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**Cleft lip and palate: Care configuration, national registration, and research
strategies**

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Abstract: A child born with a cleft lip and palate will face 20 years or more of hospital care and surgery. This is a global problem with about 10 million people affected worldwide. Various models of care exist around the condition and the best configurations of services within an economy need to be optimised. We provide examples of how centralised care can improve outcomes, provide an opportunity to establish national registries and then emphasise the opportunities for building research platforms of relevance. The default of any cleft service should be to centralise care and enable cleft teams sufficient volume of patients to develop proficiency and measure the quality of outcomes. The latter need to be benchmarked against the better centres in Europe. Two areas of concern for those with cleft are morbidity/mortality and educational attainment. These two issues are placed in context within the literature and wider approaches using population genetics. Orthodontists have always played a key role in developing these initiatives and are core members of cleft teams with major responsibilities for these children and their families.

Keywords: cleft lip and palate, centralisation, outcomes, education, cancer

Introduction

The impact of COVID-19 will have left many orthodontists reeling from some devastating financial issues and limited provision of care for their patients. It will be important as we emerge from this virus pandemic that the most vulnerable groups of our patients are given priority. This will include children born with cleft lip and/or palate (CL+/P) and those with significant craniofacial issues. Orthodontists have played a significant role in changing the care of these children in several health systems across the world. They are often recognised as custodians of data, have been willing to ask questions and make brave challenges on the quality of outcomes. There are significant benefits from improving treatment for these children particularly in centralised models and which can yield improved outcomes as well as establishing a platform for registration and research. This paper will seek to demonstrate contributions from orthodontists and highlight information of relevance to parents and families of those living with cleft.

Epidemiology and aetiology

CL+/P is a global issue where approximately every three minutes, a child will be born with some form of oro-facial clefting. In the world, over 10 million lives are affected by the condition. The cause of clefting is unknown, there are known racial and geographic variations and there are associations with environmental exposures and socioeconomic status (for seminal reviews see Mossey et al., 2009 [1]; Dixon et al., 2011 [2]). New Zealand Maori, American Native and Asian populations have the highest reported birth prevalence rates, which are often as high as 1 in 500. [2, 3] European-derived populations have intermediate prevalence rates at approximately 1 in 1,000, and African-derived populations have the lowest prevalence rates at approximately 1 in 2,500. [1]

The frequency of CL+/P also differs by gender and laterality. There is a 2:1 male to female ratio for clefts involving the lip, approximately a 1:2 male to female ratio for clefts of the palate only and a 2:1 ratio of left to right sided clefts among unilateral cleft lip cases. Approximately 70% of all cases of CL+/P and 50% of cases of cleft palate only are non-syndromic. Oro-facial clefts can be divided by phenotype into cleft lip (CL), with and without cleft palate and these clefts may be complete or incomplete, unilateral (UCLP), or bilateral (BCLP). Cleft palate (CPO) can also occur in isolation [2] [Figure 1].

