Prenatal and Perinatal Risk Factors for Autism

A Review and Integration of Findings

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Objective: To review the evidence for the presence of prenatal and perinatal factors that affect the risk of autism and autism spectrum disorders.

Data Sources: Relevant articles were identified by searching MEDLINE, screening reference lists of original studies, and searching major journals likely to publish epidemiological studies on the topic.

Study Selection: For inclusion in this review, studies required (1) a well-defined sample of cases drawn from population-based registers or cohorts; (2) standardized, prospectively collected obstetric information from birth records or registers; (3) comparison subjects drawn from the general population with information on obstetric complications collected from the same source; and (4) a standardized format for presentation of data, allowing for comparisons among studies.

Main Exposures: Parental characteristics and obstetric complications.

Main Outcome Measures: Rates of autism and autism spectrum disorders.

Results: Seven epidemiological studies were identified that fulfilled inclusion criteria. The parental characteristics associated with an increased risk of autism and autism spectrum disorders included advanced maternal age, advanced paternal age, and maternal place of birth outside Europe or North America. The obstetric conditions that emerged as significant fell into 2 categories: (1) birth weight and duration of gestation and (2) intrapartum hypoxia.

Conclusions: Evidence to suggest that parental age and obstetric conditions are associated with an increased risk of autism and autism spectrum disorders is accumulating. Although not proven as independent risk factors for autism, these variables should be examined in future studies that use large, population-based birth cohorts with precise assessments of exposures and potential confounders.

Arch Pediatr Adolesc Med. 2007;161:326-333
neurological and psychiatric disorders, including Down syndrome, dyslexia, mental retardation, and schizophrenia, as well as with developmental difficulties, such as speech and language problems, internalizing problems, attention problems, social problems, hyperactivity. Despite significant research into the potential role of pregnancy and birth complications in the origin of autism, the causal nature of these associations is still disputed. This dispute may be due to several current methodological limitations of studies that have examined associations between parental characteristics and obstetric conditions and risk of autism.

First, many early studies that examined perinatal risk factors in autism had small sample sizes and consequently lacked the statistical power to detect meaningful differences. Second, most studies used clinical rather than epidemiological samples, and such designs are especially prone to selection bias and ascertainment bias. Third, different perinatal conditions may have different roles in the cause of autism. However, many studies use aggregated scores of perinatal and obstetric conditions, such as obstetric suboptimality. Aggregation of conditions might increase the likelihood of nondifferential misclassification of exposure and possibly attenuate the estimate of true associations. Finally, some investigators relied on crude prenatal exposure data, such as maternal reporting of events that occurred during pregnancy. Maternal recall is prone to bias, because mothers of children with autism are more likely to recall prenatal and perinatal events than mothers of controls. This differential recall is likely to bias the true measure of association away from the null hypothesis and lead to spurious positive results. Even when misclassification of exposure by the parent is not conditioned on whether or not the child has autism, it may still bias the results and attenuate a true association.

We sought to systematically review the evidence for the presence of prenatal and perinatal factors that affect the risk of autism and ASDs. We have chosen to focus this review on studies that used large, population-based epidemiological samples to explore associations between prenatal and perinatal variables and the risk of autism and ASDs. The focus on such studies has several advantages. First, these studies have sufficient statistical power to detect differences in rates of autism between those exposed to adverse prenatal and perinatal events and those unexposed. Second, when subjects are drawn from clinical samples, as compared with the general population, selection bias and lack of information on potential confounders are more likely to occur and threaten the internal validity of the study. Third, results may be generalized to the underlying population with significantly less constraints. Finally, such studies typically use standardized measures of exposures and valid and reliable ascertainment of outcome (autism), whereas studies of clinical samples usually rely on data collected non-systematically.

This review summarizes the findings from all of the epidemiological studies published to date. We also endeavor to draw evidence-based conclusions, elucidate further the nature and extent of prenatal and perinatal risk in autism, and suggest directions of future research.

