

Review Article**A Systematic Review on Environmental Factors associated with Autism Spectrum Disorder in Bangladesh***Md. Shahid Khan¹, Shafi Mohammad Tareq², Mohammad Alamgir Kabir³***Abstract**

Objective: Exposure to different environmental factors appears to be widespread, detrimental to human brain development and a potential risk factor for autism spectrum disorder (ASD). We conducted a systematic review on the relationship between environmental factors and ASD in Bangladesh. **Methods:** This paper reviews the evidence on modifiable environmental factors that have been associated, in some studies, with ASD, including socio-demographic and physical environmental factors exposures during prenatal and postnatal periods. Besides, this review is restricted to human studies with at least 50 cases of ASD, having a valid comparison group, conducted within the past two decades. Moreover, literatures searched using three electronic databases (PubMed, Google Scholar, and Biomed Central) from August 2020 to January 2021, based on the PRISMA guidelines. Literatures screened by two distinguished reviewers (Khan MS; Tareq SM), and resolved differences by consensus and further discussion with third reviewer based on requirements. Then selected the eligible 21 studies based on inclusion criteria's. Two of the reviewers independently screened articles, extracted data for descriptive information and assessed risk of bias by using the Newcastle-Ottawa scale (NOS). **Results:** There is no article found with poor quality in NOS. The overall quality of the studies is high. There are strong association between ASD risk and some factors such as advanced maternal age, lead exposure during pregnancy and early childhood, blood Arsenic level of ASD children. Though few factors are related to increased risk of ASD; so far, no specific environmental factor has been found associated with increased risk of ASD with large power of study. **Conclusion:** There is appears to be a lack of such type of study in developing countries like Bangladesh. Therefore, nationwide widespread research needed to address the modifiable environmental risk factors for ASD.

Keywords: Environmental Factors, Autism Spectrum Disorders, Bangladesh

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Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders commonly occur among males¹. ASD includes severe developmental disorders characterized by atypical socialization, restricted and repetitive behaviors, and interests².

The global prevalence of ASD has been increasing

over the past few decades³⁻⁷, and now it is estimated to be 1–3% in developed countries⁸⁻¹¹. In Bangladesh, 17 per 10,000 babies have ASD¹², where it is observed 1.5/1000 in another study (30/1000 in Dhaka city and 7/10,000 in rural area)¹³. Prevalence of the ASD at rural community in Bangladesh is found 0.75/1000 children (0.075%)¹³⁻¹⁵.

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ASD shows high heritability of ~80%¹⁶. Twin studies suggested that 80–90% of ASD is caused by heritable factors, while estimated 40–50% of variance is found by different environmental factors^{9,17}. Besides, Hansen et al. found up to 40% rise in prevalence of ASD in Denmark due to yet unknown environmental causes¹⁸. Studies of environmental factors of ASD risk, compared to genetic studies, are in their infancy¹⁷, and inconclusive yet^{19,20}.

Several environmental factors (pre-natal and post-natal) become a concern for ASD though it is largely a genetic disorder. Thus, factors affecting environment are contribute to the alteration of genes associated with ASD²¹. Numerous previous studies on environmental factors of ASD risk have been limited by small sample size, retrospective review or cross-sectional design, indirect measurement of exposure¹⁷. To prevent ASD, it is important to identify the modifiable environmental risk factors²² which will represent potential targets for environmental pollution reduction efforts to reduce the risk of ASD Development and severity. Besides, the prevalence of ASD has risen significantly in recent years though it is not properly prioritized in developing countries, like Bangladesh. The aim of this systematic review is to recapitulate the evidence from included studies regarding the socio-demographic factors and physical environmental factor exposures during prenatal and postnatal periods for ASD risk comparison to controls and to explore the real scenario in Bangladesh compared to other countries.

Methods

Search strategy: The authors searched literatures on Environmental Factors and ASD using the three electronic databases (PubMed and Google Scholar and Biomed Central) from August 2020 to January 2021 based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines²³. The authors also gathered some additional records from other sources.

The search was restricted to peer-reviewed full text Journal publications in English, related to Environmental Factors and Autism Spectrum Disorder. Study review and selection were completed independently by two distinguished reviewers (Khan MS & Tareq SM), with disagreements resolved through consensus and further discussion with third reviewer based on requirements.

Inclusion criteria: To persuade review requirements and reduce selection bias, articles were eligible if (1) observational (case-control, cohort) studies (having a valid comparison group); (2) participants birth date not before 1997; (3) only human studies; (4) minimum 50 ASD cases; (5) focus on potential socio-demographic and physical environmental factors exposure during prenatal and postnatal periods in association with ASD; (6) a study published from January 2011 to December 2020 to focus on recent research.

Exclusion criteria: Studies were excluded if (1) birth before 1997; (2) old data/ data taken before 1997; (3) cohort studies without control; (4) abstracts, thesis, case reports, comments, reviews, or conference proceedings.

Study selection and data extraction: All retrieved articles (286) were first organized by title. The titles and abstracts of all references were screened independently by key reviewer (Khan MS) after removing 37 duplicates, and a publication was excluded if the reviewers unanimously found that it did not meet the given eligibility criteria (Figure1). Tow of the reviewers reviewed full texts independently and the disagreement was resolved by discussion or consensus with the other reviewer. **Data synthesis:** Identified different environmental factors for ASD risk (association or data/percentage) were sorted by socio-demographic and physical environmental factors exposures during prenatal and postnatal periods.

Quality Assessment:

The risk of bias assessed using the Newcastle-Ottawa Scale (NOS) for evaluating the quality of included studies in this review²⁵ and it is recommended by the Cochrane Collaboration & by a systematic review on 2015^{26,14}. The NOS quality instrument is scored by awarding a star for each answer that is marked with an asterisk below²⁷. Authors rated the quality of the studies (good, fair and poor) by awarding stars in each domain following the guidelines of the NOS^{28,29}. Another rating that studies receive a score of 6 or above is considered as high quality for quality of strength²⁴. Quality assessment was checked independently by two distinguished reviewers (Khan MS, Tareq SM), and any disagreements were solved by the third one.

Results

21 eligible studies were included in the present study using the PRISMA flow chart (Figure 1).

