Perinatal and Neonatal Risk Factors for Autism: A Comprehensive Meta-analysis

WHAT'S KNOWN ON THIS SUBJECT: Autism etiology is unknown, although perinatal and neonatal exposures have been the focus of epidemiologic research for more than 40 years. Although studies show that obstetrical and neonatal complications may increase autism risk, the specific complications and magnitude of effect have been inconsistent.

WHAT THIS STUDY ADDS: Our study provides the first review and meta-analysis of all 64 studies of perinatal and neonatal risk factors for autism published through March 2007.

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ABBREVIATIONS
RR—relative risk
CI—confidence interval

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abstract

BACKGROUND: The etiology of autism is unknown, although perinatal and neonatal exposures have been the focus of epidemiologic research for over 40 years.

OBJECTIVE: To provide the first review and meta-analysis of the association between perinatal and neonatal factors and autism risk.

METHODS: PubMed, Embase, and PsycInfo databases were searched for studies that examined the association between perinatal and neonatal factors and autism through March 2007. Forty studies were eligible for the meta-analysis. For each exposure, a summary effect estimate was calculated using a random-effects model. Heterogeneity in effect estimates across studies was examined, and, if found, a meta-regression was conducted to identify measured methodological factors that could explain between-study variability.

RESULTS: Over 60 perinatal and neonatal factors were examined. Factors associated with autism risk in the meta-analysis were abnormal presentation, umbilical-cord complications, fetal distress, birth injury or trauma, multiple birth, maternal hemorrhage, summer birth, low birth weight, small for gestational age, congenital malformation, low 5-minute Apgar score, feeding difficulties, meconium aspiration, neonatal anemia, ABO or Rh incompatibility, and hyperbilirubinemia. Factors not associated with autism risk included anesthesia, assisted vaginal delivery, postterm birth, high birth weight, and head circumference.

CONCLUSIONS: There is insufficient evidence to implicate any 1 perinatal or neonatal factor in autism etiology, although there is some evidence to suggest that exposure to a broad class of conditions reflecting general compromises to perinatal and neonatal health may increase the risk. Methodological variations were likely sources of heterogeneity of risk factor effects across studies. *Pediatrics* 2011;128: 344–355

The etiology of autism is unknown. Although the estimated 60% to 92% concordance rate in monozygotic twins compared with the 0% to 10% rate in dizygotic twins underscores the importance of genetic influences, the incomplete concordance in monozygotic twins also indicates a role of environmental factors.[1,2] It is now believed that the mechanism underlying autism etiology is most likely polygenic and potentially epistatic and that environmental factors may interact with genetic factors to increase risk.[3,4]

Although the distinctive neuropathology remains elusive, studies[3,5] have shown macroscopic, microscopic, and functional brain abnormalities. These various brain abnormalities suggest that the etiologically relevant period may be in utero or possibly in early infancy.[3] Obstetrical and delivery factors as well as neonatal exposures have been the focus of a significant amount of epidemiologic research on the possible risk factors for autism. Although many studies support the hypothesis that obstetrical and neonatal complications may increase the risk of autism,[6] the specific complications, magnitude of effect, and overall conclusions of these studies have been inconsistent. These inconsistencies may be a result of methodological variations, including diagnostic criteria, comparison groups, sample size, and exposure-assessment methods.

The purpose of this study is to provide a systematic review and meta-analysis of the epidemiologic literature on the relationship between perinatal and neonatal complications and exposures and autism. A review article by Kolevson et al[6] discusses 7 studies on this topic, drawn from population-based registers or cohorts with prospectively collected obstetric information. Our study provides the first review and meta-analysis of all 64 studies of perinatal and neonatal risk factors for autism published through March 2007. We have previously published a similar review and meta-analysis[7] of prenatal exposures in relation to autism, which focused on conditions during pregnancy only. The current report complements our previous article by addressing all variables assessed at approximately the onset of labor through delivery and the neonatal period.

METHODS

Data Sources and Review Methods

The PubMed, Embase, and PsycInfo databases were searched using the key words "autism" in combination with "prenatal" or "perinatal" or "pregnancy" or "neonatal," limited to peer-reviewed studies published in any language through March 2007. The search identified 698 studies in PubMed, 176 in Embase, and 416 in PsycInfo. The literature search sought to identify all epidemiologic studies that have examined the association of pregnancy and delivery factors and neonatal complications to the risk of autism. On the basis of a review of all abstracts, 83 articles were identified as potentially relevant and were reviewed further. Those studies that were not reviewed included case series, animal studies, autism prevalence studies, medical hypotheses, studies of other psychiatric diseases (eg, schizophrenia), and studies of unrelated exposures (eg, demographics, familial psychiatric diseases, genetics, or infant behaviors). A total of 41 additional potential articles were identified after screening the reference lists of articles. Among 124 studies reviewed, we excluded those that did not include a comparison group ($n = 13$) or formal statistical analyses ($n = 3$), did not examine exposures during pregnancy or the first month of life ($n = 10$), grouped their autism cases with other childhood psychotic disorders ($n = 15$), and were review or commentary articles ($n = 18$). The control group had to be nonautistic but could be otherwise abnormal. In total, 65 studies[2,8–71] were eligible for inclusion in the review. Two studies[13,28] reporting on the same data set were considered together, resulting in 64 studies for review. This report focuses on the perinatal and neonatal factors because a previous publication[7] reviewed the prenatal exposures.