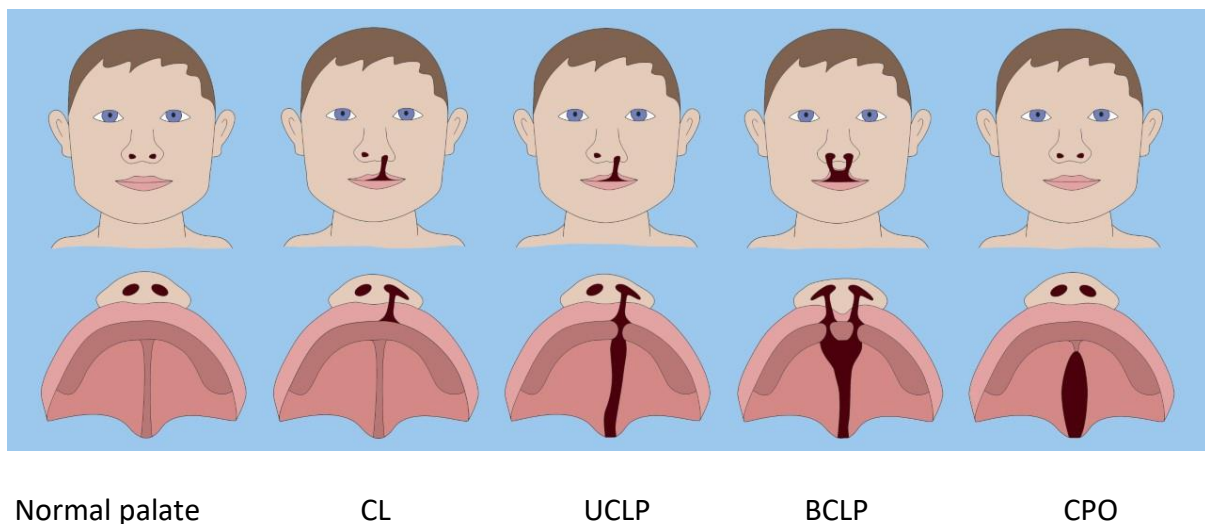


Figure 1: Cleft phenotypes showing an intact and normal palate, cleft lip (CL) unilateral cleft lip and palate (UCLP), bilateral cleft lip and palate (BCLP) and cleft palate only (CPO).

Illustration by Dr Hywel Naish

The frequency of these phenotypes varies by population and it highlights the importance of registrations and surveillance since these specific entities may provide epidemiological and genetic clues as to cause and best treatment. In European populations about 50% of all clefts are CPO, 10% CL, 25% UCLP and 10% BCLP. The remaining 5% are median clefts or variants. Cleft lip and CPO may have different aetiologies and there is evidence from familial studies and epidemiology that there are genetic differences. Twin studies have shown that concordance for CL, cleft lip, and palate (CLP) and CPO are higher in monozygotic than dizygotic twin pairs suggesting a genetic influence. Recurrence risk in families is a further pointer to genetic influence in non-syndromic clefting. [4] Accurate phenotyping is crucial to understanding both the epidemiology and aetiology of cleft lip and palate because the power to detect effects is weakened when all clefts are treated as a single entity.

Genome Wide Association Studies (GWAS) search the genome for single-nucleotide polymorphisms that occur more frequently in people with a particular disease/trait than in people without the disease/trait. They are a promising way to study complex, common diseases in which many genetic variations contribute to a person's risk. GWAS have provided major advances but the early published reports treated CL+/P as one group and had relatively low numbers. [5-7] This reflects how difficult it is to collect large samples for those born with cleft. There is also the issue of whether the cleft types are genetically distinct and how are subclinical phenotypes accounted for? Microforms of cleft can be seen in teeth, lip muscle defects, lip pits as well as three-dimensional facial images and brain imaging. There are emerging strong and coherent arguments for considering detailed dental phenotypes as an

important part of describing clefts and thereby enhancing genetic studies. There are also surrogate measures such as speech, hearing, educational attainment, social adjustment, and professional development. [2] If detailed information is to be collected longitudinally then cohort studies are needed with significant funding and commitment. We have achieved this through service development and reconfiguration, and this has helped answer the question as to whether all clefts are the same?

There is good evidence that different subtypes of orofacial cleft have distinct aetiologies, but the precise molecular mechanisms underlying these are unknown. Given the key role of epigenetic processes such as DNA methylation in embryonic development, it is likely that aberrant DNA methylation may also play a part in the development of orofacial clefts (*easy start to understanding epigenetics*). [9] We used blood samples from children with different cleft subtypes to demonstrate distinct DNA methylation profiles and found four genomic regions differentially methylated in CL compared to CLP, in CPO compared to CLP and in CPO compared to CL. These regions included several which mapped to genes that have previously been implicated in the development of orofacial clefts (for example, *TBX1*, *COL11A2*, *HOXA2*, *PDGFRA*). These distinct methylation profiles in different cleft subtypes might reflect differences in their aetiologies, or causal genetic and environmental factors. [9,10]

Infrastructure and capacity to treat cleft lip and palate

Treatment of a child born with a cleft requires significant input from several specialists over 20 years and beyond. The most pressing initial needs deal with feeding and support for the family which usually comes from specialist nursing; thereafter surgical repair is required as well as early preventative advice from paediatric dentists. Surgical repair of the lip is usually at three months, the palate 6 to 9 months with alveolar bone grafting required as the upper canine starts to develop, usually around 7-9 years of age. Further surgery may also be required

to aid speech, revise primary surgery and/or repair fistulae. Speech and language therapy, psychology, restorative dentistry, and orthodontic treatment are needed variously as the child develops. These different specialties work best as a team with appropriate integration of professional services support staff. [11]

