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Maternal Factors influencing the Development of Cleft Lip and/or Palate in Fetus – A Narrative Review

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Abstract

Cleft lip and cleft palate are congenital anomalies originating from improper fusion of the lips and palate in the fetus during gestation. Although the exact etiology remains elusive, various genetic, maternal, nutritional, and environmental factors may contribute to the development of cleft lip and/or palate (CL±P) in infants. In this context, understanding the maternal factors that influence the development of CL±P is crucial to educate mothers on preventive measures. Our study reviews the literature between 2010 and 2023, retrieved from PubMed and Google Scholar, investigating maternal factors associated with the risk of cleft in offspring. Out of 74 identified publications, we analyzed 31 studies, excluding duplicates and those not meeting the review objective. The factors assessed include maternal tobacco exposure, occupational exposure, bereavement, pollutants, multivitamin intake, serum levels, metal exposure, obesity, and maternal diseases. Our review found a strong correlation between CL±P and maternal tobacco exposure, caffeine intake during pregnancy, exposure to pesticides and dust, threatened abortion,

arsenic exposure, exposure to polycyclic aromatic hydrocarbons, herpes simplex infection, and gravidity. Conversely, protective factors against oral cleft occurrence included periconceptional folic acid intake, timely vaccinations, and a higher socioeconomic status. This review offers a comprehensive overview of maternal factors impacting the occurrence of clefts in offspring, providing key insights for early detection strategies and counseling of pregnant and expectant women.

Keywords: Cleft-Palate, Risk Factor, Pregnancy Risk, Maternal Factors, Cleft Lip And/Or Palate

Background

The Centers for Disease Control and Prevention states that "Cleft lip and cleft palate are birth defects that occur when a baby's lip or mouth do not form properly during pregnancy. Together, these birth defects commonly are called oro-facial clefts" (1). Worldwide, the incidence of cleft lip with or without cleft palate (CL±P) is 1 in 1000 live births (2). In India, the incidence is 1 in every 781 live births and every year about 35000 neonates are born with CL±P (3). The development of CL±P is a congenital malformation which occurs during the eighth week of gestation. During this period when there is failed fusion of the maxillary processes with the lower edges of the lateral nasal prominences, it results in the development of cleft lip. This fusion failure is due to the inadequate migration of neural crest cells (4). If the failure of fusion occurs on one side of the lips then it is known as unilateral cleft lip and when the cleft occurs on both sides of the lips it is known as bilateral cleft lip. The inability of the lateral palatine processes to fuse with one another causes cleft palate. This may be caused by the palatal shelves growing abnormal, unable to rise over the tongue, failing to make contact with one another due to an abnormally wide head, failing to fusion, or rupturing after fusion(4).

Etiology of CL±P is scientifically understood by a combination of genetic, maternal, nutritional, and environmental factors, however its exact cause is yet unknown. A child born with CL±P can be both emotional trauma to the child and the family. Hence the factors that influence the development of CL±P should be controlled to prevent the incidence. In this article, we aimed at reviewing the current literature on the various maternal factors that are influencing the development of CL±P in newborns.

Objective

To review the various maternal factors that influences the development of CL±P in offspring.

Materials and methods

We conducted a literature search in PubMed and Google Scholar for articles published from 2010 up till 2023 reporting the various maternal factors that influence the development of CL±P in fetuses.

Search strategy

The search was executed with the keywords: 'maternal', 'maternal factor', 'maternal risk', 'mother', 'left lip', 'cleft palate', 'oral cleft', 'orofacial cleft', 'child', 'infant', 'offspring', 'newborn', 'gene', 'genome', 'genetic' along with Boolean operators AND,OR,NOT. The detailed search strategy for specific database in given in Table 1.The search for the published literature was carried out in May 2023. Thus, the upper limit of publication time for selecting studies for this review was identified as of May 2023.

The search strategy yielded 74 results.

Table 1 Narrative review search strategy

Sn.	Name of the Database	Number	Keywords used in search
1	PubMed	1	(maternal[Title] OR mother[Title] OR maternal factor[Title] OR maternal risk[Title])
		2	"cleft lip"[MeSH Terms] OR "cleft palate"[MeSH Terms] OR "oral cleft"[Title] OR "orofacial cleft"[Title]
		3	"newborn"[Title/Abstract] OR "infant"[Title/Abstract] OR "child"[Title/Abstract] OR "offspring"[Title/Abstract]
		4	"genes"[MeSH Terms] OR "genes"[All Fields] OR "gene"[All Fields] OR "genome"[MeSH Terms] OR "genome"[All Fields] OR "genomes"[All Fields] OR "genome s"[All Fields] OR "genomically"[All Fields] OR "genomics"[MeSH Terms] OR "genomics"[All Fields] OR "genomic"[All Fields] OR "genotype"[MeSH Terms] OR "genotype"[All Fields] OR "genotypes"[All Fields] OR "genotypic"[All Fields] OR "genotype s"[All Fields] OR "genotyped"[All Fields] OR "genotyper"[All Fields] OR "genotypical"[All Fields] OR "genotypically"[All Fields] OR "genotyping"[All Fields] OR "genotypings"[All Fields] OR "genotypization"[All Fields]
		5	2010/01/01:2023/12/31[Date - Publication]
		6	((((#1) AND (#2)) AND (#3)) NOT(#4)) AND (#5)
2	Google scholar	1	allintitle: maternal cleft child OR infant OR offspring OR newborn -gene -genotypes -genetic -genome