Dr Gardener abstracted each article on 2 separate occasions spaced 1 year apart. For each study, the following information was recorded: (1) study design (cohort or case control); (2) sample size and description (eg, clinic based or population based); (3) comparison group description (eg, matching criteria, sibling control subjects, healthy versus abnormal control subjects, and diagnoses of abnormal control subjects); (4) autism diagnostic criteria and mode of reporting (eg, *Diagnostic and Statistical Manual of Mental Disorders–Third Edition* versus *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition*, parental report versus medical record review versus study physician assessment, and diagnostic measures used); (5) risk factors examined and mode of reporting (eg, parental interview and medical record review); (6) covariates in multivariate models; and (7) study results, including indicators of statistical significance, prevalence of exposures among case and control subjects, rates or risks of autism across exposure levels, relative risks (RRs) and 95% confidence intervals (CIs). Studies were classified as prospective versus retrospective if exposures were assessed and recorded before or after the onset of autism. For the quantitative review, we counted the number of studies that examined each perinatal and neonatal factor in relation to the risk of autism and the number of null findings, significant positive findings, and significant negative findings.

Statistical Analysis

Meta-analysis

Of 64 studies reviewed, 40[8–47] were appropriate for inclusion in this meta-analysis. A total of 24 studies were excluded because they did not report RRs and CIs or did not provide information needed to calculate them. The statistical methods for this study have been described in detail previously.[7] A separate meta-analysis was conducted for each exposure variable that was examined in 2 or more studies. For each exposure, a summary effect estimate was calculated using a random-effects model.[72] Because power to detect heterogeneity is low in meta-analyses such as these,[73] we took a conservative approach and used random-effects models to form CIs because random-effects models account for any observed heterogeneity regardless of whether the heterogeneity is statistically significant.

If an effect estimate was reported without the corresponding 95% CI, the confidence bounds were derived from the *P* value provided. If no *P* value was provided, then a *P* value of .05 or .50 was assumed for factors that did and did not reach statistical significance. Because of the rarity of many of the exposures and small sample sizes, there were tables in some (<5%) of the meta-analyses with 0 cell counts. In these instances, .5 was added to each cell of the 2 × 2 table.[74]

Meta-regression

Meta-regression is an analysis of whether study-level characteristics (ie, variations in methodology across studies) can explain heterogeneity in effect estimates reported across studies for the same risk factor–outcome association. It is an important aspect of a meta-analysis to indicate whether the summary effect estimates and 95% confidence bounds are an adequate representation of the results in the literature or whether stratified analyses on the basis of study design differences are more appropriate.

For each risk factor assessed in multiple studies, we examined the heterogeneity in the RRs estimated across studies using the Q statistic.[72,75] Because of the limited power of this test,[73] a liberal *P* value of <.10 was used to identify meta-analyses that required additional examination to assess potential sources of heterogeneity. If we found evidence of suggested heterogeneity, a meta-regression[76] was conducted.

Meta-regression relates the effect estimate of each study to its design characteristic or methodology, to determine whether variability in study designs across studies may account for differences in reported associations across studies (ie, between-study effect modification) for each given risk factor.[76] The study characteristics that were examined included the following: diagnostic criteria (inclusion of spectrum disorders: yes versus no); exposure information quality (0 = retrospective exposure assessment, 1 = mix of retrospective and prospective exposure assessment, and 2 = prospective exposure assessment); control for confounding (0 = univariate analysis, 1 = control for select demographic factors, birth order, or IQ and 2 = full multivariate analysis or matching with sibling control subjects); normal versus abnormal control subjects; and case selection (clinic based versus population based). A total of 19 studies used broad diagnostic criteria, of which 9 were clinic based and 10 were population based, whereas 45 studies used narrow diagnostic criteria (autism only), of which 29 were clinic based and 16 were population based. If effect modification was suggested for a given study characteristic ($P < .10$), then a stratified analysis was performed.

Publication bias was assessed for each factor by conducting tests for funnel plot asymmetry.[77] Two statistical approaches were used to examine the association between study size and the effect of the exposure: the Begg test[78] and the Egger test.[79]

RESULTS

Table 1 lists the perinatal and neonatal factors that were not included in the meta-analysis because of the unavailability of 2 or more effect estimates and 95% CIs, as well as an indication of whether they were associated with autism in the studies in which they were examined. Table 2 lists the perinatal and neonatal factors included in the meta-analysis, as well the number of null findings, significant positive findings, and significant negative findings (reduced risk). For each factor examined in the meta-analysis, Table 2 reports the summary effect estimate and 95% CI from the random-effects model and the *P* value for the test of heterogeneity.

