World Birth Defects Day 2023

Many Birth Defects – One Voice

Orofacial Clefts

Birth defects, also known as congenital anomalies or congenital malformations, are structural or functional anomalies that occur during intrauterine life, and can be identified during pregnancy, at birth or after birth[1]. Birth defects vary widely in severity, from relatively minor defects to lethal ones. It is estimated that between 3% - 6% of infants worldwide are born with a major birth defect every year[2], of which around 240,000 die within the first 28 days of life[3]. For many birth defects the underlying aetiology is still unknown, however, for some the occurrence may be reduced or prevented by taking appropriate measures before and during pregnancy. Preventative measures include adopting a healthy lifestyle, healthy eating, avoiding alcohol and smoking in pregnancy and adequate vitamin intake, to name a few.

World Birth Defects Day (WBDD) was first held on March 3rd 2015, and since then organisations from around the world mark this day with the aim of raising awareness about the impact of birth defects as well as increase opportunities for their prevention. This year marks the observance of the 8th edition of World Birth Defects Day. Further information about WBDD can be found at: https://www.worldbirthdefectsday.org/.

In Malta, surveillance of birth defects occurs through the Malta Congenital Anomalies Register of the Directorate for Health Information and Research (DHIR). Further information about the Register can be found at: https://deputyprimeminister.gov.mt/en/dhir/Pages/Registries/birthdefects.aspx.

Health professionals may notify new cases of birth defects through the secure portal found here: https://deputyprimeminister.gov.mt/en/dhir/Pages/Notifications/nocaf.aspx.

Orofacial Clefts – Cleft Lip and Cleft Palate

Orofacial clefts are a significant public health issue due to their widespread prevalence, the costs associated with their complex rehabilitation and treatment, not to mention the emotional burden on parents and their families[4].

Orofacial clefts are common head and neck congenital anomalies which occur when the tissues of the lip or the roof of the mouth do not join up before birth. These structures normally develop between the fourth to seventh and sixth to ninth weeks of pregnancy respectively.

Despite orofacial clefts being a relatively common congenital anomaly, they are generally not lethal anomalies. In an Australian study by Bell et al (2015)[5], survival rates of infants born with orofacial clefts and those born without were compared and the authors concluded that orofacial clefts (with or without other additional minor anomalies) did not influence infant or long-term survival rates. Infant survival rate was lower only in those children who had an orofacial cleft and additional major anomalies.

Orofacial clefts can be classified as either cleft palate or cleft lip, with or without cleft palate.

Cleft palate is a fissure in the secondary palate and can affect the soft palate alone or both the soft and hard palate. In cleft palate alone, the lip remains intact. ***Cleft lip*** is characterised by a partial or complete fissure in the upper lip. Most cases of cleft lip are unilateral (80-85% of cases) and occur on the left side[6]. A cleft lip without cleft palate can extend backwards into the gums up to the level of the incisive foramen. When a cleft lip extends posteriorly into the secondary palate, the condition is then referred to as ***cleft lip with cleft palate***.

Overall, cleft lip is more common than cleft palate. While cleft palate alone is more common in females, both cleft lip alone and cleft lip with cleft palate are more common in boys[7].

Figure 1: Diagrammatic representation of the different types of Cleft Lip and Cleft Palate[8]

