# Risk Factors of Children with Autism Spectrum Disorder (ASD) in Palembang, Indonesia

*by* Nita Parisa

**Submission date:** 08-Feb-2022 07:32AM (UTC+0700)
**Submission ID:** 1757274903
**File name:** 21-Article_Text-134-1-10-20201018.pdf (223.33K)
**Word count:** 3945
**Character count:** 19603

SCIENTIA PSYCHIATRICA

eISSN (Online): 2715-9736

**Scientia Psychiatrica**

Journal Homepage: www.scientiapsychiatrica.com

# Risk Factors of Children with Autism Spectrum Disorder (ASD) in Palembang, Indonesia

**Leonardo Satria[1], Ziske Maritska[2*], Nita Parisa[3]**

[1] Undergraduate, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
[2] Department of Biology Medicine, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
[3] Department of Pharmacology, Faculty of Medicine, Sriwijaya, Palembang, Indonesia

**ARTICLE INFO**

**Keywords:**
ASD
Children
Risk Factors
Palembang

**Corresponding author:**
E-mail address:
*ziske_maritska@unsri.ac.id*
All authors have reviewed and approved the final version of the manuscript.

*https://doi.org/10.37275/scipsy.v1i4.21*

**ABSTRACT**

**Background:** Autism Spectrum Disorder (ASD) is a group of nervous system development disorders with polygenic inheritance patterns, characterized by a type of dysfunctional in social communication and limited also repetitive behaviors. Risk factors for ASD can be divided into two categories in general: genetic, and environmental factors. To date, a study about risk factors of ASD in Indonesia, let alone Palembang, is limited. Therefore, this study wished to investigate the risk factors of children with ASD in Dr. Mohammad Hoesin Hospital, Palembang. **Method:** This study is an observational descriptive study. Samples were children with ASD who went to Dr. Mohammad Hoesin Hospital, Palembang. The primary data obtained from a semi-structured interview with parents/guardians of children with ASD, while secondary data obtained from their medical records. **Result:** The most common risk factors identified in this study are the paternal age and maternal age ≥ 30 years at the time of conception (59,8% and 40.2%), and the history of cesarean delivery (27,8%). **Conclusion:** This study concludes that the occurrence of ASD in Palembang is multifactorial, involving both genetic and environmental risk factors.

## 1. Introduction

Autism Spectrum Disorder (ASD) formerly known as Pervasive Developmental Disorders, is a group of heterogeneous phenotypes of nervous system development disorders with polygenic inheritance patterns, characterized by the type of dysfunctional in social communication and limited also repetitive behaviors.[1] Epidemiological data estimate the global prevalence of ASD reaches 1 in 160 people.[2] Whereas statistical data from the US Centers for Disease Control and Prevention (CDC) released in March 2014 identified about 1 in 59 American children experiencing ASD.[3]

ASD is a multifactorial genetic disorder, meaning it has more than one risk factor involved. In general, these factors are divided into 2 major groups, genetic factors, and environmental factors. When it comes to genetic factors, there is a lot of genes related to ASD, for example, *CHD8*, *ARID1B*, *SHANK3,* and *NLGN 3/4.*[4]

In the case of ASD, the environmental factors can be broadly divided into three categories based on the period, those are *pre-natal, peri-natal,* and *post-natal.* In pre-natal factors, there is a TORCH infection related to brain damage and the immune system. Advanced paternal and maternal age also related to gene mutations.[5] Gestational bleeding and hypertension during pregnancy related to placental insufficiencies and hypoxia can cause ASD as

well.[6,7,8] Last is diabetes during pregnancy that related to cell apoptotic and oxidative stress.[9] The *peri*-natal factors are the childbirth method (cesarean delivery) related to a pregnancy complication, asphyxia that related to hypoxia[7,8], and prematurity that related to organ maturity.[5] For *post-natal* factors, there are low birth weights (LBW) that related to nutrition[7] and hypoxia condition, and then *neonatal* jaundice and postnatal infection that related to brain damage[5,10]

## 2. Research Methods

This is an observational descriptive study with cross-sectional study design, i.e. data collecting is only done once at a certain time to find out risk factors in ASD children in one of the national referral hospitals in Indonesia, which is Dr. Mohammad Hoesin Hospital, during 1 January 2014 - 31 December 2018.

