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Pre-, peri- and neonatal risk factors for autism

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Key words
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Conflict of interest
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Abstract

Objective. To identify pre-, peri- and neonatal risk factors for pervasive developmental disorders (PDD). *Methods*. We 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. *Results*. During 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. *Discussion*. Despite 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 hypothsesis 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.

Abbreviations: AOR, adjusted odd ratio; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases; IQ, intellectual quotient; LBW, low birthweight; PDD, pervasive developmental disorders.

Introduction

Autism and other pervasive developmental disorders (PDD) are common behavioral syndromes characterized by impairments in social interaction, abnormalities in verbal and nonverbal communication, and restricted and stereotyped interests and behaviors. Their onset occurs in early childhood and often results in severe lifelong impairments. In the USA, the Autism and Developmental Disabilities Monitoring Network reported an overall average prevalence of autism spectrum disorders in nine of 1000 children aged 8 years, with a 57% increase in prevalence between 2002 and 2006 (1), which demostrates that PDD is an urgent public health concern (1).

The first research on a link between complications during pregnancy and autism by Pasamanick et al. dates back to 1956, only a few years after the syndrome was first described (2). Since then, various conclusions have been suggested in studies on autism risk factors but have failed to clarify the relation between autism and adverse exposures during the pre-, peri- and neonatal periods. Increasing evidence also suggests a role of genetic factors in the origins of autism. Therefore, it remains unclear whether certain complications at birth are

causal, play a secondary role in shaping clinical expression in individuals with genetic vulnerability, or represent some of the shared causal factors in the development of PDD.

Numerous considerations surrounding PDD make research on pre-, peri- and neonatal factors worthwhile. Firstly, concordance in monozygotic twin pairs is incomplete, suggesting that nonheritable factors contribute to the risk of autism (3). For example, pregnancy-induced central nervous system insults may result in relevant epigenetic changes. Secondly, increasing evidence indicates that the prevalence of PDD has increased over the past 20 years at a rate not explained by improved detection of PDD in the population (4). This phenomenon raises the probability that environmental factors play a role (5). Thirdly, a growing body of literature suggests that histological and anatomical disturbances in the brain play an important role in the etiology of PDD (6,7). Such research suggests that, irrespective of the cause of these structural anomalies, the etiologically relevant period could be the early in utero stages, similar to auto-immune processes during pregnancy that lead to biological differences (8). Fourthly, the proportion of children with a major gene defect is limited to a small proportion of PDD cases. Thus, a multifactorial approach towards PDD risk may serve as a more appropriate perspective in the study of the genesis of autism. Additionally, these genetic anomalies appear not to be specific for autism but rather to share a role in the etiology of intellectual disability (9) and perhaps schizophrenia (10). An explanation for how two children with the same genetic vulnerability develop autism rather than intellectual disability or schizophrenia remains elusive. Finally, identification of environmental factors for autism during pregnancy carries clinical implications in terms of primary prevention.

To draw conclusions about the role of obstetric factors and the magnitude of their effect, analysis of the current data is warranted. Brasic and Holland (11) detailed a reliable procedure to identify case–control reports to be used for meta-analytic purposes. However, a review of 156 articles (11) yielded only two studies that fulfilled that defined set of criteria, and those two studies had discordant results (12,13). Kolevzon et al. defined another set of criteria (14). Seven studies from various countries were selected. Four of the seven studies were prospective, population-based cohort studies; the others were retrospective. Three studies had a partially overlapping sample. The authors identified the following four categories of risk factors: advanced parental age; maternal place of birth outside Europe or North America; low birthweight (LBW) and preterm delivery; and intrapartum asphyxia. Recently, Gardener et al. published a systematic review and meta-analysis of 64 studies published prior to March 2007 (15). Although those studies covered a full scope of pregnancy and birth complications, the authors presented results on pregnancy-related risk factors only. Criteria for inclusion in their meta-analysis were less strict than those of previous studies (11,14). The selected studies did not always use operational criteria for PDD defined by International Classification of Diseases, Tenth Revision (ICD-10; World Health Organization, 1993) and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994; 16,17). Forty studies were eligible for that meta-analysis (15), and the authors provided information about relative risk level and confidence intervals. For each factor, a summary effect estimate was calculated and heterogeneity was examined. A meta-regression analysis accounted for methodological factors that contributed to study variability. The results of the Gardener study are incorporated into this review.

The present review of case–control studies aimed to estimate the differential impact of pre-, peri- and neonatal factors. Our goal was to identify which factors are relevant to a better understanding of the pathogenesis of PDD and their early detection.

Material and methods

Study selection

Relevant studies on pre-, peri- and neonatal hazards in autism were identified from the bibliographies of recent reviews (11,14,15). Additionally, a PubMed search was conducted through March 2011 using the following keywords: 'autistic disorder', 'Asperger's syndrome', 'prenatal', 'perinatal', 'neonatal', 'obstetric'. 'risk' and 'familial'. A separate search was performed for specific variables, such as 'birth defect' and 'clinical severity'. We selected the case–control studies that explored pre-, peri- or neonatal risk factors. We excluded case reports, letters to the editor, animal models and experiments, genetic studies and studies on biomarkers. We did not include publications on the season of birth, and we determined that research on exposure to toxins during pregnancy would not be exhaustive. Using a similar set of inclusion criteria, our results matched results of the Gardener meta-analysis (15), with the addition of articles published from March 2007 through March 2011. From the body of research selected, we identified the well-designed, population-based studies by using Kolevzon's criteria in addition to the reporting on adjusted odd ratios (AOR; 14). Flowcharts illustrating the inclusion and exclusion criteria are presented in Figure 1.