Three decades ago in the United Kingdom (UK) it was recognised that outcomes were not as good as those seen in the best European cleft centres [12] and various professional and parent help groups succeeded in pressuring the Government to commission a study known as the Clinical Standards Advisory Group (CSAG). After a clear demonstration of poor outcomes, the Government recognised there was a need for change. [13]

Essentially the 57 cleft centres were reduced to 16 managed clinical networks across the UK and the 1200 children born each year with some form of cleft are treated in these centres. This has allowed proficiency and efficiency to develop and a follow up study some 15 years after this centralisation of services showed up to a 50% improvement in some outcomes. There is no room for complacency, there are still some areas of care that need attention. For instance, dental caries remained at very high levels post-centralisation and a significant preventative strategy needs to be developed for this wholly preventable disease. [4] Non-syndromic children born with CL+/P tend to have a lower oral- health related quality of life (OHRQoL) than a general non-cleft population which extends into adulthood. [15]

Centralisation of care and research

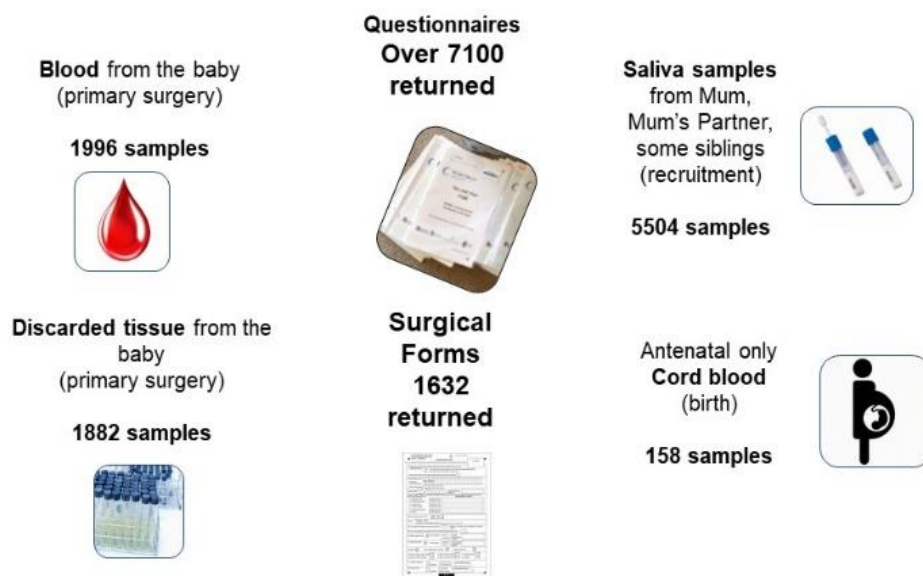
There have been other positive consequences of this centralisation in relation to research. One of the recommendations from the CSAG report was to develop a national registry for children born with a cleft. This registry (Cleft Registry and Audit NETwork, CRANE www.crane-database.org.uk) has been running since 2000 and now has over 22,000 cleft birth registrations. If this is compared to the excellent Scandinavian registries in Sweden and

Denmark, then the scale is significant. It took over 50 years for the Danish registry to recruit seven thousand children and by dint of a slightly larger population, Sweden recruited nearly 8,000 cleft births over 50 years. These two registries are made even more powerful through the ability to link to other health databases as well as social data such as education. The UK by virtue of its population size is ideally placed to recruit large numbers of cleft births and should be able to answer questions on the treatment of these children as well as the outcomes.