Data obtained were secondary data from medical records and primary data from semi-structured interviews with families of ASD inpatients and outpatients at Dr. Mohammad Hoesin Hospital in 2014 - 2018.

The inclusion criteria were all parents with ASD children at Dr. Mohammad Hoesin Hospital who was willing to participate in the study. Parents interviewed by telephone and the conversation was recorded. The exclusion criteria for this study were ASD children with cerebral palsy and down syndrome.

## 3. Results

This study identified 301 children with ASD, where 97 of them suited the inclusion and exclusion criteria. Those ninety-seven children had dominant male demographic characteristics (87.63%), with age under five years old (73.20%) as shown in table 1.

Genetic factors in this study were family history, while environmental factors in this study were paternal age, maternal age, prenatal infection, gestational bleeding, hypertension during pregnancy, gestational diabetes, cesarean delivery, premature, asphyxia, low birth weight, postnatal infections, and neonatal jaundice as can be seen in table 2.

From the results of the identification of various risk factors for ASD children, the most common risk factors are the age of the father over 30 years at the time of conception, which is 58 children, the second is the mother's age ≥ 30 years during the conception period, which is 39 children, and the least is gestational diabetes, where no risk factors for gestational diabetes were found in the subjects.

**Table 1: Demographic characteristics of ASD children in RSMHfor the period 1 January 2014 - 31 December 2018 (n = 97)**

| Demographic Characteristics | n | % |
|---|---|---|
| **Age** | | |
| 0-11 months | 1 | 1 |
| 12 months – 59 months | 71 | 73,20 |
| 60 months – 72 months | 11 | 11,35 |
| 6 years– 18 years | 14 | 14,45 |
| **Sex** | | |
| Male | 85 | 87,63 |
| Female | 12 | 12,37 |

**Table 2 : Characteristics of risk factors for ASD children in RSMH for the period 1 January 2014 - 31 December 2018 (n = 97)**

| Risk Factor | N | (%) |
|---|---|---|

| | | |
|---|---|---|
| Genetic Factor | | |
| ASD Family History | | |
| Yes | 13 | 13,4 |
| No | 84 | 86,6 |
| Environment Factor | | |
| Paternal Age | | |
| Age ≥30 | 58 | 59,8 |
| Age <30 | 39 | 40,2 |
| Maternal Age | | |
| Age ≥30 | 39 | 40,2 |
| Age <30 | 58 | 59,8 |
| Prenatal Infection | | |
| Yes | 8 | 8,2 |
| No | 89 | 91,8 |
| Gestational Bleeding | | |
| Yes | 4 | 4,1 |
| No | 93 | 95,9 |
| Pregnancy Hypertension | | |
| Yes | 9 | 9,3 |
| No | 88 | 90,7 |
| Gestational Diabetes | | |
| Yes | 0 | 0 |
| No | 97 | 100 |
| Caesar Delivery | | |
| Yes | 27 | 27,8 |
| No | 70 | 72,2 |
| Premature | | |
| Yes | 9 | 9,3 |
| No | 88 | 90,7 |
| Asphyxia | | |
| Yes | 9 | 9,3 |
| No | 88 | 90,7 |
| LBW | | |
| Body Weight <2500 g | 15 | 15,5 |
| Body Weight <2500 g | 82 | 84,5 |
| Neonatal Jaundice | | |
| Yes | 4 | 4,1 |
| No | 93 | 95,9 |
| Postnatal Infection | | |
| Yes | 6 | 6,2 |
| No | 91 | 93,8 |
| Multifactorial | | |
| Environment + Genetic Factor | 12 | 12,4 |

## 4. **DISCUSSION**

Most children with ASD were male, with a percentage of 87, 63%. It is relevant to various theories that ASD distribution is more prevalent in males than females. The prevalence of ASD in men reaches 4-5 times more often than women. The exact theory on this case has not yet been found, whether male sex is susceptible to ASD or female gender is a protective factor or even both theories are true.

