INTRODUCTION
Cardiovascular diseases (CVDs) are on the rise globally and cause one-third of deaths worldwide, with 80% of such mortality in developing countries.1 The burden of CVD is primarily driven by dyslipidemia, hypertension, obesity, diabetes, physical inactivity, poor diet, and smoking.1 The CVDs burden is anticipated to burgeon in the coming years.2 Orofacial clefts (OFCs) or cleft lip and palate defects are the commonest congenital malformation of the head & neck and one of the most frequent congenital disabilities globally.3,4 The disorder is of enormous medical, surgical, or cosmetic importance in addition to the colossal health care cost. They can occur as syndromic or non-syndromic forms with the latter being the more common.3,4

The estimated prevalence of OFCs in Nigeria is about 0.5:1000 live births.5-7 It occurs in about 1 in 700 live births globally while it accounted for 3,800 deaths globally in 2017 or 3.8 per 100,000 person death from the Global Burden of Disease (GBD) 2017 estimates.8,9 Furthermore, the highest prevalence at birth of OFCs is among the native American and Asian (1 in 500 live births), while the lowest prevalence is among the populations of African descent, with approximately 1 in 2,500 live births.10

The usual male: female ratio was 2:1 in the various OFC variants such as cleft lip and/or cleft lip and palate.9 The Nigerian craniofacial anomalies study, Nigeria CRAN, showed a male: female ratio of 1.19:1 of all OFCs.7

Pre-conceptional, as well as conceptional maternal cardiovascular risk factors (CRFs) may predispose to the development of cleft palate in the offspring. Such increased causality or the CRFs interlink with OFCs may be the strong link to the possibility of reversal of the epidemiological burden for OFCs or just the continuous presence of cases as CVDs/CRFs are on the increase. The key CRFs linked to OFCs includes alcohol use, obesity and smoking with obesity and smoking each having 6% population attributable risk factors.11 Cardiovascular conditions in the form of congenital heart diseases usually present alongside this condition in newborns.

Cleft lip and/or cleft palate may arise in isolation or association with a syndrome and CRFs, and Congenital heart diseases(CHDs) are associated with both syndromic and non-syndromic OFCs although commoner in the former.4,12

OROFAcial CLEFTS AND CARDIOVASCULAR RISK AND DISEASES: THE CAUSAL RELATIONSHIP AND ASSOCIATIONS
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ABSTRACT
There is a complex interplay between orofacial clefts (OFCs) or cleft of the lip and palate and cardiovascular risk factors and cardiac diseases. The presence of maternal cardiovascular risk factors serves as a potent predisposing factor to the development of OFCs during foetal development in addition to the fact that various congenital anomalies are associated with OFCs either in syndromic or non-syndrome relationship. This article narratively explores this complex interplay, which is not uncommon.

Keywords: Cleft lip and palate, Cardiovascular diseases, Obesity, Hypertension, Natal, Prenatal
Primordial: Predisposing Cardiovascular Risk Factors

The development of OFCs in offspring is associated with the presence of pre-conceptional maternal cardiovascular risk factors particularly obesity, dietary patterns, maternal hypertension, maternal diabetes mellitus and smoking (passive and non-passive) (See Table 1).\textsuperscript{10,11,13}

A systematic review and meta-analysis of a collection of data spanning forty-three years from North America, Europe and Australia revealed a significant association between maternal obesity, as measured by the Body Mass Index (BMI), and having a pregnancy complicated by cleft palate.\textsuperscript{14} Maternal obesity was noted to lead to the development of foetal cleft palate (OR, 1.23; 95% CI, 1.03-1.47; P=.02) or cleft lip and

Table 1: Table highlighting studies demonstrating the link of cardiovascular risk factors and OFCs

