Risk factors for autism spectrum disorders in individuals born pre-term: a systematic review and meta-analysis of population-based studies.

Bo YANG [1], Nina ZAKS [2], Sven SANDIN [3], Benjamin H.K. YIP [1]

[1] The Jockey Club School of Public Health and Primary Care, Department of Medicine, The Chinese University of Hong Kong

[2] Department of Psychiatry, Icahn School of Medicine at Mount Sinai

[3] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

[4] The Jockey Club School of Public Health and Primary Care, Department of Medicine, The Chinese University of Hong Kong

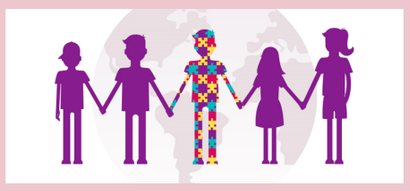
Abstract

Preterm birth is a leading risk factor for autism spectrum disorder (ASD). It is proposed that risk factors associated with and/or underlying preterm birth may themselves be linked to ASD outcome, potentially comprising an ASD subtype of distinct environmental origin. The aim of this systematic review and meta-analysis is to summarize the existing literature on environmental risk factors associated with ASD outcome in cohorts of preterm born infants.

Ovid MEDLINE, Embase, and Web of Science were searched for qualifying studies up to September 2020. Original studies examining the associations between ASD and pre-, peri-, and post-natal factors in preterm-born children were included. A total of 18 eligible studies were identified and included in a qualitative synthesis, and six were meta-analysed.

Our overall findings indicate that this topic is under-studied. Preterm cohorts are lacking, and among those existing, there is little overlap in examined exposures. We did find that male sex, low birth weight, and inflammatory biomarkers were consistently significantly associated with increased ASD risk in the available literature. Other risk factors require further investigation due to lack of replication.

What is autism spectrum disorder?



Autism spectrum disorders (ASD) are a diverse group of conditions. They are characterised by some degree of difficulty with social interaction and communication. Other characteristics are atypical patterns of activities and behaviours, such as difficulty with transition from one activity to another, a focus on details and unusual reactions to sensations.

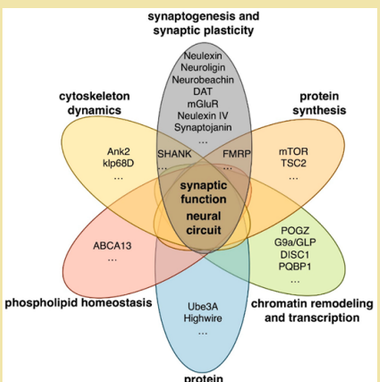
Causes and risk factors

Genetic factors

- Heritability estimated at over 80%
- More than 100 genes or genomic regions associated
- Having certain genetic conditions

Environmental factors

- Increased parental age
- Neonatal hypoxia
- Preterm birth



Method

The work comprises a systematic review and meta-analysis reported using the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines. The systematic review was registered on PROSPERO (registration number: CRD42020214689) in November 2020.

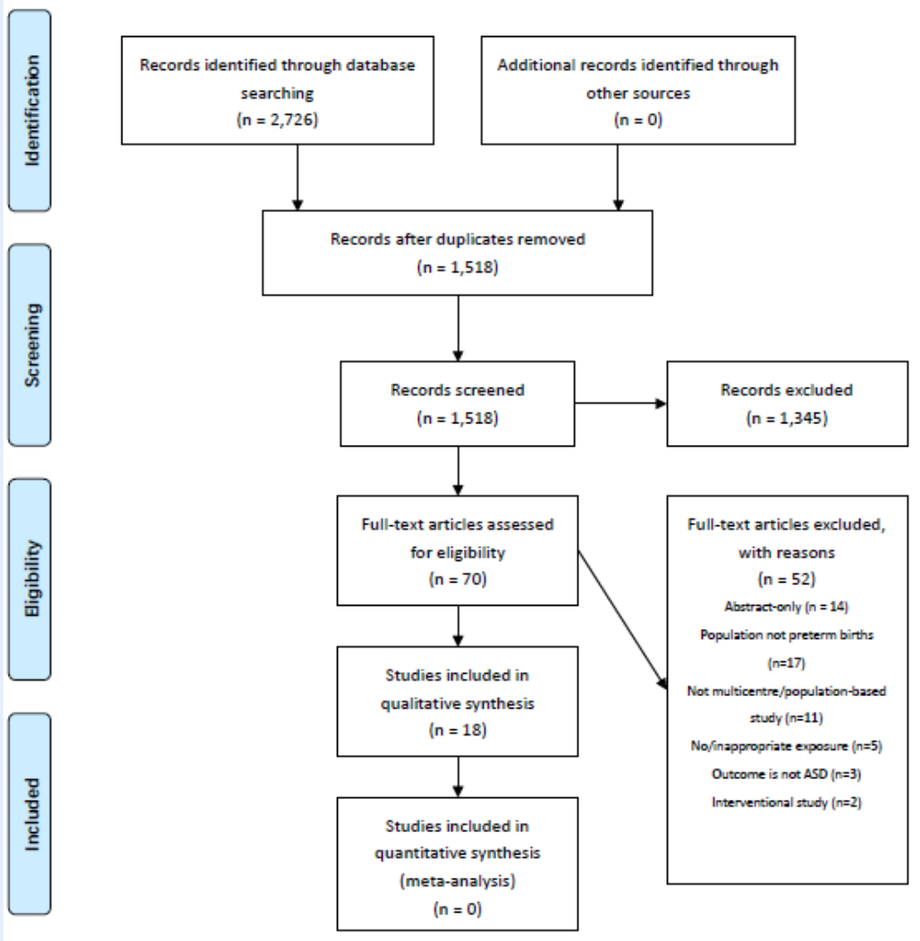
Cohort, case-control, and cross-sectional studies that examined the associations between pre-, peri-, and post-natal factors and ASD in preterm samples were included. Only population-based studies published in English were eligible. No geographical restrictions were applied.