Several theories support this, where the first is sexual hormones; estrogen, and testosterone. The hormone testosterone is known to have an effect in the production of the fetus which will later develop be a male, this hormone affects physical development, brain, neurotransmitters, immune function, and other functions. When there is a dysfunctional of the hormone testosterone in the fetus, it will affect the development of the fetus. While the hormone estrogen

is known to be a regulator of gene expression, the binding of the estrogen hormone and its receptors can penetrate the cell nucleus.

The second is the influence of chromosomes, men only have one X chromosome while the female has two X chromosomes. When there is a dysfunctional on the X chromosome, men will manifest the condition immediately, whereas women have a second X chromosome as a backup. In genetic research, copy number variations (CNV) are found in women as many as 10-15 while in men only 2-35.[11] This study is in line with several studies such as those conducted by Hisle-Gorman where they get a male gender distribution of 79.9%.[12] Another study conducted by Maia with a similar percentage of 80.2% of the majority of men[13] and the last research by Pangestu in Semarang received a percentage of 73.3% for male sex.[7]

There have been many studies on genetic factors that influence the incidence of ASD. Some of these genes are NEGR1, PTBP2, CADPS, KCNN2, KM2TE, MACROD2, SHANK3, CHD8, ARID1B, and many other genes that are expected to reach 1000 genes that affect ASD cases4.[14] These genes will later be inherited in the family both simplex and multiplex. In a study conducted by Sven et al, they concluded that ASD's genetic heritability was 50% and would increase 10 times as much as having an ASD sibling.[15] Schaefer et al's study state that ASD genetic heritability is 70% -90% and is influenced by many factors.[16]

Advanced father age of 30 years and over had a risk factor with the most distribution, which was 58 people (59.8%). Relevant with the theory which states that at senior-aged father, genetic mutations are very susceptible. This is because men constantly produce sperm and in old age, sperm quality begins to decrease. However, for the exact cause of genetic mutations occur, it still cannot be proven.[5,17] The results obtained in this study are higher than the results of research conducted by Zhang et al., where they got 39 of 95 (41,1%).[8] In the study from Semarang by Pangestu et al, they got 19 of 45 people (42.2%).[7] However, these results are lower in percentage compared to studies conducted by Hadjkacem et al, who got 33 out of 50 people (66%).[18]

Advanced mother age 30 years and over was one of the risk factors that were often found in this study, as many as 39 people from 97 people (40.2%). This is relevant to the theory which states that senior-aged mother is related to genetic mutations and chromosomes that are prone to occur, but the exact cause of genetic mutations and chromosomes cannot be proven yet. Also, the senior-aged mother is related to problems and complications during pregnancy which will cause fetal distress and hypoxia in the fetus so that free radical buildup occurs and oxidative stress occurs.[5,7] The percentage of results obtained in this study is higher than in some previous studies. The means in his study in India found 1 of 33 mothers (3%) elder,[19] then Hisle-Gorman et al in his study in Virginia received 1184 out of 8760 mothers of ASD children (13, 5%)[12], and Zhang et al. In their study in China, 23 out of 95 mothers are elders.[8] However, this percentage is lower than the study conducted by Pangestu et al in Semarang, Indonesia, where they got the results of 31 of 45 mothers who were elderly while pregnant (68.9%).[7]

In this study it was found that the number of maternal infections during pregnancy was 8 or 8.2% of the total data, the types of infections obtained in this study were rubella, toxoplasma, and then other infections were not explained further. This is consistent with the theory that the mother's infection during pregnancy can affect the fetus organically, which directly attacks the brain and neuron cells or through inflammatory mediators that are released during the infection in the form of cytokines. During fetal development, cytokines function in brain development, so that imbalance of cytokines will cause brain development disorders.[5] The percentage of results in this study is similar to the study conducted by Saranya et al in India wherein their study the percentage of prenatal infections was 9%,