Data extraction

The following characteristics of each study were recorded: (a) study design, including a prospective vs. a retrospective approach and a description of the databases; (b) sample size and characteristics, including diagnosis classification, clinical assessment, inclusion and exclusion criteria; (c) a description of the control group (healthy controls, IQ matches, siblings); (d) a description of the risk factors, including the format of

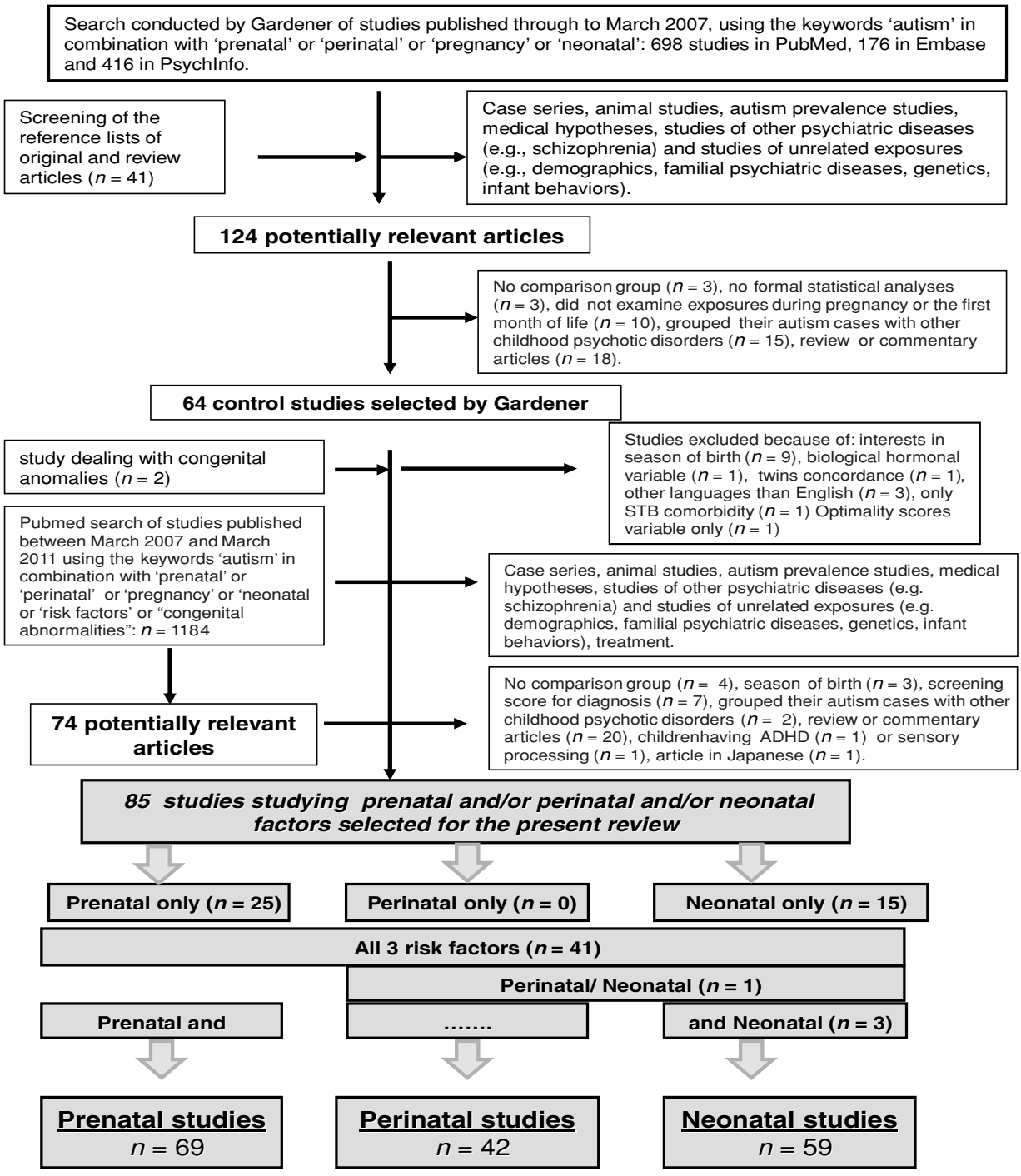

Figure 1. Flowchart of the studies included in the present systematic review of pre-, peri- and neonatal risk factors of pervasive develomental disorders.

these risks and the presence of aggregated scores; (e) source of obstetric information (parental interview, medical record, birth certificate); and (f) statistically significant results with or without multivariate adjustment. For each variable, we distinguished all statistically significant results from nonsignificant results. After a brief analysis of the factors that could explain any inconsistency, we extracted the well-designed, population-based studies for which an independent risk

factor emerged in the adjusted analysis. Unfortunately, the AOR varied according to the design and purpose of each study. Adjustment could be performed with either all significant variables or only some of the well-defined, confounding variables, such as parental age, parity and family factors. A total of 85 studies were included (12,13,18–100).

