Research in Developmental Disabilities 34 (2013) 3004–3013

Contents lists available at SciVerse ScienceDirect

Research in Developmental Disabilities

Prenatal, perinatal and neonatal risk factors of Autism Spectrum Disorder: A comprehensive epidemiological assessment from India

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ARTICLE INFO

Article history:
Received 21 February 2013
Received in revised form 2 May 2013
Accepted 14 June 2013
Available online 29 June 2013

Keywords:
Autism Spectrum Disorder
Risk factors
Prenatal
Perinatal
Neonatal
India

ABSTRACT

Incidence of Autism Spectrum Disorder (ASD) is increasing across the globe and no data is available from India regarding the risk factors of ASD. In this regard a questionnaire based epidemiological assessment was carried out on prenatal, perinatal and neonatal risk factors of ASD across 8 cities in India. A retrospective cohort of 942 children was enrolled for the study. 471 children with ASD, under age of 10, were analyzed for pre-, peri-, and neonatal factors and were compared with the observations from equal number of controls. The quality control of the questionnaire and data collection was done thoroughly and the observations were computed statistically. A total of 25 factors were evaluated by unadjusted and adjusted analysis in this study. Among the prenatal factors considered, advanced maternal age, fetal distress and gestational respiratory infections were found to be associated with ASD and had an odds ratio of 1.8. Evaluation of perinatal and neonatal risk factors showed labor complications, pre-term birth, neonatal jaundice, delayed birth cry and birth asphyxia to be associated with ASD with an odds ratio greater than 1.5. This important study, first of its kind in Indian population gives a firsthand account of the relation of pre-, peri- and neonatal risk factors on ASD from an ethnically and socially diverse country like India, the impact of which was unknown earlier. This advocates additional focused investigations on physiological and genetic changes contributed by these risk factor inducing environments.

Abbreviations: ASD, Autism Spectrum Disorder; DSMIV, Diagnostic and Statistical Manual of Mental disorders IV; ICD-10, International Classification of Diseases-10; CARS, Childhood Autism Rating Scale; OR, odds ratio; CI, confidence intervals; P, probability value.

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http://dx.doi.org/10.1016/j.ridd.2013.06.019

1. Introduction

Autism is a neurodevelopmental disorder characterized by impaired social interaction and communication, associated with restricted and repetitive behavior (Zhang et al., 2010). Autism is becoming a growing challenge in developing countries like India as well, and the earlier notion of it being uncommon is no longer justified. It poses a much greater and serious challenge in countries like India, because of the severity of the impact on the affected individuals and their families, along with the economic burden that it imposes coupled with lack on scientific know how about the disorder (Daley, 2004). Due to lack of awareness about the condition, often, misdiagnosis or inclusion of ASD under the general category of mental retardation and/or speech and language disorders is commonly noticed (Singhi & Malhi, 2001). Globally, a number of systematic population surveys and routine monitoring systems in various countries since 1990s have indicated a rise in prevalence from 0.7% to 1% (Chakrabarti & Fombonne, 2001; Fombone, 2002). According to Centers for Disease Control and Prevention (CDC) – recent study from 14 communities, 1 in 88 children in the United States have been identified as having an Autism Spectrum Disorder (ASD) (CDC, 2012), indicating a rise in the past two decades. But this may not be the true picture as the prevalence estimates from Asian countries like China (0.003–0.17%), Japan (0.011–0.21%) and South Korea (2.64%) vary widely across time and country (Kim et al., 2011; Sun & Allison, 2010). Based on the studies in Asian countries, nearly 1.7–2 million individuals are estimated to be affected (Karande, 2006; Krishnamurthy, 2008) with ASD in India. With such high estimated figures, it becomes a necessity to look into the probable risk factors of ASD in Indian population as well.

The extreme complexity in the behavioral, developmental and associated medical conditions across ASD indicates existence of multiple unknown causal factors. Studies based on concordance rates among monozygotic twins and families suggest a possible role of both genetic and environmental factors in the etiology of ASD (Bailey et al., 1995; Guinchat et al., 2012; Parner, Schendel, & Thorsen, 2008). Despite significant research in the field, the etiology of ASD is not well established. The neuropathology of ASD remains unclear and the reported brain abnormalities among children with ASD indicate a probable link with disturbances in the *in utero* period (Gardener, Spiegelman, & Buka, 2011; Minshew & Williams, 2007; Pardo & Eberhart, 2007). Hence, it is imperative to focus of prenatal, perinatal events as risk factors for ASD.

There has been a huge focus on pre- and perinatal events as risk factors in various studies across the globe, wherein disruptions and disorders of pregnancy, labor complications, fetal distress, low birth weight and premature birth have been studied and implicated in ASD (Bilder, Pinborough-Zimmerman, Miller, & McMahon, 2009; Bolton et al., 1997; Bryson, Smith, & Eastwood, 1988; Buchmayer et al., 2009; Burd, Severud, Kerbeshian, & Klug, 1999; Burstyn, Sithole, & Zwaigenbaum, 2010; Cryan, Byrne, O'Donovan, & O'Callaghan, 1996; Deb et al., 1997; Deykin & MacMahon, 1980; Dodds et al., 2011; Dubovický, 2010; El-Baz et al., 2011; Finegan & Quarrington, 1979; Gardener et al., 2011; Ghaziuddin, Shakal, & Tsai, 1995; Gillberg & Gillberg, 1983; Glasson et al., 2004; Guinchat et al., 2012; Hultman, Sparén, & Cnattingius, 2002; Johnson et al., 2010; Juul-Dam, Townsend, & Courchesne, 2001; Kinney, Munir, Crowley, & Miller, 2008; Kolevzon, Gross, & Reichenberg, 2007; Kröger et al., 2011; Kuban et al., 2009; Larsson et al., 2005; Lord, Mulloy, Wendelboe, & Schopler, 1991; Losh, Esserman, Anckarsäter, Sullivan, & Lichtenstein, 2012; Maimburg & Vaeth, 2006; Mason-brothers et al., 1987; Nelson, 1991; Ornitz, 1985; Piven et al., 1993; Schendel & Bhasin, 2008; Stein, Weizman, Ring, & Barak, 2006; Wallace, Anderson, & Dubrow, 2008; Zambrino, Balottin, Bettaglio, Gerardo, & Lanzi, 1995; Zwaigenbaum et al., 2002). Despite several studies being conducted worldwide to analyze the risk factors of ASD, the results are not conclusive.