0.8% adrift from the results obtained in this study.[19] Yet these results are much less than the studies conducted by Pangestu et al in Semarang and Hisle-Gorman et al in Virginia where they got a percentage of mothers who have infections as much as 68.9% and 40%.[7,12]

Gestational bleeding is one of the complications during pregnancy, it is related to the state of fetal hypoxia due to placental insufficiency.[6,7] In this study, it was found that 4 out of 97 mothers had experienced gestational bleeding or around 4.1% of the total data. In a study conducted by Amirhossein et al in a systematic review, they obtained four journals that said vaginal bleeding during pregnancy was one of the factors causing ASD.[20] Another study conducted by Saras et al. found no risk factors for bleeding during gestation in 33 studies samples.[19] However, in a study conducted by Pangestu et al in Semarang, they found 29 bleeding from 45 samples studied or about 64.4% of the total data. This is much more than what was found in this study.[7]

Hypertension in pregnancy at any gestational age affects the supply of oxygen and nutrients to the fetus so that it experiences a state of hypoxia and oxidative stress.[8] This is related to ASD cases. This study found a percentage of 9.3% of the total data. Other studies conducted by Hadjkacem et al got similar results to this study, namely 10% of the total sample.[18] Yet research conducted by Hisle-Gorman et al in Virginia gets more results, namely 18.1% of the total sample.[12] Whereas the research conducted by Saras et al only obtained 6% of the total data which means less than this study.[19]

The condition of DM is closely related to brain malformations and neurodevelopmental disorders. The hyperglycemic condition in the intrauterine negatively impacts the development of the fetus's brain.[9] However, in this study, no samples were found with diabetes during pregnancy. In a study conducted by Xiang in California, they obtained 877 samples with hyperglycemia during pregnancy from 5287 events of ASD or 16.58% of all data,[21] research by Hadjkaem in Brazil obtained 8% of overall data18 and most recent research by Hisle-Gorman et al in Virginia obtained a percentage of 17.3%.[12]

Cesarean delivery is the most common perinatal risk factor found in this study, 27 of 97 samples, or 27.8% of the total data. Cesareanean delivery was not directly related to ASD, cesarean delivery was related to other risk factors discussed or not discussed in this study, such as prenatal infections, macrosomia due to gestational diabetes, narrow maternal pelvis, placenta previa, and other factors that would cause fetal distress.[7,8] Another case with Benjamin et al, where observational studies conducted in five countries with a sample size of approximately five million births, get a percentage of only 3.2% of all children born with ASD conditions.[22] This finding is less than this study.

Prematurity associated with immature organs, especially the lungs, which will lead to respiratory distress and damage brain neuron cells.[5] In this study, nine samples were born preterm or 9.3% of the data. Other studies show a higher percentage than this study, research conducted by Zhang et al had a percentage of 16.9%[8], research conducted by Saranya et al had a percentage of 18.2%[19], research conducted by Hadjkacem et al had a percentage of 18%[18], research conducted by Maia et al. had a percentage of 17.8%[13] and research conducted by Hisle-Gorman has a percentage of 13.4%[12]. However, the research conducted by Benjamin et al has a smaller percentage than this study, which was only 3.6% of samples born preterm[22].

