# Clinical Characteristics and Cognitive Functioning of Hungarian Children Born with Orofacial Clefts

Doctoral (PhD) Dissertation

**Dr. Kinga Amália Sándor-Bajusz**

University of Pécs, OGYDHT Pécs

**Doctoral School of Clinical Neurosciences**

Head of Doctoral School: Prof. Dr. József Janszky

Psychiatry Program **(B-1/2012)**

Thesis Supervisor: Prof. Dr. Györgyi Csábi

Program Director: Prof. Dr. Tamás Tényi


Pécs, 2023

# Table of Contents

# Abstract

Orofocial clefts are the most common congenital abnormality of the craniofacial structures. They are defined as syndromic or non-syndromic clefts based on the underlying etiology. The optimal clinical care of these patients is ensured by a multidisciplinary team, and a long-term treatment plan in which well-timed cleft repair surgeries are of priority. In both syndromic and non-syndromic cases, the defect is associated with additional medical conditions and/or a higher risk for mental disorders that further complicate the overall care of these patients. The aim of the current thesis work was to analyze the clinical and mental health outcomes of children born with orofacial clefts, which was achieved in three levels by: (1) evaluating the impact of genetic syndromes on the algorithm of cleft repair surgeries, (2) identifying a subpopulation of children of non-syndromic orofacial clefts at risk for abnormal neurodevelopment, and (3) by summarizing the available evidence on brain structural differences in individuals with orofacial clefts and their controls.

Az ajak- és szájpadhasadék a koponya- és az arc leggyakoribb veleszületett rendellenessége. Az etiológia alapján szindrómás és nem szindrómás ajak-és szájpad hasadékot különíthetünk el. E betegek optimális klinikai ellátását multidiszciplináris team munka és hosszú távú kezelési terv biztosítja, amelyben a jól időzített műtéti beavatkozások élveznek prioritást. Mind a szindrómás, mind a nem szindrómás esetekben a defektus további egészségügyi állapotokkal és/vagy a mentális zavarok magasabb kockázatával jár együtt, ami tovább nehezíti e betegek általános ellátását. Jelen vizsgálatunk célja az ajak- és szájpadhasadékkal született gyermekek klinikai és mentálhigiénés állapotának, valamint a betegség kimenetelének elemzése volt, melyet három aspektusból vizsgáltunk: (1) a genetikai szindrómák hatásának értékelése a hasadékjavító műtétek algoritmusára, (2) a nem szindrómás ajak- és szájpadhasadékkal született gyermekek azon alcsoportjának azonosítása, akiknél fennáll az idegfejlődési zavar kockázata, és (3) az ajak-és szájpad hasadékkal született egyének és kontrollok agyszerkezeti különbségeiről rendelkezésre álló bizonyítékok összegzése.

# Abbreviations

ADHD: Attention deficit hyperactivity disorder

ASD: Autism spectrum disorder

BA: Branchial arch

CBCL: Child Behavior Checklist

CHD: Congenital heart disorder

cIN: Cortical interneuron

CL: Cleft lip

CLP: Cleft lip and palate

CNS: Central nervous system

CNV: Copy number variants

CP: Cleft palate

CPT: Continuous Performance Task

EF: Executive function

FNP: Frontonasal process

FS-IQ: Full-scale IQ.

GWAS: Genome-Wide Association Studies

HCAR: Hungarian Congenital Abnormality Registry

ID: Intellectual disorder

IQ: Intelligence Quotient

LNP: Lateral nasal prominence

MD: Mean difference

MNP: Medial nasal prominence

MP: Maxillary prominence

MRI: Magnetic resonance imaging

NDD: Neurodevelopmental disorders

OFC: Orofacial cleft

OMIM: Online Mendelian Inheritance in Man database

PRI: Perceptual Reasoning Index

PRS: Pierre Robin syndrome

PSI: Processing Speed Index

SD: Standard deviation(s)

SES: Socio-economic status

SMCP: Submucous cleft palate

TOL: Tower of London

VCI: Verbal Comprehension Index

WGS: whole genome sequencing

WISC-IV: Wechsler Intelligence Scale for Children, Fourth Edition

WMI: Working Memory Index

22q11.2 DS: 22q11.2 Deletion Syndrome

# Introduction

Orofacial clefts (OFCs) are the most common congenital abnormality that affect the development of the craniofacial structures. The anomaly is characterized by the presence of a cleft on the lip and/or palate. OFCs are defined as syndromic or non-syndromic clefts and can be further classified as cleft lip (CL), cleft palate (CP), and combined cleft lip and palate (CLP). The optimal clinical care of children with OFCs is carried out by a multidisciplinary team that ensures an individualized long-term treatment plan. Specialists including pediatric surgeons, oral and maxillofacial surgeons, plastic surgeons, dentists, orthodontics, otolaryngologists, speech, and language pathologists work together on a case-by-case basis to provide carefully coordinated and well-timed interventions for these children. The multidisciplinary Cleft Team of the University of Pécs (further mentioned as the Pécs Cleft Team) has over 25 years of experience in treating this population and is an important center for cleft patient care in Hungary.

Cleft research and clinical experience both underline that syndromic and non-syndromic OFCs represent two distinct groups of patients that clinically differ in etiology, severity, timing of treatment, and prognosis. Children with syndromic OFCs often present with additional complications that affect the timing of their cleft repair including failure to thrive, feeding and respiratory difficulties. As a result, the cleft repair protocol used for non-syndromic OFCs is often altered for syndromic patients. Children with non-syndromic OFCs have a higher risk for later neuropsychiatric disabilities compared to the general population. This observed risk was explained by the presence of multiple chronic stressors present in the life of children with OFCs and their families, including repetitive cleft repair surgeries, aesthetics, and functional consequences such as speech difficulties. However, these underlying mechanisms have not been able to further explain the atypical neurodevelopment and the higher risk for mental difficulties observed in some of these children. Delays in developmental milestones, learning difficulties in preschool, and brain structural differences identified with MRI indicate a primary dysfunction of early developmental processes involving both facial and brain structures.

# Review of the literature

## Clinical classification of orofacial clefts

OFCs present as either cleft lip (CL) with or without cleft palate (CLP), or isolated cleft palate (CP) (Bjørnland et al., 2021). The International Classification of Diseases (ICD-10) classifies OFC into three groups: Group Q35 representing CP, group Q36 as CL, and group Q37 as CLP (World Health Organization., 2004).

CL can occur as uni- or bilateral-sided cleft, and can affect the lip only (i.e., isolated), or extend into the alveolus (Bjørnland et al., 2021). CLP can present as uni- or bilateral (BCLP), and CP can involve the soft and/or the hard palate (Bjørnland et al., 2021). Bifid uvula is the mildest form of CP and may be an indicator of an underlying submucous cleft palate (SMCP) (Bjørnland et al., 2021) (Figure 1/I. and Figure 1/II.).

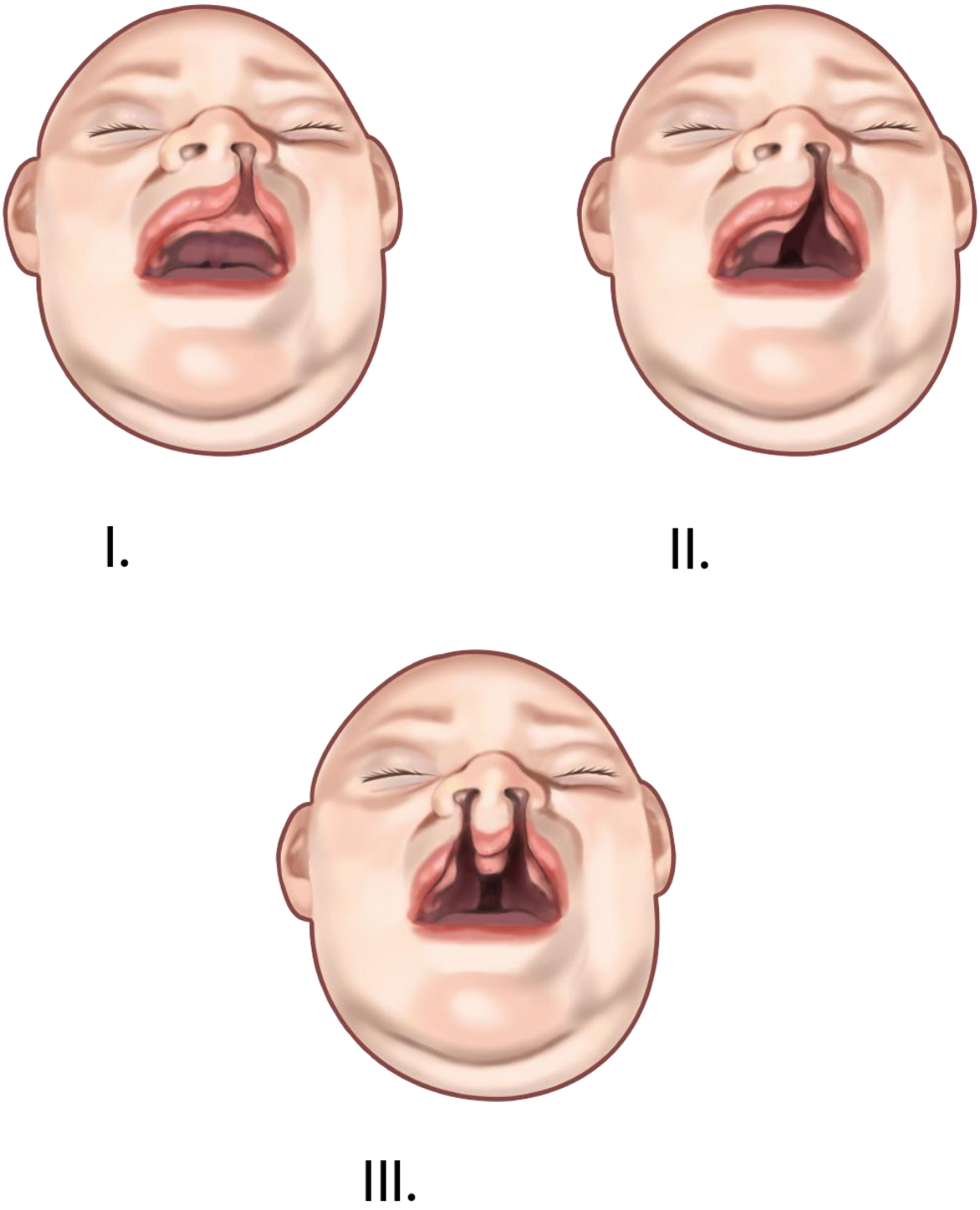


**Figure 1/I.** Types of orofacial clefts. I: unilateral cleft lip, II: unilateral combined cleft lip and palate, III: Bilateral combined cleft lip and palate.

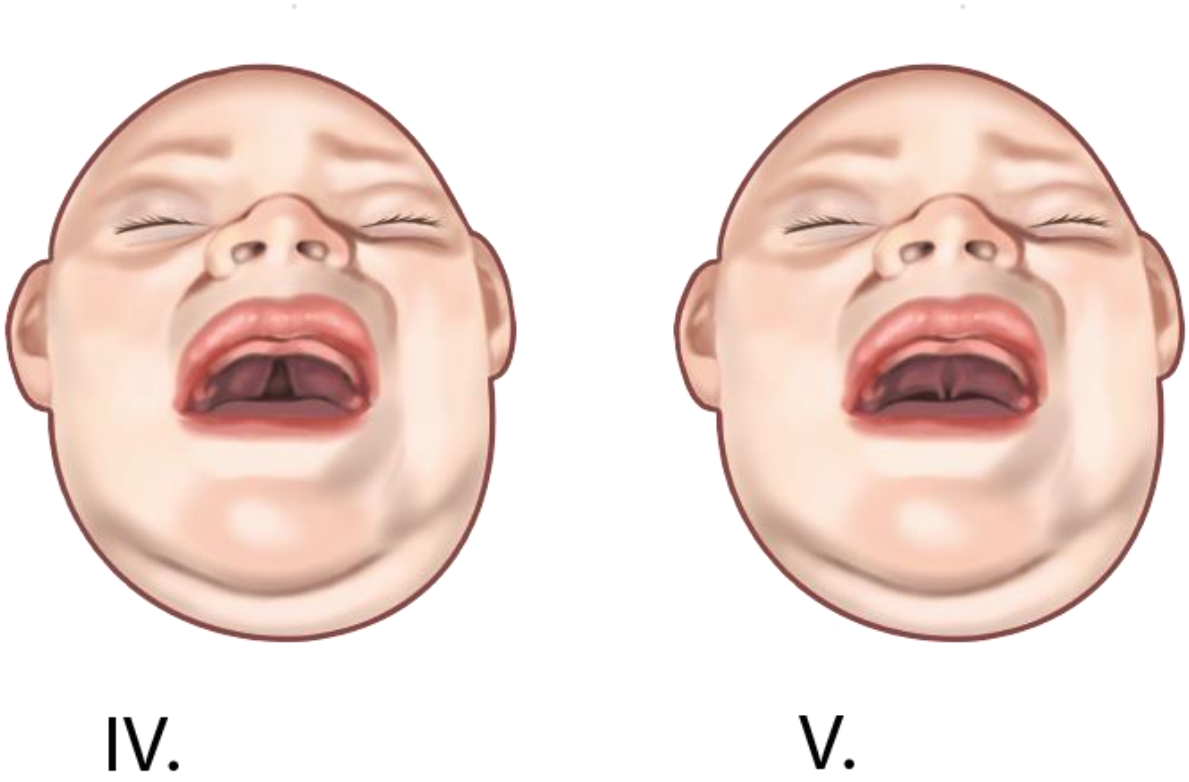


**Figure 1/II.** Types of orofacial clefts. IV: cleft palate, V: submucosal cleft palate.

## Epidemiology of orofacial clefts

Orofacial clefts are the most common congenital anomaly of the craniofacial structures (Bjørnland et al., 2021). The incidence of OFCs is 1 in 700 live births, which translates into approximately 220,000 newborns per year globally (Mossey et al., 2011). The incidence varies between countries, ethnicity, geographical and socioeconomical factors (Ji et al., 2020; Bjørnland et al., 2021). The prevalence of OFCs in Hungary is estimated to be 2.02 per 1000 live births (Ács et al., 2020). A recent study has revealed a global prevalence of 0.45 for CLP, 0.30 for CL, and 0.33 for CP (Salari et al., 2022).

In about 70% of cases, OFCs occur as isolated findings also termed as non-syndromic OFCs (Mossey and Modell, 2012; Saleem et al., 2019). A cleft is defined as syndromic when the defect is associated with monogenic or chromosomal syndromes. Syndromic OFCs represent about 30% of cleft cases (Mossey and Modell, 2012; Saleem et al., 2019). CP presents the highest prevalence of additional congenital anomalies, followed by CLP and lowest for CL (Mossey & Modell, 2012). The most common associated defects for CLP and CP include congenital heart disorders (CHD), vertebral column and limb abnormalities (Mossey & Modell, 2012). Approximately 50% of CP and 70% of CLP cases are estimated to be non-syndromic (Bjørnland et al., 2021).

The sex distribution varies according to the form of the cleft, with a male predilection for CLP and a female predilection for CP (Mossey & Modell, 2012). The explanation for these gender differences is unclear, however they may be related to the differences in timing of crucial stages in craniofacial development in utero between males and females (Mossey and Modell, 2012; Pool et al., 2021). CL is unilateral in 90% of cases with a left sided predilection, independent of severity of defect, ethnic group, or sex (Mossey and Modell, 2012; Lithovius et al., 2014; Bjørnland et al., 2021). CLP occurs bilaterally in approximately 30% of cases whereas 10% of cases in CL are bilateral (Mossey & Modell, 2012). Unilateral CL or CLP, and bilateral CLP are more common in males (Lithovius et al., 2014).

## Embryology and neural crest migration

The development of the midface occurs from the fourth until the seventh week of gestation (Ji et al., 2020). During this period, cranial neural crest cells start their ventral migration from the dorsal part of the cephalic neural tube towards the branchial arch 1 and frontonasal processes (Figure 2/I) (Ji et al., 2020). This migration is the hallmark for the commencement of craniofacial development. The upper jaw is made up of three structures at this stage: the medial (MNP) and lateral (LNP) nasal prominences, and the maxillary prominence (MP) derived from the anterior branchial arch 1 (BA1) (Ji et al., 2020). Cells of the distal part of the MNP will form intermaxillary segments that will gradually extend posteriorly into the oral cavity to form the primary palate (Li et al., 2017; Ji et al., 2020). The MP will also extend to the oral cavity to form a pair of palatal shelves (secondary palate), and these will fuse in the midline, with the nasal septum, and with the anteriorly located primary palate (Li et al., 2017; Ji et al., 2020). The posterial BA1 will develop onto the mandibulary prominences which are the primordial structures of the lower jaw (Ji et al., 2020). The primary palate will form the philtrum and the upper incisor region that is anterior to the incisive foramen. The secondary palate will develop into the rest of the hard and soft palate (Li et al., 2017). The secondary palate has therefore different embryological origins than the primary palate and the lip, which is the reason why OFCs may present as isolated cleft palate (without lip involvement) and cleft lip with or without palatal clefting (CLP) (Bjørnland et al., 2021).

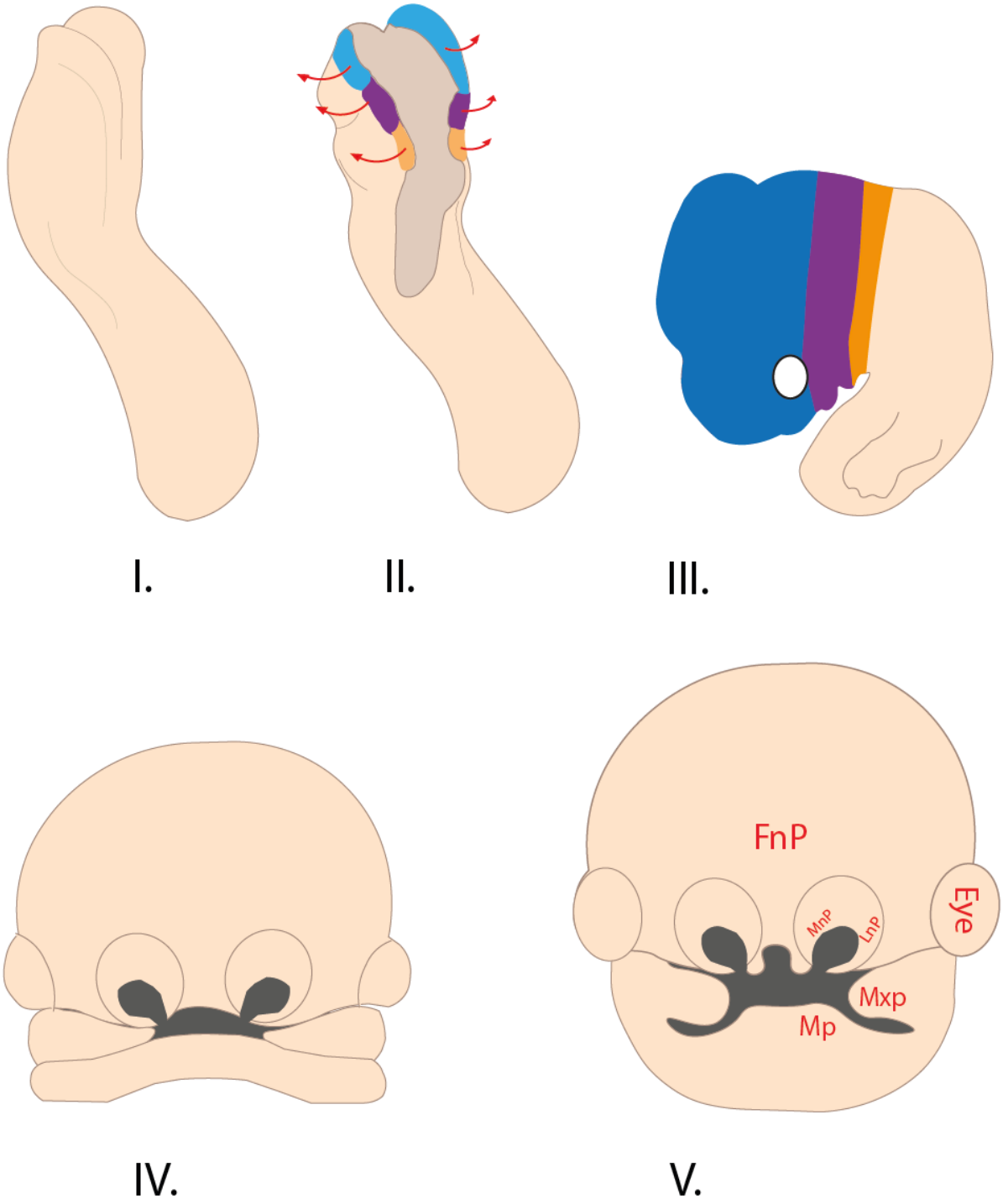


**Figure 2/I**. Summarized process of neural crest cell migration and craniofacial formation. The neural plate rises to form a neural tube, which induces the neural crest cells (I.-II.). Primordial craniofacial structures (III-IV.) further develop into the medial and lateral nasal prominences (MNP, LNP), maxillary prominences (Mxp), and mandibular prominences (Mp) (V.), FNP: Frontonasal prominence. Adapted from: (Kouskoura et al., 2011; Fitriasari and Trainor, 2021).