Inclusion criteria

Studies meeting the following criteria were included in the review:

1. Published in peer-reviewed journals
2. Available in electronic databases
3. Studies describing the maternal factors associated with oral cleft in offspring
4. Study outcome on child born with Non-syndrome oral cleft

Exclusion criteria

Studies meeting the following criteria were excluded in the review:

1. Review studies
2. Animal studies
3. Studies excluding the impact of maternal factors on the likelihood of oral cleft in children
4. Studies on genes and genotype
5. Conference abstracts
6. Books

Screening

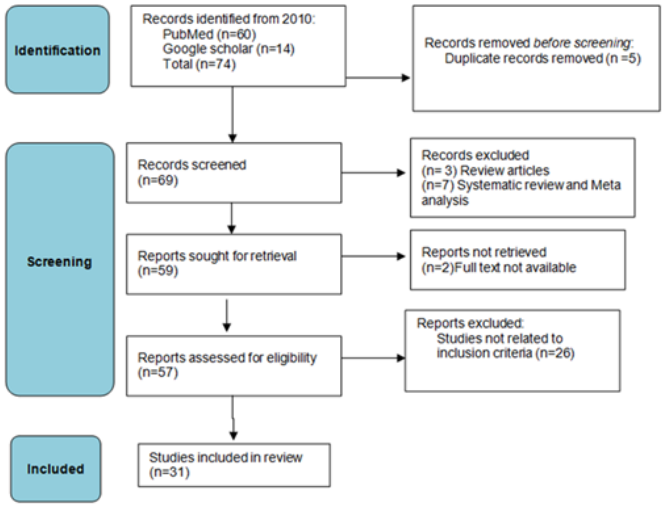
The search titles were scrutinized for duplicates. Initially, the article titles were read and screened as per their relevance to the topic. Then the abstracts of the relevant titles were read and screened. The full texts of

the selected abstracts were screened for inclusion criteria.

Search results

There were no restriction like age of the participants, study location and pregnancy trimester. Search in the databases revealed 74 titles out which 5 duplicate records were removed with publication limitation since 2010. The total number of titles screened were 69 and 10 articles were excluded as they were review articles (including systematic review and meta-analysis) Thus, abstracts of 59 studies were read in the second stage, 57 articles were taken for full-text screening, and out of those 31studies were included in the final review that focused on the various maternal factors influencing CL±P in infants. The flowchart of the study selection process in explained in Figure 1 [5].

Figure 1: Flowchart of the study selection process



Data extraction

The following data were extracted from the screened studies: publication year, study location, study design, study objective, study duration, sample size, maternal factors and outcome. The data extracted are presented in Table 2

Table 2: Results of literature review on the maternal factors influencing the development of CL±P in infants

Sn	Authors and Study title	Year of publication	Study location	Study design	Study objective	Study duration	Sample size	Maternal Factors	Outcome and Key findings
1.	Dien VHA et al.,2018 [6].	2018	South Vietnam	Hospital-based case-control study	To investigate the associations between maternal exposures in the first trimester and oral clefts	October 2014-November 2015	170cases/ 170 controls	Passive smoking	Increased risk of oral clefts in univariate analysis, but not in multivariable analysis (adjusted OR [aOR] = 1.68; 95% CI, 0.53–5.37)
								Liver intake	No association
								Caffeinated beverages	OR = 5.89; 95% CI, 1.08–32.00)
								Periconceptional use of folic acid & multivitamins	Reduced risk of oral clefts (aOR = 0.01; 95% CI, 0.00–0.09 and aOR = 0.03; 95% CI, 0.01–0.13, respectively)
2.	Spinder N et al.,2017 [7].	2017	Northern	case-malformed	To investigate the	population-based	387 cases, 1135	Pesticides	aOR* = 1.7, 95% confidence interval

			Netherlands	control study	relationship between periconceptional maternal occupational exposure and the risk of mouth clefts in offspring	birth defects registry between 1997 and 2013	chromosomal control and 4352 non-chromosomal malformed controls		[CI] 1.0–3.1
								Dust	aOR* = 1.3, 95% CI 1.1–1.6 (aOR*-Adjusted Odds Ratio)
3.	Suhl J et.,2018 [8].	2018	10 US sites located in Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah.	Population-based case–control study	To develop exposure algorithms and explore relations between maternal arsenic exposure from occupation, drinking water, and diet, and OFCs in offspring.	National Birth Defects Prevention Study (NBDPS) October 1997–December 2011	mothers of OFC cases (N = 435) and unaffected controls (N = 1267	Maternal occupational arsenic exposure	Cleft Palate: Odds ratio 4.8(1.6,14.5)[a] [a]crude estimate and 95% CI
								Maternal Exposure to occupational inorganic arsenic	Cleft Palate: OR8.6(1.1,65.1)[b,c] [b]exact logistic regression analysis used [c]adjusted for maternal education at delivery
4.	Yin S et al.,2022 [9].	2022	Beijing and two provinces (Shandong and Shanxi) in northern China	multicenter case-control study	To explore the associations between levels of eight Alkali elements (AEs) and alkaline earth elements	October 1, 2010, and January 31, 2019	Maternal serum of 130 OFC cases and 260 non-malformed controls	Maternal serum sodium	Odds of OFCs increased by 2.08-fold (1.10–3.93) and 2.35-fold (1.24–4.45) for sodium
								Maternal serum strontium	Odds of OFCs increased by 1.98-fold (1.04–3.77) and 1.92-fold (1.21–3.61) for strontium