The meta-analysis identified several perinatal and neonatal factors that were associated with an increased risk for autism. These included abnormal presentation in general (RR: 1.44, $P = .02$), breech presentation (RR: 1.81, $P = .004$), umbilical-cord complications (eg, prolapsed cord, cord wrapped around the neck; RR: 1.50, $P = .05$), fetal distress (RR: 1.52, $P = .01$), birth injury or trauma (RR: 4.90, $P = .01$), multiple birth (RR: 1.77, $P = .002$), maternal hemorrhage (RR: 2.39, $P = .003$), summer birth (RR: 1.14, $P = .02$), low birth weight (<2500 g; RR: 1.63, $P = .002$), very low birth weight (<1500 g; RR: 3.00, $P < .001$), small for gestational age (RR: 1.35, $P = .001$), congenital malformations (RR: 1.80, $P < .001$), low 5-minute Apgar score (RR: 1.67, $P = .001$), meconium aspirated (RR: 7.34, $P = .001$), feeding difficulties (RR: 3.35, $P = .01$), neonatal anemia (RR: 7.87, $P = .02$), ABO or Rh incompatibility (RR: 3.70, $P < .001$),

TABLE 1 Review of Perinatal and Neonatal Risk Factors not Eligible for Meta-analysis

Perinatal and Neonatal Risk Factors Examined in Only 1 Study	
No association with autism	Premature rupture of membranes, delayed labor, loss of amniotic fluid on the day before delivery, analgesia during labor, green amniotic fluid, acidosis pH <7.2 in cord blood, shoulder dystocia, cephalopelvic disproportion, near dead at birth, blue baby, blood t4 level (thyroxine), hypoglycemia, hypocalcemia, polycythemia, hyponatremia, infantile vomiting, intracranial hemorrhage, elevated serum IgM, macrocephaly, hydrocephaly, abnormal fetal cardiac activity, blood poisoning, and incubator use
Positive association with autism	No labor, stimulated breathing at birth, asphyxia, baby held back, Apgar score ≤6, colic, quiet and sleepy, encephalopathy, and hemolytic disease
Negative association with autism	Infected amniotic fluid

Perinatal and Neonatal Risk Factors Examined in Multiple Studies[a]	
Perinatal/neonatal factor (number of studies)	Results across studies[b]
Labor complications (3)	3, null results
Delivery complications (5)	3, null results, 2, significant positive results, $P < .05$
Birth length (3)	3, null results
Clinical dysmaturity (2)	1, null results, 1, significant positive results, $P < .05$
Poor condition at birth (2)	1, null results, 1, significant positive results, $P < .05$
Apgar <9 (2)	2, null results
Difficulty regulating temperature (2)	2, null results
Septicemia or meningitis (3)	3, null results

[a] Although these factors were examined in multiple studies, effect estimates and CIs were available for fewer than 2 studies.
[b] Total number of studies included in the review: 64.

and hyperbilirubinemia (RR: 1.87, $P = .05$). Cesarean delivery was associated with a 26% increased risk of autism that did not reach statistical significance ($P = .06$).

Heterogeneity ($P < .10$) in effect estimates across studies was observed for many factors including prolonged labor, induced or augmented labor, precipitous labor, Cesarean delivery, abnormal presentation, amniotic fluid not clear or meconium staining, multiple births, season of birth, preterm birth, postterm birth, low birth weight, low 1-minute Apgar score, weak or no crying after birth, respiratory distress, elevated temperature, hyperbilirubinemia, medical intervention during the neonatal period, and oxygen treatment or resuscitation. Table 3 shows the results of the regression analyses that examined the potential between-study sources of heterogeneity for those risk factors that showed heterogeneity in effect estimates across studies ($P < .10$). Heterogeneity in effect estimates across studies for prolonged labor, Cesarean delivery, and multiple births could not be explained by between-study variability in any of the methodological characteristics examined.

The observed relationship between the induction of labor and risk of autism was significantly different for clinic-based compared with population-based studies. Specifically, a significant 72% increased risk of autism was observed in relation to induced labor among the 3 clinic-based studies, with no association observed in the population-based studies. It is interesting to note that a significant elevated risk also was observed in relation to precipitous labor in the clinic-based studies but not in the 2 population-based studies. Potential recall bias in 1 retrospective study[30] also may have driven the summary effect estimate above the null for precipitous labor.

The timing of exposure assessment may have influenced the effect estimates for abnormal presentation. Although a significant 56% increased risk was observed in relation to abnormal fetal presentation in 9 prospective studies, no association was observed in 3 studies that assessed exposure in some or all participants retrospectively.

The meta-regression analysis suggested that the use of an abnormal (eg, Down's syndrome, physical handicaps) versus normal comparison group may account for the heterogeneity in effect estimates for several neonatal factors, including preterm birth, postterm birth, low 1-minute Apgar score, weak or no crying after birth, respiratory distress, resuscitation, medical intervention in the first month, as well as meconium staining. For all of these factors, the use of a normal comparison group (versus abnormal control subjects) resulted in a larger effect estimate, indicating a more positive association between these neonatal complications and the risk of autism. In fact, among the studies that used normal comparison groups, weak or no crying after birth, respiratory distress, and oxygen treatment or resuscitation were all significantly associated with an elevated risk of autism.