Research reports on epidemiology of ASD from India are not available (Sharan, 2006). Analysis of such risk factors is pertinent in India, as the above mentioned risk conditions like fetal distress inducing conditions and labor complications are well documented to be prevalent with significant impact on survival and development of children in India (Kumar & Bhat, 1996; March of Dimes, 2012; NFHS-3, 2007; Singh, Singh, & Shikha, 2007). However, the exact impact of these conditions as risk factors for ASD needs to be established. Moreover, globalization, secondary to industrialization and the enhanced communication pathways, had led to significant cultural, political and economic changes, requiring an individual to adapt to these changing scenarios (Banerjee, 2009). This need for adaptation contributes to increased mental stress among individuals for gaining resources to cope (Banerjee, 2009). Mental stress, in turn, has reflected in stressful pregnancies due to associated psychosocial stress among Indian women (UNICEF, 2006). Hence, it is imperative to understand the implications of these on the pre-, peri events and disease etiology from India.

Thus, the aim of our study is to perform a population based cohort study to characterize the pre-, peri- and neonatal risk factors and assess their association with ASD in Indian population. The data generated in this study is the first epidemiological report from India and the results obtained strengthens similar observations from other studies reporting pre-, peri- and neonatal risk factors of ASD.

2. Methods

The study was conducted by following Code of human research ethics guidelines laid down by Indian Council of Medical Research [ICMR] (ICMR, 2006). An informed consent was taken from the participating parent after detailed explanation of the rationale behind the study and about the questions in the questionnaire. Care was taken to ensure confidentiality of the data collected. This study was approved by Institutional Human Ethics Committee (IHEC).

2.1. Sampling data

Simple random sampling was done between September 2010 and December 2012 from individuals across 8 major Indian cities. The sample frame consisted of centers dealing with children with ASD for cases and schools with intellectually normal children in the case of controls. The center selection was carried out based on the size, probability of finding children from various socio-economic backgrounds and to have a better distribution with wider presence across the country.

The sample size calculation for an expected ASD population size of around 2 million was found to be 385 (given $\alpha = 0.05$), and predicting a 20% refusal rate for participation in the study, a total of 471 cases were enrolled for the analysis. An equal number of controls were recruited to achieve a case: control ratio of 1:1.

2.2. Data sources

In India, an estimated 26 million children are born every year, of which about 10 million (42%) go unregistered (UNICEF, 2006). Even today, in rural areas, births occur at home rather than at hospitals or primary health care centers contributing to unregistered cases. Lack of public awareness and no demand for civil registration documents (birth certificates) is also one of the biggest challenges and the reason for low levels of registration. Even for those registered, registration is usually done by the local body – The Municipal Corporation, and the birth certificate issued includes only name of the child, place and time of birth. Sometimes the place of birth of the child and the place where the child is brought up might differ due to cultural practices leading to decreased monitoring of the health conditions thereafter. Due to all the above mentioned constraints a single point of data collection through registered structured records was not possible. So, various independent organizations were approached for data collection across India to carry out our study.

2.2.1. Case ascertainment and enrollment

The information about major centers where children with ASD are enrolled was obtained from The National trust – Government of India, Psychiatric departments of various hospitals across 8 major cities (Hyderabad, Chennai, Mumbai, Bangalore, New Delhi, Mysore, Ahmedabad, Guntur), institutes like National Institute for the Mentally Handicapped (NIMH), various autism centers and by a thorough internet search. Collaborations were established with 65 centers across 8 cities for data collection which covered various hospitals, autism clinics, autism schools, special schools, therapy clinics. These included Government run or recognized centers and Institutes, large Non-governmental organizations (NGOs) where children from various lower economic backgrounds enroll due to the lower costs involved in therapies and other smaller centers, therapy clinics, large and small schools dealing with children with ASD. These centers were preferred as they maintain direct and sustained contact with the families and individuals with ASD (Daley, Singhal, & Krishnamurthy, 2013).

Our study included children between 2 and 10 years of age across India. The criterion for age selection is based on the fact that the first signs of the disorder are normally seen even before the child is 3 years old (Boyd, Odom, Humphreys, & Sam, 2010; Mefford, Batshaw, & Hoffman, 2012). Concrete diagnosis is usually available between 3 and 4 years of age, though certain conditions like the Asperger's Syndrome may have a delayed diagnosis at around 5–6 years (CDC, 2008). Many children with behavioral abnormalities reported either by parents, relatives, general practitioners, psychologists, and schools are referred to specialists in child psychiatry for further evaluation and diagnosis. The psychiatrists are well trained to use the internationally accepted classification systems such as Diagnostic and Statistical Manual of mental disorders IV (DSM IV) and International classification of diseases 10 (ICD 10) (Daley & Sigman, 2002). Apart from those two, ISAA – Indian Scale for Assessment of ASD is also used by psychiatrists across the nation (Patra & Arun, 2011) for diagnosis and giving certification. Childhood Autism Rating Scale (CARS) is also used commonly to classify case status (Rellini, Tortolani, Trillo, Carbone, & Montecchi, 2004). Upon diagnosis, a report is provided to the parent regarding the ASD evaluation. Children with ASD, as reported by the parent and confirmed by the diagnostic report constituted our study sample. Within each center, the response rate of the participating parents was 95% and the non respondents were usually parents of those children who were not born in India or who were above 10 years of age, or because of their unwillingness to participate due to personal perceptions. Children under a suspicion for ASD but with no formal diagnosis, children with Cerebral Palsy and Down syndrome, were excluded from the study.

2.2.2. Enrolment of control subjects

The control populations (age and gender matched) were identified randomly across 8 major cities in India between September 2010 and December 2012. The enrolment was done parallel to the recruitment of children with ASD. All the children were typically developing according to our assessment and did not have any history of learning or psychiatric disabilities. Data was collected by establishing collaborations with schools (regular, government run and private school) as these represented all sections of the society from rural to urban from low socio-economic status to high socio-economic status (Muralidharan & Kremer, 2006). Also, data was collected by visiting houses randomly across the cities. Most of the children enrolled attended regular government and private schools and were progressing well as per teacher and parent's report.

2.3. Questionnaire

2.3.1. Design

A questionnaire was designed based on the probable risk factors of ASD from existing literature and those likely to be specific to Indian environment. Care was taken to analyze and include the most relevant and specific risk factors and not a meager dependence on the already available data from literature.

2.3.2. Validation

The designed questionnaire was initially pilot tested with a convenient sample. This pilot tested questionnaire was modified according to the results obtained and were subjected to further validation procedures like construct and reliability testing. For construct validation, percentage agreement and content validity index was calculated and for reliability testing, internal consistency as well test–retest procedure was followed. The results obtained were conclusive and met all requirements to be used as a psychometric instrument for carrying out questionnaire based epidemiological study. The data for the questionnaire validation is communicated for publication elsewhere.

