respectively). Additional variables that were associated with ASD included general anesthesia (GA), parity number, and amniocentesis (P-value < 0.05). Stratification of CS deliveries to those, which were conducted with and without GA, revealed that only CS + GA elevate the risk of ASD (OR = 1.618, 95% CI: 1.176-2.226). Further stratification of the CS + GA deliveries to emergency and elective surgeries revealed a slightly higher risk associated with emergency surgeries (OR = 1.97 vs. 1.56 respectively), however this difference was not statistically significant (Breslow-Day test of homogeneity P-value = 0.174). Finally, repeating these analyses in subgroups of children with ASD according to their DSM-V severity levels, indicated that exposure to CS + GA affects only the most severely diagnosed children with ASD (OR = 2.52; 95% CI = 1.488 - 4.275). Conclusion(s): Our findings indicate that the reported association between CS and ASD is restricted only to CS performed with GA. Nevertheless, our subgroup analysis suggests that exposure to GA during CS is unlikely causing to ASD, but rather contributes to the manifestation of additional symptoms that worsen the clinical condition of children with ASD. Copyright © 2018

**Database:** EMBASE

### 3. Perinatal Factors Associated with Autism Spectrum Disorder in Jamaican Children.

**Author(s):** Saroukhani, Sepideh; Samms-Vaughan, Maureen; Lee, MinJae; Bach, MacKinsey A; Bressler, Jan; Hessabi, Manouchehr; Grove, Megan L; Shakespeare-Pellington, Sydonnie; Loveland, Katherine A; Rahbar, Mohammad H

**Source:** Journal of autism and developmental disorders; Sep 2019

**Publication Date:** Sep 2019

**Publication Type(s):** Journal Article

**PubMedID:** 31538260

Available at [Journal of autism and developmental disorders](#) - from SpringerLink - JUSTICE Consortium Package

**Abstract:**Mode of delivery, preterm birth, and low birth weight (LBW) are hypothesized to be associated with autism spectrum disorder (ASD) in the offspring. Using data from 343 ASD cases (2-8 years) and their age- and sex-matched typically developing controls in Jamaica we investigated these hypotheses. Our statistical analyses revealed that the parish of residence could modify the association between cesarean delivery and ASD, with a difference found in this relationship in Kingston parish [matched odds ratio (MOR) (95% confidence interval (CI)) 2.30 (1.17-4.53)] and other parishes [MOR (95% CI) 0.87 (0.48-1.59)]. Although the associations of LBW and preterm birth with ASD were not significant, we observed a significant interaction between LBW and the household socioeconomic status. These findings require replication.

**Database:** Medline

### 4. Lifestyle factors, diet and attention-deficit/hyperactivity disorder in Spanish children - an observational study.

**Author(s):** San Mauro Martin, Ismael; Sanz Rojo, Sara; Garicano Vilar, Elena; González Cosano, Lourdes; Conty de la Campa, Raquel; Blumenfeld Olivares, Javier Andrés

**Source:** Nutritional neuroscience; Sep 2019 ; p. 1-10

**Publication Date:** Sep 2019

**Publication Type(s):** Journal Article

**PubMedID:** 31479410

**Abstract:**Background: The aetiology of Attention Deficit Hyperactivity Disorder (ADHD) continues to be debated, although several contributing factors have been acknowledged. Objective: Assess the association between weight, birth attributes, exercise and sleep habits, dietary intake and adherence to a Mediterranean diet, and impulsive behaviour on Spanish ADHD children. Establish whether specific food groups (not just adherence to the Mediterranean diet) associate with impulsive behaviour. Methods: This observational cross-sectional study included 57 ADHD children from Madrid (Spain). Demographic, clinical data, sleep, exercise and technology-use habits were obtained. Anthropometric measurements included height and weight. Adherence to the Mediterranean diet was assessed using the KIDMED test. Barratt Impulsivity Scale version-11c was used to assess impulsivity. Subjects were divided into three groups for analysis, according to their age (6-10 years, children; 11-13 years, pre-adolescents; 14-16 years, adolescents). Results: There were clear associations between those who had higher BIS scores and who slept less at weekends ( $49.4 \pm 10.16$  vs.  $43.8 \pm 12.51$ ), who adhered poorly to the Mediterranean diet ( $49.9 \pm 11.72$  vs.  $41.6 \pm 16.52$ ), who used internet and technological devices for  $>3$  h/day ( $45.5 \pm 13.6$  vs.  $44.7 \pm 12.11$ ), who were born with  $>2.5$  kg ( $46.1 \pm 11.61$  vs.  $42.9 \pm 15.29$ ), who were delivered by caesarean ( $45.1 \pm 12.78$  vs.  $44.7 \pm 12.5$ ) and who were not breastfed ( $45.0 \pm 13.38$  vs.  $44.8 \pm 12.39$ ). Subjects exercising more than 3 days a week also scored slightly higher ( $45.4 \pm 14.02$  vs.  $44.6 \pm 11.85$ ) in the BIS.

Conclusion: There is a need to follow up the link between ADHD and sleep onset difficulties, dietary patterns, technological habits, perinatal factors, breastfeeding and birth delivery mode.

**Database:** Medline

## **5. The role of pre-, peri-, and postnatal risk factors in bipolar disorder and adult ADHD**

**Author(s):** Tole F.; Kopf J.; Schroter K.; Palladino V.S.; Reif A.; Kittel-Schneider S.; Jacob C.P.

**Source:** Journal of Neural Transmission; Sep 2019; vol. 126 (no. 9); p. 1117-1126

**Publication Date:** Sep 2019

**Publication Type(s):** Article

**PubMedID:** 30758784

Available at [Journal of neural transmission \(Vienna, Austria : 1996\)](#) - from SpringerLink - Medicine

**Abstract:**Gene-environment-development interactions are suggested to play a crucial role in psychiatric disorders. However, it is not clear if there are specific risk gene interactions with particular pre-, peri-, and postnatal risk factors for distinct disorders, such as adult attention-deficit-/hyperactivity disorder (aADHD) and bipolar disorder (BD). In this pilot study, the first aim was to investigate retrospective self-reports of pre-, peri-, and postnatal complications and risk factors from 126 participants (aADHD, BD, and healthy controls) and their mothers. The second aim was to investigate possible interaction between the previously published common risk gene variants of ADHD in the ADGRL3 (=LPHN3) gene (rs2305339, rs1397548, rs734644, rs1397547, rs2271338, rs6551665, and rs2345039) and shared risk gene variants of aADHD and BD in the DGKH gene (DGKH rs994856/rs9525580/rs9525584 GAT haplotype) and pre-, peri-, and postnatal risk factors in comparison to a healthy control group. After correction for multiple comparison, the following pre-, peri-, and postnatal risk factors remained statistically significant ( $p \leq 0.0036$ ) between healthy controls and ADHD and BD patients as one group: unplanned pregnancies, psychosocial stress of the mother during pregnancy, mode of delivery, shared decision-making regarding medical procedures during the delivery, perinatal bonding, number of crybabies, and quality of mother-child and father-child relationship. There were no significant environment-gene interactions. In our preliminary data, similar risk factors were found to be significantly associated with both disorders in comparison to healthy controls. However, larger and longitudinal studies and standardized and validated instruments to get a better understanding of the interaction of pre-, peri-, and postnatal complications and mental health in the offspring are needed. Copyright © 2019, Springer-Verlag GmbH Austria, part of Springer Nature.

**Database:** EMBASE

## **6. Exposure to General Anesthesia May Contribute to the Association between Cesarean Delivery and Autism Spectrum Disorder.**

**Author(s):** Huberman Samuel, Maayan; Meiri, Gal; Dinstein, Ilan; Flusser, Hagit; Michaelovski, Analiya; Bashiri, Asher; Menashe, Idan

**Source:** Journal of autism and developmental disorders; Aug 2019; vol. 49 (no. 8); p. 3127-3135

**Publication Date:** Aug 2019

**Publication Type(s):** Journal Article

**PubMedID:** 31053992

Available at [Journal of autism and developmental disorders](#) - from SpringerLink - JUSTICE Consortium Package

**Abstract:**Cesarean section (CS) has been consistently associated with susceptibility to autism spectrum disorder (ASD), however, the underlying mechanism for this association remains vague. Here, we studied various pre-peri-and-neonatal factors among 347 children with ASD, 117 children with other developmental delays (DD), and 2226 age, sex and ethnicity matched controls. We found that CS is significantly associated with an increased risk of ASD but not DD ( $p = 0.019$  and  $p = 0.540$  respectively). Furthermore, we show that only CS performed with general anesthesia (GA) elevated the risk of ASD with no significant difference between indicated and non-indicated surgeries (aOR = 1.537; 95% CI 1.026-2.302, and aOR = 1.692; 95% CI 1.057-2.709,  $p_{diff} = 0.865$ ). We therefore suggest that exposure to GA during CS may explain the association between CS and ASD.

**Database:** Medline

## **7. Meta-analysis found that studies may have overestimated Caesarean section risks for attention-deficit hyperactivity disorder by ignoring confounding factors.**

**Author(s):** Xu, Lian-Lian; Zhang, Xue; Zhou, Guo-Lin; Jiang, Chun-Min; Jiang, Hai-Yin; Zhou, Yuan-Yue

**Source:** Acta paediatrica (Oslo, Norway : 1992); Aug 2019

**Publication Date:** Aug 2019

**Publication Type(s):** Journal Article

**PubMedID:** 31472095

Available at [Acta paediatrica \(Oslo, Norway : 1992\)](#) - from Wiley Online Library

**Abstract:**AIM Epidemiological studies on associations between Caesarean sections (C-sections) and attention-deficit hyperactivity disorder (ADHD) have been inconsistent, and we performed a meta-analysis. METHODS We systematically searched PubMed and Embase to December 2018 and included nine hospital-based and population registry studies published in 2011-2018. These covered a total study cohort of more than 2.5 million people in eight countries: Australia, Brazil, Denmark, Finland, Germany, Sweden, Turkey and the UK. The analysis provided summary odds ratios (ORs) and 95% confidence intervals (CI) while taking heterogeneity into account. RESULTS We found that C-sections were associated with a small increase in the risk of ADHD (OR 1.14, 95% CI 1.11, 1.17, I<sup>2</sup> 0%) in offspring. In subgroup analyses, the association remained for both infants born after elective C-sections (OR, 1.15, 1.11, 1.19, I<sup>2</sup> 0%) and emergency C-sections (OR, 1.13, 1.1, 1.17, I<sup>2</sup> 45.4%). However, these were only marginally significant when we pooled data from siblings from other pregnancies (OR, 1.06, 1.00-1.13, I<sup>2</sup> 0%), implying that the association was due to confounding. CONCLUSION The statistically significant association between C-sections and ADHD in children can be partially explained by unmeasured confounding. Further research controlling for important confounders is required before firm conclusions can be drawn.

**Database:** Medline

## **8. The association between mode of birth delivery and attention-deficit/hyperactivity disorder: a systematic review protocol of epidemiological evidence.**

**Author(s):** Klugarová, Jitka; Janoušková, Kateřina; Procházka, Martin; Hálek, Jan; Šibravová, Věra; Klugar, Miloslav

**Source:** International journal of evidence-based healthcare; Jun 2019; vol. 17

**Publication Date:** Jun 2019

**Publication Type(s):** Journal Article

**PubMedID:** 31283578

Available at [International journal of evidence-based healthcare](#) - from Ovid (LWW Total Access Collection 2019 - with Neurology)

Available at [International journal of evidence-based healthcare](#) - from Unpaywall

**Abstract:**Caesarean section is currently the most frequently performed intervention after episiotomy in obstetrics and one of the most common abdominal operations overall. Rates of caesarean section have been rising globally. Given the increasing rate worldwide it is therefore necessary and important to understand how caesarean section affects child development. Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioural disorder in children. ADHD is characterized by a combination of symptoms including inattention, impulsivity and hyperactivity. Caesarean section may affect psychological development through changes in microbiota or stress response, and birth by caesarean section can be associated with a small increased risk of ADHD. In the current literature, there is no systematic review or protocol of the systematic review answering the question of whether the mode of delivery has influence on the risk of ADHD development. The objective of this review is to synthesize the best available evidence regarding the epidemiological association between the mode of delivery (caesarean section versus vaginal delivery) as exposure and ADHD as the outcome. A three-step strategy will be utilized in this review, aiming to find both published and unpublished studies. The initial search will be conducted using the MEDLINE, CINAHL and EMBASE. The second search will involve 21 databases and sources. Following the Preferred Reporting Items for Systematic Review and Meta-analysis statement analysis of title, abstracts and full texts, critical appraisal and data extraction will be carried out on selected studies using standardized instruments developed by Joanna Briggs Institute. All steps will be performed by two independent reviewers. If possible, statistical meta-analysis using Joanna Briggs Institute within the System for the Unified Management, Assessment and Review of Information will be pooled. Statistical heterogeneity will be assessed. The results will be disseminated by publishing in a peer-reviewed journal. Ethical assessment is not needed - we will search/evaluate the existing sources of literature.

