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# The Role of Prenatal Environmental Risk Factors in Autism Spectrum Disorder Severity: Insight from Lead Exposure, Tobacco Smoke, and Low Birth Weight

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Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition influenced by interactions between genetic susceptibility and environmental exposures during critical developmental periods. However, evidence regarding how environmental factors relate to ASD severity remains limited. This study aimed to examine the associations between urinary lead (Pb) levels, prenatal cigarette smoke exposure, history of low birth weight (LBW), and ASD severity, providing insights into potential environmental influences on clinical outcomes. A cross-sectional study was conducted among 43 children diagnosed with ASD attending a special needs school (SLB C) in Banjarbaru, South Kalimantan, Indonesia. Urinary Pb concentrations were measured using UV–Visible spectrophotometry. Information on prenatal cigarette smoke exposure and birth history was obtained through structured parental interviews. ASD severity was assessed using the Childhood Autism Rating Scale, Second Edition (CARS-2), and classified as mild–moderate or severe. Higher urinary Pb levels, prenatal cigarette smoke exposure, and a history of LBW were significantly associated with ASD severity, highlighting potential environmental risk factors that may influence clinical presentation and management strategies. In conclusion, among children with ASD in this school-based population, environmental and perinatal factors were associated with differences in ASD severity. While these findings are promising, emphasizing the need for further research can foster a sense of hope and motivation among researchers, clinicians, and students. Due to the cross-sectional design, causal inferences cannot be drawn. Further studies using longitudinal designs and objective exposure measurements are warranted.

**Keywords:** Autism, Cigarette, Heavy metal, Lead, Low birth weight

## INTRODUCTION

ASD is a highly complex neurodevelopmental disorder characterized by deficits in social interaction, communication, and unusual behavioural patterns. It appears during early childhood and has a significant impact on both individuals and society (Abdelkader et al., 2024). Given the rising incidence, understanding its prevalence and risk factors is vital for public health planning and intervention. The Canters for Disease Control (CDC) estimates that 1 in 44 children are diagnosed with ASD, while data from the United States (US) shows a higher figure, with 1 in 36 children diagnosed with ASD. Currently, the global prevalence of ASD is estimated at 0.6% of the total global population (Bozkurt et al., 2025; Sousamli et al., 2024), underscoring the urgent need for targeted research and policy responses.

The exact prevalence of ASD in Indonesia remains unknown. Women's Empowerment and Child Protection states that there are 2 new cases of ASD per 1,000 population, and 10 cases of ASD per 1,000 population

(Astuti & Suminar, 2022). Furthermore, with Indonesia's current population of 237.5 million and a population growth rate of 1.14%, the prevalence of ASD in Indonesia is estimated at 2.4 million. It is predicted to increase by 500 people per year since 2010 (Ramadhanty et al., 2024). Understanding local prevalence is essential for developing effective public health strategies and allocating resources appropriately.

The exact aetiology of ASD remains unclear, but most scientists worldwide believe an interaction between genetic and non-genetic factors, such as environmental influences, causes it. Recognizing these risk factors is crucial, as it highlights the importance of research in this area. Several genetic mutations have been confirmed to be associated with ASD, but most cases lack a clear genetic pathogenesis. Furthermore, some evidence supports the idea that environmental factors occurring early in life play a significant role in the development of ASD. Some frequently reported risk factors include gestational diabetes, hormonal imbalances, infections during pregnancy, exposure to environmental pollutants such as heavy metals, exposure to medications, nutritional deficiencies, advanced parental age, and a family history of mental illness (Wang et al., 2025). Several other factors have also been reported in previous studies, including LBW babies, maternal behaviours such as smoking or exposure to second-hand smoke, and exposure to heavy metals, such as lead (Pb). Additionally, several population studies or meta-analyses have shown that exposure to lead and second-hand smoke, the most studied heavy metals and environmental factors, are strongly associated with ASD (Chen et al., 2023; Goel & Aschner, 2021; Khan et al., 2025; Stojsavljevic et al., 2023).