2.4. Collection

An informed consent was taken from parents of the participating children (both cases and controls) prior to the study. The various methods followed for data collection include:

1. *Direct interaction*: We directly interacted with parents (literate and illiterate), explained the questionnaire, took informed consent and collected the data. This constituted major part of the data collection.
2. *By trained staff*: Teachers of special schools and clinics were educated thoroughly about the questionnaire, the wording and the relevance. They helped the parents to fill the questionnaire by translating the terms into the local dialect and by explaining the doubts regarding the questions. Either the teachers filled the questionnaire on behalf of the parent or the parents themselves filled them. 40% of the parents took the questionnaires to home, checked the medical records available with them and filled the responses.

Detailed explanation of questionnaire as given above coupled with parent's cooperation ensured minimum missing data. Though the age group under consideration was in range of 2–10, 70% of the children (cases and controls) were below 7 years of age minimizing the bias due to memory recall. The quality control of our questionnaire-based study was ensured by comparing the data collected from questionnaire with the medical records available for a convenient percentage of study population ($\sim$20%) and was found to show 100% consistency.

2.5. Statistical analysis

Statistical analysis of all risk factors was done using SAS 9.1.3 (SAS Institute, Inc, Cary NC) version. To explore the collective effect of several variables simultaneously, logistic regression (Univariable, Multivariable) was used to calculate odds ratios and 95% confidence intervals (CIs) at $\alpha = 5\%$. Frequency of occurrence of risk factor in cases and controls dictates the analysis pattern used. Only if the frequency of occurrence is at least 5, multivariable analysis was carried out. In all other conditions only univariable analysis was performed by using Fisher's exact test. A conditional logistic regression by adjusting gender, maternal age and child's birth year was performed for variables with frequency at least 5 as well as for categorical variables such as birth weight and gestation term. Reference standards considered for analysis were 30 years and above for parental age (Grether, Anderson, Croen, Smith, & Windham, 2009) less than 37 weeks for Abnormal gestational term and less than 2, 500 g for low birth weight category respectively (Muthayya, 2009; UNICEF, 2004). The model accuracy for the adjusted analysis was calculated to be $R^2 = 0.651$, which indicate it to be a good model.

2.6. Variables analyzed

1. *Parental factors*: Advanced maternal and paternal age at the time of child birth.
2. *Prenatal characteristics*: Conditions during pregnancy like gestational diabetes, high blood pressure, gestational infections like urinary tract, gastrointestinal and respiratory tract infections, fetal distress inducing conditions like amniotic fluid loss, bleeding during gestation and other suboptimal intrauterine conditions were analyzed in the study.
3. *Perinatal characteristics*: Labor characteristics like Induced or prolonged labor, pre-mature membrane rupture; Breech presentation, Nuchal cord, and delivery types including forceps or vacuum suction mediated delivery were analyzed in the study.
4. *Neonatal characteristics*: We analyzed the birth weight and gestational term, birth asphyxia, delayed birth cry, neonatal jaundice, eczema and seizures immediately after birth.

3. Results

A total of 942 participants (471 cases and 471 controls) were included in the study with age group ranging from 2 to 10 years. The average age at which the ASD was diagnosed was found to be 3 years in our study.

3.1. Parental factors

According to the statistical analysis, there was association found between advanced maternal age (OR: 1.80 [95% CI: 1.27, 2.54], $P = 0.0008$) and ASD (Table 1). Among the mothers of ASD cases 354 (75.1%) were below 30 years and 117 (24.8%) mothers were 30 years and above. While considering the control population, 397 (84.2%) mothers were below 30 years while 74 (15.7%) mothers were 30 years and above. With respect to paternal age analysis, 148 (31.4%) fathers were below 30 years and 323 (68.5%) fathers were 30 years and above among cases, while among controls 161 (34.1%) fathers were below 30 years and 310 (65.8%) fathers were 30 years and above.

3.2. Prenatal characteristics

Six maternal conditions during gestation were analyzed for their association with ASD by unadjusted analysis. Out of them clinical conditions like hypertension (1.69% in cases and 0.2% in controls) and gestational infections like respiratory tract infections (4% in cases and 1.0% in controls), were found to be significant with odds ratio of 1.8 (Table 1). Fetal distress is induced by many factors, understanding of the synergistic effect of all these factors seems logical. The occurrence of fetal distress was higher among cases when compared to controls (23.7% in cases and 4.2% in controls), and the logistic regression analysis (Table 1) presented it to be significant with an odds ratio of 5.50 ([95% CI – 2.44, 1.40], $P < 0.0001$). On the other hand, gestational diabetes, gastro-intestinal infections and urinary tract infections did not show significant association with ASD (Table 1) due to low number of controls.

3.3. Perinatal characteristics

Two assisted delivery methods and five complications observed during labor were analyzed (Table 2). Co-occurrence of more than one labor complication is not uncommon, hence understanding the collective impact of labor complications as risk factor for ASD seems logical. The occurrence of labor complications were higher among cases when compared to controls (15% in cases and 2.3% in controls) and the logistic regression analysis presented it to be significant with an odds ratio of 5.48 ([95% CI – 2.99, 11.57], $P < 0.0001$) but univariable analysis of individual factor was not significant enough. Moreover, analyses of various assisted delivery methods were did not show any significant association with ASD.

3.4. Neonatal characteristics

Neonatal risk factors included the birth weight of the child, gestational age, delayed birth cry, birth asphyxia, neonatal jaundice, seizures and eczema (Table 2). Among the factors analyzed, pre-term birth (14.1% in cases and 6.1% in controls), delayed birth cry (5.2% in cases and 1.2% in controls), birth asphyxia (11.2% in cases and 1.0% in controls), and neonatal

Table 1
Univariable analysis of parental and prenatal factors of ASD.

	Cases		Controls		Odds ratio [95% confidence interval]	*P*-value
	Number	%	Number	%		
Parental factors						
Mother's age						
<30	354	75.1	397	84.2		
≥30	117	24.8	74	15.7	1.80 [1.27, 2.54]	0.0008[a]
Father's age						
<30	148	31.4	161	34.1		
≥30	323	68.5	310	65.8	0.97 [0.72, 1.30]	0.86
Prenatal factors						
Gestational diabetes	5	1	4	0.8	0.71 [0.34, 4.79]	1.27[a]
Hypertension	8	1.69	1	0.2	7.93 [0.98, 63.74]	0.05[a]
Fetal distress	112	23.7	20	4.2	5.50 [2.44, 12.40]	<0.0001
Amniotic fluid loss	27	5.7	2	0.4	10.16 [2.34, 43.94]	0.001[a]
Bleeding	19	4	8	1.6	1.11 [0.40, 3.05]	0.83
Suboptimal intrauterine conditions	66	13.9	10	2.1	6.18 [2.99, 12.78]	<0.0001
Infections during pregnancy						
Gastro-intestinal	16	3.3	9	1.9	1.77 [0.77, 4.08]	0.17
Respiratory tract	19	4	5	1.0	4.79 [1.61, 14.22]	0.004[a]
Urinary tract	9	1.9	3	0.6	3.05 [0.82, 11.35]	0.09[a]

[a] Fisher's Exact test was used to obtain P values when frequency of occurrence was less than 5.