| Study                                                                 | Authors                | Year of publication | Type of study | Country/countries | Sample size | Key cardio-vascular risk factors                                                                 |
|----------------------------------------------------------------------|------------------------|---------------------|---------------|-------------------|-------------|--------------------------------------------------------------------------------------------------|
| Association Between Maternal Diabetes Mellitus and Newborn Oral Cleft Diabetes mellitus and birth defects | Correa et al.\textsuperscript{17} | 2008                | Case-control  | United States of America | 17,925 (15,030 cases, 4,895 controls) | Maternal pre-gestational diabetes mellitus                                                      |
| Native American Oral clefts, consanguinity, parental tobacco and alcohol use: a case-control study in Rio de Janeiro, Brazil | Leite et al.\textsuperscript{40} | 2009                | Case-control  | Brazil             | 822 (274 cases, 548 controls)           | Maternal cigarette smoking, Maternal Alcohol Abuse                                             |
| Risk factors for oral clefts: a population-based case-control study in Shenyang, China | Wang et al.\textsuperscript{41} | 2009                | Case-control  | China              | 586 cases 1172 control mothers          | Maternal diet                                                                                   |
| Maternal Factors and Disparities Associated with Oral Clefts         | Lebby et al.\textsuperscript{30} | 2010                | Cohort        | United States of America | 3,23 (Case 1654 Control 1654)          | Maternal cigarette smoking, Pregnancy-associated hypertension Maternal pre-pregnancy obesity |
| Increased risk of orofacial clefts associated with maternal obesity: a case-control study and Monte Carlo-based bias analysis | Stott-Miller et al.\textsuperscript{42} | 2010                | Case-control  | United States of America | 20,223 (2,153 cases, 18,070 controls) | Maternal cigarette smoking, Pregnancy-associated hypertension Maternal pre-pregnancy obesity |
| Maternal malnutrition, environmental exposure during pregnancy and the risk of nonsyndromic orofacial clefts | Jia et al.\textsuperscript{43} | 2011                | Case-control  | China              | 934 (537 cases, 221 controls)           | Maternal (passive) smoking                                                                      |
| Orofacial Clefts and Risk Factors in Tehran, Iran: A Case-Control Study | Taghavi et al.\textsuperscript{44} | 2012                | Case-control  | Saudi-Arabia       | 600 (300 cases, 300 controls)           | Maternal cigarette passive smoking                                                            |
| Maternal Snuff Use and Smoking and the Risk of Oral Cleft Malformations - A Population-Based Cohort Study | Gunnerbeck et al.\textsuperscript{45} | 2014                | Registry survey | Sweden             | 975,866 (1,761 cases of oral clefts)    | Maternal snuff use, Maternal cigarette smoking                                                |
| Association between maternal smoking, gender, and cleft lip and palate | Martelli et al.\textsuperscript{46} | 2015                | Case-control  | Brazil             | 1519 (843 cases, 676 controls)          | Maternal smoking                                                                               |
| Maternal Risk Factors Associated with the Development of Cleft Lip and Cleft Palate in Mexico: A Case-Control Study | Angulo-Castro et al.\textsuperscript{47} | 2017                | Case-control  | Mexico             | 48 (24 cases, 24 controls)              | Maternal cigarette smoking, Maternal Alcohol Abuse                                             |
| Maternal underweight and obesity and risk of orofacial clefts in a large international consortium of population-based studies Hebah | Kutbi et al.\textsuperscript{13} | 2017                | Population-based | Northern Europe, United States of America | 15,535 (4943 cases and 10,592 controls) | Maternal pre-pregnancy obesity                                                                 |
palate (OR, 1.20; 95% CI, 1.03-1.40; P=.02)\textsuperscript{14} Other studies also established the predisposition of maternal diabetes mellitus to OFCs. A large study over a ten-year period, among Swedish women, found a similar result even after adjustment for year of birth, parity, maternal age, and maternal smoking.\textsuperscript{15} In this case, however, the presence of another major co-existing anomaly alongside cleft palate showed a stronger association with obesity.\textsuperscript{15} Although the reason for this association is unknown, it has been attributed to undetected type 2 diabetes.\textsuperscript{15} (Table 1).\textsuperscript{16, 17}

Maternal western dietary pattern during the preconception period has also been shown to be a risk factor. A case-control study among a female Dutch population showed that diets rich in meat, pizza, potatoes, legumes, French fries, and low in fruits were shown to correlate with cleft palate in the offspring when compared with diets associated with high intake of fish, vegetables, garlic and nuts.\textsuperscript{18} This is unconnected with low maternal serum levels of vitamin B12 and folic acid associated such diet.\textsuperscript{18}

Hyperhomocysteinemia, which is associated with low levels of folic acid, is a known risk factor for heart disease.\textsuperscript{18} Similarly, studies have demonstrated an association between hyperhomocysteinaemia and cleft palate,\textsuperscript{18} while many studies have demonstrated the beneficial effect of maternal folic acid supplementation variables.\textsuperscript{27} There was a demonstrable dose-response smoking risk for OFCs in first trimester especially with combined defect of both lips and palate rather than solitary defects.\textsuperscript{27-29} The link with alcohol intake, particularly in the first trimester, may not be unconnected with retinoic acid production.\textsuperscript{28, 29} Unlike

\begin{table}[h]
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\begin{tabular}{|c|c|c|c|}
\hline
\textbf{ Syndromes} & \textbf{Aetiology} & \textbf{Associated cardiovascular disorder} & \textbf{Present congenital heart diseases associations} \\
\hline
\textbf{Loeys–Dietz syndrome}\textsuperscript{39, 48} & Genetic- autosomal dominant. Mutation in TGFBR1, TGFBR2, SMAD3, TGFBR2, and TGFBR3 & Aortic aneurysm, Aortic dissection, aortic root dilation, arterial tortuosity, mitral valve prolapse & patent ductus arteriosus and atrial septal defect \\
\hline
\textbf{Malpuech facial clefting syndrome}\textsuperscript{40} & Genetic autosomal recessive COLLEC11 and MASP1 genes mutation &  & patent ductus arteriosus and atrial & ventricular septal defect \\
\hline
\textbf{Treacher Collins syndrome or mandibulofacial dysostosis or Franceschetti-Zwahlen-Klein syndrome}\textsuperscript{49} & Genetic- autosomal dominant. TCOF1, POLR1C, or POLR1D mutation &  & Sinus of Valsalva aneurysm \\
\hline
\textbf{Oculoauriculovertebral spectrum (Goldenhar syndrome)}\textsuperscript{50, 51} & Autosomal dominant, sporadic & Ventricular septal defect, atrial septal defect, pulmonary stenosis, tetralogy of Fallot atrial/ventricular septal defect &  \\
\hline
\textbf{Oculofaciocardiodental syndrome}\textsuperscript{52} & X-linked dominant & Tetralogy of Fallot, double outlet right ventricle with aortoventricular canal, patent ductus arteriosus, ventricular septal defect and atrial septal defect with or without cleft mitral valve &  \\
\hline
\textbf{CHARGE syndrome}\textsuperscript{53} & Mutation of CHD7 gene &  &  \\
\hline
\end{tabular}
\caption{OFCs Syndromes and some congenital cardiac anomalies}
\end{table}