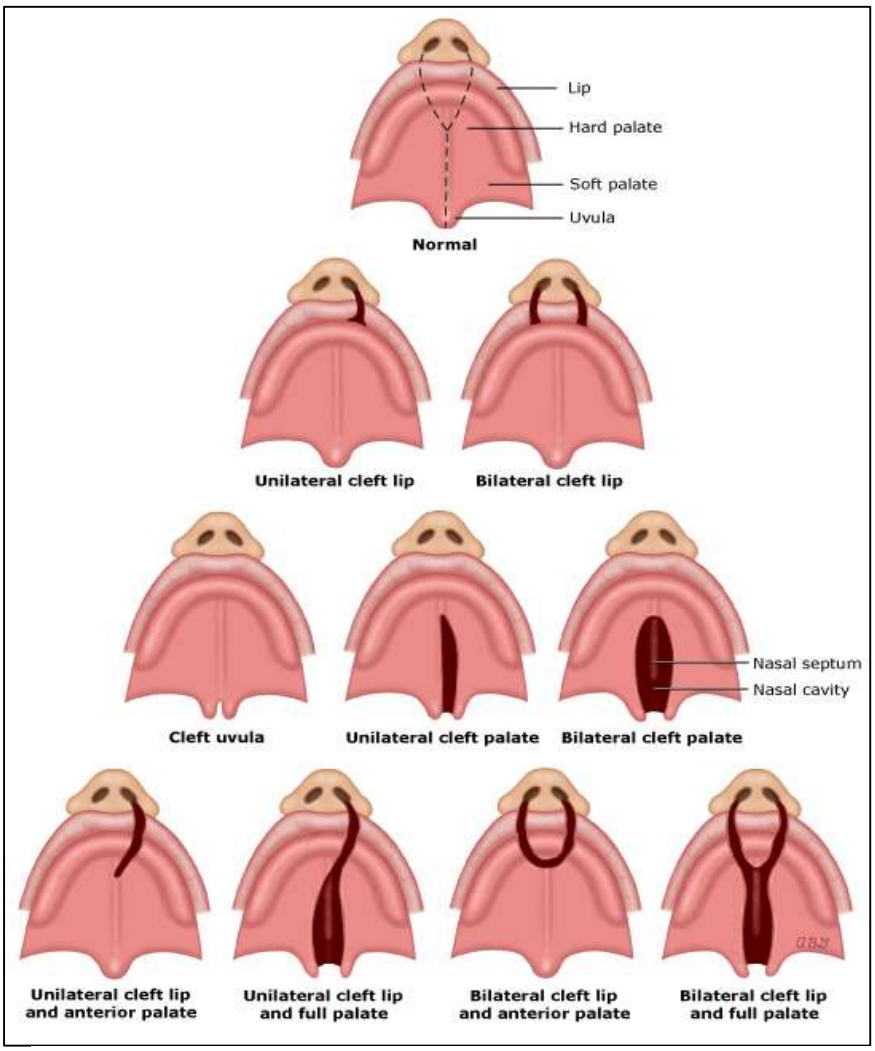


Image taken from : Etiology, prenatal diagnosis, obstetric management, and recurrence of cleft lip and/or palate - UpToDate

The majority of orofacial clefts occur in isolation, but some may be part of a recognised genetic syndrome or sequence, such as Pierre Robin Sequence, Stickler syndrome, Teacher Collins syndrome, Velocardiofacial syndrome or Van der Woude syndrome.

Aetiology of Orofacial Clefts

The underlying aetiology of syndromic and non-syndromic clefts differs.

Syndromic OFCs are typically associated with genetic mutations or chromosomal abnormalities[9]. The cause for non-syndromic orofacial clefts is believed to be multifactorial, with a complex interplay of both genetic and environmental factors. Risk factors for orofacial clefts include maternal obesity[10], increased parental age[11], strict maternal vegetarian diet[12], anti-epileptics[13] , the anti-emetic Ondansetron[14], Diabetes Mellitus[15] and maternal smoking[16].

The Role of Folic Acid Supplementation in Reducing the Risk of Orofacial Clefts

Folic Acid (vitamin B9) is an essential vitamin for fetal growth and development. Folic acid intake is well documented to be important for reducing the risk of certain birth defects, such as neural tube defects. Similar to neural tube defects, orofacial clefts are caused by developmental failures that involve neural crest migration. Several studies have therefore investigated the association between folic acid supplementation and orofacial clefts.