**Database:** Medline

## 9. Prenatal and perinatal risk factors and the clinical implications on autism spectrum disorder

**Author(s):** Chien Y.-L.; Tsai W.-C.; Chiu Y.-N.; Gau S.S.-F.; Chou M.-C.; Chou W.-J.; Wu Y.-Y.

**Source:** Autism; Apr 2019; vol. 23 (no. 3); p. 783-791

**Publication Date:** Apr 2019

**Publication Type(s):** Article

**PubMedID:** 29950101

**Abstract:** Prenatal and perinatal factors may increase the risk of autism spectrum disorder. However, little is known about whether unaffected siblings of probands with autism spectrum disorder also share the phenomenon and whether the prenatal/perinatal factors are related to the clinical severity of autistic symptoms. We compared the frequency of prenatal and perinatal factors among 323 probands with autism spectrum disorder (mean age +/- standard deviation, 10.7 +/- 3.5 years; males, 91.0%), 257 unaffected siblings (11.7 +/- 4.5; 42.8%), and 1504 typically developing controls (8.9 +/- 1.6 years; 53.1%); and investigated their effects on the severity of autistic symptoms. We found that probands with autism spectrum disorder and their unaffected siblings had more prenatal/perinatal events than typically developing controls with higher numbers of prenatal/perinatal factors in probands than in unaffected siblings. The prenatal/perinatal events were associated with greater stereotyped behaviors, social-emotional problems, socio-communication deficits, and overall severity. We also found that six prenatal/perinatal factors (i.e. preeclampsia, polyhydramnios, oligoamnios, placenta previa, umbilical cord knot, and gestational diabetes) were associated with the severity of autistic symptoms, particularly stereotyped behaviors and socio-communication deficits. Our findings suggest that prenatal and perinatal factors may potentially moderate the clinical expression of autism spectrum disorder. The underlying mechanism warrants further research. Copyright © The Author(s) 2018.

**Database:** EMBASE

## 10. Investigating the effects of cesarean delivery and antibiotic use in early childhood on risk of later attention deficit hyperactivity disorder.

**Author(s):** Axelsson, Paul Bryde; Clausen, Tine Dalsgaard; Petersen, Anne Helby; Hageman, Ida; Pinborg, Anja; Kessing, Lars Vedel; Bergholt, Thomas; Rasmussen, Steen Christian; Keiding, Niels; Løkkegaard, Ellen Christine Leth

**Source:** Journal of child psychology and psychiatry, and allied disciplines; Feb 2019; vol. 60 (no. 2); p. 151-159

**Publication Date:** Feb 2019

**Publication Type(s):** Journal Article

**PubMedID:** 30136734

**Abstract:** BACKGROUND Increasing attention deficit hyperactivity disorder (ADHD) incidence has been proposed to be caused by factors influencing microbiota in early life. We investigated the potential causality between ADHD and two surrogate markers for changes in children's microbiota: birth delivery mode and early childhood antibiotic use. METHOD This population-based, prospective cohort study linked nationwide registers of data for native Danish singleton live births in Denmark from 1997 to 2010. Exposure variables were delivery mode and antibiotic use during the first 2 years of life. The main outcome measure was ADHD diagnosis or redeemed ADHD medication prescriptions. For statistical analysis, we used both advanced sibling models and a more traditional approach. RESULTS We included 671,592 children, followed from their second birthday in the period 1999-2014 for 7,300,522 person-years. ADHD was diagnosed in 17,971. In total, 17.5% were born by cesarean delivery, and 72% received antibiotic treatment within their first 2 years of life. In the

adjusted between-within sibling survival model, mode of delivery or antibiotics had no effect on ADHD when compared with vaginal delivery or no antibiotic treatment as hazard ratios were 1.09 (95% confidence interval 0.97-1.24) for intrapartum cesarean, 1.03 (0.91-1.16) for prelabor cesarean, 0.98 (0.90-1.07) for penicillin, and 0.99 (0.92-1.06) for broader spectrum antibiotics. In a sibling-stratified Cox regression, intrapartum cesarean was associated with increased ADHD risk, but other exposures were not. In a descriptive, nonstratified Cox model, we found increased risk for ADHD for all exposures. CONCLUSIONS Detailed family confounder control using the superior between-within model indicates that cesarean delivery or use of antibiotics during the first 2 years of life does not increase ADHD risk. Therefore, our study suggests that changes in children's microbiota related to cesarean delivery or antibiotic use, do not cause ADHD.

**Database:** Medline

### **11. Is cesarean section delivery associated with autism spectrum disorder?**

**Author(s):** Al-Zalabani, Abdulmohsen H; Al-Jabree, Amani H; Zeidan, Zeidan A

**Source:** Neurosciences (Riyadh, Saudi Arabia); Jan 2019; vol. 24 (no. 1); p. 11-15

**Publication Date:** Jan 2019

**Publication Type(s):** Journal Article

**PubMedID:** 30842394

Available at [Neurosciences \(Riyadh, Saudi Arabia\)](#) - from Europe PubMed Central - Open Access

Available at [Neurosciences \(Riyadh, Saudi Arabia\)](#) - from Unpaywall

**Abstract:** OBJECTIVE To investigate a correlation between birth by caesarean section and autism spectrum disorder (ASD). METHODS A case-control study with a case to control ratio of 1:2 was performed in Al-Madina Al-Munawarah city, Kingdom of Saudi Arabia during the year 2016. The cases were selected according to the eligibility criteria and children attending a well-baby clinic in the same hospital, were chosen as the control group subjects. Data was collected from the medical records and an interview-based questionnaire was administered to the mothers. The chi-square test was used for bivariate analysis and logistic regression to estimate the crude and adjusted odds ratios (ORs). RESULTS Eighty-seven cases of ASD and 174 control group subjects were included in the current study. Approximately 39% (n=34) of the 87 children with ASD were delivered by cesarean section compared to 21% (n=36) of the 174 children in the control group. After adjusting for potentially confounding factors, the adjusted OR was 2.9 (95% confidence interval [CI]: 1.57-5.35). CONCLUSION An association between delivery by cesarean section and ASD was found in this study, in support of the findings of other studies. It is recommended that preventive measures are adopted to avoid unnecessary cesarean sections.

**Database:** Medline

## **12. Relation between Infant Microbiota and Autism?: Results from a National Cohort Sibling Design Study**

**Author(s):** Axelsson P.B.; Clausen T.D.; Lokkegaard E.C.L.; Petersen A.H.; Keiding N.; Hageman I.; Kessing L.V.; Pinborg A.; Bergholt T.; Rasmussen S.C.

**Source:** Epidemiology; Jan 2019; vol. 30 (no. 1); p. 52-60

**Publication Date:** Jan 2019

**Publication Type(s):** Article

**PubMedID:** 30273187

Available at [Epidemiology \(Cambridge, Mass.\)](#) - from Ovid (LWW Total Access Collection 2019 - with Neurology)

**Abstract:**Background: Hypotheses concerning adverse effects of changes in microbiota have received much recent attention, but unobserved confounding makes them difficult to test. We investigated whether surrogate markers for potential adverse microbiota change in infancy affected autism risk, addressing unobserved confounding using a sibling study design. Method(s): This is a population-based, prospective cohort study including all singleton live births in Denmark from 1997 to 2010. The exposure variables were cesarean delivery and antibiotic use in the first 2 years of life. The outcome was a subsequent autism diagnosis. We used the between- and within-sibling model and compared it with sibling-stratified Cox models and simpler standard Cox models that ignored sibship. Result(s): Of our study population including 671,606 children, who were followed for up to 15 years (7,341,133 person-years), 72% received antibiotics, 17.5% were delivered by cesarean, and 1.2% (8,267) developed autism. The standard Cox models predicted that both cesarean (compared with vaginal) delivery and antibiotics increased the risk of autism. In the sibling-stratified Cox model, only broader spectrum antibiotics were associated with increased risk of autism: hazard ratio (HR) = 1.16 (95% confidence interval = 1.01, 1.36). The between-within model estimated no exposure effects: intrapartum cesarean HR = 1.06 (0.89, 1.26); prelabor cesarean HR = 0.97 (0.83, 1.15); exclusively penicillin HR = 1.05 (0.93, 1.18); and broader spectrum antibiotics HR = 1.05 (0.95, 1.16). Conclusion(s): The between-within model rendered more precise estimates than sibling-stratified Cox models, and we believe that it also provided more valid estimates. Results from these preferred models do not support a causal relation between antibiotic treatment during infancy, cesarean delivery, and autism. See video abstract at, <http://links.lww.com/EDE/B432>. Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

**Database:** EMBASE

**13. Lower Apgar scores and Caesarean sections are related to attention-deficit/hyperactivity disorder.**

**Author(s):** Sucksdorff, Minna; Lehtonen, Liisa; Chudal, Roshan; Suominen, Auli; Gissler, Mika; Sourander, Andre

**Source:** Acta paediatrica (Oslo, Norway : 1992); Oct 2018; vol. 107 (no. 10); p. 1750-1758

**Publication Date:** Oct 2018

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 29604108

Available at [Acta paediatrica \(Oslo, Norway : 1992\)](#) - from Wiley Online Library

**Abstract:**AIMWe examined the associations between prenatal, birth-related and newborn risk factors and attention-deficit/hyperactivity disorder (ADHD).METHODSIn this population-based study, 10 409 subjects diagnosed with ADHD by 31 December 2011 and 39 124 controls, born between 1 January 1991 and 31 December 2005, were identified from Finnish nationwide registers. Perinatal data were obtained from the Birth Register. Conditional logistic regression was used to examine the associations after controlling for confounders.RESULTSLower Apgar scores were associated with a higher risk of ADHD, with odds ratios of 1.12 (95% confidence intervals 1.06-1.19) for one-minute Apgar scores of 7-8, 1.17 (95% CI 1.02-1.35) for scores of 5-6 and 1.41 (95% CI 1.18-1.68) for scores of 0-4, compared to Apgar scores of 9-10. Elective Caesarean sections were associated with an increased risk of ADHD with an adjusted odds ratio of 1.15 (95% CI 1.05-1.26). Other identified risk factors were breech presentation, induced labour and admission to a neonatal intensive care unit. Low umbilical artery pH did not increase the risk of ADHD.CONCLUSIONElective Caesareans and perinatal adversities leading to lower Apgar scores increased the risk of ADHD. Future research to identify the mechanisms behind these findings is warranted.

**Database:** Medline

#### **14. Frequency of risk factors and coexisting abnormalities in a population of Egyptian children with autism spectrum disorder**

**Author(s):** Meguid, Nagwa Abdel; Nashaat, Neveen Hassan; Hashem, Heba S.; Khalil, Mai M.

**Source:** Asian Journal of Psychiatry; Feb 2018; vol. 32 ; p. 54-58

**Publication Date:** Feb 2018

**Publication Type(s):** Journal Peer Reviewed Journal Journal Article

**PubMedID:** 29216607

**Abstract:**Background: Many risk factors interact together during the critical period of development and govern the future phenotype of autism spectrum disorder (ASD). Furthermore, co-occurring abnormalities among individuals with ASD vary a lot so as their abilities. Aim of work: To investigate possible risk factors and to determine the prevalence of coexisting abnormalities in a sample of Egyptian ASD children and their influence on the severity and their communication performance. Methods: The diagnosis and severity of ASD for participants (N=80) was performed by DSM-5, ADIR and CARS. They were investigated regarding the possible risk factors and coexisting abnormalities. A detailed history taking, clinical examination, the Arabic preschool language scale, cognitive abilities assessment and other additional instrumental measures such as EEG were used. Results: Caesarian section and neonatal jaundice were the most common risk factors. The severity of ASD was positively related to maternal and paternal ages. Developmental language disorder, intellectual disability, attention deficit hyperactivity disorder, sleep disorder and EEG changes were more frequently detected among studied cases. The CARS scores were significantly higher in ADHD and EEG changes groups. The most severely affected CARS items in the groups with these disorders were determined. Conclusion: High parental ages has an impact on the severity of ASD. ADHD, sleep disorder, and EEG changes seem to have an impact on certain elements of the adaptive behavior especially the communicative performance of ASD individuals. We recommend to seriously investigate co-morbid abnormalities and consider them during the process of management of ASD for proper intervention plans. (PsycINFO Database Record (c) 2018 APA, all rights reserved) (Source: journal abstract)

**Database:** PsycINFO

## **15. Is cesarean section associated with risk for autism spectrum disorder?**

**Author(s):** Gross R.

**Source:** European Neuropsychopharmacology; Oct 2017; vol. 27

**Publication Date:** Oct 2017

**Publication Type(s):** Conference Abstract

**Abstract:** Introduction: Autism is a chronic neurodevelopmental disorder characterized by social and language impairments, and stereotyped repetitive patterns of behavior. Prevalence rates of autism have increased markedly worldwide including Israel. While most plausible neurodevelopmental theories of autism focus predominantly on genetic factors, data from epidemiological studies emphasize the importance of non-genetic risk factors for autism. Objective(s): To summarize current updated delivery-related risk factors for autism. Objective(s): To summarize current updated delivery-related risk factors for autism spectrum disorder (ASD). Method(s): We summarized published findings from epidemiological studies by searching MEDLINE and by screening bibliographies of original and review articles on this topic. In addition, we present original data on the association between mode of delivery and risk of ASD from our own original research, the International Collaboration for Autism Registry Epidemiology (iCARE) database. Using population-based registries of four Nordic countries and Western Australia, our study population included 4987390 singletons surviving their first year of life, which included 671646 CS deliveries and 31073 ASD children. We used logistic regression to estimate odds ratios (OR) and their 95% confidence intervals (CI) for CS, adjusted for gestational age, site, maternal age and birth year. Stratified analyses were conducted by both gestational age subgroups and by the week of gestation. We compared emergency versus planned CS to investigate their potential difference in the risk of ASD. Result(s): A positive association between CS and ASD has been shown in several earlier studies, but the results have varied in effect size. A recent meta-analysis reported that delivery by CS was associated with a 23% increased risk of ASD when compared with vaginal delivery. Compared with vaginal delivery, the overall adjusted odds ratio (OR) for ASD in cesarean section (CS) delivery was 1.26 (95% CI 1.22-1.30). CS was significantly associated with risk of ASD for each week of gestation, from week 36 to 42, and results were consistent across study sites (OR ranged 1.16-1.38). There was no statistically significant difference between emergency and planned CS in the risk of ASD. Results were similar one when firstborns were included in the analysis. We observed no significant interaction with sex of the newborn [1]. Data on other modes of assisted delivery will also be reported in this presentation. Conclusion(s): Emergency or planned CS is consistently associated with an increased risk of ASD from gestational weeks 36 to 42 when compared with vaginal delivery. Thus, the observed risk during this gestational period cannot be attributed to effects of preterm birth for children delivered by CS. The likelihood that the finding was confounded by the indication for CS is significantly diminished by the fact that there were no differences in the risk of autism between planned and emergency CS. Possible mechanisms, including microbiomic dysregulation in the newborn, as well as potential clinical and public health implications, will be discussed.

