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Have Secular Changes in Perinatal Risk Factors Contributed to the Recent Autism Prevalence Increase? Development and Application of a Mathematical Assessment Model

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Abstract

BACKGROUND—A 57% increase in the U.S. prevalence of autism spectrum disorders (ASD) for 8-year-old children born in 1994 versus 1998 was recently reported.

METHODS—To quantify the possible contributions of given risk/predictive factors on the recent ASD prevalence increase, we formulated a mathematical model based on the baseline risk factor prevalence (RFP), the proportionate change in RFP (cRFP), and the magnitude of the association between the risk factor and ASD [estimated relative risk (RR)]. We applied this model to several pregnancy-related factors (preterm, very preterm, low and very low birth weight, multiple birth, cesarean delivery, breech presentation, and assisted reproductive technology use). RFP and cRFP estimates for each factor were obtained from U.S. population-based surveillance datasets. Estimated RRs were obtained from a series of systematic literature reviews.

RESULTS—We estimate that each risk factor examined, alone or in various combinations, accounted for a very small proportion (<1%) of the ASD increase. Additionally, hypothetical scenarios indicate RFP, cRFP, and RR all need to be sizable for a risk factor to appreciably influence ASD prevalence.

CONCLUSIONS—Thus, although various pregnancy factors have been found to be associated with ASDs, the contribution of many of these factors to the recently observed ASD increase is likely minimal.

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Keywords

Autistic Disorder; Prevalence; Pregnancy; Risk Factors

Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders including autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified, characterized by impairments in social interactions and communication and restricted, repetitive and stereotyped patterns of behavior which typically emerge in the first few years of life (1). The reported prevalence of ASD has increased markedly in recent decades, both in the United States and other industrialized countries. Although prevalence rates for childhood autism generally ranged from 2 to 5 cases per 10,000 children in studies conducted during the 1960s to 1980s (2–5), studies published in the late 1990s to early 2000s reported prevalence rates for autism and/or ASDs as much as 10-fold higher (30–60 cases per 10,000) than the earlier estimates (5–10). Most recently, prevalence rates reached 1% (11, 12).

The reasons for the prevalence increase are not completely understood, but likely include a broadening of diagnostic criteria. Before 1980, no standard diagnostic criteria were available for autism. Additionally, although the American Psychiatric Association did publish standard criteria in 1980, these have been purposefully revised several times since 1980: The criteria for autistic disorder were redefined to include a wider array of behaviors; and milder disorders on the autism spectrum were added (1, 13–15). The term “autism spectrum disorder” thus gained favor in clinical practice. In concert with these shifts in diagnostic criteria, there were concurrent increases in available diagnostic services, increased awareness of the condition among parents and medical and education professionals, a growing acceptance that autism can co-occur with other conditions, and the addition of autism as a specific special education eligibility category in public school programs in the early 1990s (13–16). Additionally, the ongoing rise in ASD prevalence has raised concerns about the possibility that etiologic risk factors might have increased and are contributing to the trend.

Recent U.S. data from the Autism and Developmental Disabilities Monitoring (ADDM) Network indicate that the trend in ASD prevalence has not abated. The ADDM system tracks ASDs in children aged 8 years residing in select U.S. population-based sites through health and education record reviews. Nine of 10 ADDM sites that collected data for the 2002 and 2006 surveillance years reported an average ASD increase of 57% (from 6.0 to 9.4 ASD cases/1000 children) (12). This is a large increase given the brief time period and the fact that it is several years beyond the widespread policy changes that directly impacted ASD diagnostic and education classifications. Thus, these data renew questions about what factors underlie the trend.

Herein we consider a subset of perinatal factors that have been implicated as risk factors for ASDs in select studies: Preterm and very preterm delivery, low and very low birth weight (LBW, VLBW), multiple birth, cesarean delivery, breech presentation, and use of assisted reproductive technology (ART) for conception. The existing evidence for each of these factors as being causal must be considered incomplete in that inconsistent findings across

studies have been reported and examination of specific population subgroups based on underlying genetic susceptibility is lacking. Nonetheless, the cumulative evidence to date points to the perinatal period as a key time frame for understanding risk factors for ASD and these perinatal risk factors are among the most well-studied to date (17). Moreover, because nearly all of these perinatal factors have been reported to have increased during part or all of the past two decades (18, 19), they are logical candidate examples to consider as potentially contributing to the increased prevalence of ASDs.

In this study, we specifically focused on the 57% increase noted in the most recent ADDM report (2006 reporting year versus 2002). Because ADDM is based on 8-year old children, the corresponding birth years for these groups were 1994 and 1998. We considered the U.S. prevalence estimates and percentage change in prevalence from 1994 to 1998 in preterm and very preterm delivery, LBW and VLBW, multiple birth, cesarean delivery, breech presentation, and ART use. We further considered how changes in each factor might have contributed to excess cases of ASD between the 1994 and 1998 U.S. birth cohorts. Beyond our specific assessment of these factors, we developed and present a framework to consider the likely impact on the ASD trend of a range of hypothesized risk factors.

METHODS

The study methods are conceptualized in three distinct stages: (1) Formulation of a mathematical model to describe the contribution of a given risk/predictive factor in explaining an ASD prevalence increase in a hypothetical population based on various risk factor attributes; (2) assessment of existing population-based data on prevalence of select prenatal and perinatal risk factors associated with ASD; and (3) systematic literature reviews to assess the magnitude of associations between select prenatal and perinatal risk factors and ASD.

Formulation of Mathematical Model

The objective for developing the model was to describe how a change in a given risk factor for ASD could influence a change in ASD prevalence. Whether and how much a given risk factor will impact ASD prevalence between two time points depends on three circumstances: (1) The baseline prevalence of the risk factor, (2) the change in the prevalence of the risk factor during the time period of interest, and (3) the magnitude of the association between the risk factor and ASD, for example as measured by the relative risk (RR).

We considered observed data from ADDM sites that document an average ASD increase of 57% over a four year time period, from 6.0 to 9.4 ASD cases/1,000 children (12). Using 6.0/1000 as the baseline ASD rate, we calculated the percentage change in ASD prevalence expected to occur in a hypothetical population as follows.

1. Given a specified risk factor population prevalence (RFP_0) in the baseline (1994) birth cohort, and a given relative risk for the risk factor–ASD association (RR), we estimated $ASDP_w$, the 2002 ASD prevalence among baseline birth cohort children who are not exposed to the factor, as

$$ASDP_u = \frac{6/1000}{[RR * RFP + (1 - RFP)]}$$

This estimate reflects our assumption of a total ASD prevalence of 6 in 1000 in 2002 and is based on the identity

$$6/1000 = ASDP_e * RFP + ASDP_u * (1 - RFP)$$

where $ASDP_e$ is the baseline prevalence of ASD among children with the exposure. Given the estimate of $ASDP_u$, we then estimated this baseline prevalence of ASD among children with the exposure as

$$ASDP_e = RR * ASDP_u$$

2. Let RFP_I be the population risk prevalence of the exposure of interest for the second birth cohort, in our example those children born in 1998, and $cRFP$ represent a specified percentage change in the RFP over the time period of interest such that

$$cRFP = \frac{(RFP_1 - RFP)}{RFP}$$

Within a hypothetical population of 100,000 children in the second (1998) birth cohort, we estimated the number with (N_{e1}) and without (N_{u1}) the exposure of interest as

$$N_{e1} = [cRFP * RFP + RFP] * 100,000$$

and

$$N_{u1} = 100,000 - N_{e1}$$

3. Under an assumption that the magnitude of the association between the risk factor and ASD is the same among the two birth cohorts, in other words that the RR is constant, the total prevalence of ASD in the second birth cohort at age 8 years, expressed per 1000 children and defined as $ASDP_I$, can be estimated as

$$ASDP_I = [ASDP_e * N_{e1} + ASDP_u * N_{u1}] / 1000$$

A crucial assumption in the model is that the RR for the association between the risk factor and ASD remains constant across the two birth cohorts. This assumption is likely reasonable if the time period of interest is relatively short, and thus the population of children born at baseline and born at follow-up are likely to be comparable in terms of unmeasured aspects of a given risk factor that might influence its association with ASD. Although the model

does not explicitly account for the impact of having different combinations of multiple risk factors, it is nonetheless possible to use estimates of RFP, cRFP, and RR that are constructed based on one or more risk factor combinations. However, there are fewer empirical data available to inform such combination estimates, and thus, greater uncertainty is introduced in the model. In addition, the model does not account for the potential impact of in- and out-migration on changes in ASD prevalence. In practice, ASD prevalence rates are calculated based on children living within certain geographic boundaries at a point in time and, thus, encompass children who were not born in the area but subsequently moved in and likewise do not include children born in the area who subsequently left. Thus, the estimates are closest to real-life for larger, more stable geographic areas, such as the entire United States versus small local populations with a potentially greater migration impact because of parent decisions related to access and quality of services for children with disabilities.