Neural crest cells are multipotent cells that will migrate ventrally to differentiate into cartilage, bone, neural tissue, melanocytes, and connective tissue of the craniofacial structures (Li et al., 2017; Ji et al., 2020). This migration is tightly controlled and guided by signalling pathways, including FGF/SHH, BMP, Wnt, MSX1, Folate, and TGFB (Ji et al., 2020; Alade et al., 2022). Neural crest cells will detach from the neural tube, loose their intercellular adhesions, and develop migration ability (Li et al., 2017; Ji et al., 2020). This is a particular migration that does not occur randomly, rather by migration streams (Ji et al., 2020). Wnt, Bmp, Fgf, Rho, cadherins, and Yap are important signalling molecules that give migration ability to the neural crest cells towards BA1, BA2 and FNP (Ji et al., 2020). A critical regulatory network that drives palatal development is the IRF6 gene-regulatory network, and includes genes implicated in non-syndromic OFCs (Alade et al., 2022).

Clefting occurs when the development of the premordial structures of the upper jaw is disrupted (Ji et al., 2020; Bjørnland et al., 2021). Lip development begins prior to that of the palate; however, its abnormal formation may affect the developing structures of the palate, which is the reason why cleft lip and palate show high comorbidity (Ji et al., 2020). Clefting of the lip occurs when the intermaxillary segments of the upper lip do not fuse with the nasal prominences during the sixth to seventh week of gestation (Ji et al., 2020; Bjørnland et al., 2021). The palate develops from the fifth to the 12th week of gestation, and clefting of the palate occurs when the palatal shelves fail to fuse during the eighth to 12th week of gestation (Bjørnland et al., 2021).

Disruptions may stem from neural crest cell defects including abnormal proliferation, migration, or survival; this causes an inadequate neural crest cell count once these cells reach the cephalic neural tube (Ji et al., 2020). They may also occur due to post-migratory disruptions affecting cell proliferation and apoptosis within the primordial structures (Ji et al., 2020). BA1 ensures a microenvironment that regulate the development of neural crest cells, including proliferation and differentiation. Disrupted development of these cells causes syndromic OFCs (Ji et al., 2020), which may arise due to abnormal microenvironment in the branchial arch causing signalling aberrations that lead to Van der Woude syndrome (Kondo et al., 2002), or intrinsic defects in the neural crest cells leading to Treacher Collins Syndrome (Jones et al., 2008; Ji et al., 2020).

## Genetics and inheritance

OFCs have a complex multifactorial background involving the interaction of genetic and environmental factors (Li et al., 2017; Ji et al., 2020; Bjørnland et al., 2021; Alade et al., 2022). The development of the face is a very sensitive process mediated by a coordination of genes, transcription factors, growth factors and signalling molecules (Li et al., 2017; Alade et al., 2022). Facial development is largely mediated by genetic factors, and the presence of environmental teratogens and maternal dietary factors during this process may greatly affect the critical role of these genes (Bjørnland et al., 2021). Smoking, alcohol, certain drugs, low folic acid intake, and viral infections are known maternal risk factors associated with clefting (Bjørnland et al., 2021). OFCs may show Mendelian, sporadic, or chromosomal inheritance (Bjørnland et al., 2021).

## Common syndromes occurring in orofacial clefts

There are over 500 identified OFC-related syndromes (Venkatesh, 2009; Bjørnland et al., 2021). Monogenic clefting syndromes are caused by defects involving a single gene, including Treacher Collins and Van der Woude syndrome (Venkatesh, 2009). Chromosomal clefting syndromes are caused by structural or numerical chromosomal abnormalities (Venkatesh, 2009). 22q11.2 Deletion Syndrome (22q11.2 DS) involves a deletion of 2.54 Mb size on the long arm of chromosome 22 (McDonald-McGinn et al., 2020; Venkatesh, 2009). Trisomy 13 and 21 are chromosomal syndromes with orofacial clefting (Venkatesh, 2009; Bjørnland et al., 2021). Common cases of clefting syndromes include Pierre Robin sequence (PRS), 22q11.2 DS, and Van der Woude syndrome (Venkatesh, 2009; Bjørnland et al., 2021).

Pierre Robin sequence (OMIM: 261800) occurs with the abnormal development of the lower jaw, leading to micrognathia, glossoptosis, wide u-shaped cleft of the secondary palate, and a volatile airway prone to airway obstruction (Venkatesh, 2009; Tan et al., 2013; Bjørnland et al., 2021). Feeding difficulties are also common in the neonatal period (Tan et al., 2013). Chromosomal anomalies and various syndromes are associated with the majority of PRS cases, most commonly Stickler syndrome (Tan et al., 2013; Baxter and Shanks, 2022). It is one of the most common birth defects occurring 1 in 8500 to 1 in 14000 births (Izumi et al., 2012).

22q11.2 Deletion syndrome is the most common microdeletion syndrome occurring in humans with a prevalence of 1:3000-1:6000 live births (Botto et al., 2003; Hwang et al., 2014). 22q11.2 DS (also known as DiGeorge syndrome, OMIM: 188400) presents with a wide phenotypic spectrum including neonatal hypocalcemia, thyroid abnormalities, CHD, and neuropsychiatric disorders including ADHD and schizophrenia (Cárdenas-Nieto et al., 2020; Davies et al., 2020). A recent systematic review has revealed that about 60% of cases have SMCP, 11% have isolated CP, 5% have a bifid uvula, and 2% have CLP (Cárdenas-Nieto et al., 2020).

Van der Woude syndrome (OMIM: 119300) is the most common single-gene cleft syndrome and is associated with the presence of fistulae of the lower lip forming lip pits as the hallmark of the disease (Venkatesh, 2009). It is caused by the mutation in the interferon regulatory factor-6 gene (IRF6) located on chromosome 1q32 (Schutte et al., 2021). Patients typically present with CL or CLP; however, some cases of bifid uvula and SMC have been reported (Schutte et al., 2021). The estimated prevalence is approximately 1 in 300 000 births (Schutte et al., 2021).

## Genetic basis of non-syndromic orofacial clefts

The last three decades of cleft research provided significant advancements to our understanding of the complex multifactorial etiology in non-syndromic OFCs. However, the exact etiopathogenesis still remains unclear (Alade et al., 2022). Challenges such as study replicability, inconsistent findings across affected populations, and incomplete penetrance across families make it difficult to establish a clear genetic etiology of non-syndromic OFCs (Alade et al., 2022). Most non-syndromic OFC cases are sporadic, which implies the significant role of de novo mutations in orofacial clefting (Alade et al., 2022).

Important pathways for craniofacial development harbor potential genes for orofacial clefting, including FGFR1 and FGF2 genes of the FGF/SHH pathway, AXIN1 and WNT9B of the Wnt pathway, MX1, Folate, TGFB and IRF6 regulatory network pathways (Alade et al., 2022).

With the increasing availability and use of Genome-Wide Association Studies (GWAS) in cleft research, over 40 risk loci were identified in non-syndromic OFCs (Alade et al., 2022). Further

studies were able to confirm genome-wide significance among candidate genes including GRHL3, PARK2, FOXC2/FOXL1, and IRF6 (Leslie et al., 2017; Huang et al., 2019). However, these risk loci account only for 20-30% of the overall heritability of non-syndromic OFCs (Leslie et al., 2017; Alade et al., 2022). This „missing heritability" may be due to epigenetics, rare genetic variants, and gene-gene interactions that cause non-syndromic OFCs (Alade et al., 2022).

A recent study using next generation sequencing, whole genome sequencing (WGS) found loss of function de novo mutations in three genes implicated in craniofacial development: ZFHX4, IRF6, and TFAP2A (Bishop et al., 2020; Alade et al., 2022).

Syndromic and non-syndromic OFCs may be also caused by copy number variations (CNVs) that may disrupt the function and expression of a gene, or alter its dosage (Maarse et al., 2012; Alade et al., 2022). CNV analyses of non-syndromic OFCs were able to demonstrate deletions and duplications of known candidate OFC genes, including FGF2, MAPK3, and SPRY1. Further CNV analyses found novel candidate genes including Isthmin 1 (Conte et al., 2016), KAT6B and MACROD2 (LEI et al., 2016), confirming the role of CNVs in the etiopathogenesis of non-syndromic OFCs (Alade et al., 2022).

## Mental disorders in the orofacial cleft population

Children born with syndromic OFCs frequently present with multisystem abnormalities that involve the musculoskeletal, cardiac, gastrointestinal, respiratory, urogenital, ocular, auditory and central nervous system (CNS) (Venkatesh, 2009; Junaid et al., 2022). CNS disorders including epilepsy, and neurodevelopmental disorders (NDD) such as autism spectrum disorder (ASD) and intellectual disability (ID) are common in syndromic children (Nopoulos et al., 2007b; Diaz-Stransky and Tierney, 2012; Kucukguven et al., 2018; Zinkstok et al., 2019; Junaid et al., 2022). The previously described 22q11.2 DS is a clefting syndrome with multisystem involvement and extensively studied for its associated high risk for neuropsychiatric disorders (Fiksinski et al., 2021). 22q11.2 DS is the strongest single genetic risk factor identified for schizophrenia, with 20-25% of individuals diagnosed in adulthood (van Duin et al., 2020; Fiksinski et al., 2021). ASD, ADHD, and mood disorders are also common mental illnesses among affected individuals (Fiksinski et al., 2021). The symptoms of 22q11.2 DS are highly variable, and this variability may be explained by incomplete penetrance, pleiotropy, and additional genetic factors including the size of the deletion; all consistent with pathogenic genetic variants (Fiksinski et al., 2021). 22q11.2 DS is currently emerging as a valuable model to study neuropsychiatric conditions (Davies et al., 2020; Fiksinski et al., 2021).

Individuals born with non-syndromic OFCs also have a higher risk for neuropsychiatric disorders compared to the general population (Richman et al., 2012; Tillman et al., 2018; Gallagher and Collett, 2019). ID, ASD, anxiety disorders and ADHD are commonly reported in these children (Nopoulos et al., 2010a; Pedersen et al., 2016; Ansen-Wilson et al., 2018; Tillman et al., 2018; Gallagher and Collett, 2019; Junaid et al., 2022). Neurodevelopmental delays have been documented in younger children including fine motor, gross motor, expressive and receptive language development (Conrad et al., 2008, 2021; Hardin-Jones and Chapman, 2011; Richman et al., 2012; Gallagher and Collett, 2019). These children are also at a high risk for learning disabilities (Tillman et al., 2018; Gallagher and Collett, 2019; Glinianaia et al., 2021) with an estimated prevalence of 30-46% (Richman and Ryan, 2003). Verbal language disability and speech difficulties have been among the reasons for this high rate of learning

disability (Richman and Ryan, 2003; Nopoulos et al., 2005; Gallagher and Collett, 2019). The basis of such deficits was previously explained by multiple stress factors including repetitive cleft repair surgeries, anesthesia, social stigma, aesthetics, and functional consequences such as speech difficulty (Gallagher and Collett, 2019). However, the underlying mechanisms for these deficits have not been clarified (Yang et al., 2012; Gallagher and Collett, 2019). The neurocognitive, psychosocial, and persisting functional difficulties such as speech and hearing greatly affects the quality of life of these patients (Feragen et al., 2014).

## Orofacial clefts and brain development

New advances in research have provided evidence of a unified primary dysfunction of normal brain and face development that could explain the higher rate of neuropsychiatric disorders in the non-syndromic OFC population (Yang et al., 2012; Ansen-Wilson et al., 2018; Gallagher and Collett, 2019).

Evidence of possible brain involvement in non-syndromic OFCs came from neuroimaging studies that found brain structural differences in individuals with non-syndromic OFCs compared to controls (Nopoulos et al., 2001, 2002a, 2005, 2007a, 2010a; Shriver et al., 2006; Boes et al., 2007; Weinberg et al., 2009, 2013; Chollet et al., 2010, 2014; Conrad et al., 2010; Tollefson and Sykes, 2010; Van Der Plas et al., 2010; Devolder et al., 2013; Adamson et al., 2014; DeVolder et al., 2014, 2015). Observational studies further confirmed cognitive deficits in some children with non-syndromic OFCs (Speltz, 2000; Nopoulos et al., 2002b, 2010b; Conrad et al., 2008, 2009; Hardin-Jones and Chapman, 2011; Richman et al., 2012; Bodoni et al., 2021), suggesting frontal and prefrontal cortical function impairment in some of these children (Nopoulos et al., 2010a; Adamson et al., 2014; Chollet et al., 2014).

## Cortical interneuronopathy in orofacial clefts

Cortical interneurons (cINs) are crucial for proper neurodevelopment as they regulate cortical maturation necessary for normal cognition, learning and memory (Le Magueresse and Monyer, 2013). cINs make roughly 10-25% of neurons in the neocortex, and dynamically modulate cortical activity through dual inhibitory and excitatory actions (Le Magueresse and Monyer, 2013; Ansen-Wilson and Lipinski, 2017). Impairement of cIN activity– such as altereted GABA signalling, excitatory-inhibitory imbalance, and neuronal dysfunction− are involved in many illnesses including neuropsychiatric disorders, executive function disorders, and seizures (Marín, 2012; Abbas et al., 2018; Ansen-Wilson et al., 2018; Ferguson and Gao, 2018; Pfisterer et al., 2020). Ansen-Winson et al. were among the first to provide evidence of a link between abnormal development of cINs and orofacial clefting (Ansen-Wilson et al., 2018). Their results revealed a shared developmental mechanism between primordial structures of the upper lip and palate and cINs, occuring in both molecular synchrony and spatiotemporal proximity. Primordial structures of the midface and cINs may therefore have shared sensitivities to genetic and/or teratogenic insults, such as prenatal alcohol exposure (Skorput et al., 2015). The authors further demonstrated that significant disruptions occur in the proliferation and migration of cINs in OFC (Figure 2/II) and affects specifically the somatostatin-producing subtype of GABAergic cINs. Gene expression analysis further revealed a relationship of known OFC genes with genes involved in cIN development. Altogether, these results provided findings for a unified maldevelopment of cIN and orofacial clefting that may explain the observed higher rate of neuropsychiatric illnesses across the non-syndromic OFC population (Ansen-Wilson et al., 2018).

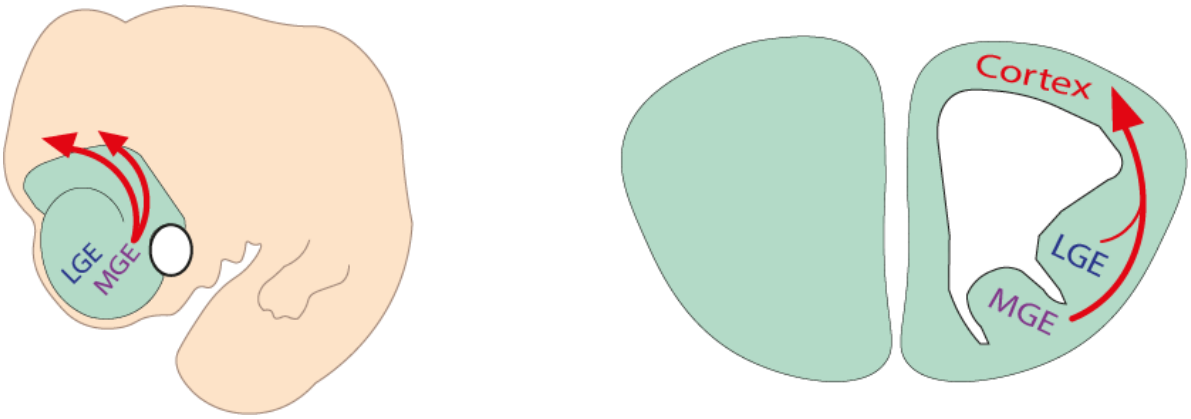


**Figure 2/II.** Migration of future cortical interneurons (cINs). Cells that arise from the medial ganglionic eminence (MGE) and the lateral ganglionic eminence (LGE) of the telencephalon (green) will migrate towards the cortex and develop into interneurons. Disruptions occur in the proliferation and migration of cINs in OFCs and affects specifically the somatostatin-producing subtype of GABAergic cINs which originate from the MGE (Ansen-Wilson et al., 2018). Adapted from (Goffinet, 2006).

# List of original publications

Study I

Sándor-Bajusz KA, Maros TB, Olasz L, Sándor GK, Hadzsiev K, Vástyán AM. The Influence of Genetic Syndromes on the Algorithm of Cleft Lip and Palate Repair - A Retrospective Study. Ann Maxillofac Surg. 2021 Jul-Dec;11(2):270-273. doi: 10.4103/ams.ams_77_21.

Study II

Sándor-Bajusz KA, Dergez T, Molnár E, Hadzsiev K, Till Á, Zsigmond A, Vástyán A, Csábi G. Cognitive functioning and clinical characteristics of children with non-syndromic orofacial clefts: A case-control study. Frontiers in Psychology. 2023 Feb 28;14:1115304. doi: 10.3389/fpsyg.2023.1115304.

Study III

Sándor-Bajusz KA, Sadi A, Varga E, Csábi G, Antonoglou GN, Lohner S. The Brain in Oral Clefting: A Systematic Review with Meta-Analyses. Frontiers in Neuroanatomy. 2022 Jun 10;16:863900. doi: 10.3389/fnana.2022.863900.

# Aims

The aim of the current thesis work was to analyze the clinical and mental outcomes of children born with orofacial clefts (OFCs).

The first study aimed to identify Hungarian syndromic OFC patients and evaluate how their genetic syndrome influenced the timing of the algorithm of cleft repair surgeries.

The second study aimed to identify a subpopulation of Hungarian children with non-syndromic OFCs that are at risk for abnormal neurodevelopment by assessing their developmental history and present cognitive functioning.

The final study aimed to summarize the available evidence on potential brain structural differences in individuals with non-syndromic OFCs and their matched controls.

# Materials, methods, and statistical analysis

## Study I

### Participants

The records of syndromic and non-syndromic CLP patients managed by the Pécs Cleft Team between January 1999 and December 2015 were analyzed retrospectively. Detailed clinical documentation of all patients, including genetic and epidemiological data, was required for inclusion in the study.

### Data collection and statistical analyses

The data were collected retrospectively without personal identifying details. Special permission was obtained and granted for data collection from the Hungarian Congenital Abnormality Registry (HCAR). The Ethics Committee of the University of Pécs waived the need for ethical approval and the need to obtain consent for this study. The reason for this waiver was the retrospective nature of this study and the anonymized nature of the data used in the study. All procedures performed in the study were conducted in accordance with the ethics standards given in the 1964 Declaration of Helsinki, as revised in 2013.

