Supplementary material appendix B: Study characteristics, level of evidence and associated risk factors

Article title	Authors	Year	DOI, website or PMCID	Country (LMIC)	Type of cleft (CL, CP, CLP)	Number of participants including controls	Participants & participant age range	Study design	Level of evidence (ASHA, 2004)	Outcomes (category risk factor & specific associated risk factors)
Antenatal determinants of oro-facial clefts in Southern Nigeria	Omo-Aghoja, V. W., Omo-Aghoja, L. O., Ugboko, V. I., Obuekwe, O. N., Saheeb, B. D. O., Feyi-Waboso, P., Onowhakpor, A.	2010	PMC2895797	Nigeria	CP, CLP	Case: 60	Newborns, children & adults 5 days - 37 years old	Transverse, cross-sectional	IIb	**Biological risks** Family history (p-value < 0.250) **Environmental risks** Maternal age (OR=3.14, CI=1.14 – 8.69) Parental age (OR=1.33, CI=0.52 – 5.25) Alcohol consumption (p-value=0.772) Low SES (p-value=0.689) Medication consumption (OR=2.35, CI=0.58 – 4.47)
Association between cleft lip and/or cleft palate and family history of cancer: A case-control study	Bui, A. H., Ayub, A., Ahmed, M. K., Taioli, E., Taub, P. J.	2018	10.1097/SAP.0000000000001331	Pakistan	CLP	Case: 137 Control: 147	Infants & toddlers < 3 years old	Case-control	IIb	**Biological risks** Family history of cancer (AOR=5.17, CI=1.57 – 17.03, p-value < 0.001) Maternal chronic illness (AOR=1.34, CI=0.44 – 4.05, p-value = 0.02) **Environmental risks** Smoking parent (AOR=2.12, CI=1.05 – 4.28, p-value = 0.001) Consanguineous marriage (AOR=1.53, CI=0.83 – 2.82, p-value = 0.03)

										Prenatal complications (AOR=4.60, CI=1.21 – 17.54, p-value = 0.01) Low SES (p-value < 0.001)
Cleft palate in HIV-exposed newborns of mothers on highly active antiretroviral therapy	Fasunla, A.J., Ogunbosi, B.O., Odaibo, G.N., Taiwo, B., Nwaorgu, O.G.B., Olaleye, D.O., Murphy, R.L., Adewole, I.F., Kanki., P., Akinyinka ,O.O.	2014	10.1111/ors.12117	Nigeria	CP	HIV-exposed: 126 HIV-unexposed: 121 Case with cleft: 3	Newborns < 37 weeks old	Qualitative, descriptive study (case report)	III	**Environmental risks** Medicine consumption (OR=10.95, CI=0.94 – 126.84; p-value = 0.07)
Genetic risk factors for orofacial clefts in Central Africans and Southeast Asians	Figueiredo, J. C., Ly, S., Raimondi, H., Magee, K., Baurley, J. W., Sanchez-Lara, P. A., Ihenacho, U., Yao, C., Edlund, C. K., van den Berg, D., Casey, G., DeClerk, Y. A., Samet, J. M., Magee, W., 3rd	2014	10.1002/ajmg.a.36693	DR Congo, Vietnam, Philippines	CLP	260	Infants & toddlers < 3 years old	Case-control	IIb	**Biological risks** Genetics: rs10787738 (p = 4.98) rs7987165 (p = 6.1)
Low incidence of nonsyndromic celft lip with or without cleft palate in females: Is homocysteine a factor?	Kumari, P., Ali, A., Sukla, K. K., Singh, S. K., Raman, R.	2013	10.1007/s12038-013-9298-7	India	CLP	Case: 318 Controlled: 281	Infants & young children Case: 1 - 9 years old. Controlled: 3 - 12.5 years old	Retrospective, cohort	IIb	**Biological risks** Homocysteine (OR=1.99, CI=1.42 – 2.77) Genetics (OR=4.9, CI=1.2 – 20.2)
Maternal exposures and risk of oral clefts in South Vietnam	Dien, V. H. A., McKinney, C. M., Pisek, A., Pitiphat, W.	2018	10.1002/bdr2.1192	South Vietnam	CL, CP, CLP	Age & gender matched Case: 170 Controlled: 170	Infants < 18 months old	Hospital-based case-control	IIb	**Environmental risks** Food consumption (OR=5.89, CI=1.08 – 32.00)