Asphyxia at birth is a state of distress in children that can be life-threatening, this condition causes hypoxia which will cause oxidative stress in the brain and damage neuronal cells in the brain. Other studies have shown that the distribution of risk factors for asphyxia can have a very high percentage, as in research conducted by Pangestu et al. had a percentage of 71.1%[7], then other research is conducted by Hisle Gorman et al with a percentage of 42.4%[12], then research conducted by Maia et al, with

a percentage of 17.4%[13]. The percentage of this research was only 9.3%, smaller than other studies. Research that had similar results was a study conducted by Zhang et al, which amounted to 11.6% but is still larger than this study.[8]

Birth weight is related to complications that occur during the prenatal period. When the supply of oxygen and nutrients does not reach the fetus, this will cause developmental disorders, especially the brain[7]. In this study, the results obtained as many as 15 samples with low birth weight or about 15.5%. Some studies got higher results compared to this study, as in the study conducted by Pangestu et al in Semarang and Maia et al in Brazil got a percentage of 51.1% and 20.9%[7,13]. While other studies had a smaller percentage of results as in the study conducted by Hadjkacem et al and Hisle-Gorman et al with a percentage of 12% and 8.8%[12,18].

High levels of bilirubin during neonates can cause deposits of bilirubin in the brain which can cause encephalopathy[10]. This study found as many as four samples that had this condition, or about 4.1%. Other studies in various countries got higher results compared to this study, such as research conducted by Zhang et al in China has a percentage of 11.6%[8], research by Saranya et al in India got 12% results[19], research by Maia et al in Brazil get a percentage of 30% [13], and last but not least is the research conducted by Hisle-Gorman in Virginia with a percentage of 38.8% [12].

Infections that occur during the neonatal period, especially infections of the brain after birth will directly affect neuronal cell damage in the brain which can cause ASD. This study obtained a percentage of results of 6.2% of the total data, where these results were less than other studies conducted by Maia et al and also Hisle-Gorman et al who got a percentage of 13.8% and 22.2% [12,13].

Of the entire sample that had genetic factors, the majority also had environmental factors. The number of samples that had multifactorial factors was 12 people or 12.4% of all data. According to existing theories, genetic factors alone in ASD cannot directly cause ASD but require environmental factors. Some environmental factors are directly related to genetic factors in ASD, such as father's age and maternal age which cause genetic mutations[5]. A study conducted by Risch et al concluded that the recurrence of ASD in one family was also influenced by environmental factors such as the distance of pregnancy and also the age of parents[23].

## 5. CONCLUSION

All cases of ASD in this study are multifactorial, in line with the theory. Both genetic and environmental factors related to the incidence of ASD. Further studies to analyze which risk factors play the most important part is needed.

## 6. REFERENCES


1. Sadock BJ, Sadock VA. Kaplan & Sadock Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry. Wolters Kluwer, Philadelphia, Pa. 2015. 3016–46 p.
2. WHO. Autism spectrum disorders & other developmental disorders: From raising awareness to building capacity. World Heal Organ Geneva, Switz. 2013;1(September):1–36.
3. Redfield RR, Kent CK, Leahy MA, Martinroe JC, Spriggs SR, Yang T, et al. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years-Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014 Surveillance Summaries Centers for Disease Control and Prevention MMWR Editorial and Production Staf. MMWR Surveill Summ. 2018;67(6):2–16.
4. Landrigan PJ. What causes autism? Exploring the environmental contribution. Curr Opin Pediatr. 2010;22(2):219–25.
5. Casanova EL, Casanova MF. Defining autism : a guide to brain, biology, and behavior. 2019. 27–100 p.
6. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: Comprehensive meta-analysis. Br J Psychiatry. 2009;195(1):7–14.
7. Pangestu N, Fibriana AI. HIGEIA JOURNAL OF PUBLIC HEALTH Aedes aegypti. 2018;2(2):331–41.
8. Zhang X, Lv CC, Tian J, Miao RJ, Xi W, Hertz-

