Correlation between Maternal Zinc Deficiency and Nonsyndromic Cleft Lip with or without Cleft Palate : A Rapid Review

Alanis Sakina Agniya Mahanani[1], Eriska Riyanti[2]*, Arlette Suzy Puspa Pertiwi[2]

1. Faculty of Dentistry, Universitas Padjadjaran, Indonesia.
2. Dept. of Paediatric Dentistry, Faculty of Dentistry, Universitas Padjadjaran, Indonesia.

Abstract

Nonsyndromic cleft lip and palate (NS CLP) is a congenital disorder with the second-highest percentage in Indonesia. One of the factors that caused it was micronutrient deficiency of the mother. Zinc deficiency during pregnancy is suspected can increase the risk of babies with CLP. This rapid review aimed to identify the correlation between maternal zinc deficiency and NS CLP. Methods: This study was conducted using PRISMA via databases: PubMed, Google Scholar, ScienceDirect, ProQuest, and Cochrane Library. All observational design study which discusses zinc deficiency and CLP with publication year from 2007 – 2022 were included. Result: Nine articles were included in this rapid review: eight with case-control design and one with cross-sectional design. Samples and methods for assessing zinc levels vary in each article. Four articles reported a positive correlation between zinc deficiency and CLP while the other five reported no correlation. The risk of bias from all articles was low to moderate. Conclusion: The included articles showed different findings on the correlation between maternal zinc deficiency and NS CLP. A definitive correlation cannot be made due to the varied samples and methods, and most articles had a moderate risk of bias.

Review (J Int Dent Med Res 2022; 15(4): 1855-1863)

Keywords: Maternal zinc, zinc deficiency, nonsyndromic clef lip with cleft palate.

Received date: 05 July 2022 **Accept date:** 14 August 2022

Introduction

Nonsyndromic cleft lip and cleft palate (NS CLP) is a congenital disorder with the second-highest percentage in Indonesia.[1] This congenital abnormality is a malformation in the form of a gap in the upper lip and palate.[2] This gap is formed in the first trisemester of pregnancy.[3] The etiology of CLP is mostly unknown, but several studies stated it is multifactorial.[4] The risk factors that play a role are genetic and environmental factors such as low socioeconomic conditions, mothers who experience nutritional deficiencies, mothers who smoke, consume alcohol, use drugs and harmful chemicals.[4,5]

Riset Kesehatan Dasar 2018 shows that the percentage of cleft lip in children aged 24-59 months is 0.12%.[6] This indicates an increase in cases from 2013 to 0.04%.[7] One of the prevention efforts is to ensure the fulfillment of the needs of vitamins and minerals, especially folic acid for women who are planning to become pregnant.[1] Besides folic acid, there are other micronutrients needed by pregnant women, one of which is zinc. Zinc is one of the most important trace elements in the body that is needed during protein synthesis, DNA synthesis, and cell division, so it plays a significant role in fetal morphogenesis and differentiation.[8,9] Therefore, the first trimester must be fulfilled because organogenesis of the lips and palate occurs rapidly during this period.[10]

However, in reality, pregnant women are included in a group prone to zinc deficiency, especially in developing countries.[11,12] The cause of zinc deficiency that often occurs is the lack of intake of foods containing zinc.[13] Including in Indonesia, consuming zinc is still little done by pregnant women.[14] This happens because zinc is only needed in very small amounts, so people still often underestimate and do not make zinc consumption an important thing.[14]

Several previous studies have examined the relationship between zinc deficiency in

Corresponding author:
Eriska Riyanti ,
Department of Paediatric Dentistry, Faculty of Dentistry, Universitas Padjadjaran, Indonesia.
E-mail: eriska.riyanti@unpad.ac.id

mothers with CLP and obtained varying results.[15] So, this rapid review study aimed to identify scientific evidence regarding the correlation between zinc deficiency and NS CLP. The results of this study are expected to clarify the correlation between maternal zinc deficiency and CLP to increase public understanding and awareness of the importance of meeting zinc needs.

Materials and methods

This rapid review was conducted following the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines.[16] This study begins by formulating research questions using the PECO format : Population (pregnant women), Exposure (mothers who have zinc deficiency), Comparison (mothers who do not have zinc deficiency), and Outcome (nonsyndromic cleft lip with or without cleft palate).[17] In order to answer the research question about the correlation between maternal zinc deficiency and nonsyndromic cleft lip with or without cleft palate, a literature search with a systematic approach was performed from February to June 2022. The electronic database used was PubMed, Google Scholar, ScienceDirect, Proquest, and Cochrane Library.