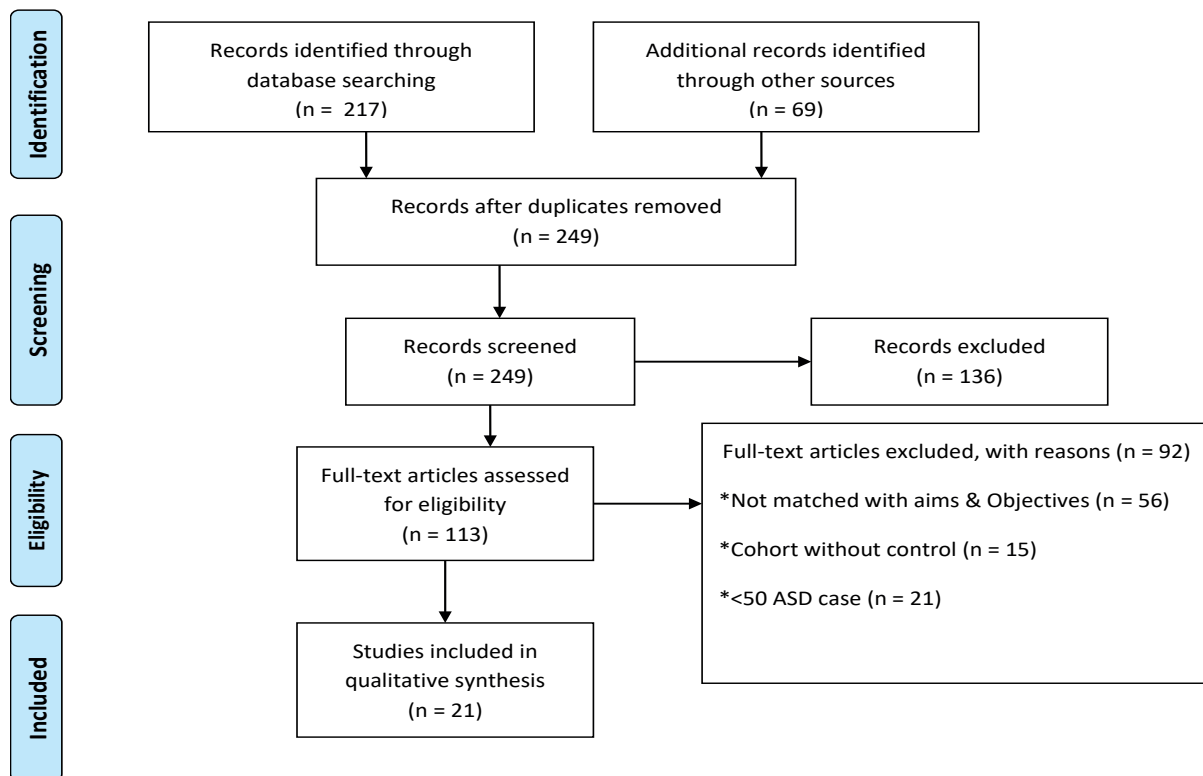


Figure 1: PRISMA Flow Diagram (Moher et al., 2009)²³

The characteristics of the included studies are sorted by publication year. The ages of samples were from two to 15 years, sample sizes ranged from 50 to 2961 participants for ASD cases and from 30 to 115632 for controls. All the studies were observational (case-control including two cohorts) in design and published during 2012-2020.

The study results are shortly summarized in Table 1. Quality scores for the studies, assessing risk of bias. 20 studies are of good quality where only one study³⁰ is fair quality based on “good, fair, poor” rating of NOS.^{28,29} Additionally, the overall qualities of strength of the studies are high based on NOS rating (≥ 6), rated by Farsad-Naeimi et al.²⁴

Among the 21 eligible studies, 17 specifically assessed socio-demographic factors and 17 assessed physical environmental factors exposures during prenatal and postnatal periods. Screening tools (total 14 standard tools/scales) and records from existing databases or registered in special schools, hospitals/clinics were used, and Clinical/Physical Assessments were done in eight studies by experts to diagnose or rate the ASD.

Socio-demographic factors (shown in figure 2):

Parental age: Total 13 studies evaluated the parental age.

Seven out of 11 studies found positive association between maternal age and ASD risk. Advanced maternal age was strongly associated with increased ASD risk with OR of 1.13 (95% CI=1.05-1.20, $p < 0.001$)³¹, with Matched Odds Ratio (MOR) = 3.13, 95% CI (1.41, 6.93, $p < 0.01$)³², and with OR of 1.80 (95%CI: 1.27, 2.54, $p = 0.0008$)³³. Besides, advanced maternal age (30.3 to ≥ 35 years) during pregnancy was significantly associated with ASD risk, where ≥ 30 years were associated without significant.^{2,34-36} However, previous two studies found no association between maternal age and ASD compared to controls.^{37,38} Moreover, two studies found maternal age of ASD was same as controls.^{39,40}

Advanced paternal age (≥ 30 years) was significant ($p = 0.01$) with ASD risk³⁷, and Rahbar et al. found it has very strong association with increased ASD risk [MOR = 2.54, 95% CI (1.34, 4.82, $p < 0.01$)]³² compared to controls. However, advanced paternal age (≥ 30 years) at child's birth was not significantly associated with ASD risk.^{33,34,36} Advanced parental age was significant among ASD cases⁴¹, while Talbott et al., (2015a)