The second major UK initiative was the development of a cohort study for children born with CLP which now recruits families to provide the information on lifestyle environment and treatment. Observational cohort studies can also be used as a high-quality design for answering questions around prevalence, natural history, and risk factors. This cohort study (known as the Cleft Collective <http://www.bristol.ac.uk/cleft-collective/>) started in 2012 and was funded through a medical charity, The Scar Free Foundation. In collaboration with those born with cleft and their families as well as the clinical teams, research protocols and questionnaires were developed and implemented within all UK cleft teams once ethical approval had been obtained. Recruitment to the study and data collection is ongoing with over 9,000 participants from more than 3,000 families recruited to date. The progress of the collection is easily understood from figure 2. In addition, there is a nested speech and language study within the Cleft Collective (Cleft Collective Speech and Language (CC-SL) study). The data collected forms a comprehensive resource of information about individuals with CL+/P and their families and is constantly expanding. The resource comprises biological samples, speech audio recordings, medical and educational records and parent and child completed questionnaires. It is available for clinical and academic communities to access and use to address a range of cleft related research questions. More information on the study and how to access the dataset is available at www.bristol.ac.uk/cleft-

[collective/professionals/access/](#). This initiative provides the basis of a longitudinal cohort study, many future projects, and worldwide collaborations. [16,17]

Figure 2: The Cleft Collective is a longitudinal cohort study of children born with cleft and their families in the UK. Blood is collected from those diagnosed through ante-natal scans (cord blood) and from the child at operation as well as discarded tissue. The cleft teams return surgical details. Families are asked to provide saliva and fill in questionnaires. The figures to date are shown against samples and questionnaires. The study is ongoing.



These approaches, where services are re-configured to provide improved outcomes and coupled with a research agenda which includes national registration and a cohort study are unique but none of this would have been possible without previous seminal work by Professors Gunvor Semb and Bill Shaw. The Eurocleft studies showed the importance of inter-centre comparisons and started to relate volume and outcomes. [12] This certainly informed the need for CSAG in the UK and the subsequent “Americleft” [18] and New Zealand studies [19,20] followed similar lines. In New Zealand, where there are 100 cleft births a year,

patients are treated in five centres some outcomes are very poor and a centralised model is the most obvious way forward. The difficulties in creating centralised care involve geography, travel, and access as well as a political will. Private health-care systems add another layer of complexity since financial imperatives often stymie clear evidence. Other initiatives from Bill Shaw and Gunvor Semb have included herculean tasks such as Scandcleft [21] and the timing of palatal surgery [TOPS] [22] where operative techniques and timing of surgery are scrutinised. These studies require global collaborations and significant finance but are starting to indicate that operator skill is of paramount importance and can override technique and timing. Two areas are highlighted to demonstrate why we need national registries and large cohort studies to answer sensitive questions accurately and confidently.

What information can we give patients and families?

When a child is born or diagnosed antenatally with a cleft parents are shocked and distressed but after the initial impact they generally will want to know what the best treatments are (and where these are delivered), what has been the cause and what does the future hold for their child? None of these are easy to answer but the information that parents and those born with cleft are given needs to be based on best available evidence. The relatively low incidence of clefting results in many studies recruiting low numbers of cases where results and interpretations may then be spurious.

Parents would be concerned if they were told “affected children have higher morbidity and mortality throughout life than do unaffected individuals” which is derived from a single short-term study (two years) of 347 cases of cleft lip and/or cleft palate. [23] After consideration of terminations and late foetal loss there was a 1% overall perinatal mortality rate for all children in the region but this was 9% for babies born with orofacial clefts and even for isolated clefts this was significantly (3 times) higher than the background population. These

figures are frightening, and a more realistic view is from the excellent Danish registry. Here over 7,000 children born with clefts have been registered and followed up in Denmark between 1936 and 1987. This was achieved with patient lists, and capture-recapture methods with ascertainment of 99% of liveborn cleft affected babies without associated anomalies or syndromes. This provides a more realistic reflection of the impact of clefting on mortality and morbidity. However, the most striking observation was an increased risk of suicide in both sexes. The cause of suicide is complex, but recognition of potential risk factors could enable treatment and prevention in people born with birth anomalies. Most attention is to the early years of health in children born with congenital malformations but as more now survive serious birth defects into adulthood then understanding the full life course of these disorders is important to provide optimal preventive health care. [24] Large population studies are needed with genetic information coupled to environmental exposures to fully map health expectations for those born with a cleft.

There was also an increased risk associated with all major causes of death but there was only a marginally increased mortality due to cancer among people with cleft lip and palate compared with the general population which did not support previous observations. [25,26]

There is evidence from epidemiological population-based studies that birth anomalies are associated with an increased incidence of cancer. [27,28] These anomalies include non-syndromic CL+/P where the evidence for increased incidence of cancers among cases and unaffected first-degree relatives is not convincing in either direction. [26-29] There are also limitations of comparing cancer incidence in non-syndromic CL+/P cases with that in the non-cleft population. Cancers are distinct and if different types are examined in cleft populations the numbers become too small for meaningful conclusions. This is even more diluted in considering syndromic and non-syndromic clefting let alone the subtypes.