Inclusion and Exclusion Criteria

Eligibility criteria were determined by a selection of articles that met the inclusion and exclusion criteria. The inclusion criteria in this study were articles that analyzed the relationship between maternal zinc deficiency and NS CLP; articles with cross-sectional, case-control, or cohort study design; published in the last 15 years (2007 – 2022); in English; and can be accessed in full text. Observational research articles with non-human subjects, case series, and systematic reviews regarding the relationship between zinc deficiency and NS CLP were excluded.

Search Strategy and Study Selection

Search articles through electronic databases using keywords that include terminology about maternal zinc deficiency ("maternal zinc", "maternal zinc deficiency", "zinc deficiency", "maternal zinc level", "maternal zinc concentration", "zinc concentration of mother", "zinc level of mother") and NS CLP ("cleft lip", "nonsyndromic cleft lip", "nonsyndromic cleft lip with or without cleft palate", " nonsyndromic orofacial cleft", "nonsyndromic oral cleft", "isolated cleft lip"). These keywords are used together using Boolean Operators (OR and AND) to combine searches.[18,19] The publication year filter (2007 – 2022) is used for each database. An additional filter used in ScienceDirect is a research article filter, while in ProQuest is a source type filter (scholarly journal).

The results of the articles identified from the five databases were then selected manually. First, eliminate duplicate articles, screen articles with irrelevant titles and abstracts and screen for articles that cannot be accessed in full text. Finally, the complete manuscript is read to be assessed for eligibility according to the content of this research.

Data Extraction and Risk of Bias Assessment

Data extraction included information about the name of the researcher, year of publication, title, research location, study design, participant characteristics, sample and method of zinc level assessment, results, conclusions, and quality assessment of each article.

The quality of the articles included in this rapid review study was assessed using the JBI Critical Appraisal Tools, which were adapted to the research design of each article. To determine quality of each article, there are 8 – 11 questions with answers "Yes", "No", or "Unclear". One person carried out this risk of bias assessment by giving a score of 1 for each question with a "Yes" answer and a score of 0 for other answers. The risk of bias from articles is categorized based on the percentage of "Yes" answers. Articles with a "Yes" percentage: (1) 49% have a high risk of bias, (2) 50% - 79% have a moderate risk of bias, and (3) 80% have a low risk of bias.[20]

Results

Study Selection

The five electronic databases search strategy identified 659 articles, which resulted in 443 after duplicate articles were removed. After screening titles and abstracts that can be accessed in full text, 21 relevant articles were obtained. Then the entire contents of these 21 articles were reviewed for eligibility. Twelve articles were omitted for the following reasons: case series articles (n = 1), review articles (n = 4), non-English articles (n = 1), articles discussing zinc gene polymorphisms (n = 2), and indirectly correlating maternal zinc deficiency with NSCLP

(n = 4). Finally, nine articles that meet the inclusion criteria will be synthesized in this study.[5,21–28] The study selection process is summarized in Figured 1.

Description of The Study Characteristics

The total number of articles synthesized in this rapid review was nine articles. There are differences in the research design: eight articles used a case-control study design and one used a cross-sectional study. In addition, the research locations in each article varied: three articles were conducted in China, while the other six articles were conducted in Indonesia, Iran, Thailand, California, Poland, and Utah. All participants in the case-control study design article consisted of a case group (mother of an infant or fetus diagnosed as having CL/P) and a control group (mother of an infant or fetus without congenital abnormalities). The number of participants varied, consisting of 48 - 595 mothers in the case group and 48 - 534 mothers in the control group. Participants in the cross-sectional design article consisted of 35 mothers and their 35 children suffering from CLP.[22] Maternal age ranged from 15 to 40 years, but 1 article did not clearly state maternal age.[5]

There are different types of samples and methods used to assess zinc levels. Two articles used blood plasma samples and the Flame Atomic Absorption Spectrometry method.[5,28] Four articles used the Inductively Coupled Plasma – Mass Spectrometry method with different samples, namely maternal whole blood, blood serum, umbilical cord, and placenta.[21,23,24,27] One article used the Inductively Couple Plasma – Atomic Emission Spectrometer method but samples were not clearly identified.[22] One article used toenail samples and the Instrumental Neutron Activation Analysis method.[25] One article used a modified food frequency questionnaire from the National Cancer Institute Health Habits and History Questionnaire.[26] The results of data extraction are presented in Table 1.

