

## **META ANALYSIS OF FACTORS AFFECTING THE BIRTH OF INFANTS WITH LABIOPALATOSCHIZIS**

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### **ABSTRACT**

Labiospalatoskizis is caused by failure in the process of joining the lips while still in the fetus. This disorder can cause many disorders such as disorders such as eating disorders, speech disorders, ear irritation, and dental and oral disorders. Many factors can cause this disorder, namely exposure to cigarette smoke and metal exposure during pregnancy. The purpose of this meta-analysis was to analyze the effect of cigarette smoke exposure and metal exposure on labiospalatoskizis events. This study was conducted by systematic review and meta-analysis. Research data is sought from several indexing including: PubMed, Science Direct, Web of Science, Springer Link and Cochrane Database. By using the search keywords "smoking AND Orofacial Clefts", "heavy metal AND labiospalatoschizis", "smoke AND metal exposure AND cleft lift AND adjusted odds ratio", and "factors AND labiospalatoskizis AND adjusted odds ratio". There were 6 articles with 2 analysis results, namely: heavy metal exposure (OR: 3.18; 95% CI: 2.45 – 4.12; p value <0.001) and secondhand smoke exposure (OR: 5.40; 95% CI: 4.26 – 6.86; p value <0.001).

Keywords: labiospalatoskizis; meta analysis; secondhand smoke

### **INTRODUCTION**

Labipalatoskizis/ Cleft lip and cleft palate are one of the most common disorders of all congenital defects. Cleft lip can occur with cleft palate or without cleft palate and is commonly referred to as "cleft lip with or without cleft palate". Cleft lip is a disorder caused by failure in the process of uniting the lips while still in the fetus. While the cleft palate occurs when the roof of the mouth does not fuse normally, causing a gap between the oral cavity and the nasal cavity. (Kummer, 2018) There are three main types of cleft lip defects, namely cleft lip (CL) where cleavage occurs only on the lips, cleft palate (CP) where cleavage occurs in the palate area, and cleft lip palate (CLP), where cleavage occurs completely from the palate to the lips. (Kusuma, 2022) The incidence of cleft lip is most likely to occur unilaterally or only on one side. The side most commonly affected by the defect is the left side. Cleft cases accompanied by cleft palate usually occur in 85% of bilateral cleft cases and 70% of unilateral cleft cases (Leslie and Merry, 2014). Cleft lip and palate are more prevalent in boys, while cleft palate is more prevalent in girls. The incidence of cleft lip with or without cleft palate is approximately 1:600 births while the incidence of cleft palate alone is approximately 1:1,000 births (Beaty et al. 2016).

The incidence of cleft lip is highest in Asian ethnicity and lowest in blacks. The Centers for Disease Control and Prevention (Centers for Disease Control and Prevention) said in Indonesia cleft lip disorder sufferers increased by an average of 7,500 people per year in Indonesia. The etiology of cleft lip (Labioschizis) and cleft palate (Palatoschizis) is a combination of genetic factors 22% and environmental factors 78%. So it is very important to ask if there is a history of heredity at the time of history and know there are things that can affect the process of pregnancy. (Afra, 2021) Until now, cleft lip and cleft palate have no known cause or are idiopathic. Cleft lip and cleft palate are suspected due to mutations in the genes forming the oral cavity and lips in infants when the gestation is 4 months old. This mutation leads to the failure of the union of tissues that make up

the palate and upper lip, which eventually forms clearly visible hemispheres in the oral cavity. However, some recent studies also suspect diet and drug use in mothers, and smoking habits, may be contributing factors to the occurrence of cleft lip and cleft palate. Cleft lip and cleft palate can result in several disorders such as eating disorders, speech disorders, ear irritation, and dental and oral disorders.(Alade, 2022)(Lacerda, 2021)(Gumilar, 2020)