METHODS

INCLUSION CRITERIA

Studies were included in the review if they fulfilled the following a priori defined set of criteria: (1) inclusion of a well-defined sample of cases drawn from population-based registries or cohorts; (2) use of standardized, prospectively collected obstetric information from birth records or registers; (3) inclusion of comparison subjects drawn from the general population with information on obstetric complications collected from the same source; and (4) use of a standardized format for presentation of data on individual obstetric complications, allowing for comparisons between studies.

SEARCH OF STUDIES

The search strategies used were (1) a computerized MEDLINE search for English-language biomedical articles that examined prenatal and perinatal conditions in autism and ASDs (the following keywords were used: autism, risk, prenatal, perinatal, obstetric, and familial); (2) screening of reference lists of original articles; and (3) a manual search of major journals likely to publish epidemiological studies on the topic, including the New England Journal of Medicine, JAMA, Lancet, BMJ, American Journal of Epidemiology, Epidemiology, Archives of General Psychiatry, American Journal of Psychiatry, and British Journal of Psychiatry.

RESULTS

We identified 7 articles that reported results from epidemiological studies that fulfilled all 4 inclusion criteria. The characteristics of the 7 studies and a summary of their main findings are presented in Table 1 and Table 2. Four of the 7 were population-based cohort studies, and 3 used a case-control study design. Five different geographic locations were represented, including Denmark, California, Sweden, Western Australia, and Israel. The 3 studies from Denmark and California have partially overlapping samples, but since they have slightly different methods and examined diverse and not always overlapping risk factors, we review the results of all 3 studies. The study by Eaton et al includes a secondary analysis of a larger cohort, but the authors restricted the analysis to a smaller set of variables than used in the main analysis. All studies included affected cases with either Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) diagnoses of autism, although 4 used a combined sample of autism and ASDs. Two of these 4 studies analyzed autism and ASDs separately.

SUMMARY OF FINDINGS

Crude estimates and adjusted estimates that take into account the effect of potential confounders are summarized in Tables 1 and 2. In this review, we focus on factors found by at least 2 studies and associated with at least a 50% increase in the risk of autism (ie, a relative risk of 1.5 or higher). Such factors are less likely to be ex-
explained by mismeasured or unmeasured confounders. When applying those criteria, 3 parental characteristics and 2 broadly defined obstetric conditions appear to be associated with an elevated risk of autism and ASDs across the 7 studies.

PARENTAL CHARACTERISTICS

The parental characteristics that emerged as significant predictors of autism and ASDs included advanced paternal age, advanced maternal age, and maternal place of birth outside Europe or North America for children born in Denmark and Sweden.

The effect of advanced paternal age was examined in 4 studies. Paternal age remained a significant risk factor for autism and ASDs in 3 of the 4 studies after controlling for confounding variables, including maternal age (range of adjusted relative risk, 1.58-3.75). In a recently published study, Reichenberg et al demonstrated a greater than 2-fold increase in the risk of ASDs with each 10-year increase in paternal age.

Advanced maternal age was one of the most frequently studied risk factors for autism and was associated with risk of autism in 6 of the 7 studies before controlling for potential confounders. Older mothers have an increased risk of obstetric complications possibly due to uterine muscle dysfunction and diminished blood supply with age. Maternal age remained an independent risk factor in 3 studies also after adjusting for other variables: the relative risk for mothers 35 years or older was 3.4 in a US cohort, 2.3 in a Denmark study, and 1.5 in an Australian study. Only the Australian study, however, took paternal age into account in the analysis.

Maternal place of birth outside Europe or North America was associated with increased risk of autism in 2 studies: 1 from Sweden (adjusted relative risk, 3.0) and 1 from Denmark (adjusted relative risk, 1.4).

OBSTETRIC CONDITIONS

The obstetric conditions that appeared to increase risk of autism fell into 2 categories: (1) birth weight and gestational age at birth (ie, duration of pregnancy) and (2) intrapartum hypoxia. Low birth weight (LBW), defined as birth weight less than 2500 g, was examined in 5 studies, but none have conferred LBW to be associated with increased risk of autism. Data on gestational age were reported in 4 studies. Birth at less than 35

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Abbreviations: ASD, autism spectrum disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases.