**Database:** EMBASE

## 16. Method of delivery, the microbiome and neurodevelopment

**Author(s):** Lamb G.V.; van Niekerk A.; Green R.J.

**Source:** Current Allergy and Clinical Immunology; Sep 2017; vol. 30 (no. 3); p. 130-141

**Publication Date:** Sep 2017

**Publication Type(s):** Review

**Abstract:**Caesarean sections, and especially elective Caesarean sections, are on the increase worldwide. The grey-matter volume of the foetal brain undergoes a linear increase of 1,4% per week from 29 weeks until 40 weeks of gestation. This is followed by an accelerated period of brain growth, during which 50% of the increase in cortical volume occurs, between 34 and 40 weeks of gestation. Between 37 and 40 weeks of gestation, cortical grey matter increases by 50% and myelinated white matter increases three-fold. According to the World Health Organisation (WHO), a baby is born prematurely if it is delivered before 37 completed weeks' gestational age (GA), or before 259 days after the last normal menstrual period. As a result, the American College of Gynecologists and Obstetricians (ACOG) has adopted a new maturity classification that refers to babies born from 37 to 39 weeks as 'early term'. Early-term neonates are at increased risk of morbidity. Prematurity is associated with impaired cortical development, and ex-premature infants never achieve the same degree of cortical folding as that seen in babies born at term. Prematurity is also a major risk factor for cerebral palsy, which occurs in 35% of cases. The increased risk is directly proportional to decreasing GA. The global prevalence of cerebral palsy is 2/1 000 births. Between 32 and 36 weeks of gestation, the risk increases to 6.75/1 000 births. Importantly for the timing of elective Caesarean section, there is still an increased risk of 1.35/1 000 births even after 36 weeks of gestation. Babies who are born in the early term period (between 37 and 39 weeks GA) will later constitute 5,5% of children with special educational needs (SEN). Even those babies born at 39 weeks GA carry an elevated risk and constitute 1,7% of total SEN cases. Normal vaginal delivery is associated with neonatal acquisition of a maternally derived microbiome that has a rich diversity. Through bacterial peptides, the microbiome stimulates immune, endocrine and neuronal cells to release cytokines and neurotransmitters, which access the central nervous system via the blood or the vagal nerve. In this way, enteric bacteria can influence mood and behaviour, sleep-wake cycles and feeding patterns. During Caesarean section, however, the foetus is colonised instead by bacteria from the mother's skin. The microbiome that results from this has far less richness and diversity. This in turn is associated with significant risk for chronic inflammatory disorders in later life. New to our understanding of chronic inflammatory disorders that result from dysbiosis is a range of neuro-developmental problems in childhood and adults. Copyright © 2017, Allergy Society of South Africa. All rights reserved.

**Database:** EMBASE

## **17. Prenatal, perinatal, and postnatal factors associated with autism: A meta-analysis**

**Author(s):** Wang C.; Geng H.; Liu W.; Zhang G.

**Source:** Medicine (United States); May 2017; vol. 96 (no. 18)

**Publication Date:** May 2017

**Publication Type(s):** Review

**PubMedID:** 28471964

Available at [Medicine](#) - from Europe PubMed Central - Open Access

Available at [Medicine](#) - from Ovid (LWW Total Access Collection 2019 - with Neurology)

Available at [Medicine](#) - from Unpaywall

**Abstract:**Background: The aim of this meta-analysis was to investigate the prenatal, perinatal, and postnatal risk factors for children autism. Method(s): PubMed, Embase, Web of Science were used to search for studies that examined the prenatal, perinatal, and postnatal risk factors for children autism. A fixed-effects model or random-effects model was used to pool the overall effect estimates. Result(s): Data from 37,634 autistic children and 12,081,416 nonautistic children enrolled in 17 studies were collated. During the prenatal period, the factors associated with autism risk were maternal and paternal age $\geq$ 35 years, mother's and father's race: White and Asian, gestational hypertension, gestational diabetes, maternal and paternal education college graduate+, threatened abortion, and antepartum hemorrhage. During perinatal period, the factors associated with autism risk were caesarian delivery, gestational age $\leq$ 36 weeks, parity $\geq$ 4, spontaneous labor, induced labor, no labor, breech presentation, preeclampsia, and fetal distress. During the postnatal period, the factors associated with autism risk were low birth weight, postpartum hemorrhage, male gender, and brain anomaly. Parity $\geq$ 4 and female were associated with a decreased risk of autism. In addition, exposure to cigarette smoking, urinary infection, mother's and father's race: Black and Hispanic, mother's country of birth outside Europe and North America, umbilical cord around neck, premature membrane rupture, 5-minutes Apgar score $<$ 7, and respiratory infection were not associated with increased risk of autism. Conclusion(s): The present meta-analysis confirmed the relation between some prenatal, perinatal, and postnatal factors with autism. All these factors were examined individually, thus it was still unclear that whether these factors are causal or play a secondary role in the development of autism. Further studies are needed to verify our findings, and investigate the effects of multiple factors on autism, rather than the single factor. Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc.

**Database:** EMBASE

**18. Caesarean section and risk of autism across gestational age: a multi-national cohort study of 5 million births.**

**Author(s):** Yip, Benjamin Hon Kei; Leonard, Helen; Stock, Sarah; Stoltenberg, Camilla; Francis, Richard W; Gissler, Mika; Gross, Raz; Schendel, Diana; Sandin, Sven

**Source:** International journal of epidemiology; Apr 2017; vol. 46 (no. 2); p. 429-439

**Publication Date:** Apr 2017

**Publication Type(s):** Research Support, N.i.h., Extramural Research Support, Non-u.s. Gov't Comparative Study Multicenter Study Journal Article

**PubMedID:** 28017932

Available at [International journal of epidemiology](#) - from Oxford Journals - Medicine

Available at [International journal of epidemiology](#) - from HighWire - Free Full Text

Available at [International journal of epidemiology](#) - from Unpaywall

**Abstract:**BackgroundThe positive association between caesarean section (CS) and autism spectrum disorder (ASD) may be attributed to preterm delivery. However, due to lack of statistical power, no previous study thoroughly examined this association across gestational age. Moreover, most studies did not differentiate between emergency and planned CS.MethodsUsing population-based registries of four Nordic countries and Western Australia, our study population included 4 987 390 singletons surviving their first year of life, which included 671 646 CS deliveries and 31 073 ASD children. We used logistic regression to estimate odds ratios (OR) and their 95% confidence intervals (CI) for CS, adjusted for gestational age, site, maternal age and birth year. Stratified analyses were conducted by both gestational age subgroups and by week of gestation. We compared emergency versus planned CS to investigate their potential difference in the risk of ASD.ResultsCompared with vaginal delivery, the overall adjusted OR for ASD in CS delivery was 1.26 (95% CI 1.22-1.30). Stratified ORs were 1.25 (1.15-1.37), 1.16 (1.09-1.23), 1.34 (1.28-1.40) and 1.17 (1.04-1.30) for subgroups of gestational weeks 26-36, 37-38, 39-41 and 42-44, respectively. CS was significantly associated with risk of ASD for each week of gestation, from week 36 to 42, consistently across study sites (OR ranged 1.16-1.38). There was no statistically significant difference between emergency and planned CS in the risk of ASD.ConclusionAcross the five countries, emergency or planned CS is consistently associated with a modest increased risk of ASD from gestational weeks 36 to 42 when compared with vaginal delivery.

**Database:** Medline

## **19. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses**

**Author(s):** Modabbernia A.; Velthorst E.; Reichenberg A.

**Source:** Molecular Autism; Mar 2017; vol. 8 (no. 1)

**Publication Date:** Mar 2017

**Publication Type(s):** Review

**PubMedID:** 28331572

Available at [Molecular autism](#) - from BioMed Central

Available at [Molecular autism](#) - from SpringerLink - Medicine

Available at [Molecular autism](#) - from ProQuest (Health Research Premium) - NHS Version

Available at [Molecular autism](#) - from Unpaywall

**Abstract:**Background: According to recent evidence, up to 40-50% of variance in autism spectrum disorder (ASD) liability might be determined by environmental factors. In the present paper, we conducted a review of systematic reviews and meta-analyses of environmental risk factors for ASD. We assessed each review for quality of evidence and provided a brief overview of putative mechanisms of environmental risk factors for ASD. Finding(s): Current evidence suggests that several environmental factors including vaccination, maternal smoking, thimerosal exposure, and most likely assisted reproductive technologies are unrelated to risk of ASD. On the contrary, advanced parental age is associated with higher risk of ASD. Birth complications that are associated with trauma or ischemia and hypoxia have also shown strong links to ASD, whereas other pregnancy-related factors such as maternal obesity, maternal diabetes, and caesarian section have shown a less strong (but significant) association with risk of ASD. The reviews on nutritional elements have been inconclusive about the detrimental effects of deficiency in folic acid and omega 3, but vitamin D seems to be deficient in patients with ASD. The studies on toxic elements have been largely limited by their design, but there is enough evidence for the association between some heavy metals (most important inorganic mercury and lead) and ASD that warrants further investigation. Mechanisms of the association between environmental factors and ASD are debated but might include non-causative association (including confounding), gene-related effect, oxidative stress, inflammation, hypoxia/ischemia, endocrine disruption, neurotransmitter alterations, and interference with signaling pathways. Conclusion(s): Compared to genetic studies of ASD, studies of environmental risk factors are in their infancy and have significant methodological limitations. Future studies of ASD risk factors would benefit from a developmental psychopathology approach, prospective design, precise exposure measurement, reliable timing of exposure in relation to critical developmental periods and should take into account the dynamic interplay between gene and environment by using genetically informed designs. Copyright © 2017 The Author(s).

**Database:** EMBASE

## **20. A systematic review of the association between the development of behavioural disorders and delivery by caesarean section**

**Author(s):** Khan N.; Moore J.

**Source:** BJOG: An International Journal of Obstetrics and Gynaecology; Mar 2017; vol. 124 ; p. 78

**Publication Date:** Mar 2017

**Publication Type(s):** Conference Abstract

Available at [BJOG : an international journal of obstetrics and gynaecology](#) - from Wiley Online Library

Available at [BJOG : an international journal of obstetrics and gynaecology](#) - from Unpaywall

**Abstract:** Introduction Autism spectrum disorder (ASD) and other developmental disorders are characterised by stereotypical behaviours, impairment in both social interaction and communication. Studies have shown an association between behavioural disorders and caesarean section. As rates of caesarean section rise, it is important to evaluate the long term effects of mode of delivery (MOD) on child development. The aim was to perform a systematic review to investigate the association between caesarean section and development of ASD and attention deficit hyperactivity disorder (ADHD). Methods We performed a systematic review of the literature using Medline, Embase and The Cochrane Library. Randomised control trials, case control and cohort studies were included with no language restrictions. Results A total of 13 studies were eligible, including 8 case control and 5 cohort studies. Ten examined ASD and 3 ADHD. Only 7 studies analysed emergency and planned caesarean sections separately. Overall, 4 studies showed an association between planned caesarean section and ASD (OR 2.05; 95% CI 1.49-2.82). One study found an association between emergency caesarean section and ASD. However, 6 studies showed no association between MOD and ASD. In the studies which analysed ADHD separately, there was no association with MOD. Conclusion There is an increased odds of developing ASD if delivered by caesarean section. Evidence from sibling control studies show no direct causal relationship. This increased risk together with the rise in caesarean section rates and impact of behavioural disorders needs to be considered. Further research is required to understand this relationship.