Although several studies have shown that prenatal, perinatal, and postnatal and environmental factors increase the risk of ASD, few have examined their influence on ASD severity. Given Indonesia's high rates of LBW, cigarette consumption, and Pb pollution, investigating these factors' impact on ASD severity is particularly relevant. This research aims to fill this gap by examining the relationship between a history of LBW, lead exposure, and cigarette smoke on the severity of ASD, emphasizing its importance for local public health efforts.

This study offers several key contributions to the existing body of research on autism spectrum disorder (ASD). It enhances our theoretical understanding by clarifying the links between certain environmental and prenatal factors—such as exposure to lead, cigarette smoke, and instances of low birth weight—and the varying levels of ASD severity, focusing specifically on a population comprised solely of individuals with ASD rather than making comparisons with those who do not have the condition. On the methodology front, this research employs an exposure-based analytical approach within a clear educational context, enabling a structured examination of ASD severity in relation to identified prenatal and environmental risk factors among students at a specialized institution. The practical implications of these findings are significant, offering actionable insights for educators, healthcare providers, and policymakers. These insights can aid in early identification of risk, the development of targeted intervention strategies, and the implementation of proactive public health measures for children with ASD. Practically, the findings are expected to provide evidence-based insights for educators, healthcare professionals, and policymakers to support early risk stratification, targeted intervention strategies, and preventive public health actions for children with ASD. By focusing on students enrolled at the SLB C Banjarbaru, the only A-accredited public special needs school for children with ASD in South Kalimantan, this study offers context-specific evidence that may inform local and regional policies while also contributing to broader discussions on environmental risk factors and ASD severity.

## METHOD

### Research Design and Population

This study was an observational, analytical, cross-sectional study conducted on children diagnosed with ASD attending Special Needs School C (SLB C) in Banjarbaru, South Kalimantan. The study was conducted from August 2024 to January 2025, with urine sampling and data collection conducted on August 5-6, 2024. The subjects were students at SLB C Banjarbaru, selected based on the following inclusion criteria: children diagnosed with ASD by a health professional; registered as active students at SLB C Banjarbaru; and Parents/guardians willing to provide written informed consent. Subjects with children with hearing impairments, attention deficit hyperactivity disorder (ADHD), or Down syndrome; Parents/guardians refusing participation; and uncooperative children, making it impossible to collect urine samples or perform clinical assessments, were excluded from this study. Each subject will then have a urine sample taken, and the patient's parents will complete a structured questionnaire containing birth history and exposure to cigarette smoke during pregnancy. The urine samples taken will be analyzed for Pb levels at the Wetland Research Center Laboratory, Faculty of Medicine and Health Sciences (FKIK), Lambung Mangkurat University (ULM).

### Outcome and Research Variables Definition

The primary outcome, ASD severity assessed by CARS-2, is central to this study and aims to inform clinicians and researchers about meaningful differences in ASD presentation. The primary exposure variable was urinary Pb levels, analyzed as an indicator of environmental Exposure linked to ASD severity, acknowledging that no safe threshold exists for children. The results of Pb level measurements were then divided into two categories, namely low and high, based on the Threshold Limit Value (TLV) for Pb levels in urine as stipulated in the Decree of the Minister of Health No. 1406/MENKES/SK/XI/2002. According to this Decree, the TLV for Pb in urine is 0.15 mg/L. Therefore, urinary Pb levels <0.15 mg/L will be categorized as low Exposure, and ≥15 mg/L as high Exposure. Other exposure variables included Exposure to cigarette smoke during pregnancy

and a history of LBW. Pregnancy-specific cigarette smoke exposure was defined as maternal Exposure to active or passive cigarette smoke during pregnancy, expressed as the duration of Exposure per week (minutes/week) based on parent/guardian reports. For categorical analysis, second-hand smoke exposure was classified as: Unexposed: 0 minutes/week, and Exposed: >0 minutes/week. This exposed vs. unexposed categorization approach aligns with common practice in international epidemiological studies assessing the impact of second-hand smoke exposure on perinatal outcomes, including low birth weight, without establishing a specific biological threshold for duration (Ramadhanty et al., 2024; Yaya & Odusina, 2025). Classifying low birth weight as 1500–2499 grams and non-LBW as ≥2500 grams ensures transparency, helping clinicians and students trust the study's approach and findings (UNICEF & WHO, 2021).