Previous studies reported a positive association between active ingredients in cigarettes and cleft lip / labiospalatoskizis / cleft lip events with risk analysis results were 1.34 (95% CI: 1.25 to 1.44) and for cleft palate (CP) the relative risk was 1.22 (95% CI: 1.10 to 1.35) (Sabbagh et al. 2015). However, the risk of exposure to cigarette smoke in pregnant women is still often underestimated, this is because there is still a debate on the results between pregnant women and passive or active smokers. (Zheng, 2019)In addition, another condition that has been analyzed as having a relationship with the incidence of labiospalatoskizis is exposure to toxic substances such as metals or radiation. Research reports that the concentration of Cr, Ni, Fe and Cu ions in the saliva of cleft lip and palate patients is several times higher compared to the control group (Mikulewicz et al. 2015) However, Research conducted by (Takeuchi et al. 2022) and (Suhl et al. 2018) states that there is no association between heavy metal exposure and labiospalatoskizis events.

Both studies had samples with non-high exposure to the heavy metal cadmium. Therefore, information is needed to educate midwives about the effects of exposure to cigarette smoke with heavy metals that may cause labioskizis, cleft lip and cleft palate, so as to conduct screening and also educate parents if the child to be born is indicated labioplatoskizis to be given further action directions. The author hopes that through making a meta-analysis of cigarette exposure and heavy metals during pregnancy to the birth of babies with labiopalatoskizis, it can increase knowledge for midwives about prevention and also education to pregnant women.

## **METHOD**

This study was conducted by systematic review and meta-analysis. This research will be conducted by searching and selecting data from the results of analysis conducted across ethnicities, races, and also locations in the world at the time of the results of the study to be selected in the period 2018-2023. Research data is sought from several indexing including: PubMed, Science Direct, Web of Science, Springer Link and Cochrane Database. By using the search keywords "smoking AND Orofacial Clefts", "heavy metal AND labiospalatoschizis", "smoke AND metal exposure AND cleft lip AND adjusted odds ratio", and "factors AND labiospalatoskizis AND adjusted odds ratio". In addition to determining keywords, article searches are carried out by determining eligibility criteria defined using the PICO (Population, Intervention, Controls/Comparisons, Outcome) model, namely:

Population :Mother pregnant

Outcome : children with LABIOSPALATOSKIZIS

Data analysis performed using Review Manager (RevMan) 5.4 software issued by Cochrane collaboration (RevMan) was used to calculate the overall mean difference, describing a 95% confident interval (CI) using an effect model, I<sup>2</sup>, or heterogeneity of data.