**Database:** EMBASE

## **21. Elective cesarean delivery at term, a significant risk factor for long-term pediatric neurological morbidity of the offspring**

**Author(s):** Baumfeld Y.; Walfisch A.; Wainstock T.; Segal I.; Sergienko R.; Landau D.; Sheiner E.

**Source:** American Journal of Obstetrics and Gynecology; Jan 2017; vol. 216 (no. 1)

**Publication Date:** Jan 2017

**Publication Type(s):** Conference Abstract

**Abstract:**OBJECTIVE: To determine whether the mode of delivery at term has an impact on the risk of long-term neurological morbidity of the offspring. STUDY DESIGN: A population-based cohort analysis was performed including all singleton term deliveries occurring between 1991-2013 at a tertiary medical center. A comparison was performed between children delivered via elective cesarean delivery (CD) and those delivered vaginally. Multiple gestations and fetuses with congenital malformations were excluded. All cases of urgent CD due to nonreassuring fetal status, non-progressive labor, prolapse of cord, preeclampsia, placenta previa, placental abruption, gestational diabetes, labor induction and failed induction, fetal growth restriction, as well as instrumental deliveries, were excluded from the analysis. Pediatric hospitalizations of the offspring up to the age of 18 years involving neurological morbidity were evaluated. A Kaplan-Meier survival curve was used to compare cumulative morbidity incidence. A Cox regression model was used to control for confounders. RESULT(S): During the study period 132 054 term deliveries met the inclusion criteria; 8.9% were via elective CD (n=11 746) and 91.1% (n=120 308) were vaginal deliveries. Hospitalizations up to the age of 18 years involving neurological morbidity were significantly more common in offspring delivered by CD as compared with those delivered vaginally (Table). Specifically, autism and movement disorders were more common in the CD group ( $p<0.001$  in both). The Kaplan-Meier survival curve demonstrated a significantly higher cumulative incidence of neurological morbidity in the CD group (Figure, log rank  $p<0.001$ ). Using a Cox proportional hazards model while controlling for maternal age, gestational age, and birth weight, elective CD at term exhibited an independent association with longterm neurological morbidity of the offspring (adjusted HR=1.32, CI 1.18-1.47,  $p<0.001$ ). CONCLUSION(S): Elective CD at term is a significant risk factor for longterm pediatric neurological morbidity of the offspring.(Figure Presented).

**Database:** EMBASE

## 22. Prenatal Risk Factors and the Etiology of ADHD-Review of Existing Evidence

**Author(s):** Sciberras E.; Mulraney M.; Coghill D.; Silva D.

**Source:** Current Psychiatry Reports; Jan 2017; vol. 19 (no. 1)

**Publication Date:** Jan 2017

**Publication Type(s):** Review

**PubMedID:** 28091799

Available at [Current psychiatry reports](#) - from SpringerLink - Medicine

Available at [Current psychiatry reports](#) - from Unpaywall

**Abstract:** While it is well accepted that attention-deficit/hyperactivity disorder (ADHD) is a highly heritable disorder, not all of the risk is genetic. It is estimated that between 10 and 40% of the variance associated with ADHD is likely to be accounted for by environmental factors. There is considerable interest in the role that the prenatal environment might play in the development of ADHD with previous reviews concluding that despite demonstration of associations between prenatal risk factors (e.g. prematurity, maternal smoking during pregnancy) and ADHD, there remains insufficient evidence to support a definite causal relationship. This article provides an update of research investigating the relationship between prenatal risk factors and ADHD published over the past 3 years. Recently, several epidemiological and data linkage studies have made substantial contributions to our understanding of this relationship. In particular, these studies have started to account for some of the genetic and familial confounds that, when taken into account, throw several established findings into doubt. None of the proposed prenatal risk factors can be confirmed as causal for ADHD, and the stronger the study design, the less likely it is to support an association. We need a new benchmark for studies investigating the etiology of ADHD whereby there is an expectation not only that data will be collected prospectively but also that the design allows the broad range of genetic and familial factors to be accounted for. Copyright © 2017, Springer Science+Business Media New York.

**Database:** EMBASE

## 23. From risk to protective factors in autism spectrum disorder: What is the evidence base?

**Author(s):** Reichenberg A.

**Source:** Journal of the American Academy of Child and Adolescent Psychiatry; Oct 2016; vol. 55 (no. 10)

**Publication Date:** Oct 2016

**Publication Type(s):** Conference Abstract

**Abstract:** Objectives: According to recent evidence, up to 40-50 percent of variance in ASD liability is determined by environmental factors. Method(s): In the present study, we conducted a systematic review and metaanalysis of environmental risk factors for ASD. We assessed the quality of evidence and compared results to recent studies on ASD risk in national sample groups from seven countries. An overview of putative mechanisms of environmental risk factors for ASD is presented. Result(s): Current evidence suggests that several environmental factors, including vaccination, maternal smoking, air pollution (in European countries), thimerosal exposure, and most likely assisted reproductive treatments, are unrelated to the risk of ASD. Birth complications that are associated with trauma or ischemia and hypoxia have shown strong links to ASD, whereas other pregnancy-related factors, such as maternal obesity, maternal diabetes, and caesarian section, have shown a weak association with risk of ASD. The reviews on nutritional elements have yielded limited useful information on the beneficial effects of folic acid, vitamin D, and omega 3. The studies on toxic elements have been largely limited by their design, but there is enough evidence for the association

between some heavy metals (most important, inorganic mercury and lead) and ASD that warrants further investigation. Mechanisms of the association between environmental factors and ASD are debated, but they may include noncausative association (including confounding factors), gene-related effect, oxidative stress, inflammation, hypoxia/ischemia, endocrine disruption, neurotransmitter alterations, and interference with signaling pathways. Conclusion(s): Environment seems to play a diverse role in the risk for ASD. Compared to genetic studies of ASD, studies of environmental risk factors are in their infancy and have significant methodological limitations. Future studies of ASD risk factors should use prospective design, precise exposure measurement, and reliable timing of exposure in relation to critical developmental periods and should take into account the interplay between gene and environment by using genetically informed designs.

**Database:** EMBASE

#### **24. Perinatal risk factors of attention deficit/ hyperactivity disorder: A population-based study**

**Author(s):** Sourander A.; Lehtonen L.; Sucksdorff M.

**Source:** Journal of the American Academy of Child and Adolescent Psychiatry; Oct 2016; vol. 55 (no. 10)

**Publication Date:** Oct 2016

**Publication Type(s):** Conference Abstract

**Abstract:** Objectives: Previous studies have shown associations between perinatal risk factors and ADHD. The results are partly controversial, and some of the obstetric factors have not been studied previously in a population-based setting. In this study, our objective was to examine the association of a variety of prenatal, birth-related, and newborn risk factors and subsequent ADHD diagnoses in a nationwide epidemiological frame. Method(s): In this population-based study, 10,409 children diagnosed with ADHD, according to International Classification of Disease criteria, and 39,124 control subjects, individually matched for sex, date of birth, and place of birth, were identified from Finnish nationwide registry. Perinatal data was obtained from the Finnish Medical Birth Register. Conditional logistic regression was used to examine the association between prenatal, birth-related, and newborn risk factors and ADHD after controlling extensively for confounding factors. Result(s): We identified several perinatal risk factors for ADHD. Declining Apgar scores increased the risk of ADHD. Elective cesarean section remained a risk factor for ADHD after controlling for confounding factors. Other identified risk factors included mother's high blood pressure, nulliparity, breech presentation, induction of labor, and the child being treated in a neonatal intensive care unit. Low umbilical artery pH did not increase the risk of ADHD. Conclusion(s): Perinatal adversities leading to lower Apgar score increase the risk of ADHD, whereas low umbilical pH does not seem to predict later ADHD. Future research is warranted to untangle the mechanisms behind these associations. The increased risk of ADHD with elective cesarean section should be taken into account while planning the appropriate mode of delivery.

**Database:** EMBASE

## **25. Increased Risk of Autism Development in Children Whose Mothers Experienced Birth Complications or Received Labor and Delivery Drugs**

**Author(s):** Smallwood M.; Sareen A.; Baker E.; Hannusch R.; Williams T.; Kwessi E.

**Source:** ASN Neuro; Aug 2016; vol. 8 (no. 4)

**Publication Date:** Aug 2016

**Publication Type(s):** Article

**PubMedID:** 27511908

Available at [ASN neuro](#) - from Europe PubMed Central - Open Access

Available at [ASN neuro](#) - from Free Medical Journals . com

Available at [ASN neuro](#) - from Unpaywall

**Abstract:**Autism spectrum disorder (ASD) is a perplexing and pervasive developmental disorder characterized by social difficulties, communicative deficits, and repetitive behavior. The increased rate of ASD diagnosis has raised questions concerning the genetic and environmental factors contributing to the development of this disorder; meanwhile, the cause of ASD remains unknown. This study surveyed mothers of ASD and non-ASD children to determine possible effects of labor and delivery (L&D) drugs on the development of ASD. The survey was administered to mothers; however, the results were analyzed by child, as the study focused on the development of autism. Furthermore, an independent ASD dataset from the Southwest Autism Research and Resource Center was analyzed and compared. Indeed, L&D drugs are associated with ASD ( $p = .039$ ). Moreover, the Southwest Autism Research and Resource Center dataset shows that the labor induction drug, Pitocin, is significantly associated with ASD ( $p = .004$ ). We also observed a synergistic effect between administrations of L&D drugs and experiencing a birth complication, in which both obstetrics factors occurring together increased the likelihood of the fetus developing ASD later in life ( $p = .0003$ ). The present study shows the possible effects of L&D drugs, such as Pitocin labor-inducing and analgesic drugs, on children and ASD. Copyright © The Author(s) 2016.

**Database:** EMBASE

## **26. Obstetric mode of delivery and attention-deficit/hyperactivity disorder: a sibling-matched study.**

**Author(s):** Curran, Eileen A; Khashan, Ali S; Dalman, Christina; Kenny, Louise C; Cryan, John F; Dinan, Timothy G; Kearney, Patricia M

**Source:** International journal of epidemiology; Apr 2016; vol. 45 (no. 2); p. 532-542

**Publication Date:** Apr 2016

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 27063604

Available at [International journal of epidemiology](#) - from Oxford Journals - Medicine

Available at [International journal of epidemiology](#) - from HighWire - Free Full Text

Available at [International journal of epidemiology](#) - from Unpaywall

**Abstract:**BACKGROUND It has been suggested that birth by caesarean section (CS) may affect psychological development through changes in microbiota or stress response. We assessed the impact of mode of delivery, specifically CS, on the development of attention-deficit/hyperactivity disorder (ADHD), using a large, population-based cohort. METHODS The study cohort consisted of all singleton live births in Sweden from 1990 to 2008 using data from Swedish national registers. Mode of delivery included: unassisted vaginal delivery (VD), assisted VD, elective CS or emergency CS. ADHD was determined using International Classification of Diseases version 10 (F90 or F98.8), or prescription for ADHD medication. We used Cox regression to assess the association between birth by CS and ADHD in the total study population, adjusting for perinatal and sociodemographic factors, then stratified Cox regression analysis on maternal identification number to assess the association among siblings. RESULTS Our cohort consisted of 1 722 548 children, and among these 47 778 cases of ADHD. The hazard ratio (HR) of the association between elective CS, compared with unassisted VD, and ADHD was 1.15 [95% confidence interval (CI): 1.11-1.20] in the cohort, and 1.05 (95% CI: 0.93-1.18) in the stratified analysis. The HR of the association between emergency CS and ADHD was 1.16 (95% CI: 1.12-1.20) in the cohort and 1.13 (95% CI: 1.01-1.26) in the stratified analysis. CONCLUSION Birth by CS is associated with a small increased risk of ADHD. However among siblings the association only remained for emergency CS. If this were a causal effect by CS, the association would be expected to persist for both types of CS, suggesting the observed association is due to confounding.

**Database:** Medline

## **27. Gestational Age at Term, Delivery Circumstance, and Their Association with Childhood Attention Deficit Hyperactivity Disorder Symptoms.**

**Author(s):** Talge, Nicole M; Allswede, Dana M; Holzman, Claudia

**Source:** Paediatric and perinatal epidemiology; Mar 2016; vol. 30 (no. 2); p. 171-180

**Publication Date:** Mar 2016

**Publication Type(s):** Research Support, Non-u.s. Gov't Research Support, N.i.h., Extramural Journal Article Research Support, U.s. Gov't, P.h.s.

**PubMedID:** 26739771

Available at [Paediatric and perinatal epidemiology](#) - from Wiley Online Library

**Abstract:**BACKGROUND Perinatal characteristics may identify subgroups of term-born children at risk for academic and behavioural difficulties. Using follow-up data from the Pregnancy Outcomes and Community Health Study, we subdivided term births according to two potential markers of perinatal risk (gestational age, delivery circumstance) and evaluated their association with attention deficit hyperactivity disorder (ADHD) symptoms. METHODS We included children born at term whose mothers completed the Conners' Parent Rating Scales-Revised-Short Form (CPRS-R-S) (n = 610; ages: 3-9 years). The CPRS-R-S yields age and sex-referenced T-scores for the two primary dimensions of ADHD (inattention, hyperactivity) and an ADHD Index that reflects both dimensions. Using general linear models, we evaluated whether: (1) term delivery defined by gestational week (reference: 39-40 weeks), or (2) term delivery circumstance defined by labour onset type and mode of delivery (reference: spontaneous labour, vaginal delivery) was associated with these problems. RESULTS Following adjustment for parity, sociodemographics, and maternal mental health both during pregnancy and at the child follow-up survey, the induced labour plus caesarean group exhibited higher inattention and ADHD Index scores relative to the spontaneous labour, vaginal delivery group (inattention: mean difference = 5.1, 95% CI 0.6, 9.7; ADHD Index: mean difference = 4.1, 95% CI 0.5, 7.8). Findings were primarily driven by male children. CONCLUSIONS Among term-born children, only those whose mothers experienced induction of labour that culminated in caesarean delivery exhibited higher levels of ADHD symptoms. Prenatal, antepartum, and/or postnatal factors associated with this delivery profile may reflect increased risk for such problems.