Four of the nine synthesized articles found an association between maternal zinc levels and NS CLP.[22,23,26,27] Four other articles did not found correlation, and one article stated that there was no definitive correlation.[5,21,24,25,28] The results of the risk of bias assessment using the JBI Critical Appraisal showed that 7 articles had a moderate risk of bias and 2 articles had a low risk of bias. None of the included article obtained the highest score based on the JBI assessment. The score range of all articles is between five and nine. The results of the risk assessment of bias are presented in Table 2.

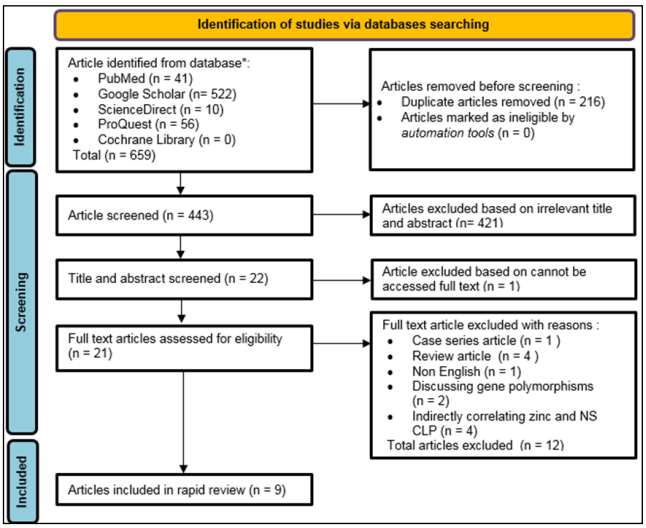

Figure 1. PRISMA diagram flow in this rapid review.

Study	Q_1[a]	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q_{10}	%Yes	Risk of bias[b]
A correlation between maternal zinc level and CLP												
Chairunas *et al.*[22]	?	✓	✓	✓	✓	?	✓	✓			75%	Moderate
Wenli Ni *et al.*[23]	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	90%	Low
Wallenstein, *et al.*[26]	x	x	?	x	✓	✓	✓	✓	?	✓	50%	Moderate
Hozyasz, *et al.*[27]	x	x	✓	✓	✓	✓	X	✓	x	✓	60%	Moderate
No correlation between maternal zinc level and CLP												
Shengju Yin, *et al.*[21]	✓	x	x	✓	✓	✓	✓	?	?	✓	60%	Moderate
Xin Pi, *et al.*[24]	✓	✓	x	✓	✓	✓	✓	✓	✓	✓	90%	Low
McKinney, *et al.*[25]	✓	✓	x	x	✓	✓	✓	x	✓	✓	70%	Moderate
Munger, *et al.*[28]	✓	✓	x	x	✓	✓	X	✓	x	✓	60%	Moderate
No definitive correlation between maternal zinc level and CLP												
Azita Tiznobaik, *et al.*[5]	✓	x	✓	x	✓	✓	X	✓	x	✓	60%	Moderate

[a]Q_1 – Q_{10} are questions 1 to 8 for article with a cross-sectional study and questions 1 to 10 for article with a case control study based on *Joanna Briggs Institute* (JBI) *Critical Appraisal*.
[b]The risk of bias is categorized based on the percentage of "yes" answers, which are as follows : 1) ≤ 49% : High 2) 50% - 79% : Moderate; 3) ≥ 80% : Low. "✓" indicate yes, "x" indicate no, "?" indicate unclear.

Table 2. JBI risk of bias assessment of synthesized articles

Discussion

The correlation between zinc deficiency as a risk factor for infants with cleft lip and palate has been debated. In this rapid review, four of the nine articles stated a correlation between maternal zinc levels and cleft lip with or without cleft palate. [22,23,26,27] Wenli Ni et al. (2019) stated that the median zinc level in the umbilical cord tissue was lower in the case group (P = 0.001).[23] Hozyasz et al. (2009) also revealed that the median zinc concentration in maternal whole blood was lower in the case group than in the control group (P = 0.07), and mothers with zinc concentrations less than 47.1 mol/L had 2.5 times the risk of infants with CLP. higher (P <

0.05).[27] The results of these two studies showed that lower maternal zinc concentrations correlated with cleft lip and palate infants.