Xu et al (2021) [17] carried out a population based case-control study in China which studied the effect of maternal folic acid supplementation and their association with non-syndromic orofacial clefts. Maternal periconceptional folic acid supplementation was found to be associated with a reduced risk for non-syndromic cleft lip with or without cleft palate (adjusted odds ratio = 0.41, 95% CI 0.33–0.51) and non-syndromic cleft lip (adjusted odds ratio = 0.42, 95% CI 0.30–0.58). The association of folic acid supplementation and non-syndromic cleft palate was non-significant however. Jayarajan et al's (2019)[18] systematic reviewed echoed the previous findings, showing there to be a strong association between high-dose folic acid administration and the prevention of isolated CL +/- CP. Millacura et al (2017) [4] carried out a meta-analysis which also showed a significant decrease in the risk for non-syndromic cleft lip +/-palate (RR=0.88, 95% CI 0.81,0.96) following folic acid fortification, with neutral effects on total orofacial clefts and cleft palate.

A systematic review by Zhou et al (2020)[19] showed an inverse association between the use of folic acid containing supplements before or during pregnancy and cleft lip with or without cleft palate (odds ratio 0.60, 95% CI 0.51-0.69, Cochrane Q p-value <.01). A small decrease in the risk for cleft palate only was also noted (odds ratio 0.88, 95% CI 0.79-0.99). The use of supplements starting after the first trimester (i.e. after the aetiologically relevant period) showed no association with non-syndromic clefts.

Overall, the literature shows that there is a beneficial association between maternal folic acid supplementation both prior to and in early pregnancy on the risk for non-syndromic cleft lip with or without cleft palate. Further research in the area is however still needed to fully understand the relationship between the two. As no significant association between folic acid supplementation and cleft palate was seen, it raises questions on whether the aetiology behind the cleft palate differs to that of cleft lip[4].

Diagnosis and Treatment of Orofacial Clefts

Orofacial clefts, especially cleft lip with or without cleft palate, can be detected with antenatal ultrasounds. Cleft palate alone is harder to diagnose antenatally using ultrasound and therefore many of these cases are diagnosed at birth[20]. Other types of minor cleft palate, such as bifid uvula or submucous cleft palate might not be diagnosed until later in life.

Treatment options for children with orofacial clefts varies depending on the severity of the cleft and the presence of other birth defects. A multidisciplinary team, consisting of surgeons, speech language pathologists, orthodontics and audiologists provide holistic care for children with orofacial clefts.

Timely surgical repair of a cleft lip or palate improves both the cosmetic appearance of the child as well as aids in breathing, language and speech development. Surgical repair is usually performed within the first 12 months of life and is considered to be a safe procedure with a relatively low risk of adverse events. Complications following cleft repair include vermilion/whistle deformity, muscular dehiscence, nasal asymmetry, palatal fistula, obstructive sleep apnoea and velopharyngeal dysfunction[21].