We applied these calculations to a range of assumptions about the baseline RFP for a risk factor (or combination of risk factors), the cRFP in a given time period, and the RR for the association between the risk factor and ASD. We assessed all combinations of the following risk factor attributes: RFP 1.0%, 5.0%, 10.0%, 20%, and 40%; cRFP 2.0%, 5.0%, 10.0%, 50.0%, and 100%; RR 1.5, 2.5, and 5.0. These represent a range of scenarios, including extreme scenarios such as a prevalent risk factor (40% at baseline) that increases dramatically at follow-up (100% increase) and has a strong association with ASD (RR of 5.0).

Assessment of Existing Data on Select Perinatal Factors

We considered six perinatal risk factors potentially associated with ASD: Conception via ART; preterm delivery (total preterm <37 weeks' gestation; moderately preterm 32–36 weeks' gestation; very preterm <32 weeks' gestation); LBW at delivery (total LBW <2500 g; moderately LBW 1500–2499 g; VLBW <1500 g); cesarean delivery; breech presentation before or at delivery; and multiple birth. U.S. population-based data for the number of infants born annually who were conceived by ART are available from the National ART Surveillance System (NASS) published reports (20, 21); the first complete NASS report was based on 1996 ART procedures and births (20). Population-based data for all other factors of interest and for total U.S. births are available from annual U.S. natality files (National Center on Health Statistics, 1994 and 1998 Public Use Natality Files and 1998 Birth Cohort Linked Birth-Infant Death File).

Using the public-use natality files, we estimated prevalence of each risk factor, other than ART, for children born in 1994 and 1998, that is, birth years corresponding to recent ASD estimates based on children aged 8 years in 2002 and 2006. We assessed these risk factors in several ways: Total prevalence (which by default does not consider whether infants born with or without a given risk factor also had the other risk factors); prevalence limited to each risk factor in absence of the other risk factors of interest; prevalence of having various combinations of two or three risk factors; and prevalence of having any of the five risk factors. For each set of 1994 and 1998 prevalence estimates, we computed percentage change between the two time points.

For each of the 1998 estimates, we also used the linked 1998 natality–infant death file to adjust the risk factor estimates to include only children who survived to age 1 year. These estimates better represent the birth cohort population at risk for an ASD, which is generally diagnosed at age 3 years or later (22, 23). The linked birth–death data file was not available for 1994 births. Thus, we present the 1998 data only to describe the amount of variation between estimates computed using the total birth cohort versus the birth cohort excluding infant deaths.

We used data from NASS reports on number of liveborn infants conceived with ART in U.S. clinics in 1998 to estimate the proportion of U.S. births attributable to ART during this timeframe. We also assessed this attributable proportion based on 1996 NASS data and assumed that the 1994 estimate would be lower than this estimate. Although these data are limited in assessing changes in ART prevalence between 1994 and 1998, they nonetheless inform the likely total prevalence of this risk factor during the general time frame.

Literature Reviews: Associations Between Select Prenatal and Perinatal Risk Factors and ASD

To assess the likely magnitude of associations between each perinatal risk factor and ASD, we systematically searched the peer-reviewed literature for English-language publications in 1994 or later. Search terms included autism combined with each of the following: ART; in vitro fertilization; infertility; preterm; birth weight; breech; cesarean; multiple birth; twin; triplet; and perinatal. Additional articles were identified from citation lists in the initially identified articles. Each article was screened by one of the authors to determine if it qualified for abstraction. Articles that qualified were those with presentation of RRs or related measures of association for one or more ASD–perinatal risk factor associations of interest or included data on either the prevalence of a risk factor among children with and without ASDs or the prevalence of ASD among children with and without a risk factor, such that an estimated RR could be calculated. Information on study type, source population, sample size, risk factor and ASD definitions, confounders considered, prevalence estimates, and RRs or related measures were abstracted from articles identified in the initial screen.

RESULTS

Formulation of Mathematical Model

Table 1 presents the expected increase in ASD prevalence based on 75 scenarios of RFP, cRFP, and RR. These data are also presented graphically in Figure 1. The RFPs range from rare to very common (1%–40%); the cRFPs range from small to very large increases (2%–100%); and the RRs indicate moderate to strong ASD associations (1.5, 2.5, 5.0). At the two extremes (RFP: 1%, cRFP: 2%, RR: 1.5 and RFP: 40%, cRFP: 100%, RR: 5.0), the ASD prevalence increase varies from 0.01% to 61.54%. However, for most scenarios assessed, the expected ASD prevalence increase is quite small; 34 of the 75 scenarios would result in an increase of less than 1%, 40 scenarios would result in an increase of less than 5%, and 56 scenarios would result in an increase of less than 10%.

Overall, 15 scenarios were assessed for each of five RFP estimates. Among the 15 scenarios illustrating uncommon risk factors (RFP = 1%), none resulted in an ASD increase of less than 5% and only three resulted in an increase of greater than 1%. Among scenarios illustrating moderately uncommon risk factors (RFP = 5%), only three resulted in an ASD increase of greater than 5% and only one of these resulted in an increase of greater than 10%. Among scenarios illustrating moderately common risk factors (RFP = 10%), four resulted in an ASD increase of greater than 5% and three resulted in an increase of greater than 10%. Among scenarios illustrating common risk factors (RFP = 20%), five resulted in an ASD increase of greater than 5%, and four resulted in an increase of greater than 10%. Finally, among scenarios illustrating very high prevalence risk factors (RFP = 40%), seven resulted in an ASD increase of greater than 5%, and five resulted in an increase of greater than 10%. Across all RFP groups, those scenarios that did result in a greater than 10% ASD prevalence increase are the least likely real-world scenarios (especially during a short timeframe): large cRFP (50% or 100%) coupled with high RR (5.0) or large RFP (20% or 40%), large cRFP (50% or 100%) and moderate or large RR (2.5 or 5.0).

Assessment of Existing Data on Select Prenatal and Perinatal Factors

The prenatal and perinatal risk factors assessed ranged in baseline (1994) prevalence from less than 1% (ART) to 21% (cesarean delivery; Table 2). In addition to ART, very preterm delivery, VLBW, breech presentation, and multiple birth all had RFPs of less than 5%. In addition to cesarean delivery, total preterm (11%), moderately preterm (9%), total LBW (7%) and moderately LBW (6%) had RFPs of greater than 5%. Various combinations of two or more factors had lower RFPs than those of individual risk factors. The RFP for having any of the risk factors (except ART) was 32%.

The 1994 to 1998 cRFPs ranged from -3.5% to greater than 35%. However, all risk factors or risk factor combinations with cRFPs of greater than 10% had RFPs of less than 5%: Multiple birth (RFP = 2.6%; cRFP = 16.7%); preterm + multiple birth (RFP = 1.4%; cRFP = 25.9%); preterm + LBW + multiple birth (RFP = 1.1%; cRFP = 19.6%); preterm + breech (RFP = 0.9%; cRFP = 18.5%); preterm + cesarean + breech (RFP = 0.8%; cRFP = 21.1%); breech without other factors (RFP = 0.3%; cRFP = 15.6%); and ART (RFP <0.5%; cRFP >35.2%).