Overall, preterm birth was not associated with the risk of autism, although there was significant heterogeneity across studies. In 5 studies with broad diagnostic criteria, preterm birth was associated with a 76% increased risk, and in 10 prospective studies preterm birth conferred a 54% increase in risk. The positive association between low birth weight and risk of autism was also driven by 10 of 14 studies that assessed birth weight prospectively, suggesting that differential recall may have resulted in bias toward the null. Finally, the use of narrow diagnostic

criteria and a clinic-based case sample were methodological characteristics that may have accounted for some of the heterogeneity in effect estimates for hyperbilirubinemia and were associated with an elevation in the effect estimate.

Publication bias was assessed for factors examined in 3 or more studies. No significant publication bias was observed using Begg's test.[78] Using Egger's test,[79] publication bias ($P < .05$) was suggested for high birth weight (>4000 g), meconium aspiration, and October to December birth. Although both tests for publication bias lacked sufficient power because of the small number of studies included in each meta-analysis, Egger's test is slightly higher powered. In the meta-analysis, high birth weight was assessed in 6 studies, quarter of birth in 4 studies, and meconium aspiration in only 3 studies. Although Egger's test indicates that publication bias may have impacted the summary effect estimates observed, ~4 significant results would be expected as a result of chance alone because 76 tests of publication bias were conducted in this meta-analysis study of prenatal, perinatal, and neonatal risk factors for autism.

Several studies examined composite indices reflecting compromised perinatal and neonatal health in general in relation to the risk of autism, although an insufficient number of studies provided the data necessary for a formal meta-analysis. Perinatal and neonatal optimality scales were used to assess the number of perinatal and neonatal complications, respectively, experienced by case and control subjects. Various scales have been developed for this line of research, and the Gillberg optimality scale[53] was used most often. The use of these scales helps solve the problem of low statistical power attributed to rare perinatal and neonatal complications. In addition,

TABLE 2 Meta-analysis of Perinatal and Neonatal Risk Factors for Autism

Perinatal and Neonatal Factors (number of studies)	Results Across Studies[a]	Summary Effect Estimate (95% CI)[b]	Heterogeneity (*P*)
Labor			
Prolonged labor (9)	5−, 3↑, 1↓	1.77 (0.76–4.14)	<.001
Induced or augmented labor (8)	6−, 2↑	1.21 (0.90–1.62)	.01
Precipitous labor (5)	4−, 1↑	1.52 (0.59–3.90)	.002
Premature rupture of membranes (7)	7−	1.30 (0.96–1.76)	.43
Delivery procedures			
Anesthesia (7)	6−, 1↑	1.32 (0.84–2.07)	.17
General anesthesia (3)		1.36 (0.87–2.13)	.81
Cesarean section (12)	8−, 3↑, 1↓	1.26 (0.99–1.60)	.06
Emergency Cesarean (4)		1.04 (0.60–1.78)	.03
Elective Cesarean (2)		1.40 (0.75–2.62)	.04
Vacuum, forceps, or assisted vaginal (14)	13−, 1↑	1.12 (0.95–1.32)	.37
Forceps (7)		1.16 (0.94–1.43)	.94
Vacuum extraction (2)		0.85 (0.43–1.69)	.77
Presentation			
Abnormal presentation (15)	10−, 5↑	1.44 (1.07–1.94)	.08
Breech (4)		1.81 (1.21–2.71)	.22
Other perinatal factors			
Cord complications (14)	13−, 1↑	1.50 (1.00–2.24)	.15
Amniotic fluid not clear or meconium staining (6)	3−, 2↑, 1↓	0.82 (0.25–2.69)	.06
Fetal distress (4)	3−, 1↑	1.52 (1.09–2.12)	.32
Birth injury or trauma (6)	6−	4.90 (1.41–16.94)	.31
Twins or multiple birth (10)	7−, 3↑	1.77 (1.23–2.55)	.01
Maternal hemorrhage (4)	3−, 1↑	2.39 (1.35–4.21)	.58
Timing of birth			
Season and month of birth (12)	6−, 6↑		
January through March (4)		1.07 (0.90–1.27)	.27
April through June (4)		1.14 (0.80–1.63)	.003
July through September (4)		1.06 (0.95–1.17)	.67
October through December (4)		0.80 (0.58–1.10)	.03
Fall (3)		0.84 (0.62–1.14)	.06
Winter (3)		0.92 (0.69–1.24)	.07
Spring (3)		1.14 (0.71–1.83)	<.001
Summer (3)		1.14 (1.02–1.26)	.68
Gestational length			
Weeks' gestation (decreased) (10)	5−, 3↑, 2↓		
Postterm (14)	7−, 6↑, 1↓	1.14 (0.58–2.24)	<.001
Preterm (17)	9−, 7↑, 1↓	1.16 (0.83–1.62)	<.001
≥4 weeks preterm (2)		2.51 (0.77–8.23)	.17
Birth weight and size			
Total birth weight (decreased) (15)	12−, 2↑, 1↓		
Low birth weight (<2500 g) (15)	8−, 7↑	1.63 (1.19–2.33)	<.001
Birth weight <2000 g (2)	1−, 1↑	2.20 (0.53–9.12)	.003
Birth weight <1500 g (3)	2−, 1↑	3.00 (1.73–5.20)	.27
High birth weight (>4000 g) (6)	6−	1.13 (0.95–1.35)	.70
Small for gestational age (10)	7−, 3↑	1.35 (1.14–1.61)	.81
Large for gestational age (4)	4−	1.11 (0.85–1.46)	.20
Small head circumference (5)	5−	1.17 (0.91–1.50)	.68
Large head circumference (5)	5−	0.88 (0.70–1.11)	.85
Clinical impression			
Congenital malformation (11)	4−, 7↑	1.80 (1.42–2.82)	.87
Irritable, floppy infant, convulsions, soft neurological signs (4)	4−	1.49 (0.64–3.47)	.84
Apgar score			
1-minute Apgar score (decreased) (5)	4−, 1↑		
Low 1-minute Apgar score (6)	4−, 1↑, 1↓	1.08 (0.71–1.64)	.01
5-minute Apgar score (decreased) (6)	4−, 2↑		
Low 5-minute Apgar score (8)	6−, 2↑	1.67 (1.24–2.26)	.48