The Online Mendelian Inheritance in Man database (OMIM) was used to identify the genetic syndromes. Epidemiological data were obtained from the HCAR. Special emphasis was placed on the syndromic features of the patients and their associated anomalies. The timing of the CL and/or CLP repair was recorded and was compared with the algorithm used for non-syndromic cleft patients. The type and timing of the surgeries or interventions unrelated to the clefts were listed and categorized. The study used descriptive statistics consisting of percentages and frequencies of the surgical interventions, presenting syndromes and participants of the study.

# Study II

## Participants

A single-center, case-controlled study was carried out at the Department of Pediatrics of the University of Pécs between July 2020 and March 2022. The study was approved by the Regional Ethics Committee of the University of Pécs (approval number: 7967-PTE 2020) and was performed according to the principles of the Declaration of Helsinki. All participating children with non-syndromic OFCs were patients of the Pécs Cleft Team. Medical geneticists examined all participants of the cleft group to rule out the presence of additional congenital malformations and/or underlying syndromes. Controls were recruited from the community of Baranya County, specifically from public elementary, high schools, and post advertisements on social media. The inclusion criteria for the OFC group consisted of the following: children with non-syndromic forms of OFC, 6–16 years old and an IQ ≥ 70. An OFC was considered non-syndromic when the cleft was the only single malformation without additional physical or developmental anomalies (Bjørnland et al., 2021). The inclusion criteria of the controls included the following: healthy children born without OFCs, 6–16 years old and IQ ≥ 70.

## Materials

The study consisted of three phases including questionnaires to collect retrospective clinical data and psychometric tools to assess executive functioning and Intelligence Quotient (IQ). Initially all psychometric tests were completed on site. The study was converted into an online platform due to restrictions related to the ongoing COVID-19 pandemic at the time. Measurements that required in-person completion (IQ test) were postponed onto a later period once the pandemic situation improved.

The Hungarian version of the Child Behavior Checklist (CBCL) was used to screen for behavioral and emotional problems in children and adolescents for the previous six months (Achenbach, 1991; Rózsa S et al., 1999). A parental questionnaire was developed for the study to collect demographic data (Appendix 1). This included prenatal and postnatal history, birth, motor and language development, education, previous psychiatric treatment, and history of somatic and neuropsychiatric disorders. Parental socio-economic data were additionally collected, including parental age, education, and employment status. Parents were also asked about a possible family history of neuropsychiatric disorders and/or any previous psychiatric treatment.

Four computer-based tests were used to assess the main domains of executive functioning. All tests were provided by the Psyway Hungarian psychometric website and all tests are standardized and norm-referenced (PsyWay, 2020). The official Hungarian version of the WISC-IV (Nagyné Réz et al., 2007) was used to measure full-scale IQ, which was important for the assessment of executive functioning (Grizzle, 2011; Ardila, 2018). Each cognitive test is summarized in Table 1.

**Table 1.** Cognitive tests used in the study to measure executive functioning.

| **Cognitive test** | **EF domain(s) measured** | **Main outcome measures used in the study** |
|---|---|---|
| Stroop test | Cognitive flexibility(Diamond, 2013; Parris, 2014; Scarpina and Tagini, 2017) | Inhibition of cognitive interference: speed and accuracy of the response |
| Tower of London | Planning ability and working memory (Bull et al., 2004; Unterrainer et al., 2004; Kaller et al., 2011; Naidoo et al., 2019) | Total correctly solved trials, total rule violation, mean execution time, average number of trials and weighted performance score |
| Corsi Block-Tapping Test | Visuo-spatial working memory (Kessels et al., 2000; Brunetti et al., 2014) | Block-span |
| Continuous Performance Task | Attention (Conners, 2014; Roebuck et al., 2016) | Detectability (%), omissions (%) and commissions (%) |

## Statistical analysis

Statistical analysis was carried out using IBM SPSS Statistics 28 Software. A descriptive statistical analysis was performed. The primary aim of the analysis was to compare the differences in the results of cognitive test for executive function assessment (London Tower, Stroop, Corsi, and Continuous Performance Test), IQ (WISC-IV), the CBCL questionnaire (Child Behavior Checklist), and the demographic parameters between the two study groups.

Occupational statuses of the parents were classified as follows: employed, not employed, or retired. Academic levels of the parents were initially grouped into basic (elementary, lower secondary education), intermediate (upper secondary) and advanced (college or university). We later grouped these levels as either higher education (upper secondary education, college, or university) or lower education (elementary, lower secondary education) to increase statistical power.

The raw score is an untransformed score from a measurement of the above listed cognitive tests and the CBCL questionnaire. The raw scores were converted into a scale called T-score scale, which assumes a normal distribution with the mean = 50 and the standard deviation = 10. The T-scores of all psychometric tests were expressed as means ± standard deviations. The categorical data of the cleft and control groups were analyzed using contingency tables and the chi-squared or Fischer's test, as appropriate. For quantitative variables, two-sided independent samples Student's t-test were used. The Welch test was applied in cases when the variance was not homogenous. Analysis of variance (ANOVA) was used to test the difference among more than two groups (e.g., in case of analysis based on the type of cleft). These variables follow a normal distribution. Statistical significance was established as a value of $p < 0.05$. Effect sizes were defined as Cohen's d value in case of two independent groups, $\eta 2$ in case of ANOVA test, and $\phi$ value in case of Chi-square test (Coe, 2002).

# Study III

## Materials

The current meta-analysis was registered in PROSPERO (International Prospective Register of Systematic Reviews; RRID:SCR_019061, identifier CRD42020167773), and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020, RRID:SCR_018721) guideline (Page et al., 2021).The data that was retrieved and analysed for this study was initially acquired by primary investigators who obtained informed consent from participants. Ethical approval was therefore deemed not necessary for the current study.

## Database searches

MEDLINE, Scopus, Cochrane Central Register of Controlled Trials, Web of Science and Embase were systematically searched in September 2020 for case-control studies that reported structural brain MRI in individuals with non-syndromic OFCs and healthy controls.

## Study selection and data extraction

The following criteria had to be met for inclusion into the study: (1) Case-control studies with humans; (2) Individuals with non-syndromic (isolated) OFCs, without restriction to age; (3) Healthy controls; (4) Structural brain differences of individuals with non-syndromic OFCs vs. their controls as a relevant outcome: structural differences had to be explored with brain MRI. No restrictions were applied for language. The publication was excluded if it had any of the following: (1) Animal studies (2) Individuals with syndromes (syndromic forms of OFCs, such as Pierre-Robin sequence or Velocardiofacial syndrome).

Two review authors independently screened studies for eligibility, extracted data and assessed risk of bias with the Newcastle-Ottawa Scale (Wells et al., 2000). Any differences between the two reviewers were settled by consensus after consulting a third author. Additional sources were also screened (hand searching, reference/citation lists) to identify articles that may potentially meet the inclusion criteria. Study setting (design, institution, country), patient demographics (number, age, sex, ethnicity, gender, type of OFCs, brain imaging details, data processing) and outcome measurement details (general and regional brain MRI measurements) were collected. Any data that were not described in the article were calculated from existing data or were obtained by contacting the authors.

The primary outcome measures were structural differences of the brain of individuals with OFCs vs. individuals without OFCs (controls) investigated via MRI. Other sought outcomes included the correlation between observed structural brain differences and alterations in neurological and/or mental functioning.

Statistical analysis

Review Manager Software Version 5.4 was used for data synthesis (Cochrane, 2020). The random-effects model was chosen a priori as the primary method to estimate all pooled estimates for studies that were comparable in design, exposure, and outcomes. This model was used to account for the differences within study populations such as age, sex, and type of OFCs. Mean Differences (MDs) and their corresponding 95% confidence intervals (CI 95%) were used for continuous outcomes.

The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots and by calculating the tau-squared and the I-squared statistics, respectively. The I-squared thresholds represented heterogeneity that may not be important (0–40%), moderate (30–60%), substantial (50–90%), or considerable (75–100%). Possible sources of heterogeneity in meta-analyses were sought through pre-specified mixed-effects subgroup analyses if at least two studies were included for a comparison (same intervention/outcome). Pre-defined subgroup analyses included: (i) age; (ii) sex; (iii) ethnicity; (iv) cleft form (non-syndromic vs. syndromic).

# Results

## Study I

Syndromes and cleft types

A total of 607 patients were managed by the cleft team during the study between 1999 and 2015. Among the patients, 25 children (4.1%) had associated anomalies and sixteen patients (2.6%) were noted to be afflicted with a particular identifiable syndrome. Ten patients (60%) were boys and six (40%) were girls of the syndromic CLP group. The majority of the syndromic CLP patients had CP only (n = 13, 81%). Seven different genetic syndromes and one sequence were present in the study. The Pierre Robin sequence occurred most often, comprising 50% of the cohort. The other syndromes observed in the cohort included: Smith-Lemli Opitz syndrome, Dandy–Walker syndrome, DiGeorge syndrome, Ectrodactyly-ectodermal dysplasia-clefting syndrome, Treacher Collins syndrome, Turner syndrome, and Weissenbacher–Zweymüller syndrome (Figure 3).

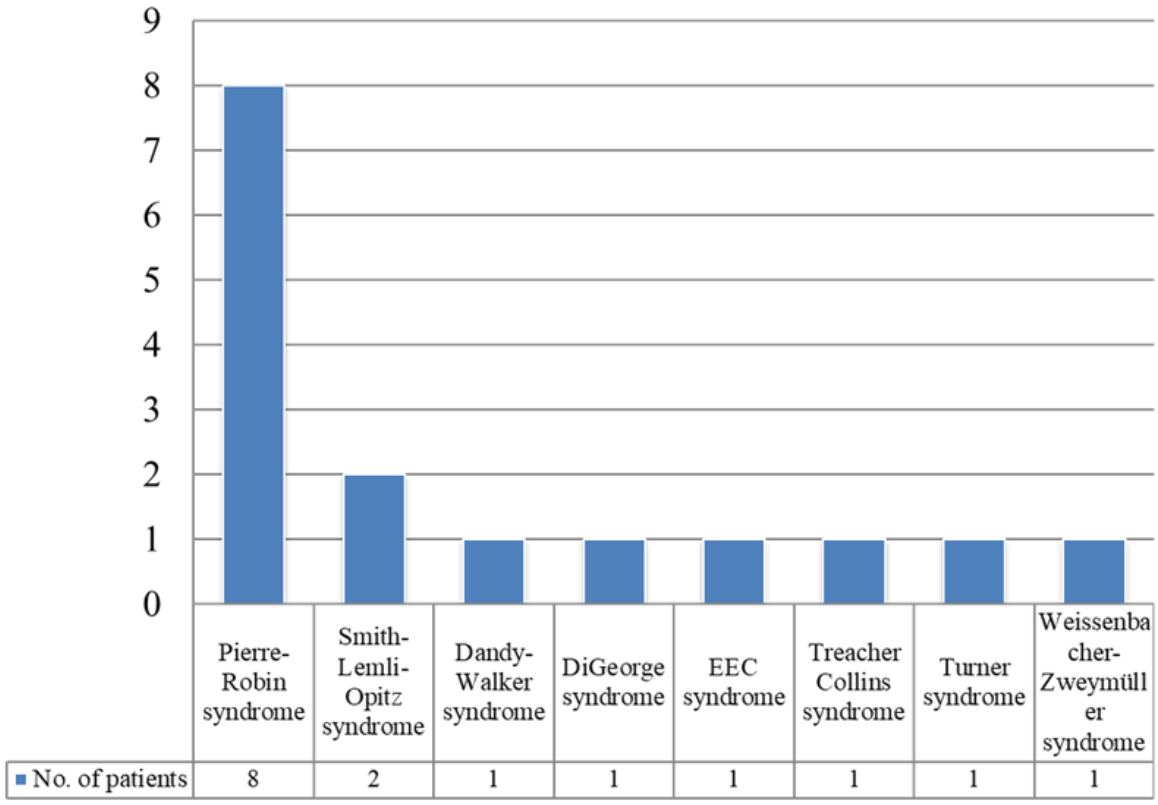


**Figure 3.** The distribution of the eight genetic syndromes present in the cohort (*Sándor-Bajusz, Maros, Olasz et al.*, Annals of Maxillofacial Surgery, 2021).

Modified treatment algorithm

The treatment algorithm used by the PCT in managing non-syndromic clefts required modification in 13 of the 16 syndromic patients (81%). The timing of the cleft repair procedure in the syndromic cohort is illustrated in Figure 4. There were notable delays in the timing of the palate repair in syndromic patients. In two syndromic patients, the palatoplasty procedure was completed much later, at four years of age. In addition, 15 patients underwent additional surgeries due to the presence of the syndromes and associated medical conditions, including heart and urogenital tract diseases (Figure 5). These operations had of necessity priority over cleft repair. Tracheostomies were needed in three patients with PRS. Secondary operations for CLP were required in six patients (37.5%). Speech improvement operations or pharyngoplasty and tympanostomy tube placements were the most common secondary operations and were mainly required by PRS patients.

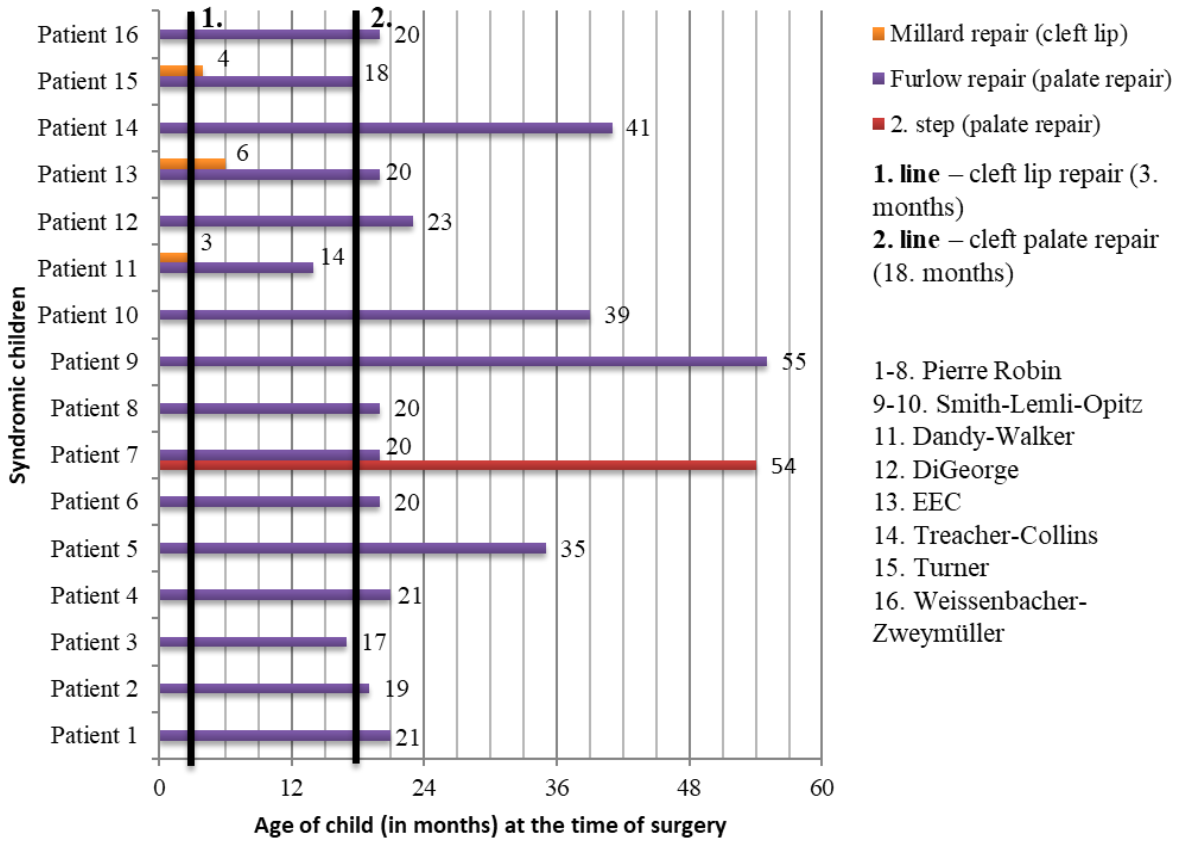


**Figure 4.** The timing of the cleft repair surgery for syndromic patients (*Sándor-Bajusz, Maros, Olasz et al.*, Annals of Maxillofacial Surgery, 2021).

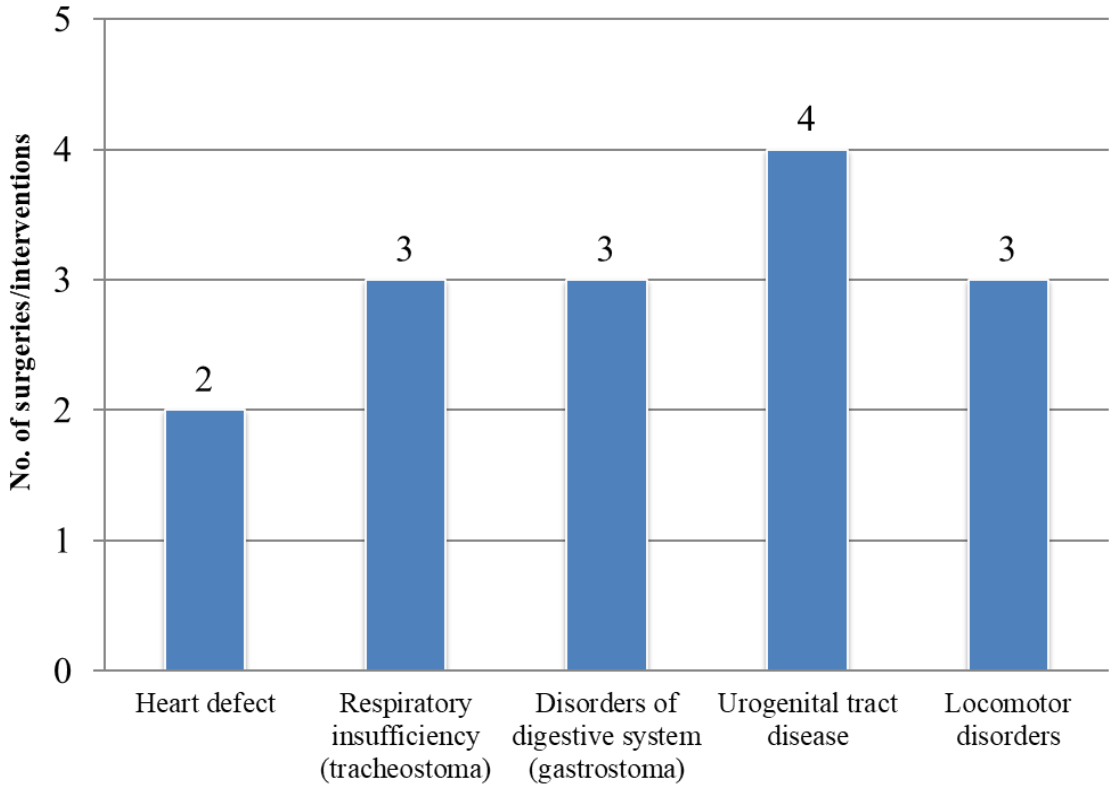


**Figure 5.** The distribution of additional surgeries for the affected organ system(s) for syndromic patients (*Sándor-Bajusz, Maros, Olasz et al.*, Annals of Maxillofacial Surgery, 2021).

# Study II

We recruited 43 children with non-syndromic OFCs and 44 controls for the study. Past medical history revealed two syndromic OFCs and these participants were excluded from the study. One participant of the cleft group was lost to follow up. The data of 84 study participants were analyzed (Figure 6).