Pregestational diabetes mellitus is also a well-known risk factor for cleft palate in the offspring.\textsuperscript{24, 25} In a United States Natality database, a population-based case-control study showed that diabetic mothers were almost 1.4 times more likely to develop cleft palate than non-diabetic mothers.\textsuperscript{15, 16, 26}

Passive and active cigarette smoking in pregnancy has been associated with the development of cleft palate. The records of 3,891,494 live births from the 1996 U.S. Natality database showed this clear predisposition to OFCs using cases-controls design of maternal smoking even after adjustment of confounding.
the smoking exposure, the association of alcohol intake with OFC is not dose responsive.28

Generally, various cardiovascular risk factors are interrelated. Western dietary patterns could predispose to obesity, and obesity may be an early pointer to diabetes mellitus. Therefore, there may be an underlying, undiagnosed impaired glucose tolerance in these populations that were studied, which most studies did not take into account. While some studies identified the role of maternal alcohol intake during pregnancy on OFCs, many are frosty by small sample sizes. Also implicated are hypertension and the usage of antihypertensive drugs36,38

Finally, cardiovascular diseases appear to be more common in the cleft palate than cleft lip,23,27 but more studies are required to confirm these.

**Associations of Orofacial Defects and Cardiovascular Diseases**

Congenital heart disease is the most frequent associated anomaly in patients with cleft palate as shown in various studies3,6,31, with atrial septal defect31,32 often being cited. Others include patent ductus arteriosus, pulmonary stenosis, tetralogy of Fallot and ventricular septal defect.33 There is a wide variation of the incidence and prevalence of congenital heart disease among neonates with cleft palate.7,34 The risk of having a congenital heart disease have been reported to be 23 times that of the general population.35

Cardiovascular disease and cleft palate can be present in conditions that can affect multiple organ systems, for example, in chromosomal defects like Edward syndrome (Trisomy 18) and Patau syndrome (Trisomy 13) particularly in the non-isolated cleft palate (Table 3).25 They can both be significant components in sequences and syndromes, notably Velocardiofacial syndrome,4,35 DiGeorge syndrome,35 and rarely, Van der Woude syndrome.4 Some genetic mutations like that in TGFBR1 or TGFBR2 genes have also been reported to cause combined cleft palate and cardiovascular disease (Table 3).36

**Orofacial Defects, Paediatric Cardiologist, and the Adult Cardiologist**

Even though an affected child may benefit form repair of the defect within a year of birth, such care may not be available in a resource-poor environment like Nigeria especially in situation of non-assess to free treatment intervention such as SMILE programme.37,38 Furthermore, it may come with a severe attendant implication which is beyond the primary care specialist that may have initially intervened. Those issues associated with OFCs may not be the initial interest of the parents and caregivers, rather the orofacial defect that pose a severe cosmetic problem. Some of the cardiovascular diseases may linger into adulthood with attendant mortality and morbidity which undermine the quality of life. For example, in Loeys-Dietz Syndrome, the OFC may be repaired while leaving a risk of widespread and aggressive arterial aneurysms later in childhood or adulthood.39

| Table 3: Orofacial clefts and chromosomal anomalies | Present congenital heart diseases associations |
|-----------------------------------------------|-----------------------------------------------|
| Chromosomal anomaly | Aetiology | Interrupted aortic arch type B, truncus arteriosus, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, pulmonary atresia with a ventricular septal defect |
| Velocardiofacial syndrome or DiGeorge syndrome | Genetic-autosomal dominant. Deletion in Chromosome 22q11 | Ventricular septal defect, Patent ductus arteriosus, transposition of great arteries, pulmonary atresia |
| Chromosome 22q11.2 deletion syndrome | Sporadic, Trisomy 18 | Ventricular septal defect, atrial septal defect, Patent ductus arteriosus |
| Edward syndrome | Sporadic, Trisomy 18 | |
| Patau syndrome | Sporadic, Trisomy 13 | |

Therefore, the excellent prognosis is underpinned not only by the initial management but also care and regular follow-up by an experienced interdisciplinary team from infancy until adulthood.

**CONCLUSION**

Cardiovascular diseases and cleft palate interrelate in various ways; although the mechanisms are unclear, more studies are required to reveal more associations. There is currently enough evidence that maternal cardiovascular risk factors are potent risk factors for foetal OFCs development in addition to the fact that many congenital heart diseases are associated with OFCs.
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