**Urine Sampling**

The urine sample used was a midstream urine sample. Before sample collection, subjects were asked to wash their hands and clean the genital area using sterile gauze to ensure sample integrity and make the process feel controlled and reliable. The initial urine sample was discarded, and the midstream urine sample was collected in a sterile urine container.

The collected urine sample was stored in a closed container, protected from light, and immediately sent to the laboratory for analysis. Analysing within 2 hours emphasizes the importance of prompt handling, which helps the team feel competent and diligent. If a delay occurred, the sample was stored at 2–8°C and analysed within 8 hours of collection.

**Analysis of Pb Levels in Urine**

Analysis of (Pb levels in urine was conducted at the Wetland Research Centre Laboratory, FKIK, ULM, using UV–Vis spectrophotometry. A 5 mL urine sample was transferred into a 50 mL volumetric flask, then treated with dithizone solution, potassium cyanide (KCN), and sodium hydroxide (NaOH) to adjust the pH Absorbance was measured at 570 nm, and Pb levels were interpolated from a standard calibration curve exhibiting a linear relationship between Pb concentration and absorbance. The urine Pb levels were then expressed in parts per million (ppm). As is known, ppm is equivalent to mg/L, which is equivalent to the standard for lead in urine as stipulated in the Decree of the Minister of Health No. 1406/MENKES/SK/XI/2002, which is 0.15 mg/L.

**Questionnaire Data Collection**

Data regarding cigarette smoke exposure during pregnancy and birth weight history were collected using a structured questionnaire completed by parents/guardians through guided interviews conducted by the researcher. To ensure data accuracy, the questionnaire was pilot-tested, and reliability was assessed using Cronbach's alpha to address potential measurement bias.

**Statistical Analysis**

Data analysis was conducted using univariate, bivariate, and multivariate analyses. Highlighting this comprehensive approach aims to reassure the study's audience of its thoroughness and robustness. The association between urinary Pb levels, cigarette smoke exposure during pregnancy, and history of LBW and ASD severity was analysed using the Chi-square ($\chi^2$) test or Fisher's exact test if the requirements for the Chi-square test were not met, with a significance level of $\alpha = 0.05$. Multivariate analysis was performed using binary logistic regression, with ASD severity as the dependent variable. Independent variables were entered using the enter method, while accounting for sample size limitations and the potential for overfitting.

**Ethical Approval**

This research has received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Lambung Mangkurat University, under the number 132/KEPK-FKIK ULM/EC/VIII/2024. Prior to the study, parents/guardians were provided with an explanation of the study's purpose, procedures, benefits, and potential risks, and signed informed consent. All subject data was anonymized to maintain confidentiality.

**RESULT AND DISCUSSION**

The school is located at Jalan Ahmad Yani Km. 20, in the Landasan Ulin Barat Village, Liang Anggang District, Banjarbaru City, South Kalimantan Province. It holds an A accreditation, underscoring its commitment to quality education and reliability, which reassures policymakers and parents of its standards. SLB C Banjarbaru Negeri Pembina, operating since March 1, 1991, under the auspices of the Education and Culture Office of South Kalimantan Province, offers a comprehensive range of educational levels. The school is equipped with specialized facilities and resources to support students with diverse needs. Currently, it accommodates 238 students in 58 classrooms. The school's inclusive approach is evident in its acceptance of students with special needs such as hearing impairment, autism, and Down syndrome. SLB C Banjarbaru offers four levels of education, from early childhood education (PAUD) to high school (SMA), ensuring a complete and holistic education for all students.

A total of 43 children with ASD were included in this study. Based on assessment using the CARS-2, participants were classified into 18 children with mild–moderate ASD and 25 children with severe ASD. Participant characteristics according to ASD severity are presented in Table 1. Male participants predominated in both groups, accounting for 72.2% of the mild–moderate ASD group and 84.0% of the severe ASD group.