Study by Chairunas et al. (2019) showed a significant correlation (P = 0.04) between maternal zinc levels and nonsyndromic CL/P infants with a moderate correlation coefficient (R = 0.35).[22] According to her study, zinc levels below the median were more frequently occurred in infants with cleft palate compared to other types of clefts.[22] Wenli Ni et al. (2019) found that higher zinc levels were associated with a reduced risk of CLP (P = 0.022) but not for CL (P = 0.161).[23] The study by Hozyasz et al. (2009) showed that low zinc concentrations were only found in mothers of infants with cleft palate.[27] Another thing was stated by Wallenstein et al. (2013), namely that mothers who did not take zinc supplements and had a low nutritional intake of zinc had a two-fold higher risk of having a baby with cleft palate (95% CI > 1.0).[26]

Based on the four study results which stated that there was a correlation between maternal zinc levels and the incidence of cleft lip and cleft palate, it was seen that a tendency for low zinc levels to be correlation with cleft palate. This tendency is related to studies which state that zinc-dependent enzymes, namely Matrix Metalloproteinases (MMP-2 and MMP-3) are needed in the process of palatogenesis.[29] MMPs play a role in tissue remodelling, migration, adhesion, and cell proliferation.[29] Tissue inhibitor MMPs (TIMPs) play a role in inhibiting the activity of MMPs and can stimulate the process of cell apoptosis.[29] If the mother's zinc deficiency causes a disturbance in the balance of MMPs and TIMPs, zinc deficiency may interfere with the process of palatal fusion.[30]

The level of zinc in the body is influenced by several factors, especially the nutritional intake of zinc.[10] Zinc intake per day, although only a little is needed to maintain stable body functions.[31] During pregnancy, the need for zinc increases which is about 11 mg/day to maintain the mother's metabolism and support fetal growth.[32] This is in accordance with the statement that pregnant women who do not consume foods containing zinc or zinc supplements as recommended have a higher risk of giving birth to babies suffering from the cleft lip with or without cleft palate.

However, four articles found no correlation, and one concludes that there is no definitive correlation between the two variables. Sengju Yin et al. (2020) and Azita Tiznobaik et al. (2018), which assessed the concentration of zinc in maternal serum and blood plasma, showed that zinc concentrations were lower in the case group, but the difference was not statistically significant (*P* = 0.210; *P* = 0.187).[5,21] Xin Pi et al. (2018) stated that there was no significant difference in the median zinc concentration in placental tissue between the case and control groups (*P* = 0.224).[24] Other studies also revealed that the average zinc concentration in the two groups was almost the same.[25,28]

Differences in results found between studies could be due to variations in the sample used to assess maternal zinc levels (serum, plasma, whole blood, placental tissue, umbilical cord, nails, and questionnaires). Until now, there has been no definitive statement regarding which sample indicators are better used to measure zinc levels.[33] Experts more often use plasma because it is easier to use and provides relatively accurate results.[34] Plasma zinc levels in women who have given birth are considered less representative of maternal zinc levels during pregnancy compared with placental and umbilical cord tissue that is part of the fetus.[23,24] The sampling time and the method used to assess zinc levels may also have contributed to the findings of different results. Another reason is to ignore other factors of the participants that can influence the study results, such as consuming food and mineral supplements.[5]

The etiology of infants with cleft lip and cleft palate remains unclear.[4] However, evidence suggests that the true etiology of CLP results from a complex and multifactorial series of events so that low maternal zinc levels cannot be seen as the only causative factor.[35] Another thing to remember is that various intrauterine environmental factors will affect fetal development, including fetal genotype.[36] Maternal zinc deficiency will affect the embryogenesis process because zinc plays a major role in biochemical reactions and gene regulation.[37] Disruption of this role can slow down transcription rate, which causes a decrease in gene expression so that there can be disturbances in forming the lips and palate.[38] Therefore, zinc deficiency in the mother is still likely to have a correlation with cleft lip and cleft palate.

This rapid review study has several

limitations. First, in selecting articles to be synthesized, only English articles were selected and published in the last 15 years, so there is a possibility of ignoring other relevant articles. Second, Africa has the highest prevalence of zinc deficiency globally, followed by Asia. None of the articles synthesized in this study was conducted in Sub-Saharan Africa. There are studies conducted in Asia, but not all of these areas are geographically deficient in zinc, so the participants involved are less relevant.[39] Third, most of the articles synthesized had a moderate risk of bias.