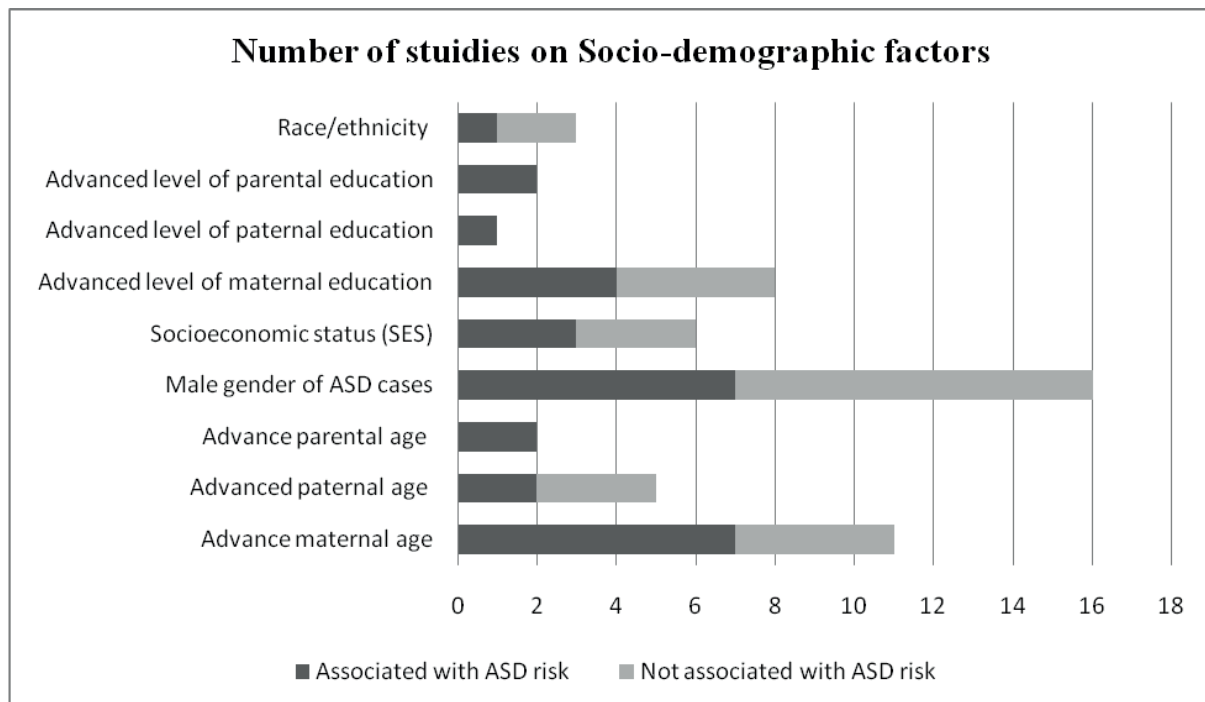


Figure 2. Number of studies on Socio-demographic factors

found it was in mixed pattern⁴².

Gender of ASD cases: Seven out of 16 studies found positive relations between male gender and ASD. Male gender was significantly associated with increased OR of ASD risk compared to controls ($p < 0.001$, OR 3.95; 95% CI 2.82, 5.53)³⁵, and with OR of 2.87 (95%CI= 1.67, 4.90)⁴¹. Several recent studies found significant or positive relations between male sex with ASD risk.^{31,36,40,43,44} However, very recent studies from USA and Jamaica found no significant/positive relations of male gender with ASD.^{2,30,32,34,37,38,39,42,45}

Socioeconomic status (SES): Only three studies out of six found a positive association between higher SES and increased ASD risk compared to controls,^{30,41,32} in which opposite findings observed in other studies.^{31,35,40}

Parental education: Four out of eight studies found positive relation between advanced level of maternal education and ASD risk compared to controls,^{2,41,32,39} where rest of the studies found opposite/mixed results.^{37,38,40,42} Only one study investigated paternal educational level and found positive trends.³² Parental advanced level

of education at child birth has also significant relations with ASD risk compared to TD controls {matched odds ratio (MOR) = 3.36, 95% CI (1.85, 6.10), $p < 0.01$ }³² and it was also significant in univariable analysis ($p < 0.01$), {MOR = 5.60, 95 % CI (2.16, 14.50)}³⁰.

Race: Maternal race was significantly different ($p < 0.0001$) between ASD and controls⁴⁰. However, race/ethnicity of ASD was similar to controls in other studies^{39,44}.

Physical environmental factors:

17 studies examined several physical environmental factors exposures such as: mercury, lead, arsenic, cadmium, zinc, copper, manganese, cyanide, air neurotoxicants, pesticides, vinyl flooring, air pollutants, sun light exposures, season of birth, and 25 endocrine disruptors, and these are demonstrated in figure 3.

Mercury: Two out of five studies revealed significant association between higher levels of blood mercury and ASD risk ($p \leq 0.001$) compared to controls,^{46,47} in which it was not significant in recent studies.^{30,43,48}

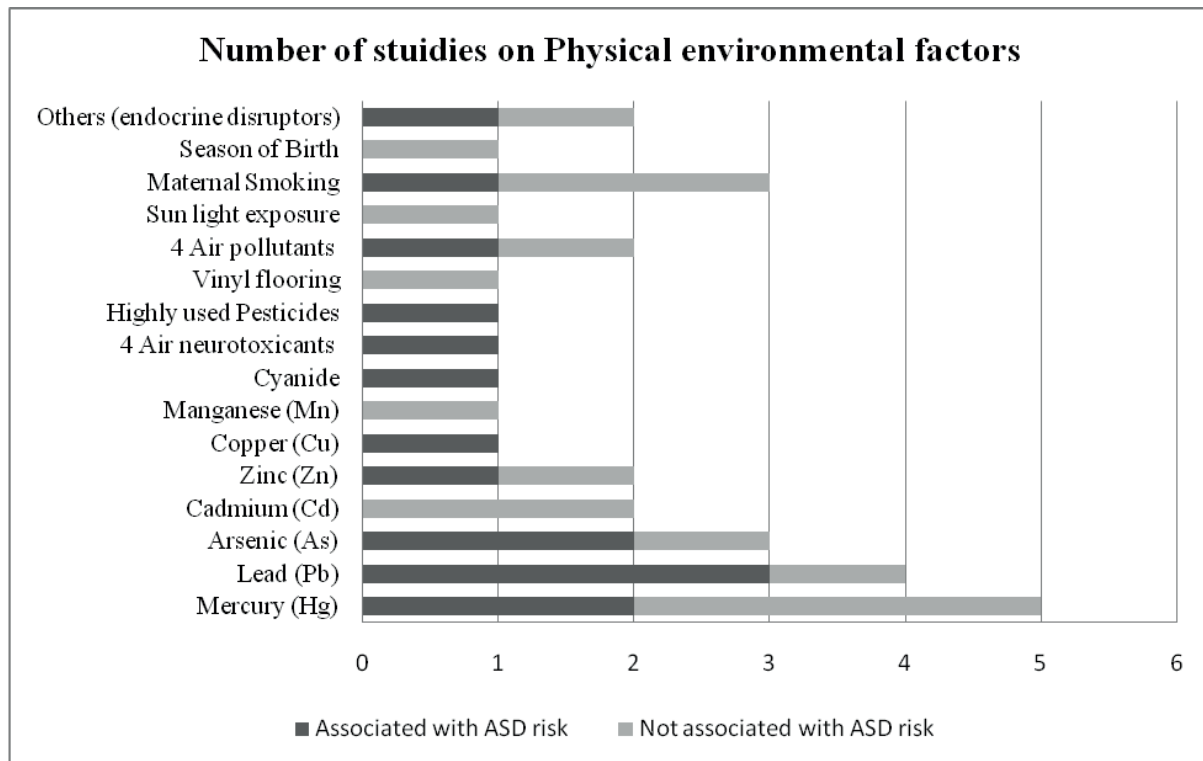


Figure 3. Number of studies on physical environmental factors

Lead: Sehgal et al. found significant/positive association between ASD in children and higher levels of lead,⁴⁸ while Talbott et al. (2015a) stated that, ASD risk increases due to lead exposure during pregnancy,⁴² and lead exposure significantly increased ASD risk compared to controls during pregnancy and early childhood ($p=0.001$)⁴⁷. However, Li et al. found, the level of blood lead was not considerably different between the two groups ($p=0.379$).⁴⁶

Arsenic: The children with ASD were significantly associated with higher level of blood arsenic compared to controls^{42,46}. However, Sehgal et al. found the geometric mean blood arsenic levels were higher in controls compared to cases ($p=0.01$)⁴⁸.