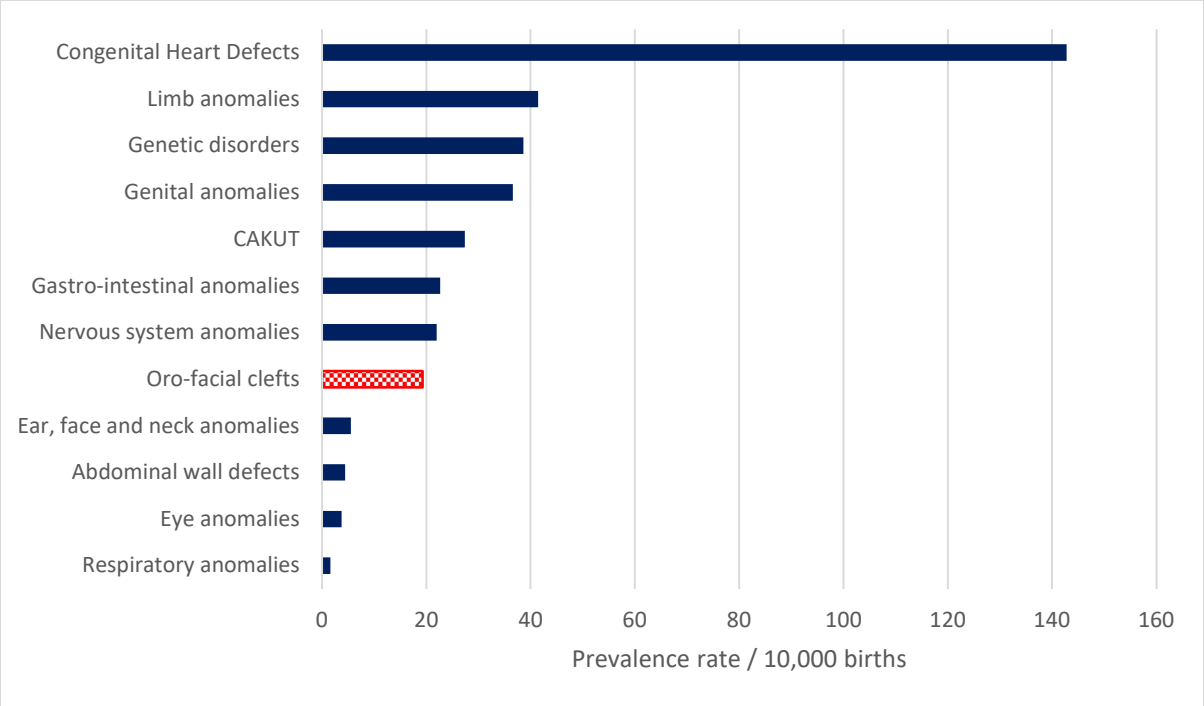
Although children born with an orofacial cleft remain at increased risk for middle ear disease, palatoplasty at an early age significantly reduces the prevalence of middle ear dysfunction and hearing loss (27.4% and 2% respectively for palatoplasty under 3 years of age vs 75% and 43.7% for palatoplasty at an older age)[22]. Birch et al (2021) examined speech outcomes following orticochea pharyngoplasty on children with cleft palate and velopharyngeal dysfunction and found that following the procedure, there was a statistically significant decrease in scores for hypernasality ($p < .001$), nasal emission ($p < .01$), and passive cleft speech characteristics ($p < .01$)[23].

Orofacial Clefts in Malta

The Malta Congenital Anomalies Register within the Directorate of Health Information and Research (DHIR) collects information on all babies born in Malta and Gozo and are diagnosed with congenital anomalies until one year of age.

During the period between 1st Jan 2000 up to 31st Dec 2020, there were a total of 172 orofacial cleft defects registered in Malta. They accounted for around 5% of all major birth defects within this period.

Figure 2: Prevalence rate of major congenital anomalies in Malta, inclusive of genetic anomalies, between 2000-2020