For most risk factors and risk factor combinations, the 1998 RFPs based on 1-year survivors were very close to the respective RFPs based on total births. However, because of the high infant mortality rates associated with very preterm delivery and VLBW, the 1-year survivor RFPs were notably lower for these risk factors.

Literature Reviews: Associations Between Select Perinatal Risk Factors and ASD

In all, 266 articles were initially identified and screened for relevant data on associations between ASD and selected risk factors and 40 were fully abstracted (24–63), some for more than one factor (Table 3). The vast majority of studies reviewed were case-control or retrospective cohort analyses in which the prevalence of a given risk factor was assessed in children with and without ASDs or autism. However, we also identified and included 6 follow-up studies in which children born extremely preterm (2 studies) or extremely LBW

or VLBW (4 studies) were later assessed for autism or potential risk for autism based on a screening tool at young ages. Although autism screeners have fairly low positive predictive value at young ages (64, 65), we nonetheless included these studies because there is currently a paucity of prospective data on the associations of interest and thus, these studies offer unique information. Although we were specifically interested in preterm, very preterm, LBW, and VLBW, we included studies with data presentation for various gestational age groupings of less than 37 weeks and birth weight groupings of less than 2500 g. We also included several studies of outcomes related to, but not specific to, breech presentation at birth, such as “nonvertex” or “abnormal” presentation or breech at midgestation. Likewise, there is a dearth of studies specific to ART treatments and we thus included studies with related data on broader groupings of infertility treatment. Most (but not all) studies were population based and, thus, included population-based comparison groups or comparisons with population norms. Sample sizes varied widely and in some studies did not seem to be sufficient to examine the outcomes of interest (as evidenced by imprecise risk estimates or very low numbers of exposed cases; Tables 3 and 4). Most studies included children with a wide birth year range and thus, are potentially limited by unmeasured secular changes in both ASD identification and obstetric practices. More than half of the studies did not control for potential confounders either through matching or analytic adjustment; this was often because the perinatal risk factor of interest here was not the primary factor of interest in the study. Further, in some studies, level of confounder adjustment was different for different perinatal factors (Table 4).

The findings of the abstracted studies are presented in Table 4. From the 22 retrospective studies with data on preterm, moderately preterm, and/or very preterm, the estimated RRs that were either directly presented or calculable from presented risk factor prevalence estimates ranged from below to well above 1.0. Most estimates were greater than 1.0, but suggested only a moderate association with autism or ASD (estimated RRs <3.0). Only one study of total preterm delivery documented a RR estimate above 3.0 [odds ratio (OR) = 4.9], and another study documented RR estimates of greater than 7.0 for two extremely preterm groups. Two prospective follow-up studies of extremely preterm infants also suggested potentially high risks for autism-related characteristics (based on screeners only) in this very select group of children.

Studies that assessed LBW, moderately LBW and/or VLBW presented similar findings. Estimated RRs from 20 retrospective studies primarily ranged from 1.0 to 3.0; only one study reported a higher RR estimate (OR = 4.2) for infants who weighed 1500 to 2000 g. Four prospective studies all suggested potentially high risks for autism or ASD symptoms in children who were born extremely LBW or VLBW.

The 12 studies that assessed multiple birth were inconsistent with six suggesting no association, four suggesting moderate associations (estimated RRs 1.7–2.7) and two suggesting possibly stronger associations (estimated RRs ≥ 4.0). However, one of these latter studies demonstrated a strong association for pervasive developmental disorder, not otherwise specified, but not autism, and the other was from a study with a complex design in which only families with two twin or non-twin siblings, both with or both without an ASD, were sampled. Thus, interpretation of the findings is difficult.

The 12 studies examining cesarean delivery and the 9 studies examining breech or related abnormal birth presentation had a fairly narrow range of RR estimates, with most falling between 1.0 and 2.0. The one study of mid-gestation ultrasounds suggested a notably lower proportion of children with autism were breech at this point in pregnancy than expected based on population norms; however, comparison with the other studies suggests that this finding is not informative to birth presentation.

Finally, the data on ART and autism are as yet quite sparse. Of the four studies reviewed herein, one suggests a potential moderate positive association, but the finding was not significant; one suggests a protective effect; and one suggests no association for ART overall, but a slight to moderate positive association in specific subgroups of women using ART. The remaining study is based on a very small number of exposed cases, but could be viewed as possibly suggestive of an association between ASD and one specific type of ART, namely, intracytoplasmic sperm injection.

DISCUSSION

As summarized in Table 5, for each factor, applying the 1994 RFP, the 1994 to 1998 cRFP, and estimated RRs from available studies of the risk factor–ASD association yields very low estimates of the likely impact the factor had on the recent ASD increase. The data indicate that each factor most likely accounted for less than 1% of the ASD increase. Although the RFP was moderately high for preterm delivery, cRFP and RR estimates were low, with the exception of one outlier. Even if we assumed that outlier represents the true association magnitude, the increase in preterm delivery during our study period would still be expected to result in only a 1.5% concomitant ASD prevalence increase. LBW had a lower RFP and cRFP than preterm, and studies suggested that the RR was similar to that observed for preterm. VLBW and multiple birth both had rather high cRFPs (9% and 17%, respectively) and, although studies of their associations with ASD have been inconsistent, limited studies have suggested the possibility of high RRs for these two outcomes. However, both factors had low RFPs. Thus, even if we assumed the most extreme RR estimates suggested by outlier studies, VLBW would still have accounted for less than a 1% ASD increase. For multiple birth, applying an outlier RR (which was based on an unusual and perhaps questionable study design), would have resulted in less than a 2% ASD increase and more reasonable RR estimates, suggest less than a 1% ASD increase. Although cesarean delivery had a high RFP, the cRFP was near 0% for this factor; thus, it could not have contributed to the ASD trend. Breech presentation had a fairly low RFP, cRFP, and estimated RR and, thus, likely had very little impact on the ASD rate. Despite a current lack of data on the RR for ART, the very low RFP makes it is highly unlikely that increased use of ART had even a 1% impact on ASD prevalence.

Even though it is well known that the perinatal risk factors we examined often co-occur, assessments of various combinations of them or the prevalence of having any one of them suggest that changes in the frequency of these factors had little impact on the current ASD trend. For each combination considered, the RFP, cRFP, or both, were too low to have impacted ASD prevalence in any meaningful way.

Potential limitations should be considered in interpreting our findings. All estimates of the impact of a risk factor on the ASD rate could have been influenced by under- or over-reporting estimates of RFP, cRFP, or RR. All RFP and cRFP estimates, except ART, were from national birth certificate files. Validation studies suggest birth certificate data are highly valid for birth weight, and method of delivery (66, 67). Gestational age is derived from several variables on the birth certificate that have also been found to be accurately abstracted from the prenatal care record (66); however, because these variables depend on maternal recall of last menstrual period and early ultrasound data, some misclassification may have impacted the preterm estimates, particularly for women with later entry into prenatal care. The factor examined here with the greatest concern in terms of data completeness is breech presentation. The sensitivity of malpresentation on the birth certificate has been reported as 65% (66); therefore, the RFP reported here is likely an underestimate. Even so, an increase in the RFP for breech from 4% to 6%, would not have impacted our interpretation. The estimated RFP for ART is from NASS, a system estimated to be more than 90% complete (19–21). Numerous studies were available to assess estimated RRs for preterm, very preterm, LBW, and VLBW and, although there was variation in findings, the majority of studies showed fairly consistent estimates; therefore, we can have a fair level of confidence in the estimated RRs for these factors. Although the available RR data were less consistent for multiple birth and were very sparse and indeterminate for ART, it is highly unlikely that either factor could have contributed much to ASD trends because of the low RFPs. Thus, despite some limitations with the data available to us for this assessment, our findings and interpretation seem to be robust.