Although population studies have found inconsistent evidence for increased incidence of cancer in non-syndromic CL+/P cases, there is a case for using population genetics to explore this further. A recent approach has been to examine the shared genetic aetiology between non-syndromic clefting and oral cavity/oropharyngeal cancers, which affect similar anatomical regions and may share aetiological risk factors. [30] This involves Mendelian randomization being used to test the possibility that common non-syndromic clefting genetic variants, a latent measure of an individual's underlying liability to non-syndromic CL+/P will influence cancer risk. A similar approach has been used to provide evidence of shared genetic influences between non-syndromic CL+/P and facial morphology. [31] Very large samples were used to estimate genetic overlap using non-syndromic CL+/P polygenic risk scores. There was evidence for an association between non-syndromic CL+/P polygenic risk scores and increased odds of oral cavity/oropharyngeal cancers but there was no confirmation of an association when UK Biobank was used in a replication study. Thus, through this analysis the major non-syndromic CL+/P risk variants are unlikely to influence oral cavity/oropharyngeal cancers. This approach is comprehensive and would need to be used with specific other cancers and specific cleft phenotypes with very large samples and population controls.

There is, in summary no strong evidence of an association between clefting and cancer. The indication of risk of suicide has not been replicated in the Swedish registry which may reflect intervention strategies ameliorating this risk.

Education

There has been for some time evidence that children born with non-syndromic CL+/P struggle with educational attainment [32] which can have wide adverse impacts on vocational, social, mental, and physical health outcomes. [33] This has the potential for an additional burden on a child born with cleft and potential intervention can be invoked if we can understand the

aetiology. However, this is complex since there have been suggestions of differences in brain structure or function [34] as well as compromised hearing, delayed speech development and the potential impact of classroom bullying and social exclusion. We also know that cleft type and gender are factors; males with CPO and females with CLP are most vulnerable [32] and girls are more negatively affected than boys. [35,36] It is difficult to make comparisons across countries and cultures but in most studies, those with CPO have the most negative outcomes, followed by those with CLP and CL only being the least affected. Objective educational measures and targets vary from country to country and dissection of the educational issues for those born with cleft requires more detailed studies, but all academic subjects have low attainment. [36-39] There is further impact in that birth order shows that younger siblings have higher risk of poor academic outcomes [40] with shared socio-economic circumstances explaining some of the observed differences in academic achievement. [36,38,39]

To start unscrambling the possible causes of this poor educational attainment we hypothesised that common variant genetic liability to non-syndromic CL+/P influences educational attainment. This research used similar methodologies to that described for facial morphology and cancer risk. [30, 31] In summary there was little evidence for shared genetic liability and common genetic variants are unlikely to predispose individuals born with non-syndromic CL+/P to low educational attainment or intelligence and interventions can be developed to improve their educational attainment. [41]

Conclusion

This brief paper has highlighted how orthodontists have been central to the care of children born with a cleft. Service configuration has a proven impact and if linked with national registration and research strategy, outcomes can be demonstrated with linkage to genetic and environmental influences. Much of the research detailed throughout this paper has been

driven by orthodontists. The effort needed to attain these goals is considerable but will positively influence the lives of a child born with a cleft.