Maternal folic acid intake and risk of nonsyndromic orofacial clefts: A hospital-based case–control study in Bangalore, India	Mendonca, V. J.	2020	10.1177/1055665619893214	India	CP, CLP	Case: 106 Control: 212	Infants, Case: birth - 9 months old. Infants, Control: birth - 3 months old	Hospital-based, case-control	IIb	**Environmental risks** Intake of multivitamin supplementation (AOR=2.93, CI=1.84 – 4.69) Smoking parent (AOR=8.16, CI=1.60 – 41.58)
Maternal tobacco exposure and development of orofacial clefts in the child: A case-control study conducted in Pakistan	Bui, A. H., Ayub, A., Ahmed, M. K., Taioli, E., Taub, P. J.	2018	10.1097/SAP.0000000000001665	Pakistan	CL, CP, CLP	Case: 297 Control: 131	Newborns, children & adults, Case: 1 day - 25 years old. Newborns & toddlers, Control: 1 day - 3 years old	Retrospective, case-control	IIb	**Biological risks** Maternal illness (AOR=1.59, CI=0.60 – 4.22) **Environmental risks** Smoking parent (AOR=1.89, CI=1.10 – 3.26) Consanguineous marriage (AOR=1.79, CI=1.13 – 2.85) Prenatal complications (AOR=2.36, CI=1.43 – 3.88) Low SES (AOR=1.36, CI=0.70 – 2.66)
Maternal risk factors associated with the development of cleft lip and/or palate in Sudan	Gendel, A. A. A., Sayed, S. A. M., Mohamme, B. H., Mohemed, A. A.	2019	https://www.researchgate.net/publication/338139231_Maternal_Risk_Factors_Associated_with_the_Development_of_Cleft_Lip_and_or_Palate_in_Sudan	Sudan	CL, CP, CLP	Case: 280	Infants & children 1 - < 10 years old	Case descriptive, cross-sectional, hospital-based	III	**Biological risks** Family history (p-value = 0.025) Maternal illness (Chi-square = 4.961, p-value = 0.042) Gender (Chi-square = 12.857, p-value = 0.001) **Environmental risks** Low SES (p-value = 0.003) Medication consumption (Chi-square = 8.718, p-value = 0.007)

	Folic acid supplementation (Chi-square = 4.973, p=0.042) Maternal age (24.3%, CI=20.06 – 28.51) Low maternal education (n=183; 65.4%)

Non-syndromic cleft lip and/or cleft palate: Epidemiology and risk factors in Lubumbashi (DR Congo), a case-control study	Mbuyi-Musanzayi, S., Kayembe, T. J., Kashal, M. K., Lukusa, P. T., Kalenga, P. M., Tshilombo, F. K., Devriendt, K., Reychler, H.	2018	10.1016/j.jcms.2018.05.006	DR Congo	CP, CLP	Geographically matched Case: 162 Control: 162	Infants Birth - 1 years old	Case-control	IIb	**Biological risks** Family history (p-value < 0.0007) Gender (males: 52%; females: 48%; ratio: 1.08) **Environmental risks** Alcohol consumption (Maternal: AOR=19.301, CI= 1.890 – 197.095; paternal: AOR=18.748, CI=3.939 – 89.229) Food consumption (AOR=38.269, CI=9.328 – 157.010) Maternal age (OR=0.744, CI=0.256 – 2.156) Paternal age (OR=1.864, CI=0.590 – 5.885) Low maternal education (AOR=9.480, CI=2.012 – 44.676) Exposure to chemicals (AOR=130.3, CI=13.2 – 1286.9)

Nonsyndromic cleft lip with or without cleft palate in arab populations: genetic analysis of 15 risk loci in a novel case-control sample recruited in Yemen	Aldhorae, K. A., Böhmer, A. C., Ludwig, K. U., Esmail, A. H., Al-Hebshi, N. N., Lippke, B., Gölz, L., Nöthen, M. M., Daratsianos, N., Knapp, M., Jäger, A., Mangold, E.	2014	10.1002/bdra.23221	Yemen	CLP	Case: 242 Control: 420	Not indicated in study.	Case-control	IIb	**Biological risks** Genetics: rs987525 (OR_{Het}=1.74, CI=1.22 – 2.47; OR_{Hom}=2.47, CI=1.55 – 3.93) rs4460498 (OR_{Het}=1.18, CI=0.75 – 1.85; OR_{Hom}=1.99, CI=1.25 – 3.16) rs4752028 (OR_{Het}=1.84, CI=1.28 – 2.66; OR_{Hom}=1.38, CI=1.38, CI=0.38 – 4.96) rs8001641 (OR_{Het}=1.22, CI=0.87 – 1.71; OR_{Hom}=2.99, CI=1.72 – 5.20)
Orofacial clefts at Bugando Medical Centre: associated factors and postsurgical complications	Buyu, Y., Manyama, M., Chandika, A., Gilyoma, J.	2012	10.1597/10-202	Tanzania	CL, CP, CLP	94	Newborns, children & adults 2 days old - 41 years old	Cohort study	III	**Biological risks** Family history (Chi-square = 27.7, p-value < .001) Birth order (Chi-square = 21.0, p-value < .001) [†]**Environmental risks**
Parental risk factors for oral clefts among Central Africans, Southeast Asians, and Central Americans	Figueiredo, J. C., Ly, S., Magee, K. S., Ihenacho, U., Baurley, J. W., Sanchez-Lara, P. A., Brindopke, F., Nguyen, T. H. D., Nguyen, V., Tangco, M. I., Giron, M., Abrahams, T., Jang, G., Vu, A., Zolfaghari, E., Yao, C. A., Foong, A., Declerk, Y. A.,	2015	10.1002/bdra.23417	DR Congo, Vietnam, Philippines, Honduras	CP, CLP	Case: 430 Control: 754	Infants & toddlers < 3 years old	Case-control	IIb	**Biological risks** Family history (AOR=4.7, CI=3.0 – 7.2) Pregestational hypertension (AOR=2.6, CI=1.3 – 5.1) Gestational seizures (AOR=2.9, CI=1.1 – 7.4)