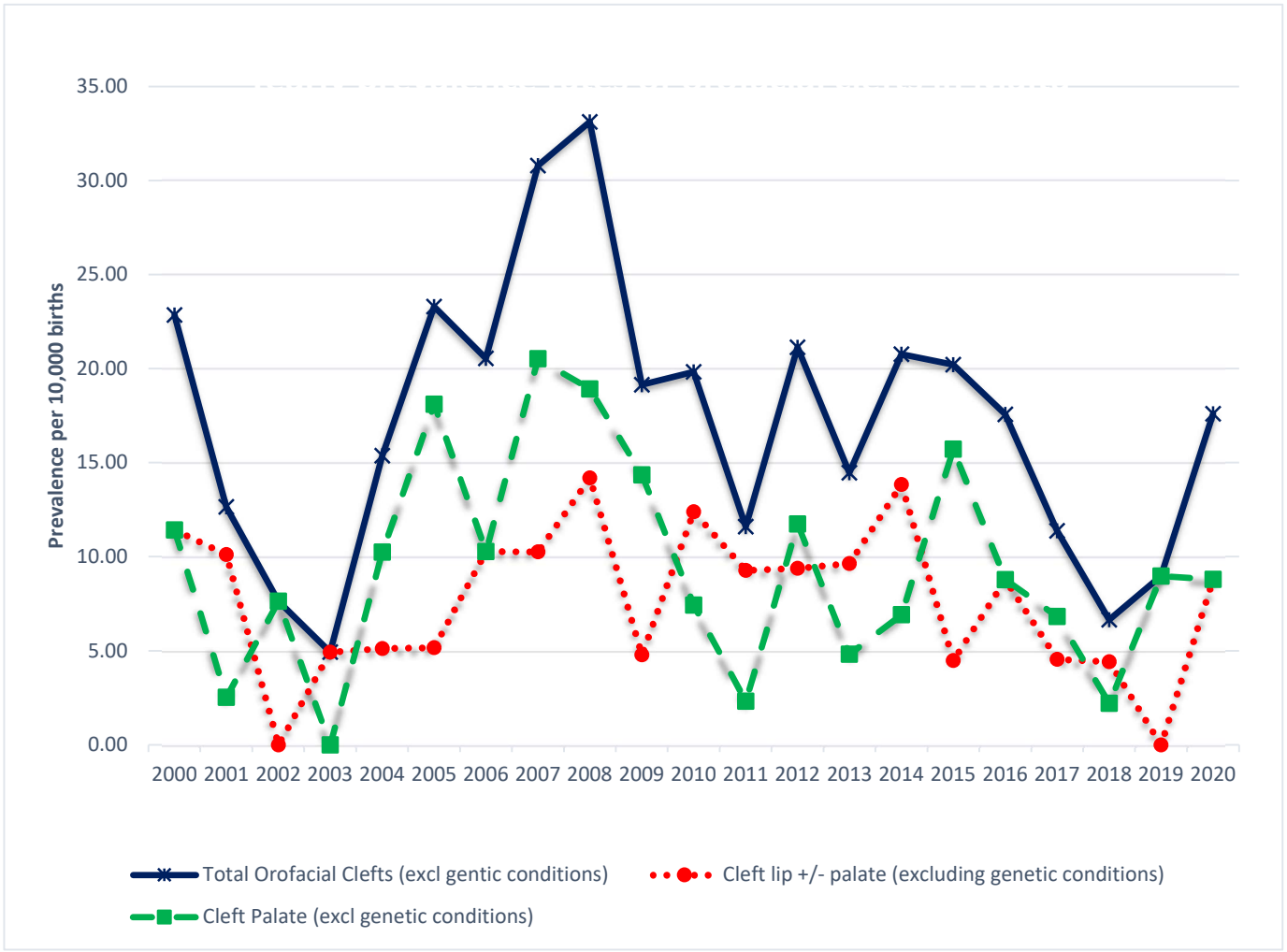
(Source: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence/export/ ; accessed on 25/1/2023)

Out of the 172 cases of orofacial clefts registered in Malta between 2000 - 2020, 147 cases (85.5%) were non-syndromic while the remaining 25 cases (14.5%) were associated with a genetic syndrome. The most commonly associated syndrome occurring with orofacial clefts was Pierre Robin Syndrome, found in 10 of the 25 syndromic cases.

Cleft palate accounted for 96 cases (55.8%) of the total number of orofacial clefts (of which, 82.3% were non-syndromic and 17.7% were syndromic), cleft lip without cleft palate accounted for 19.8% (of which there were 34 cases, all non-syndromic) and cleft lip with cleft palate accounted for 24.4% (42 cases) of the total (of which 81% were non-syndromic and 19% were syndromic).

The overall population prevalence rate in Malta for non-syndromic orofacial clefts between 2000 – 2020 was 17.1 per 10,000 births. For Cleft palate alone, the prevalence across this period was 7.7 per 10,000 births and the prevalence for cleft lip, with or without cleft palate, was 9.4 per 10,000 births[24].