Table 2
Univariable analysis of perinatal and neonatal factors of ASD.

	Cases		Controls		Odds ratio [95% confidence interval]	*P*-value
	Number	%	Number	%		
Perinatal factors						
Assisted delivery						
Forceps mediated delivery	7	1.4	1	0.2	3.76 [0.41, 34.17]	0.23[a]
Vacuum mediated delivery	3	0.6	1	0.2	1.66 [0.14, 18.97]	0.68[a]
Labor complications	71	15	11	2.3	5.48 [2.99, 11.57]	<0.0001
Induced labor	9	1.9	1	0.2	4.76 [0.55, 40.71]	0.15[a]
Prolonged labor	13	2.7	1	0.2	6.07 [0.73, 50.25]	0.09[a]
Pre-matured membrane rupture	1	0.2	1	0.2	0.41 [0.018, 9.69]	0.58[a]
Breech presentation of the child	5	1	1	0.2	2.26 [0.22, 23.21]	0.49[a]
Cord around neck of the child	8	1.6	1	0.2	1.95 [0.21, 17.96]	0.55[a]
Other complications of labor and delivery	35	7.4	6	1.2	6.30 [2.59, 15.28]	<0.0001
Neonatal factors						
Pre-term birth	67	14.1	29	6.1	2.11 [1.29, 3.42]	0.002
Low birth weight	64	13.5	45	9.5	1.13 [0.73, 1.76]	0.56
Delayed birth cry	25	5.2	6	1.2	3.22 [1.26, 8.25]	0.01
Birth asphyxia	53	11.2	5	1.0	11.15 [3.88, 32.01]	<0.0001[a]
Neonatal jaundice	64	13.5	17	3.6	3.58 [2.02, 6.35]	<0.0001
Seizures	11	2.3	1	0.2	6.23 [0.74, 51.87]	0.09[a]
Eczema	1	0.2	2	0.4	0.10 [0.004, 2.74]	0.17[a]

[a] Fisher's Exact test was used to obtain P values when incidence was less than 5.

Table 3
Adjusted analysis of risk factors of ASD.

	aOR	95% Confidence Interval	*P*-value
Parental factors			
Father's age	1.05	[0.76, 1.46]	0.73
Mother's age	1.59	[1.09, 2.32]	0.01[a,**]
Fetal distress	5.13	[3.03, 8.69]	<0.0001****
Gestational infections			
Respiratory infection	3.80	[1.18, 12.29]	0.02**
Gastro intestinal infection	2.24	[0.54, 9.26]	0.26
Labor complications	4.52	[2.27, 9.01]	<0.0001****
Neonatal factors			
Pre-term birth	1.78	[1.07, 2.93]	0.02*
Low birth weight	1.13	[0.71, 1.79]	0.60
Birth asphyxia	10.63	[3.69, 30.59]	<0.0001****
Neonatal Jaundice	2.89	[1.58, 5.28]	0.0006****
Delayed birth cry	2.68	[0.99, 7.25]	0.05*

Results were from multiple logistic regression model and adjusted for maternal age at delivery, gender and birth year.
aOR – adjusted odds ratio.
* Significant values.
[a] Significance of Advanced maternal age was calculated by adjusting gender and birth year only.

jaundice (13.5% in cases and 3.6% in controls) were significantly associated with ASD and had an odds ratio of greater than 1.1.

3.5. Adjusted analysis

Adjusted analysis with maternal age at gestation, gender and birth year of the child was also carried out for the factors with minimum frequency of 5 in both the case and control group for the calculation of adjusted odds ratio (aOR). The factors considered were parental age – father and mother; fetal distress, gestational infections – respiratory and gastro-intestinal, labor complications and neonatal factors – pre-term birth, low birth weight, birth asphyxia, neonatal jaundice, and delayed birth cry (Table 3). The factors which were significant after adjusted analysis were mother's age at gestation (aOR – 1.59), fetal distress (aOR – 5.13), respiratory infections (aOR – 3.80), labor complications (aOR – 4.52), pre-term birth (aOR – 1.78), birth asphyxia (aOR – 10.63), neonatal jaundice (aOR – 2.89) and delayed birth cry (aOR – 2.68). Our results suggest that even after adjustment of gender, maternal age and birth year, the factors remained significant with odds ratios greater than 1.5, indicating true association, as was the case in univariable analysis.

4. Discussion

This is the first study to analyze the prenatal, perinatal and neonatal risk factors of ASD in Indian population. We conducted a questionnaire-based case–control epidemiological study. The strength of the current study lies in its large country wide data collection with validated questionnaire, precise confirmation of the ASD diagnosis by physicians, active participation of parents and volunteers (teachers and therapists) from various schools and hospitals in filling up of the questionnaire, personalized monitoring of collection, meticulous data analysis and also structured attempts to minimize the missing data.

Previous studies had reported significant association of prenatal, perinatal and neonatal risk factors with ASD but no study has been conducted in India to evaluate the risk factors associated during pre- and perinatal conditions with ASD. We analyzed the association of parental age with ASD and found that advanced maternal age of 30 years and above to be significantly associated with ASD with the odds ratio 1.59 times higher for advanced maternal age compared to mother's who are below 30 years of age. This could be due to the fact that among women, advancement of age predisposes them to abnormalities in biological mechanisms, like alteration in hormonal factors affecting the in utero environment, epigenetic changes and nucleotide repeat instability, etc. (Anello et al., 2009). The synergistic effect of all these factors could affect fetal brain development leading to ASD (Anello et al., 2009; Durkin et al., 2008). But our study did not find any significant association of paternal age with ASD, even though earlier studies from other countries have shown association of paternal age with ASD (Burd et al., 1999; Reichenberg et al., 2006; Shelton et al., 2010).

Our study also analyzed the effect of various gestational infections like respiratory, gastro-intestinal and urinary tract infections with ASD. Of the three, we found the association of respiratory tract infection with ASD with an odds ratio of 3.8. The immune responses of the mother to these infections elicit the release of cytokines, which can cross the trans-placental barrier and can modulate neural function, survival, apoptosis, and expression of transmitters and neurotrophins in developing brain (Depino, 2006). Cytokines also affect neural cell proliferation and differentiation, impairments of which are known to be associated with ASD (Ashwood et al., 2011).