					(AEEs) in maternal serum during pregnancy and occurrence of fetal OFCs.			Maternal serum potassium	Odds of OFCs decreased by 0.54-fold (0.29–0.98) and 0.42-fold (0.22–0.78) for potassium
5.	Yoshida S., et al 2020 [10].	2020	Japan	Prospective, population-based nationwide cohort study.	To determine whether a relationship exists between maternal nutrient or multivitamin intake and oro-facial clefts	Recruitment period started in January 2011 and lasted until March 2014	98 787 eligible mother–child pairs of the Japan Environment and Children's Study	Multivitamin intake before pregnancy	(RR=1.71; 95% CI 1.06 to 2.77)
								During the first trimester	(RR=2.00; 95% CI 1.18 to 3.37)
								Multivitamin intake after the first trimester	Not significant (RR=1.34; 95% CI 0.59 to 3.01)
								Maternal micronutrient intake via food	Not associated with the incidence of oro-facial clefts in offspring
6.	Ács L et al., 2020 [11].	2020	Hungary	Hungarian Case-Control Surveillance of Congenital Abnormalities	The aim of this study was to estimate possible maternal risk factors in the origin of Isolated cleft palate (CPO).	The Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) between 1980 and 2009	751 cases with isolated CPO, 1196 matched controls and 57 231 population controls	Anemia complicating pregnancy	OR: 1.8 [95% CI: 1.3-2.7]
								threatened abortion	OR: 4.9 [95% CI: 3.1-7.9]
								severe nausea-vomiting	OR: 3.2 [95% CI: 2.6-4.0]
								Smoker mothers	18.64% in the CPO group while 8.44% and 8.94% in the matched (OR: 2.5 [95% CI: 1.9-3.3]) and population (OR: 2.3 [95% CI: 1.9-2.8]) control groups, respectively
								Influenza	OR: 2.95, 1.75-4.95
								acute upper	OR:2.5, 95%

								respiratory infections	CI:1.9-3.1
								acute lower respiratory infections	OR:2.4, 95% CI:1.4-4.2
								urogenital infections	OR:2.0, 95% CI:1.4-2.8
								pulpitits	OR: 7.85, 2.80-22.03
								herpes simplex infection in the mothers	OR:14.8, vCI:5.7-38.5 for CPO
								Maternal Graves' disease	OR: 4.30, 1.74-10.62
								epilepsy	OR: 4.64, 2.44-8.82
								migraine	OR: 2.82, 1.18-6.76
								essential hypertension	OR: 2.33, 1.32-4.10
								cholelithiasis	OR: 3.15, 1.16-8.60
								urolithiasis	OR:4.2, 95% CI:1.7-10.2
7.	Zhao J et.,2018 [12].	2018	Wuhan, China	Cohort	To evaluate whether high levels of maternal exposure to $PM_{2.5}$, PM_{10}, O_3, CO and SO_2 are related to increased risk of oral clefts	2011 to 2013	105,927 births, 133 with oral clefts, and 105,794 without any malformations during the study period	PM2.5	(aORs $_{2nd\ month}$ = 1.34, CI:1.19-1.49; aORs $_{3rd\ month}$=1.14, CI:1.02-1.28)
								PM10	(aORs $_{2nd\ month}$ =

									1.11, CI:1.00-1.23)
								CO	(aORs 2nd month = 1.31, CI:1.14-1.51 aORs 3rd month = 1.17, CI:1.03-1.33)
								O3	(aORs 2nd month = 1.21, CI: 1.03-1.42; aORs 3rd month = 1.18, CI: 1.02-1.37)
8.	Kim J., 2016 et al [13].	2016	Texas	Case-Control Study	To examine the association between maternal occupation and risk of orofacial clefts in offspring	Texas Birth Defects Registry and vital records for 1999 to 2009 deliveries	cases (n= 4207) controls (n = 6000)	Maternal business/finance occupations	Cleft palate only crude OR 1.73 (1.01–2.96)
								Architecture and engineering occupations	Cleft palate only aOR 2.9 CI (1.4 - 5.9)
								Janitor	CLP cleft lip with or without cleft palate aOR 3.58 CI:1.28–10.03
								Maids	CLP cleft lip with or without cleft palate aOR 1.94 CI:1.00–3.75
								Secretaries and administrative assistants	CLP cleft lip with or without cleft palate aOR 0.63 CI:0.41–0.97
9.	Xu W et al.,2021 [14].	2021	Chengdu, China	case–control study	To the association of maternal periconceptional folic acid supplementation (FAS) with the risk of	October 2010 and September 2015	807 singletons affected by NsOC and 8070 healthy neonates	Maternal periconceptional FAS	Decreased risk of NsCL/P (aOR = 0.41, 95% CI 0.33–0.51) NsCL (aOR = 0.42, 95% CI 0.30–0.58) and NsCLP (aOR = 0.41, 95%