Cadmium: There was no significant association between cadmium exposure and ASD risk ($p<0.05$)^{46,48}.

Zinc and Copper: Li et al. (2014) found significantly lower mean serum zinc levels in children with ASD ($p<0.001$)⁴⁵. However, Sehgal et al. found it was higher in ASD case ($p=0.02$)⁴⁸. Besides, mean serum copper levels were significantly higher in children with ASD compared to controls ($p<0.001$)⁴⁵.

Manganese: No significant association was found

between mean blood manganese concentrations (BMC) and ASD in univariable general linear model (GLM) analysis ($p=0.29$), or in adjusted multivariable GLM analysis ($p=0.48$).³²

Cyanide: Significant association was found between ASD risk and cyanide exposure (OR 1.32) during pregnancy for singleton births of interviewed cases only.⁴²

Four Air neurotoxins (Styrene, chromium, methylene chloride, Polycyclic aromatic hydrocarbons (PAHs)): The adjusted OR for higher levels of ambient styrene in living areas during pregnancy for the interviewed case-control analysis (OR 2.04; 95 % CI = 1.17–3.58, $p=0.013$) and for the birth certificates (BC controls) analysis (OR 1.61; 95 % CI = 1.08–2.40, $p=0.018$) were associated with increased risk of ASD. In the BC comparison, higher ambient levels of chromium also elevated OR of 1.60 (95 % CI = 1.08–2.38, $p=0.020$), and OR of 1.52 was for interviewed analysis (OR = 1.52, 95 % CI = 0.87–2.66). There were borderline ORs for the BC comparison for methylene chloride (OR = 1.41, 95 % CI = 0.96–2.07, $p=0.082$) and PAHs (OR = 1.44, 95 % CI = 0.98–2.11, $p=0.064$).⁴²

Highly used Pesticides: Pesticides exposure within 2000 m from the maternal residence during

prenatal and infantile period was associated with increased OR for ASD. Some pesticide substances exposure in the first year of life increased the odds for the ASD with ID by up to 50%.²

Vinyl flooring: Number of rooms with vinyl flooring during prenatal and early postnatal period ($p=0.16$) was not significant among ASD compared to TD.³⁷

Four Air pollutants ($PM_{2.5}$, PM_{10} , Ozone (O_3), and NO_2): Mid-pregnancy air pollution was not associated with any neurodevelopmental groups including ASD in recent study in the USA.³⁴ However, from three months before pregnancy through year two exposure to $PM_{2.5}$ was associated with an approximate 50% increase risk of childhood ASD ($p=0.046$).³⁸

Sun light exposure: Duration of sun exposure/week was not significant with autistic children compared to controls ($P=0.49$), and serum 25-hydroxy vitamin D has no significant correlations with the duration of sun exposure/week ($P=0.96$).⁴⁹

Maternal Smoking: Maternal smoking during pregnancy or in 3 months prior to pregnancy (24.6% of ASD and 10.5% of controls) was associated with ASD risk,³⁸ or mixed pattern between two groups.⁴² Moreover, percentage of

maternal smoking during prenatal period was closer in both groups (38.9% in ASD & 34.4% in control) ($p=0.16$).⁴⁰

Season of Birth: Season of birth ($p=0.29$) was not associated with ASD risk.⁴⁴

Others: Hamra et al. found no association between prenatal exposures to 25 endocrine disruptor chemicals (EDCs) and ASD, with OR of near 1.00 in both primary and secondary analysis.³⁹ However, higher level of IL-4 was associated with increased odds of severe ASD (OR=1.40, 95% CI, 1.03, 1.91), and IL-1 β was associated with increased odds of mild/moderate ASD (OR=3.02, 95% CI, 1.43, 6.38).⁴⁴

Discussion

Considering published literature, this study appears to be the first systematic review conducted in Bangladesh to appraise the environmental factors of ASD risk. The study findings are inconsistent. The figure 4 presents the environmental factors investigated by ≥ 3 studies. This review demonstrated the various associations between exposures and ASD, in which the potential exposures can be modified at the individual or societal level, and tried to explore the real scenario in Bangladesh compared to other countries.