TABLE 2 Continued

Perinatal and Neonatal Factors (number of studies)	Results Across Studies[a]	Summary Effect Estimate (95% CI)[b]	Heterogeneity (*P*)
Neonatal Status			
Feeding difficulties (3)	2 ↑, 1 —	3.35 (1.33–8.40)	.22
Weak or no crying after birth or slow to cry (3)	2 —, 1 ↑	1.84 (0.19–17.58)	<.001
Meconium aspirated (3)	2 —, 1 ↑	7.34 (2.30–23.47)	.73
Respiratory distress or no breathing after birth (13)	9 —, 4 ↑	1.84 (0.80–4.21)	<.001
Neonatal medical conditions			
Anemia (4)	3 —, 1 ↑	7.87 (1.43–43.36)	.50
Neonatal infection (2)	2 —	0.35 (0.09–1.44)	.57
Elevated temperature (2)	1 —, 1 ↑	2.84 (0.52–15.64)	.01
ABO or Rh incompatible (5)	4 —, 1 ↑	3.70 (1.90–7.23)	.83
Hyperbilirubinemia or jaundice (14)	11 —, 3 ↑	1.39 (0.97–1.97)	.001
Jaundice (4)		1.06 (0.80–1.40)	.52
Hyperbilirubinemia (6)		1.87 (1.01–3.47)	.001
Phototherapy (2)		1.65 (0.86–3.19)	.09
Seizures (5)	4 —, 1 ↓	2.72 (0.70–10.53)	.43
Microcephaly (3)	3 —	1.40 (0.19–10.35)	.36
Heart defect (2)	2 —	1.59 (0.86–2.93)	.39
Medical treatment			
Medical intervention in the first month (7)	1 —, 4 ↑, 2 ↓	1.34 (0.81–2.21)	.003
Oxygen treatment or resuscitation (10)	8 —, 2 ↑	1.38 (0.65–2.94)	<.001

Null results: —; significant positive results ($P < .05$): ↑; significant negative results ($P < .05$): ↓.

[a] Total number of studies included in the review: 64.

[b] Total number of studies included in the meta-analysis: 40.

the use of optimality scores allows investigators to examine the hypothesis that general compromises to fetal and neonatal development, rather than specific exposures, increase the risk of autism. Of 8 studies that used perinatal optimality scales, only 1 reported reduced perinatal optimality among autism cases. However, reduced neonatal optimality was associated with an increased risk of autism in 8 of 11 studies that examined neonatal optimality scores.

DISCUSSION

The current study is the first meta-analysis of the relationship between perinatal and neonatal factors and risk of autism. Over 60 perinatal and neonatal factors have been studied in relation to autism in 64 epidemiologic studies, of which 40 studies were eligible for meta-analysis. Few of these factors have been examined in multiple well-designed studies. Therefore, attempted replication in methodologically rigorous studies remains necessary for many perinatal and neonatal variables. Most perinatal and neonatal factors examined in multiple studies have shown inconsistent results, and the preponderance of findings overall have not been statistically significant. The factors with the strongest evidence for an association with autism risk included abnormal fetal presentation, umbilical-cord complications, fetal distress, birth injury or trauma, multiple birth, maternal hemorrhage, summer birth, low birth weight, small for gestational age, congenital malformation, low 5-minute Apgar score, feeding difficulties, meconium aspiration, neonatal anemia, ABO or Rh incompatibility, and hyperbilirubinemia. In contrast, the factors with the strongest evidence against a role in autism risk included anesthesia use during delivery, assisted vaginal delivery, postterm birth, high birth weight, and head circumference.

Heterogeneity in effect estimates across studies was observed for several of the risk factors examined, and variability in study design characteristics may have accounted for the observed heterogeneity for many of these variables. There were some potentially important early risk factors for autism that were not found in most individual studies but are highlighted in these stratified analyses, including oxygen resuscitation and respiratory distress at birth.