Results

Prenatal risk factors

In Table 1 we summarize prenatal (familial and pregnancy) risk factors based on Gardener's meta-analysis (15) and on studies published since March 2007. The following four familial factors were consistently associated with autism: advanced maternal age and advanced paternal age, both as independent risk factors; primiparous women; and having a mother born outside Europe, North America or Australia.

Regarding pregnancy, the following three risk factors emerged from Gardener's meta-analysis: bleeding; medication during pregnancy; and diabetes. Recent data confirm the association of medication and bleeding but not diabetes with autism (83). Pre-eclampsia, vomiting, infection and stress during pregnancy still need to be studied more thoroughly. Except for paternal age (over 40 years) with an AOR of around 3, all other documented AORs were between 1.5 and 2.

Perinatal risk factors

Most authors used an empirical definition of the perinatal period that included time of delivery. The purpose of distinguishing this period from the prenatal period lies in the potential contribution of external, mechanical procedures and the consequences of birth complications to the fetus. Although the relation between perinatal and prenatal risk factors is not easy to delineate, complications during delivery could at the very least serve as the observable event of a final, causal pathway, thus revealing previously unnoticed prenatal insults or abnormal fetal development. We present the various perinatal risk factors that emerged in more than two publications and distinguish a pathological duration of pregnancy (preterm and post-term pregnancies) and delivery-related risk factors (Table 2). During the perinatal period, the predominant risk factors were preterm birth, breech presentation and planned cesarean section. All the documented AOR were between 1.3 and 2.8. Nevertheless, in a stratified analysis the AOR for preterm birth increased by as much as 5 in a group of girls born before 33 weeks (72).

Neonatal risk factors

Numerous neonatal factors were suspected and investigated as possible risk factors for autism. We classified them as follows: (a) LBW and size; (b) poor condition at birth, including low Apgar scores and hypoxia; and (c) other conditions, such as hyperbilirubinemia, encephalopathy and birth defects. Table 3 lists the potential risks, including positive and negative findings, from studies of these potential risk factors. During the neonatal period, the risk factors for PDD were low Apgar scores, neonatal encephalopathy, hyperbilirubinemia, birth defect and baby small for gestational age. The documented AORs were below 3 for most variables, but between 3 and 5 for neonatal encephalopathy and up to 9 for hyperbilirubinemia in children born at term.

Low birthweight, usually defined as less than 2500 g, led to inconsistent results. Nevertheless, in a stratified analysis, Schendel et al. credited LBW with an independent twofold increased risk for autism in children born at term and a 7.1 risk for girls born at term (72). Moreover, four population-based studies reported an association between autism and being small for gestational age (usually defined as a weight at birth less than 2 SD below the expected weight on customized curves). No studies have yet explored intrauterine growth restriction.

Discussion

No individual factor in the neonatal and perinatal periods has been consistently validated as a risk factor for autism. However, some have been associated with autism in several studies and should be considered as potential risk factors that provide small contributions to the etiology or causal pathway of autism (Table 4). Although heterogeneous results implicate a variety of events, the differences observed in the optimality scores indicate that rather than focusing on a single factor, future studies should investigate combinations of factors.

Some of the risk factors listed in Table 4 warrant individual discussion. Firstly, the prevalence of cesarean sections has increased in recent decades, for both social and medical reasons. The current data do not enable us to untangle the true effect of cesarean section from the underlying indications to this operative procedure (such as failure to progress in labor, fetal distress, multiple pregnancies, breech presentation and the increasing trend of women requesting a cesarean section). It appears that if mechanical interventions in delivery serve as environmental factors, the magnitude of those effects is low. Progress in neonatal management has led to increased survival of preterm infants, but as a consequence of this a growing number of severe disabilities may be anticipated during childhood. The contribution of increasing survivors of extreme prematurity to the dramatically increasing prevalence of autism has to be questioned. Regarding prematurity, evidence that moderate preterm birth (34–37 weeks gestation) is an independent risk factor has only emerged in three studies and has carried a moderate effect magnitude. However, the risk seems to increase and to be more reliable in cases of more severe preterm birth. Similar observations can be made for LBW babies. However, it is difficult to

Table 1. Prenatal risk factors for autism as reported by Gardener (13) or in at least two recent studies (since March 2007) after adjusted analyses.