Figure 3: Yearly prevalence rates (per 10,000 births) of Orofacial Clefts in Malta between 2000 - 2020



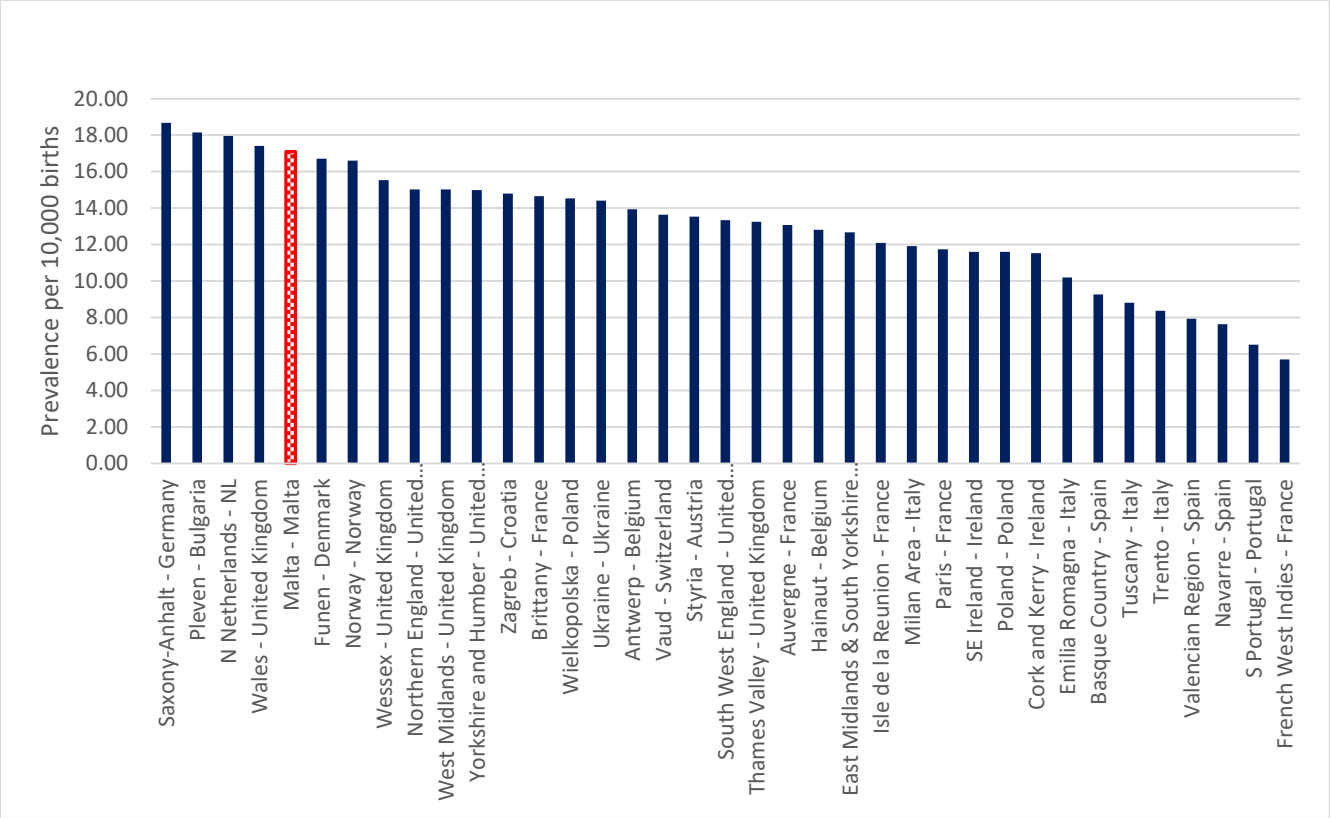
(Source: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence/export/ ; accessed on 25/1/2023)

Orofacial Clefts in Europe

The prevalence of orofacial clefts across Europe varies greatly. The following graphs show the total prevalence for orofacial clefts, cleft palate and cleft lip with or without cleft palate for the members of EUROCAT, a European Network of population-based registries for the epidemiological surveillance of congenital anomalies[25]. The presented rates include only those defects that do not form part of a genetic syndrome (i.e. only the non-syndromic cases).