The model illustrated in Table 1 could be extended to estimate the impact of other risk factors, combination of risk factors, or identification-related factors. For a candidate risk factor to have had a large influence on the ASD prevalence, the RFP, cRFP, and estimated RR would all need to be fairly sizable. Only one scenario that we assessed (RFP = 40%; cRFP = 100%; RR = 5.0) would result in an ASD prevalence increase close to the recently observed 57% increase and only four additional scenarios would result in an ASD increase above 25%. These scenarios each met at least two of the three most extreme conditions we assessed: RFP of 40%, cRFP of 100%, and RR of 5.0. Although it is difficult to imagine a single environmental risk factor that might meet such criteria, it was beyond the scope of this review to systematically review all factors previously implicated as potential autism risk factors. Additionally, although these extremes would seem unrealistic when applying the model to an assessment of a 4-year prevalence change, as we did, they might not be unrealistic if this model were applied to much longer time periods, such as decades.

We lacked data to subdivide the impact estimates for the perinatal factors we assessed by population characteristics. However, if data were available to derive estimates of RFP, cRFP, and RR, the model could be used to assess the potential impact on various population subsets, such as children born to parents identified as having a genetic variation associated with increased ASD risk. Here we present effects on the total population prevalence, a summary measure across various population subsets.

These findings highlight the complexity in identifying the multiple factors that might contribute to increases in ASD prevalence. Although studies consistently indicate preterm

delivery and LBW are risk factors for ASD and limited studies implicate multiple birth, cesarean delivery, breech presentation, and ART as possible risk factors, none have sufficient values for RFP, cRFP, or RR to have contributed substantively to the recently observed ASD prevalence increase in the U.S. population.

Selected Abbreviations and Acronyms

ADDM	Autism and Developmental Disabilities Monitoring
ART	assisted reproductive technology
ASD	autism spectrum disorder
cRFP	change in RFP
LBW	low birth weight
NASS	National ART Surveillance System
OR	odds ratio
RFP	risk factor prevalence
RR	relative risk
VLBW	very low birth weight

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FIGURE 1.

Estimated relative change in ASD prevalence according to the population prevalence of a risk factor (RFP), the change in risk factor prevalence over time (cRFP), and the estimated relative risk for the association between the risk factor and ASD (RR).

TABLE 1

Estimated risk factor impact on ASD prevalence according to the population prevalence of risk factor (RFP), the change in risk factor prevalence over time (cRFP), and the relative risk for the association between the risk factor and ASD (RR)

Baseline RFP (%)	cRFP (%)	RR	Increase in ASD Prevalence Expected (%)
1.0	2.0	1.5	0.010
1.0	5.0	1.5	0.025
1.0	10.0	1.5	0.050
1.0	50.0	1.5	0.249
1.0	100.0	1.5	0.498
1.0	2.0	2.5	0.030
1.0	5.0	2.5	0.074
1.0	10.0	2.5	0.148
1.0	50.0	2.5	0.739
1.0	100.0	2.5	1.478
1.0	2.0	5.0	0.077
1.0	5.0	5.0	0.192
1.0	10.0	5.0	0.385
1.0	50.0	5.0	1.923
1.0	100.0	5.0	3.846
5.0	2.0	1.5	0.049
5.0	5.0	1.5	0.122
5.0	10.0	1.5	0.244
5.0	50.0	1.5	1.220
5.0	100.0	1.5	2.439
5.0	2.0	2.5	0.140
5.0	5.0	2.5	0.349
5.0	10.0	2.5	0.698
5.0	50.0	2.5	3.488
5.0	100.0	2.5	6.977
5.0	2.0	5.0	0.333
5.0	5.0	5.0	0.833
5.0	10.0	5.0	1.667
5.0	50.0	5.0	8.333
5.0	100.0	5.0	16.667
10.0	2.0	1.5	0.095
10.0	5.0	1.5	0.238
10.0	10.0	1.5	0.476
10.0	50.0	1.5	2.381
10.0	100.0	1.5	4.762
10.0	2.0	2.5	0.261
10.0	5.0	2.5	0.652

Baseline RFP (%)	cRFP (%)	RR	Increase in ASD Prevalence Expected (%)
10.0	10.0	2.5	1.304
10.0	50.0	2.5	6.522
10.0	100.0	2.5	13.043
10.0	2.0	5.0	0.571
10.0	5.0	5.0	1.429
10.0	10.0	5.0	2.857
10.0	50.0	5.0	14.286
10.0	100.0	5.0	28.571
20.0	2.0	1.5	0.182
20.0	5.0	1.5	0.455
20.0	10.0	1.5	0.909
20.0	50.0	1.5	4.545
20.0	100.0	1.5	9.091
20.0	2.0	2.5	0.462
20.0	5.0	2.5	1.154
20.0	10.0	2.5	2.308
20.0	50.0	2.5	11.538
20.0	100.0	2.5	23.077
20.0	2.0	5.0	0.889
20.0	5.0	5.0	2.222
20.0	10.0	5.0	4.444
20.0	50.0	5.0	22.222
20.0	100.0	5.0	44.444
40.0	2.0	1.5	0.333
40.0	5.0	1.5	0.833
40.0	10.0	1.5	1.667
40.0	50.0	1.5	8.333
40.0	100.0	1.5	16.667
40.0	2.0	2.5	0.750
40.0	5.0	2.5	1.875
40.0	10.0	2.5	3.750
40.0	50.0	2.5	18.750
40.0	100.0	2.5	37.500
40.0	2.0	5.0	1.231
40.0	5.0	5.0	3.077
40.0	10.0	5.0	6.154
40.0	50.0	5.0	30.769
40.0	100.0	5.0	61.538

TABLE 2

Prevalence of select prenatal and perinatal factors in 1994 and 1998*

Risk Factor	1994 Prevalence (%)	1998 Prevalence (%)	% Change 1994 to 1998	1998 Prevalence 1- year survivors (%)
Total preterm, <37 wks [†]	11.01	11.59	5.27	11.22
Moderately preterm, 32–36 wks	9.10	9.63	5.82	9.60
Very preterm, <32 wks	1.91	1.96	2.62	1.62
Total LBW, <2500 g	7.28	7.57	3.98	7.18
Moderately LBW, 1500–2499 g	5.95	6.13	3.03	6.07
VLBW, <1500 g	1.33	1.45	9.02	0.11
Multiple birth (plurality ≥ 2)	2.57	3.00	16.73	2.92
Cesarean delivery (primary or repeat)	21.19	21.15	−0.19	21.08
Breech presentation	3.74	3.87	3.48	3.79
Preterm + LBW	4.66	5.01	7.51	4.65
Preterm + multiple birth	1.39	1.75	25.90	1.67
Preterm + LBW + multiple birth	1.12	1.34	19.64	1.26
Preterm + cesarean delivery	3.20	3.65	14.06	3.54
Preterm + breech	0.92	1.09	18.48	1.01
Preterm + cesarean delivery + breech	0.76	0.92	21.05	0.88
Cesarean delivery + breech	3.19	3.25	1.88	3.22
Preterm only (w/o other listed risk factors)	4.78	4.85	1.46	4.86
LBW only (w/o other listed risk factors)	1.69	1.63	−3.55	1.62
Cesarean delivery only (w/o other listed risk factors)	14.70	14.30	−2.72	14.35
Breech only (w/o other listed risk factors)	0.32	0.37	15.63	0.37
Any of the above risk factors	31.58	31.67	0.28	31.37
None of the listed risk factors	68.42	68.33	−0.13	68.63
ART	<0.54 (1996 rate)	0.73	>35.19	Not available

* All estimates except those for ART were derived from public use U.S. natality data files for 1994 or 1998. ART estimates were from the National ART Surveillance System (NASS) in 1996 (first year of complete reporting) and 1998.