Bleeding during gestation, amniotic fluid loss or any other suboptimal intrauterine conditions have been implicated to cause fetal distress (Kaur & Kaur, 2012). According to Indian National Family Health Survey – 3 (NFHS – 3) there is rise in vaginal bleeding among women from both urban and rural areas (NFHS-3, 2007). Vaginal bleeding has been found to be associated with high rate of fetal loss and adverse infant outcomes like prematurity, intrauterine growth retardation (IUGR), still birth and neonatal death (Karim, Bakhtawar, Butta, & Jalil, 1998; Sipilä, Hartikainen-Sorri, Oja, & Wendt, 2005) indicating fetal distress. Fetal hypoxia is one of the manifestations of this fetal distress and has been reported to induce conditions like placental abruption, threatened premature delivery, emergency caesarean section, forceps delivery, spontaneous abortion to varying degrees of cerebral damage (Kinney et al., 2008). Also, amniotic fluid loss which is generally termed as oligohydramnios has been implicated to cause pregnancy complications like ruptured membranes and placental insufficiency as well as congenital anomalies (Chhabra, Dargan, & Bawaskar, 2007). Such instances of stressful conditions during pregnancy are conceptualized to be on a rise in major metropolitan cities of India in the last decade (Dole et al., 2003). According to our study, fetal distress has been found significantly associated with ASD and the odds ratio was estimated to be 5.13. Our findings are consistent with previous findings that fetal distress induced during pregnancy is associated with etiology of ASD. Thus, any suboptimalities of the fetus during gestation as indicated above can have adverse effect on the development of the fetus. Though our investigation identified hypertension to be a risk factor for ASD in univariable analysis, but we could not draw any conclusions due to low representation in the control group.

According to NFHS-3, pregnancy complications are on rise among Indian women and so is the maternal mortality due to these complications (RGI, 2006). Obstructed and prolonged labor has been reported to cause asphyxia resulting in infant death or brain damage (Ashford, 2002). Also nuchal cord has been reported to be a risk factor for mild, chronic, pre-labor fetal hypoxia (Hashimoto & Clapp, 2003) and is associated with a subclinical deficit in neurodevelopmental performance at 1 year of age (Clapp, Lopez, & Simonean, 1999). Premature-membrane rupture has been reported to be involved in causing fetal distress (Kaur & Kaur, 2012) and moderate to severe neurodevelopmental impairments in infants (Spinillo et al., 1995) as well. Our study reports that more labor complications arising due to pre-matured membrane rupture or breech presentation of the child or Nuchal cord or induction of labor and prolonged labor and other labor or delivery complications were observed among mothers of children with ASD rather than in control population with an odds ratio of 4.52. Thus, complications occurring during labor affect the neurodevelopment of the fetus and infant in later stages and can contribute towards the risk of ASD.

The analysis of neonatal factors gave significant results with respect to delayed birth cry, birth asphyxia, pre-term birth and Neonatal Jaundice with an odds ration of greater than 1.1. In India, 50% of all child mortality is due to pre-term births and other associated complications (March of Dimes, 2012). Neonatal consequences of preterm delivery reported include developmental delay, hearing impairment and intraventricular hemorrhage etc (Marlow, Wolke, Bracewell, & Samara, 2005; Ward & Beachy, 2003; Wood, Marlow, Costeloe, Gibson, & Wilkinson, 2000). Also, an increased incidence of attention deficit hyperactivity disorder (ADHD) and other behavioral abnormalities have been observed among children born preterm (Bhutta, Cleves, Casey, Cradock, & Anand, 2002). Thus, pre term birth seems to be a good risk factor candidate to be explored. Our finding shows that pre term birth of less than 37 weeks is significantly associated with ASD with odds ratio of 2.11, and is consistent with the other studies reporting association of preterm birth with ASD.

Our results are at par with other studies (Maimburg & Vaeth, 2006; Zhang et al., 2010) reporting a link between neonatal jaundice and ASD with an odds ratio of 2.89. Neonatal jaundice is due to accumulated bilirubin (mostly conjugated)

physiologically or pathologically, and has been implicated to cause damage to the central nervous system and also can lead to bilirubin encephalopathy (Maimburg & Vaeth, 2006; Zhang et al., 2010). Delayed birth cry and birth asphyxia are also significantly associated with odds ratio of 2.68 and 10.63. Delayed birth cry and birth asphyxia are known to induce hypoxic conditions leading to neurological consequences also (Low, 2004; Nelson, 1991).

Our study did not find any significant association of low birth weight (<2500 g) with ASD. Among neonatal factors, low birth weight and preterm birth are considered to be predictors of an adverse prenatal environment (Zhang et al., 2010). Low birth weight has been reported to be a risk factor for psychiatric disorders like ADHD, anxiety symptoms, etc. (Botting, Powls, Cooke, & Marlow, 2006; Hack, Klein, & Taylor, 1995). Surprisingly in the Indian population, unlike other studies low birth weight was not a major risk factor. This could be due to the fact that underweight children are not unusual even in the control population. Also, due to the exclusion criteria used where cases with cerebral palsy and intellectual disabilities were not included in the study where the frequencies of occurrence of low birth weight children are equally higher (Mervis, Decoufle, Murphy, & Yeargin-Allsopp, 2008).

Though this study gives comprehensive data from the Indian population, it is limited by certain constraints like vastness of the region with multiple ethnicities, no published report on incidence and prevalence, the non-availability of structured and reliable record keeping on maternal and fetal conditions in the country, dependence on maternal memory for data acquisition, etc. Thus, there is a need for further extension of this study to address these limitations. Nevertheless, many of our reports are consistent with other reports that prenatal, perinatal and neonatal environment plays a very important role in neurodevelopment and etiology of ASD.

5. Conclusion

Our study categorically implicates many pre, peri and neonatal conditions to be risk factors for ASD independently and collectively, adding important country specific information to existing literature. Out of all the factors analyzed, advanced maternal age, fetal distress and gestational respiratory infections were found to be associated with ASD and had an odds ratio of 1.8. Evaluation of perinatal and Neonatal risk factors showed labor complications, pre-term birth, neonatal jaundice, delayed birth cry and birth asphyxia to be associated with ASD and had an odds ratio greater than 1.5. This study, being the first representation from a multi ethnic and multidimensional society like India becomes noteworthy. This adds impetus to the fact that additional focused investigations are necessary on physiological and genetic changes contributed by these risk factor inducing environments. Such a high number of risk factors being implicated in India also necessitate the true understanding of the actual incidence of ASD in this country.