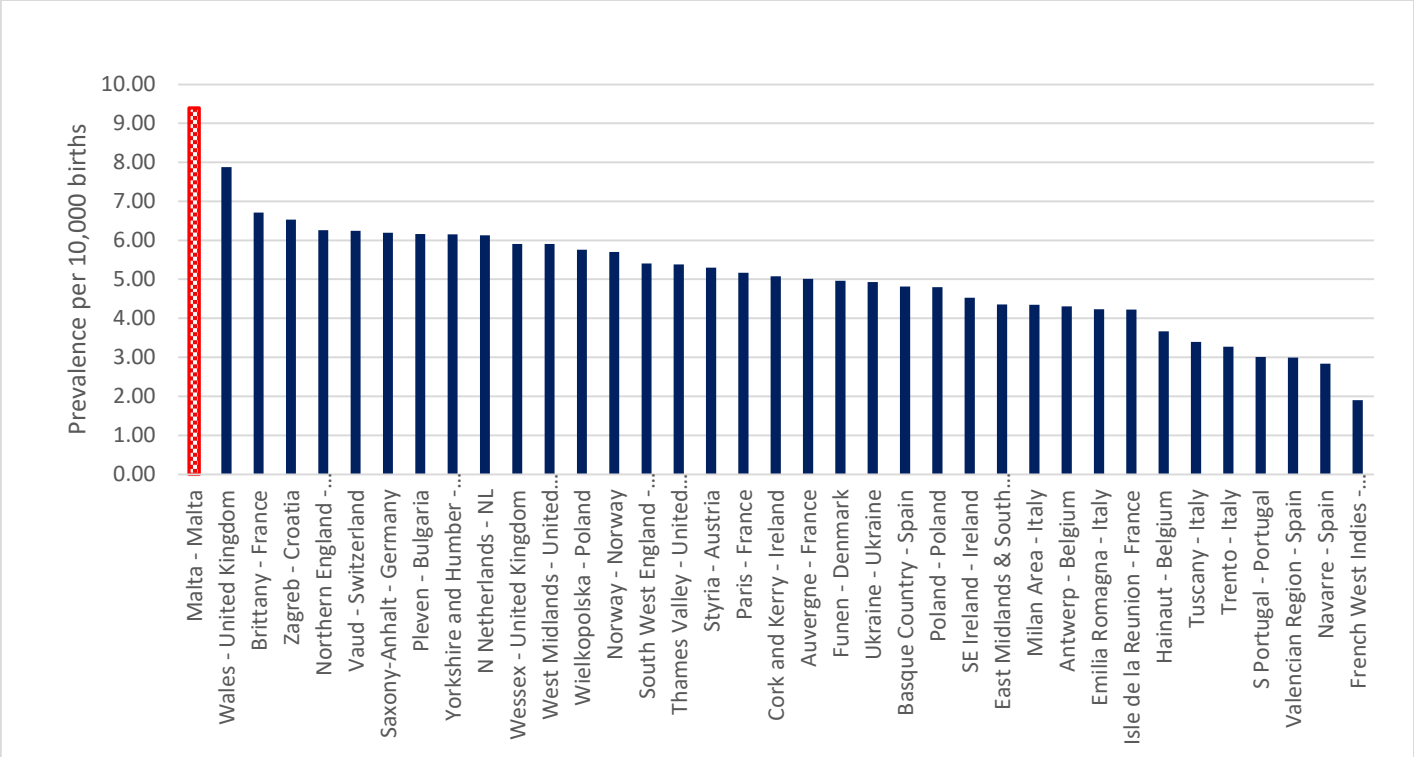
Figure 4: Prevalence of non-syndromic total Orofacial Clefts reported by participating European Registries (2000 – 2020)

(Source: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence/export/ ; accessed on 25/1/2023)