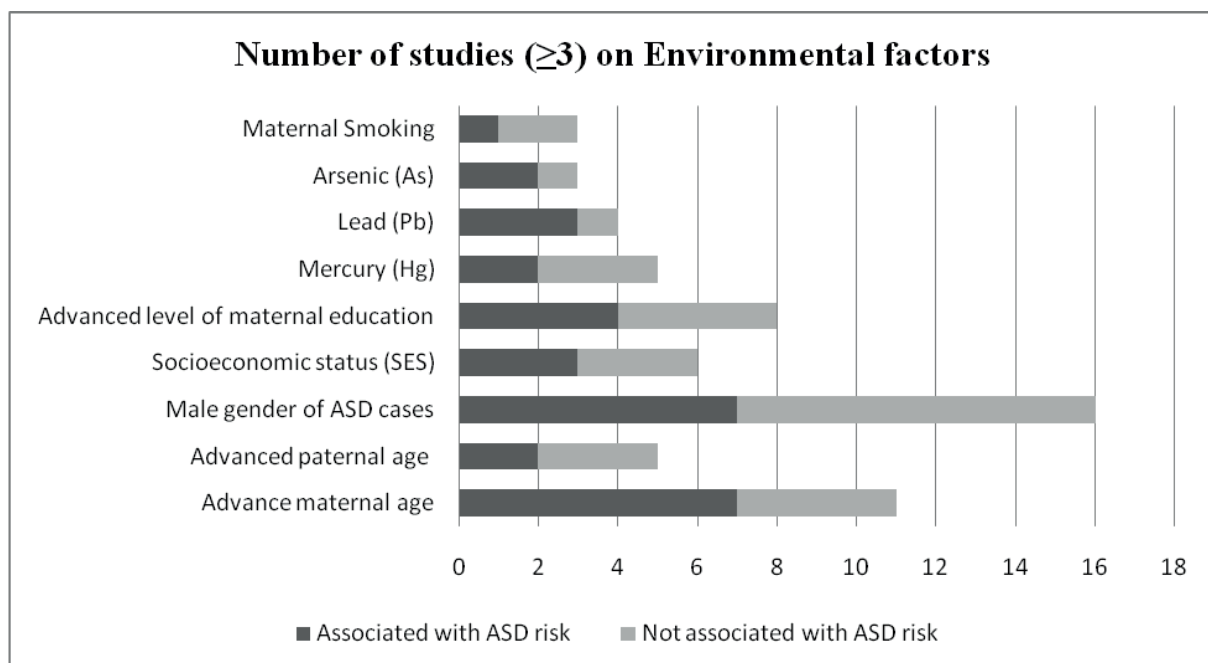


Figure 4. Number of studies (≥ 3) on Environmental factors

Socio-demographic factors: Most studies among 13 found positive association between advanced parental age and ASD risk in this review. Relationships between male genders ($k=16$), and

SES ($k=6$) with ASD risk found mixed results in the present review. There was positive relation between advanced level of maternal (four out of eight studies) education and ASD without

significant results, where race/ethnicity was inconclusive ($k=3$) in this review. Stewart (2019) found that, detection of ASD is related with many socio-demographic variables (geographic location, race/ethnicity, and socio-economic status, maternal education and age at the time of child's birth.⁵⁰

Physical environmental factors: This review found, Hg has less evidence with the development of ASD (two out of five studies) and this finding is similar to De Palma et al.⁵¹ Three out of four studies found significant association between ASD and lead exposure during pregnancy and early childhood, while two studies out of three found ASD was significant for level of blood arsenic in the present review. Wang et al. found in their SR & MA that, there is consistent evidence for inorganic arsenic (iAs) exposure, and inconsistent evidence of lead exposure for ASD risk.⁵²

Prenatal and infant exposure to several common ambient pesticides within 2000 m of their mother's residence increase the offspring's risk of ASD compared to controls ($k=1$) in this study. Tessari et al. recommended that, a possible association between pesticides and ASD by some evidence, though it is not conclusive.⁵³

PM_{2.5} exposure from three months before pregnancy through year two was associated with increased risk of childhood ASD ($k=1$) and mid-pregnancy air pollution exposures ($k=1$) was not significant with ASD risk in this review.

In this review, BMC ($k=1$), level of Cd exposure ($k=2$), vinyl flooring during prenatal and early postnatal period and Phthalates in dust at house ($k=1$), duration of sun exposure/week ($k=1$), season of birth ($k=1$) were not significant with ASD risk. Maternal smoking during pregnancy or in 3 months prior to pregnancy ($k=3$) were inconclusive with ASD risk in the present review. However, De Palma et al. found limited evidence for cadmium exposures with ASD risk.⁵¹ Also, the total dust phthalate esters (PAEs) levels in schools and kindergartens were significantly higher than those in homes.⁵⁴

Serum copper levels were significantly higher in ASD ($k=1$) where serum zinc levels ($k=2$) were inconclusive in this study. Frye et al. stated that, ASD is associated with zinc deficiency both prenatally and postnatally, and also found lower prenatal and postnatal copper and copper-zinc ratio in children with ASD as compared with

TD children.⁵⁵ However, Bölte et al. stated that, altered zinc-copper cycles increase offspring vulnerability to ASD,⁵⁶ and little evidence was found for ASD risk with hair metal concentration of copper in other study.⁵¹

Only two EDCs {Interleukin (IL)-1 β and IL-4} were associated with increased OR for severity of ASD in this review ($k=2$). Cytokine profiles have complex roles in neurodevelopment, and dysregulated levels may be indicative of genetic differences and environmental exposures or their interactions that relate to ASD.⁴⁴

The strong association between ASD with pollutants in more recent years (2000–2013) indicates the uprising environmental pollutions in developed world^{57,58} as well as its serious alarming for developing countries like Bangladesh. Bangladesh has the most polluted air in the world and Dhaka is the second most polluted capital city. The density of airborne particulate matter (PM) has reached 247 micrograms per cubic metre (mcm) in Dhaka (five times more than acceptable level of 50 PM/mcm) set by the National Ambient Air Quality Standard (NAAQS) of Bangladesh^{59,60}. Thus, to assess the role of environmental factors for the development of autism in Bangladesh, further studies are needed with larger sample size.

Strengths and limitations:

This is the first systematic review conducted in Bangladesh in this topic. A comprehensive search conducted in three relevant databases and gathered all potential investigated factors. The individual qualities of all studies are good except one study³⁰ in NOS^{28,29} and the qualities of strength are also high (≥ 6)²⁴. However, many potential studies of environmental risk factors related to ASD excluded for this review due to exclusion criteria's, which might have limited and negatively affected the number of references analyzed. In addition to, many studies were conducted in the USA ($k=9$), pointing to a global research bias. Moreover, only one study was found in this review from Bangladesh.

Conclusion

This review suggests strong evidence ($k\geq 3$) for advanced maternal age and advanced maternal education during pregnancy, lead exposure during pregnancy and early childhood with ASD risk. The present study demonstrates evidence for few socio-demographic and physical environmental factors