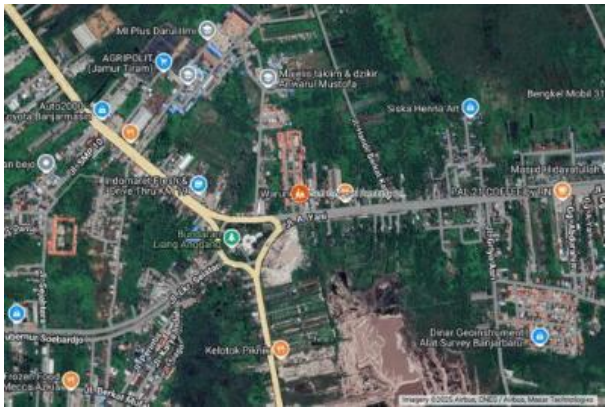

**Figure 1**. Screenshot of the location of SLB C Negeri Pembina, South Kalimantan Province

**Table 1.**
Subject Characteristics

| | **Autism** | |
|---|---|---|
| | **Mild-Moderate Autism (n =18)** | **Severe Autism (n = 25)** |
| Male, n (%) | 13 (72.2) | 21 (84.0) |
| Age (Year) mean ± SD | 11.0 ± 2.1 | 10.0 ± 2.3 |
| Age (Year) median (IQR) | 11 (10–13) | 11 (8–12) |
| Birth Weight (gram) mean ± SD | 2566.7 ± 421.5 | 3108.0 ± 512.4 |
| Birth Weight (gram) median (IQR) | 2350 (2100–2900) | 3100 (2800–3400) |
| Urinary Pb Level (µg/L), mean ± SD | 18.6 ± 4.7 | 25.7 ± 6.2 |
| Urinary Pb Level (µg/L), median (IQR) | 17.5 (15.0–22.0) | 28.0 (22.0–30.0) |

The mean age in the mild–moderate ASD group was 11.0 ± 2.1 years, with a median of 11 years (IQR: 10–13). In the severe ASD group, the mean age was 10.0 ± 2.3 years, with a median of 11 years (IQR: 8–12). The mean birth weight in the mild–moderate ASD group was 2566.7 ± 421.5 g, with a median of 2350 g (IQR: 2100–2900). In contrast, the mean birth weight was higher in the severe ASD group, at 3108.0 ± 512.4 g, with a median of 3100 g (IQR: 2800–3400). Urinary Pb levels also differed between groups. The mean urinary Pb concentration in the mild–moderate ASD group was 18.6 ± 4.7 µg/L, with a median of 17.5 µg/L (IQR: 15.0–22.0). In the severe ASD group, the mean urinary Pb concentration was 25.7 ± 6.2 µg/L, with a median of 28.0 µg/L (IQR: 22.0–30.0).

Bivariate analyses examining differences in environmental and perinatal factors according to ASD severity are presented in Table 2. The results showed that a higher proportion of participants with elevated urinary Pb levels was observed in the severe ASD group compared with the mild–moderate ASD group, and this difference was statistically significant (p = 0.003). Prenatal cigarette smoke exposure (>0 minutes per week) was also more frequently observed in the severe ASD group than in the mild–moderate ASD group, with a statistically significant difference (p = 0.004). Conversely, a history of low birth weight (LBW) was more common in the mild–moderate ASD group than in the severe ASD group, and this difference was also statistically significant (p = 0.016). Multivariate logistic regression analysis was conducted to identify factors independently associated with ASD severity, as presented in Table 3. The results indicated that prenatal cigarette smoke exposure was significantly associated with ASD severity. Exposure to cigarette smoke increased the odds of severe ASD by 8.87 times compared with no exposure (OR = 8.87; 95% CI: 1.20–65.60; p = 0.033). In addition, urinary Pb levels and history of LBW were also significantly associated with ASD severity, although the direction and magnitude of the associations differed across variables (Table 3).