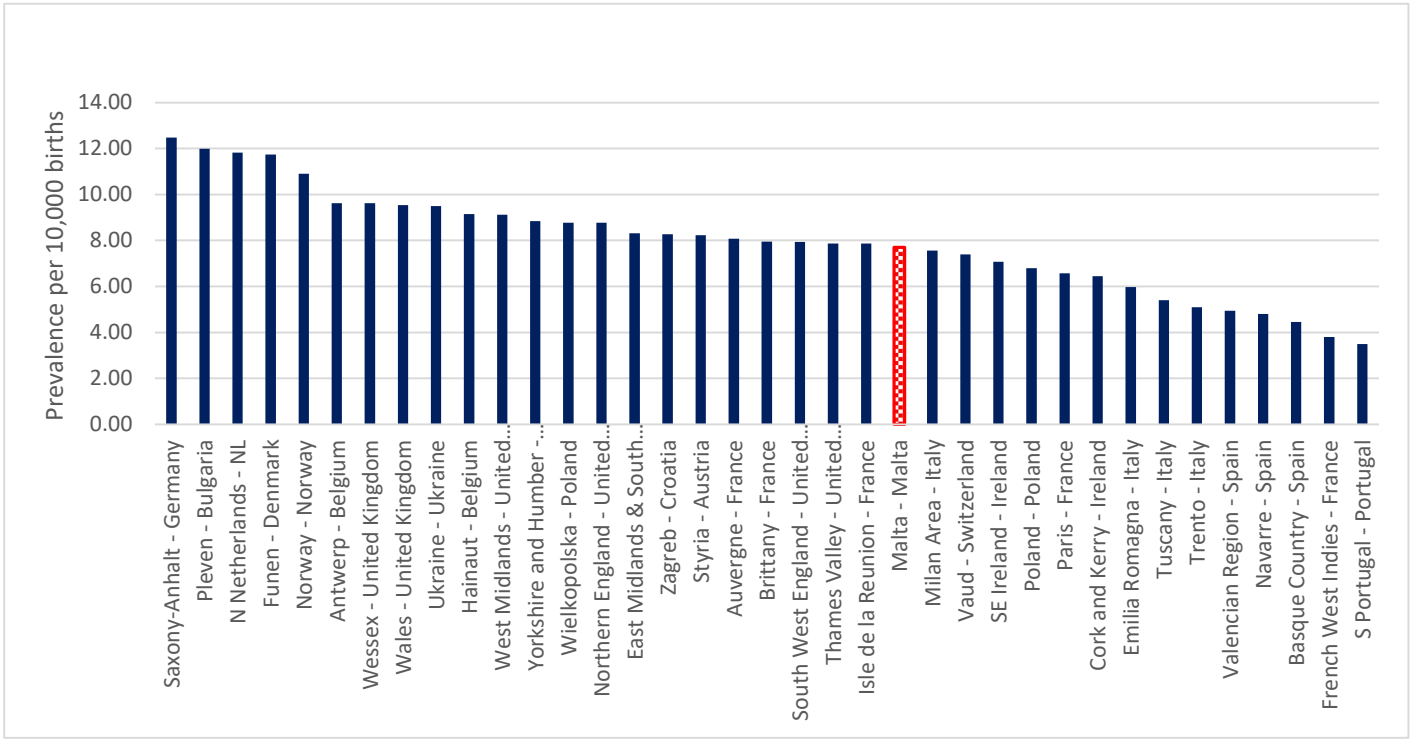
Malta reports a high rate for non-syndromic orofacial clefts (5th amongst EUROCAT members), mainly fuelled by the fact that Malta has the highest prevalence rate for non-syndromic cleft palate (Figure 5). Figure 6 shows the prevalence rate for Cleft Lip +/- cleft palate wherein Malta has a slightly lower rate compared to the EUROCAT average.

Figure 5: Prevalence of non-syndromic Cleft Palate reported by participating European Registries (2000 – 2020)



(Source: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence/export/ ; accessed on 25/1/2023)

Figure 6: Prevalence of non-syndromic Cleft Lip with or without Cleft Palate reported by participating European Registries (2000 – 2020)



(Source: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence/export/ ; accessed on 25/1/2023)

Conclusion

Orofacial clefts are one of the most common birth defects, both worldwide and in Malta, and impose a heavy burden on the overall health and quality of life on the affected individuals and their families. Understanding the underlying aetiology and the drawing up of subsequent policies aimed at reducing the prevalence of these birth defects is a key public health initiative aimed to reduce the burden on those directly and indirectly affected by this condition.

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