References

1. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. *Lancet*. 2009;374(9703):1773-85.
2. Dixon MJ, Marazita ML, Beaty TH, Murray JC. Cleft lip and palate: understanding genetic and environmental influences. *Nat Rev Genet*. 2011;12(3):167-78.
3. Thompson JM, Stone PR, Sanders M, van der Zee H, Borman B, Fowler PV. The incidence of Orofacial Cleft in live births in New Zealand. *N Z Med J*. 2016;129(1440):64-71.
4. Sivertsen A, Wilcox AJ, Skjaerven R, Vindenes HA, Abyholm F, Harville E, Lie RT. Familial risk of oral clefts by morphological type and severity: population-based cohort study of first-degree relatives. *BMJ*. 2008;336(7641):432-4.
5. Birnbaum S, Ludwig KU, Reutter H, Herms S, Steffens M, Rubini M, Baluardo C, Ferrian M, Almeida de Assis N, Alblas MA, Barth S, Freudenberg J, Lauster C, Schmidt G, Scheer M, Braumann B, Bergé SJ, Reich RH, Schiefke F, Hemprich A, Pötzsch S, Steegers-Theunissen RP, Pötzsch B, Moebus S, Horsthemke B, Kramer FJ, Wienker TF, Mossey PA, Propping P, Cichon S, Hoffmann P, Knapp M, Nöthen MM, Mangold E. Key susceptibility locus for nonsyndromic cleft lip with or without cleft palate on chromosome 8q24. *Nat Genet*. 2009;41(4):473-7.
6. Grant SF, Wang K, Zhang H, Glaberson W, Annaiah K, Kim CE, Bradfield JP, Glessner JT, Thomas KA, Garris M, Frackelton EC, Otieno FG, Chiavacci RM, Nah HD, Kirschner RE, Hakonarson H. A genome-wide association study identifies a locus for nonsyndromic cleft lip with or without cleft palate on 8q24. *J Pediatr*. 2009;155(6):909-13.

7. Mangold E, Ludwig KU, Birnbaum S, Baluardo C, Ferrian M, Herms S, Reutter H, de Assis NA, Chawa TA, Mattheisen M, Steffens M, Barth S, Kluck N, Paul A, Becker J, Lauster C, Schmidt G, Braumann B, Scheer M, Reich RH, Hemprich A, Pötzsch S, Blaumeiser B, Moebus S, Krawczak M, Schreiber S, Meitinger T, Wichmann HE, Steegers-Theunissen RP, Kramer FJ, Cichon S, Propping P, Wienker TF, Knapp M, Rubini M, Mossey PA, Hoffmann P, Nöthen MM. Genome-wide association study identifies two susceptibility loci for nonsyndromic cleft lip with or without cleft palate. *Nat Genet.* 2010;42(1):24-6.
8. Sharp GC, Stergiakouli E, Sandy J, Relton C. Epigenetics and Orofacial Clefts: A Brief Introduction. *Cleft Palate Craniofac J.* 2018;55(6):795-797.
9. Sharp GC, Ho K, Davies A, Stergiakouli E, Humphries K, McArdle W, Sandy J, Davey Smith G, Lewis SJ, Relton CL. Distinct DNA methylation profiles in subtypes of orofacial cleft. *Clin Epigenetics.* 2017; 9:63.
10. Howe LJ, Richardson TG, Arathimos R, Alvizi L, Passos-Bueno MR, Stanier P, Nohr E, Ludwig KU, Mangold E, Knapp M, Stergiakouli E, Pourcain BS, Smith GD, Sandy J, Relton CL, Lewis SJ, Hemani G, Sharp GC. Evidence for DNA methylation mediating genetic liability to non-syndromic cleft lip/palate. *Epigenomics.* 2019;11(2):133-145.
11. Scott JK, Leary SD, Ness AR, Sandy JR, Persson M, Kilpatrick N, Waylen AE. Perceptions of team members working in cleft services in the United kingdom: a pilot study. *Cleft Palate Craniofac J.* 2015 Jan;52(1):e1-7.
12. Shaw WC, Brattström V, Mølsted K, Prahll-Andersen B, Roberts CT, Semb G. The Eurocleft study: intercenter study of treatment outcome in patients with complete cleft lip and palate. Part 5: discussion and conclusions. *Cleft Palate Craniofac J.* 2005;42(1):93-8.