[†] Gestational age was calculated based on the estimate of the last menstrual period (LMP) or clinical estimate of gestational age if LMP was missing.

TABLE 3

Summary of studies of risk factor-ASD associations that met study criteria for full abstraction

Author, year	Study population and design, and sample size	Birth years	Outcomes assessed					
			PTD/vPTD	LBW/vLBW	MB	C-S	Breech	ART
Cryan et al., 1996 (24)	Case-control study, Ireland; 49 cases autistic disorder (DSM III) from several clinics; 49 matched controls	Not stated	X					
Burd et al., 1999 (26) and Klug et al., 2003 (25)	Case-control study, North Dakota, USA; 78 cases of ASD (DSM III, IV) from state registry; 390 matched birth population controls	1968–1990	X	X				
Matsuishi et al., 1999 (27)	Case control study, Japan; 18 cases of autistic disorder (DSM-III) from 1 hospital, NICU survivors; 214 controls from same NICU cohort	1983–1987			X	X	X	X
Juul-Dam et al., 2001 (28)	Retrospective cohort analysis, California, USA; 51 autism and 13 PDD-NOS cases (DSM-IV and ADOS) from ongoing study compared with population norms in 1995	Not stated	X	X	X	X	X	X
Eaton et al., 2001 (29)	Retrospective cohort analysis, Denmark; 116 autism and 279 Asperger cases (ICD-8); 102,905 reference births from population	1973–1993	X	X		X	X	X
Greenberg et al., 2001 (30)	Retrospective cohort analysis, Autism Genetic Resource Exchange, USA; 166 children with ASD (ADD); % twin pairs in families selected because 2 siblings have ASD compared with % twin pairs in sample of families in which 2 siblings have diabetes and population norms for twinning in Europe, 1991	Not stated			X			
Hultman et al., 2002 (31)	Nested case-control study, Sweden; 408 cases of infantile autism (ICD-9) from national registry; 2040 matched birth population controls	1974–1993	X	X	X	X		
Croen et al., 2002 (32)	Retrospective cohort analysis, California, USA; 4381 cases full-spectrum autism (DSM III, IV) from state service agency compared with birth population	1989–1994		X	X			
Hallmayer et al., 2002 (33)	Retrospective cohort analysis, Western Australia; 451 ASD cases (DSM) from registry compared with birth population	1980–1995			X			
Cederlund and Gillberg, 2004 (34)	Retrospective review, Sweden; 100 males with Asperger disorder (ICD-10) from clinic compared with population norms in 2001	1967–1988	X	X		X	X	X
Msall et al., 2004 (35)	Follow-up study of ELBW (<1251 g) infants who survived to 8-year, multiple centers, USA; 215 assessed for autism (parent report)	1986–1987		X				
Glasson et al., 2004 (36)	Case control study, Western Australia; 465 ASD cases (DSM) from registry; 1313 matched birth population controls	1980–1995				X	X	X
Larsson et al., 2005 (37)	Case-control study, Denmark; 698 cases infantile autism (ICD-8 or 10) from national registry; 17,450 matched population controls	1973–1994	X	X	X		X	X
Sugie et al., 2005 (38)	Case-control study, Japan; 225 cases of autistic disorder (DSM-IV) from clinic; 1580 typically developing controls assessed at same clinic	1980–1999	X					
Indredavik et al., 2005 (39)	Follow-up of VLBW infants who survived to 14–15 year, Norway; 55 screened for psych symptoms (DSM-IV, ASSQ); 66 term controls w/birth weight >10%ile for gestational age	1986–1988		X				
Guillem et al., 2006 (40)	Retrospective cohort analysis, Isere County, France; 289 cases PDD (French system) from national registry compared with population norms	1980–1993	X					

Author, year	Study population and design, and sample size	Birth years	Outcomes assessed					
			PTD/vPTD	LBW/vLBW	MB	C-S	Breech	ART
Stein et al., 2006 (41)	Case control study, Israel; 206 autism cases (ICD-8, DSM-III, -IV) from parent registry; 152 control births to women working in medical center	1970–1998	X	X				X
Wier et al., 2006 (42)	Case control study, California, USA; 417 ASD cases (ICD-9) from pediatric clinic; 2067 frequency-matched controls	1995–1999	X	X	X			
Maimburg & Vaeth, 2006 (43)	Case control study, Denmark; 473 cases infantile autism (ICD-8, -10) from registry; 4730 matched birth population controls	1990–1999	X	X	X	X	X	
Brimacombe et al., 2007 (44)	Retrospective cohort analysis, New Jersey, USA; 164 ASD cases (DSM-IV, ADOS, ADI-r, ARS) from clinic compared with population norms in 2000	~1983–2001	X	X	X	X		
Hobbs et al., 2007 (45)	Retrospective analysis of ultrasound data, Utah, USA; 45 cases of autistic disorder (DSM-IV) from community sources compared with population norms	1988–2002					X	
Knoester et al., 2007 (46)	Retrospective cohort analysis, The Netherlands; ASD (parent report) compared in 87 ICSI singletons, 81 IVF singletons, 85 naturally conceived singletons, and population norm for ASD	1996–1999						X
Maimburg and Vaeth, 2007 (47)	Case control study, Denmark. 461 cases of infantile autism (ICD-8, -10) from registry; 461 matched birth population controls	1990–1999						X
Schendel and Bhasin, 2008 (48)	Case-control study, metropolitan Atlanta, USA; 565 ASD cases (DSM-IV) from registry; 578 frequency-matched birth population controls	1981–1993	X	X				
Leonard et al., 2008 (49)	Retrospective cohort analysis, Western Australia; 169 ASD w/ID cases (DSM-IV) from agency registry; 217,252 birth population controls without ID	1983–1992	X	X				
Williams et al., 2008 (50)	Case control study, New South Wales, Australia; 182 cases of autistic disorder (DSM-IV) from registry compared with 1996 birth population	1990–1999	X	X	X			
Moster et al., 2008 (51)	Retrospective cohort analysis, Norway. Birth populations linked to insurance registries to assess ASD (n = 425) + other disability rates	1967–1983	X					
Limperopoulos et al., 2008 (52)	Follow-up of VLBW infants who survived to 18–24 mos (corrected age), 2 hospitals, Boston, USA; 91 screened for autism (M-CHAT)	1998–2003		X				
Van Naarden Braun et al., 2008 (53)	Retrospective cohort analysis, 11 sites, USA; 1626 cases of ASD (DSM-IV) from registry compared with population norms	1994			X			
Bilder et al., 2009 (54)	Case-control study, Utah, USA; 132 ASD cases (DSM-IV) from registry; 13,200 matched birth population controls	1994	X	X		X	X	
May-Benson et al., 2009 (55)	Retrospective record review, Massachusetts, USA; 467 ASD cases (clinic eval) from clinic compared with 1000 sensory processing disorder (SPD) cases and population norms	Not stated	X	X		X	X	
Kuban et al., 2009 (56)	Follow-up of extremely preterm infants (<28 wk)s who survived to 2 years (corrected age), 14 centers, USA; 988 screened for autism (M-CHAT)	2002–2004	X					
Boulet et al., 2011 (57)	Retrospective cohort analysis, USA; National Health Interview Survey; total N = 87,578; ~350 w/autism diagnosis (parent reported; exact n not stated)	1979–2002		X				
Hack et al., 2009 (58)	Follow-up of ELBW infants (<1000 g) who survived to 8 year, Ohio, USA; 219 screened for autism and Asperger disorder via Child Symptom Inventory; 176 NBW controls	1992–1995		X				