					nonsyndromic cleft lip with or without cleft palate (NsCL/P), and cleft palate (NsCP)				CI 0.31–0.54)
								maternal FAS started before and after the last menstrual period (LMP)	inversely associated with NsCL/P (before LMP, aOR = 0.43, 95% CI 0.33–0.56; after LMP, aOR = 0.41, 95% CI 0.33–0.51)
								maternal FAS initiating before LMP	NsCP (aOR = 0.52, 95% CI 0.30–0.90)
10.	Yin S et al., 2020 [15].	2020	Northern China (Beijing, Shandong, and Shanxi)	Multicenter case–control study	To examine associations between concentrations of iron (Fe), zinc (Zn), selenium (Se), cuprum (Cu), cobalt (Co), and molybdenum (Mo) in maternal serum and risk for OFCs in offspring	Recruited between October 1, 2010 and January 31, 2019	130 cases of OFCs and 260 non malformed controls	Higher concentrations of molybdenum (Mo) and cobalt (Co) in maternal serum	With odds ratios and 95% confidence intervals of 0.37 (0.20-0.66) for the second tertile of Mo, 0.28 (0.15-0.54) for the third tertile of Mo, 0.54 (0.29-1.00) for the second tertile of Co, and 0.47 (0.25-0.87) for the third tertile of Co, with the lowest tertile as the referent, there was a dose-dependent reduction in the risk for OFCs.
11.	Bui AH et al.,2018 [16].	2018	Cleft Hospital and Bashir Hospital in Gujrat, Pakistan	case-control study	To evaluate the association between maternal tobacco exposure and development of orofacial	December 2015 to December 2016	297 patients with OFC and 131 control subjects	maternal tobacco exposure	P < 0.001

					clefts (OFCs) in the child in a Pakistani population				
								complications during pregnancy	P < 0.001
								maternal hypertension	P = 0.01
								mother not on physician-recommended medications	P < 0.001
								mother not receiving vaccinations (tetanus)	P < 0.001
								consanguineous marriage	P < 0.001 OR, 1.79; 95% CI, 1.13–2.85
								lower socioeconomic status	P < 0.001
								having a smoking parent	OR, 1.89; 95% confidence interval [CI], 1.10–3.26
								complications during pregnancy	OR, 2.36; 95% CI, 1.43–3.88
								receiving vaccinations	OR, 0.31; 95% CI, 0.16–0.63
								higher socioeconomic status	OR, 0.20; 95% CI, 0.05–0.74
12.	Liu FH.,et al 2021 [17].	2021	Liaoning province	Population-based case-control study	To relate the association between maternal sulfur dioxide (SO_2) exposure and	Maternal and Child Health Certificate Registry of Liaoning	3086 patients with Oral Clefts and 7950 controls	Maternal SO2 exposure during the 3 months before conception	(odds ratio = 1.38, 95% confidence interval: 1.15–1.65; P for trend < 0.01)

					the risk of oral clefts (OCs) in offspring during 3 months before conception, the first trimester of pregnancy, and their single months	Province from 1 January 2010 to 31 December 2015			
13.	Wei Y et al.,2019 [18].	2019	Four provinces in China Shanxi Hebei Jiangsu Zhejiang	Case-control study	To explore association between uranium and thorium concentrations in maternal scalp hair grown from 3 months before to 3 months after conception, namely during the periconceptional period and the risk of orofacial clefts (OFCs) in offspring.	Subjects from Shanxi province were recruited from 2003 to 2016, whereas those from Hebei, Zhejiang, and Jiangsu provinces were enrolled from 2003 to 2007.	153 women whose pregnancies were affected by OFCs (cases) and 601 women who delivered infants without birth defects (controls)	Thorium in maternal hair	The Adjusted Odds Ratio at highest, upper, and lower quartile versus the lowest quartile were 2.63 (95% CI, 1.41–4.92), 1.98 (95% CI, 1.03–3.79), and 2.73 (95% CI, 1.46–5.12), respectively
								Uranium in maternal hair	No association

14.	Ingstrup KG et al., [19].	2013	Denmark	population-based cohort study	Is maternal bereavement (emotional stress) in the antenatal period associated with the risk of oral cleft in the offspring?	Several national registers in Denmark from 1978 to 2008	Of 1771663 children 35118 (2%) were born to mothers who experienced bereavement in the exposure window from 1 year before pregnancy to the end of the first trimester. 3043 children with a cleft	Maternal bereavement from 1 year before conception to the end of the first trimester	OR 1.28, 95% (CI): 1.01; 1.61
15.	Munger RG et al., 2021 [20].	2021	Thiruvallur, Kanchipuram, and Chennai districts of Tamil Nadu state, India	Case–control study	To test the hypotheses that low maternal vitamin B12 status and low folate status are each associated with an increased risk of isolated cleft lip with or without cleft palate (CL+P)	blood tests gathered during the period May to July 2014, and the included births of case and controls were between January 2012 and September 2013	Case-mothers of CL+P children (n = 47) and control-mothers of unaffected children (n = 50)	Low vitamin B12 (combination of both plasma vitamin B_{12} and MMA levels)	OR = 6.54, 95% CI, 1.33-32.09
16.	Gunnerbeck A et a.,2014	2014	Sweden	Population-based cohort	To determine if maternal	Swedish Medical	n = 1086213	mothers habit of	Adjusted OR 1.48 [1.00–2.21]