Although there is insufficient evidence to implicate any 1 perinatal or neonatal factor in autism etiology, the studies using optimality scales provide some evidence to suggest that exposure to multiple neonatal complications may increase autism risk. It also is important to note that the observed association between perinatal and neonatal complications and risk of autism may actually reflect the consequences of previous prenatal complications. As mentioned, we previously published a meta-analysis of prenatal risk factors for autism, in which we found that few prenatal risk factors were associated with the risk of autism. The strongest prenatal factors included advanced maternal and paternal age at birth, maternal gestational bleeding, gestational diabetes, being first born versus third born or later, maternal prenatal medication use, and maternal birth abroad.[7] The perinatal and neonatal complications identified in the current analysis may be the result of previous prenatal complications and/or may operate in combination with prior prenatal complications to impact autism risk. Additional research that considers the joint and independent effects of adverse conditions during these various time periods is required to address these possibilities.

This study suggests that several perinatal and neonatal complications may be related to autism risk, either alone, in combination, or per-

haps only in those who are genetically vulnerable. However, the correlated occurrence of many of these complications limits the ability to determine which factors, if any, are independently associated with autism. For example, Cesarean deliveries are more common in pregnancies with abnormal fetal presentation, fetal distress, and multiple birth.[80,81] Congenital malformations, low birth weight, abnormal presentation, and low Apgar score also are interrelated.[36] Most studies did not use multivariate analyses to simultaneously control for all obstetrical factors examined, and a different set of factors was examined in each study. It is possible that increasing rates of some obstetrical factors, such as Cesarean delivery, low birth weight, multiple birth, and neonatal resuscitation, may be contributing factors to the rising prevalence of autism.[81]

The obstetrical complications that have emerged as significant risk factors for autism in the current meta-analysis suggest a possible role of fetal and neonatal hypoxia. In particular, growth retardation, fetal distress, umbilical-cord wrapping around the neck, low Apgar score, respiratory distress, resuscitation, meconium aspiration, and Cesarean delivery are all potential risk factors that also may be associated with an increased risk of hypoxia.[6,24,26,36,38,82] Although some brain abnormalities observed in individuals with autism may reflect a potential role of oxygen deprivation during development, this possibility requires additional examination. Hypoxia also has been shown to increase dopaminergic activity, and there is evidence for dopamine overactivation in autism.[83]

The current meta-analysis indicates that low birth weight and being small for gestational age are significantly associated with an increased risk of au-

TABLE 3 Analysis of Effect Modification by Study Characteristics: Perinatal and Neonatal Risk Factors With Heterogeneity, $P < .10$

Perinatal and Neonatal Risk Factors with Heterogeneity, $P < .10$	Significant Sources of Between-Study Heterogeneity: Study Characteristics, $P < .10$[a]	Summary Effect Estimate (95% CI)
Prolonged labor	None	1.77 (0.76–4.14)
Induced/augmented labor		1.21 (0.90–1.62)
	Population based ($P = .03$)	
	4 Studies: population based	0.99 (0.72–1.35)
	3 Studies: clinic based	1.72 (1.17–2.54)
Precipitous labor		1.52 (0.59–3.90)
	Population based ($P < .001$)	
	2 Studies: population based	0.71 (0.45–1.11)
	3 Studies: clinic based	4.10 (1.95–8.62)
	Exposure data collection ($P < .001$)	
	4 Studies: prospective	0.78 (0.52–1.16)
	1 Study: mix of retrospective and prospective	5.33 (2.12–13.40)
Cesarean delivery	None	1.26 (0.99–1.60)
Abnormal presentation		1.44 (1.07–1.94)
	Exposure data collection ($P = .03$)	
	9 Studies: prospective	1.56 (1.17–2.08)
	3 Studies: retrospective and mixed	0.75 (0.32–1.76)
Amniotic fluid not clear or meconium staining		0.82 (0.25–2.69)
	Abnormal and multivariate versus univariate analysis ($P = .03$)	
	3 Studies: normal control subjects and multivariate analysis or sibling control subjects	1.10 (0.50–2.39)
	1 Study: abnormal comparison group and univariate analysis	0.08 (0.01–0.72)
Twins or multiple birth	None	1.77 (1.23–2.55)
April–June birth		1.14 (0.80–1.63)
	Population based ($P < .001$)	
	2 Studies: population based	0.86 (0.77–0.97)
	2 Studies: clinic based	1.69 (1.20–2.38)
October–December birth	None	0.80 (0.58–1.10)
Fall birth		0.84 (0.62–1.14)
	Population based or multivariate versus univariate analysis ($P = .03$)	
	2 Studies: population based and univariate analysis	0.99 (0.88–1.11)
	1 Study: clinic based and sibling control subjects	0.52 (0.30–0.91)
Winter birth	None	0.92 (0.69–1.24)
Spring birth	None	1.14 (0.71–1.83)
Postterm birth		1.14 (0.58–2.24)
	Abnormal ($P = .02$)	
	9 Studies: normal control subjects	1.40 (0.77–2.56)
	1 Study: abnormal control subjects	0.25 (0.14–0.44)
Preterm birth		1.16 (0.83–1.62)
	Abnormal ($P = .003$)	
	14 Studies: normal control subjects	1.30 (0.99–1.71)
	1 Study: abnormal control subjects	0.31 (0.17–0.57)
	Exposure data collection ($P = .02$)	
	10 Studies: prospective	1.54 (1.14–2.06)
	5 Studies: retrospective and mixed	0.74 (0.41–1.35)
	Diagnostic criteria ($P < .001$)	
	10 Studies: narrow diagnostic criteria	0.81 (0.55–1.20)
	5 Studies: broad diagnostic criteria	1.76 (1.44–2.16)
Low birth weight (<2500 g)		1.61 (1.18–2.19)
	Exposure data collection ($P = .01$)	
	10 Studies: prospective	2.03 (1.39–2.96)
	4 Studies: retrospective and mixed	0.86 (0.58–1.29)