Author, year	Study population and design, and sample size	Birth years	Outcomes assessed					
			PTD/vPTD	LBW/vLBW	MB	C-S	Breech	ART
Zhang et al., 2010 (59)	Case control study, Han children in China; 95 autism cases (CARS >30) from special education class; 95 frequency-matched controls from regular education class	~1986–2004	X	X		X		
Johnson et al., 2010 (60)	Follow-up of extremely preterm infants (<26 wks), who survived to 11 year, UK and Ireland; 189 screened for ASD and autism (SCQ 15 and 22); 140 term-born controls	1995	X					
Mann et al., 2010 (61)	Retrospective cohort analysis, South Carolina, USA; 472 ASD cases (ICD-9) from Medicaid billing registry; 87,205 birth population controls	1996–2002	X	X				
Hvidtjorn et al., 2010 (62)	Retrospective cohort analysis, Denmark; 3619 ASD cases (ICD-8, -10) from registry compared with birth population controls	1995–2003						X
Dodds et al., 2010 (63)	Retrospective cohort analysis, Canada; 924 ASD cases (ICD-9, -10) from registry; 128,809 birth population controls	1990–2002	X	X	X	X		

ADOS = autism diagnostic observation schedule; ADI-r = autism diagnostic interview revised; ARS = autism rating scale; ART = assisted reproductive technology; ASSQ = autism spectrum screening questionnaire; CARS = childhood autism rating scale; C-S = cesarean section; DSM = Diagnostic and Statistical Manual of Mental Disorders; ELBW = extremely low birth weight; ICD = International Classification of Diseases; ICSI = intracytoplasmic sperm injection; ID = intellectual disability; IVE = in vitro fertilization; LBW = low birth weight (< 2500 g unless otherwise specified); MCHAT = modified checklist for autism in toddlers; NBW = normal birth weight; preterm < 37 weeks gestation unless otherwise specified; NICU = neonatal intensive care unit; PTD = preterm delivery; PDD-NOS = pervasive developmental disorder; not otherwise specified; SCQ = social communications questionnaire; VLBW = very low birth weight (< 1500 g unless otherwise specified); very preterm < 32 weeks gestation unless otherwise specified.

TABLE 4

Findings from abstracted studies

Author, Year	Confounders assessed	Findings
Preterm and very preterm delivery		
Cryan et al., 1996 (24)	Matched for sex, birth year	Preterm 4% autism vs. 6% control, calc RR 0.7
Burd et al., 1999 (26) and Klug et al., 2003 (25)	Matched for birth month and year, and sex.	Preterm 12% ASD vs. 5% control, OR 2.7 (0.97–7.6)
Juul-Dam et al., 2001 (28)	None	Preterm 10% autism vs. 8% PDD-NOS vs. 11% population, calc RR 0.9 (NS) and 0.7 (NS)
Eaton et al., 2001 (29)	None	Preterm RR autism 1.4 (NS), Asp 1.5 (NS)
Hultman et al., 2002 (31)	Matched for sex, birth year, birth hospital; further adjustment for several maternal/perinatal factors.	Preterm 10% autism vs. 6% control (sign); aOR 0.9 (0.5–1.6)
Cederlund and Gillberg, 2004 (34)	None	Preterm 9% Asp vs. 4% population, calc RR 2.3
Larsson et al., 2005 (37)	Matched for sex, birth year, age; further adjustments for perinatal factors, parental psych history, SES	<35 wk: 6% autism vs. 2% control, aRR 2.5 (1.6–3.9); 35–36 wk: 3% vs. 3% aRR 1.1 (0.6–1.8)
Sugie et al., 2005 (38)	None	Preterm 5% autism vs. 5% control, calc RR 1.0
Guillem et al., 2006 (40)	None	Preterm 10% total PDD vs. 12% autism without associated medical conditions vs. 5% population calc RRs: 2.0 and 2.4 (sign)
Stein et al., 2006 (41)	None	Preterm 13% autism vs. 20% control calc RR 0.7 (NS)
Wier et al., 2006 (42)	Freq matched for sex, birth year, birth hospital	Mod preterm 9% ASD vs. 5%, control, calc RR 1.8 (sign); very preterm 2% vs. 1%, calc RR 2.0 (sign)
Maimburg and Vaeth, 2006 (47)	Matched for sex, birth year, birth county; further adjustments for parental age, country of origin, several perinatal factors	Preterm 8% autism vs. 6% control (sign), aOR 1.7 (0.6–4.4)
Brimacombe et al., 2007 (44)	None	Preterm 17% ASD vs. 9% population calc RR 1.9 (sign)
Schendel and Bhasin, 2008 (48)	Freq matched for birth year; further adjustments for multiplicity, parity, sex, child age, birth defects, maternal age, race, education	Mod preterm 9% ASD vs. 9% control, aOR 0.8 (0.5–1.4); very preterm 5% vs. 2%, aOR 1.9 (0.8–4.4)
Leonard et al., 2008 (49)	None, but limited to Caucasian singletons	Mod preterm OR 0.5 (0.2–1.3); very preterm OR 0.8 (0.1–5.5)
Williams et al., 2008 (50)	Sex, multiplicity, maternal age, country origin	Preterm unadjusted OR 2.3 (1.5–3.7) aOR ~2.0 (aOR presented in figure without exact value)
Moster et al., 2008 (51)	Sex, birth year, multiplicity, maternal marital status, age, maternal/paternal education, country of origin	34–36 wk: aRR 0.8 (0.4–1.4); 31–33 wk: aRR 1.0 (0.2–3.0); 28–30 wk: aRR 7.3 (2.7–17.6); 23–27 wk: aRR 9.7 (1.5–36.2)
Bilder et al., 2009 (54)	Matched for sex; further adjustments for maternal age, parity	Preterm 13% ASD vs. 13% control, aOR 0.9 (0.5–1.6)
May-Benson et al., 2009 (55)	None	Preterm 16% ASD vs. 12% SPD vs. 13% population, calc RRs 1.3 (NS), 1.2
Kuban et al., 2009 (56)	None	21% pos MCHAT in total ext preterm sample; 10% pos MCHAT in subset without major motor, cognitive, visual, hearing impair.; no control group but 5.7% pos MCHAT cited from community sample in other study [Kleinman et al., 2008 (64)]
Zhang et al., 2010 (59)	Freq matched for sex, birth year.	Preterm (<35 wks) 17% autism vs. 4% control, OR 4.9 (1.6–15.3)
Johnson et al., 2010 (60)	None	Pos SCQ for ASD in 16% ext preterm vs. 3% control, calc RR 5.3; Pos SCQ for autism in 8% ext preterm vs. 0% control