## RESULT AND DISCUSSION

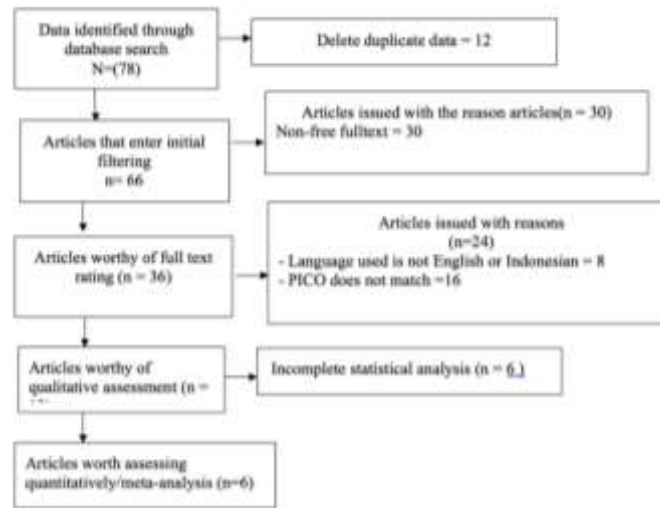


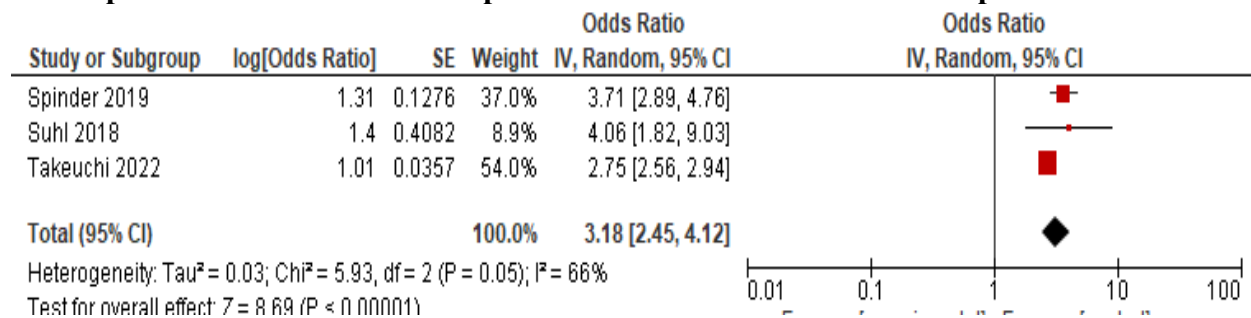
Figure 1. PRISMA flow diagram

Table 1.  
Summary Source

Study	Variables under study	Result
(Spinder, 2019)	Exposure to environmental pollutants during pregnancy includes: solvents, glycol ethers, pesticides, and some other heavy metals	The results showed that there was a relationship between occupational exposure to pesticides or metals and congenital anomalies in babies born. In the incidence of labiospalatoskizis the incidence ratio is (OR: 1.95, 95%CI: 1.38–2.75).
(Zheng, 2019)	Exposure to cigarette smoke during pregnancy, in the sense of passive smoking	Secondhand smoke exposure correlated with a significantly increased risk for malformations of the digestive system (1.17 [1.05–1.32]), nervous system (1.74 [1.33–2.29]), and cardiovascular system (2.10 [1.32–3.35]) and labiospalatoskizis (1.87 [1.47–2.39]).
(Oldereid, 2018)	The smoking habit of the father / husband when the wife is pregnant	A father who smoked was found to be associated with increased SGA, birth defects such as congenital heart defects, and orofacial cleft (labiospalatoskizis), cancer, brain tumors and acute lymphoblastic leukemia.
(Takeuchi, 2022)	Examining heavy metal exposure in 192 children born with labiospalatoskizis conditions, these metals include: Hg, Pb, Cd and Mn	Low levels of metals were found in the blood (for example, the median Pb levels were 5.85, 6.22, and 5.75 µg/L, respectively). Multivariate analysis showed that levels of none of the four heavy metals in the mother's blood during pregnancy were associated with the risk of cleft L/P in the offspring; The adjusted odds ratios (increments per 1 µg/L) with 95% intervals were 0.96 (0.91–1.03), 1.01 (0.94–1.08), 1.00 (0.61–1.63) and 1.00 (0.97–1.03) for, respectively. Results were consistent across all sensitivity analyses
(Garland, 2020)	Analyze behavioral risk factors (exposure to cigarette smoke), and biological hazards that can interfere with fetal orofacial development.	Exposure to cigarette sap or pregnant women who become passive smokers are at risk of giving birth to children with labiospaltoschizis disorders of CL/P (OR = 1.37, 95% CI: 1.26, 1.49) and CPO (OR = 1.24, 95% CI: 1.12, 1.38).