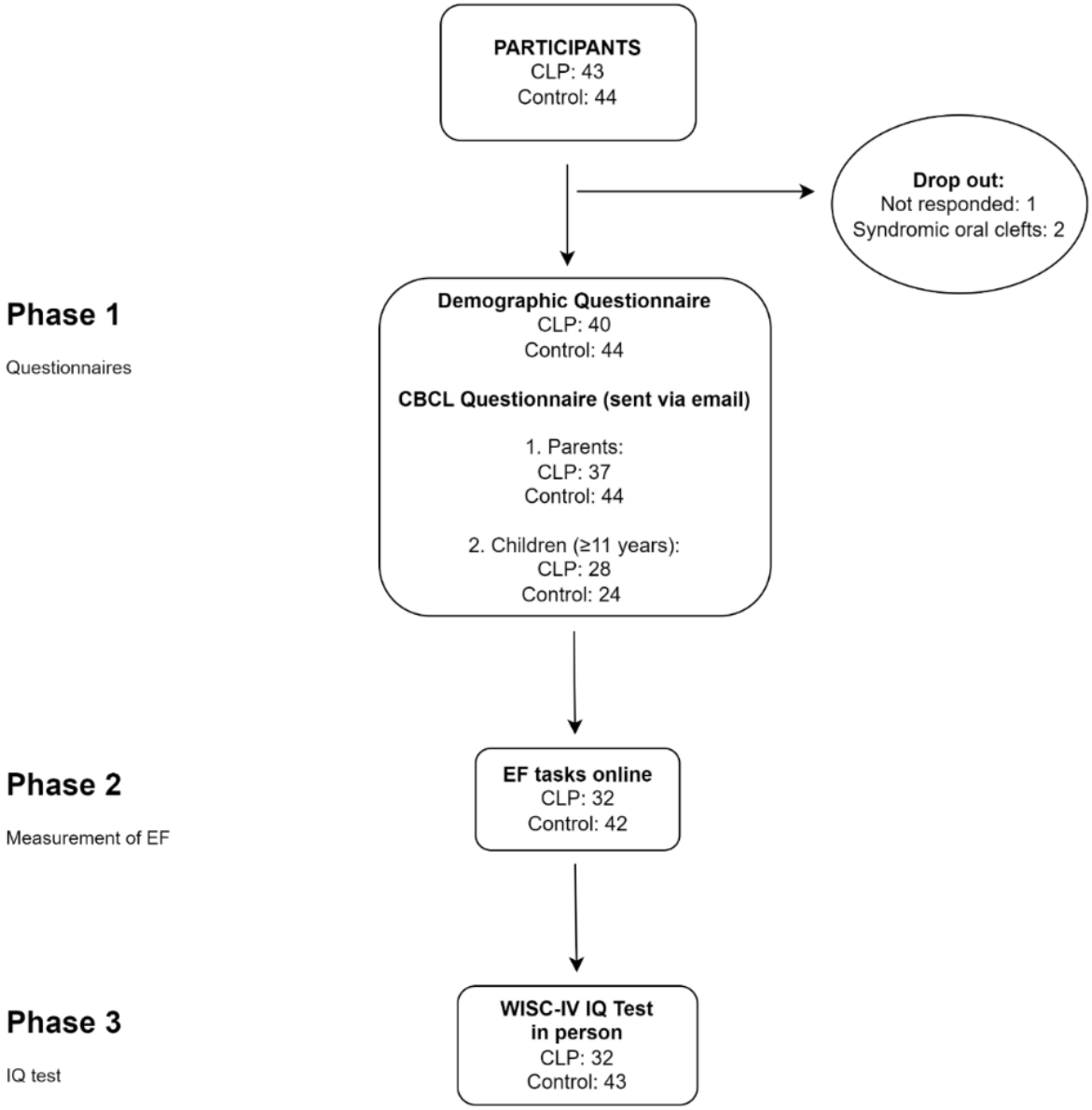


**Figure 6.** Study flow. The analyses were divided into three phases. The number of the participants are provided for each phase (CLP: cleft lip and/or palate group, EF: Executive function, IQ: Intelligence Quotient) (*Sándor-Bajusz, Dergez, Molnár, et al.,* Frontiers in Psychology, 2023).

Child Behavioral Checklist

Two dimensions of the Self-Report CBCL showed significant differences between the groups: Cleft children reported higher symptoms of affective problems, while controls reported greater symptoms of externalization, somatic, attention, oppositional, and behavioral problems. (Table 2). Parents of controls reported higher symptoms across all scales of the CBCL compared to parents of the cleft group, with small effect sizes (Table 3).

**Table 2.** Results of the CBCL Self-Report. Data are presented as means and standard deviations (SD) (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **Scales** | **Group** | ***n*** | **Mean±SD** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **Internalization** | Control | 28 | 52.57±10.57 | 0.64 | 0.13 |
| | Cleft | 24 | 54.17±14.00 | | |
| **Externalization** | Control | 28 | 53.29±8.68 | 0.024* | 0.65 |
| | Cleft | 24 | 47.83±8.05 | | |
| **Affective problems** | Control | 28 | 50.39±8.42 | 0.39 | 0.24 |
| | Cleft | 24 | 53.08±13.10 | | |
| **Anxiety** | Control | 28 | 49.50±10.16 | 0.69 | 0.11 |
| | Cleft | 24 | 50.71±11.75 | | |
| **Somatic problems** | Control | 28 | 51.60±11.54 | 0.46 | 0.21 |
| | Cleft | 24 | 49.42±9.37 | | |
| **Attention deficit/hyperactivity** | Control | 28 | 54.89±10.83 | 0.24 | 0.33 |
| | Cleft | 24 | 51.67±8.29 | | |
| **Oppositional defiance** | Control | 28 | 54.25±10.60 | 0.048* | 0.56 |
| | Cleft | 24 | 48.13±11.15 | | |
| **Behavioral problems** | Control | 28 | 51.32±7.61 | 0.19 | 0.37 |
| | Cleft | 24 | 48.46±7.90 | | |

**Table 3.** Results of the CBCL Parental Report. Data are provided in means (M) and standard deviations (SD) (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **Scales** | **Group** | ***n*** | ***M*±*SD*** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **Internalization** | Control | 44 | 54.15±15.70 | | |
| | Cleft | 37 | 51.51±10.08 | 0.31 | 0.23 |
| **Externalization** | Control | 44 | 50.18±7.72 | | |
| | Cleft | 37 | 47.49±8.36 | 0.15 | 0.32 |
| **Affective problems** | Control | 44 | 54.98±14.42 | | |
| | Cleft | 37 | 52.57±10.26 | 0.35 | 0.21 |
| **Anxiety** | Control | 44 | 51.16±13.44 | | |
| | Cleft | 37 | 49.78±9.56 | 0.54 | 0.12 |
| **Somatic problems** | Control | 44 | 54.91±14.64 | | |
| | Cleft | 37 | 54.12±13.09 | 0.74 | 0.08 |
| **Attention deficit/hyperactivity** | Control | 44 | 52.49±12.04 | | |
| | Cleft | 37 | 49.97±8.06 | 0.31 | 0.23 |
| **Oppositional defiance** | Control | 44 | 51.27±9.82 | | |
| | Cleft | 37 | 47.54±9.51 | 0.11 | 0.36 |
| **Behavioral problems** | Control | 44 | 49.29±6.79 | | |
| | Cleft | 37 | 47.38±7.62 | 0.25 | 0.26 |

## Demographic data of children

### Cleft status

Three subtypes of OFCs were present in the cleft group: 45% with cleft lip and palate (CLP), 37.5% with cleft lip (CL) and 17.5% with cleft palate (CP). Left-sided (32.5%) and bilateral (32.5%) OFCs were the most common. Overall, 29.16% of the cleft group reported their repaired OFCs as a current medical condition. All participants of the cleft group had repaired clefts, and none of these children had persistent hearing deficiency. More than half of the cleft group was represented by boys (56.6%), while controls had more girl participants (67.7%, $p = 0.031$, $\phi = 0.24$). There were no significant differences between the age of cleft versus controls (Table 4).

**Table 4.** Demographic data of the study groups. Data are presented as means and standard deviations (SD). The number of participants is provided for each variable (n). Units are provided for each measurement. Overall academic score was provided according to the 5-point grade system used in Hungary, which defines 1 as insufficient, 2 as sufficient, 3 as satisfactory, 4 as good, and 5 as excellent (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **Variable** | **Cleft group (mean ± SD)** | ***n*** | **Control group (mean ± SD)** | ***n*** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|---|
| **Age** | 12.00±2.62 | 39 | 11.77±2.63 | 44 | 0.69 | 0.09 |
| **Education** | | | | | | |
| Academic year | 6.17±2.38 | 39 | 6.06±2.75 | 44 | 0.99 | 0.04 |
| Overall academic score | 4.45±0.51 | 38 | 4.46±0.58 | 43 | 0.95 | 0.02 |
| **Birth** | | | | | | |
| Week of delivery | 38.97±2.19 | 39 | 39.20±1.62 | 44 | 0.59 | 0.12 |
| APGAR score 1 | 8.88±0.62 | 36 | 8.97±0.52 | 41 | 0.58 | 0.16 |
| APGAR score 2 | 9.77±0.59 | 36 | 9.97±0.15 | 41 | 0.031* | 0.48 |
| Birth weight (g) | 3414.87±614.58 | 39 | 3488.31±618.23 | 44 | 0.59 | 0.12 |
| Birth height (cm) | 51.76±4.08 | 38 | 50.43±3.32 | 44 | 0.11 | 0.36 |
| Head circumference (cm) | 34.75±1.51 | 16 | 34.43±1.90 | 30 | 0.57 | 0.19 |
| **Motor development** | | | | | | |
| Rolls over (months) | 3.97±0.93 | 39 | 4.17±1.02 | 40 | 0.37 | 0.20 |
| Sits (months) | 6.50±1.55 | 38 | 7.29±2.00 | 41 | 0.06 | 0.44 |
| Crawls (months) | 8.61±1.74 | 38 | 8.47±1.80 | 41 | 0.73 | 0.08 |
| Walks (months) | 11.88±1.38 | 39 | 12.02±1.64 | 43 | 0.68 | 0.09 |
| Potty-trained (years) | 2.71±0.84 | 39 | 2.34±0.54 | 42 | 0.008* | 0.53 |
| **Language development** | | | | | | |
| First words (months) | 15.00 ±7.65 | 39 | 13.50±4.83 | 37 | 0.53 | 0.23 |
| Two-word phrases (months) | 24.43±9.77 | 38 | 19.52±6.11 | 34 | 0.039* | 0.60 |
| Coherent sentences (year) | 2.50±0.75 | 38 | 2.22±0.59 | 38 | 0.055 | 0.41 |
| **Parental SES** | | | | | | |
| Gravidity of mother | 2.44±1.37 | 39 | 2.66±1.94 | 44 | 0.99 | 0.13 |
| Mother's age | 42.79±4.43 | 39 | 44.67±4.57 | 43 | 0.063 | 0.42 |
| Father's age | 45.71±5.06 | 39 | 48.13±5.24 | 43 | 0.037* | 0.47 |

## Past psychiatric history and academic performance

We observed a higher proportion of psychiatric disorders in the cleft group (15%) compared to controls (4.5%; $p = 0.14$, $\phi = 0.18$). The cleft group received previous psychiatric therapy more often (15%) than controls (0%; $p = 0.009$, $\phi = 0.29$). The reported psychiatric diagnoses were ADHD (50%), borderline personality disorder (12.5%), learning disability (12.5%), depression (12.5%) and anxiety disorder (12.5%). Children in the cleft group required additional support for learning, psychological and physical well-being during their education more often than controls ($p < 0.001$, $\phi = 0.49$), specifically speech and language therapy ($p < 0.001$, $\phi = 0.51$). Overall, 4.5% of controls reported having a psychiatric comorbidity, which included dyslexia (50%) and ADHD (50%).

Preschool integration was significantly more difficult for the cleft group compared to controls ($p = 0.025$, $\phi = 0.26$). Both study groups did well later in preschool without requiring grade repetition ($p = 0.96$, $\phi = 0.005$). Children of the cleft group were examined by pedagogical professional services more often than controls ($p < 0.001$, $\phi = 0.49$). Participants in the cleft group required special education plans more often than controls ($p = 0.016$, $\phi = 0.29$). There were no differences in the rate of elementary grade repetition between clefts and controls ($p = 0.60$, $\phi = 0.073$). We observed no differences in the overall academic score; both clefts and controls achieved a good overall score in the current academic year (Table 4).

## Pregnancy and developmental history

All participating children were born full-term via uncomplicated births. Apgar score at 5 min was lower in the cleft group ($p = 0.031$, $d = 0.48$, Table 4). No differences were observed in the total number of pregnancies, and natural and caesarian delivery ($p = 0.63$, $\phi = 0.05$). No differences were observed in the week of delivery, head circumference and birthweight between the two study groups (Table 4). The need for postnatal supportive care did not differ between clefts and controls (respiratory support, surfactant therapy, phototherapy, antibiotics, and transfusions; $p = 0.23$, $\phi = 0.13$).

Mothers of the cleft group reported feeding ($p = 0.007$, $\phi = 0.29$) and hearing ($p < 0.001$, $\phi = 0.51$) difficulties more often than mothers of controls. The cleft group developed motor skills (roll over, sitting) later than controls, however the effect sizes were small (Table 4). The cleft group was potty trained at an older age than controls ($p = 0.008$, $d = 0.53$, Table 4). Parents of the cleft group reported that their children were able to form two-word sentences at a later age compared to reports of parents of controls ($p = 0.039$, $d = 0,60$, Table 4). First words and coherent sentences were also spoken later by children in the cleft group (Table 4).

## Demographic data of parents

Parents of the control group were older at the time of assessment than those of the cleft group (Table 4). Most parents of clefts (70.0%) and controls (69.8%) were married, and no differences were observed between the relationship statuses of parents of both groups ($p = 0.47$, $\phi = 0.08$). The employment statuses of fathers ($p = 0.42$, $\phi = 0.25$) and mothers ($p = 0.86$, $\phi = 0.19$) did not differ between the two groups.

## Past psychiatric and academic history

The majority of reported psychiatric diagnoses in the family of the cleft group were depression (75%) and anxiety disorders (25%). History of psychiatric disorders was more often reported by parents of controls (27.3%) compared to clefts (7.5%; $p = 0.010$, $\phi = 0.39$). One parent of the control group reported to have history of anxiety, but most parents did not further specify

these conditions. Fathers of the control group achieved a higher degree of education than fathers of the cleft group who had lower secondary education ($p = 0.024$, $\phi = 0.25$). There were no differences in the mother's level of education between the two study groups ($p = 0.29$, $\phi = 0.12$). Most parents completed high school and/or had a university degree.

Cognitive functioning

The CPT revealed differences between the two groups: the cleft group scored lower on detectability (%) than controls ($p = 0.022$, $d = 0.55$, Table 5). They also missed more targets than controls ($p = 0.058$, $d = 0.46$, Table 5). We did not observed differences for the remaining cognitive test results (Tables 6–8). Controls scored higher on the PRI and WMI subtests of the IQ test (Table 9). None of the participants scored below average in any of the dimensions of the WISC-IV.

**Table 5.** Results of the CPT (Continuous Performance Task). Data are presented as means and standard deviations (SD) (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **Performance measures** | **Group** | ***n*** | **Mean±SD** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **Detectability (%)** | control | 41 | 59.46±14.90 | 0.022* | 0.55 |
| | cleft | 32 | 51.03±15.66 | | |
| **Omission errors (%) (missed targets)** | control | 41 | 59.54±13.00 | 0.058 | 0.46 |
| | cleft | 32 | 53.84±11.84 | | |
| **Commission errors (%) (false response without target)** | control | 41 | 52.00±12.21 | 0.47 | 0.17 |
| | cleft | 32 | 54.28±14.49 | | |

**Table 6.** Results of the Stroop test. Data are provided in means (M) and standard deviations (SD) (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **Interference** | ***Group*** | ***n*** | ***M*±*SD*** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **Speed** | control | 42 | 48.93±6.66 | 0.48 | 0.16 |
| | cleft | 32 | 47.67±8.59 | | |
| **Accuracy** | control | 42 | 46.21±14.63 | 0.28 | 0.26 |
| | cleft | 32 | 49.72±12.52 | | |

**Table 7.** Corsi Block Span Test. Data are provided in means (M) and standard deviations (SD) (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **Performance measure** | **Group** | ***n*** | ***M*±*SD*** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **Block Span** | control | 42 | 53.67±11.39 | 0.50 | 0.16 |
| | cleft | 32 | 55.38±9.60 | | |

**Table 8.** Results of the TOL (Tower of London Task). Data are provided in means (M) and standard deviations (SD) (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **Performance measures** | **Group** | ***n*** | ***M*±*SD*** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **Total correctly solved trials** | control | 40 | 49.03±11.88 | 0.70 | 0.09 |
| | cleft | 31 | 47.81±14.84 | | |
| **Total rule violation** | control | 40 | 49.03±11.88 | 0.77 | 0.07 |
| | cleft | 31 | 49.90±12.88 | | |
| **Mean execution time** | control | 40 | 37.53±15.84 | 0.97 | 0.01 |
| | cleft | 31 | 37.35±16.41 | | |
| **Average number of trials** | control | 40 | 41.18±14.68 | 0.51 | 0.16 |
| | cleft | 31 | 43.48±14.38 | | |
| **Weighted performance score** | control | 40 | 54.93±11.73 | 0.83 | 0.05 |
| | cleft | 31 | 54.32±11.18 | | |

**Table 9**. The IQ scores of both study groups. Data are provided in means (M) and standard deviations (SD). All four indexes of the IQ were measured, and a full-scale IQ (FS-IQ) score is provided below (VCI: Verbal Comprehension Index, PRI: Perceptual Reasoning Index, WMI: Working Memory Index, PSI: Processing Speed Index) (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| | **Group** | ***n*** | ***M*±*SD*** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **Age** | Control | 43 | 11.60±2.74 | 0.48 | 0.17 |
| | Cleft | 32 | 12.03±2.39 | | |
| **VCl** | Control | 43 | 116.91±10.75 | 0.66 | 0.10 |
| | Cleft | 32 | 115.72±12.35 | | |
| **PRI** | Control | 43 | 109.16±12.90 | 0.35 | 0.22 |
| | Cleft | 32 | 106.63±9.60 | | |
| **WMI** | Control | 43 | 107.12±13.87 | 0.29 | 0.25 |
| | Cleft | 32 | 103.78±12.47 | | |
| **PSI** | Control | 43 | 102.88±10.00 | 0.59 | 0.12 |
| | Cleft | 32 | 104.22±11.47 | | |
| **FS-lQ** | Control | 43 | 112.72±12.05 | 0.49 | 0.16 |
| | Cleft | 32 | 110.81±11.12 | | |

Subgroup analysis of the cleft group

We hypothesized that the more complex cleft subtypes would obtain lower scores on the IQ test, and present with a history of atypical neurodevelopment, psychiatric disorders, and academic difficulties. We further assumed that early interventions for speech and language would positively impact cognitive development, and the later would be reflected in the IQ score of these children.

A total of 10 girls and 30 boys were tested in the cleft group (Table 10). Boys became potty-trained earlier (2.39 years) than girls (3.50 years; $p = 0.037$, $d = 0.79$). Hearing difficulties were in highest proportion for CP (57.1%) than for CL (13.3%) and CLP (44.4%) however with small effect size ($p = 0$ 0.063, $d = 0.36$). In the analysis according to types of clefts, CLP was the subtype that was most often referred to special education services: CLP in 72%, CL in 40%, and CP in 14% of the cases ($p = 0.023$, $d = 0.29$). CLP subtype was also diagnosed with psychiatric comorbidities in highest proportion (22.2%) compared to CL (13.3%) and CP (0%) ($p = 0.53$, $d = 0.22$). CLP subtype had additionally received previous psychiatric care in highest proportion (22.2%) compared to the rest of the cleft subtypes ($p = 0.61$, $d = 0.23$). Bilateral (30.8%) and left-sided clefts (15.4%) presented the highest proportion of psychiatric diagnoses ($p = 0.27$, $d = 0.35$).