Author, Year	Confounders assessed	Findings
Mann et al., 2010 (61)	None	Preterm 13% ASD vs. 9% control, calc RR 1.4 (sign)
Dodds et al., 2010 (63)	None	Preterm 8% ASD vs. 6% control, RR 1.4 (1.1–1.8)
Low and very low birth weight		
Burd et al., 1999 (26) and Klug et al., 2003 (25)	Matched for birth month and year, and sex.	LBW 14% ASD vs. 6% control, OR 2.4 (1.1–5.1)
Juul-Dam et al., 2001 (28)	None	LBW 4% autism vs. 0% PDD-NOS vs. 7% population, calc RR autism 0.6 (NS)
Eaton et al., 2001 (29)	None	LBW RR autism 2.8 (sign), Asp 1.5 (NS)
Hultman et al., 2002 (31)	Matched for sex, birth year, birth hospital	LBW 9% autism vs. 5% control, OR 2.2 (1.4–3.2)
Croen et al., 2002 (32)	Sex, multiplicity, parity, maternal age, race, education, birth place	LBW 7% autism vs. 6% population, a RR 1.1 (0.9–1.2)
Cederlund and Gillberg, 2004 (34)	None	LBW 8%, stated to be similar to population estimates (data not shown)
Msall et al., 2004 (35)	None	Parent-reported autism in 4% total ELBW infants, 0.8% ELBW infants w/favorable vision, and 9% ELBW infants with unfavorable vision status; no control group
Larsson et al., 2005 (37)	Matched for sex, birth year, age	2001–2500 g: 6% autism vs. 4% control, RR 1.8 (1.3–2.5); 1501–2000 g: 4% vs. 1%, RR 4.2 (2.7–6.6); <1500 g: 2% vs. 0.6%, RR 4.0 (2.3–6.9)
Indredavik et al., 2005 (39)	None	Symptoms Asp disorder in 7% VLBW vs. 0% control
Stein et al., 2006 (41)	None	LBW 8% autism vs. 13% control, calc RR 0.6 (NS); VLBW 1.9% vs. 1.3%, calc RR 1.5 (NS)
Wier et al., 2006 (42)	Freq matched for sex, birth year, birth hospital	MLBW 6% ASD vs. 4% control, calc RR 1.5 (NS); VLBW 2% vs. 1%, calc RR 2.0 (NS)
Maimburg and Vaeth, 2006 (47)	Matched for sex, birth year, birth county; further adjustments for parental age, country of origin, several perinatal factors	LBW 10% autism vs. 4% control, aOR 3.0 (1.7–5.1)
Brimacombe et al., 2007 (44)	None	LBW 8% ASD vs. 8% population, calc RR 1.0 (NS)
Schendel and Bhasin, 2008 (48)	Freq matched for birth year; further adjustments for multiplicity, parity, sex, child age, birth defects, maternal age, race, education	LBW 12% ASD vs. 5% control, aOR 2.3 (1.3–4.1)
Leonard et al., 2008 (49)	None, but limited to Caucasian singletons	2000–2499 g: 0.9 (0.3–2.5); 1500–1999 g: 0.9 (0.1–6.5); 1000–1499 g: 1.9 (0.3–13.7)
Williams et al., 2008 (50)	None	LBW OR 1.5 (0.8–2.6)
Limperopoulos et al., 2008 (52)	None	25% pos MCHAT in VLBW sample; no control group
Bilder et al., 2009 (54)	Matched for sex; further adjustments for maternal age, parity, gestational age	LBW 11% ASD vs. 6% control, aOR 1.9 (0.97–3.8)
May-Benson et al., 2009 (55)	None	LBW 8% ASD vs. 5% SPD vs. 8% population, calc RRs 1.6 (NS), 1.0; VLBW 1.8% ASD vs. 1.5% SPD vs. 1.5% population, calc RRs 1.2 (NS), 1.2
Boulet et al., 2011 (57)	Child age, sex, race, maternal education, income, survey year	2000–2400 g: aOR for autism 1.4 (0.8–2.7); 1500–1999 g: aOR 2.2 (1.1–4.5); 1000–1499 g: aOR 1.6 (0.5–4.5)
Hack et al., 2009 (58)	Freq. matched for child age, race, sex	Symptoms of autistic disorder 2% ELBW vs. 0.6% NBW, OR 3.1 (0.3–27.9); symptoms of Asp disorder 1% ELBW vs. 0 NBW
Zhang et al., 2010 (59)	Freq. matched for sex, birth year; further adjustments for paternal age	LBW 20% autism vs. 13% control, aOR 1.5 (0.7–3.1)
Mann et al., 2010 (61)	None	LBW 13% ASD vs. 9% control, calc RR 1.4 (sign)
Dodds et al., 2010 (63)	None	LBW 6% ASD vs. 5% control, RR 1.2 (0.95–1.6)
Multiple birth		

Author, Year	Confounders assessed	Findings
Matsuishi et al., 1999 (27)	None	Multiple birth 0% autism vs. 10% control (NS)
Juul-Dam et al., 2001 (28)	None	Multiple birth 0% autism vs. 8% PDD-NOS vs. 2% population, calc RR (PDD-NOS) 4.0 (NS)
Greenberg et al., 2001 (30)	None	DZ twinning 7.5% if both siblings autism vs. 7.2% if both siblings PDD/Asp vs. 0.15% if both siblings diabetes vs. 1.6% population, calc RRs (ASDs) 4.7, 4.5; MZ twinning 14% both siblings autism vs. 10% both siblings PDD/Asp vs. 2.0% both siblings diabetes vs. 0.8% population, calc RRs (ASDs) 17.5, 12.5; total twinning 22.6% both siblings autism vs. 18.1% both siblings PDD/Asp vs. 2.3% both siblings diabetes vs. 2.4% population, calc RRs (ASDs) 9.4, 7.5
Hultman et al., 2002 (31)	Matched for sex, birth year, birth hospital; further adjustment for several maternal/ perinatal factors	Twinning 3% autism vs. 2% control, aOR 0.7 (0.3–1.6)
Croen et al., 2002 (32)	Sex, birth weight, parity, maternal age, race, education, birth place	Multiple birth 4% autism vs. 2% population, aRR 1.7 (1.4–2.0)
Hallmayer et al., 2002 (33)	None	Twinning 3.0% ASD vs. 3.5% autism vs. 2.6% population, calc RRs 1.2, 1.3 (NS)
Larsson et al., 2005 (37)	Matched for sex, birth year, age	Multiple birth 2.7% autism vs. 2.5% population, OR 1.1 (0.7–1.8)
Wier et al., 2006 (42)	Freq matched for sex, birth year, birth hospital	Multiple birth 8% ASD vs. 3% control, calc RR 2.7 (sign)
Brimacombe et al., 2007 (44)	None	Multiple birth 10% ASD vs. 4% population, calc RR 2.5 (sig)
Williams et al., 2008 (50)	Sex, gestational age, maternal age, country of origin	Multiple birth aOR 2.5 (1.1–5.5)
Van Naarden Braun et al., 2008 (53)	Maternal age using indirect standardization.	Multiple birth Obs/Exp 1.1 (0.8–1.4)
Dodds et al., 2010 (63)	None	Multiple birth 2.0% ASD vs. 2.3% control, RR 0.8 (0.5–1.3)
Cesarean delivery		
Matsuishi et al., 1999 (27)	None	C-S 6% autism vs. 12% control, calc RR 0.5 (NS)
Juul-Dam et al., 2001 (28)	None	C-S 24% autism vs. 15% PDD-NOS vs. 21% population, calc RRs 1.1 (NS) and 0.7 (NS)
Eaton et al., 2001 (29)	None	C-S RR autism 1.6 (NS), Asp. 1.1 (NS)
Hultman et al., 2002 (31)	Matched for sex, birth year, birth hospital; further adjustment for several maternal/ perinatal factors	C-S 21% autism vs. 13% control. aOR 1.6 (1.1–2.3)
Cederlund and Gillberg, 2004 (34)	None	C-S 18% Asp vs. 10% population, calc RR 1.8
Glasson et al., 2004 (36)	Matched for sex, birth year; further adjustments for parity, maternal age, fetal distress, threatened abortion	Elective C-S 13% ASD vs. 10% control, aOR 1.8 (1.3–2.5); emergency C-S 12% vs. 9%, unadjusted OR 1.6 (1.1–2.2), aOR not provided for emergency C-S.
Maimburg and Vaeth, 2006 (47)	Matched for sex, birth year, birth county; further adjustments for parental age, country of origin, several perinatal factors	Scheduled C-S 7% autism vs. 5% control, aOR 1.0 (0.6–1.6); unscheduled C-S 11% autism vs. 8% control, aOR 1.2 (0.7–1.9)
Brimacombe et al., 2007 (44)	None	C-S 30% ASD vs. 27% population, calc RR 1.1 (NS)
Bilder et al., 2009 (54)	Matched for sex; further adjustments for maternal age, parity, gestational age	Primary C-S 18% ASD vs. 10% control, aOR 1.7 (1.03–2.7); repeat C-S 6% ASD vs. 7% control, aOR 0.7 (0.03–2.7)
May-Benson, et al., 2009 (55)	None	C-S 22% ASD vs. 18% SPD vs. 30% population, calc RRs 1.2 (NS), 0.7
Zhang et al., 2010 (59)	Freq matched for sex, birth year; further adjustments for paternal age	C-S 50% autism vs. 36% control, aOR 1.8 (0.98–3.4)
Dodds et al., 2010 (63)	None	C-S 24% ASD vs. 21% control, RR 1.2 (1.1–1.4)