	[21].			study	use of snuff is associated with an increased risk of oral cleft malformations in the infant and whether cessation of snuff use or smoking before the antenatal booking influences the risk	Birth Register from 1999 through 2009	1761 cases of oral clefts	snuff	
								Maternal smoking	Adjusted OR 1.19 [1.01–1.41]
								Mothers who stopped using snuff before the antenatal booking	Adjusted OR 0.71 [0.44–1.14]
								Mothers who stopped smoking before the antenatal booking	Adjusted OR 0.88 [0.73–1.05]
17.	Li Z et al.,2010 [22].	2010	4 counties (Pingding, Xiyang, Taigu, Zezhou) of Shanxi Province in China	Population-based case-control study	To Examin the association between maternal passive smoking and the risk of CL/P among nonsmoking women in China	data collected between January 2003 and December 2006.	88 infants with CL/P and 651 infants with no major external birth defects.	Maternal passive smoking	OR 1.8 (CI1.1–2.8)
								exposure levels of 1–6 times per week	Adjusted ORs 1.6 (0.9 –2.9)
								>6 times per week (at least 1 cigarette each time)	Adjusted ORs 2.8 (1.5–5.2)
18.	Langlois PH et al., 2013 [23].	2013	US	Case-control study.	Evaluate whether there is an association between maternal occupational exposure to polycyclic aromatic hydrocarbons (PAHs) and oral cleftsin offspring	1997–2002 data from the National Birth Defects Prevention Study	2989 controls(3.5% exposed), 805 cases of CL±P (5.8% exposed) and 439 cases of CP (4.6% exposed)	Maternal Occupational Exposure to Polycyclic Aromatic Hydrocarbons	For CL±P OR was 1.47 (95% CI 1.02–2.12) adjusted for maternal education OR for Cleft Palate were not statistically significant.

19.	Zhou Y et a.,2018 [24].	2018	Arizona, Florida, New York (excluding New York City), and Texas.	Retrospective registry based study	To evaluatewhether maternal exposure to elevated levels of $PM_{2.5}$ and ozone during early pregnancy is associated with a higher prevalence of orofacial defects among offspring	Birth data from 2001 to 2007	4.7 million births	$PM_{2.5}$ concentration	Each 10 µg/m3 increase in PM2.5 concentration was significantly associated with cleft palate alone (OR =1.43, 95% CI: 1.11–1.86)
									No significant association for cleft lip with or without cleft palate
								Ozone exposure	No significant association for cleft lip with or without cleft palate and cleft palate only
20.	Materna-Kiryluk A et al.,2011 [25].	2011	Poland	case–control cohort	To examine the relationship between maternal reproductive history and the newborn's risk of isolated congenital malformations	Polish Registry of Congenital Malformations collected during 2 years (2005 and 2006)	2584 mothers of cases, controls was 4017	Maternal gravidity	Cleft lip with or without cleft palate (OR = 1.21, [95% CI 1.09, 1.36], P = 0.0005)
									Isolated cleft palate (OR = 1.18, [95% CI 1.02, 1.37], P = 0.03
21.	Huybrechts KFet al.,2018 [26].	2018	United States	Retrospective cohort study	To evaluate the association between ondansetron exposure during pregnancy and risk of	2000–2013 nationwide Medicaid Analytic eXtract	cohort consisted of 1,816,414 pregnancies contributed by 1,502,895	Ondansetron dispensing during the first trimester, the period of organogenesis	Absolute risks of oral clefts were 11.1 (10.6 – 11.6) and 14.0 (11.6 – 16.5) per 10,000 (1,912 unexposed and 124 exposed cases)

					congenital malformations .		women enrolled in Medicaid		Adjusted relative risk RR was 1.24 (1.03 – 1.48) and the Risk difference RD was 2.7 (0.2 – 5.2 per 10,000 births)
22.	Takeuchi M et al.,2022 [27].	2022	Japan	nested case–control study	To investigate whether maternal exposure to heavy metals was associated with the risk of isolated cleft L/P in offspring.	Recruitment period for the study was January 2011 to March 2014	Of 104,062 fetal records,192 were children with isolated cleft L/P and 1,920 matched controls	Exposure to 4 heavy metals four metals (mercury [Hg], lead [Pb], cadmium [Cd], and manganese [Mn]) in the mother's blood during pregnancy	No association with isolated cleft L/P
23.	Munger RG et al.,2016 [28].	2016	Utah, USA	State-wide case-control study	To determine whether biomarkers related to one-carbon metabolism, including concentrations of plasma and erythrocyte folate, plasma PLP, and plasma tHcy in mothers, were associated with risk of clefts in their children	Conducted in Utah during 2000 to 2005 in collaboration with the Utah Birth Defects Network (UBDN), a state-wide birth defects registry operated by the Utah Department of	653 case mothers (73.1%) and 782 control mothers (54.8%)	Plasma folate (PF) Plasma pyridoxal-5′-hosphate (PLP; active vitamin B_6) Erythrocyte folate	All cleft types combined, highest versus lowest PF quartile (odds ratio [OR], 0.35; 95% confidence interval [CI], 0.23–0.53; p-trend < 0.001) for PF In the highest versus lowest PLP quartile, risk of CP with other malformations was lower (OR, 0.25; 95% CI, 0.07–0.95) for PLP; active vitamin B_6) Quartile 3,>60 months interval between birth of index child and