The results of this rapid review indicate that there is still a difference in the presence or absence of a correlation between maternal zinc deficiency and nonsyndromic cleft lip with or without cleft palate. Definitive conclusions cannot be made based on the articles that have been synthesized. However, in this rapid view, authors suspect that maternal zinc deficiency still has the opportunity to have a correlation with cleft lip and cleft palate, considering that the etiology of CLP is multifactorial. Suggestions for future research regarding the correlation between maternal zinc deficiency and CLP is to consider the geographical location of the study, which can represent areas of zinc deficiency. Another consideration is the timing of the assessment of zinc levels in pregnant women during the first trimester to provide more relevant results from the correlation between zinc deficiency in mothers and nonsyndromic cleft lip with or without cleft palate.

Conclusions

The results of this rapid review indicate that there is still a difference in the presence or absence of an association between zinc deficiency in the mother and nonsyndromic cleft lip with or without cleft palate. Definitive conclusions cannot be made based on the articles that have been synthesized because the sample and research methods varied and most articles had a moderate risk of bias.

Acknowledgements

The authors received no financial or other support of any research grant for this article.

Declaration of Interest

The authors report no conflict of interest.

No.	Study (Year)	Article title	Study design	Partisipant characteristic	Sample and method	Result	Conclusion
1.	Shengju Yin, et al.[21] (2020)	Selected essential trace element in maternal serum and risk for fetal orofacial clefts	Case - control	**Case group** : mother of fetuses or newborns with orofacial cleft confirmed at delivery or prenatal diagnosis in 3 provinces in northern China (n = 130) **Control group** : mother of nonmalformed fetuses or infant living in the same province with a first day of last menstruation close to case group (n = 260) **Age of mother (Cases / Controls):** - < 25 years (36 / 88) - 25 – 29 years (57 / 92) - 30 – 34 years (23 / 55) - ≥ 35 years (14 / 25)	**Sample :** Serum **Zinc level assessment method :** the Inductively Coupled Plasma – Mass Spectrometry	Consentration of Zn lower in cases but these differences did not statistical significance (*P* = 0,210). No association were found between concentration of Zn and risk of OFC (OR = 0.98; 95% CI 0.54 – 1.77 for second tertile and OR = 0.66; 95% CI 0.35 – 1.24 for thirs tertile). Increased levels of all six trace elements are associated with a reduced risk of orofacial clefts when considered together.	No association was observed between levels of Zn and risk for OFCs in either statistical model.

2.	Chairunas, et al.[22] (2019)	Correlation between zinc level of mothers and case of babies with non-syndromic cleft lip and palate	Cross-sectional	Thirty-five mothers and their babies with cleft lip and palate were treated at RSHS and several hospitals in Bandung. **Age of mother :** - 15 – 19 years (n = 3) - 20 – 24 years (n = 4) - 25 – 29 years (n = 12) - 30 – 34 years (n = 10) - 35 – 40 years (n = 4) - ≥ 40 years (n = 2)	**Sample :** Not mentioned **Zinc level assessment method:** Inductively Couple Plasma – Atomic Emission Spectrometer	The mean maternal zinc was higher than babies. The test showed significant correlation (P = 0.04 and R = 0.35).	There was moderate correlation between zinc level mothers and babies with NS CLP.
3.	Wenli Ni, et al.[23] (2019)	Association between selected essential trace element concentration in umbilical cord and risk for cleft lip with or without cleft palate : a case control study	Case - control	**Case group** : mothers and babies with CLP from Sanxi Province, northern China (n = 88). **Control group** : mothers and babies with no congenital malformation was matched by sex, place of residence, and the date of the last menstrual period (± 4 month) of the cases mother (n = 200). **Mothe's age when pregnancy:** Cases : 26,55 ± 4,94 years Controls : 26,90 ± 4,70 years	**Sample :** Umbilical cord **Sampling time :** At the time of delivery **Zinc level assessment method:** the Inductively Coupled Plasma – Mass Spectrometry	The median level of Zn in umbilical cord tissues cases (49.72 µg/g) were lower than those in controls (54.79 µg/g); P = 0.001. Higher level of ZN were associated with reduced risk for CL/P (OR = 0.44; 95% CI = 0.20 – 0.93; P = 0.032) and CLP (OR = 0.35; 95% CI = 0.14 – 0.86; P = 0.022) but not for CL (P = 0.161).	Higher levels of Zn was associated with reduced risk for CLP.
No.	**Study (Year)**	**Article title**	**Study design**	**Partisipant characteristic**	**Sample and method**	**Result**	**Conclusion**
4.	Azita Tiznobaik, et al.[5] (2018)	Relationship between plasma zinc concentration of maternal zinc durinf pregnancy and the risk for orofacial cleft	Case - control	**Case group**: mothers of children with cleft lip in Iran (n = 48). **Control group**: mothers of children with no congenital malformation (n = 48). **Criteria** : - None had previous use of alcohol, cigarette, or any teratogenic drugs. - None had a history of the birth of children with congenital malformation. - BMI < 30 kg / m^2	**Sample** : Plasma **Interval time between delivery and sampling (max) :** 5 years **Zinc level assessment method:** Flame atomic absorption spectrometry.	Plasma Zn level in cases was (16.87 ± 8.17 µmol/L) and in controls was (19.28 ± 8.83 µmol/L) that was statistically similar (T = -1.329, P = 0187). T-test showed that the two group did not have a significant difference (OR = 1.66; 95% CI = 0.61 – 4.54).	Despite lower zinc plasma levels in women of the case group, the difference in concentration of this element was not statistically significant between so there is no definitive relationship.
5.	Xin Pi, et al.[24] (2018)	Higher concentration of selenium in placental tissues is associated with reduced risk for orofacial clefts	Case - control	**Case group**: mothers and babies with CLP from Sanxi Province, northern China (n = 103). **Control group**: mothers and babies with no congenital malformation was matched by sex, place of residence, and the date of the last menstrual period (± 4 month) of the cases mother (n = 206). **Age of mother (Cases / Controls):** - < 25 years (44 / 91) - 25 – 29 years (41 / 63) - ≥ 30 years (17 / 51)	**Sample :** Placental tissue **Sampling time :** At the time of delivery **Zinc level assessment method:** the Inductively Coupled Plasma – Mass Spectrometry	No significant differences in Zn concentration ere foung between the group (P = 0.224). No association was observed between placental Zn and risk of OFC (OR= 0,90; 95% CI = 0.50 – 1.60).	No association was observed between levels of Zn in placental and risk for OFCs