**Table 2.**
Results of the analysis of the influence of several factors on Autism using the Chi-Square test

| **Risk Factor** | **Autism Group** | | | | **P value** |
|---|---|---|---|---|---|
| | Mild-Moderate | | Severe | | |
| **Urinary Pb level** | n | % | n | % | |
| Low | 14 | 77.8 | 8 | 32 | 0.003 |
| High | 4 | 22.2 | 17 | 68 | |
| **Cigarette Smoke Exposure** | n | % | n | % | 0.004 |
| Exposed | 3 | 16.7 | 15 | 60 | |
| Not Exposed | 15 | 83.3 | 10 | 40 | |
| **History of LBW** | n | % | n | % | |
| LBW | 10 | 55.6 | 5 | 20 | 0.016 |
| Not LBW | 8 | 44.4 | 20 | 80 | |

**Table 3.**
Results of multivariate logistic regression analysis between urinary Pb levels, exposure to cigarette smoke, and history of LBW and Autism

| Risk Factor | B | Exp (B) | P Value | 95% CI for Exp (B) | |
|---|---|---|---|---|---|
| | | | | *Lower* | *Upper* |
| **Urinary Pb Level** | -3.387 | 0.034 | 0.007 | 0.003 | 0.395 |
| **Cigarette Smoke Expsoure** | 2.182 | 8.866 | 0.033 | 1.198 | 65.600 |
| **History of LBW** | -2.526 | 0.080 | 0.032 | 0.008 | 0.803 |

This study demonstrates an association between environmental and perinatal factors and differences in ASD severity, classified as mild–moderate ASD and severe ASD based on CARS-2. These insights are valuable for researchers aiming to understand ASD variability and may inspire further investigation into these factors.

The study population was predominantly male, with a mean age ranging from 10 to 11 years. This finding is consistent with the literature reporting that both the prevalence of ASD and the severity of its symptoms are more frequently observed in males than in females. Large-scale epidemiological studies in the United States have shown that ASD prevalence in boys is approximately four times higher than in girls, with sex-related differences also evident in clinical symptom expression (Grosvenor et al., 2024; Napolitano et al., 2022) These differences are thought to be related to biological, genetic, and hormonal factors that influence sex-specific neurodevelopmental vulnerability (Hong et al., 2025).

The results further indicate that higher urinary Pb levels were more frequently observed in the severe ASD group compared with the mild–moderate ASD group. This finding supports existing evidence that Pb exposure is associated with increased severity of neurobehavioral disturbances—such as hyperactivity, attention deficits, and executive dysfunction—which are core components of the autism symptom spectrum (Briffa et al., 2020; Tizabi et al., 2023).

Several studies suggest that Pb exposure does not necessarily correlate with ASD occurrence in a dichotomous manner, but is more closely related to the degree of symptom severity among children with underlying neurodevelopmental vulnerability. Thus, Pb is more appropriately viewed as a severity-modifying factor rather than a singular causal determinant of ASD (Tizabi et al., 2023).

From a biological perspective, Pb is known to disrupt calcium homeostasis and synaptogenesis, induce oxidative stress and neuroinflammation, and alter neurotransmitter function. These mechanisms may exacerbate central nervous system dysfunction during early developmental periods, providing a strong biological rationale for the observed association between higher Pb levels and increased ASD symptom severity rather than mere diagnostic status (Briffa et al., 2020; Sekartaji et al., 2024).

This study also found that prenatal cigarette smoke exposure was more frequently observed among children with severe ASD, and this association remained evident in multivariate analysis. This finding aligns with studies reporting that prenatal exposure to cigarette smoke is associated with altered brain development and early behavioural changes resembling autism-related symptoms, including impaired emotional regulation, hyperactivity, and communication difficulties (Zhong et al., 2022).

In contrast to studies comparing autistic and non-autistic children, several recent investigations emphasize that prenatal exposures—including cigarette smoke—are associated with greater ASD symptom severity and increased behavioural comorbidities among children with ASD (Pham et al., 2022). Toxic components of cigarette smoke, such as nicotine and carbon monoxide, may induce foetal hypoxia, placental inflammation, and oxidative stress, thereby disrupting neural maturation and intensifying the clinical phenotype of ASD (Berger et al., 2021). Moreover, prenatal cigarette smoke exposure has been linked to epigenetic alterations associated with long-term neurological function, which may influence the expression of neurodevelopmental symptoms from childhood through adolescence (Pham et al., 2022). Collectively, these findings reinforce the view that prenatal cigarette smoke exposure represents a critical environmental factor that modulates ASD symptom severity.