13. CSAG. Cleft lip and/or palate, Report of a CSAG Committee. London: HMSO 1998
14. Ness AR, Wills AR, Waylen A, Smallridge J, Hall AJ, Sell D, Sandy JR. Closing the Loop on Centralization of Cleft Care in the United Kingdom. *Cleft Palate Craniofac J.* 2018;55(2):248-251.
15. Queiroz Herkrath AP, Herkrath FJ, Rebelo MA, Vettore MV. Measurement of health-related and oral health-related quality of life among individuals with nonsyndromic orofacial clefts: a systematic review and meta-analysis. *Cleft Palate Craniofac J.* 2015;52(2):157-72.
16. Stock NM, Humphries K, Pourcain BS, Bailey M, Persson M, Ho KM, Ring S, Marsh C, Albery L, Rumsey N, Sandy J. Opportunities and Challenges in Establishing a Cohort Study: An Example From Cleft Lip/Palate Research in the United Kingdom. *Cleft Palate Craniofac J.* 2016;53(3):317-25.
17. Wren Y, Humphries K, Stock NM, Rumsey N, Lewis S, Davies A, Bennett R, Sandy J. Setting up a cohort study in speech and language therapy: lessons from The UK Cleft Collective Speech and Language (CC-SL) study. *Int J Lang Commun Disord.* 2018;53(3):421-430.
18. Long RE Jr, Hathaway R, Daskalogiannakis J, Mercado A, Russell K, Cohen M, Semb G, Shaw W. The Americleft study: an inter-center study of treatment outcomes for patients with unilateral cleft lip and palate part 1. Principles and study design. *Cleft Palate Craniofac J.* 2011;48(3):239-43.
19. Fowler PV, Keall H, Kennedy D, Healey D, Thompson JMD. Dental arch relationship outcomes for children with complete unilateral and complete bilateral cleft lip and palate in New Zealand. *Orthod Craniofac Res.* 2019;22(3):147-152.

20. Thompson JMD, Stone PR, Williams K 3rd, Sanders M, Mason N, Pope R, Fowler PV. Nasolabial outcomes in a nationwide study of orofacial cleft in New Zealand. *Orthod Craniofac Res.* 2019;22(3):194-200.
21. Semb G, Enemark H, Friede H, Paulin G, Lilja J, Rautio J, Andersen M, Åbyholm F, Lohmander A, Shaw W, Mølsted K, Heliövaara A, Bolund S, Hukki J, Vindenes H, Davenport P, Arctander K, Larson O, Berggren A, Whitby D, Leonard A, Neovius E, Elander A, Willadsen E, Bannister RP, Bradbury E, Henningsson G, Persson C, Eyres P, Emborg B, Kisling-Møller M, Küseler A, Granhof Black B, Schöps A, Bau A, Boers M, Andersen HS, Jeppesen K, Marxen D, Paaso M, Hölttä E, Alaluusua S, Turunen L, Humerinta K, Elfving-Little U, Tørdal IB, Kjöll L, Aukner R, Hide Ø, Feragen KB, Rønning E, Skaare P, Brinck E, Semmingsen AM, Lindberg N, Bowden M, Davies J, Mooney J, Bellardie H, Schofield N, Nyberg J, Lundberg M, Karsten AL, Larson M, Holmefjord A, Reisæter S, Pedersen NH, Rasmussen T, Tindlund R, Sæle P, Blomhoff R, Jacobsen G, Havstam C, Rizell S, Enocson L, Hagberg C, Najar Chalien M, Paganini A, Lundeborg I, Marcusson A, Mjönes AB, Gustavsson A, Hayden C, McAleer E, Slevan E, Gregg T, Worthington H. A Scandcleft randomised trials of primary surgery for unilateral cleft lip and palate: 1. Planning and management. *J Plast Surg Hand Surg.* 2017;51(1):2-13.
22. Shaw W, Semb G, Lohmander A, Persson C, Willadsen E, Clayton-Smith J, Trindade IK, Munro KJ, Gamble C, Harman N, Conroy EJ, Weichart D, Williamson P. Timing Of Primary Surgery for cleft palate (TOPS): protocol for a randomised trial of palate surgery at 6 months versus 12 months of age. *BMJ Open.* 2019;9(7):e029780.
23. Ngai CW, Martin WL, Tonks A, Wyldes MP, Kilby MD. Are isolated facial cleft lip and palate associated with increased perinatal mortality? A cohort study from the West Midlands Region, 1995-1997. *J Matern Fetal Neonatal Med.* 2005;17(3):203-6.