**Table 10.** Demographical data of the orofacial cleft group. CLP: cleft lip and palate, CP: cleft palate only, CL: cleft lip (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **Variable** | ***n*** |
|---|---|
| **Age** | |
| Younger group (6-11 years) | 18 |
| Older group (12-16 years) | 22 |
| **Sex** | |
| Male | 30 |
| Female | 10 |
| **Type of orofacial cleft** | |
| CLP | 18 |
| CP | 7 |
| CL | 15 |
| **Side of orofacial cleft** | |
| Right | 8 |
| Left | 13 |
| Bilateral | 13 |
| Midline | 6 |

Parental socioeconomic status and children's cognitive performance

We explored variables of parental SES that may influence the outcome of academic and cognitive performance of the OFC group. Children who had fathers with a high academic background reached a higher overall academic average ($p = 0.005$, $d = 1.02$). Children with mothers of a high academic background also reached a higher overall academic average (Table 11). The same pattern was observed for the IQ scores: children who scored higher on almost all indexes of the IQ had parents with a higher academic background (Tables 12 and 13). A total of 44.4% of cleft children with single parents had a psychiatric condition(s), while only 6.5% had psychiatric condition(s) when raised by married parents ($p = 0.016$, $d = 0.44$).

**Table 11.** Parental level of education in relation to overall academic average of the cleft group (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **Level of education** | | ***n*** | **Mean±SD** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **Father** | High | 25 | 4.60±0.42 | 0.005* | 1,02 |
| | Low | 14 | 4.11±0.57 | | |
| **Mother** | High | 29 | 4.62±0.42 | <0.001* | 1.88 |
| | Low | 10 | 3.85±0.38 | | |

**Table 12.** Fathers level of education in relation to the IQ scores of the cleft group. Data are provided in means (M) and standard deviations (SD). FS-IQ: Full-scale IQ, VCI: Verbal Comprehension Index, PRI: Perceptual Reasoning Index, WMI: Working Memory Index, PSI: Processing Speed Index (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **IQ Indexes** | **Fathers level of education** | ***n*** | ***M*±*SD*** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **FS-IQ** | Low | 11 | 103.82±9.11 | 0.011* | 1.04 |
| | High | 20 | 114.15±10.61 | | |
| **VCI** | Low | 11 | 111.36±10.54 | 0.20 | 0.50 |
| | High | 20 | 117.20±12.63 | | |
| **PRI** | Low | 11 | 101.82±10.33 | 0.044* | 0.77 |
| | High | 20 | 109.10±8.57 | | |
| **WMI** | Low | 11 | 97.09±10.75 | 0.028* | 0.88 |
| | High | 20 | 107.35±12.38 | | |
| **PSI** | Low | 11 | 97.91±9.87 | 0.026* | 0.90 |
| | High | 20 | 107.45±11.33 | | |

**Table 13.** Mothers level of education in relation to the IQ scores of the cleft group. Data are provided in means (M) and standard deviations (SD). FS-IQ: Full-scale IQ, VCI: Verbal Comprehension Index, PRI: Perceptual Reasoning Index, WMI: Working Memory Index, PSI: Processing Speed Index (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **IQ Indexes** | **Mothers level of education** | ***n*** | ***M*±*SD*** | ***p* value** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **FS-IQ** | Low | 7 | 101.71±6.70 | 0.015* | 1.25 |
| | High | 24 | 113.04±10.96 | | |
| **VCI** | Low | 7 | 109.71±9.25 | 0.18 | 0.64 |
| | High | 24 | 116.71±12.52 | | |
| **PRI** | Low | 7 | 96.29±6.78 | 0.001* | 1.73 |
| | High | 24 | 109.51±8.39 | | |
| **WMI** | Low | 7 | 96.29±9.62 | 0.078 | 0.85 |
| | High | 24 | 105.88±12.78 | | |
| **PSI** | Low | 7 | 101.86±12.67 | 0.58 | 0.23 |
| | High level | 24 | 104.70±11.52 | | |

Speech and language therapy and the IQ score

We explored the effect of speech and language therapy on IQ scores and overall academic average. FS-IQ and VCI scores were higher for children who received therapy (Table 14). Overall academic average was higher for cleft participants who did not receive therapy, although with small effect size (Table 14). A one-way ANOVA was performed to compare the effect of the affected side of the cleft (left, right, bilateral and midline) on IQ scores. We observed differences for continuous variables in WMl when tested by the affected side ($p = 0.037$, $\eta 2 = 0.27$, Table 15).

**Table 14.** Effect of speech and language therapy on IQ scores and overall academic average. FS-IQ: Full-scale IQ, VCI: Verbal Comprehension Index, PRI: Perceptual Reasoning Index, WMI: Working Memory Index, PSI: Processing Speed Index (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| **Cognitive performance** | **Speech and language therapy** | ***n*** | **Mean±SD** | ***p value*** | **Cohen's *d*** |
|---|---|---|---|---|---|
| **FS-IQ** | No | 16 | 107.06±10.77 | 0.077 | 0.66 |
| | Received | 15 | 114.13±10.68 | | |
| **VCI** | No | 16 | 109.44±10.73 | 0.005* | 1.10 |
| | Received | 15 | 121.20±10.63 | | |
| **PRI** | No | 16 | 104.50±10.67 | 0.24 | 0.43 |
| | Received | 15 | 108.67±8.44 | | |
| **WMI** | No | 16 | 102.38±13.88 | 0.55 | 0.22 |
| | Received | 15 | 105.13±11.54 | | |
| **PSI** | No | 16 | 103.63±9.02 | 0.83 | 0.07 |
| | Received | 15 | 104.53±14.22 | | |
| **Overall academic average** | No | 18 | 4.54±0.48 | 0.22 | 0.40 |
| | Received | 21 | 4.33±0.56 | | |

**Table 15.** Results of one-way ANOVA which was performed to compare the effect of the affected side of the cleft on IQ. VCI: Verbal Comprehension Index, PRI: Perceptual Reasoning Index, WMI: Working Memory Index, PSI: Processing Speed Index, FS-IQ: Full-scale IQ (*Sándor-Bajusz, Dergez, Molnár et al.,* Frontiers in Psychology, 2023).

| | ***n*** | **Affected side** | ***M*±*SD*** | ***p*** | ***η²*** |
|---|---|---|---|---|---|
| **FS-IQ** | 5 | right | 118.00±12.31 | 0.34 | 0.12 |
| | 12 | left | 108.83±9.01 | | |
| | 10 | midline | 107.60±12.25 | | |
| | 4 | bilateral | 113.25±12.20 | | |
| **VCI** | 5 | right | 116.60±14,54 | 0.85 | 0.029 |
| | 12 | left | 116.83±9.55 | | |
| | 10 | midline | 112.30±14.84 | | |
| | 4 | bilateral | 115.25±11.90 | | |
| **PRI** | 5 | right | 112.80±7.95 | 0.33 | 0.12 |
| | 12 | left | 106.33±8.94 | | |
| | 10 | midline | 103.00±11.44 | | |
| | 4 | bilateral | 108.00±8.16 | | |
| **WMI** | 5 | right | 117.20±10.99 | 0.037 | 0.27 |
| | 12 | left | 98.17±11.24 | | |
| | 10 | midline | 103.50±11.11 | | |
| | 4 | bilateral | 104.00±13.54 | | |
| **PSI** | 5 | right | 108.00±10.02 | 0.36 | 0.11 |
| | 12 | left | 100.58±9.65 | | |
| | 10 | midline | 103.30±12.91 | | |
| | 4 | bilateral | 111.50±14.98 | | |

# Study III

## Systematic literature review

A total of 257 records were identified following the database searches. Of this total, 245 records underwent title and abstract screening following duplicate removal and 32 records were retrieved and assessed for eligibility. Two records were additionally identified by handsearching, and only one met the inclusion criteria (Yang et al., 2012). Three records included individuals diagnosed with Van der Woude syndrome (Nopoulos et al., 2000, 2002a, 2005). These records were included in the current systematic review as none of the syndromic individuals exceeded 15% of total cleft participants. The study selection process is shown in the flow diagram of Figure 7.

Fifteen records seemed to meet the inclusion criteria; however, they were excluded during the full-text screening process. The reasons for exclusion were as follows: absence of a control group (n = 3) (Shen and Huang, 1996; Mueller et al., 2007; Zheng et al., 2019), conference abstracts or commentaries (n = 4) (Chollet et al., 2010; Tollefson and Sykes, 2010; DeVolder et al., 2014, 2015), wrong study population that only included syndromic cases of OFCs (n = 2) (Nopoulos et al., 2007c, 2007b), absence of neuroimaging (n = 5) (Čeponien≐ et al., 1999; Scott et al., 2005; Kummer et al., 2007; Conrad et al., 2008; Watkins et al., 2018), or neuroimaging other than brain MRI (n = 1 (Becker et al., 2008). The study characteristics are presented in Tables 16 and 17. The study size ranged between 24 and 234 participants. Most of the participants were males of Caucasian ethnicity, and the majority were children.

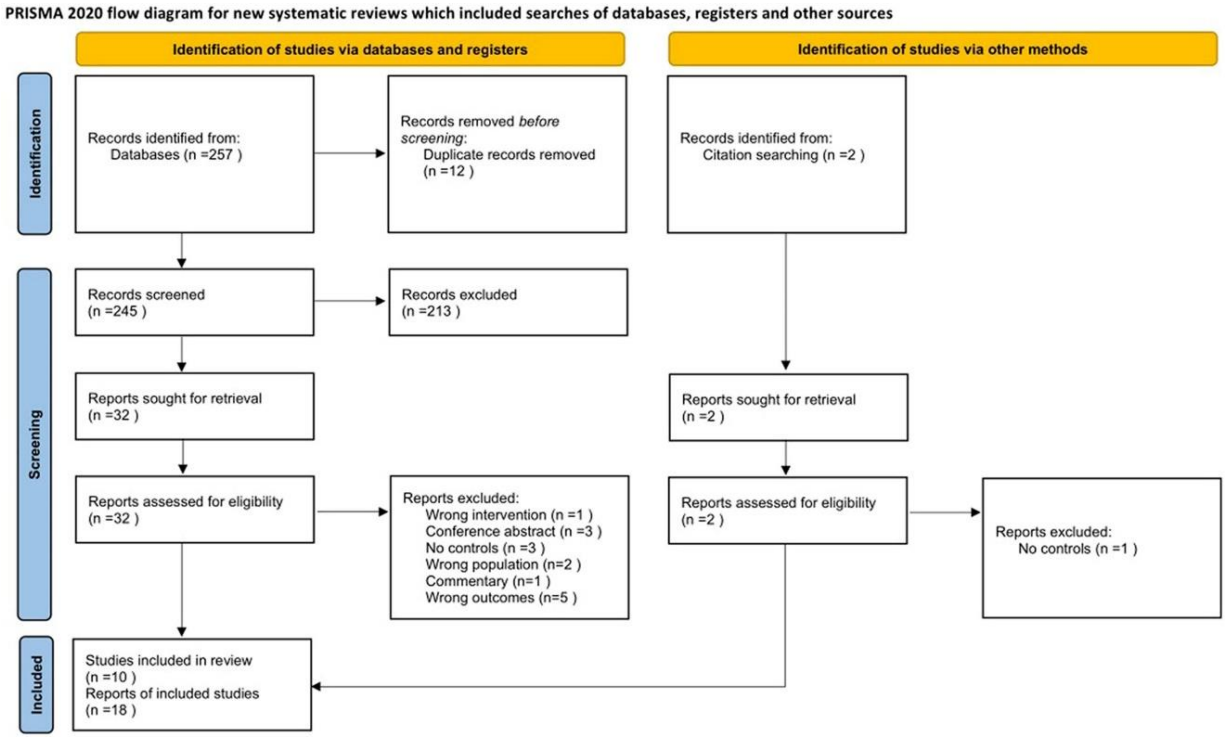


**Figure 7.** Flow diagram of the study selection process (*Sándor-Bajusz, Sadi, Varga et al.*, Frontiers in Neuroanatomy, 2022).

**Table 16.** Characteristics of included studies (*Sándor-Bajusz, Sadi, Varga et al.*, Frontiers in Neuroanatomy, 2022).

| References | Country | Study participants present in another reference? | Inclusion | Exclusion | N |
|---|---|---|---|---|---|
| Nopoulos et al. (2000) | United States | No | Adult males (18 +) with non-syndromic oral clefts | Congenital syndromes | 28 |
| Nopoulos et al. (2001) | United States | No | Adult males with non-syndromic oral clefts | Congenital syndromes | 124 |
| Nopoulos et al. (2002) | United States | No | Non-syndromic oral clefts | Congenital syndromes | 92 |
| Nopoulos et al. (2005) (Nopoulos, 2002A) | United States | Same study cohort as (Nopoulos et al., 2002) | Adult males (18 +) with non-syndromic clefts | Congenital syndromes | 92 |
| Shriver et al. (2006) (Nopoulos, 2002B) | United States | Same patient population as (Nopoulos et al., 2002) | Adult males (18 +) with non-syndromic oral clefts | Genetic syndrome, serious, active medical or neurologic disease or active substance abuse/dependence, psychiatric disorders | 89 |
| Nopoulos et al. (2007c) | United States | No | Children with non-syndromic oral clefts | Braces (artifact in MRI scan), IQ < 70, genetic syndrome | 148 |
| Boes et al. (2007) (Nopoulos, 2007A) | United States | Subset of cleft participants from Nopoulos et al. (2007c) | Boys with non-syndromic oral clefts | Genetic syndromes, serious medical or neurological disease | 73 |
| Weinberg et al. (2009) | United States | No | Adult males (18 +) | N/A | 86 |
| van der Plas et al. (2010) (Nopoulos, 2007E) | United States | Participants of both groups were part of another study (Nopoulos et al., 2007c) | Children with unilateral CLP or CL only | CP, bilateral CLP or CL, genetic syndromes, serious medical and neurological disease | 90 |
| Nopoulos et al. (2010) (Nopoulos, 2007B) | United States | Subset of cleft participants from Nopoulos et al. (2007c) | Boys with non-syndromic oral clefts | Braces (creates artifact in MRI scan), IQ < 70, genetic syndrome | 110 |
| Conrad et al. (2010) (Nopoulos, 2007C) | United States | Cleft MRI results from Nopoulos et al. (2007c) | Children with non-syndromic oral clefts | Genetic syndromes, significant hearing loss (requiring a hearing aid), braces, history of head trauma, brain tumor or epilepsy. | 86 |
| DeVolder et al. (2013) (Nopoulos, 2007D) | United States | Subset of participants of two previous studies from Nopoulos et al. (2007c) and Conrad et al. (2010) | Children with non-syndromic oral clefts | Braces (artifact in MRI scan), IQ < 70 | 234 |
| Yang et al. (2012) | China | No | Full-term birth, uncomplicated delivery, non-syndromic oral cleft | Congenital syndromes, other chronic health disorders | 54 |
| Weinberg et al. (2013) | United States | No | Males, non-syndromic oral clefts, limited to 18–50 year old | Congenital syndromes | 64 |
| Adamson et al. (2014) | Australia | No | Children with non-syndromic oral clefts | Genetic syndromes | 52 |
| Chollet et al. (2014) (Nopoulos, 2007F) | United States | MRI data from previous study by Nopoulos et al. (2007c) | Children with non-syndromic oral clefts | Braces, FSIQ < 70, genetic syndromes | 96 |
| Bodoni et al. (2021) | Brazil | No | Children with non-syndromic oral clefts | Sensory or motor problems, psychiatric disorders, claustrophobia, contraindications to MRI | 24 |
| Li et al. (2020) | China | No | N/A | Brain structural abnormalities, neurological or psychiatric disorders, and MRI contraindications | 69 |

*N, population size; CLP, Cleft lip and palate; CP, Cleft palate; CL, Cleft lip.*

**Table 17.** Demographic data of included studies (*Sándor-Bajusz, Sadi, Varga et al.*, Frontiers in Neuroanatomy, 2022).

| References | Demographic measures of clefts | | | | Demographic measures of controls | | |
|---|---|---|---|---|---|---|---|
| | Age: mean (SD) | Gender (%) | Ethnicity (%) | Cleft subtype (N) | Age: mean (SD) | Gender (%) | Ethnicity (%) |
| Nopoulos et al. (2000) | 33.7 (7.3) | Male (100%) | Caucasian (100%) | CL (1), CPO (5, one is syndromic), CLP (8, one is syndromic) | 33.1 (7.7) | Male (100%) | Caucasian (100%) |
| Nopoulos et al. (2001) | 30.3 (N/A) | Male (100%) | Caucasian (100%) | CPO (15), CLP (34, three are syndromic) | 27.3 (N/A) | Male (52%), female (48%) | N/A |
| Nopoulos et al. (2002) | 30.1 (7.04) | Male (100%) | Caucasian (100%) | CPO (14), CLP (32, three are syndromic) | 28.8 (7.60) | Male (100%) | Caucasian (100%) |
| Nopoulos et al. (2005) (Nopoulos, 2002A) | 30.1 (7.04) | Male (100%) | Caucasian (100%) | CPO (14), CLP (32, three are syndromic | 28.8 (7.60) | Male (100%) | Caucasian (100%) |
| Shriver et al. (2006) (Nopoulos, 2002B) | 30.1 (7.04) | Male (100%) | Caucasian (100%) | CPO (14), CLP (32, three are syndromic) | 28,8 (7.60) | Male (100%) | Caucasian (100%) |
| Nopoulos et al. (2007c) | 12.1 (3.26) | Male (67.57%), female (33.33%) | White (90.5%), Asian American (8, 1%), Hispanic (1.4%) | CL (18), CPO (23), CLP (33) | 12.3 (3.08) | Male (67.57%), female (33, 33%) | White (87.8%), Asian American (5.4%), Hispanic (6.8) |
| Boes et al. (2007) (Nopoulos, 2007A) | 9.98 (1.64) | Male (100%) | Provided for both study groups: African (1.37%), Asian (1.37%), Asian American (4.11%), Caucasian (89.04%), Hispanic (1,37%), and mixed (2.74%). | CL (8), CPO (7), CLP (15) | 10.68 (1.45) | All male | See oral cleft group |
| Weinberg et al. (2009) | 30.1 (7.1) | Male (100%) | Caucasian (100%) | CPO (14), CLP (31) | 28.8 (7.5) | All male | Caucasian (100%) |
| van der Plas et al. (2010) (Nopoulos, 2007E) | Separated by cleft side: Right, 13 (2.68); left cleft, 11.7 (2.80) | Male (100%) | N/A | CL (9), CLP (24) | 12,2 (3.01) | All males | N/A |
| Nopoulos et al. (2010) (Nopoulos, 2007B) | 11.9 (3.3) | Male (100%) | Caucasian (95%; detailed info N/A) | CL (11), CPO (13), CLP (26) | 12.1 (2.7) | All males | See oral cleft group |
| Conrad et al. (2010) (Nopoulos, 2007C) | 13.27 (3.28) | Male, (59%) female (41%) | White (70%) Asian American (9%), Hispanic (5%), multiracial (7%) unknown (9%) | CL (7), CPO (11), CLP (25) | 13.28 (3.27) | Males (59%), females, (41%) | White: 37 (86%), multiracial: 1 (2%), unknown: 5 (12%) |
| DeVolder et al. (2013) (Nopoulos, 2007D) | Male: 13.44 (4.61), female: 14.11 (3.80) | Male: (61.68%). female: (38.31%) | N/A | CL (22), CP (31), CLP (52) | Male: 13.04 (3.92), female: 13.65 (3.82) | Males (50.39%), females: 63 (49.60%) | N/A |
| Yang et al. (2012) | 15.6 months (5.7 months) | Male: 24 (88.9%), female: 3 (11.1%) | Han Chinese (100%) | CL (2), CP (6), CLP (19) | 15.6 months (5.7 months) | Same as oral cleft group | Han Chinese (100%) |
| Weinberg et al. (2013) | 32.3 (7.4) | All male | N/A | N/A | 29.1 (7.9) | All male | N/A |
| Adamson et al. (2014) | 10.40 (2.57) | Males: 11 (42.31%) Females: 15 (57.69%) | N/A | N/A | 10, 52 (1.72) | Male (61, 54%), female (38.46%) | N/A |
| Chollet et al. (2014) (Nopoulos, 2007F) | CP: 11.7 (± 3.2), CLP: 12.7 (± 3.1) | Male (66, 67%), female (33, 33%) | Caucasian (82%), Asian American (8%), African American (1%), Hispanic/Latino (2%), Native Hawaiian/Pacific Islander (1%), biracial (4%), N/A (1%) | CP (22), CLP (35) | 12.5 (3.0) | Male (69.23%) female (30.77%) | See oral cleft group |
| Bodoni et al. (2021) | 13 (1) | Male (58, 33%), female (41, 67%) | N/A | CLP (12) | 13 (2) | Male (58.33%), female (41.67%) | N/A |
| Li et al. (2020) | Group B before therapy: 24 (4.92)*, group A after therapy 22.8 (5.4)* | Male: 26 (57.78%) female:19 (42.22%) | N/A | N/A | 22 (1.58)* | Male: 15 (62.50%), female: 9 (37.50%) | N/A |

*N, population size; CLP, Cleft lip and palate; CP, Cleft palate; CL, Cleft lip.*
**Data were calculated from median (IQR) values with statistical tool developed by Wan et al. (2014) and Luo et al. (2018).*

Risk of bias

The overall risk of bias ranged from medium to high. Selection of cleft participants, their comparators and the assessment of exposure were described in half of the studies. Information on recruitment and reasons for dropout were not available in most studies. Only one study reported blinding personnel of group status during MRI scanning (Nopoulos et al., 2007a). The risk of bias assessment of included studies are shown in Table 18.