6.	McKinney, et al.[25] (2016)	Case – control study of nutritional and environmental factors and the risk of oral clefts in Thailand	Case - control	**Case group**: mothers of infanrs with nonsyndromic CLP (< 24 month) seen in Center of Cleft Lip – Cleft Palate and Craniofacial Deformities, Thailand (n = 95). **Control group**: mothers of infants with no congenital malformation were matched by age, birth weight, and place of conception of the cases mother (n = 95). **Age of mother (Cases / Controls):** - < 25 years (37 / 32) - 25 – 34 years (43 /50) - ≥ 35 years (15 / 12)	**Sample:** Toenail **Sampling time:** ± 3 month after delivery **Zinc level assessment method:** Instrumental Neutron Activation Analysis	Zinc concentration were similar for cases (62 ppm) and controls (60 ppm) (*P* = 0.19). Toenal zinc concentration were not associated with CL/P (OR = 1.0; 95% CI = 0.99 – 1.1; *P* = 0.28).	Toenal zinc concentration were not associated with risk of CL/P.

No.	Study (Year)	Article title	Study design	Partisipant characteristic	Sample and method	Result	Conclusion
7.	Wallenstein, et al.[26] (2013)	Periconceptional nutrient intakes and risk of orofacial clefts in California	Case - control	**Case group:** mothers of infants with CLP and prenatally diagnosed that occurred in California (n = 595). **Control group**: mothers of infants with nonmalformed were selected randomly and matched by cases (n = 534).	**Method :** Food frequency questionnaire modified from National Cancer Institute Health Habits and History Questionnaire. **Interview time :** < 6 weeks after the baby is born	Vitamin supplement intake was associated with a modestly decreased risk of clefts buat the CI = 1.0. Among women who did not take Zn supplement, lower dietary intake was associated with at least a twofold increased risk of CLP CL (95% CI > 1.0).	Nutrient intake during periconceptional period may be associated with risk of CLP.
8.	Hozyasz, et al.[27] (2009)	Relation between the concentration of zinc in maternal whole blood and the risk of an infant being born with orofacial cleft	Case - control	**Case group**: mothers of children with nonsyndromic CLP (n = 116). **Control group** mothers of children with no congenital malformation (n = 64). **Criteria :** - All participants were white and omnivorous. - None took mineral supplements **Age of mother:** - Cases : 24 – 30 years - Controls : 24 – 32 years	**Sample :** Maternal whole blood **Interval time between delivery and sampling (median):** - Cases : 3 years - Controls : 6,3 years **Zinc level assessment method:** the Inductively Coupled Plasma – Mass Spectrometry	Zn concentration in blood lower in cases than controls (53.1 µmol/L vs. 55.5 µmol/L; *P* = 0.07) Mothers with a whole blood zinc concentration of < 47.1 µmol/L had a risk 2.5 times higher of having a child with OFC (OR = 2.53; 95% CI = 1.03 – 6.23; *P* = 0.04).	An association between concentration of maternal zinc and the risk of orofacial cleft.