Risk factors	Positive studies (univariate analysis, since March 2007)	Negative/null studies (univariate analysis, since March 2007)	P/T[a]	Adjusted effect estimates[b]
Familial risk factors				
Advanced maternal age	Bilder (2009; 79), Buchmayer (2009; 83), Burstyn (2010; 91), Croen (2007; 64), Dawson (2009; 80), Durkin (2008; 76), Grether (2009; 84), Haglund (2011; 99), King (2009; 81), Mann (2009), Shelton (2010; 87), Williams (2008; 69)	Croen (2008; 73), Hultman (2011; 93), Karmel (2010; 92), Tsuchiya (2008; 74), Sasanfar (2010; 86), Zhang (2010, 95)	20/47	Gardener (2009; 15) (>35 vs. <35): 1.6 (1.32–1.95)
				Gardener (2009; 15) (>40 vs. <30): 2.1 (1.48–2.86)
Advanced paternal age	Croen (2007; 64), Dawson (2009; 80), Durkin (2008; 76), Grether (2009; 84), Hultman (2011; 93), King (2009; 81), Sasanfar (2010; 86), Shelton (2010; 87), Tsuchiya (2008; 74), Williams (2008; 69), Zhang (2010, 95)		15/20	Gardener (2009; 15) (35+ vs. 25–29): 1.34 (1.16–1.54) Gardener (2009; 15) (40+ vs. <30): 3.10 (0.95–9.49)
Mother born abroad	Buchmayer (2009; 83), Haglund (2011; 99), Williams (2008; 69), Hultman (2011; 93),		7/9	Gardener (2009; 15): 1.58 (1.14–2.19) Haglund (2011; 99): 2.2 (1.6–3.1)
Parity	Bilder (2009; 79), Croen (2008; 73), Dawson (2009; 80), Durkin (2008; 76), Hultman (2011; 93), Sasanfar (2010; 86), Zhang (2010, 95)	Buchmayer (2009; 83), Burstyn (2010; 91), Haglund (2011; 99)	15/30[c]	Gardener (2009; 15): first vs. ≥ third 1.61 (1.42–1.82)
Pregnancy risk factors				
Diabetes		Buchmayer (2009; 83), Burstyn (2010; 91), Dodds (2011; 100)	1/9	Gardener (2009; 15): 2.07 (1.24–3.47)
Bleeding	Burstyn (2010; 91), Dodds (2011; 100)	Bilder (2009; 79), Burstyn (2010; 91),	8/21	Gardener (2009; 15): 1.81 (1.14–2.86)
Psychotropic drugs	Dodds (2011; 100)		6/16	Gardener (2009; 15): 1.46 (1.08–1.96)
Pre-eclampsia	Buchmayer (2009; 83), Burstyn (2010; 91), Dodds (2011; 100), Mann (2010, 90)		5/17	Buchmayer (2009; 83): 1.64 (1.08–2.49) Burstyn (2010; 91):1.49 (1.00–2.23) Mann (2010, 90): 1.69 (1.26–2.28)

Other risk factors with at least one positive result reported since March 2007 and no more than one significant AOR (P/T) are as follows: hypertension/edema (*n*=2/15); infection (5/20); nausea (3/8[c]); stress during pregnancy (3/4); Rhesus sensitivity (2/11); smoking during pregnancy (*n*=2/10); threatened abortion (3/4); and weight gain during pregnancy (2/6).

Other risk factors with no recent positive results and for which no statistically significant AOR was reported by Gardener are as follows (number of studies): fever (*n*=5); physical injury (*n*=4); anemia (*n*=4); proteinuria (*n*=4); any illness during pregnancy (*n*=6); placental complication (*n*=9); number of prenatal visits (*n*=2); 1+ prenatal complications (*n*=2); genitourinary tract infection (*n*=3); previous miscarriage (*n*=40); and previous fetal loss (abortion, miscarriage, stillbirth; *n*=15).

Risk factors not evoked by Gardener and examined in only single studies are as follows: work with computers (95); X-ray exposure (95); tocolytic therapy (95); malnutrition (95); oligoamnios (79); and ultrasound exposure (85).

[a]Statistically significant positive results/total.

[b]Effect estimates were Relative Risk and Odds Ratio. When significant, only Gardener's AOR is indicated for one risk factor.

[c]Indicates that *p*-value includes positive/negative and/or mixed results.

Table 2. Perinatal risk factors for autism, as reported in at least two positive studies.