**Table 18.** Risk of bias (RoB) assessment using the Newcastle-Ottawa Scale (*Sándor-Bajusz, Sadi, Varga et al.,* Frontiers in Neuroanatomy, 2022).

| Studies | Selection | | | | Comparability | Outcome | | | Total quality score |
|---|---|---|---|---|---|---|---|---|---|
| Author, year | Is the case definition adequate? | Representativeness of the cases | Selection of controls | Definition of controls | Comparability of cases and controls on the basis of design or analysis | Ascertainment of outcome | Same method of ascertainment for cases and controls | Non-response rate | 9 = Low RoB; 7–8 = Medium RoB; < 6 = High RoB |
| Nopoulos et al. (2000) | * | * | * | * | ** | * | * | * | 6 |
| Nopoulos et al. (2001) | * | * | * | * | ** | * | * | * | 5 |
| Nopoulos et al. (2002) | * | * | * | * | ** | * | * | * | 7 |
| Nopoulos et al. (2007c) | * | * | * | * | ** | * | * | * | 8 |
| Weinberg et al. (2009) | * | * | * | * | ** | * | * | * | 5 |
| Yang et al. (2012) | * | * | * | * | ** | * | * | * | 7 |
| Weinberg et al. (2013) | * | * | * | * | ** | * | * | * | 6 |
| Adamson et al. (2014) | * | * | * | * | ** | * | * | * | 8 |
| Bodoni et al. (2021) | * | * | * | * | ** | * | * | * | 7 |
| Li et al. (2020) | * | * | * | * | ** | * | * | * | 4 |

*Total quality score of 9 indicates low RoB, 7–8 medium RoB and ≤ 6 high RoB (Wells et al., 2000; Muka et al., 2020). The asterisks represent the scores under each dimension of the Newcastle-Ottawa Scale.*

## Meta-analyses

Five studies were comparable in terms of study design, exposure, and outcome. Studies were pooled using a random-effect meta-analysis. All five studies segmented the brain according to all or one of the following: intracranial volume was divided into total brain tissue and cerebrospinal fluid; the brain tissue was divided into the cerebrum and cerebellum; the cerebrum was subdivided into the frontal, parietal, temporal, and occipital lobes. Most studies used the Talairach Atlas-based method for measures of general and regional brain tissue. Most studies used three different sequences (T1-weighted, T2-weighted, and/or proton density images) with comparable parameters to classify tissue into gray matter, white matter, and cerebrospinal fluid.

## Studies investigating global measurements

These measurements included three anatomical groups: total brain volumes (including MRI volumes of the cerebrum and cerebellum), cerebral volumes (only MRI volumes of the cerebrum), and cerebellar volumes (only MRI volumes of the cerebellum).

The cleft group had lower total brain gray matter volume compared to controls (MD: −41.14 cm3; 95% CI: −57.36 to −24.92; n = 2; 172 participants; I2: 0%) (Figure 8). The cerebellum was significantly smaller in OFCs compared to controls (MD: −12.46 cm3; 95% CI: −18.26, −6.67; n = 3; 354 participants; I2: 0%, n = 3) (Figure 9).

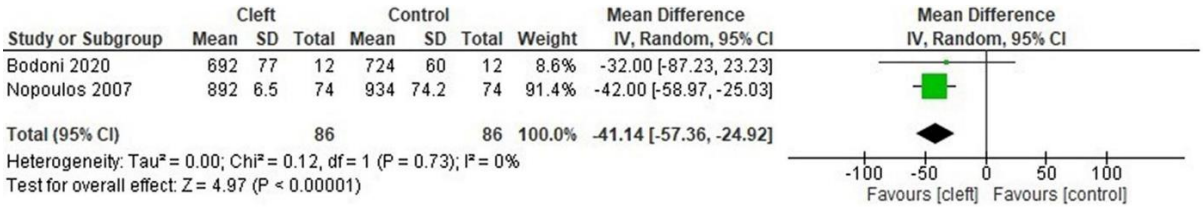


**Figure 8.** Forest plot for total brain gray matter volume ($cm^3$) (*Sándor-Bajusz, Sadi, Varga et al.,* Frontiers in Neuroanatomy, 2022).

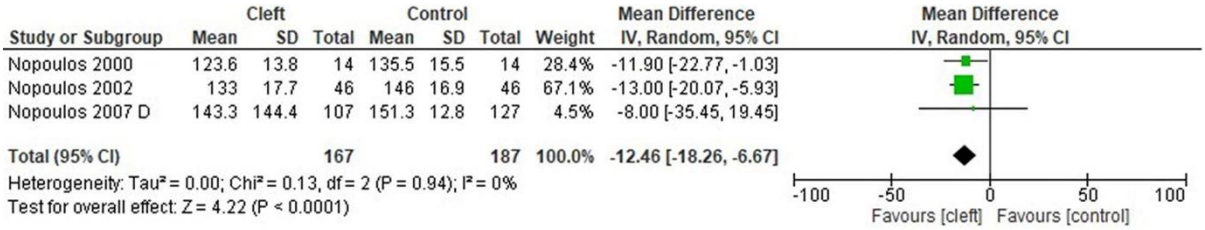


**Figure 9.** Forest plot for total volume of the cerebellum ($cm^3$) (*Sándor-Bajusz, Sadi, Varga et al.,* Frontiers in Neuroanatomy, 2022).

Overall brain size (MD: −38.86 cm3; 95% CI: −83.88 to 6.16; n = 4;322 participants; I2: 48%), total white matter volume (MD: −21.93 cm3; 95% CI: −64.20 to 20.33; n = 2; 172 participants; I2: 69%), total volume of the cerebrum (MD: −22.42 cm3; 95% CI: −66.40 to 21.56; n = 3; 268 participants; I2: 58%), cerebral white matter (MD: −5.08 cm3; 95% CI: −20.19 to 10.03; n = 2; 146 participants; I2:0%), and gray matter volume of the cerebrum (MD: −6.45 cm3; 95% CI: −25.17 to 12.27; n = 2; 202 participants; I2: 0%), did not differ between OFCs and controls.

Studies investigating regional measurements

Measurements included the frontal, temporal, parietal, and occipital lobes. Smaller temporal lobes were found for the cleft group compared to controls (MD: −10.53 cm3; 95% CI: −18.23 to −2.82; n = 2; 120 participants; I2: 0%) (Figure 10). The cleft group had significantly smaller occipital lobes compared to controls (MD: −7.39 cm3; 95% CI: −12.80 to −1.99; n = 2; 120 participants; I2: 0%) (Figure 11).

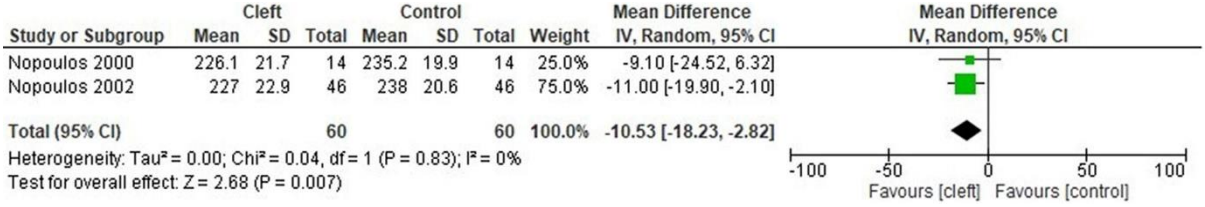


**Figure 10.** Forest plot for temporal lobe volume ($cm^3$) (*Sándor-Bajusz, Sadi, Varga et al.,* Frontiers in Neuroanatomy, 2022).

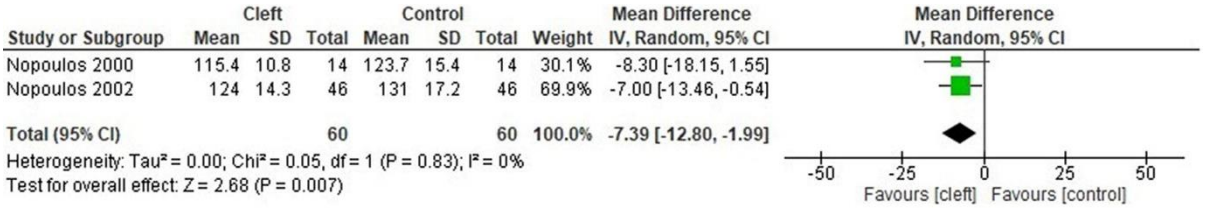


**Figure 11.** Forest plot for occipital lobe volume ($cm^3$) (*Sándor-Bajusz, Sadi, Varga et al.,* Frontiers in Neuroanatomy, 2022).

The following regional sizes did not differ between clefts and controls: the size of the frontal lobe (MD: 18.27 cm3; 95% CI: −12.62 to 49.16; n = 2; 120 participants I2: 0%), frontal gray matter volume (MD: 4.77 cm3; 95% CI: −7.84 to 17.38; n = 2; 165 participants; I2: 0%), the two components of the ventrofrontal cortex; the straight gyrus (MD: −0.17 cm3; 95% CI: −1.35 to 1.00; n = 2; 165 participants; I2: 90%) and orbitofrontal cortex (MD: −0.99 cm3; 95% CI: −2.69 to 0.71; n = 2; 165 participants; I2: 0%), the parietal lobe (MD: 4.91 cm3; 95% CI: −4.29 to 14.10; n = 2; 120 participants; I2: 0%), and superior temporal plane (STP) (left side MD: −0.37 cm3; −1.78 to 1.04; n = 2; 143 participants; I2: 66%. Right side MD: 0.20 cm3; 95% CI: −0.21 to 0.60; n = 2; 143 participants; I2: 0%).

## Studies investigating mental and cognitive functioning

Heterogeneity of methods and outcomes prevented statistical pooling for meta-analyses for most secondary outcomes, except for IQ scores. All studies used the Wechsler Intelligence Scale of different editions. Significantly lower FS-IQ scores were as observed in individuals with OFCs compared to controls (MD: −12.58; FS-IQ; 95% CI: −21.98 to -3.17; n = 2; 234 participants; I2 = 84%) (Figure 12). The rest of the secondary outcomes are illustrated in Table 19**.**

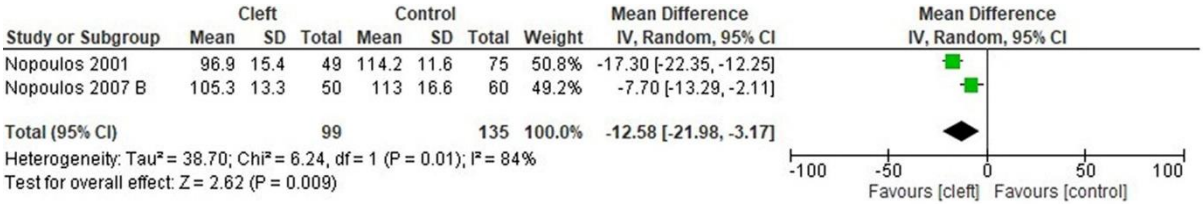


**Figure 12.** Forest plot for full-scale IQ scores (*Sándor-Bajusz, Sadi, Varga et al.*, Frontiers in Neuroanatomy, 2022).

**Table 19.** Psychometric tools used to measure psychosocial functioning (*Sándor-Bajusz, Sadi, Varga et al.*, Frontiers in Neuroanatomy, 2022).

| Study | Outcome | Results | Validated |
|---|---|---|---|
| Nopoulos (2002A) | Social function measured with the Psychiatric Symptoms You Currently have-Baseline tool (PSYCH-base), and the relationship to brain volumes. | Social function was measured only for cleft subjects (recreational interests and activities; relationship with friends and peers; relationship with family members). Twenty-six percent of oral cleft subjects rated relationship with friends as poor. Thirteen percent of oral cleft subjects rated their relationship with family members as poor. Six percent of subjects rated recreational participation as poor. No significant differences of social function between CLP and CP subtypes. Significant correlation was observed between smaller surface of the OF and social dysfunction in cleft subjects ($P = 0.003$). | Yes |
| Nopoulos (2007B) | Pediatric Behavior Scale derived hyperactivity/impulsivity/inattention (HII) scores and its relationship to the volume of the vmPFC. | The cleft group showed significantly elevated scores in HII compared to controls ($P = 0.021$). Boys of the control group with the lowest right vmPFC volume scored the highest on the HII ($P = 0.041$). In the cleft group, boys with the highest volume of the right vmPFC achieved the highest HII scores ($P = 0.005$). | Yes |
| Noppulos (2002B) | Boston Naming Test, Rey Auditory-Verbal Learning Test, Rey–Osterreith Complex Figure Test, Stroop Test. Relationship of test performance and brain volumes. | Lower test performance on the Boston Naming Task correlated with greater STP volume for oral cleft subjects, but not significant ($P = 0.074$). No correlations observed in the other tests. | Yes |
| Bodoni et al. (2021) | RAVEN, Rey Complex Figure, Wisconsin. Relationship between test performance and brain volumes. | Cleft group performed significantly worse on the Raven test compared to controls, and had non-verbal intelligence scores below average ($P = 0.006$). Raven test correlated positively with decreased cortical thickness of right pars orbitalis in oral clefts. Rey Complex Figure Test—Memory scores in oral cleft subjects showed significant positive correlation to decreased cortical thickness in: left supramarginal gyrus, right supramarginal gyrus, left superior parietal lobule, left inferior parietal lobule, right inferior parietal lobule, right middle temporal gyrus, right pars orbitalis, right superior temporal gyrus, and right rostral middle frontal gyrus ($P \leq 0.05$). | Yes |
| Nopoulos (2007A) | Self-Description Questionnaire: SDQ-1 and relationship to brain volumes. | Boys with oral clefts had significantly poorer peer relations in the self-reported SDQ-1 score ($P = 0.002$). Significant correlation between small SG measures and self-reported low peer relation scores was observed ($P \leq 0.05$). | Yes |
| Nopoulos (2007C) | Speech measured by hypernasality, articulation proficiency, and nasalance. Relationship between performance and brain volumes. | Boys had greater impaired speech than girls in all three domains. These differences reached significance only for the hypernasality rating ($P = 0.003$). Speech and structure correlations for boys with oral clefts were significant for cerebellar volume and articulation ($P = 0.015$), and those with worse articulations had smaller cerebellar volumes. | N/A |

*CLP, Cleft lip and palate; CP, Cleft palate; OFC, orbitofrontal cortex; vmPFC, Ventro-medial prefrontal cortex.*

Subgroup analysis

Four meta-analyses demonstrated moderate to considerable levels of heterogeneity. We performed the analysis to identify possible sources of the heterogeneity observed in the main analyses. Subgroup analysis was feasible for only two meta-analyses (Figures 13 and 17). Subgroup analyses were performed for age, sex, ethnicity, non-syndromic, and mixed (syndromic and non-syndromic) OFCs.

The non-syndromic subgroup had significantly smaller total brain volume compared to controls. However, this significant difference was not seen in the mixed subgroup (syndromic and non-syndromic cases) (MD: −77.06 cm3; 95% CI: −115.47 to −38.64; n = 2; 202 participants; I2 = 0%; Figure 13). The same phenomenon was observed for age (children vs. adults), sex (male only vs. mixed) and ethnicity (Caucasian vs. mixed) (Figures 14–16). These factors may be possible sources of the heterogeneity seen in the main analysis. A decrease in heterogeneity was found in the subgroup analysis of mixed OFCs for cerebral volume (MD: −0.80 cm3; 95%CI: −40.88 to 39.29; n = 2; 120 participants; I2 = 0%; Figure 17). The same phenomenon was observed for age (children vs. adults) and sex (male vs. male and female).

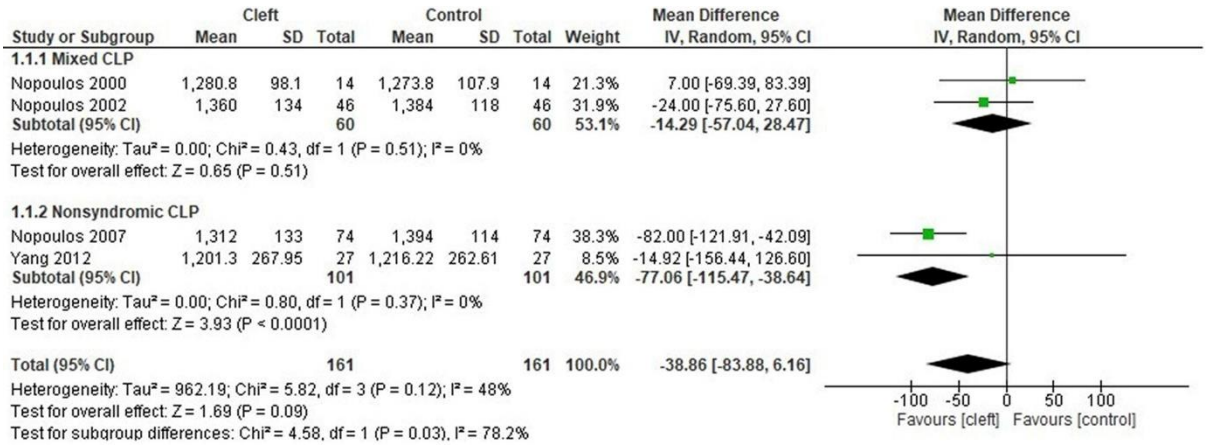


**Figure 13.** Forest plot for total brain volume ($cm^3$) with subgroup analysis (non-syndromic vs. mixed) (*Sándor-Bajusz, Sadi, Varga et al.*, Frontiers in Neuroanatomy, 2022).