TABLE 3 Continued

Perinatal and Neonatal Risk Factors with Heterogeneity, $P < .10$	Significant Sources of Between-Study Heterogeneity: Study Characteristics, $P < .10$[a]	Summary Effect Estimate (95% CI)
Birth weight < 2000 g	None	2.20 (0.53–9.12)
Low 1–minute Apgar score		1.08 (0.71–1.64)
	Abnormal ($P = .003$)	
	5 Studies: normal control subjects	1.25 (0.93–1.67)
	1 Study: abnormal control subjects	0.21 (0.07–0.62)
Weak or no crying after birth or slow to cry		1.84 (0.19–17.58)
	Abnormal ($P < .001$)	
	2 Studies: normal control subjects	5.93 (2.75–12.80)
	1 Study: abnormal control subjects	0.34 (0.17–0.68)
Respiratory distress or no breathing after birth		1.84 (0.84–4.21)
	Abnormal ($P = .04$)	
	7 Studies: normal control subjects	2.95 (1.14–7.61)
	2 Studies: abnormal control subjects	0.48 (0.24–0.94)
Hyperbilirubinemia or jaundice		1.39 (0.97–1.97)
	Diagnostic criteria ($P = .05$)	
	8 Studies: narrow diagnostic criteria	1.63 (1.12–2.37)
	2 Studies: broad diagnostic criteria	0.86 (0.53–1.40)
Medical intervention in the first month		1.34 (0.81–2.21)
	Abnormal ($P = .01$)	
	5 Studies: normal control subjects	1.58 (1.09–2.30)
	1 Study: abnormal control subjects	0.18 (0.05–0.67)
Oxygen treatment or resuscitation		1.38 (0.65–2.94)
	Abnormal ($P = .001$)	
	6 Studies: normal control subjects	1.89 (1.06–3.37)
	1 Study: abnormal control subjects	0.22 (0.11–0.46)

[a] Exposure data collection refers to the effect modification by exposure measurement (prospective versus retrospective). Diagnostic criteria refers to the effect modification by diagnostic criteria (narrow versus broad). Multivariate versus univariate analysis refers to effect modification by the degree of control for covariates. Population based refers to the effect modification by population-based versus clinic-based samples. Abnormal refers to the effect modification by use of a normal comparison group versus an abnormal comparison group. None refers to no effect modification ($P < .10$) by any of the above study characteristics.

tism. The association with low birth weight was particularly strong among prospective studies. Birth weight is commonly studied as an indicator of fetal growth and development and is affected by many prenatal factors, only some of which may be etiologically relevant. In addition to autism, low birth weight has been associated with a variety of psychiatric, cognitive, and behavioral problems.[84–93]

Season or month of birth was significantly related to the risk of autism in 6 of 12 studies. Although the seasonal trends varied across studies, March[10,23,60,64] and August[10] were both suggested as birth months associated with an elevated risk of autism. The meta-analysis of season of birth only included a small subset of the studies that examined this association, and it indicated a potential elevated risk of autism associated with summer birth. Although the biological mechanism underlying this association is unclear, a relationship may be caused by seasonal variation in viral or other infections, nutritional factors, or vitamin deficiencies. Therefore, maternal infections and vitamin and nutrient consumption during pregnancy should be examined further in future prospective cohort studies.

Several investigators have questioned the causal nature of the observed relationship between perinatal and neonatal complications and autism. Confounding by birth order has been suggested because prenatal, perinatal, and neonatal complications are more often observed in first-, fourth-, and later-born offspring, and an increased risk of autism has been reported among those who are born first, fourth, and later.[50,71] Although some studies have shown that associations were attenuated and no longer significant after adjusting for parity,[39,59] other studies[50,71] have shown that the positive relationship persists. A second noncausal hypothesis is that obstetrical and neonatal complications may occur as a result of the autistic condition in the offspring or as a consequence of other factors (eg, genetic factors) that are the true causal determinants of autism.[50] In this epiphenomena explanation, perinatal complications simply reflect the abnormalities of autistic fetal development (autism causes suboptimality) or the same familial factors cause both autism and obstetrical and neonatal complications. The study conducted by Bolton et al[50] provided strong evidence in support of the shared-risk hypothesis because there was an association between composite prenatal, perinatal, and neonatal suboptimality and measures of autism severity and familiality, and the suboptimality scores in the cases were highly correlated with that of their affected siblings. In addition, probands with increased prenatal, perinatal, and neonatal complications had more family members with the broader autism phenotype, which was characterized as similar yet milder impairments in language, communication, and social skills or repetitive stereotyped interests and behaviors compared with diagnostic criteria for autism. However, this finding was not replicated in a second study by Zwaigenbaum et al.[71] The shared-risk hypothesis also was supported by the findings in the Zwaigenbaum et al study that indicated more composite prenatal, perinatal, and neonatal adversity among unaffected siblings of children with pervasive developmental disorders that had high

familial loading for the broader autism phenotype.[71]