The search strategy consisted of subject headings and keywords for ASD, premature birth, and gestational age. The search was conducted in Ovid MEDLINE, Embase, and Web of Science on 21 September 2020.

Data extraction and study quality assessment was conducted independently and then jointly by two study authors. Study quality was assessed using the validated Newcastle-Ottawa scale.

To present a more precise estimate of certain risk factors on ASD outcome, we performed meta-analyses including six different studies that examined overlapping risk factors including male sex and low birth weight.

Figure 1. Flow chart for the literature search



Results

Most of the studies were carried out in the USA (n=13). Taiwan and Sweden reported two studies each, and the UK reported one. Eight were multi-centre cohort studies, of which seven used data from the Extremely Low Gestational Age Newborn Study (ELGAN). The remaining one is based on the Late and Moderate Preterm Birth Study. Four studies used regional healthcare registry data. Four studies adopted information from National registers in Taiwan and Nordic countries. The remaining two studies were cross-sectional and extracted data from the National Survey of Children's Health in US.

Prenatal risk factors

Histologic chorioamnionitis was associated with ASD in Venkatesh et al., an ELGAN study. This risk was increased with mild or moderate grade of chorionic plate and umbilical cord inflammation.Using a subset of data from the 2016 National Survey of Children's Health, 6–11 year old children had a higher incidence of **toxic stress**, which increased the incidence of ASD in both the preterm and full-term samples.

Perinatal risk factors

Children exposed to **antepartum and intrapartum complications** were at increased risk of ASD in Getahun et al.study. The risk was even greater when both antepartum and intrapartum conditions were present.

Across five Nordic countries (N=4,987,390), emergency or planned **caesarean section** (CS) was associated with 1.26 times increased risk of ASD when compared with vaginal delivery. There was no statistically significant difference between emergency and planned CS in the risk of ASD.

Cervical-vaginal infection in those born very preterm was associated with increased risk of ASD with accompanying intellectual disability (ID+) but not with ASD without accompanying ID (ID-). On the other hand, **antibiotics** were associated with decreased risk of ASD with ID- but not ID+.

Postnatal risk factors

Low birth weight (LBW) was reported by four studies to be associated with increased ASD risk. Similar to LBW, **male sex** has long been regarded as a dominant risk factor for ASD. Four studies reported a significant association between male sex and autism in preterm samples. Notably, in Joseph et al., male sex increased risk for ASD+/ID+ and ASD-/ID+ but not ASD+/ID-, distinct from their findings on LBW.

Brain damage is hypothesized to increase the risk of ASD, a neurodevelopmental disorder. **Cerebral dysfunction** caused by brain damage was found to be associated with increased ASD risk by Hwang et al.

Meta-analytic assessments

According to our meta-analyses, male sex was associated with an elevated risk of ASD in the preterm population (2.79 [2.07, 3.76]). We also observed a significant association between LBW and ASD risk (2.11 [1.34, 3.32]). Heterogeneity was modest in the sex analysis (I^2=46%) and substantial (I^2=73%) in the LBW analysis.

Figure 2. Forest plot of meta-analysis on the associations between male sex and autism spectrum disorders in preterm born population

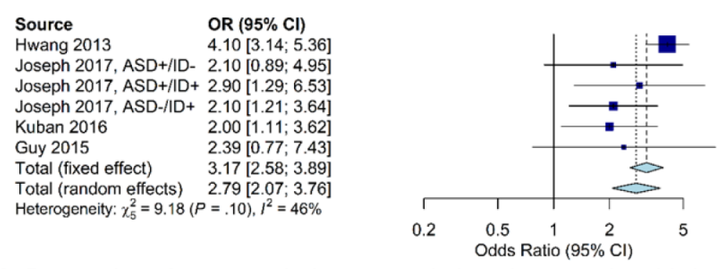
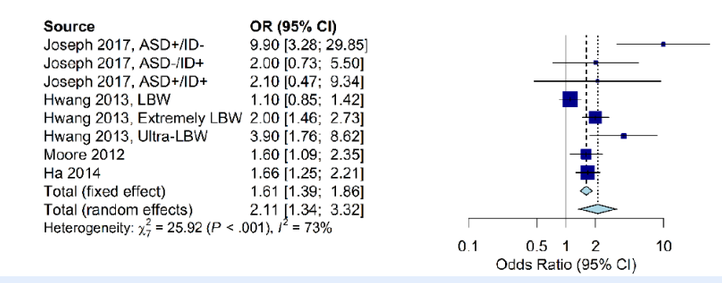


Figure 3. Forest plot of meta-analysis on associations between low birth weight and autism spectrum disorders in preterm born population



Summary

Across studies, male sex, low birth weight, and inflammation were consistently associated with increased ASD risk. Many other significant exposures across the prenatal, perinatal, and postnatal periods were identified but require further investigation.

Strength and Limitations

A strength of this review is the grouping of risks into three stages, pre-, peri-, and postnatal factors, enables interpretation of risk across time. This led us to identifying inflammation as a significant ASD risk factor across all three stages.

The primary limitation is the small number of studies included. Few studies have used preterm subjects as their target population, and even fewer examined ASD outcome. Considering the low prevalence of ASD, statistical power of many of the included studies is low. Another issue is the extremely limited overlap in examined exposures among the 18 included studies. Of 33 unique exposures, only two exposures were studied frequently enough to meta-analyze. An additional limitation of such research is the varying diagnostic criteria of both exposure and outcome, which contributes substantially to precision of findings.