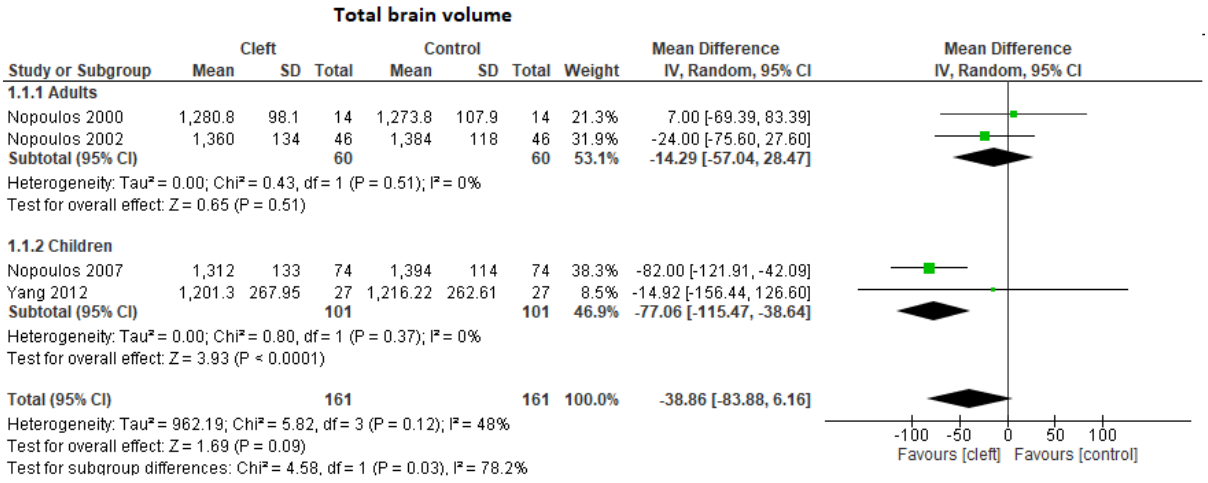


**Figure 14.** Forest plot for total brain volume ($cm^3$) with subgroup analysis (adults versus children) (*Sándor-Bajusz, Sadi, Varga et al.*, Frontiers in Neuroanatomy, 2022).

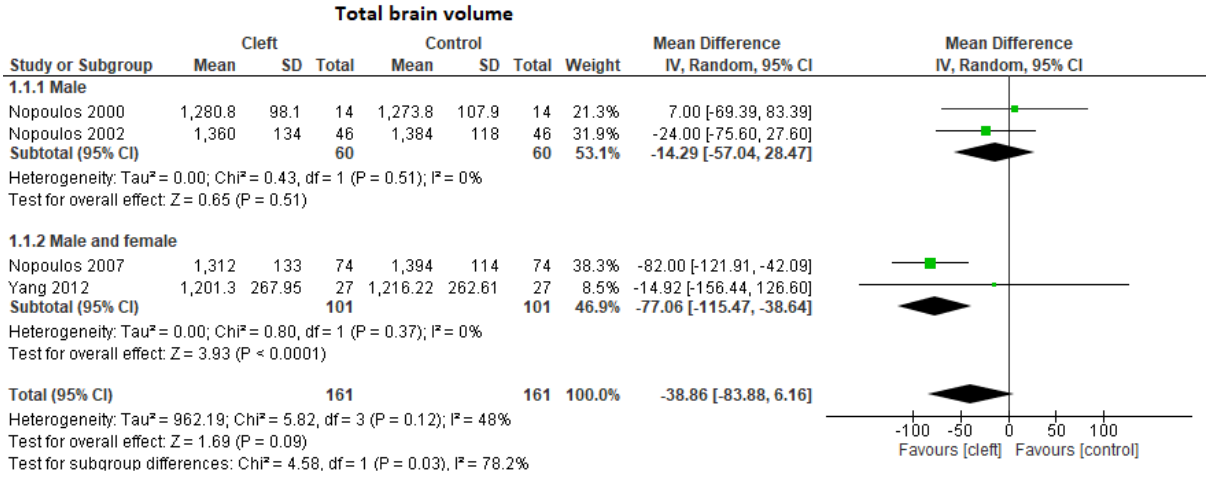


**Figure 15.** Forest plot for total brain volume ($cm^3$) with subgroup analysis (male versus male and female) (*Sándor-Bajusz, Sadi, Varga et al.*, Frontiers in Neuroanatomy, 2022).

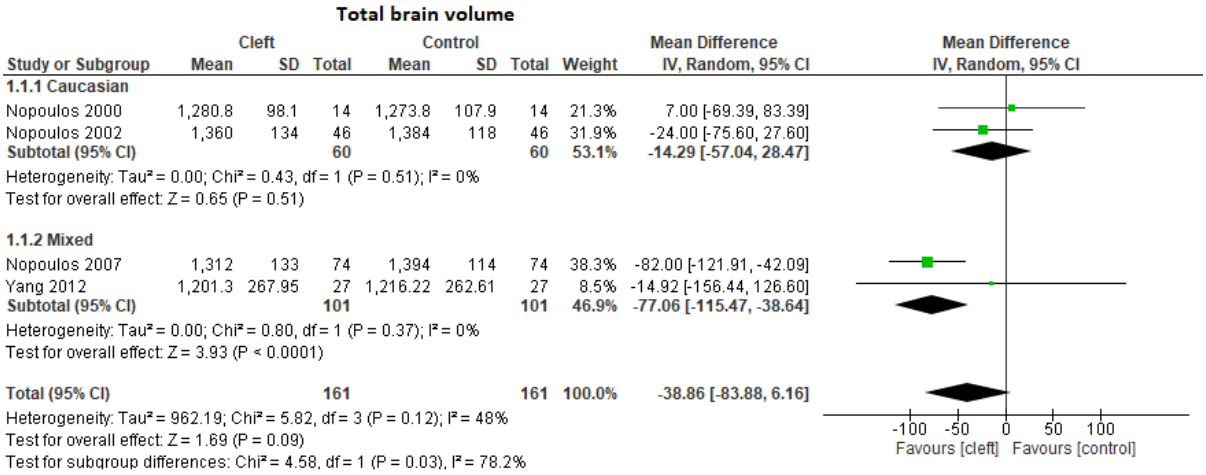


**Figure 16.** Forest plot for total brain volume ($cm^3$) with subgroup analysis (Caucasian versus mixed) (*Sándor-Bajusz, Sadi, Varga et al.*, Frontiers in Neuroanatomy, 2022).

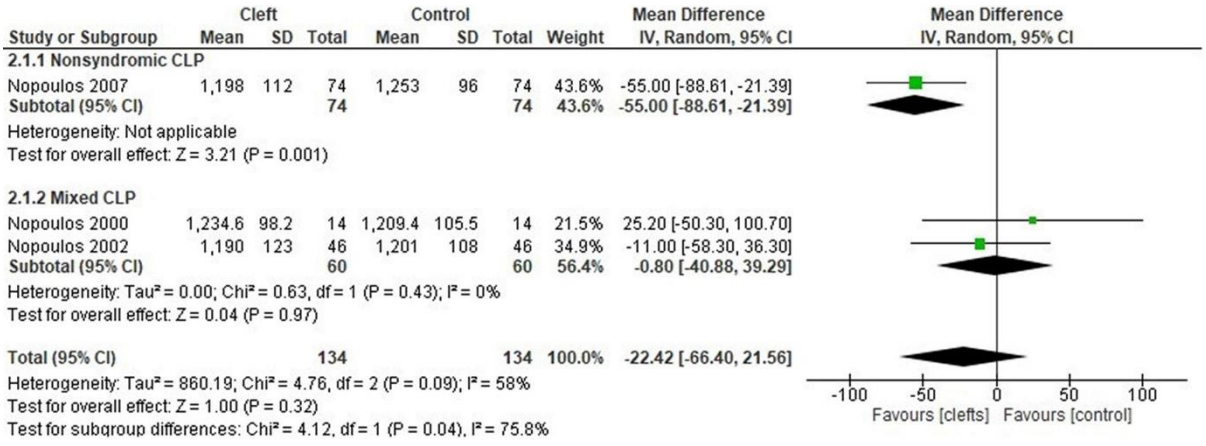


**Figure 17.** Forest plot for total volume of the cerebrum ($cm^3$) with subgroup analysis (non-syndromic vs. mixed) (*Sándor-Bajusz, Sadi, Varga et al.*, Frontiers in Neuroanatomy, 2022).

# Summary of new findings and discussion

## Study I

- The Cleft Team needed to modify the treatment algorithm for primary and/or secondary operations in the majority (81%) of the syndromic patients.
- The main causes of the delay in palatoplasty for PRS patients were airway issues and feeding problems. In other syndromic patients, cardiorespiratory and urogenital interventions had priority and therefore caused a delay in the timing of the primary cleft operations.
- The observed high rate (37.5%) of the secondary operations such as speech improvement surgery and ancillary procedures such as placement of tympanostomy tubes for the syndromic OFC patients is in accordance with the literature (Godbout et al., 2014; Hardwicke et al., 2016; Lehtonen et al., 2016; Gustafsson et al., 2020; Kocaaslan et al., 2020).
- Velopharyngeal insufficiency and speech problems were more common conditions in syndromic patients, especially in patients with PRS. This finding explains the high rate of pharyngoplasties and tympanostomies in these patients (Godbout et al., 2014; Hardwicke et al., 2016; Gustafsson et al., 2020; Kocaaslan et al., 2020).
- The percentage of the syndromic OFC patients managed by the PCT was 2.6% during the study. This number is below the 10%-30% prevalence of syndromic OFC described in the literature (Sárközi et al., 2005; Venkatesh, 2009; Saleem et al., 2019).
- Interestingly, two very rare syndromes both Ectrodactyly-ectodermal dysplasia-clefting syndrome and Weissenbacher–Zweymüller syndrome were present in the syndromic cohort (Galil et al., 1991; Bigatà et al., 2003; Malvankar et al., 2012). A center for rare congenital diseases was subsequently established in Pécs during the latter half of the study period, in 2009, which may explain the more current appearance and reporting of these rare syndromes.

### Strengths and limitations

The main limitation is the retrospective nature of the current study; the quality of the data depends on the availability and accuracy of the patient's medical records, and the study may be subjected to selection bias as the cases are self-selected from previous records. However, the current study has several strengths. We analyzed data of the Pécs Cleft Team collected over a period of 16 years. Our cohort included two very rare cleft syndromes. We identified and characterized important factors that may contribute to the delay of surgical interventions for syndromic clefts in an otherwise internationally well-established treatment algorithm for cleft patients.

## Study II

- The postnatal period was uneventful for the two study groups. Apgar score at 5 min was lower for the cleft group than for controls, but clinically within the normal range.
- There was a tendency of a slower onset of developmental milestones in children with OFCs; potty-training and the use of two-word phrases presented at a later age compared to controls, also within clinical ranges.
- Children with OFCs experienced difficulties integrating into preschool, and most required additional support for learning, psychological and physical well-being throughout their education. Difficulties with speech and language development are known to be a consequence related to the primary defect; however, studies highlight the possibility of a central auditory dysfunction, which may cause developmental issues that affect these skills (Čeponien≐ et al., 1999; Yang et al., 2012; Conrad et al., 2021). Based on our results, children with non-syndromic OFCs initially have a slower development and experience difficulties integrating into preschool; however, it seems that they go through a "catch-up phase" around school age and perform well−almost equal to their peers−throughout elementary and high school.
- Psychiatric diagnoses varied across cleft subtypes and the affected side: the highest proportion of psychiatric diagnoses were observed in CLP and bilateral-sided clefts. These observations may suggest that the more complicated clefts are more likely to present with psychiatric comorbidities (Pedersen et al., 2016; Gallagher et al., 2018).
- We did not observe psychiatric comorbidities in CP children, which is in contrast with previous observations (Nilsson et al., 2015; Pedersen et al., 2016; Tillman et al., 2018; Gallagher and Collett, 2019). Interestingly, less than half (29.16%) of the cleft group participants recognized their repaired OFC as a disease or medical condition. This may indicate that the causative stressor is in fact something other than the physical awareness of the defect itself (Aleksieva et al., 2021).
- Children with non-syndromic OFCs reported symptoms of internalizing disorders (affective, anxiety), in contrast to symptoms of externalizing disorders reported by controls (attention, oppositional, behavioral) (Table 2).
- Retrospective analysis of past medical history revealed that children with non-syndromic OFCs were clinically diagnosed with psychiatric disorders at a higher proportion and received psychiatric support more often than controls. Larger cohort studies have previously described this observation (Pedersen et al., 2016; Tillman et al., 2018). While there is a clear difference in the proportion of psychiatric disorders between our two study groups, this is not statistically detectable, and the effect size is small. A larger sample may provide conclusive evidence of this observation.
- Children with non-syndromic OFCs scored lower on the CPT and missed targets more often than controls (omission errors, **Table 5**). The results raise the possibility of an underlying attention deficit in these children described previously by other studies (Nopoulos et al., 2010; Pedersen et al., 2016).
- Controls scored higher on the PRI and WMI IQ subtests than cleft children.
- Subgroup analysis of the cleft group revealed significant relationships between parental SES and IQ scores: children of parents with a higher educational background scored

significantly higher on the IQ test, specifically reflected in perceptual reasoning and the FS-IQ score.

- We observed a significant association between early intervention and IQ: children who received speech and language therapy achieved higher scores specifically reflected in the verbal component (VCI) of the WISC-IV (Table 14).
- We further observed the influence of family structure on mental health outcomes: children raised by single parents were diagnosed with psychiatric conditions more often than children raised by married parents.

## Strengths and limitations

This study has important limitations. The small sample size of the study limited us to further explore relationships within gender, cleft subtype and affected side. The sample size varied across the different phases of the study. Most of the children in the cleft group were represented by males. The retrospective nature of the questionnaires may have created bias in the data provided. We could not assess the baseline level of executive functioning prior to the interventional programs (speech and language therapy), and we may observe an overall "corrected" level of cognitive functioning. However, this study has several strengths. Our study is the first to provide data on cognitive performance and clinical characteristics of Hungarian children with non-syndromic OFCs across a wide age-range. We were able to provide data on neurodevelopmental differences in children with non-syndromic OFCs in early infancy and the preschool period. We further demonstrated how these children, despite having previous difficulties during early infancy, can "catch-up" to their peers and perform well. Early intervention, additional help in school and proper parental support seem to have a strong effect on proper cognitive development for this patient population. Our observations suggest the presence of attention deficit in children with non-syndromic OFCs in support of the higher proportion of ADHD diagnosis seen in this population compared to controls. Assessing the executive system at an earlier stage of development, prior to interventional programs, may be useful to screen and identify individuals within the cleft population who are at risk for atypical neurodevelopment.

## Study III

- Subjects with OFCs had smaller total gray matter, cerebellum, temporal lobes, and occipital lobes on brain MRI compared to controls.
- Individuals with OFCs had lower FS-IQ scores compared to matched controls.
- Most studies controlled for confounders such as age and/or sex to control for brain growth and development; however, only half of the studies controlled for subjects and/or parent's sociodemographic level (Nopoulos et al., 2000, 2002a, 2007a; Li et al., 2020; Bodoni et al., 2021).
- The risk of bias for the included studies was moderate to high. Most included studies did not analyze cleft subtypes separately which was likely due to the small sample size across subgroups.
- The total gray matter volume was significantly smaller in the cleft group (Figure 8), an interesting outcome as the total brain and cerebral volume did not significantly differ between the two groups. This observation may be explained by the following hypotheses:

  (1) Shifts in brain tissue distribution in individuals with non-syndromic OFCs have been shown previously (Nopoulos et al., 2007a). This phenomenon was suggested to occur due to a "compensatory overgrowth" of either brain tissue component unaffecting total brain size (Nopoulos et al., 2002). The cerebellum was also significantly smaller in the cleft group; however, the gray or white matter volumes of the cerebellum could not be analyzed separately due to the lack of data in studies. The OFC group may additionally have a smaller cerebellar cortex (i.e., gray matter), a difference which may not affect the overall tissue size of the "compensated" brain.

  (2) Subgroup analysis revealed a significantly smaller brain and cerebrum in studies with exclusively non-syndromic OFC participants. These differences were not observed in studies with mixed syndromic participants (Figures 13, 17).

- Non-syndromic OFCs may have smaller total brain and cerebrum, but the presence of syndromic individuals might have influenced this outcome.
- Some effects of OFCs may have remained hidden as a consequence to the small number of studies for most outcomes. A few studies have included syndromic OFCs, notably Van der Woude syndrome. There have been documented cases of cognitive deficits and brain structural abnormalities of Van der Woude syndrome (Nopoulos et al., 2007c; Rincic et al., 2016), and their inclusion may have an impact on the results of the non-syndromic cleft population.
- Previous systematic reviews have shown an increased risk of neurodevelopmental and academic difficulties in individuals with non-syndromic OFCs (Hunt et al., 2005; Al-Namankany and Alhubaishi, 2018; Gallagher and Collett, 2019). These studies, however, highlight the difficulty of summarizing the available evidence due to the lack of uniformity and consistency across studies. It has been proposed that syndromes and additional conditions related to the cleft should be analyzed in a separate group to

observe if the additional condition is of any way a confounding variable affecting cognitive functioning (Feragen et al., 2014). Future studies should consider the assessment of brain structural data in reference to the subtype of OFCs, the side affected, additional congenital malformations or comorbidities, anamnestic data on neurodevelopment, age, and gender.

## Strengths and limitations

Our study has several important limitations. Most studies did not report participation rate or investigate the differences between participants and dropouts. We could not analyze structural brain differences across the subtypes of OFC and gender due to the small sample sizes. Most participants were Caucasian and originated from one register (University of Iowa Cleft Lip and Palate Registry). The clinic-based recruitment and the absence of blinding during the MRI procedures may have introduced bias. It was not possible to isolate data of the syndromic cases from the overall data of respective studies. Furthermore, the impact of surgical interventions on the developing brain could not be analyzed due to lack of data regarding the timing of the surgery, age of the patient, type of cleft repair surgery and anesthesia exposure. Only one study included the cleft repair status of its participants (Yang et al., 2012). Demographic factors, such as age and/or sex of the participants were provided by most of the included studies; however, there was a lack of detailed information of parental socio-economic factors including education and financial backgrounds. Parental socio-economic factors are known to strongly relate to the child's neurodevelopment (Noble et al., 2015; Rakesh and Whittle, 2021), and may be a crucial factor in the developing brain of children with OFCs. It is unclear how brain structural differences affect psychosocial functioning due to the variable assessment tools used in the included studies. The meta-analyses combined data across studies to estimate the effect of OFCs on brain structure. The main limitations of these meta-analyses are the incomplete reporting of study designs and the variable definition of the patient population across the studies. The interpretation and synthesis of the included studies may have been influenced by these factors. Applicability of our results may be affected due to the limited data for certain subgroups, such as cleft type and gender.

The current review has several strengths. To the best of our knowledge, this is the first study to have assessed the overall empirical evidence of brain imaging studies in OFCs carried out for over two decades. We were able to highlight possible sources of heterogeneity including sex, ethnicity, age, and syndromic cases of OFCs.

# Future directions

The future will underscore the importance of dedicated cleft teams with multidisciplinary expertise and experience in cleft excellence. The application of early interventions, special educational programmes, and proper parental support will aim at the goal of attaining outcomes where most children with OFCs develop and perform as well as their peers. Future studies with increasing sophistication may greatly benefit the clinical field in establishing more refined timely therapeutic interventions. These include such possible approaches as robotic surgical platforms (Al Omran et al., 2019), simplified rapid genetic testing, and early screening of executive functions to carefully monitor neurodevelopmental trajectories as a part of the complex therapy applied to OFC patients.

Stem cell-based interventions are becoming increasingly recognized in the medical field. They may in the future, offer novel approaches to the clinical care of OFC patients. Stem-cells may be used for example, in reconstructions to replace missing orofacial hard and soft tissues in the defects left behind the wake of malformations caused by the presence of a cleft (Sándor et al., 2014). Stem cells may also in the future, provide a new model for cleft research to monitor interneuronal development and identify key gene/protein pathways that are altered or dysregulated in these individuals (Drouin-Ouellet et al., 2017; Stüssel et al., 2022).

# Conclusions

Treating syndromic OFC patients is by nature, more complex than treating non-syndromic cleft patients. Syndromic patients require more attention and support for their multiple potential special needs from both the family and the health care facility, including the cleft teams. The surgical treatment of certain associated anomalies, such as heart defects and respiratory insufficiency, has priority over the timing of the reconstruction of the cleft lip and/or cleft palate in syndromic patients. The presence of a genetic syndrome may therefore notably affect the treatment algorithm of cleft repair surgeries.