Table 1: Characteristics of included studies

S/N	Author and publication year (ref No.)	Study population (country)	Study Design (observational)	Sample size	Study population birth year/ age (year)	Environmental Exposures/ interventions	Exposure time	Main findings/outcomes	Quality of strength in NOS*
1	Volk et al. 2020	USA	CC**	ASD without ID (199), ASD with ID (180), ID without ASD (164), and healthy controls (414)	January 2000 to June 2003	Air pollutants: PM2.5, PM10, ozone (O3), and NO2	Prenatal/ during pregnancy	NDD was not associated with mid-pregnancy air pollution. Only IL-6 associated with ASD with ID even after adjusting for air pollution exposure.	High
2	Gil-Hernández et al. 2020	Córdoba, Spain	CC**	54/54	2–6 years	Mercury (Hg)	Not reported	No correlations between Hg in hair and Urine concentrations in the ASD group	High
3	Maia et al. 2019	Brazil	CC**	253/886	2-15 years	postnatal factors	Birth to present age.	Advanced maternal age, and male gender were significantly associated with ASD.	High
4	Hamra et al. 2019	California, USA	CC**	491 ASD, 155 ID, 73 controls	January 2000 to June 2003, (4–9 years)	25 endocrine disruptor chemicals	Prenatal	No association found between endocrine disruptor chemicals exposures and ASD.	High
5	Sehgal et al. 2019	Northern India.	CC**	60/60	3-12 years	Blood Heavy Metal (Hg, Pb, Zn, As, Cd)	Before, during pregnancy and postnatal	No significant association between exposure and ASD.	High
6	von Ehrenstein et al. 2019	California (USA)	CC**	2961/ 35 370	1998-2010	11 highly used pesticides within 2000 m from the maternal residence	Prenatal and infant	Pesticides exposure associated with increased OR for ASD.	High
7	Soke et al. 2019	USA	CC**	673/876	2.5-5.75 years (30–68 months)	Prenatal and Postnatal factors	Prenatal and Postnatal periods	Maternal race was different between ASD and controls.	High
8	Oommen et al. 2018	Northern and Eastern regions, KSA	CC**	100/100	3-10 years	Socio-demographic data and social history	Prenatal to postnatal	Maternal age during pregnancy was weakly associated with increased OR for ASD.	High
9	Li H et al. 2018	Han ethnics, China	CC**	180/184	3-8 years	Hg, As, Cd, Pb	Not reported	ASD children had significantly higher levels of Hg and As and a lower level of Cd, while Pb was not significantly different between the two groups.	High
10	Krakowiak et al. 2017	California, USA	CC**	214 ASD, 62 TD, and 27 DD as control	2–5 years	17 cytokines and chemokines of neonatal blood	Not reported	Race/ethnicity, season of Birth was not significant, male gender was significant. Higher level of IL-4 & IL-1 β was associated with increased odds of ASD.	High
11	Talbott et al. 2015a	Southwestern Pennsylvania, USA	CC**	Analytic group (217/224), BC controls (216/ 4,971)	January 2005 to December 2009	30 air neurotoxins	Pregnancy, first and second year of life	Living in areas with higher levels of styrene and chromium during pregnancy was associated with increased risk of ASD	High
12	Khanom et al. 2015	Dhaka city, Bangladesh	CC**	99/198	5-7 years	Socio-demographic data and Gestational Diabetes Mellitus (GDM)	During pregnancy	ASD had significantly older parents and higher socioeconomic status.	High
13	Philippat et al. 2015	California, US	CC**	50 ASD, 27 DD, 68 TD	2-5 years	Phthalate concentrations in house dust	Pre- and early post-natal	Phthalates in dust were not associated with ASD.	High

14	Talbott et al. 2015b	Southwestern Pennsylvania, USA	CC**	217/226	January 2005 to December 2009	Fine particulate matter (PM _{2.5})	Prenatal and early childhood	Both prenatal and postnatal exposures to pm _{2.5} associated with increased OR for ASD risk.	High
15	Rahbar et al. 2014	Jamaica	CC**	109/109 TD	2–8 years	Blood manganese concentrations (BMC)	Not reported	No significant association between mean BMC in ASD	High
16	Li SO et al. 2014	China	CC**	60/60	January 2011 to December 2013	Zn and Cu	Not reported	The significant lower mean serum Zn levels, and higher mean serum Cu levels found in ASD.	High
17	Alabdali et al. 2014	Saudi Arabia	CC**	52/30	3–12 years	Toxic heavy metals: Pb and Hg	Pregnancy and early childhood	Hg and Pb levels significantly associated with ASD.	High
18	Maramara et al. 2014	New Jersey, USA	Cohort (CC**)	268/115632	1998–2006	14 pre- and perinatal risk factors	Prenatal and perinatal	Advanced maternal age (≥35 years) was significantly higher among ASD.	High
19	Mamidala et al. 2013	India	Cohort (CC**)	192/471	Under 10 years	25 Prenatal, perinatal and neonatal risk factors	Prenatal, perinatal and neonatal	Advanced maternal age significantly associated with increased OR for ASD.	High
20	Rahbar et al. 2013	Jamaica	CC**	65/65	2–8 years	Blood Hg level	Early Childhood	Geometric mean blood Hg concentrations was not associated with increased OR for ASD.	High
21	Mostafa GA & AL-Ayadhi LY. 2012	Riyadh, KSA	CC**	50/30	5–12 years	25-hydroxy vitamin D	Not reported	Lower serum levels of 25-hydroxy vitamin D significantly associated with ASD risk.	High

*Quality of strength in Newcastle–Ottawa Scale (NOS).

**CC = Case-Control

with ASD risk, lack of large-scale study especially in developing countries like Bangladesh indicate to a critical need of further nationwide extensive research to address the modifiable environmental risk factors for better clinical recommendation and management.

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expertise and assistance throughout this review.

Conflict of interest: None declared.

Ethical issue: As this study was done based on secondary data, no ethical approval was needed.

Contribution of authors: The authors were involved equally in literature search, review, compilation, manuscript writing, revision and finalizing.

References

1. Ali AA, Cui X, Pertile RAN, Li X, Medley G, Alexander SA, et al. Developmental vitamin D deficiency increases foetal exposure to testosterone. *Mol Autism*. 2020;11(1):96.
2. von Ehrenstein OS, Ling C, Cui X, Cockburn M, Park AS, et al. Prenatal and infant exposure to ambient pesticides and autism spectrum disorder in children: population based case-control study. *BMJ* 2019;364:l962.
3. CDC. Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators; Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum

- disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010. *MMWR Surveill Summ* 2014;63(2):1-21.
4. French LR, Bertone A, Hyde KL, Fombonne E. Epidemiology of Autism Spectrum Disorders. In: Buxbaum JD, Hof PR. (eds.). *The Neuroscience of Autism Spectrum Disorders*. San Diego: Elsevier; 2013: pp.3-24.
5. Nassar N, Dixon G, Bourke J, Bower C, Glasson E, de Klerk N, et al. Autism spectrum disorders in young children: effect of changes in diagnostic practices. *Int J Epidemiol*. 2009;38(5): 1245-1254.
6. Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *Lancet*. 2006;368(9531):210–215.
7. Lauritsen MB, Pedersen CB, Mortensen PB. The incidence and prevalence of pervasive developmental disorders: a Danish population-based study. *Psychol Med*. 2004;34(7):1339-46.
8. Baio J, Wiggins L., Christensen DL, J Maenner M, Daniels J, Warren Z, et al. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 Sites, United States, 2014. *MMWR Surveillance summaries* 2018; 67(6): 1-23. Retrieved on April 6, 2021 from <https://www.cdc.gov/mmwr/volumes/67/ss/ss6706a1.htm>.
9. Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, et al. The changing epidemiology of autism spectrum disorders. *Annu Rev Public Health* 2017;38:81–102.
10. Sealey LA, Hughes BW, Sriskanda AN, Guest J, Gibson A, Johnson-Williams L, et al. Environmental factors in the development of autism spectrum disorders. *Environ Int*. 2016;88:288-298.
11. Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcin C, et al. Global prevalence of autism and other pervasive developmental disorders. *Autism Res* 2012; 5(3):160–79.
12. Molla MAM. Autism prevalence high in urban areas. *The Daily Star*, 13 July 2018. Retrieved on 6th April 2021 from <https://www.thedailystar.net/frontpage/autism-prevalence-high-urban-areas-1604551>.
13. Rahman F, Akhter S, Biswas A, Abdullah AM. Study on Prevalence of Autism in Bangladesh. Technical Report (Researchgate) 2016; retrieved from:10.13140/RG.2.2.33709.33765.
14. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med*. 2015;8(1):2-10.
15. Akhter S, Hussain AHME, Shefa J, Kundu GK, Rahman F, Biswas A. Prevalence of Autism Spectrum Disorder (ASD) among the children aged 18-36 months in a rural community of Bangladesh: A cross sectional study. *F1000Res*.2018;7:424.
16. Sandin S, Lichtenstein P, Kuja-Halkola R, Hultman C, Larsson H, Reichenberg A. The heritability of autism spectrum disorder. *JAMA*. 2017;318(12):1182-1184.
17. Modabbernia A, Velthorst E, & Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. *Mol Autism*. 2017;8(1):13.
18. Hansen SN, Schendel DE, Parner ET. Explaining the Increase in the Prevalence of Autism Spectrum Disorders: The Proportion Attributable to Changes in Reporting Practices. *JAMA Pediatr*. 2015;169(1):56–62.
19. Gialloreti LE, Mazzone L, Benvenuto A, Fasano A, Alcon A G, Kraneveld A, et al. Risk and Protective Environmental Factors Associated with Autism Spectrum Disorder: Evidence-Based Principles and Recommendations. *J Clin Med*. 2019;8(2):217.
20. Al-Hamdan AZ, Preetha PP, Albashaireh RN, Al-Hamdan MZ, Crosson WL. Investigating the effects of environmental factors on autism spectrum disorder in the USA using remotely sensed data. *Environ Sci Pollut Res Int* 2018;25(8):7924-7936.
21. Bhandari R, Paliwal JK, Kuhad A. Neuropsychopathology of Autism Spectrum Disorder: Complex Interplay of Genetic, Epigenetic, and Environmental Factors. In book: *Personalized Food Intervention and Therapy for Autism Spectrum Disorder Management*. *Adv Neurobiol*.2020;24:97-141.
22. Jung Y, Lee AM, McKee SA, Picciotto MR. Maternal smoking and autism spectrum disorder: meta-analysis with population smoking metrics as moderators. *Sci Rep*. 2017;7(1):4315.
23. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:2535.

24. Farsad-Naeimi A, Asjodi F, Omidian M, Askari M, Nouri M, Pizarro AB, et al. Sugar consumption, sugar sweetened beverages and Attention Deficit Hyperactivity Disorder: A systematic review and meta-analysis. *Complement Ther Med*. 2020;53:102512.
25. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomised studies in meta-analyses. Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada 2011. Retrieved on 6th July 2021 from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
26. Higgins JPT, Green S (Eds.). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Retrieved on 6th July 2021 from www.handbook.cochrane.org.
27. Gierisch JM, Beadles C, Shapiro A, McDuffie JR, Cunningham N, Bradford D, et al. Health Disparities in Quality Indicators of Healthcare Among Adults with Mental Illness [Internet]. Washington (DC): Department of Veterans Affairs (US); 2014 Oct. Appendix B, Newcastle-Ottawa Scale Coding Manual for Cohort Studies.
28. Sharmin S, Kypri K, Khanam M, Wadolowski M, Bruno R, Mattick RP. Parental Supply of Alcohol in Childhood and Risky Drinking in Adolescence: Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2017;14(3):287.
29. Newcastle-Ottawa Quality Assessment Form for Cohort Studies. Retrieved in 6th July 2021 from <https://www.ncbi.nlm.nih.gov/books/NBK115843/bin/appe-fm3.pdf>.
30. Rahbar MH, Samms-Vaughan M, Loveland KA, Ardjomand-Hessabi M, Chen Z, Bressler J, et al. Seafood consumption and blood mercury concentrations in Jamaican children with and without autism spectrum disorders. *Neurotox Res*. 2013;23(1): 22-38.
31. Oommen A, AlOmar RS, Osman AA, Aljofi HE. Role of environmental factors in autism spectrum disorders in Saudi children aged 3-10 years in the Northern and Eastern regions of Saudi Arabia. *Neurosciences (Riyadh)* 2018;23(4):286-291.
32. Rahbar MH, Samms-Vaughan M, Dickerson AS, Loveland KA, Ardjomand-Hessabi M, Bressler J, et al. Blood manganese concentrations in Jamaican children with and without autism spectrum disorders. *Environ Health* 2014;13:69.
33. Mamidala MP, Polinedi A, P T V PK, Rajesh N, Vallamkonda OR, Udani V, et al. Prenatal, perinatal and neonatal risk factors of Autism Spectrum Disorder: a comprehensive epidemiological assessment from India. *Res Dev Disabil*. 2013;34(9):3004-13.
34. Volk HE, Park B, Hollingue C, Jones KL, Ashwood P, Windham GC, et al. Maternal immune response and air pollution exposure during pregnancy: insights from the Early Markers for Autism (EMA) study. *J NeurodevDisord*. 2020;12(1):42.
35. Maia FA, Oliveira LMM, Almeida MTC, Alves MR, Saeger VSA, Silva VBD, et al. Autism spectrum disorder and postnatal factors: a case-control study in Brazil. *Rev Paul Pediatr*. 2019;37(4):398-405.
36. Maramba LA, He W, Ming X. Pre- and perinatal risk factors for autism spectrum disorder in a New Jersey cohort. *J Child Neurol*. 2014;29(12):1645-51.
37. Philippat C, Bennett DH, Krakowiak P, Rose M, Hwang HM, Hertz-Picciotto I. Phthalate concentrations in house dust in relation to autism spectrum disorder and developmental delay in the Childhood Autism Risks from Genetics and the Environment (CHARGE) study. *Environ Health* 2015;14:56.
38. Talbott, EO, Arena VC, Rager JR, Clougherty JE, Michanowicz DR, Sharma RK, et al. Fine particulate matter and the risk of autism spectrum disorder. *Environ Res* 2015;140:414-20.
39. Hamra GB, Lyall K, Windham GC, Calafat AM, Sjödin A, Volk H, et al. Prenatal Exposure to Endocrine-disrupting Chemicals in Relation to Autism Spectrum Disorder and Intellectual Disability. *Epidemiology (Cambridge, Mass.)* 2019;30(3):418-426.
40. Soke GN, Maenner M, Windham G, Moody E, Kaczaniuk J, DiGuseppi C, et al. Association Between Breastfeeding Initiation and Duration and Autism Spectrum Disorder in Preschool Children Enrolled in the Study to Explore Early Development. *Autism Res*. 2019;12(5):816-829.
41. Khanom F, Chowdhury S, Ahmed S, Moniruzzaman M, Ahmed MM. Association of autism spectrum disorder and gestational diabetes mellitus of mothers in Bangladesh. *Indian J Comm Health*. 2015;27(3):391-397.
42. Talbott EO, Marshall LP, Rager JR, Arena VC, Sharma RK, Stacy SI. Air toxics and the risk of autism spectrum disorder: the results of a population based case-control study in southwestern Pennsylvania.