Acknowledgements

This research was completely funded by University Grants Commission, India. We would also like to extend our acknowledgement to Department of Science and Technology, India for funding the research scholar. We would like to thank Dr. M. Gowri Devi, Professor and HOD Department of Psychiatry, Niloufer Hospital for permitting us for data collection. Our extended appreciation to Mr. V. Shankaran, Mr. C. N. Rahul, Ms. N. Geetanjali and Dr. S. Kalidasan for helping us in the collection of control questionnaires. Our sincere gratitude to various autism schools, therapy center, organizations in India, for extending support for data collection and to carry out the research successfully.

References

Anello, A., Reichenberg, A., Luo, X., Schmeidler, J., Hollander, E., Smith, C. J., et al. (2009). Brief report: Parental age and the sex ratio in autism. *Journal of Autism and Developmental Disorders, 39*(10), 1487–1492.

Ashford, L. (2002). *Hidden suffering: Disabilities from pregnancy and childbirth in less developed countries*. Population Reference Bureau: MEASURE Communication.

Ashwood, P., Krakowiak, P., Hertz-Picciotto, I., Hansen, R., Pessah, I., & Van de Water, J. (2011). Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. *Brain, Behavior, and Immunity, 25*(1), 40–45.

Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators; Centers for Disease Control and Prevention. (2012). Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. MMWR Surveillance Summaries, 6, pp. 11–19.

Bailey, A., Le Couteur, A., Gottesman, I., Bolton, P., Simonoff, E., Yuzda, E., et al. (1995). Autism as a strongly genetic disorder: Evidence from a British twin study. *Psychological Medicine, 25*(01), 63–77.

Banerjee, B. (2009). Physical hazards in employment and pregnancy outcome. *Indian Journal of Community Medicine, 34*(2), 89–93.

Bhutta, A. T., Cleves, M. A., Casey, P. H., Cradock, M. M., & Anand, K. J. S. (2002). Cognitive and behavioral outcomes of school-aged children who were born preterm. *JAMA: The Journal of the American Medical Association, 288*(6), 728–737.

Bilder, D., Pinborough-Zimmerman, J., Miller, J., & McMahon, W. (2009). Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. *Pediatrics, 123*(5), 1293–1300.

Bolton, P. F., Murphy, M., MacDonald, H., Whitlock, B., Pickles, A., & Rutter, M. (1997). Obstetric complications in autism: Consequences or causes of the condition? *Journal of the American Academy of Child & Adolescent Psychiatry, 36*(2), 272–281.

Botting, N., Powls, A., Cooke, R. W., & Marlow, N. (2006). Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birthweight children at 12 years. *Journal of Child Psychology and Psychiatry, 38*(8), 931–941.

Boyd, B., Odom, S., Humphreys, B., & Sam, A. (2010). Infants and toddlers with autism spectrum disorder: Early identification and early intervention. *Journal of Early Intervention, 32*(2), 75–98.

Bryson, S. E., Smith, I. M., & Eastwood, D. (1988). Obstetrical suboptimality in autistic children. *Journal of the American Academy of Child & Adolescent Psychiatry, 27*(4), 418–422.

Buchmayer, S., Johansson, S., Johansson, A., Hultman, C. M., Sparén, P., & Cnattingius, S. (2009). Can association between preterm birth and autism be explained by maternal or neonatal morbidity? *Pediatrics, 124*(5), e817–e825.