The study also revealed differences in the distribution of low birth weight (LBW) history between the mild–moderate and severe ASD groups. LBW has long been associated with adverse neurodevelopmental outcomes, including cognitive and behavioural impairments that may contribute to variability in ASD symptom severity (Johnson et al., 2021; Sari et al., 2022). LBW reflects suboptimal intrauterine conditions—such as chronic hypoxia, inflammation, and nutritional deficiency—that play a crucial role in foetal brain development. These conditions may increase early neurological vulnerability and subsequently influence the clinical expression of ASD during childhood (Johnson et al., 2021). Accordingly, LBW in this study is more appropriately interpreted as a marker of neurodevelopmental vulnerability that may modulate symptom severity rather than as a direct cause of ASD.

This study also revealed that prenatal cigarette smoke exposure showed the strongest association with ASD severity compared with urinary Pb levels and LBW history. While these associations are noteworthy, it is important to emphasize that the cross-sectional design limits causal inference, and these findings should be interpreted as correlations rather than definitive causes. This clarification helps readers understand the study's scope and avoid overestimating causality.

Several methodological limitations must be explicitly acknowledged when interpreting this study's findings.

First, the cross-sectional design, combined with the absence of a non-autistic control group, precludes causal inference and limits interpretation to associations within different levels of ASD severity. As a result, the observed relationships between environmental and prenatal exposures and ASD severity cannot be interpreted as evidence of etiological pathways. Instead, the findings should be understood as indicative of severity-related variation within an ASD population, which restricts generalizability beyond this specific clinical group. Second, the reliance on parental recall to obtain information on prenatal cigarette smoke exposure and birth weight introduces the possibility of recall bias and misclassification. Such measurement error may attenuate or inflate observed associations, thereby affecting the precision and internal validity of the estimates. Consequently, the strength of the reported associations should be interpreted with caution.

Third, although the CARS-2 is a validated instrument for assessing ASD severity, the potential for misclassification remains, particularly among children with scores near diagnostic thresholds. This limitation may lead to non-differential classification error, which could reduce the sensitivity of detecting true differences across severity levels. Fourth, residual confounding cannot be excluded. Important factors such as maternal nutritional status, exposure to other environmental toxicants, socioeconomic status, and genetic susceptibility were not directly measured. The absence of these variables may limit the ability to fully isolate the independent contribution of the three investigated risk factors, thereby affecting the robustness of the conclusions. Taken together, these limitations indicate that the findings should not be interpreted as establishing causality, but rather as providing hypothesis-generating evidence that supports the need for longitudinal, multi-centre, and mechanistically informed studies to clarify causal pathways and strengthen external validity.

## CONCLUSION

This study demonstrates that higher urinary lead Pb levels, prenatal cigarette smoke exposure, and a history of LBW were significantly associated with differences in ASD severity, particularly with severe ASD compared to mild–moderate presentations. Among the examined factors, prenatal cigarette smoke exposure exhibited the strongest association with ASD severity in multivariate analysis, suggesting a potentially prominent role of early-life environmental toxicant exposure in modulating clinical severity. These findings contribute to the growing body of evidence indicating that environmental and perinatal factors may influence the heterogeneity of ASD expression rather than its occurrence alone. Importantly, the results highlight that variations in exposure burden may be linked to differential symptom severity within an already diagnosed ASD population. While the cross-sectional design and sampling framework limit causal interpretation, the observed associations provide meaningful evidence supporting the need for more rigorous longitudinal investigations. Future research should employ prospective cohort or case–control designs, incorporate objective biomarkers of toxicant exposure such as, validated Pb biomarkers, and include larger, more representative samples to clarify causal pathways and better understand how environmental and perinatal exposures contribute to ASD severity modulation.

## SUGGESTION

Furthermore, the research underscores the pressing need for more effective prevention strategies. These strategies should include comprehensive public education on exposure risks and the necessity for stricter pollution control policies. The study also presents an opportunity for the development of early screening and intervention programs, particularly for the most vulnerable groups. By implementing these measures, we can strive to enhance public health and reduce the prevalence of Autism in the future.

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