Methodological limitations that may have impaired the precision and validity of the results of the studies in this review include small sample size, nonnormal control groups (eg, Down's syndrome), broad disease definition, and retrospective parental recall of exposures. Of 64 studies included, only 19 had over 80% power to detect an RR of 2 for an exposure with 10% prevalence. A total of 19 studies used broad diagnostic criteria, resulting in the inclusion of case subjects with other autism spectrum disorders, which may limit the ability to detect associations due to etiologic heterogeneity. A total of 21 studies assessed the exposure variables retrospectively, resulting in the high possibility of recall bias. However, the use of medical records also has the limitation of being incomplete. Finally, the majority of studies included only univariate analyses and did not assess potential confounding. These methodological weaknesses also were likely sources of heterogeneity of effects across studies. A possible additional source of heterogeneity of effects across studies was variability in the definitions of risk factors across studies. In fact, risk factor definitions and criteria often were lacking in the manuscripts reviewed. As mentioned, when possible we analyzed both broad variable definitions (eg, abnormal presentation at birth) and narrow variable definitions (eg, breech presentation).

This meta-analysis has a few limitations. First, only published data were used. Second, of 64 studies reviewed, only 40 reported the data necessary for inclusion in the meta-analysis. Within these 40 studies, the investigators did not report the necessary data for a meta-analysis on all factors examined. And although 40 studies were included in the meta-analysis overall, for each factor there generally were fewer than 6 studies included, limiting the statistical power to detect heterogeneity across studies and potential effect modification by study characteristics. Third, because of the rarity of many of the exposures examined and the small sample sizes in many studies, there were several instances of 0 cell counts within studies. The relatively small addition of 0.5 to the cell counts may have had an impact on the overall results because of the small sample sizes. Fourth, a few studies only reported an effect estimate and an indication of whether the results were statistically significant. In these cases, the CIs were estimated on the basis of assumptions regarding the actual P value ($P = .05$ if significant, $P = .50$ if not significant). In the case of statistically significant findings, these assumptions resulted in estimated confidence limits that were wider, less precise, and therefore more conservative than might have been expected. Fifth, the tests of publication bias were underpowered because of the limited number of studies in each meta-analysis. Finally, many studies simply examined all available perinatal and neonatal data using designs with methodological weaknesses and without a priori hypotheses or knowledge about reproductive epidemiology. As a result, significant associations observed due to chance are possible in this meta-analysis.

The current review and meta-analysis was not restricted to studies with particular methodological strengths. In addition, individual study characteristics were examined in meta-regressions rather than assigning studies aggregate quality scores. These strategies are consistent with the recommendations proposed by the Meta-Analysis of Observational Studies in Epidemiology Group, which advocated the use of broad inclusion criteria for studies along with regression analyses to relate specific study design characteristics to outcome.[94] This maximizes the amount of data available for review. In addition, different methodological considerations are relevant for each exposure. However, the increased probability for heterogeneity of results using the broad inclusion criteria is important to note.

CONCLUSIONS

Autism is a devastating condition with no known cure. The rising prevalence, coupled with the severe emotional and financial impact on the families, underscores the need for large, prospective, population-based studies with the goal of elucidating the early-life modifiable risk factors.

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GAIN DESPITE PAIN: *This weekend I hope to complete my first and, likely, last marathon. As a self-proclaimed non-runner, preparation for running 26.2 miles has not been without some challenges. So far, I have gone through two pairs of shoes, two cortisone injections, one month of physical therapy, and four visits to orthopedic surgeons. As I await the beginning of the race, I keep asking myself why I endure all the pain associated with running. According to an article in* The New York Times *(Fitness & Nutrition: May 16, 2011), why people endure pain while exercising is complicated. For some, the motivation to run or exercise may be derived from a desire to reach a painful state. But, pain is a complex concept. People often report stopping exercise because of pain. Most of the time, however, the signals that trigger us to stop running or other types of exercise are from a group of nerve fibers called ergoreceptors that respond to byproducts released by exercising muscles. The muscles aren't in "pain" but are fatigued. The brain recognizes these signals and slows or stops exercise before muscle damage occurs. However, if an athlete continues to exercise, as elite athletes may do, a second group of nerve fibers, the nociceptive nerve fibers, which respond to much higher levels of muscle metabolites than the ergoceptive fibers, can be triggered. Nociceptive signals are associated with deep muscle pain. This has been confirmed in experiments in which metabolites from fatigued muscle cells were injected into the thenar eminence of healthy adults. At low concentrations, subjects complained of a sensation of heaviness or exhaustion. At higher concentrations the subjects complained of heat and an aching sensation. While muscle fatigue, interpreted as pain, is the body's way of telling us to stop exercising, many athletes continue to exercise knowing the satisfaction of feeling exhausted at the end of a workout. Others continue through the fatigue waiting for the euphoria that can accompany intense exercise. As for me, I am not looking to experience true deep physical pain when I run in the marathon. However, I look forward to both the intense satisfaction from finishing the race despite the fatigue and the reward of a "runners high".*

Noted by LHC, medical student (want to add this)