	Samet, J. M., Magee, W., III									**Environmental risks** Maternal age (AOR=1.2, CI=1.0 – 1.3) Maternal education (primary school: AOR=2.4, CI=1.6 – 2.8; secondary school: AOR=1.6, CI=1.2 – 2.2) Smoking parent (AOR=1.5, CI=1.1 – 1.9) Exposure to chemicals (agricultural chemicals: AOR=2.7, CI=1.1 – 6.7; industrial chemicals: AOR=3.9, CI=2.0 – 7.6)
Prevalence and evaluation of environmental risk factors associated with cleft lip and palate in a central Indian population	Kalaskar, R., Kalaskar, A., Naqvi, F. S., Tawani, G. S., Walke, D. R.	2013	http://search.ebscohost.com.uplib.idm.oclc.org/login.aspx?direct=true&db=ddh&AN=87856059&site=ehost-live&scope=site	India	CP, CLP	Case: 88 Control: 88	Mothers 15 - 47 years old	Case-control	IIb	**Environmental risks** Food consumption (Chi-square, p-value = .00) Medicine consumption (Chi-square, p-value = .00)
Risk factors for orofacial clefts in India: A case–control study	Neogi, S. B., Singh, S., Pallepogula, D. R., Pant, H., Kolli, S. R., Bharti, P., Datta, V., Gosla, S. R., Bonanthaya, K., Ness, A., Kinra, S., Doyle, P., Gudlavalleti, V. S. M.	2017	: 10.1002/bdr2.1073	India	CLP	Geographically matched Case: 157 Control: 628	Infants, Case: birth - 4 months old Newborns, Control: birth - 2 days old	Hospital-based, matched case-control	IIb	**Biological risks** Family history (AOR=15.48, CI=4.36 – 54.96) Birth order (AOR=2.55, CI=1.25 – 5.21) **Environmental risks**

										Food consumption (AOR=4.47, CI=1.83 – 10.98)
Risk factors of non-syndromic orofacial clefts in Sudan during 2016-2017	Ali, M. A. M., Hamid, M. M. M.	2019	http://search.ebscohost.com.uplib.idm.oclc.org/login.aspx?direct=true&db=a9h&AN=136630644&site=ehost-live&scope=site	Sudan	CL, CP, CLP	Case: 144 Control: 144	Mothers 11 - 50 years old	Descriptive, case-control	IIb	**Biological risks** Family history (OR=6.95, CI=4.68 – 7.26, p-value = 0.003) **Environmental risks** Maternal education (p-value = 0.001) Lack of folic acid supplementation (p-value = 0.018) Low SES (p-value = 0.042) Consanguineous marriage (OR=2.70, CI=2.03 – 3.37, p-value = 0.003)
The role of environmental factors in the etiology of nonsyndromic orofacial clefts	Eshete, M., Butali, A., Abate, F., Hailu, T., Hailu, A., Degu, S., Demissie, Y., Gravem, P. E., Derbew, M., Mossey, P., Bush, T., Deressa, W.	2020	: 10.1097/SCS.0000000000005924	Ethiopia	CL, CP, CLP	Case: 359 Control: 401	Infants & toddlers A few days - 4 years old	Unmatched, case-control	IIb	**Biological risks** Maternal illness (AOR=0.194, CI=0.053 – 0.712) **Environmental risks** Prenatal complications (AOR=0.179, CI=0.091 – 0.352) Exposure to radiation (AOR=0.375, CI=0.142 – 0.990)

OR = odds ratio
AOR = adjusted odds ratio
OR_{Hom} = odds ratio homozygous
OR_{Het} = odds ratio heterozygous
CI = confidence interval
SES = Socioeconomic status
† = category risk factor investigated but no risk factors were found to be associated with CL/P