Risk factors	Positive studies (univariate analysis)	Negative or null studies (univariate analysis)	P/T[a]	Adjusted effect estimates[b]
Prematurity and postmaturity				
Preterm birth				
<37 weeks	Brimacombe (2007; 63), Buchmayer (2009; 83), Dodds (2011; 100), Durkin (2008; 76), Guillem (2006; 62), Finegan (1979; 21), Haglund (2011; 99), Hultman (2002; 44), Maimburg (2006; 61), Mann (2010, 90), Wilkerson (2002; 45), Williams (2008; 69)	Bilder (2009; 79), Burstyn (2010; 91), Cryan (1996; 13), Eaton (2001; 41), Juul-Dam (2001; 40), Lord (1991; 32), Laxer (1988; 28), Larsson (2005; 50), Schendel (2008; 72), Stein (2006; 57), Wier (2006; 59)	12/23	Buchmayer (2009; 83),[c]: 1.44 (1.07–1.94) Durkin (2008; 76): 1.4 (1.2–1.17) Williams (2008; 69): 2.2 (1.5–3.5)
<35 weeks	Larsson (2005; 50), Zhang (2010, 95)	Eaton (2001; 41)	2/3	Larsson (2005; 50): 2.57 (1.64–4.03)
<33 weeks	Schendel (2008; 72), Eaton (2001; 41)	Wier (2006; 59), Karmel (2010; 92)	2/4	Schendel (2008; 72),[d]: 5.4 (1.1–27.7)
<28 weeks <26 weeks	Durkin (2008; 76), Johnson (2010; 88)		1/1 1/1	Durkin (2008; 76): 2.8 (1.6–3.9)
Post-term	Cryan (1996; 13), (male) Laxer (1988; 28), Lobasher (1970; 16), Lord (1991; 32), Sugie (2005; 56), Zambrino (1997; 37)	Bryson (1988; 27), Finegan (1979; 21), Juul-Dam (2001; 40), Hultman (2002; 44), Larsson (2005; 50), Mason-Brothers (1990; 30), Maimburg (2008; 75), Stein (2006; 57), Zhang (2010, 95)	6/15	
Delivery-related risk factors				
Breech presentation	Bilder (2009; 79), Burstyn (2010; 91), Finegan (1979; 21), Larsson (2005; 50), Levy (1988; 29), Maimburg (2006; 61), Wilkerson (2002; 45)	Deykin (1980; 23), Eaton (2001; 41), Gillberg (1983; 12), Juul-Dam (2001; 40), Lord (1991; 32), Mason-Brothers (1990; 30), Matsuishi (1999; 39), Piven (1993; 34), Stein (2006; 57), Bryson (1988; 27)	7/17	Burstyn (2010; 91): 1.31 (1.02–1.69) Bilder (2009; 79): 2.10 (1.11–3.97) Larsson (2005; 50): 1.63 (1.18–2.26)
Induced labor	Dodds (2011; 100), Glasson (2004; 48); Juul-Dam (2001; 40)	Burstyn (2010; 91), Brimacombe (2007; 63), Laxer (1988; 28), Mason-Brothers (1990; 30), Maimburg (2008; 75), Stein (2006; 57)	3/9	Dodds (2011; 100): 1.22 (1.03–1.44)
Precipitous labor	Finegan (1979; 21), Juul-Dam (2001; 40)	Deykin (1980; 23), Glasson (2004; 48), Stein (2006; 57)	2/5	
Prolonged labor	Juul-Dam (2001; 40), Finegan (1979; 21), Eaton (2001; 41), Karmel (2010; 92), Brimacombe (2007; 63), Wilkerson (2002; 45)	Deykin (1980; 23), Dodds (2011; 100), Laxer (1988; 28), Lord (1991; 32), Mason-Brothers (1990; 30), Stein (2006; 57)	5/11	
Cesarean section, all indications	Bilder (2009; 79), Brimacombe (2007; 63), Dodds (2011; 100), Eaton (2001; 41), Hultman (2002; 44), Zhang (2010, 95)	Burstyn (2010; 91), Finegan (1979; 21), Gillberg (1983; 12), Laxer (1988; 28), Lord (1991; 32), Mason-Brothers (1990; 30), Matsuishi (1999; 39)	6/13	Hultman (2002; 44): 1.6 (1.1–2.3)
Scheduled cesarean	Burstyn (2010; 91), Glasson (2004; 48), Haglund (2011; 99), Maimburg (2008; 75),		4/4	Glasson (2004; 48): 1.83 (1.32–2.5) Burstyn (2010; 91): 1.23 (1.01–1.49)

Table 2. Continued.

Risk factors	Positive studies (univariate analysis)	Negative or null studies (univariate analysis)	P/T[a]	Adjusted effect estimates[b]
Meconium	Bryson (1988; 27), Matsuishi (1999; 39)	Bilder (2009; 79), Finegan (1976), Gillberg (1983; 12), Levy (1988; 29), Lord (1991; 32), Maimburg (2006; 61), Mason-Brothers (1990; 30), Piven (1993; 34)	2/10	
Fetal distress	Glasson (2004; 48), Hultman (2010; 93),	Bilder (2009; 79), Brimacombe (2007; 63), Sugie (2005; 56)	2/5	Glasson (2004; 48): 1.52 (1.12–2.06) Hultman (2010; 93): 1.44 (1.02–2.05)

Delivery-related risk factors for autism that resulted in one positive result are as follows: cephalo-pelvic disproportion (48); cord complication (12,18,20,21,22,28,29,30,32,34,39,40,48,57,95); epidural anesthesia (12,20,27,48); forceps (12,18,21,23,28,30,32,34,40,48,57,94,99); placental insufficiency (41); placental abruption (30,57); postpartum hemorrhage (22,29,39,48,61); premature rupture of membranes (30,57,48,95); preterm birth <31 weeks (100); and unscheduled cesarean (22,48,57,61,99).

Delivery-related risk factors for autism that resulted in no positive results are as follows: vacuum extraction (12,21,23,32,34,40,44,48,57,61); vaginal birth after previous cesarean section (79); acidosis with a pH <7.20 in cord blood (61); pathological fetal heart rate in labor (61); umbilical cord infection (57); placenta calcified (21); abnormal placenta (57); placenta previa (13,27); placental infarcts (28,83); infected amniotic fluid (57); puncture of fetal membranes (61); general anesthesia (21,32,48); anesthesia, nonspecific (27,34) and trauma during delivery (12,21,28,34,40,49,83); and preterm birth <36 weeks (38).

[a]Statistically significant positive results/total.

[b]Effect estimate were Relative Risk and Odds Ratio.

[c]Adjusted for mother/pregnancy characteristics only.

[d]Girls only.

Table 3. Neonatal risk factors for autism, as reported in at least two positive studies.