**Database:** Medline

## **28. Obstetric mode of delivery and attention-deficit/hyperactivity disorder: A sibling control study**

**Author(s):** Curran E.A.; Khashan A.S.; Kenny L.C.; Cryan J.F.; Dinan T.G.; Kearney. P.M.; Dalman C.

**Source:** Reproductive Sciences; Mar 2016; vol. 23 (no. 1)

**Publication Date:** Mar 2016

**Publication Type(s):** Conference Abstract

Available at [Reproductive Sciences](#) - from Unpaywall

**Abstract:**INTRODUCTION: Birth by Caesarean section(CS) may affect psychological development through changes in gut microbiota or stress response. Our objective was to assess the impact of mode of delivery, specifically birth by CS on the development of attention-deficit/ hyperactivity disorder(ADHD), using data from the Swedish national registers. METHOD(S): Mode of delivery included: unassisted vaginal delivery(VD), assisted VD, elective CS or emergency CS. ADHD was determined using International Classification of Diseases version 10(F90 or F98.8), or prescription for ADHD medication. The study cohort included all singleton live births in Sweden from 1990-2008. We used Cox regression for data analysis in the total cohort, adjusting for perinatal and socio-demographic factors. We then stratified our Cox regression analysis by maternal ID to assess the association among sibling matches. RESULT(S): There 1,722,548 children in our cohort, and 47,778 cases of ADHD(2.8%). 1,241,366 families were included in the sibling-matched analysis including 6,976 families discordant on both mode of delivery and ADHD. When compared to unassisted VD, there was little evidence of an association between assisted VD and ADHD in the total cohort(HR=1.02; [95%CI:0.98-1.06]) or sibling-matched(HR=1.05; [95%CI:0.93-1.18]) analyses. For elective CS, the HR was 1.15(95% CI:1.11-1.20) in the total cohort, and 1.05(95%CI:0.93-1.18) with sibling-matched analysis. For emergency CS, the HR was 1.16(95%CI:1.12-1.20) in the total cohort and 1.13(95%CI:1.01-1.26) with the sibling-matched analyses. CONCLUSION(S): The observed association between CS and ADHD persisted in sibling-matched analyses for emergency, but not elective CS. As emergency CS begins after the onset of labour, babies are likely exposed to microbiota of the birth canal and experience the raised stress hormones associated with delivery. If there were a true causal effect of CS through either of these mechanisms we would expect the association to remain for elective CS, where neither of these exposures occurs. The persistence of the effect of emergency CS is more likely related to factors that led to the emergency rather than the procedure itself (confounding by indication).

**Database:** EMBASE

## **29. Obstetrical Mode of Delivery and Childhood Behavior and Psychological Development in a British Cohort.**

**Author(s):** Curran, Eileen A; Cryan, John F; Kenny, Louise C; Dinan, Timothy G; Kearney, Patricia M; Khashan, Ali S

**Source:** Journal of autism and developmental disorders; Feb 2016; vol. 46 (no. 2); p. 603-614

**Publication Date:** Feb 2016

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 26412364

Available at [Journal of autism and developmental disorders](#) - from SpringerLink - JUSTICE Consortium Package

Available at [Journal of autism and developmental disorders](#) - from ProQuest (Health Research Premium) - NHS Version

Available at [Journal of autism and developmental disorders](#) - from EBSCO (Psychology and Behavioral Sciences Collection)

**Abstract:**The association between mode of delivery [specifically birth by Cesarean section (CS)] and induction of labor (IOL) psychological development at age 7 was assessed [including autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD) and behavioral difficulties]. The Millennium cohort study, a nationally representative UK cohort of children (including 13,141 children), was used. There was no association between planned CS and ASD [aOR 0.58; (95 % CI 0.19-1.79)] or ADHD [aOR 0.54; (95 % CI 0.18-1.64)] analyses. Induced vaginal delivery was significantly associated with behavioral difficulties in unadjusted [OR 1.26; (95 % CI 1.03-1.54)], but not adjusted analysis [OR 1.15; (95 % CI 0.82-1.60)]. There was no association between mode of delivery and ASD or ADHD in this cohort. Further research is needed to understand the relationship between mode of delivery and IOL and psychological development.

**Database:** Medline

### **30. Previous Exposure to Anesthesia and Autism Spectrum Disorder (ASD): A Puerto Rican Population-Based Sibling Cohort Study.**

**Author(s):** Creagh, O; Torres, H; Rivera, K; Morales-Franqui, M; Altieri-Acevedo, G; Warner, D

**Source:** Boletín de la Asociación Médica de Puerto Rico; 2015; vol. 107 (no. 3); p. 29-37

**Publication Date:** 2015

**Publication Type(s):** Journal Article

**PubMedID:** 26742193

**Abstract:**BACKGROUND Autism Spectrum Disorder (ASD) is characterized by impaired social interaction and communication, and by restricted and repetitive behavior, that begins usually before a child is three years old.<sup>1</sup> Researchers have shown that prevalence rates in the U.S. may be as high as 1 in 68.<sup>52</sup> A number of studies have examined the effects of early exposure to anesthesia on brain development and subsequent impairment in neurocognitive function; yet, little is known about the possible effects of anesthetic agents on social-behavioral functioning. The association between exposure to anesthesia either in uterus, during the first years of life, or later and development of Autistic Spectrum Disorder (ASD) or its severity was determined in a retrospective population based cohort study. OBJECTIVES Identify if children who had previous exposure to anesthesia either in uterus, first years of life during their developing brain years, or later, are at risk of developing ASD and its severe form of the disease. METHODS Data was obtained from structured interviews administered to a sample of 515 parents/guardians distributed in two groups: ASD = 262 children diagnosed with this condition and Non-ASD: 253 children (siblings of ASD group) without diagnosis ( $p = 0.8069$ ) when comparing exposure to anesthesia in uterus to subsequent severe form of ASD. Of the 262 ASD patients, 99 had exposure to anesthetics before their diagnosis, while in Non-ASD population, 110 had exposure to anesthesia, demonstrating no statistically significant association between both groups ( $p = 0.2091$ ). Out of 99 ASD patients exposed to anesthesia prior to their diagnosis, 72 were exposed before age 2. When compared to the 110 Non-ASD patients exposed to anesthesia, 86 had exposure during this developing brain period, which indicates no statistically significant association ( $p = 0.4207$ ). In addition, most of the ASD children exposed to anesthesia during developing brain were diagnosed with mild degree of the disorder when compared to ASD children without any previous exposure to anesthesia ( $p = 0.9700$ ) during the same period. When the exposure occurred after age 2, ASD children developed mild form of the disorder as compared with ASD children without any previous exposure to anesthesia ( $p = 0.1699$ ) in that period. CONCLUSIONS Children under early exposure to anesthesia in uterus, first 2 years of life, or later are not more likely to develop neither ASD nor severe form of the disorder. INDEX WORDS: Anesthesia, Autism Spectrum Disorder, Puerto Rico. (95% confidence interval) that freely decided to participate and agreed to a consent form. Variables studied, include: demographics, diagnosis and severity of ASD, exposure to anesthesia, method of childbirth, and age of exposure. Children less than 2 years of age were considered into have developing brain period. Data was analyzed using Chi-square or Fisher exact test. RESULTS In contrast to non-ASD group, most of the children within ASD group were male, 76% ( $p = 0.0001$ ). With regards to methods of childbirth, 64% of the ASD population were vaginal delivery (VD; Non-anesthesia exposure group) and 36% cesarean delivery (CD) compared to non-autistic population with 71% VD and 29% CD, which demonstrates no statistical difference between both groups ( $p = 0.1113$ ). Out of the 36% of ASD population that underwent CD, 7% were performed using general anesthesia and 93% regional anesthesia, while the 29% of the CD of non-ASD, 5% were performed using general anesthesia and 95% regional anesthesia. This reveals no statistical significance ( $p = 0.7569$ ) with the development of ASD and the type of anesthesia used when comparing ASD with non-ASD patients. In view of severity of autism, in VD, 56% of ASD population had mild form of the disorder, 34% moderate, and 10% severe; while CD had a 54% mild form of the disorder, 33% moderate, and 13% severe. This shows no statistical association.

**Database:** Medline

**31. Risk of Autism Associated With General Anesthesia During Cesarean Delivery: A Population-Based Birth-Cohort Analysis**

**Author(s):** Chien L.-N.; Lin H.-C.; Shao Y.-H.J.; Chiou S.-T.; Chiou H.-Y.

**Source:** Journal of Autism and Developmental Disorders; 2015; vol. 45 (no. 4); p. 932-942

**Publication Date:** 2015

**Publication Type(s):** Article

**PubMedID:** 25256350

Available at [Journal of autism and developmental disorders](#) - from SpringerLink - JUSTICE Consortium Package

Available at [Journal of autism and developmental disorders](#) - from ProQuest (Health Research Premium) - NHS Version

Available at [Journal of autism and developmental disorders](#) - from EBSCO (Psychology and Behavioral Sciences Collection)

**Abstract:**The rates of Cesarean delivery (C-section) have risen to >30 % in numerous countries. Increased risk of autism has been shown in neonates delivered by C-section. This study examined the incidence of autism in neonates delivered vaginally, by C-section with regional anesthesia (RA), and by C-section with general anesthesia (GA) to evaluate the risk of autism associated with C-section and obstetric anesthesia. During a mean follow-up of 4.3 years, the incidence of autism was higher in neonates delivered by C-section with GA than in neonates delivered vaginally, with an adjusted risk of 1.52 (95 % confidence interval 1.18-1.94). However, the adjusted risk of autism in neonates delivered by C-section with RA and in neonates delivered vaginally was nonsignificantly different. Copyright © 2014, Springer Science+Business Media New York.

**Database:** EMBASE

### **32. Association Between Obstetric Mode of Delivery and Autism Spectrum Disorder: A Population-Based Sibling Design Study.**

**Author(s):** Curran, Eileen A; Dalman, Christina; Kearney, Patricia M; Kenny, Louise C; Cryan, John F; Dinan, Timothy G; Khashan, Ali S

**Source:** JAMA psychiatry; Sep 2015; vol. 72 (no. 9); p. 935-942

**Publication Date:** Sep 2015

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article

**PubMedID:** 26107922

Available at [JAMA psychiatry](#) - from Unpaywall

**Abstract:**IMPORTANCEBecause the rates of cesarean section (CS) are increasing worldwide, it is becoming increasingly important to understand the long-term effects that mode of delivery may have on child development.OBJECTIVETo investigate the association between obstetric mode of delivery and autism spectrum disorder (ASD).DESIGN, SETTING, AND PARTICIPANTSPerinatal factors and ASD diagnoses based on the International Classification of Diseases, Ninth Revision (ICD-9),and the International Statistical Classification of Diseases, 10th Revision (ICD-10),were identified from the Swedish Medical Birth Register and the Swedish National Patient Register. We conducted stratified Cox proportional hazards regression analysis to examine the effect of mode of delivery on ASD. We then used conditional logistic regression to perform a sibling design study, which consisted of sibling pairs discordant on ASD status. Analyses were adjusted for year of birth (ie, partially adjusted) and then fully adjusted for various perinatal and sociodemographic factors. The population-based cohort study consisted of all singleton live births in Sweden from January 1, 1982, through December 31, 2010. Children were followed up until first diagnosis of ASD, death, migration, or December 31, 2011 (end of study period), whichever came first. The full cohort consisted of 2,697,315 children and 28,290 cases of ASD. Sibling control analysis consisted of 13,411 sibling pairs.EXPOSURESObstetric mode of delivery defined as unassisted vaginal delivery (VD), assisted VD, elective CS, and emergency CS (defined by before or after onset of labor).MAIN OUTCOMES AND MEASURESThe ASD status as defined using codes from the ICD-9 (code 299) and ICD-10 (code F84).RESULTSIn adjusted Cox proportional hazards regression analysis, elective CS (hazard ratio, 1.21; 95% CI, 1.15-1.27) and emergency CS (hazard ratio, 1.15; 95% CI, 1.10-1.20) were associated with ASD when compared with unassisted VD. In the sibling control analysis, elective CS was not associated with ASD in partially (odds ratio [OR], 0.97; 95% CI, 0.85-1.11) or fully adjusted (OR, 0.89; 95% CI, 0.76-1.04) models. Emergency CS was significantly associated with ASD in partially adjusted analysis (OR, 1.20; 95% CI, 1.06-1.36), but this effect disappeared in the fully adjusted model (OR, 0.97; 95% CI, 0.85-1.11).CONCLUSIONS AND RELEVANCETHis study confirms previous findings that children born by CS are approximately 20% more likely to be diagnosed as having ASD. However, the association did not persist when using sibling controls, implying that this association is due to familial confounding by genetic and/or environmental factors.