Burd, L., Severud, R., Kerbeshian, J., & Klug, M. G. (1999). Prenatal and perinatal risk factors for autism. *Journal of Perinatal Medicine, 27*(6), 441–450.
Burstyn, I., Sithole, F., & Zwaigenbaum, L. (2010). Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada. *Chronic Diseases in Canada, 30*(4), 125–134.
Centers for Disease Control and Prevention. Autism Spectrum Disorders – Signs and Symptoms. (2012). Retrieved March 29, 2012, from http://www.cdc.gov/NCBDDD/autism/facts.html
Chakrabarti, S., & Fombonne, E. (2001). Pervasive developmental disorders in preschool children. *JAMA: The Journal of the American Medical Association, 285*(24), 3093–3099.
Chhabra, S., Dargan, R., & Bawaskar, R. (2007). Oligohydramnios: A potential marker for serious obstetric complications. *Journal of Obstetrics & Gynecology, 27*(7), 680–683.
Clapp, J. F., Lopez, B., & Simonean, S. (1999). Nuchal cord and neurodevelopmental performance at 1 year. *Journal of the Society for Gynecologic Investigation, 6*(5), 268–272.
Cryan, E., Byrne, M., O'Donovan, A., & O'Callaghan, E. (1996). Brief report: A case–control study of obstetric complications and later autistic disorder. *Journal of Autism and Developmental Disorders, 26*(4), 453–460.
Daley, T. C. (2004). From symptom recognition to diagnosis: Children with autism in urban India. *Social Science & Medicine, 58*(7), 1323–1335.
Daley, T. C., & Sigman, M. D. (2002). Diagnostic conceptualization of autism among Indian psychiatrists, psychologists, and pediatricians. *Journal of Autism and Developmental disorders, 32*(1), 13–23.
Daley, T. C., Singhal, N., & Krishnamurthy, V. (2013). Ethical considerations in conducting research on autism spectrum disorders in low and middle income countries. *Journal of Autism and Developmental Disorders.*
Deb, S., Prasad, K. B. G., Seth, H., & Eagles, J. M. (1997). A comparison of obstetric and neonatal complications between children with autistic disorder and their siblings. *Journal of Intellectual Disability Research, 41*(1), 81–86.
Depino, A. M. (2006). Maternal infection and the offspring brain. *The Journal of Neuroscience, 26*(30), 7777–7778.
Deykin, E. Y., & MacMahon, B. (1980). Pregnancy, delivery, and neonatal complications among autistic children. *Archives of Pediatrics & Adolescent Medicine, 134*(9), 860–864.
Dodds, L., Fell, D. B., Shea, S., Armson, B. A., Allen, A. C., & Bryson, S. (2011). The role of prenatal, obstetric and neonatal factors in the development of autism. *Journal of Autism and Developmental Disorders, 41*(7), 891–902.
Dole, N., Savitz, D. A., Hertz-Picciotto, I., Siega-Riz, A. M., McMahon, M. J., & Buekens, P. (2003). Maternal stress and preterm birth. *American Journal of Epidemiology, 157*(1), 14–24.
Dubovický, M. (2010). Neurobehavioral manifestations of developmental impairment of the brain. *Interdisciplinary Toxicology, 3*(2), 59–67.
Durkin, M. S., Maenner, M. J., Newschaffer, C. J., Lee, L. C., Cunniff, C. M., Daniels, J. L., et al. (2008). Advanced parental age and the risk of autism spectrum disorder. *American Journal of Epidemiology, 168*(11), 1268–1276.
El-Baz, F., Ismael, N. A., & El-Din, S. M. N. (2011). Risk factors for autism: An Egyptian study. *Egyptian Journal of Medical Human Genetics, 12*(1), 31–38.
Finegan, J. A., & Quarrington, B. (1979). Pre-, peri-, and neonatal factors and infantile Autism. *Journal of Child Psychology and Psychiatry, 20*(2), 119–128.
Fombone, E. (2002). Prevalence of childhood disintegrative disorder. *Autism, 6*(2), 149–157.
Gardener, H., Spiegelman, D., & Buka, S. L. (2011). Perinatal and neonatal risk factors for autism: A comprehensive meta-analysis. *Pediatrics, 128*(2), 344–355.
Ghaziuddin, M., Shakal, J., & Tsai, L. (1995). Obstetric factors in Asperger syndrome: Comparison with high-functioning autism. *Journal of Intellectual Disability Research, 39*(6), 538–543.
Gillberg, C., & Gillberg, I. C. (1983). Infantile autism: A total population study of reduced optimality in the pre-, peri-, and neonatal period. *Journal of Autism and Developmental Disorders, 13*(2), 153–166.
Glasson, E. J., Bower, C., Petterson, B., de Klerk, N., Chaney, G., & Hallmayer, J. F. (2004). Perinatal factors and the development of autism: A population study. *Archives of General Psychiatry, 61*(6), 618.
Grether, J. K., Anderson, M. C., Croen, L. A., Smith, D., & Windham, G. C. (2009). Risk of autism and increasing maternal and paternal age in a large North American population. *American Journal of Epidemiology, 170*(9), 1118–1126.
Guinchat, V., Thorsen, P., Laurent, C., Cans, C., Bodeau, N., & Cohen, D. (2012). Pre-, peri- and neonatal risk factors for autism. *Acta Obstetricia et Gynecologica Scandinavica, 91*(3), 287–300.
Hack, M., Klein, N. K., & Taylor, H. G. (1995). Long-term developmental outcomes of low birth weight infants. *The Future of Children,* 176–196.
Hashimoto, K., & Clapp, J. F. (2003). The effect of nuchal cord on amniotic fluid and cord blood erythropoietin at delivery. *Journal of the Society for Gynecologic Investigation, 10*(7), 406–411.
Hultman, C. M., Sparén, P., & Cnattingius, S. (2002). Perinatal risk factors for infantile autism. *Epidemiology, 13*(4), 417–423.
ICMR. (2006). *Ethical guidelines for biomedical research on human participants.* New Delhi: Indian Council of Medical Research.
International Institute for Population Sciences (IIPS) and Macro International. (2007). National Family Health Survey (NFHS-3) (2005-2006). India: Key Findings. Mumbai: IIPS.
Johnson, S., Hollis, C., Kochhar, P., Hennessy, E., Wolke, D., & Marlow, N. (2010). Autism spectrum disorders in extremely preterm children. *The Journal of Pediatrics, 156*(4), 525–531.
Juul-Dam, N., Townsend, J., & Courchesne, E. (2001). Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. *Pediatrics, 107*(4), e63.
Karande, S. (2006). Autism: A review for family physicians. *Indian Journal of Medical Sciences, 60*(5), 205–215.
Karim, S. A., Bakhtawar, I., Butta, A. T., & Jalil, M. (1998). Effects of first and second trimester vaginal bleeding on pregnancy outcome. *Journal of Pakistan Medical Association, 48*(2), 40–42.
Kaur, J., & Kaur, K. (2012). Conditions behind fetal distress. *Annals of Biological Research, 3*(10), 4845–4851.
Kim, Y. S., Leventhal, B. L., Koh, Y. J., Fombonne, E., Laska, E., Lim, E. C., et al. (2011). Prevalence of autism spectrum disorders in a total population sample. *American Journal of Psychiatry, 168*(9), 904–912.
Kinney, D. K., Munir, K. M., Crowley, D. J., & Miller, A. M. (2008). Prenatal stress and risk for autism. *Neuroscience & Biobehavioral Reviews, 32*(8), 1519–1532.
Kolevzon, A., Gross, R., & Reichenberg, A. (2007). Prenatal and perinatal risk factors for autism: A review and integration of findings. *Archives of Pediatrics & Adolescent Medicine, 161*(4), 326–333.
Krishnamurthy, V. (2008). A clinical experience of autism in India. *Journal of Developmental & Behavioral Pediatrics, 29*(4), 331–333.
Kröger, A., Hänig, S., Seitz, C., Palmason, H., Meyer, J., & Freitag, C. M. (2011). Risk factors of autistic symptoms in children with ADHD. *European Child & Adolescent Psychiatry, 20*(11-12), 1–10.
Kuban, K. C., O'Shea, T. M., Allred, E. N., Tager-Flusberg, H., Goldstein, D. J., & Leviton, A. (2009). Positive screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in extremely low gestational age newborns. *The Journal of Pediatrics, 154*(4), 535–540.
Kumar, A., & Bhat, B. V. (1996). Epidemiology of respiratory distress of newborns. *Indian Journal of Pediatrics, 63*(1), 93–98.
Larsson, H. J., Eaton, W. W., Madsen, K. M., Vestergaard, M., Olesen, A. V., Agerbo, E., et al. (2005). Risk factors for autism: Perinatal factors, parental psychiatric history, and socioeconomic status. *American Journal of Epidemiology, 161*(10), 916–925.
Lord, C., Mulloy, C., Wendelboe, M., & Schopler, E. (1991). Pre-and perinatal factors in high-functioning females and males with autism. *Journal of Autism and Developmental Disorders, 21*(2), 197–209.
Losh, M., Esserman, D., Anckarsäter, H., Sullivan, P. F., & Lichtenstein, P. (2012). Lower birth weight indicates higher risk of autistic traits in discordant twin pairs. *Psychological Medicine, 42*(5), 1091–1102.
Low, J. A. (2004). Determining the contribution of asphyxia to brain damage in the neonate. *Journal of Obstetrics and Gynaecology Research, 30*(4), 276–286.
Maimburg, R. D., & Vaeth, M. (2006). Perinatal risk factors and infantile Autism. *Acta Psychiatrica Scandinavica, 114*(4), 257–264.
March of Dimes, PMNCH, Save the Children, WHO. (2012). Born too soon: The global action report on preterm birth. Geneva: World Health Organization.