Risk factors	Positive studies (univariate analysis)	Negative or null studies (univariate analysis)	P/T[a]	Adjusted effect estimates[b]
Birthweight and growth				
Low birthweight	Burd (1999; 38), Burstyn (2010; 91), Croen (2002; 43), Deykin (1980; 23), Eaton (2001; 41), Finegan (1979; 21), Haglund (2011; 99), Hultman (2002; 44), Hultman (2010; 93), Karmel (2010; 92), Knobloch (1975; 19), Larsson (2005; 50), Maimburg (2006; 61), Schendel (2008; 72)	Bilder (2009; 79), Brimacombe (2007; 63), Croen (2005; 52), Dodds (2011; 100), Juul-Dam (2001; 40), Levy (1988; 29), Mason-Brothers (1990; 30), Mann (2010; 90), Wier (2006; 59), Williams (2008; 69), Stein (2006; 57), Zhang (2010; 95)	14/27	Burstyn (2010; 91): 1.3 (1.1–1.75) Maimburg (2006; 61): 3.0 (1.7–5.1) Schendel (2008; 72),[d,f]: 7.1 (1.6–32.6)
Lower birthweight	Burd (1999; 38), Karmel (2010; 92), Mann (2010; 90), Mason-Brothers (1990; 30),[e] Wilkerson (2002; 45)	Bryson (1988; 26), Cryan (1996; 13), Croen (2005; 52, 2007; 64, 2008; 73), Gillberg (1983; 12), Glasson (2004; 48), Links (1980; 25), Torrey (1975; 20), Lobasher (1970; 18), Lord (1991; 32), Sugie (2005; 56)	5/17	
Small for gestational age	Buchmayer (2009; 83), Eaton (2001; 41), Hultman (2002; 44), Hultman (2010; 93), Larsson (2005; 50)	Durkin (2008; 76), Dodds (2011; 100), Gillberg (1983; 12), Glasson (2004; 48), Haglund (2011; 99), Karmel (2010; 92), Mann (2009), Piven (1993; 34), Williams (2008; 69)	5/14	Buchmayer (2009; 83): 1.86 (1.32–2.63) Hultman (2002; 44): 2.1 (1.1–3.9) Larsson (2005; 50): 1.32 (1.0–1.68)

Table 3. Continued.

Risk factors	Positive studies (univariate analysis)	Negative or null studies (univariate analysis)	P/T[a]	Adjusted effect estimates[b]
Head circonference	Courchesne (2003; 46), Karmel (2010; 92)	Glasson (2004; 48), Hazlet (2005; 55), Hultman (2002; 44), Laxer (1988; 28), Mason-Brothers (1990; 30), Torrey (2004; 49)	2/8	
Poor condition at birth				
Suboptimal Apgar 5	Bryson (1988; 26), Buchmayer (2009; 83), Burstyn (2010; 91), Finegan (1979; 21), Hultman (2002; 44), Larsson (2005; 50), Maimburg (2006; 61)	Bilder (2009; 79), Bryson (1988; 26), Burd (1999; 38), Dodds (2011; 100), Eaton (2001; 41), Gillberg (1983; 12), Haglund (2011; 99), Torrey (1975; 20), Juul-Dam (2001; 40), Karmel (2010; 92), Levy (1988; 29), Maimburg (2008; 75), Mason-Brothers (1990; 30), Matsuishi (1999; 39), Piven (1993; 34), Williams (2008; 69)	7/23	Larsson (2005; 50): 1.97 (1.15–3.36) Hultman (2002; 44): 3.2 (1.2–8.2)
Suboptimal Apgar 1	Finegan (1979; 21), Glasson (2004; 48), Williams (2008; 69)	Burd (1999; 38), Eaton (2001; 41), Torrey (1975; 20), Karmel (2010; 92), Levy (1988; 29), Maimburg (2008; 75), Mason-Brothers (1990; 30), Matsuishi (2005)	3/11	
Transfer to special care	Guillem (2006; 62), Deykin (1980; 23), Maimburg (2006; 61), Matsuishi (2005)	Glasson (2004; 48), Levy (1988; 29), Mason-Brothers (1990; 30)	4/7	Maimburg (2006; 61): 1.8 (1.3–2.7)
Markers of hypoxia				
Lack of first cry, breath or oxygen; blue baby	Brimacombe (2007; 63), Bryson (1988; 27), Glasson (2004; 48), Stein (2006; 57), Zhang (2010; 95)	Deykin (1980; 23), Laxer (1988; 28), Matsuishi (2005), Stein (2006; 57)	5/9	
Respiratory distress syndrome or assisted ventilation or asphyxia	Bryson (1988; 27), Buchmayer (2009; 83), Dodds (2011; 100), Finegan (1979; 21), Juul-Dam (2001; 40), Gillberg (1983; 12), Sugie (2005; 56)	Bilder (2009; 79), Laxer (198), Levy (1988; 29), Lord (1991; 32), Maimburg (2006; 61), Mason-Brothers (1990; 30), Matsuishi (1999; 39), Piven (1993; 34), Sugie (2005; 56), Williams (2008; 69)	7/17	
Other specific conditions at birth				
Hyperbilirubinemia	Buchmayer (2009; 83), Finegan (1979; 21), Juul-Dam (2001; 40), Maimburg (2008; 75), Maimburg (2010; 94), Sugie (2005; 56), Zhang (2010; 95)	Brimacombe (2007; 63), Bryson (1988; 27), Croen (2005; 52), Deykin (1980; 23), Laxer (1988; 28), Lobasher (1970; 18), Lord (1991; 32), Mason-Brothers (1990; 30), Matsuishi (2005), Williams (2008; 69), Piven (1993; 34)	7/18	Maimburg (2008; 75): 3.7 (1.3–10.5) 9 (1.14–71)[f] Buchmayer (2009; 83): 1.32 (1.01–1.72)[c]
Neonatal encephalopathy	Badawi (2006; 58), Buchmayer (2009; 83), Dodds (2011; 100), Maimburg (2008; 75)		4/4	Buchmayer (2009; 83): 3.06 (1.56–5.99) Dodds (2011; 100): 5.59 (2.32–13.51) Maimburg (2008; 75): 3.1 (1.1–8.7)
Birth defects	Buchmayer (2009; 83), Dawson (2009; 80), Dodds (2011; 100), Guillem (2006; 62), Hultman (2002; 44), Lauritsen (2002; 42), Maimburg (2006; 61), Schendel (2009; 82), Stein (2006; 57), Tripi (2008; 71), Wier (2006; 59), Links (1980; 25)	Bilder (2009; 79), Deykin (1980; 23), Juul-Dam (2001; 40), Mason-Brothers (1990; 30)	12/ 16	Dawson (2009; 80): 1.6 (1.1–2.4) Schendel (2009; 82): 1.7 (1.2–2.4) Wier (2006; 59): 1.7 (1.1–2.4) Hultman (2002; 44): 1.8 (1.1–3.1) Maimburg (2006; 61): 1.9 (1.1–3.5)