Picciotto I, et al. Prenatal and perinatal risk factors for autism in China. J Autism Dev Disord. 2010;40(11):1311–21.
9. Wan HM, Zhang CM, Li HM, Luan SM, Liu CM. Association of maternal diabetes with autism spectrum disorders in offspring: A systemic review and meta-analysis. Medicine (Baltimore) [Internet]. 2018;97(2):e9438. Available from: http://ovidsp.ovid.com/?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovftt&AN=00005792-201801120-00012 http://eu.alma.exlibrisgroup.com/view/uresolver/44SAL_INST/openurl?sid=OVID:ovftdb&id=pmid:&id=doi:10.1097%2FMD.0000000000009438&issn=0025-7974&isbn=&volume=97&iss
10. BELL RAF. Nelson. Textbook of Pediatrics. Archives of Disease in Childhood. 2009. 93–4 p.
11. Ferri SL, Abel T, Brodkin ES. Sex Differences in Autism Spectrum Disorder: a Review. Curr Psychiatry Rep. 2018;20(2).
12. Hisle-Gorman E, Susi A, Stokes T, Gorman G, Erdie-Lalena C, Nylund CM. Prenatal, perinatal, and neonatal risk factors of autism spectrum disorder. Pediatr Res. 2018;84(2):190–8.
13. Maia FA, Oliveira LMM, Almeida MTC, Alves MR, De Araújo Saeger VS, Da Silva VB, et al. Autism spectrum disorder and postnatal factors: A case-control study in Brazil. Rev Paul Pediatr. 2019;37(4):398–405.
14. Stefansson H, Stefansson K, Steinberg S, Bragi Walters G, Genet Author manuscript N. Identification of common genetic risk variants for autism spectrum disorder HHS Public Access Author Manuscript. Nat Genet [Internet]. 2019;51(3):431–44. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6454898/pdf/nihms-1015648.pdf
15. Hultman CM, Reichenberg A. The Familial Risk of Autism. 2015;311(17):1770–7.
16. Schaefer GB. Clinical Genetic Aspects of ASD Spectrum Disorders. 2016;1–14.
17. Zager D, David F. Cihak A, Stone-MacDonald A. Autism Spectrum Disorders : Identification, Education, and Treatment. 4th edition. 2017;1–22.
18. Hadjkacem I, Ayadi H, Turki M, Yaich S, Khemekhem K, Walha A, et al. Prenatal, perinatal and postnatal factors associated with an autism spectrum disorder. J Pediatr (Versão em Port [Internet]. 2016;92(6):595–601. Available from: http://dx.doi.org/10.1016/j.jpedp.2016.08.011
19. Ravi S, Chandrasekaran V, Kattimani S, Subramanian M. Maternal, and birth risk factors for children screening positive for autism spectrum disorders on M-CHAT-R. Asian J Psychiatr [Internet]. 2016;22(2016):17–21. Available from: http://dx.doi.org/10.1016/j.ajp.2016.04.001
20. Modabbernia A, Velthorst E, Reichenberg A. Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. Vol. 8, Molecular Autism. Molecular Autism; 2017. p. 1–16.
21. Xiang AH, Wang X, Martinez MP, Walthall JC, Curry ES, Page K, et al. Association of Maternal Diabetes With Autism in Offspring. 2017;91101(14):1425–34.
22. Hon B, Yip K, Leonard H, Stock S, Stoltenberg C, Francis RW, et al. Neurocognitive Development and Mental Health Caesarean section and risk of autism across gestational age : a multi-national cohort study of 5 million births. 2017;(December 2016):429–39.
23. N. R, T.J. H, M. A, L.A. C, J.K. G, G.C. W. Familial recurrence of autism spectrum disorder: Evaluating genetic and environmental contributions. Am J Psychiatry [Internet]. 2014;171(11):1206–13. Available from: http://ajp.psychiatryonline.org/doi/pdfplus/10.1176/appi.ajp.2014.13101359%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014905510

.

# Risk Factors of Children with Autism Spectrum Disorder (ASD) in Palembang, Indonesia

ORIGINALITY REPORT

| 0% | 0% | 0% | 0% |
|---|---|---|---|
| SIMILARITY INDEX | INTERNET SOURCES | PUBLICATIONS | STUDENT PAPERS |

PRIMARY SOURCES

| | | | |
|---|---|---|---|
| Exclude quotes | On | Exclude matches | < 3% |
| Exclude bibliography | On | | |