**Database:** Medline

### **33. Obstetric mode of delivery and autism spectrum disorders in Sweden: A sibling design study**

**Author(s):** Curran E.A.; Kenny L.; Dalman C.; Kearney P.M.; Khashan A.S.; Cryan J.F.; Dinan T.G.

**Source:** European Journal of Epidemiology; Aug 2015; vol. 30 (no. 8); p. 722

**Publication Date:** Aug 2015

**Publication Type(s):** Conference Abstract

Available at [European journal of epidemiology](#) - from SpringerLink - Medicine

Available at [European journal of epidemiology](#) - from ProQuest (Health Research Premium) - NHS Version

Available at [European journal of epidemiology](#) - from Unpaywall

**Abstract:**Objective: As rates of caesarean section (CS) are rising worldwide, it is becoming increasingly important to understand any long-term effects CS may have on child development, such as autism spectrum disorder (ASD). ASD is also on the rise and has been associated with perinatal factors, such as obstetric mode of delivery. Consequently, we investigated the association between obstetric mode of delivery and autism spectrum disorder (ASD) using a large, population-based cohort. Method(s): The study cohort consisted of all singleton live births in Sweden between 1982 and 2010. Perinatal factors were retrieved from the Swedish Medical Birth Register, and ASD diagnoses based on the International Classification of Disease versions 9 and 10 were identified from the National Patient Register. We conducted stratified Cox regression analysis to examine the impact of mode of delivery on ASD, adjusting for perinatal and socio-economic factors. This was followed by sibling design study, which examined association between mode of delivery and ASD among sibling pairs discordant for autism and mode of delivery. The sibling study analysis was performed using conditional logistic regression. Analyses were first partially adjusted for year of birth, then further adjusted for infant gender, maternal age, 5 min Apgar score, maternal and paternal citizenship, small or large for gestational age, birth order, social welfare, family income, and parental psychiatric illness both affective and non-affective. Sibling design analysis was adjusted for all factors with the exception of maternal citizenship, as it was the same for both siblings. Result(s): The final cohort included 2,697,315 births, and 28,290 cases of ASD. In adjusted Cox regression analysis, elective (HR = 1.21; [95 % CI: 1.15-1.27]) and emergency (HR = 1.16; [95 % CI: 1.10-1.20]) CS were associated with ASD but assisted vaginal delivery (VD) was not (HR = 1.03; [95 % CI = 0.98-1.07]). The sibling design study included 13,411 sibling pairs discordant on ASD. In adjusted conditional logistic regression, using siblings as controls, elective CS (OR = 0.89; [95 % CI: 0.76-1.04]), emergency CS (OR = 0.97; [95 % CI: 0.85-1.11]) and assisted VD (OR = 0.91; [95 % CI: 0.82-1.02]) were all not associated with ASD. Conclusion(s): This study confirms previous findings that children born by CS are about 20 % more likely to be diagnosed with ASD after adjustment for known confounders. However, the association did not persist when using sibling controls, implying that this relationship is not causal, but may be due to residual confounding by shared familial factors such as genetic predisposition or environmental influences.

**Database:** EMBASE

### 34. Is birth a critical period in the pathogenesis of autism spectrum disorders?

**Author(s):** Ben-Ari Y.

**Source:** Nature Reviews Neuroscience; Jul 2015; vol. 16 (no. 8); p. 498-505

**Publication Date:** Jul 2015

**Publication Type(s):** Review

**PubMedID:** 26152864

Available at [Nature reviews. Neuroscience](#) - from ProQuest (Health Research Premium) - NHS Version

Available at [Nature reviews. Neuroscience](#) - from EBSCO (Psychology and Behavioral Sciences Collection)

**Abstract:**Birth is associated with a neuroprotective, oxytocin-mediated abrupt excitatory-to-inhibitory GABA shift that is abolished in autism, and its restoration attenuates the disorder in offspring. In this Opinion article, I discuss the links between birth-related stressful mechanisms, persistent excitatory GABA actions, perturbed network oscillations and autism. I propose that birth (parturition) is a critical period that confirms, attenuates or aggravates the deleterious effects of intrauterine genetic or environmental insults. Copyright © 2015 Macmillan Publishers Limited. All rights reserved.

**Database:** EMBASE

### 35. Pre-and perinatal risk factors in attention-deficit/ hyperactivity disorder and autism spectrum disorders

**Author(s):** Freitag C.; Evers J.

**Source:** European Child and Adolescent Psychiatry; Jun 2015; vol. 24 (no. 1)

**Publication Date:** Jun 2015

**Publication Type(s):** Conference Abstract

Available at [European child & adolescent psychiatry](#) - from SpringerLink - Medicine

Available at [European child & adolescent psychiatry](#) - from ProQuest (Health Research Premium) - NHS Version

Available at [European child & adolescent psychiatry](#) - from EBSCO (Psychology and Behavioral Sciences Collection)

Available at [European child & adolescent psychiatry](#) - from Unpaywall

**Abstract:**Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) frequently co-occur. Twin studies have shown a substantial genetic component of this overlap. Given the role of preand perinatal risk factors especially for ADHD aetiology, the aim of the present study was to elicit overlap and specificity of associated pre- and perinatal environmental risk factors on ASD and AD(H)D. Method(s): Age and sex matched children and adolescents, aged 4-18 years old, from five comparison groups were included into the present study. N = 42 ASD without AD(H)D; N = 30 ASD with ADD (inattentive ADHD subtype); N = 35 ASD with ADHD combined subtype; N = 37 ADD without ASD and N = 47 ADHD without ASD. Pre- and perinatal risk factors were obtained by a semistructured medical history interview with the primary caregiver and from medical records. The following pregnancy related risk factors were analysed: maternal smoking, alcohol, drug use, different medications, diabetes, high blood pressure, accidents, bleedings. The following perinatal risk factors were studied: oxytocin, Caesarean section, birth weight, perinatal infection, length of stay in incubator. Result(s): Preliminary analyses showed disorder specific risk factors for ADHD combined subtype (with and without ASD), especially smoking during pregnancy, and for the

inattentive ADHD subtype, especially low birth weight. No disorder specific pre- or perinatal environmental risk factors were elicited for ASD. Conclusion(s): The assessed pre- and perinatal environmental risk factors seem to play a major role only for AD(H)D, but not for ASD. The major limitation of the study is the retrospective assessment of many risk factors. The strength of the study is the inclusion of several differential groups with and without ASD and/or AD(H)D.

**Database:** EMBASE

**36. Research review: Birth by caesarean section and development of autism spectrum disorder and attention-deficit/hyperactivity disorder: a systematic review and meta-analysis.**

**Author(s):** Curran, Eileen A; O'Neill, Sinéad M; Cryan, John F; Kenny, Louise C; Dinan, Timothy G; Khashan, Ali S; Kearney, Patricia M

**Source:** Journal of child psychology and psychiatry, and allied disciplines; May 2015; vol. 56 (no. 5); p. 500-508

**Publication Date:** May 2015

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article Review Systematic Review

**PubMedID:** 25348074

Available at [Journal of child psychology and psychiatry, and allied disciplines](#) - from EBSCO (Psychology and Behavioral Sciences Collection)

**Abstract:**BACKGROUND Given the growing prevalence of birth by Caesarean section (CS) worldwide, it is important to understand any long-term effects CS delivery may have on a child's development. We assessed the impact of mode of delivery on autism spectrum disorders (ASD) and attention-deficit/hyperactivity disorder (ADHD).METHODS We conducted a systematic review of the literature in PubMed, Embase, CINAHL, PsycINFO and Web of Science up to 28 February 2014. No publication date, language, location or age restrictions were employed.RESULTS Thirteen studies reported an adjusted estimate for CS-ASD, producing a pooled odds ratio (OR) of 1.23 (95% CI: 1.07, 1.40). Two studies reported an adjusted estimate for CS-ADHD, producing a pooled OR of 1.07 (95% CI: 0.86, 1.33).CONCLUSIONS Delivery by CS is associated with a modest increased odds of ASD, and possibly ADHD, when compared to vaginal delivery. Although the effect may be due to residual confounding, the current and accelerating rate of CS implies that even a small increase in the odds of disorders, such as ASD or ADHD, may have a large impact on the society as a whole. This warrants further investigation.

**Database:** Medline

### **37. Obstetrical mode of delivery and childhood mental illness and behavior in a british cohort**

**Author(s):** Curran E.A.; Kenny L.C.; Khashan A.S.; Cryan J.F.; Dinan T.G.; Kearney P.M.

**Source:** Reproductive Sciences; Mar 2015; vol. 22

**Publication Date:** Mar 2015

**Publication Type(s):** Conference Abstract

**Abstract:**INTRODUCTION: Given the high rates of birth by Caesarean section (CS), it is important to understand any possible long-term effects on child development. Our objective was to assess the association between planned CS and autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD) and behavioral difficulties among 7 year old children. METHOD(S): We used data from the Millennium cohort study, a representative UK cohort. ASD and ADHD were parent-reported based on a diagnosis by a doctor or health care professional. Behavioral difficulties were measured using the Strengths and Difficulties Questionnaire (SDQ) scores. The impact of mode of delivery and induction of labor on ASD, ADHD and abnormal SDQ scores were modelled using logistic regression, and adjusted for variables relating to pregnancy and delivery, maternal health and mental health and demographic/socioeconomic factors. RESULT(S): There was no association between planned CS and ASD in unadjusted (OR=1.06; [95%CI:0.56-2.03]) or adjusted (OR=0.73; [95%CI:0.34-1.06]) analysis. Similarly, there was no association between planned CS and ADHD in unadjusted (OR=0.97; [95%CI:0.44-1.74]) or adjusted (OR=0.68; [95%CI:0.29-1.58]) analyses. In unadjusted analysis, induction of labor was significantly associated with abnormal SDQ scores (OR=1.26; [95%CI:1.03-1.54]). This association lost significance in the fully adjusted model (OR=1.19; [95%CI:0.95-1.50]). CONCLUSION(S): We found no association between mode of delivery and ASD or ADHD in this cohort. Induction of labor was associated with behavioral difficulties in unadjusted analysis, but this relationship was not significant in the adjusted model.

**Database:** EMBASE

### **38. Familial, Social and Environmental Risk Factors in Autism: A Case-Control Study.**

**Author(s):** Jahan, A; Rezina-Parvin, S Z; Bugum, D

**Source:** Bangladesh Medical Research Council bulletin; Dec 2014; vol. 40 (no. 3); p. 113-117

**Publication Date:** Dec 2014

**Publication Type(s):** Journal Article

**PubMedID:** 26402976

**Abstract:**This case-control study was done to identify the correlation between the familial, social and environmental risk factors and autism. This hospital and specialized centre based study done from January 2002 to November, 2004. Thirty two children from the autism group and 14 children from the control group were enrolled. Mean age were 3.75 yrs. and 2.83 yrs. respectively. Significant proportion of children were in the highest birth orders, 68.8% in autism and 78.6% in the control group. Full-term children were 96.9% and 92.9% respectively. 53.1% children in the autism and 57.1% in the normal speech delay group were born by cesarean sections. Higher education of parents in autism group was statistically significant ( $p < 0.05$ ). Too much watching TV, inadequate opportunity to mix with peers and inadequate interactive relationship with the family members in the early childhood were significantly ( $p = 0.001$ ) related to the development of autism.

**Database:** Medline

### **39. Are caesarean sections, induced labor and oxytocin regulation linked to Autism Spectrum Disorders?**

**Author(s):** Gialloreti, Leonardo Emberti; Benvenuto, Arianna; Benassi, Francesca; Curatolo, Paolo

**Source:** Medical hypotheses; Jun 2014; vol. 82 (no. 6); p. 713-718

**Publication Date:** Jun 2014

**Publication Type(s):** Journal Article

**PubMedID:** 24685110

**Abstract:**The etiology of Autism Spectrum Disorders (ASDs) continues to be elusive. While ASDs have been shown to be heritable, several environmental co-factors, such as, e.g. pre- or perinatal adverse events, could play a role in the pathogenesis of the disorder as well. Prevalence of ASDs appears to have increased in the last three decades, but the causes of this surge are not fully understood. As perinatal adverse events have increased as well, they have been regarded as logical contributors to the risen prevalence of ASDs. Over the last three decades there has been also a considerable increase in the rates of induced labor and caesarean sections (CS). However, even if a causal association between CS and ASDs increase has been suggested, it has not yet been proven. Nevertheless, we hypothesize here that such an association is actual and that it might help to explain a part of the increase in ASD diagnoses. Our assumption is based on the wider epidemiological picture of ASDs and CS, as well as on the possible biological plausibility of this correlation, by postulating potential epigenetic and neurobiological mechanisms underpinning this relationship. Today, several observations point toward the existence of epigenetic dysregulation in ASDs and this raises the issue of the role of environmental factors in bringing about epigenetic modifications. Epigenetic dysregulations in some brain neuropeptide systems could play a role in the behavioral dysfunctions of ASDs. Particularly, some evidence suggests a dysregulation of the oxytocinergic system in autistic brains. Perinatal alterations of oxytocin (OT) can also have life-long lasting effects on the development of social behaviors. Within the perinatal period, various processes, like pitocin infusion or CS, can alter the OT balance in the newborn; OT dysregulation could then interact with genetic factors, leading ultimately to the development of ASDs. Large long-term prospective studies are needed to identify causal pathways for ASDs and examine whether and how (epi-)genetic susceptibility interacts with obstetric risk factors in the development of ASDs. A better understanding of such a potential interplay could become paradigmatic for a wide range of genetic-environmental interactions in ASDs.

**Database:** Medline

#### **40. Population attributable fractions for three perinatal risk factors for autism spectrum disorders, 2002 and 2008 autism and developmental disabilities monitoring network.**

**Author(s):** Schieve, Laura A; Tian, Lin H; Baio, Jon; Rankin, Kristin; Rosenberg, Deborah; Wiggins, Lisa; Maenner, Matthew J; Yeargin-Allsopp, Marshaly; Durkin, Maureen; Rice, Catherine; King, Lydia; Kirby, Russell S; Wingate, Martha S; Devine, Owen

**Source:** Annals of epidemiology; Apr 2014; vol. 24 (no. 4); p. 260-266

**Publication Date:** Apr 2014

**Publication Type(s):** Journal Article

**PubMedID:** 24529515

Available at [Annals of epidemiology](#) - from Unpaywall

**Abstract:****PURPOSE**Numerous studies establish associations between adverse perinatal outcomes/complications and autism spectrum disorder (ASD). There has been little assessment of population attributable fractions (PAFs).**METHODS**We estimated average ASD PAFs for preterm birth (PTB), small for gestational age (SGA), and Cesarean delivery (CD) in a U.S. population. Average PAF methodology accounts for risk factor co-occurrence. ASD cases were singleton non-Hispanic white, non-Hispanic black, and Hispanic children born in 1994 (n = 703) or 2000 (n = 1339) who resided in 48 U.S. counties included within eight Autism and Developmental Disabilities Monitoring Network sites. Cases were matched on birth year, sex, and maternal county of residence, race-ethnicity, age, and education to 20 controls from U.S. natality files.**RESULTS**For the 1994 cohort, average PAFs were 4.2%, 0.9%, and 7.9% for PTB, SGA, and CD, respectively. The summary PAF was 13.0% (1.7%-19.5%). For the 2000 cohort, average PAFs were 2.0%, 3.1%, and 6.7% for PTB, SGA, and CD, respectively, with a summary PAF of 11.8% (7.5%-15.9%).**CONCLUSIONS**Three perinatal risk factors notably contribute to ASD risk in a U.S. population. Because each factor represents multiple etiologic pathways, PAF estimates are best interpreted as the proportion of ASD attributable to having a suboptimal perinatal environment resulting in PTB, SGA, and/or CD.