Table 3. Continued.

Risk factors	Positive studies (univariate analysis)	Negative or null studies (univariate analysis)	P/T[a]	Adjusted effect estimates[b]
Neonatal or congenital infections	Buchmayer (2009; 83), Atladottir (2010; 89)	Bryson (1988; 27), Dodds (2011; 100), Gillberg (1983; 12), Matsuishi (2005), Piven (1993; 34), Williams (2008; 69)	2/8	Atladottir (2010; 89): 1.5 (1.03–2.32)[d]

Neonatal risk risk factors for autism that resulted in one positive result (reference) are as follows: fetal hypoxia (91); gastrointestinal diseases (39,47,57); intracranial hemorrhage (30,39,83,100); hypoglycemia (39,75,83); and Apgar 1<5 (30,39,69).
Neonatal risk factors for autism that resulted in no positive results are as follows: hemolytic disease (21); elevated IgM (39,97); anemia (12,21,27,100); near-death situation (41); poor condition at birth (23); Apgar 5<5 (30,39,69,100) and resuscitation needed (18,27,69); aspiration (21); exchange transfusion (75); difficulties regulating temperature (34); and trauma (83).
[a]Statistically significant positive results/total.
[b]Effect estimates were Relative Risk and Odds Ratio.
[c]Adjusted for mother/pregnancy characteristics only.
[d]Girls.
[e]Males only.
[f]Term birth.

Table 4. Pre-, peri- and neonatal risk factors in autism: summary of the most robust results.

Family factors	Parental age Parity Mother born abroad
Maternal pregnancy factors	Bleeding Pre-eclampsia
Delivery factors	Breech presentation Scheduled cesarean Small for gestational age
Baby with adverse conditions	Prematurity Low Apgar Hyperbilirubinemia Low birthweight/slow growth Encephalopathy Birth defects

consider preterm birth and LBW as truly being independent from other potential risks, such as being small for gestational age at birth. The phenomenon of being small for gestational age has heterogeneous etiologies, including genetic factors and placental insufficiency (44,101); therefore, the reason for an increased risk of autistic disorders among these children is not clear. In the study by Durkin et al., the mean parental age of autistic children was correlated in unadjusted analyses with birthweight, gestational age and preterm birth (76). Buchmayer et al. showed that a possible association between autism and preterm birth was mediated by prenatal factors or neonatal complications (83). Mann et al. identified the following three main maternal characteristics that predisposed to LBW and preterm birth (90): maternal genitourinary tract infection (102); antenatal tobacco use (102); and pre-eclampsia and eclampsia (103). Upon assessing these variables as potential risk factors, neither genitourinary tract infections nor antenatal tobacco was associated with an increased risk for autism. In contrast, the presence of pre-eclampsia or eclampsia appeared to be a strong risk factor, only partly mediated by birthweight. Schendel et al. observed that the risk associated with LBW newborns was even higher with other developmental disabilities than it is in autism. This finding led her to hypothesize that coexisting autism as a co-morbidity could be an unrecognized feature of very low birthweight infants and eventual developmental disability (82). Recently, Limperopoulos et al. followed a cohort of preterm children with severe preterm delivery and LBW (less than 1500 g) and found a high prevalence of children with a positive initial screening for autism at 20 months (104). In multivariate analyses, a higher score was associated with LBW and gestational age, male gender, prenatal infection, chorioamnionitis, illness severity on admission and abnormal MRI (cerebellar hemorrhagic injury, combined supra- and infratentorial parenchymal damage). These findings were consistent with a previous study in which an isolated cerebellar hemorrhagic injury was found in one-third of preterm children with a positive autism screening test (105). Another recent study noted that a low Apgar score at one minute was specifically associated with an increased risk for autism among LBW babies (106).