9.	Munger, et al.[28] (2008)	Plasma zinc concentration of mothers and the risk of oral clefts in their children in Utah	Case control	–	**Case group**: mothers had a child liveborn or stillborn with an OC (n = 410). **Control group**: mothers without a history of a cleft-affected pregnancy were renadomly selected using Utah birth certificate and matching sex and births by month and year to cases (n = 447). **Mother's age when delivery (mean) :** 27,2 (±5,5 SD) years	**Sample :** Plasma **Zinc level assessment method:** Flame atomic absorption spectrometry. **Interval time between delivery and sampling (mean) :** - Cases : 3,7 years - Controls : 4,3 years	Mean PZns of all groups were similar Low PZn was found in 59% of cases and 62% of controls (< 11 µmol/L). The risk of CLP was not significantly different with PZn for each cleft type in case group.	No association was found between zinc status and oral cleft. Poor maternal zinc status may become a risk factor only when zinc status is highly compromised.

Tabel 1. Study characteristics of literature research.

References

1. InfoDATIN: Kelainan Bawaan. Jakarta. Kemenkes RI. Pusat Data dan Informasi Kementerian Republik Indonesia. 2018.
2. Wilson-Nagrani C, Richmond S, Paternoster L. Non-syndromic Cleft Lip and Palate Polymorphisms Affect Normal Lip Morphology. Front Genet. 2018;9(413):1-12.
3. Kurniati M, Airlangga U, Malahayati U, et al. BMP4 SNP Rs17563 T>C Gene Polymorphism on Non-Syndromic Cleft Lip/Palate in an Indonesia Population. J Int Dent Med Res. 2021;14(2):595-599.
4. A Oner D, Tastan H. Cleft lip and palate: Epidemiology and etiology. Otorhinolaryngol Neck Surg. 2020;5(4):1-5.
5. Tiznobaik A, Taheri S, Momenimovahed Z, Shirinzad M, Dalband M, Noorafrooz A. Relationship between Plasma Concentration of Maternal Zinc during Pregnancy and the Risk for Orofacial Cleft. Asian J Pharm. 2018;12(2):1-5.
6. Laporan Nasional Riskesdas 2018. Jakarta. Kemenkes RI. Badan Penelitian dan Pengembangan Kesehatan. 2019:433-434.
7. Laporan Nasional Riskesdas 2013. Jakarta. Kemenkes RI. Badan Penelitian dan Pengembangan Kesehaan. 2013:229-230.
8. National Institutes of Health Office of Dietary Supplement. Zinc. Available at https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/#h5. Published 2021. Accessed September 10, 2021.
9. Karimi A, Bagheri S, Nematy M, Saeidi M. Zinc Deficiency in Pregnancy and Fetal Impact of the Supplements on Pregnancy Outcomes. Iran J Neonatol. 2012;3(2):77-83.
10. Mousa A, Naqash A. Macronutrient and Micronutrient Intake during Pregnancy : An Overview of Recent Evidence. Nutrient. 2019;11(2):443-446.
11. Uwitonze AM, Ojeh N, Murererehe J, Atfi A, Razzaque MS. Zinc adequacy is essential for the maintenance of optimal oral health. Nutrients. 2020;12(4):1-14.
12. Plum LM, Rink L, Hajo H. The essential toxin: Impact of zinc on human health. Int J Environ Res Public Health. 2010;7(4):1342-1365.
13. Saper RB, Rash R. Zinc: An essential micronutrient. Am Fam Physician. 2009;79(9):768-772.
14. Herman S. Review on the problem of zinc defficiency , program prevention and its prospect. Media Litbang Kesehat. 2009;19(2):S75-S83.
15. Tamura T, Munger RG, Corcoran C, Nepomuceno B, Solon F, Bacayao JY. Plasma Zinc Concentrations of Mothers and the Risk of Nonsyndromic Oral Clefts in Their Children : A Case-Control Study in the Philippines. 2005;73(9):612-616.
16. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372(160):1-36.
17. Dobbins M. Rapid Review Guidebook - Steps for Conducting a Rapid Review. Hamilton: National Collaborating Centre for Methods and Tools; 2017:5-19.