**Database:** Medline

#### **41. Obstetric risk factors and autism spectrum disorders in Finland.**

**Author(s):** Polo-Kantola, Päivi; Lampi, Katja M; Hinkka-Yli-Salomäki, Susanna; Gissler, Mika; Brown, Alan S; Sourander, Andre

**Source:** The Journal of pediatrics; Feb 2014; vol. 164 (no. 2); p. 358-365

**Publication Date:** Feb 2014

**Publication Type(s):** Research Support, Non-u.s. Gov't Research Support, N.i.h., Extramural Journal Article

**PubMedID:** 24183209

Available at [The Journal of pediatrics](#) - from Patricia Bowen Library & Knowledge Service West Middlesex University Hospital NHS Trust (lib302631) Local Print Collection [location] : Patricia Bowen Library and Knowledge Service West Middlesex university Hospital.

**Abstract:****OBJECTIVE**To examine the relationship between obstetric risk factors and childhood autism, Asperger syndrome, and other pervasive developmental disorders (PDDs).**STUDY DESIGN**Registry-based case-control study from all singleton births in Finland from 1990-2005. Cases with childhood autism, Asperger syndrome, or PDD (n = 4713) were identified from the Finnish Hospital Discharge Register. Each case was matched to 4 controls on sex, date of birth, and place of birth. Information on obstetric risk factors was from the Finnish Medical Birth Register. Conditional logistic regression models were used for statistical analyses.**RESULTS**When adjusted with confounders, childhood autism was associated with maternal high blood pressure (OR 1.49, 95% CI

1.1-2.1,  $P = .018$ ), Apgar scores less than 7 (1 minute, OR 1.46, 95% CI 1.1-2.0,  $P = .021$ ), and neonatal treatment with monitoring (OR 1.40, 95% CI 1.02-1.9,  $P = .038$ ). PDD was associated with induced labor (OR 1.25 95% CI 1.1-1.5,  $P = .007$ ), planned cesarean delivery (OR 1.34, 95% CI 1.1-1.7,  $P = .009$ ), 1-minute Apgar scores 7-8 (OR 1.22, 95% CI 1.1-1.4,  $P = .008$ ) and less than 7 (OR 1.34, 95% CI 1.03-1.8,  $P = .032$ ), and neonatal intensive care unit treatment (OR 1.52, 95% CI 1.2-2.0,  $P = .003$ ). Asperger syndrome was associated only with 1-minute Apgar scores 7-8 (OR 1.19, 95% CI 1.03-1.4,  $P = .018$ ). **CONCLUSIONS** Low Apgar scores as well as conditions requiring neonatal special follow-up are important risk factors for childhood autism and PDD. These findings suggest that fetal distress is a potential risk factor for these disorders, but not for Asperger syndrome.

**Database:** Medline

#### **42. Association of autism with induced or augmented childbirth in North Carolina birth record (1990-1998) and education research (1997-2007) databases**

**Author(s):** Gregory S.G.; Anthopolos R.; Miranda M.L.; Osgood C.E.; Grotegut C.A.

**Source:** JAMA Pediatrics; Oct 2013; vol. 167 (no. 10); p. 959-966

**Publication Date:** Oct 2013

**Publication Type(s):** Review

**PubMedID:** 23938610

Available at [JAMA pediatrics](#) - from Unpaywall

**Abstract:**Importance: One in 88 children in the United States is diagnosed as having autism spectrum disorder. Significant interest centers on understanding the environmental factors that may contribute to autism risk. **OBJECTIVE(S):** To examine whether induced (stimulating uterine contractions prior to the onset of spontaneous labor) and/or augmented (increasing the strength, duration, or frequency of uterine contractions with spontaneous onset of labor) births are associated with increased odds of autism. **DESIGN, SETTING, AND PARTICIPANTS:** We performed an epidemiological analysis using multivariable logistic regression modeling involving the North Carolina Detailed Birth Record and Education Research databases. The study featured 625 042 live births linked with school records, including more than 5500 children with a documented exceptionality designation for autism. **EXPOSURES:** Induced or augmented births. **MAIN OUTCOMES AND MEASURES:** Autism as assessed by exceptionality designations in child educational records. **RESULT(S):** Compared with children born to mothers who received neither labor induction nor augmentation, children born to mothers who were induced and augmented, induced only, or augmented only experienced increased odds of autism after controlling for potential confounders related to socioeconomic status, maternal health, pregnancy-related events and conditions, and birth year. The observed associations between labor induction/augmentation were particularly pronounced in male children. **CONCLUSIONS AND RELEVANCE:** Our work suggests that induction/augmentation during childbirth is associated with increased odds of autism diagnosis in childhood. While these results are interesting, further investigation is needed to differentiate among potential explanations of the association including underlying pregnancy conditions requiring the eventual need to induce/augment, the events of labor and delivery associated with induction/augmentation, and the specific treatments and dosing used to induce/augment labor (eg, exogenous oxytocin and prostaglandins).

**Database:** EMBASE

#### **43. Epidemiology of autistic disorder in Bahrain: prevalence and obstetric and familial characteristics.**

**Author(s):** Al-Ansari, A M; Ahmed, M M

**Source:** Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit; Sep 2013; vol. 19 (no. 9); p. 769-774

**Publication Date:** Sep 2013

**Publication Type(s):** Journal Article

**PubMedID:** 24313037

Available at [Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit](#) - from Free Medical Journals . com

Available at [Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit](#) - from ProQuest (Health Research Premium) - NHS Version

Available at [Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit](#) - from Unpaywall

**Abstract:**European and North American studies show that the prevalence of autistic disorder is increasing. This study was performed to identify the prevalence of autistic disorder in Bahrain, and determine some of the demographic and family characteristics. Using a case-control design, 100 children who received a diagnosis of autistic disorder according to DSM-IV-TR during the period 2000-2010 were selected. An equal number of controls who had received a diagnosis of nocturnal enuresis and no psychopathology were selected, matched for sex and age group. The prevalence of autistic disorder was estimated as 4.3 per 10,000 population, with a male:female sex ratio of 4:1. Significantly more cases than controls were delivered by caesarean section and had mothers who suffered prenatal complications. The prevalence estimate in Bahrain is comparable to previous reports using similar methods. Obstetric complications and caesarean section delivery may be associated with autistic disorder.

**Database:** Medline

#### **44. Prenatal and perinatal risk factors in autistic disorders**

**Author(s):** Al-Jammas, Ilham Khattab; Al-Dobooni, Rabei M. Y.

**Source:** Arab Journal of Psychiatry; Nov 2012; vol. 23 (no. 2); p. 108-114

**Publication Date:** Nov 2012

**Publication Type(s):** Journal Peer Reviewed Journal Journal Article

**Abstract:**Background: Recent evidence suggests higher prevalence of autistic disorder in association with certain prenatal and perinatal factors or adversities. Objectives: 1) to investigate the relationship between autistic disorders and certain prenatal and perinatal conditions, and 2) to identify possible risk factors which could be preventable. Patients and Method: A case-control study of fifty autistic children and fifty non-autistic children, who presented with speech delay to the Psychiatric Research unit at Mosul Medical College and to pediatric outpatient clinic during the period between 10 th May 2011 to 10 th April 2012. Detailed prenatal and perinatal history was taken from the parents of each patient and control group. Statistical tests were used to calculate Odd ratio, 95% Confidence interval, and p-value. Results: The autistic group was predominantly male. M: F ratio 3.5:1. Urban people accounted for 96% of the sample. Six prenatal and perinatal risk factors were identified. These were: advanced maternal age ( $p=0.000$ ), advanced paternal age ( $p=0.004$ ), delivery by cesarean section ( $p=0.02$ ), neonatal asphyxia ( $p=0.000$ ), neonatal convulsions ( $p=0.03$ ), and history of previous admission to neonatal intensive care unit ( $p=0.001$ ). Conclusion and recommendations: The study confirms the presences of some prenatal and perinatal risk factors are associated with autistic disorders. The investigators hope that a better ante-natal, obstetric, and neonatal care may play an important role in protection from this disorder in a significant number of children. (PsycINFO Database Record (c) 2016 APA, all rights reserved) (Source: journal abstract)

**Database:** PsycINFO

#### **45. Early environmental risk factors for children diagnosed and treated for ADHD: Western Australian population linkage study**

**Author(s):** Silva D.; Colvin L.; Bower C.

**Source:** Journal of Paediatrics and Child Health; May 2012; vol. 48 ; p. 10

**Publication Date:** May 2012

**Publication Type(s):** Conference Abstract

Available at [Journal of Paediatrics and Child Health](#) - from Wiley Online Library

**Abstract:**Background: Attention Deficit Disorder (ADHD) is the commonest developmental disorder in childhood with high heritability, although early environmental factors may be an important causal pathway in understanding the aetiology of ADHD. Mandatory notification of all children with ADHD commenced on stimulant medication (SM) in Western Australia (WA) was introduced in August 2003. Aim(s): To provide an overview of the data linkage opportunities in WA relating to ADHD and to investigate the maternal, pregnancy and newborn risk factors for children prescribed SM for ADHD. Method(s): This is a population-based, record-linkage case-control study where between August 2003 and December 2007, 16 883 children and adolescents (cases) aged 4-25 years had been prescribed stimulant medication in WA for ADHD and were recorded on the Monitoring of Drugs Dependency System (MODDS) database. A stratified random sample of birth records with no linkage to MODDS formed a comparison group (32 728). Case and comparison records were linked to the Midwives, Hospital Morbidity, Mortality, Mental Health, Emergency, Corrective Services and Education databases, and de-identified linked data files were provided for analysis. Finding(s): Mothers of case children were significantly more likely to be young (OR 1.63 CI; 1.48-1.78), single (OR 1.51; CI 1.41-1.62), smoke in pregnancy (OR 2.00; CI 1.72-2.33), have complications in pregnancy with threatened preterm labour (OR 2.40; CI 1.73-3.33) and have smaller babies of lower gestational

age compared to the comparison group. There was a small non-significant difference associated with acute emergency events around delivery (emergency caesarean sections, prolapsed cord, foetal distress) and no significant difference for maternal gestational diabetes and premature rupture of membranes. Conclusion(s): Data linkage at the population level can be a valuable source of information on perinatal risk factors associated with ADHD. This data linkage study will improve our understanding of early environmental risk factors which may enhance our understanding of complex gene-environment interactions.

**Database:** EMBASE

#### **46. Association of adverse antenatal and perinatal events with occurrence of Autism: A Case Control Study**

**Author(s):** Al-Farsi Y.M.; Al-Farsi O.A.; Al-Shafae M.A.; Al-Khaduri M.M.; Al-Sharbati M.M.; Waly M.I.; Deth R.C.

**Source:** FASEB Journal; Apr 2012; vol. 26

**Publication Date:** Apr 2012

**Publication Type(s):** Conference Abstract

**Abstract:**Background: Early life events, especially during perinatal and neonatal period, have been proposed as important factors in the etiologic pathways of autism. Objective(s): To evaluate the association between selected antenatal and perinatal adverse events and autism spectrum disorders (ASD). Method(s): A retrospective case-control study has been nested on ongoing prospective cohort study, and it included 102 ASD cases and 102 controls. Result(s): Adjusted odds ratios (OR) were generated from logistic regression models. ASD was found to be associated with social problems during pregnancy (OR = 1.39; 95% CI 1.01, 4.2), serious illness or trauma (OR = 1.5; 95% CI 1.02, 3.2), medication intake during pregnancy (OR = 1.6; 95% CI 0.96, 4.6), and premature delivery (OR = 1.7; 95% CI 1.1, 2.6). No evidence has been obtained for a significant association with gestational diabetes, anemia, and exposure to X-ray, or caesarian section. Conclusion(s): This study indicates that adverse early life events might be associated with increased risk of ASD.