Author, Year	Confounders assessed	Findings
Breech presentation (and related)		
Matsuishi et al., 1999 (27)	None	Abnormal presentation (defined only as “e.g., breech”) 0% autism vs. 21% control (NS)
Juul-Dam et al., 2001 (28)	None	Nonvertex presentation 4% autism vs. 8% PDD-NOS vs. 4% population, calc RRs 1.0 (NS) and 2.0 (NS)
Eaton et al., 2001 (29)	None	Presentation other than head or back of head RR autism 1.9 (NS), Asp. 1.3 (NS)
Cederlund and Gillberg, 2004 (34)	None	Breech 5% Asp vs. 2%–3% population, calc RR 2.0
Glasson et al., 2004 (36)	Matched for sex, birth year	Breech 7% ASD vs. 5% control, OR 1.5 (0.98–2.4)
Larsson et al., 2005 (37)	Matched for sex, birth year, age; further adjustments for perinatal factors, parental psychiatric history, SES	Breech 8% autism vs. 5% control, aOR 1.6 (1.2–2.3)
Maimburg and Vaeth, 2006 (47)	Matched for sex, birth year, birth county; further adjustments for parental age, country of origin, several perinatal factors	Fetal presentation irregular (not further defined) 19% autism vs. 14% control (sign), aOR 1.2 (0.9–1.7)
Hobbs et al., 2007 (45)	None	Midgestation ultrasounds in autism sample 9% breech vs. 50% expected, calc RR 0.2 (sign)
Bilder et al., 2009 (54)	Matched for sex; further adjustments for maternal age, parity, gestational age	Breech 9% ASD vs. 4% control, aOR 2.1 (1.1–4.0)
May-Benson et al., 2009 (55)	None	Breech 6% ASD vs. 5% SPD vs. 5% population, calc RRs 1.2 (NS), 1.2
Assisted reproductive technology (and related)		
Stein et al., 2006 (41)	None	Medical tx infertility 14% autism vs. 8% control, calc RR 1.8 (NS)
Knoester et al., 2007 (46)	None	3.4% ICSI children had ASD vs. 0% IVF vs. 1.2% NC vs. 0.3% population, Calc RRs (ICSI-ASD) 2.8, 11.3
Maimburg and Vaeth, 2007 (47)	Matched for sex, birth year, birth county; further adjustments for mat age, country of origin, parity, multiplicity, birth weight, gestational age, birth defect	Assisted conception (all types, as reported on b record) 2% autism vs. 5% control, aOR 0.4 (0.1–0.98)
Hvidtjørn et al., 2010 (62)	Maternal age education, parity, smoking, body weight, multiplicity	IVF or OI without IVF aHRR 1.1 (0.97–1.3) IVF aHRR 1.0 (0.8–1.3); OI without IVF aHRR 1.2 (0.99–1.4); Subsets: in female infants OI aHRR 1.6 (1.03–2.36); treatments with FSH medication verified (IVF or OI) aHRR 1.4 (1.2–1.8); IVF for ovulation factor infertility unadjusted HRR 1.6 (0.8–3.4); IVF for mixed/unspecified infertility unadjusted HRR 1.5 (1.1–2.0)

ART = assisted reproductive technology; aOR = adjusted odds ratio; aRR = adjusted relative risk; calc RR = calculated relative risk and indicates that only proportions were specified in manuscript and these were used to calculate a RR; C-S = cesarean section; DZ = dizygotic; ELBW = extremely low birth weight; FSH = follicle stimulating hormone; HRR = hazard rate ratio; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization; LBW = low birth weight (< 2500 g unless otherwise specified); MCHAT = modified checklist for autism in toddlers; MLBW = moderately low birth weight (1500–2499 g unless otherwise specified); mod preterm defined as 32–36 weeks gestation unless otherwise specified; MZ = monozygotic; NBW = normal birth weight; preterm < 37 weeks gestation unless otherwise specified; NC = natural conception; NS = non-significant (recorded here only if “NS” or $P > .05$ specifically indicated in manuscript); OI = ovulation induction infertility treatment; OR = odds ratio; PDD-NOS = pervasive developmental disorder; not otherwise specified; RR = relative risk; SCQ = social communications questionnaire; SES = socioeconomic status; sign = statistically significant (recorded here only if statistically significant or $P > .05$ specifically indicated in manuscript); VLBW = very low birth weight (< 1500 g unless otherwise specified); very preterm < 32 weeks gestation unless otherwise specified.

TABLE 5

Summary assessment of perinatal risk factors and potential contribution to ASD increase

Risk factor	1994 RFP estimate (%)	1994– 1998 cRFP estimate (%)	Estimated RR summary	Estimated ASD increase (based on RFP, cRFP, and RR)
Preterm (total) and/or mod preterm	11 9	5 6	22 retrospective studies: 17 preterm, 5 mod preterm, 1 both Preterm: 7 est RRs 0.7 to 1.3; 10 est RRs 1.4 to 2.7 1 outlier: est RR = 4.9 Mod preterm: est RRs 0.5 to 1.8	0.26%—if RR 1.5 0.50%—if RR 2.0 0.90%—if RR 3.0 1.50%—if RR 4.9 (assumes outlier correct)
Very preterm/extremely preterm	2	3	4 retrospective studies Very preterm est RRs 0.8 to 2.0 E preterm est RRs 7.3 and 9.7 2 prospective ASD screening studies suggest high RR: ~5.0	0.06%—if RR 2.0 0.22%—if RR 5.0 0.46%—if RR 10.0 (assumes outliers correct)
LBW (total)/mod LBW	7 6	4 3	20 retrospective studies: 16 LBW, 4 mod LBW LBW: 6 est RRs 0.6 to 1.2; 10 est RRs 1.4 to 3.0 Mod LBW: 3 est RRs 0.9 to 2.2; 1 outlier: est RR 4.2	0.14%—if RR 1.5 0.26%—if RR 2.0 0.49%—if RR 3.0 0.73%—if RR 4.2 (assumes outlier correct)
VLBW/ELBW	1.5	9	6 retrospective studies est RRs 1.2 to 4.0 4 prospective ASD screening studies suggest high RR: 4 to 7	0.13%—if RR 2.0 0.51%—if RR 5.0 0.74%—if RR 7.0
Multiple birth	3	17	12 studies 1 study: in ASD group 0% were MB 5 est RRs 0.7 to 1.3; 4 est RRs 1.7 to 2.7 2 est RRs 4.0 (both had methodologic limitations)	0.35%—if RR 1.7 0.83%—if RR 2.7 1.82%—if RR 5.0 (assumes outliers correct)
Cesarean delivery	21	0	12 studies 6 est RRs 0.5 to 1.2; 6 est RRs 1.6 to 1.8	0% because cRFP = 0%
Breech presentation	4	4	9 studies of presentation at birth 1 study: in ASD group 0% were breech 8 est RRs 1.2 to 2.1 1 study midgestation ultrasound est RR 0.2	0.15%—if RR 2.0
ART (and related)	~0.5	~35	4 studies 2 est RRs 1.8 and 11.3 (but based on very small sample) 1 est RR 0.4 1 est RRs 1.0 to 1.2 overall, but est RRs 1.4 to 1.6 within subsets based on child sex, medication type, or infertility diagnosis	0.17%—if RR 2.0 1.51%—if RR 10.0 (assumes outlier correct)

ART = assisted reproductive technology; ASD = autism spectrum disorder; cRFP = change in risk factor prevalence; ELBW = extremely low birth weight; Est = estimated; mod = moderately; LBW = low birth weight; MB = multiple birth; RFP = risk factor prevalence; RR = relative risk; VLBW = very low birth weight.