						Health (UDOH)			collection of maternal blood specimen 0.16 (0.07–0.37) Quartile 4 ,>36–≤60 months 0.21 (0.07–0.63); >60 months, 0.63 (0.30–1.25) for Erythrocyte folate
24.	Liu FH et al .,2020 [29].	2020	Liaoning Province	Case-control study	associations between maternal preconception and first trimester exposure to particulate matter with a diameter ≤10 µm (PM10) and the risk of oral cleft (OC)	Maternal and Child Health Certificate Registry between 2010 and 2015. P	3086 OC cases and 7950 controls	Maternal PM10 exposure 3 months preconception	Risk for oral cleft per 10 µg/m3 increment: R=1.04, 95% CI 1.01 to 1.07; highest vs lowest quartile: OR=1.23, 95% CI 1.04 to 1.45
								Maternal PM10 exposure First trimester	Risk for oral cleft per 10 µg/m3 increment: OR=1.05, 95% CI 1.02 to 1.08; highest vs lowest quartile: OR=1.37, 95% CI 1.15 to 1.64
25.	Zhang B et al.,2011 [30].	2011	China	Case-control study	To investigate whether maternal and paternal cigarette smoking during early pregnancy could increase the risk of delivering an infant with an orofacial cleft.	2006 to 2009	304 infants born with an isolated non syndromic oral cleft and 453 non-malformed controls	Maternal smoking from 1 to 10 cigarettes per day before pregnancy	Relative Odds Ratio 3.30 (95% CI, 1.17-9.33) in CLO and 3.12 (95% CI, 1.24-7.84) in CLP Unadjusted odds ratio is 3.64 (95% CI, 1.01e13.19) and the adjusted OR is 7.00 (95% CI, 1.44e34.13) in CLO
26.	Stott-Miller M et al.,2011 [31].	2011	Washington State	Case control study	to evaluate whether infants born to obese or diabetic women are at	Washington State birth certificate and hospitalisa	Cases were infants born with orofacial clefts (n =	Obese women	Adjusted OR 1.26; 95% confidence interval 1.03, 1.5 small increased risk of isolated orofacial clefts in their

					higher risk of non-syndromic orofacial clefting	tion data for the years 1987–2005	2153) and controls infants without orofacial clefts (n = 18 070)		offspring compared with normal-body mass index women
27.	Kruse T et al.,2020 [32].	2020	Germany	Cohort	To compare the incidence of right-sided versus left-sided, and unilateral versus bilateral, nonsyndromic clefting in the affected offspring of smoking and nonsmoking mothers.	2005-2019	587 patients with a unilateral cleft and 255 with a bilateral cleft	Maternal Smoking	Right-sided CLP, CL+A (reference category: left-sided) The adjusted OR for Both boys and girls OR1.642 CI 1.048-2.572 For girls adjusted OR 2.819 CI 1.391-5.714 Bilateral CLP, CL+A (reference category: unilateral) the adjusted OR 1.981 CI 1.056-3.716
28.	Huber JC Jr., et al 2013 [33].	2013	Georgia, Arkansas, California, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah	Population-based case–control study	To examine the relationship between maternal dietary intake of nitrates, nitrites (including plant and animal sources as separate groups), and nitrosamines and several types of birth defects in offspring	participants had estimated delivery dates from October 1, 1997 through December 31, 2005	6544 mothers of infants with neural tube defects (NTD)s, oral clefts (OC)s, or limb deficiencies (LD)s and 6807 mothers of unaffected control infants	Animal Nitrite	Adjusted odds ratios Quartile 1 vs Quartile 4 for Cleft lip with or without cleft palate (95% CI) adjusted OR 1.24 CI (1.05-1.48) Adjusted odds ratios Quartile 1 vs Quartile 4 for ceft lip only adjusted OR 1.32 CI (1.01-1.72)
29.	Ramakrishnan A et al., 2013	2013	Texas	Case control	to examine the	delivered between	6,045 non-	High estimated	Not associated with oral clefts,

	[34].				association between estimated maternal residential exposure to benzene, toluene, ethyl benzene, and xylene (BTEX) and the risk of oral clefts among offspring.	1999 and 2008 were obtained from the Texas Birth Defects Registry	syndromic isolated oral cleft cases (3,915 cleft lip with or without cleft palate [CL±P] and 2,130 non-syndromic isolated cleft palate [CP] cases	maternal exposure to benzene	compared with low estimated exposure (CL ± P adjusted OR = 0.95; 95% CI = 0.81 - 1.12; CP adjusted OR = 0.85; 95% CI = 0.67 - 1.09).
30.	McKenzie LM et al.,2014 [35]	2014	rural Colorado	retrospective cohort study	examined associations between maternal residential proximity to Natural Gas Development NGD and birth outcomes	births occurring from 1996 through 2009	124,842 births	natural gas well counts within a 10-mile radius of maternal residence	No association was found between exposure and oral clefts.
31.	Boyles AL et al.,2011 [36]	2011	Norway	nested case–control study within the Norwegian Mother and Child Cohort Study.	To explore the relationship of the birth defects to inhibition of folic acid binding to folate receptor α (FRα), as well as possible effects of parental demographics or prenatal	1999 to 2008	mothers of children with an Neural Tube Defects NTD (n= 11), cleft lip with or without cleft palate (CL/P, n= 72), or cleft	inhibition of folic acid binding to folate receptor α (FRα)	no increased risk of oral facial clefts from inhibited folic acid binding to FRα (CL/P aOR = 0.7, 95% CI 0.6–1.0; CPO aOR = 1.1, 95% CI 0.8–1.4

					exposures.		palate only (CPO, n= 27), and randomly selected mothers of controls (n= 221)		

Maternal risk factors for CL±P in newborns

Maternal tobacco exposure

Passive smoking

The hospital based case control research conducted in South Vietnam by Dien VHA et al [6] showed that passive smoking was related with more risk of cleft when analyzed as univariate but was not significantly associated when adjusted to confounders. The limit for categorizing smoking exposure in this study was 15 minutes per day. Another case control study done reported strong association on maternal passive smoking as a risk factor for CL±P adjusting for confounding factors like maternal occupation, periconceptional flu or fever, infant sex. The limit for categorizing smoking exposure in this study was exposure to passive smoking 1-6 times a week and more than 6 times a week [22]. Most of maternal tobacco exposure in Bui AH et al study is to a great extent owing to fatherly cigarette smoking and described association with risk of CL±P in infants [16].