**Database:** EMBASE

#### **47. Pre-, peri- and neonatal risk factors for autism.**

**Author(s):** Guinchat, Vincent; Thorsen, Poul; Laurent, Claudine; Cans, Christine; Bodeau, Nicolas; Cohen, David

**Source:** Acta obstetricia et gynecologica Scandinavica; Mar 2012; vol. 91 (no. 3); p. 287-300

**Publication Date:** Mar 2012

**Publication Type(s):** Research Support, Non-u.s. Gov't Journal Article Review

**PubMedID:** 22085436

Available at [Acta obstetricia et gynecologica Scandinavica](#) - from Wiley Online Library

**Abstract:**OBJECTIVETo identify pre-, peri- and neonatal risk factors for pervasive developmental disorders (PDD).METHODSWe searched the Medline database through March 2011 for relevant case-control and population-based studies on pre-, peri- and neonatal hazards related to PDD, including autism. We identified 85 studies for this review. Data were extracted systematically and organized according to risk factors related to family history, pregnancy, gestational age, delivery, birth milestones and the neonate's condition at birth.RESULTSDuring the prenatal period, risk factors for PDD were advanced maternal or paternal ages, being firstborn vs. third or later, maternal prenatal medication use and mother's status as foreign born. During the perinatal and neonatal periods, the risk factors for PDD were preterm birth, breech presentation, planned cesarean section, low Apgar scores, hyperbilirubinemia, birth defect and a birthweight small for gestational age. The influence of maternal pre-eclampsia, diabetes, vomiting, infections and stress during pregnancy requires further study in order to determine risk for PDD.DISCUSSIONDespite evidence for the association of some pre-, peri- and neonatal risk factors associated with PDD, it remains unclear whether these risks are causal or play a secondary role in shaping clinical expression in individuals with genetic vulnerability. A plausible hypothesis is that improvements in obstetric and neonatal management have led to an increased rate of survivors with pre-existing brain damage. Given the variety of risk factors, we propose that future studies should investigate combinations of multiple factors, rather than focusing on a single factor.

**Database:** Medline

#### **48. Attention-deficit/hyperactivity disorder after early exposure to procedures requiring general anesthesia**

**Author(s):** Sprung J.; Flick R.P.; Bojanic K.; Wilder R.T.; Warner D.O.; Katusic S.K.; Colligan R.C.; Welch T.L.; Olson M.D.; Hanson A.C.; Schroeder D.R.; Barbaresi W.J.

**Source:** Mayo Clinic Proceedings; Feb 2012; vol. 87 (no. 2); p. 120-129

**Publication Date:** Feb 2012

**Publication Type(s):** Article

**PubMedID:** 22305025

Available at [Mayo Clinic proceedings](#) - from Europe PubMed Central - Open Access

Available at [Mayo Clinic proceedings](#) - from ProQuest (Health Research Premium) - NHS Version

Available at [Mayo Clinic proceedings](#) - from Unpaywall

**Abstract:**Objective: To study the association between exposure to procedures performed under general anesthesia before age 2 years and development of attention-deficit/hyperactivity disorder (ADHD). Patients and Methods: Study patients included all children born between January 1, 1976, and December 31, 1982, in Rochester, MN, who remained in Rochester after age 5. Cases of ADHD diagnosed before age 19 years were identified by applying stringent research criteria. Cox proportional hazards regression assessed exposure to procedures requiring general anesthesia (none, 1, 2 or more) as a predictor of ADHD using a stratified analysis with strata based on a propensity score including comorbid health conditions. Result(s): Among the 5357 children analyzed, 341 ADHD cases were identified (estimated cumulative incidence, 7.6%; 95% confidence interval [CI], 6.8%-8.4%). For children with no postnatal exposure to procedures requiring anesthesia before the age of 2 years, the cumulative incidence of ADHD at age 19 years was 7.3% (95% CI, 6.5%-8.1%). For single and 2 or more exposures, the estimates were 10.7% (95% CI, 6.8%-14.4%) and 17.9% (95% CI, 7.2%-27.4%), respectively. After adjusting for gestational age, sex, birth weight, and comorbid health conditions, exposure to multiple (hazard ratio, 1.95; 95% CI, 1.03-3.71), but not single (hazard ratio, 1.18; 95% CI, 0.79-1.77), procedures requiring general anesthesia was associated with an increased risk for ADHD. Conclusion(s): Children repeatedly exposed to procedures requiring general anesthesia before age 2 years are at increased risk for the later development of ADHD even after adjusting for comorbidities. © 2012 Mayo Foundation for Medical Education and Research.

**Database:** EMBASE

**49. Have secular changes in perinatal risk factors contributed to the recent autism prevalence increase? Development and application of a mathematical assessment model.**

**Author(s):** Schieve, Laura A; Rice, Catherine; Devine, Owen; Maenner, Matthew J; Lee, Li-Ching; Fitzgerald, Robert; Wingate, Martha S; Schendel, Diana; Pettygrove, Sydney; van Naarden Braun, Kim; Durkin, Maureen

**Source:** Annals of epidemiology; Dec 2011; vol. 21 (no. 12); p. 930-945

**Publication Date:** Dec 2011

**Publication Type(s):** Journal Article

**PubMedID:** 22000328

Available at [Annals of epidemiology](#) - from Unpaywall

**Abstract:**BACKGROUND A 57% increase in the U.S. prevalence of autism spectrum disorders (ASD) for 8-year-old children born in 1994 versus 1998 was recently reported. METHODS To quantify the possible contributions of given risk/predictive factors on the recent ASD prevalence increase, we formulated a mathematical model based on the baseline risk factor prevalence (RFP), the proportionate change in RFP (cRFP), and the magnitude of the association between the risk factor and ASD [estimated relative risk (RR)]. We applied this model to several pregnancy-related factors (preterm, very preterm, low and very low birth weight, multiple birth, cesarean delivery, breech presentation, and assisted reproductive technology use). RFP and cRFP estimates for each factor were obtained from U.S. population-based surveillance datasets. Estimated RRs were obtained from a series of systematic literature reviews. RESULTS We estimate that each risk factor examined, alone or in various combinations, accounted for a very small proportion (<1%) of the ASD increase. Additionally, hypothetical scenarios indicate RFP, cRFP, and RR all need to be sizable for a risk factor to appreciably influence ASD prevalence. CONCLUSION Thus, although various pregnancy factors have been found to be associated with ASDs, the contribution of many of these factors to the recently observed ASD increase is likely minimal.

**Database:** Medline

**50. Risk factors correlated with Autistic Spectrum Disorders**

**Author(s):** Dobrescu I.; Rad F.; Ciobanu C.; Trutescu C.

**Source:** European Child and Adolescent Psychiatry; Jun 2011; vol. 20

**Publication Date:** Jun 2011

**Publication Type(s):** Conference Abstract

Available at [European Child & Adolescent Psychiatry](#) - from SpringerLink - Medicine

Available at [European Child & Adolescent Psychiatry](#) - from ProQuest (Health Research Premium) - NHS Version

Available at [European Child & Adolescent Psychiatry](#) - from EBSCO (Psychology and Behavioral Sciences Collection)

**Abstract:**Introduction: Autistic Spectrum Disorders (ASD) are neurodevelopmental disorders, the result of a complex interactions between genes involved in brain development and environmental factors. ASD is frequently correlated with environmental factors acting in pre-, peri- and postnatal period, an extremely vulnerable period for brain development. Objective(s): To identify possible risk factors correlated with ASD. Method(s): We performed a retrospective study on a sample of 100 patients, 3-6 years old, diagnosed with ASD (based on ADI-R diagnostic tool) inpatient or outpatient in Child and Adolescent Psychiatry Department, "Prof Dr. Al. Obregia" Psychiatry Hospital, Bucharest, Romania. We followed the presence of risk factors in pre-, peri- and postnatal period: parent's age, presence of a major psychiatric disorders at one of the parents, maternal exposure during pregnancy to

alcohol, smoking or toxic substance, imminent abortion, caesarian section, hypoxia at birth, neonatal infections. The same risks factors were followed in a group of 100 children with typically development, similar at age and gender. Dates were statistical processed to evidence a possible connection between risk factors and ASD. Result(s): The results are still in progress. From preliminary results we can conclude that risk factors described above occur more frequent in ASD sample.

**Database:** EMBASE

### **51. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders.**

**Author(s):** Bilder, Deborah; Pinborough-Zimmerman, Judith; Miller, Judith; McMahon, William

**Source:** Pediatrics; May 2009; vol. 123 (no. 5); p. 1293-1300

**Publication Date:** May 2009

**Publication Type(s):** Journal Article Research Support, U.s. Gov't, P.h.s.

**PubMedID:** 19403494

Available at [Pediatrics](#) - from Patricia Bowen Library & Knowledge Service West Middlesex University Hospital NHS Trust (lib302631) Local Print Collection [location] : Patricia Bowen Library and Knowledge Service West Middlesex university Hospital.

**Abstract:**OBJECTIVETo investigate prenatal, perinatal, and neonatal risk factors for autism spectrum disorders by using participants identified through broad ascertainment and reliable classification methods.METHODSThe targeted population was 8-year-old children born in 1994 and residing in 1 of the 3 most populous counties in Utah who were identified as having an autism spectrum disorder on the basis of methodology used by the 2002 Autism and Developmental Disabilities Monitoring Network. Of those identified, 132 children (115 boys, 17 girls) had birth certificate records available. Each child was matched by gender and birth year to 100 controls (11 500 boys, 1700 girls) from the birth certificate database in a nested case-control design. Birth certificate records of participants and controls were surveyed for 23 potentially pathologic prenatal, perinatal, and neonatal factors.RESULTSThe prenatal factors that occurred significantly more frequently among children with autism spectrum disorders were advanced maternal age and parity. Increased duration of education among mothers of children with autism spectrum disorders was small but statistically significant. Significant perinatal factors were breech presentation and primary cesarean delivery. When corrected for breech presentation, a known indication for cesarean delivery, the association between primary cesarean delivery and autism spectrum disorders was eliminated. There were no significant associations found between autism spectrum disorders and neonatal factors.CONCLUSIONSIn the absence of other complications suggesting fetal distress, the association between breech presentation and autism spectrum disorders in this study suggests a shared etiology rather than causal relationship. Additional investigation focused on both genetic and environmental factors that link these autism spectrum disorder risk factors individually or collectively is needed.

**Database:** Medline

## **52. Perinatal factors and the development of autism: A population study**

**Author(s):** Glasson E.J.; Hallmayer J.F.; Bower C.; Petterson B.; De Klerk N.; Chaney G.

**Source:** Archives of General Psychiatry; Jun 2004; vol. 61 (no. 6); p. 618-627

**Publication Date:** Jun 2004

**Publication Type(s):** Article

**PubMedID:** 15184241

Available at [Archives of general psychiatry](#) - from Unpaywall

**Abstract:**Background: Autism is considered to have a genetic basis, although exposure to certain stimuli in the prenatal period has been implicated to be causal in some cases. Some investigations have shown an association with obstetric complications but findings have been inconsistent owing to differences in sampling and methods. Objective(s): To examine the association of obstetric factors with autism spectrum disorders for a cohort of children, using obstetric data contained in a statutory database collected at the time of birth. Design(s): Subjects born in Western Australia between 1980 and 1995 and diagnosed with an autism spectrum disorder by 1999 were included as cases (n=465). Siblings of the cases (n=481) and a random population-based control group (n=1313) were compared with the cases on obstetric information contained in the Maternal and Child Health Research Database of Western Australia. Result(s): Compared with control subjects, cases had significantly older parents and were more likely to be firstborn. Case mothers had greater frequencies of threatened abortion, epidural caudal anesthesia use, labor induction, and a labor duration of less than 1 hour. Cases were more likely to have experienced fetal distress, been delivered by an elective or emergency cesarean section, and had an Apgar score of less than 6 at 1 minute. Cases with a diagnosis of autism had more complications than those with pervasive developmental disorder not otherwise specified or Asperger syndrome. Nonaffected siblings of cases were more similar to cases than control subjects in their profile of complications. Conclusion(s): Autism is unlikely to be caused by a single obstetric factor. The increased prevalence of obstetric complications among autism cases is most likely due to the underlying genetic factors or an interaction of these factors with the environment.

**Database:** EMBASE

## Strategy 787909

#	Database	Search term	Results
1	Medline	(autism OR autistic OR ADHD OR "attention deficit disorder").ti,ab	68324
20	Medline	exp "ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY"/	27730
2	Medline	exp "AUTISTIC DISORDER"/ OR exp "AUTISM SPECTRUM DISORDER"/	28106
3	Medline	(1 OR 2)	71817
4	Medline	(cesarean* OR caesarean* OR "c section" OR cesarian* OR caesarian*).ti,ab	59788
5	Medline	exp "CESAREAN SECTION"/	44108
6	Medline	(4 OR 5)	72161
7	Medline	(3 AND 6)	71
8	EMBASE	(autism OR autistic OR ADHD OR "attention deficit disorder").ti,ab	92306
9	EMBASE	exp "AUTISTIC DISORDER"/ OR exp "AUTISM SPECTRUM DISORDER"/	66592
23	EMBASE	exp "ATTENTION DEFICIT DISORDER"/	59021
10	EMBASE	(8 OR 9)	108379
11	EMBASE	(cesarean* OR caesarean* OR "c section" OR cesarian* OR caesarian*).ti,ab	86297
12	EMBASE	exp "CESAREAN SECTION"/	92473

13	EMBASE	(11 OR 12)	111181
14	EMBASE	(10 AND 13)	249
15	PsycINFO	(autism OR autistic OR ADHD OR "attention deficit disorder").ti,ab	75876
16	PsycINFO	exp "AUTISM SPECTRUM DISORDERS"/	42091
17	PsycINFO	(15 OR 16)	78361
18	PsycINFO	(cesarean* OR caesarean* OR "c section" OR cesarian* OR caesarian*).ti,ab	1960
19	PsycINFO	(17 AND 18)	35
21	Medline	(1 OR 20 OR 2)	80586
22	Medline	(6 AND 21)	75
24	EMBASE	(23 AND 13)	105
25	PsycINFO	exp "ATTENTION DEFICIT DISORDER"/	26411
26	PsycINFO	(18 AND 25)	9