All of these recent studies highlight the possibility that the numerous factors associated with both preterm birth and autistic disorders may be interrelated through causal pathways. For a better appraisal of the magnitude of risk of

preterm birth and LBW for autism, future studies should include children with co-morbid congenital anomalies. Moreover, one likely outcome is that among certain subgroups of children, some of these risk factors may be masked when the study design includes both term and preterm children. As Buchmayer et al. found different contributing factors for preterm vs. term births, future studies should be designed to include stratified analysis of gestational age (83).

Finally, looking for an association between autism and hyperbilirubinemia is worthwhile for several reasons. Hyperbilirubinemia is thought to exert toxicity on the basal ganglia and cerebellum, two structural brain regions that have been identified as important in the development of autism. Also, a disparity exists concerning the management of this condition, and changes in disease management have led to less aggressive treatment. Such a trend could produce an increment of neurodevelopment sequelae that may account for the increasing prevalence of autism. Hyperbilirubinemia is a neonatal factor that is more distinctive from the prenatal period than are other neonatal factors. Recent, well-designed studies indicate that Rhesus incompatibility might not be the key to understanding hyperbilirubinemia in autism (66,70,73,107). Causes of hyperbilirubinemia in autism require further research.

Discrepancies across studies can partly be explained by the heterogeneity of study design and methodological limitations. Many studies had recruitment and design problems. Firstly, the population of PDD could either be recruited from a population-based registry or from clinical samples at medical centres, inducing unavoidable selection bias. The age at the time of inclusion in studies also led to some differences. Specifically, we may see a possible overestimation of risk factors in younger populations because parents could seek care more rapidly after pre-, peri- and neonatal complications compared with those for whom diagnosis came later (69). On the contrary, it is more difficult to gather valid obstetric information and obtain a reliable diagnosis for older children. The second problem concerns the case ascertainment that led to a great variability between the populations studied. The definition of autism varied according to diagnostic classification. A few studies described a standardized assessment with PDD diagnostic tools, somatic examination for children and new assessments. Most studies based the reliability of diagnosis on retrospective data supplied by parents or medical records. Moreover, depending on authors, the clinical group either constituted children with a broad diagnosis of PDD (52) or a diagnosis restricted to infantile autism (75). Finally, variability of the exclusion criteria (such as co-morbid genetic and neurodevelopmental disorders) may lead to a loss of information about the genesis of autism in some children, especially in those for whom a malformation could be a marker of prenatal insults. Moreover, some evidence points towards a nonspecific impact of perinatal factors on autism and intellectual disability.

The data collection process also was accompanied by various problems. In some studies, data were derived from multiple pieces of clinical information. Other studies were based only on the parents' interview, which may introduce information bias (28,45). The format of the data itself was often problematic (definitions, a lack of cut-off scores, categorical vs. continuous variables). The lack of a standardized measure of exposure impeded comparison among studies. Several studies used an overall optimality score to implicate the role of obstetric complications in autism. Such a score incorporated an aggregated score of various perinatal and obstetric conditions. This approach may have resulted in nondifferential misclassification, preventing a normative definition of the different types of complications, and underestimated true associations with individual factors (12,35,36,108). Moreover, although an item-by-item analysis could be performed, these weighted scales do not cover certain categories of perinatal factors.

The definition of controls was another factor that contributed to variability among studies. The incidence of obstetric complication could be compared with healthy controls, non-autistic disabled patients, siblings or national statistics (63). Using unaffected siblings as controls may help to identify risk factors and to control for hereditary background, family environment and maternal predisposition to complications in pregnancy or birth (21,23,27,30,32,34,35,36,48,108). These studies excluded sporadic cases of autism for which obstetric factors could share the same etiology as autism itself and, generally, such studies were even more difficult to carry out with adequate sample sizes. A large proportion of studies did not use non-affected controls matched for IQ or corrected for sex ratio (21). However, using a group of non-autistic disabled patients may reduce the magnitude of nonspecific factors potentially involved in several neurodevelopmental disorders.

The final limitation in the comparison of these publications lay in the fact that distributions of children with PDD by factors such as birthweight, primiparous pregnancy and parental age have probably changed over the past 20 years. Therefore, statistically significant changes in risk factor prevalence may change the distribution among autistic children and increase the heterogeneity of results in recent studies and older ones. In the future, this concern should encourage the design of new, large, prospective studies rather than a homogenization of older data.

Conclusion

Despite recent advances in autism genetics, this present review indicates that several risk factors, such as those relevant to the pre-, peri- and neonatal period, may confer a small risk

for autism. Nonetheless, distinguishing whether these risks should be regarded as strictly environmental or related to a genetic vulnerability is not possible. Determining the contribution of these risk factors may improve detection, earlier treatment and better prevention of the disease.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Description of the studies included in the reviews according to the following characteristics: country were the study was conducted, first author's name and year of publication, number of subjects (*N*), origins of the obstetrical data, psychiatric diagnosis and classifications used, control population characteristics, intellectual quotient included in the analysis (IQ), neurodevelopmental comorbidities excluded or not, adjusted odd ratio calculated (AOC).

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