*The studies from Denmark have partially overlapping samples.
weeks was associated with increased risk of autism in 1 study\textsuperscript{32} (adjusted relative risk, 2.6). Being small for gestational age or having LBW or slow growth was associated with a 2-fold increase in risk in 2 studies (range of adjusted relative risk, 1.6-2.1).\textsuperscript{26,30} Birth weight and gestational age were combined in 1 study\textsuperscript{26} to reflect the joint effects of these 2 variables and formulated into a separate variable called weight or growth risk. One of the other studies\textsuperscript{32} found only gestational age at birth (adjusted relative risk, 1.3) but not LBW to be associated with autism.

Several obstetric variables may act as surrogates of fetal hypoxia, including low Apgar score, fetal distress, cesarean delivery, threatened abortion, and bleeding during pregnancy. Measures of hypoxia were examined in 4 of the 7 studies. Findings from all 4 studies suggested that an Apgar score of less than 7 predicts autism.\textsuperscript{26,30-32} In 3 of the 4 studies, a low Apgar score remained a significant risk factor in the adjusted analyses (range of adjusted relative risk, 1.7-3.2).\textsuperscript{26,30,32}

In 1 study, several pregnancy complications were associated with an increased risk of autism, including bleeding, cesarean delivery, and congenital malformations.\textsuperscript{30} Two of the 7 studies identified cesarean delivery as an independent risk factor for autism (range of adjusted relative risk, 1.6-1.8).\textsuperscript{26,31} In addition, a history of abortion\textsuperscript{30} or threatened abortion\textsuperscript{31} similarly increased the risk of autism. Finally, bleeding during pregnancy\textsuperscript{30} and fetal distress\textsuperscript{31} emerged as 2 other significant risk factors for autism in separate studies. Taken together, the studies suggest that hypoxia-related obstetric complications and fetal hypoxia may possibly increase the risk of autism.

### COMMENT

According to our review, 3 parental characteristics and 2 obstetric conditions emerge as potential risk factors for autism: namely, paternal age, maternal age, maternal immigration, growth restriction, and newborn hypoxia. In analyses that adjusted for confounding variables, these factors usually remained statistically significant.

Several variables were interpreted to reflect hypoxia, however, including low Apgar score, fetal distress, cesarean delivery, maternal hypertension, and bleeding during pregnancy. In this section, we discuss the potential risk factors identified in this review and attempt to understand their etiological relevance to autism.

### ADVANCED PATERNAL AGE

Several studies\textsuperscript{13,34-39} of clinical samples have reported advanced paternal age in individuals with autism or childhood psychosis. The results of this review show that 3 of the 4 population-based studies\textsuperscript{28,29,32} to examine paternal age reported a significant association with risk of autism and ASDs. The fourth study\textsuperscript{33} also found that paternal age was older in fathers of case patients with autism compared with fathers of controls, although this re-
lationship was statistically weaker in the adjusted analysis. Thus, advancing paternal age is consistently associated with increased risk of autism and ASDs.

Advanced paternal age has been associated with several congenital disorders, including Apert syndrome,48 craniosynostosis,49 situs inversus,50 syndactyly,51 cleft lip and/or palate,44,45 hydrocephalus,46 neural tube defects,46 and Down syndrome.37 In addition, advanced paternal age has been associated with schizophrenia52 and decreased intellectual capacities in the offspring.46 The most widely proposed mechanism underlying these congenital anomalies is known as the “copy error” hypothesis, first proposed by Penrose.49 After puberty, spermatocytes divide every 16 days, which is known as the “copy error” hypothesis, first proposed by Penrose.49 After puberty, spermatocytes divide every 16 days, and by the age of 35 years, approximately 540 cell divisions have occurred. As a result, de novo genetic mutations that result from replication errors and defective DNA repair mechanisms are believed to propagate in successive clones of spermatocytes. These mutations accumulate with advancing paternal age and thus help explain how this disorder, which has a large genetic component, can be maintained in the population despite reduced reproduction in affected individuals.

**ADVANCED MATERNAL AGE**

Increased maternal age has also been associated with several developmental disorders, including Down syndrome,53 dyslexia,54 and mental retardation of unknown cause.55 Brain damage of the fetus or neonate may also be more likely to occur in older mothers.50 Early case-control studies56,57 of autism have reported mixed results with respect to a proposed association between advanced maternal age and autism. Our review indicated that 3 epidemiological studies26,27,31 found advancing maternal age to be associated with increased risk of autism or ASDs, although results are not consistent across studies. One of the 3 studies26 found maternal age to be specifically associated only with Asperger syndrome.