24. Christensen K, Juel K, Herskind AM, Murray JC. Long term follow up study of survival associated with cleft lip and palate at birth. *BMJ*. 2004;328(7453):1405.
25. Zack M, Adami HO, Ericson A. Maternal and perinatal risk factors for childhood leukemia. *Cancer Res*. 1991;51(14):3696-701.
26. Zhu JL, Basso O, Hasle H, Winther JF, Olsen JH, Olsen J. Do parents of children with congenital malformations have a higher cancer risk? A nationwide study in Denmark. *Br J Cancer*. 2002;87(5):524-8.
27. Bjørge T, Cnattingius S, Lie RT, Tretli S, Engeland A. Cancer risk in children with birth defects and in their families: a population based cohort study of 5.2 million children from Norway and Sweden. *Cancer Epidemiol Biomarkers Prev*. 2008;17(3):500-6.
28. Carozza SE, Langlois PH, Miller EA, Canfield M. Are children with birth defects at higher risk of childhood cancers? *Am J Epidemiol*. 2012;175(12):1217-24.
29. Bille C, Winther JF, Bautz A, Murray JC, Olsen J, Christensen K. Cancer risk in persons with oral cleft--a population-based study of 8,093 cases. *Am J Epidemiol*. 2005 Jun 1;161(11):1047-55
30. Howe LJ, Hemani G, Lesueur C, Gaborieau V, Ludwig KU, Mangold E, Brennan P, Ness AR, St Pourcain B, Davey Smith G, Lewis SJ. Evaluating shared genetic influences on nonsyndromic cleft lip/palate and oropharyngeal neoplasms. *Genet Epidemiol*. 2020.
31. Howe LJ, Lee MK, Sharp GC, Davey Smith G, St Pourcain B, Shaffer JR, Ludwig KU, Mangold E, Marazita ML, Feingold E, Zhurov A, Stergiakouli E, Sandy J, Richmond S, Weinberg SM, Hemani G, Lewis SJ. Investigating the shared genetics of non-syndromic cleft lip/palate and facial morphology. *PLoS Genet*. 2018 Aug 1;14(8):e1007501.

32. Broder HL, Richman LC, Matheson PB. Learning disability, school achievement, and grade retention among children with cleft: a two-center study. *Cleft Palate Craniofac J.* 1998;35(2):127-31.
33. Davies NM, Dickson M, Davey Smith G, van den Berg GJ, Windmeijer F. The causal effects of education on health outcomes in the UK Biobank. *Nat Hum Behav.* 2018;2(2):117-125.
34. Nopoulos P, Langbehn DR, Canady J, Magnotta V, Richman L. Abnormal Brain Structure in Children With Isolated Clefts of the Lip or Palate. *Arch Pediatr Adolesc Med.* 2007;161(8):753.
35. Persson M, Becker M, Svensson H. Academic achievement in individuals with cleft: a population-based register study. *Cleft Palate Craniofac J.* 2012;49(2):153-9.
36. Persson M, Becker M, Conrad AL, Svensson H. Female and Male Differences in Academic Achievement in Individuals With Cleft: A Population-Based Register Study. *Cleft Palate Craniofac J.* 2018;55(2):196-203.
37. Fitzsimons KJ, Copley LP, Setakis E, Charman SC, Deacon SA, Dearden L, van der Meulen JH. Early academic achievement in children with isolated clefts: a population-based study in England. *Arch Dis Child.* 2018;103(4):356-362.
38. Wehby GL, Collet B, Barron S, Romitti PA, Ansley TN, Speltz M. Academic achievement of children and adolescents with oral clefts. *Pediatrics.* 2014;133(5):785-92.
39. Wehby GL, Collett BR, Barron S, Romitti P, Ansley T. Children with oral clefts are at greater risk for persistent low achievement in school than classmates. *Arch Dis Child.* 2015;100(12):1148-54.

40. Collett BR, Wehby GL, Barron S, Romitti PA, Ansley TN, Speltz ML. Academic Achievement in Children With Oral Clefts Versus Unaffected Siblings. *J Pediatr Psychol*. 2014;39(7):743-751.
41. Dardani C, Howe LJ, Mukhopadhyay N, Stergiakouli E, Wren Y, Humphries K, Davies A, Ho K, Weinberg SM, Marazita ML, Mangold E, Ludwig KU, Relton CL, Davey Smith G, Lewis SJ, Sandy J, Sharp GC. Cleft lip/palate and educational attainment: cause, consequence or correlation? A Mendelian-randomization study. *Int J Epidemiol*. 2020:dyaa047.
- 42.