Maternal snuff/ smoking

The population based case control study on the incidence of isolated cleft palate (CPO) in infants and maternal-related factors reported that the extent of smoker mothers was 18.64% in the CPO while 8.44% and 8.94% in the matched control population [11]. Nearly 1.45% mothers were smokers in Bui BS et al study with p value 0.005 when compared to controls [16]. Increased risk of oral clefts was observed with early pregnancy maternal snuff use and smoking. The authors also observed that no higher risk of offspring with cleft was seen in mothers who terminated snuff or smoking in antenatal period [21].Zhang B et al reported increased risk of CL±P to maternal smoking of 1 - 10 cigarettes/day before pregnancy [30]. Kruse T et al analyzed that smoking mother had right sided and bilateral clefts in offspring compared to controls. Sex definite analyses established significant association only for girls [32].

Caffeinated beverages

Mothers drinking beverages that have caffeine had an increased risk of giving birth to a child with an oral cleft compared to nondrinkers [6].

Maternal multi-vitamin supplements

Supplementing with multivitamins during pregnancy was linked to decreased likelihood of developing oral clefts in newborns[6]. A prospective nationwide cohort study in Japan with 98,787 eligible mother–child pairs reported that intake of multivitamin before pregnancy resulted in Relative Risk ratio RR=1.71; 95% CI 1.06 to 2.77, intake during 1st trimester RR=2.00; 95% CI 1.18 to 3.37 indicating a rise in the number of babies born with clefts. After the first trimester, there was no significant association for multivitamin consumption and cleft. Maternal micronutrient consumption by means of food was not related with the frequency of clefts in infants. Pregnant women and those

meaning to become pregnant ought to be informed concerning the likely dangers of multivitamin supplementation [10].

Low Maternal Vitamin B12 status

A case control study in Tamil Nadu, India reported that Low vitamin B_{12} defined by combination of plasma vitamin B_{12} and methylmalonic acid levels had more association with case-mothers [20].

Maternal Exposure to pesticides

A registry based case control study in Netherlands showed increased association of risk between maternal occupational exposure to pesticides and clefts in offspring when compared with non chromosomal controls [7]

Maternal Exposure to dust

When compared with non chromosomal controls, oral clefts in infants was significantly related to maternal occupational exposure to dust [7].

Maternal arsenic exposure

Suhl et al explored the Data from National Birth Defects Prevention Study (NBDPS) to assess the association between maternal arsenic exposure from occupation, drinking water, and diet to development of oral clefts in infants. The study concluded that maternal occupational arsenic exposure and Cleft Palate, as well as maternal dietary arsenic exposure and CL/P, were found to have positive associations [8].

Maternal polycyclic aromatic hydrocarbons exposure

Increased risk of CL±P was reported in occupational maternal exposure to polycyclic aromatic hydrocarbons adjusted for maternal education [22].

Maternal serum

The study on associating maternal serum alkali and alkaline earth elements during pregnancy reported higher concentration of sodium and strontium in maternal serum during pregnancy are related with expanded chances of oral clefts, though higher concentration of potassium is related with diminished chances of oral cleft. Additionally, when other elements are at higher levels, a higher level of rubidium is a risk factor for cleft in newborn [9].Yin S et al associated reduced risk of oral cleft with increased molybdenum (Mo) in maternal serum [15].

Threatened abortion

Higher association to threatened abortion as a risk for CL±P in infants was reported when compared to controls in a population based study [11].

Maternal diseases during pregnancy

Maternal anemia and severe nausea-vomiting was linked to an increased chance of CPO in the infants. Epilepsy, Graves' disease, migraine and essential hypertension, common cold, acute respiratory infections, influenza, pulpitis, cholecystitis, acute urinary tract infections, herpes simplex infection and pelvic inflammatory diseases during pregnancy were also associated with increased risk for developing CPO. This study suggests that during the first trimester, maternal diseases and lifestyle factors play an important role in the formation of CPO [11].

Maternal air pollution exposure

A study on the relationship between air pollutants and cleft risk in China reported exposure to particulate matter $PM_{2.5}$, PM_{10} and Carbon Monoxide CO were associated with CL±P and $PM_{2.5}$ associated with CPO [12].Another study conducted in four U.S states reported that CPO was significantly linked with each 10 g/m3 increase for PM2.5 concentration but does not influence for CL±P [24].Study conducted in Liaoning Province, reported exposure to PM_{10} during three months preconception and the first trimester increases the risk of oral clefts [29].

Maternal Occupation

Association between CPO with maternal occupation being business/finance, architecture/engineering and for CLP with cleaning related maternal occupation were observed. CLP and office, administrative jobs showed negative association [13].

Maternal Sulfur Dioxide (SO_2) Exposure

Positive association between maternal SO_2 exposure 3 months prior conception to oral cleft in infants is [17].