One possible mechanism for the association between advanced maternal age and neurological and psychiatric disorders involves nucleotide repeat instability.56 Trinucleotide or triplet repeats are 3 nucleotides consecutively repeated within a region of DNA and have been found to undergo a type of genetic mutation, termed a dynamic or expansion mutation. In this type of mutation, through mechanisms that occur during DNA replication and are only partially understood, the number of triplets in a repeat increases.53 Unlike repeats of normal length, in which length changes only rarely from one generation to the next, expanded repeats tend to be unstable and will typically become longer over successive generations. During the past decade, nearly 20 diseases caused by a trinucleotide repeat expansion have been identified, as well as other diseases caused by related mutations, including Huntington disease and fragile X syndrome. More recently, trinucleotide repeats have been associated with the risk of autism.54,55

**MATERNAL IMMIGRATION**

Two studies28,30 identified an increased risk of autism in children whose mothers were born outside Europe or North America. This finding is consistent with previous work by Gillberg and Gillberg56 in a Swedish population-based study to examine autism in immigrants. This increased risk has been suggested to indicate the presence of an underlying infectious cause because mothers may not receive immunizations in their new country and thereby lack immunity to certain infections during pregnancy that are otherwise uncommon in the country of origin.56,57 Another possible explanation for this effect is selective migration of people with genetic vulnerability to autism. This explanation would appear less likely, however, given that immigration requires integration into a new culture and acquisition of a new language, both skills that are presumably lacking in people with ASDs. However, Gillberg et al57 have suggested that men with social impairments may more easily establish an intimate relationship with someone from another country. This theory finds indirect support in work by Lauritzen et al,26 who examined parental countries of birth and found the effect of maternal country of origin to have a greater effect than paternal country of origin. However, the studies that demonstrated a maternal immigration effect in autism were conducted in Nordic countries. Sweden and Denmark may receive immigrants from similar countries, and replication in other geographic regions is necessary before these results can be generalized.

**LBW AND GESTATIONAL AGE**

Low birth weight is considered a marker for newborns at high risk for later neurological, psychiatric, and neuropsychological problems because it is a likely indicator of fetal growth problems and has been associated with prenatal risk factors, intrapartum complications, and neonatal disease.58 Low birth weight is a particularly attractive marker because it is measured routinely and rather accurately and has been associated with a variety of cognitive difficulties and psychiatric outcomes in children, including speech and language problems;16,17 internalizing problems, attention problems, social problems;18 hyperactivity,21,22 and learning disabilities.59 There is also a substantial literature base on the relationship between LBW and intelligence. Most studies38,60 have demonstrated that, compared with normal-birth-weight children, LBW children have lower mean IQ scores. Recent studies61 further suggest that birth weight is associated with IQ across the entire birth weight range. However, our review suggests that LBW is not associated with increased risk of autism. Low-birth-weight infants represent an etiologically heterogeneous group, and LBW is often an indicator of earlier intrauterine effects.62 Premature infants are also typically physically small, and therefore the association between birth weight and gestational age is important to consider. Similar to LBW, gestational age and particularly being small for gestational age have been associated with adverse health outcomes, including developmental delays and later intellectual impairments in childhood and adolescence.63-65 Evidence from case-control studies that used clinical samples of autistic children to explore an association between gestational age and autism is not consistent. Abnormal gestational age,
including prematurity and postmaturity, has been associated with an increased risk of autism in some studies, but not all. Among the epidemiological studies within the scope of our review, only 4 examined gestational age as a potential risk factor for autism. Two studies found a significant association between being small for gestational age and autism, and another study found an increased risk of autism in very light or slow-growth infants. In summary, despite biological plausibility and fairly consistent findings that document a relationship between gestational age and the risk of autism, large population-based epidemiological samples with comprehensive data on potential confounders and plausible mediators are needed for a more conclusive investigation of these factors.