18. " What is a Boolean Operator ?". Available at "https://library.alliant.edu/screens/boolean.pdf". Accessed September 10, 2021
19. Database Search Tips: Boolean operators. Available at "https://libguides.mit.edu/c.php?g=175963&p=1158594". Accessed September 10, 2021.
20. Goplen CM, Verbeek W, Kang SH, et al. Preoperative opioid use is associated with worse patient outcomes after Total joint arthroplasty : a systematic review and meta-analysis. BMC Musculoskelet Disord. 2019;20(234):1-12.
21. Yin S, Wang C, Wei J, et al. Selected essential trace elements in maternal serum and risk for fetal orofacial clefts. Sci Total Environ. 2020;712(4):1-7.
22. Chairunas, Effendi SH, Yusuf HY, Riyanti E, Suhanda R, Nandini N. Correlation between zinc level of mothers and case of babies with non-syndromic cleft lip and palate. Indian J Public Heal Res Dev. 2019;10(11):1868-1872.
23. Ni W, Yang W, Yu J, et al. Association between selected essential trace element concentrations in umbilical cord and risk for cleft lip with or without cleft palate: A case-control study. Sci Total Environ. 2019;661(4):196-202.
24. Pi X, Wei Y, Li Z, et al. Higher concentration of selenium in placental tissues is associated with reduced risk for orofacial clefts. Clin Nutr. 2019;38(5):2442-2448.
25. McKinney CM, Pisek A, Chowchuen B, et al. Case–control study of nutritional and environmental factors and the risk of oral clefts in Thailand. Birth Defects Res Part A - Clin Mol Teratol. 2016;106(7):624-632.
26. Wallenstein MB, Shaw GM, Yang W, Carmichael SL. Periconceptional nutrient intakes and risks of orofacial clefts in California. Pediatr Res. 2013;74(4):457-465.
27. Hozyasz KK, Kaczmarczyk M, Dudzik J, Bulska E, Dudkiewicz Z, Szymanski M. Relation between the concentration of zinc in maternal whole blood and the risk of an infant being born with an orofacial cleft. Br J Oral Maxillofac Surg. 2009;47(6):466-469.
28. Munger RG, Tamura T, Johnston KE, Feldkamp ML, Pfister R, Carey JC. Plasma zinc concentrations of mothers and the risk of oral clefts in their children in Utah. Birth Defects Res Part A - Clin Mol Teratol. 2009;85(2):151-155.
29. Smane L, Pilmane M, Akota I. Apoptosis and MMP-2, TIMP-2 expression in cleft lip and palate. Stomatologija. 2013;15(4):129-134.
30. Smane-Filipova L, Pilmane M, Akota I. MMPs and TIMPs expression in facial tissue of children with cleft lip and palate. Biomed Pap. 2016;160(4):538-542.

31. Gabriel P, Rink L. Zinc and the immune system. Proc Nutr Soc. 2000;59(4):541-552.
32. Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health : An integrative review. J Res Med Sci. 2013;18(2):144-157.
33. Wieringa FT, Dijkhuizen MA, Fiorentino M, Laillou A, Berger J. Determination of zinc status in humans: Which indicator should we use? Nutrients. 2015;7(5):3252-3263.
34. Sandstrom B. Diagnosis of zinc deficiency and excess in individuals and populations. Food Nutr Bull. 2001;22(2):133-137.
35. Shkoukani MA, Chen M, Vong A. Cleft lip - A comprehensive review. --. 2013;1(53):1-10.
36. Prescott NJ, Winter RM, Malcolm S. Nonsyndromic cleft lip and palate: Complex genetics and environmental effects. Ann Hum Genet. 2001;65(6):505-515.
37. Terrin G, Canani RB, Di Chiara M, et al. Zinc in early life: A key element in the fetus and preterm neonate. Nutrients. 2015;7(12):10427-10446.
38. Cousins RJ. A role of zinc in the regulation of gene expression. Proc Nutr Soc. 1998;57(02):307-311.
39. Gupta S, Brazier AKM, Lowe NM. Zinc deficiency in low- and middle-income countries: prevalence and approaches for mitigation. J Hum Nutr Diet. 2020;33(5):624-643.