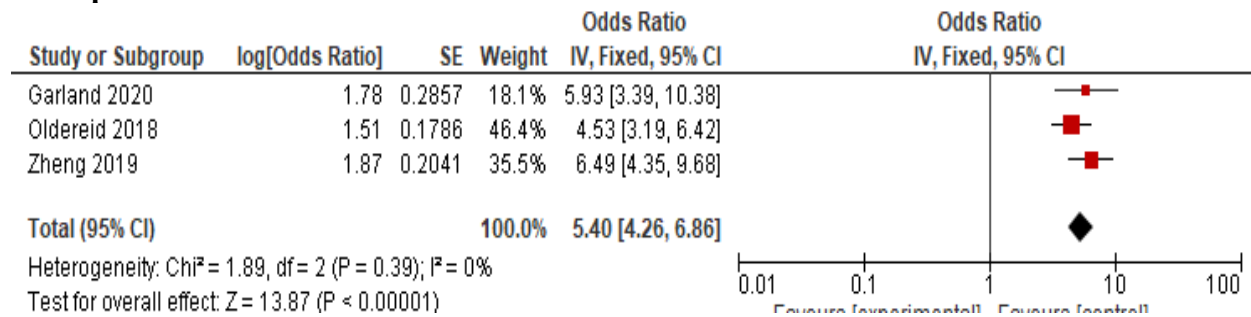
(Suhl, 2018)	Analyze exposure to cadmium metal during the mother's work and also Work history or exposure for 3 months after conception and follow the baby's birth conditions	Cumulative exposure to cadmium metal in the high category is associated with labiospalatoskizis events with the results of multivariate analysis showing an adjusted odds ratio of 1.4 (95% confident interval: 0.6, 3.2).
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### Forest plot of influence of metal exposure factors on incidence of labiospalatoskizis



Based on the results of the meta-analysis, it was found that exposure to various heavy metals can increase the risk of labiospalatoskizis events up to 3 times compared to pregnant women who have never been exposed to heavy metals and are statistically significant (OR: 3.18; 95% CI: 2.45 – 4.12; *p value* <0.001).

### Forest plot of the influence of cigarette smoke exposure factors on the incidence of labiospalatoskizis



Based on the results of the meta-analysis, it was found that exposure to cigarette smoke or when pregnant women become passive smokers can increase the risk of labiospalatoskizis events up to 5 times compared to pregnant women who have never been exposed to cigarette smoke and are statistically significant (OR: 5.40; 95% CI: 4.26 – 6.86; *p value* <0.001).

### Mechanism of exposure to cigarettes and heavy metals during pregnancy with the incidence of Labiospalatoskizis.

There are several mechanisms hypothesized about how tobacco smoke and heavy metals may increase the risk of labiospalatoskizis. The first mechanism is the expression of genes involved in cell cycle regulation, DNA repair, and oxidative stress responses have been affected by tobacco smoke. In addition, tobacco smoke can induce *proteasome-mediated* degradation of proteins that mediate DNA methylation in first-branch curved cells (BA1) (Garland et al. 2020). Endogenous compounds in tobacco plants, such as nicotine, as well as pyrolysis products such as polycyclic aromatic hydrocarbons (PAHs), dioxins, carbon monoxide, pesticides, and heavy metals such as cadmium can be present in tobacco smoke. One possible mechanism to be induced is AHR

activation. Exposure to heavy metals can cause labiospalatoskizis, believed to act teratogenically through the induction of oxidative stress and disruption of redox-sensitive signaling pathways. (Anggriant, 2022)

Nicotine and carbon monoxide can cause fetal hypoxia, a condition known to be labiospalatoskizis. Nicotine is a vasoconstrictor that can damage uterine vascular function and affect blood flow and oxygen delivery to the fetus while carbon monoxide can prevent oxygen transport by forming carboxyhemoglobin in red blood cells (Yin, 2019) Fetal hemoglobin has a greater affinity for carbon monoxide compared to adult hemoglobin, forming 10-15% more carboxyhemoglobin than the mother, exposure to heavy metals and cigarettes can cause labiospalatoskizis through inhibition of steroid anabolism . (Mbuyi-Musanzayi, 2018) Tobacco smoke can interfere with signaling pathways and the development of polymorphisms of genes encoding developmental ligands, such as transformation *Growth Factor Alpha* (TGFA), *Transforming Growth Factor Beta 3* (TGFB3), and *morphogenetic proteins 4* (BMP4) for bone, Variants that affect GxE smoking TGFA and TGFB3 which encodes ligands that regulate TGF- $\beta$  signaling which is essential for lip and palatal development.(Reynolds, 2020)

TGFB3 regulates fusion in MES and cell proliferation. Variants in TGFB3, in the context of smoking, have been associated with cleft lip and *Submucous Cleft Palate* (SMCP). In addition to growth factors, polymorphisms in other OFC-related genes have been implicated in smoking and orofacial clefts. Fetal homozygous mutations (allele 4) in *MSX1*, an important transcription factor for neural crest specification, were found to provide the greatest susceptibility to labiospalatoschizis events when the mother was exposed to smoke and heavy metals during pregnancy (Garland M. A., 2020)(Kawalec, 2015).