**Hypoxic Conditions**

Several investigators have hypothesized that a set of perinatal conditions that indicate prolonged or acute oxygen deprivation (hypoxia) to the fetus may be a major risk factor for neuropsychological and neuropsychiatric disturbances. Murray and Harvey reported that regions in the brain are especially vulnerable to perinatal insult, including the basal ganglia, the hippocampus, and the lateral ventricles. Neuroimaging studies have shown that the lateral ventricles in particular are larger in patients with autism compared with controls. Brains of individuals with autism have also been shown to exhibit morphological hippocampal abnormalities. Prenatal and perinatal conditions associated with fetal hypoxia are likely to be heterogeneous in origin and may include, in addition to overt fetal distress, conditions such as maternal hypertension, gestational diabetes, cord encircling of the neck, and prolonged labor.

Some indirect evidence also supports an association between hypoxia and hypoxia-related conditions and autism. Juul-Dam and colleagues found increased frequency of oxygen treatment among newborns who later developed autism and other pervasive developmental disorders, but this association was no longer significant after controlling for multiple comparisons. Similar results, although not statistically significant, were reported by Gillberg and Gillberg. Among the epidemiological studies reviewed in this article, increased frequency of several variables that may reflect hypoxia-related conditions was detected in case patients with autism. One study found significant associations with pregnancy-induced hypertension, bleeding, cesarean delivery, congenital malformations, and daily smoking during pregnancy. The association with cesarean delivery should be considered with caution because it might be confounded by the indication to perform cesarean delivery, such as a significant obstetric complication. Other studies identified provoked abortion, threatened abortion, and fetal distress as significant risk factors. However, most of these studies assessed only a few potentially hypoxic conditions.

Before concluding, several limitations of this review are worth noting. First, our results were based on a limited number of studies. Second, diagnostic criteria varied across studies and may now be considered outdated in some (e.g., ICD-8 and DSM-III), although Madsen et al in their 2002 study on measles-mumps-rubella vaccination and autism found that a change in classification system from ICD-8 to ICD-10 did not have a major influence on the overall results. Similarly, the risk factors characterized in this review were evident across studies using different classification methods. Furthermore, case assessments typically did not include gold standard measures such as the Autism Diagnostic Interview—Revised or the Autism Diagnostic Observation Schedule—Generic, yet most studies report high reliability and validity of case sources. Third, our conclusions were based only on data collected and reported by the reviewed studies. Other potentially relevant risk factors may have been overlooked. Fourth, the generalizability of the identified risk factors is limited by the difficulty of applying conclusions drawn from diverse ethnic populations, especially with a vastly heterogeneous disease such as autism. Finally, the specificity of the results may be called into question because several other neurodevelopmental diseases, as noted, may similarly be associated with the identified risk factors.

**Conclusions**

Future studies should continue to explore whether parental characteristics and obstetric conditions are associated with an increased risk of autism and ASDs. The parental characteristics identified through this review that are likely to have a true association with autism include advancing paternal and, to a lesser extent, advancing maternal age. Because of a growing body of evidence supporting the presence of abnormal fetal brain development in ASDs, future studies should investigate obstetric conditions such as newborn hypoxia and LBW. A broader autism phenotype, with characteristic social, language, and behavioral impairments, has been implicated. Future studies may also seek to assess the impact of prenatal and perinatal risk factors on dimensional outcomes related to the autism phenotype in the general population. Given the inconsistency present in some results, it is especially important for future studies to use large, population-based birth cohorts and to allow for precise and detailed assessments of exposures and potential confounders. Perhaps the most important potential confounder to consider is genetic susceptibility to autism. Genetic susceptibility, a well-known risk factor for autism, may be associated with obstetric suboptimality. To determine whether prenatal and perinatal exposures are independent risk factors for autism, a measure of genetic susceptibility should be included in future studies. To date there are no known genes for autism, and therefore a detailed family history should be sought. Such a history would allow for the assessment of genetic susceptibility as a confounder and would also help researchers examine the interaction of autism susceptibility genes with nonheritable, potentially preventable prenatal and perinatal risk factors for autism and ASDs.

**Accepted for Publication:** November 30, 2006.

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