Maternal Scalp Hair

Wei Y et al reported Thorium exposure periconception may increase the likelihood of cleft in newborn. [18].

Maternal bereavement

Before pregnancy and during the 1st trimester, maternal bereavement resulted in higher risk of cleft in offspring [19].

Maternal ozone exposure

A study in China reported ozone exposure to risk of CPO in infants [12]. Another study on the maternal exposure relation to incidence of CLP in United States reported ozone concentration had no statistical significance relation with CL±P or CPO [24].

Maternal gravidity

A case control cohort in Poland reported significant association between maternal gravidity and CL±P [25].

Maternal Ondansetron Use

Cohort study by Huybrechts KF et al., reported increased risk for oral clefts and maternal 1st trimester ondansetron use [26].

Maternal Heavy Metal Exposure

Takeuchi M et al reported that exposure to mercury, lead, cadmium and manganese during pregnancy is associated with cleft risk [27].

Maternal Obesity

Women with obesity reported small increased risk of isolated clefts in newborn compared with normal-body mass index women concluding that these results might be due to bias or confounding [31].

Maternal dietary intake of nitrates, nitrites and nitrosamines

Huber JC Jr et al conducted a case control study and concluded that odds of oral clefts are not significantly related to nitrate, nitrosamine and nitrate maternal dietary intake [33].

Maternal Exposure To Benzene, Toluene, Ethyl Benzene, And Xylene (BTEX)

Ramakrishnan A et al reported that among offspring in Texas (1999-2008), no association was observed between maternal exposure to BTEX and oral clefts [34].

Maternal Residential Proximity To Natural Gas

A large cohort study in rural Colorado by McKenzie LM et al reported no association was estimated between exposure and oral clefts [35].

Protective maternal factor for CL±P

Folic acid/ folate intake

Periconceptional maternal folic acid supplementation (FAS) was linked to lower chance of developing oral clefts [6]. Decreased risk of non-syndrome CL±P and non-syndrome cleft lip was seen in periconceptional folic acid supplementation. Also, FAS intake before last menstrual period was found to reduce the incidence of CPO [14]. The mean difference in case and control maternal plasma folate, erythrocyte folate, plasma pyridoxal-5'-phosphate and total plasma homocysteine concentrations widened over time, and low maternal blood folate concentration was linked to higher risk of clefts. [28].Boyles AL et al reported no elevated risk of oral clefts from inhibited folic acid binding to folate receptor α [36].

Maternal Vaccination

Maternal vaccination for tetanus during pregnancy reported protective maternal factor reporting lower risk

of CL±P in infants. The authors also state that it's likely that prior tetanus immunization served as a stand-in for other necessary immunizations, such the flu shot, which may have prevented processes like febrile infections that cause hyperthermia and shielded against the development of OFC. [16].

Issues to be addressed:

The potential protective factor for CL±P is identified to be FAS intake. Under the National Rural Health Mission /Reproductive Child Health II Programme all pregnant and lactating women are provided with one tablet (containing 100 mg of elemental iron and 0.5 mg of Folic Acid) daily for 100 days to prevent anemia (37). Additional awareness should be given to pregnant women that periconception of FAS can reduce the risk of developing CL±P in their offspring. The focus to eliminate congenital birth defects with active mapping of CL±P across various districts and states evaluating the national and state prevalence with nationwide cleft birth registry should be initiated and monitored for higher incidences.

Limitation

Our review focused on the various maternal factors influencing CL±P in newborns and our literature search was limited to 2 databases. Further systematic review critically evaluating the study quality should be done for the reliability of the results. In this study we limited to maternal factors, future reviews on paternal factors should also be reviewed for influencing CL±P in newborns.

Conclusion

This review included various maternal factors like maternal exposure to tobacco, maternal occupational exposure, pollutants, multi-vitamins, maternal serum level, exposure to metals, obesity, maternal diseases etc. Strong association to maternal tobacco exposure, intake of caffeinated beverages during pregnancy, maternal exposure to pesticides and dust, threatened abortion, maternal arsenic exposure, polycyclic aromatic hydrocarbons exposure and maternal gravidity for increased incidence of clefts in newborns is identified. Parental tobacco cessation counselling should be encouraged for to be parents and pregnant mothers regarding smoking, passive smoking and snuff use. Maternal periconceptional folic acid intake, receiving vaccinations and higher socioeconomic status were identified to be significant protective factor for incidence of oral clefts in offspring. Intake of folic acid during pregnancy should be encouraged. Occupational exposures should be monitored with awareness programmes. We identified only one study conducted in Tamil Nadu on vitamin B12 being a protective factor for CL±P. This review presents summary of broad view on various influencing maternal factors over clefts in offspring to be considered in prevention, education and perinatal care of pregnant mothers.

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Supplement

Detailed information on study inclusion and exclusion:

Sn.	Studies retrieved from PubMed	Fulfilled eligibility for study	Reason for study exclusion
1.	Xuan Z, Zhongpeng Y, Yanjun G, Jiaqi D, Yuchi Z, Bing S, Chenghao L. Maternal active smoking and risk of oral clefts: a meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Dec;122(6):680-690. doi: 10.1016/j.oooo.2016.08.007. Epub 2016 Aug 18. PMID: 27727103.		Review
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10.	Blanco R, Colombo A, Suazo J. Maternal obesity is a risk factor for orofacial clefts: a meta-analysis.		Meta analysis

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