- Environ Health.2015;14:80.
43. Gil-Hernández F, Gómez-Fernández AR, la Torre-Aguilar MJ, Pérez-Navero JL, Flores-Rojas K, Martín-Borreguero P, et al. Neurotoxicity by mercury is not associated with autism spectrum disorders in Spanish children. *Ital J Pediatr*. 2020;46(1):19.
 44. Krakowiak P, Goines PE, Tancredi DJ, Ashwood P, Hansen RL, Hertz-Picciotto I, et al. Neonatal Cytokine Profiles Associated With Autism Spectrum Disorder. *Biol Psychiatry* 2017;81(5):442-451.
 45. Li SO, Wang JL, Bjørklund G, Zhao WN, Yin CH. Serum copper and zinc levels in individuals with autism spectrum disorders. *Neuroreport* 2014;25(15):1216-20.
 46. Li H, Li H, Li Y, Liu Y, Zhao Z. Blood Mercury, Arsenic, Cadmium, and Lead in Children with Autism Spectrum Disorder. *Biol Trace Elem Res*. 2018;181(1):31-37.
 47. Alabdali A, Al-Ayadhi L, El-Ansary A. A key role for an impaired detoxification mechanism in the etiology and severity of autism spectrum disorders. *Behav Brain Funct* 2014;10(1):1-11.
 48. Sehgal R, Gulati S, Gupta YK, Sapra S, Mehta M, Pandey RM, et al. Blood Heavy Metal Levels in Children with Autism Spectrum Disorder: A Cross-Sectional Study From Northern India. *J. Nepal Paediatr. Soc*. 2019;39(1):6-14.
 49. Mostafa GA, & Al-Ayadhi LY. Reduced serum concentrations of 25-hydroxy vitamin D in children with autism: relation to autoimmunity. *J Neuroinflammation* 2012;9:201.
 50. Stewart L. Association of socio-demographic characteristics with autism spectrum disorder: measurement and identification timing in the U.S. A dissertation submitted to Johns Hopkins University, 2019; retrieved on 6th July 2021 from <https://jscholarship.library.jhu.edu/bitstream/handle/1774.2/61472/STEWART-DISSERTATION-2019.pdf?sequence=1>.
 51. De Palma G, Catalani S, Franco A, Brighenti M, Apostoli P. Lack of correlation between metallic elements analyzed in hair by ICP-MS and autism. *J Autism Dev Disord*. 2012;42(3):342–353.
 52. Wang M, Hossain F, Sulaiman R, Ren X. Exposure to Inorganic Arsenic and Lead and Autism Spectrum Disorder in Children: A Systematic Review and Meta-Analysis. *Chem Res Toxicol*. 2019;32(10):1904-1919.
 53. Tessari L, Angriman M, Díaz-Román A, Zhang J, Conca A, Cortese S. Association Between Exposure to Pesticides and ADHD or Autism Spectrum Disorder: A Systematic Review of the Literature. *J Atten Disord*. 2020; doi:10.1177/1087054720940402.
 54. Huang CN, Chiou YH, Cho HB, Lee CW. Children's exposure to phthalates in dust and soil in Southern Taiwan: A study following the phthalate incident in 2011. *Science of The Total Environment* 2019;696:33685.
 55. Frye RE, Cakir J, Rose S, Delhey L, Bennuri SC, Tippet M, et al. Early life metal exposure dysregulates cellular bioenergetics in children with regressive autism spectrum disorder. *Transl Psychiatry* 2020;10(1):1-12.
 56. Bölte S, Girdler S, Marschik PB. 2019. The contribution of environmental exposure to the etiology of autism spectrum disorder. *Cell Mol Life Sci*. 2019;76(7):1275–1297.
 57. Ritz B, Liew Z, Yan Q, Cui X, Virk J, Ketzel M, et al. Air pollution and Autism in Denmark. *Environ Epidemiol*. 2018;2(4):e028.
 58. Roberts AL, Lyall K, Hart JE, Laden F, Just AC, Bobb JF, et al. Perinatal Air Pollutant Exposures and Autism Spectrum Disorder in the Children of Nurses' Health Study II Participants. *Environ Health Perspect*. 2013;121(8):978-984.
 59. Khan S. Air pollution causing hazards to local environment. *The Financial Express*, Tuesday, 29 August 2020, retrieved on 23rd November 2021 from <https://thefinancialexpress.com.bd/views/air-pollution-causing-hazards-to-local-environment-1598711955>.
 60. Taylor MJ, Rosenqvist MA, Larsson H, Gillberg C, D'Onofrio BM, Lichtenstein P, et al. Etiology of Autism Spectrum Disorders and Autistic Traits Over Time. *JAMA Psychiatry*. 2020;77(9):936-943.