Marlow, N., Wolke, D., Bracewell, M. A., & Samara, M. (2005). Neurologic and developmental disability at six years of age after extremely preterm birth. *New England Journal of Medicine, 352*(1), 9–19.
Mason-brothers, A. N. N. E. , Ritvo, E. R., Guze, B., Mo, A., Freeman, B. J., Funderburk, S. J., et al. (1987). Pre-, peri-, and postnatal factors in 181 autistic patients from single and multiple incidence families. *Journal of the American Academy of Child & Adolescent Psychiatry, 26*(1), 39–42.
Mefford, H. C., Batshaw, M. L., & Hoffman, E. P. (2012). Genomics, intellectual disability, and autism. *New England Journal of Medicine, 366*(8), 733–743.
Mervis, C. A., Decoufle, P., Murphy, C. C., & Yeargin-Allsopp, M. (2008). Low birthweight and the risk for mental retardation later in childhood. *Paediatric and Perinatal Epidemiology, 9*(4), 455–467.
Minshew, N. J., & Williams, D. L. (2007). The new neurobiology of autism: Cortex, connectivity, and neuronal organization. *Archives of Neurology, 64*(7), 945.
Muralidharan, K., & Kremer, M. (2006). *Public and private schools in rural India*. Cambridge, MA: Harvard University, Department of Economics.
Muthayya, S. (2009). Maternal nutrition & low birth weight-what is really important. *Indian Journal of Medical Research, 130*(5), 600–608.
Nelson, K. B. (1991). Prenatal and perinatal factors in the etiology of autism. *Pediatrics, 87*(5), 761–766.
Ornitz, E. M. (1985). Neurophysiology of infantile autism. *Journal of the American Academy of Child Psychiatry, 24*(3), 251–262.
Pardo, C. A., & Eberhart, C. G. (2007). The neurobiology of autism. *Brain Pathology, 17*(4), 434–447.
Parner, E. T., Schendel, D. E., & Thorsen, P. (2008). Autism prevalence trends over time in Denmark: Changes in prevalence and age at diagnosis. *Archives of Pediatrics & Adolescent Medicine, 162*(12), 1150.
Patra, S., & Arun, P. (2011). Use of Indian scale for assessment of autism in child guidance clinic: An experience. *Indian Journal of Psychological Medicine, 33*(2), 217–219.
Piven, J., Simon, J., Chase, G. A., Wzorek, M., Landa, R., Gayle, J., et al. (1993). The etiology of autism: Pre-, peri-and neonatal factors. *Journal of the American Academy of Child & Adolescent Psychiatry, 32*(6), 1256–1263.
Registrar General of India in Collaboration with Centre for Global Health Research, Canada. (2006). Maternal mortality in India: 1997–2003, trends, causes and risk factors. Sample Registration System, Registrar General of India and Centre for Global Health Research, University of Toronto, Canada.
Reichenberg, A., Gross, R., Weiser, M., Bresnahan, M., Silverman, J., Harlap, S., et al. (2006). Advancing paternal age and autism. *Archives of General Psychiatry, 63*(9), 1026–1032.
Rellini, E., Tortolani, D., Trillo, S., Carbone, S., & Montecchi, F. (2004). Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC) correspondence and conflicts with DSM-IV criteria in diagnosis of autism. *Journal of Autism and Developmental Disorders, 34*(6), 703–708.
Schendel, D., & Bhasin, T. K. (2008). Birth weight and gestational age characteristics of children with autism, including a comparison with other developmental disabilities. *Pediatrics, 121*(6), 1155–1164.
Sharan, P. (2006). Need for epidemiological work on autism in India. *Journal of the Indian association of Child and Adolescent Mental Health, 2*(3), 700–701.
Shelton, J. F., Tancredi, D. J., & Hertz-Picciotto, I. (2010). Independent and dependent contributions of advanced maternal and paternal ages to autism risk. *Autism Research, 3*(1), 30–39.
Singh, U., Singh, N., & Shikha, S. (2007). A prospective analysis of etiology and outcome of preterm labor. *Journal of Obstetrics and Gynecology of India, 57*(1), 48–52.
Singhi, P., & Malhi, P. (2001). Clinical and neurodevelopmental profile of young children with autism. *Indian Pediatrics, 38*(4), 384.
Sipilä, P., Hartikainen-Sorri, A. L., Oja, H., & Wendt, L. (2005). Perinatal outcome of pregnancies complicated by vaginal bleeding. *BJOG: An International Journal of Obstetrics & Gynaecology, 99*(12), 959–963.
Spinillo, A., Capuzzo, E., Stronati, M., Ometto, A., Orcesi, S., & Fazzi, E. (1995). Effect of preterm premature rupture of membranes on neurodevelopmental outcome: Follow up at two years of age. *BJOG: An International Journal of Obstetrics & Gynaecology, 102*(11), 882–887.
Stein, D., Weizman, A., Ring, A., & Barak, Y. (2006). Obstetric complications in individuals diagnosed with autism and in healthy controls. *Comprehensive Psychiatry, 47*(1), 69–75.
Sun, X., & Allison, C. (2010). A review of the prevalence of autism spectrum disorder in Asia. *Research in Autism Spectrum Disorders, 4*(2), 156–167.
UNICEF India – Child protection – Why is birth registration important? (2006) http://www.unicef.org/india/child_protection_1650.htm (Accessed on January 3rd 2013).
United Nations Children's Fund and World Health Organization, Low Birthweight: Country, regional and global estimates. UNICEF, New York, 2004.
Wallace, A. E., Anderson, G. M., & Dubrow, R. (2008). Obstetric and parental psychiatric variables as potential predictors of autism severity. *Journal of Autism and Developmental Disorders, 38*(8), 1542–1554.
Ward, R. M., & Beachy, J. C. (2003). Neonatal complications following preterm birth. *BJOG: An International Journal of Obstetrics & Gynaecology, 110*, 8–16.
Wood, N. S., Marlow, N., Costeloe, K., Gibson, A. T., & Wilkinson, A. R. (2000). Neurologic and developmental disability after extremely preterm birth. *New England Journal of Medicine, 343*(6), 378–384.
Zambrino, C. A., Balottin, U., Bettaglio, E., Gerardo, A., & Lanzi, G. (1995). Obstetrical subopttmality in children with autism: An Italian sample. *Journal of Autism and Developmental Disorders, 25*(5), 553–555.
Zhang, X., Lv, C. C., Tian, J., Miao, R. J., Xi, W., Hertz-Picciotto, I., et al. (2010). Prenatal and perinatal risk factors for autism in China. *Journal of Autism and Developmental Disorders, 40*(11), 1311–1321.
Zwaigenbaum, L., Szatmari, P., Jones, M. B., Bryson, S. E., Maclean, J. E., Mahoney, W. J., et al. (2002). Pregnancy and birth complications in autism and liability to the broader autism phenotype. *Journal of the American Academy of Child & Adolescent Psychiatry, 41*(5), 572–579.