## CONCLUSION

Exposure to secondhand smoke can increase the risk of labiospalatoskizis events by up to 5 whereas heavy metal exposure can increase labiospalatoskizis events by up to 3 times and both are statistically significant

## REFERENCES

- Spinder, N. P. (2019). Congenital anomalies in the offspring of occupationally exposed mothers: a systematic review and meta-analysis of studies using expert assessment . *Human Reproduction*, 34(5), 903-919.
- Zheng, Z. X. (2019). Congenital malformations are associated with secondhand smoke among nonsmoking women: A meta-analysis. *Birth*, 46(2), 222-233.
- Oldereid, N. B. (2018). The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis. *Human reproduction update*, 24(3), 320.
- Takeuchi, M. Y. (2022). Association of maternal heavy metal exposure during pregnancy with isolated cleft lip and palate in offspring: Japan Environment and Children's Study (JECS) cohort study. *Plos one*, 17(3), e0265648.
- Garland, M. A. (2020). Environmental mechanisms of orofacial clefts. *Birth defects research*, 112(19), 1660-1698.

- Suhl, J. R. (2018). Maternal occupational cadmium exposure and nonsyndromic orofacial clefts. *Birth defects research*, 110(7), 603-609.
- Anggriant, V. R. (2022). The Correlation between High-Risk Pregnancy > 35 Years Old with Labioschizis Congenital Disorders. *Journal of Medical and Health Studies*, 3(3), 32-38.
- Yin, X. e. (2019). Maternal alcohol consumption and oral clefts: a meta-analysis. *British Journal of Oral and Maxillofacial Surgery*, 57(9), pp.839–846.
- Reynolds, K. Z. (2020). Genetics and signaling mechanisms of orofacial clefts. *Birth defects research*, 112(19), 1588-1634.
- Garland, M. A. (2020). Role of epigenetics and miRNAs in orofacial clefts. *Birth defects research*, 112(19), 1635-1659.
- Kawalec, A. e. (2015). Risk factors involved in orofacial cleft predisposition-review. *Open Medicine (Poland)*, 10(1), pp.163–175.
- Mbuyi-Musanzayi, S. K. (2018). Non-syndromic cleft lip and/or cleft palate: Epidemiology and risk factors in Lubumbashi (DR Congo), a case-control study. *Journal of Cranio-Maxillofacial Surgery*, 46(7), 1051-1058.
- Kummer, A. (2018). A Pediatrician's Guide to Communication Disorders Secondary to Cleft Lip/Palate. *Pediatric Clinics of North America*, 65(1), pp.31–46.
- Kusuma, D. C. (2022). Asuhan Neonatus Dan Bayi Baru Lahir Dengan Kelainan Bawaan. *Global Eksekutif Teknologi*.
- Afra, H. A. (2021). Article Review: Analysis of Patients with Labioschisis or Cleft Lip Review Artikel: Analisis Penderita Labioschisis atau Bibir Sumbing. In *Prosiding Seminar Nasional Biologi*, (pp. (Vol. 1, No. 2, pp. 1401-1407)).
- Gumilar, M. S. (2020). Bibir Sumbing Labioschisis. *PENYAKIT GIGI MULUT*, 12.
- Alade, A. A. (2022). Genetic and epigenetic studies in non-syndromic oral clefts. *Oral diseases*, 28(5), 1339-1350.
- Lacerda, R. H. (2021). Maternal Smoking Leads to Larger Cleft Palate Defects. *Frontiers in Dental Medicine*, 1, 632037.