Some Hungarian children with non-syndromic OFCs seem to be at risk for atypical cognitive and speech development compared to children not born with OFCs. Future studies with large sample sizes are needed to further explore this underlying etiology to identify this at-risk subpopulation, since not all children with non-syndromic OFCs present with such difficulties. Longitudinal studies are further needed to provide more evidence of baseline cognitive functioning to study early signs of atypical neurodevelopment and the effect of early interventions.

There may be structural brain differences between individuals with non-syndromic clefts and controls based on the available evidence, which may indicate a co-occurring brain involvement in orofacial clefts. Structural brain MRI studies may provide evidence on how the type and degree of clefts plays a role with later cognitive development and functioning. Improvement in study design, size, methodology, and participant selection may allow a more thorough analysis and decrease study heterogeneity.

# Acknowledgements

The research of the current thesis was carried out at the Department of Pediatrics of the University of Pécs, Hungary.

First and foremost, I would like to express my sincere gratitude to the University of Pécs, Prof. Dr. József Janszky and Prof. Dr. Tamás Tényi, and to Prof. Dr. Tamás Decsi, Clinical Director of the Department of Pediatrics, for providing this unique opportunity to learn and experience academic research in medicine.

I would like to express my deepest gratitude to my corresponding Supervisor, Prof. Dr. Györgyi Csábi, for always being there when I needed her support, reviewing my progress constantly, and guiding me through my PhD studies.

A special thanks to all the co-authors of the three publication that provided the basis for this thesis; Thank you Dr. Attila Vástyán, Dr. Kinga Hadzsiev, Prof. Dr. György Sándor, Dr. Barna Teodor, Dr. Anna Zsigmond, Dr. Ágnes Till, Edit Molnár, Dr. Tímea Dergez, Dr. Szimonetta Lohner, Dr. Georgios Antonoglou, Dr. Eszter Varga, and Dr. Asaad Sadi for the outstanding team work and diligence you provided for each project.

A very special thanks to the members of the Pécs Cleft Team, especially Dr. Attila Vástyán, for all your support and the amazing opportunity to be a part of your team. I would like to thank the members of the University Hospital Cleft Lip and Palate Centre in Oulu, Finland for making it possible for me to visit.

I would like to thank the patients of the Pécs Cleft Clinic who despite their own challenges are willing to participate in research. Without your contribution, cleft research in Hungary would not be possible.

I would like to highlight the following truly exceptional people from the University of Pécs; Dr. Szimonetta Lohner, Dr. Tímea Dergez, Edina Mendl, and Ildikó Csölle, who have shown immense support and have given me guidance during the most challenging times as a PhD student.

A special thanks to Dr. Karolina Pircs, Kilian Gutiérrez, Dr. Raul Alelú-Paz, Dr. Ariel Cariaga Martinez, and Dr. Jacob Vorstman, who took their time to teach me the most important aspects of neuropsychiatric research, and have truly inspired me to continue future research as a clinician.

I want to give my deepest appreciation to my parents, Prof. Dr. György Sándor and Dr. Cecilia Bajusz, for providing me with the best parental support and guidance throughout this journey. I would like to thank my siblings Enikő Sándor and Hunor Sándor, and my significant other, Gergely Sámson, for their support and keeping me sane throughout the whole process. I would further like to thank all my dear friends, specifically Laetitia Verville, for her support and amazing art skills which have greatly increased the value of this thesis.

This work was financially supported by the University of Pécs and the ÚNKP-21-3 New National Excellence Program of the Ministry for Culture and Innovation from the Source of the National Research, Development, and Innovation Fund.

# References


1. Abbas, A. I., Sundiang, M. J. M., Henoch, B., Morton, M. P., Bolkan, S. S., Park, A. J., et al. (2018). Somatostatin Interneurons Facilitate Hippocampal-Prefrontal Synchrony and Prefrontal Spatial Encoding. *Neuron* 100, 926-939.e3. doi: 10.1016/j.neuron.2018.09.029.
2. Achenbach, T. M. (1991). Manual for the Child Behavior Checklist/ 4—18 and 1991 profile. *Burlington: University of Vermont, Department of Psychiatry.*
3. Ács, L., Bányai, D., Nemes, B., Nagy, K., Ács, N., Bánhidy, F., et al. (2020). Maternal-related factors in the origin of isolated cleft palate—A population-based case-control study. *Orthod Craniofac Res* 23, 174–180. doi: 10.1111/ocr.12361.
4. Adamson, C. L., Anderson, V. A., Nopoulos, P., Seal, M. L., and Da Costa, A. C. (2014). Regional Brain Morphometric Characteristics of Nonsyndromic Cleft Lip and Palate. *Dev Neurosci* 36, 490–498. doi: 10.1159/000365389.
5. Al Omran, Y., Abdall-Razak, A., Ghassemi, N., Alomran, S., Yang, D., and Ghanem, A. M. (2019). Robotics in Cleft Surgery: Origins, Current Status and Future Directions. *Robot Surg* 6, 41–46. doi: 10.2147/RSRR.S222675.
6. Alade, A., Awotoye, W., and Butali, A. (2022). Genetic and epigenetic studies in non-syndromic oral clefts. *Oral Dis* 28, 1339–1350. doi: 10.1111/odi.14146.
7. Aleksieva, A., Begnoni, G., Verdonck, A., Laenen, A., Willems, G., and Cadenas de Llano-Pérula, M. (2021). Self-Esteem and Oral Health-Related Quality of Life within a Cleft Lip and/or Palate Population: A Prospective Cohort Study. *Int J Environ Res Public Health* 18. doi: 10.3390/ijerph18116078.
8. Al-Namankany, A., and Alhubaishi, A. (2018). Effects of cleft lip and palate on children's psychological health: A systematic review. *J Taibah Univ Med Sci* 13, 311–318. doi: 10.1016/j.jtumed.2018.04.007.
9. Ansen-Wilson, L. J., Everson, J. L., Fink, D. M., Kietzman, H. W., Sullivan, R., and Lipinski, R. J. (2018). Common basis for orofacial clefting and cortical interneuronopathy. *Transl Psychiatry* 8, 8. doi: 10.1038/s41398-017-0057-7.
10. Ansen-Wilson, L. J., and Lipinski, R. J. (2017). Gene-environment interactions in cortical interneuron development and dysfunction: A review of preclinical studies. *Neurotoxicology* 58, 120–129. doi: 10.1016/j.neuro.2016.12.002.
11. Ardila, A. (2018). Is intelligence equivalent to executive functions? *Psicothema* 30, 159–164. doi: 10.7334/psicothema2017.329.
12. Baxter, D., and Shanks, A. (2022). *Pierre Robin Syndrome.* . StatPearls [Internet]. Treasure Island (FL): StatPearls.
13. Becker, D. B., Coalson, R. S., Sachanandani, N. S., Fair, D., Lugar, H. M., Kirchner, L. E., et al. (2008). Functional neuroanatomy of lexical processing in children with cleft lip and palate. *Plast Reconstr Surg* 122. doi: 10.1097/PRS.0b013e3181881f54.
14. Bigatà, X., Bielsa, I., Artigas, M., Azón, A., Ribera, M., and Ferrándiz, C. (2003). The ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC): report of five cases. *Pediatr Dermatol* 20, 113–8. doi: 10.1046/j.1525-1470.2003.20203.x.
15. Bishop, M. R., Diaz Perez, K. K., Sun, M., Ho, S., Chopra, P., Mukhopadhyay, N., et al. (2020). Genome-wide Enrichment of De Novo Coding Mutations in Orofacial Cleft Trios. *The American Journal of Human Genetics* 107, 124–136. doi: 10.1016/j.ajhg.2020.05.018.
16. Bjørnland, T., Nørholt, S. E., Rasmusson, L., and Sándor, G. K. (2021). "Nordic Textbook of Oral and Maxillofacial Surgery," in (Munksgaard). Available at: https://books.google.hu/books?id=aR1rzgEACAAJ.
17. Bodoni, P. S. B., Leoni, R. F., do Vale, A. B., da Silva, P. H. R., Meira Junior, S. G., Richieri Costa, A., et al. (2021). Neuropsychological functioning and its relationship with

brain anatomical measures of children and adolescents with non-syndromic cleft lip and palate. *Child Neuropsychology* 27, 2–16. doi: 10.1080/09297049.2020.1776240.
18. Boes, A. D., Murko, V., Wood, J. L., Langbehn, D. R., Canady, J., Richman, L., et al. (2007). Social function in boys with cleft lip and palate: Relationship to ventral frontal cortex morphology. *Behavioural Brain Research* 181, 224–231. doi: 10.1016/J.BBR.2007.04.009.
19. Botto, L. D., May, K., Fernhoff, P. M., Correa, A., Coleman, K., Rasmussen, S. A., et al. (2003). A Population-Based Study of the 22q11.2 Deletion: Phenotype, Incidence, and Contribution to Major Birth Defects in the Population. *Pediatrics* 112, 101–107. doi: 10.1542/peds.112.1.101.
20. Brunetti, R., Gatto, C. del, and Delogu, F. (2014). eCorsi: implementation and testing of the Corsi block-tapping task for digital tablets. doi: 10.3389/fpsyg.2014.00939.
21. Bull, R., Espy, K. A., and Senn, T. E. (2004). A comparison of performance on the Towers of London and Hanoi in young children. *J Child Psychol Psychiatry* 45, 743–754. doi: 10.1111/j.1469-7610.2004.00268.x.
22. Cárdenas-Nieto, D., Forero-Castro, M., Esteban-Pérez, C., Martínez-Lozano, J., and Briceño-Balcázar, I. (2020). The 22q11.2 Microdeletion in Pediatric Patients with Cleft Lip, Palate, or Both and Congenital Heart Disease: A Systematic Review. *J Pediatr Genet* 09, 001–008. doi: 10.1055/s-0039-1698804.
23. Čeponien≐, R., Hukki, J., Cheour, M., Haapanen, M.-L., Ranta, R., and Näätänen, R. (1999). Cortical auditory dysfunction in children with oral clefts: relation with cleft type. *Clinical Neurophysiology* 110, 1921–1926. doi: 10.1016/S1388-2457(99)00152-2.
24. Chollet, M. B., DeLeon, V. B., Conrad, A. L., and Nopoulos, P. (2014). Morphometric analysis of brain shape in children with nonsyndromic cleft lip and/or palate. *J Child Neurol* 29. doi: 10.1177/0883073813510603.
25. Chollet, M. B., Nopoulos, P., Conrad, A., and DeLeon, V. (2010). Brain morphology of children with cleft lip and/or palate. *The FASEB Journal* 24. doi: 10.1096/fasebj.24.1_supplement.300.3.
26. Cochrane (2020). Review Manager (RevMan) [Computer program]. Version 5.4. *The Cochrane Collaboration*.
27. Coe, R. (2002). It's the effect size, stupid: what '"effect size"' is and why it is important. aper Presented at the British Educational Research Association Annual Conference. in, ed. R. Coe (Exeter). Available at: http://www.leeds.ac.uk/educol/documents/00002182.htm [Accessed January 28, 2023].
28. Conners, C. K. (2014). Conners CPT3, Continuous Performance Test 3rd Edition.
29. Conrad, A. L., Canady, J., Richman, L., and Nopoulos, P. (2008). Incidence of Neurological Soft Signs in Children with Isolated Cleft of the Lip or Palate. *Percept Mot Skills* 106, 197–206. doi: 10.2466/pms.106.1.197-206.
30. Conrad, A. L., Dailey, S., Richman, L., Canady, J., Karnell, M. P., Axelson, E., et al. (2010). Cerebellum structure differences and relationship to speech in boys and girls with nonsyndromic cleft of the lip and/or palate. *Cleft Palate-Craniofacial Journal* 47. doi: 10.1597/08-228.
31. Conrad, A. L., Richman, L., Nopoulos, P., and Dailey, S. (2009). Neuropsychological Functioning in Children with Non-Syndromic Cleft of the Lip and/or Palate. *Child Neuropsychology* 15, 471–484. doi: 10.1080/09297040802691120.
32. Conrad, A. L., Wermke, K., Eisenmann, M., Kuhlmann, E., Benavides, A., Koscik, T., et al. (2021). Preliminary evaluation of pre-speech and neurodevelopmental measures in 7–11-week-old infants with isolated oral clefts. *Pediatr Res* 89, 85–90. doi: 10.1038/s41390-020-0887-5.
33. Conte, F., Oti, M., Dixon, J., Carels, C. E. L., Rubini, M., and Zhou, H. (2016). Systematic analysis of copy number variants of a large cohort of orofacial cleft patients identifies

candidate genes for orofacial clefts. *Hum Genet* 135, 41–59. doi: 10.1007/s00439-015-1606-x.
34. Davies, R. W., Fiksinski, A. M., Breetvelt, E. J., Williams, N. M., Hooper, S. R., Monfeuga, T., et al. (2020). Using common genetic variation to examine phenotypic expression and risk prediction in 22q11.2 deletion syndrome. *Nat Med* 26, 1912–1918. doi: 10.1038/s41591-020-1103-1.
35. DeVolder, I., Conrad, A., Magnotta, V., and Nopoulos, P. (2015). Difficulties in timing perception related to abnormal brain structure in children and adolescents with nonsyndromic cleft lip and/or cleft palate. *Cleft Palate-Craniofacial Journal* 52, e110. Available at: https://www.embase.com/search/results?subaction=viewrecord&id=L617894309&from=export.
36. DeVolder, I., Conrad, A., Richman, L., Magnotta, V., and Nopoulos, P. C. (2014). White Matter Structure in Individuals With Isolated Cleft Lip and/or Palate: A Diffusion Tensor Imaging Study. in doi: https://doi.org/10.1597/1545-1569-51.3.11.
37. Devolder, I., Richman, L., Conrad, A. L., Magnotta, V., and Nopoulos, P. (2013). Abnormal cerebellar structure is dependent on phenotype of isolated cleft of the lip and/or palate. *Cerebellum* 12. doi: 10.1007/s12311-012-0418-y.
38. Diamond, A. (2013). Executive Functions. *Annu Rev Psychol* 64, 135–168. doi: 10.1146/annurev-psych-113011-143750.
39. Diaz-Stransky, A., and Tierney, E. (2012). Cognitive and behavioral aspects of Smith-Lemli-Opitz syndrome. *Am J Med Genet C Semin Med Genet* 160C, 295–300. doi: 10.1002/ajmg.c.31342.
40. Drouin-Ouellet, J., Pircs, K., Barker, R. A., Jakobsson, J., and Parmar, M. (2017). Direct Neuronal Reprogramming for Disease Modeling Studies Using Patient-Derived Neurons: What Have We Learned? *Front Neurosci* 11, 530. doi: 10.3389/fnins.2017.00530.
41. Feragen, K. B., Stock, N. M., and Rumsey, N. (2014). Toward a Reconsideration of Inclusion and Exclusion Criteria in Cleft Lip and Palate: Implications for Psychological Research. *The Cleft Palate-Craniofacial Journal* 51, 569–578. doi: 10.1597/12-326.
42. Ferguson, B. R., and Gao, W.-J. (2018). PV Interneurons: Critical Regulators of E/I Balance for Prefrontal Cortex-Dependent Behavior and Psychiatric Disorders. *Front Neural Circuits* 12. doi: 10.3389/fncir.2018.00037.
43. Fiksinski, A. M., Schneider, M., Zinkstok, J., Baribeau, D., Chawner, S. J. R. A., and Vorstman, J. A. S. (2021). Neurodevelopmental Trajectories and Psychiatric Morbidity: Lessons Learned From the 22q11.2 Deletion Syndrome. *Curr Psychiatry Rep* 23, 13. doi: 10.1007/s11920-021-01225-z.
44. Fitriasari, S., and Trainor, P. A. (2021). Diabetes, Oxidative Stress, and DNA Damage Modulate Cranial Neural Crest Cell Development and the Phenotype Variability of Craniofacial Disorders. *Front Cell Dev Biol* 9. doi: 10.3389/fcell.2021.644410.
45. Galil, A., Carmi, R., Goldstein, E., Porter, B., Bar Ziv, J., and Chemke, J. (1991). Weissenbacher-Zweymuller syndrome: long-term follow-up of growth and psychomotor development. *Dev Med Child Neurol* 33, 1104–9. doi: 10.1111/j.1469-8749.1991.tb14834.x.
46. Gallagher, E. R., and Collett, B. R. (2019). Neurodevelopmental and Academic Outcomes in Children With Orofacial Clefts: A Systematic Review. *Pediatrics* 144. doi: 10.1542/peds.2018-4027.
47. Gallagher, E. R., Siebold, B., Collett, B. R., Cox, T. C., Aziz, V., and Cunningham, M. L. (2018). Associations between laterality of orofacial clefts and medical and academic outcomes. *Am J Med Genet A* 176, 267–276. doi: 10.1002/ajmg.a.38567.
48. Glinianaia, S. V., McLean, A., Moffat, M., Shenfine, R., Armaroli, A., and Rankin, J. (2021). Academic achievement and needs of school-aged children born with selected

congenital anomalies: A systematic review and meta-analysis. *Birth Defects Res* 113, 1431–1462. doi: 10.1002/bdr2.1961.
49. Godbout, A., Leclerc, J. E., Arteau-Gauthier, I., and Leclerc, L.-D. (2014). Isolated versus Pierre Robin Sequence Cleft Palates: Are They Different? *The Cleft Palate-Craniofacial Journal* 51, 406–411. doi: 10.1597/12-261.
50. Goffinet, A. M. (2006). What makes us human? A biased view from the perspective of comparative embryology and mouse genetics. *J Biomed Discov Collab* 1, 16. doi: 10.1186/1747-5333-1-16.
51. Grizzle, R. (2011). "Wechsler Intelligence Scale for Children, Fourth Edition," in *Encyclopedia of Child Behavior and Development*, eds. S. Goldstein and J. A. Naglieri (Boston, MA: Springer US), 1553–1555. doi: 10.1007/978-0-387-79061-9_3066.
52. Gustafsson, C., Vuola, P., Leikola, J., and Heliövaara, A. (2020). Pierre Robin Sequence: Incidence of Speech-Correcting Surgeries and Fistula Formation. *The Cleft Palate-Craniofacial Journal* 57, 344–351. doi: 10.1177/1055665619874991.
53. Hardin-Jones, M., and Chapman, K. (2011). Cognitive and Language Issues Associated with Cleft Lip and Palate. *Semin Speech Lang* 32, 127–140. doi: 10.1055/s-0031-1277715.
54. Hardwicke, J. T., Richards, H., Cafferky, L., Underwood, I., Horst, B. ter, and Slator, R. (2016). Outcomes of Cleft Palate Repair in Patients with Pierre Robin Sequence. *Plast Reconstr Surg* 137, 927–935. doi: 10.1097/01.prs.0000475829.32402.a8.
55. Huang, L., Jia, Z., Shi, Y., Du, Q., Shi, J., Wang, Z., et al. (2019). Genetic factors define CPO and CLO subtypes of nonsyndromicorofacial cleft. *PLoS Genet* 15, e1008357. doi: 10.1371/journal.pgen.1008357.
56. Hunt, O., Burden, D., Hepper, P., and Johnston, C. (2005). The psychosocial effects of cleft lip and palate: a systematic review. *Eur J Orthod* 27, 274–285. doi: 10.1093/ejo/cji004.
57. Hwang, V. J., Maar, D., Regan, J., Angkustsiri, K., Simon, T. J., and Tassone, F. (2014). Mapping the deletion endpoints in individuals with 22q11.2 Deletion Syndrome by droplet digital PCR. *BMC Med Genet* 15, 106. doi: 10.1186/s12881-014-0106-5.
58. Izumi, K., Konczal, L. L., Mitchell, A. L., and Jones, M. C. (2012). Underlying Genetic Diagnosis of Pierre Robin Sequence: Retrospective Chart Review at Two Children's Hospitals and a Systematic Literature Review. *J Pediatr* 160, 645-650.e2. doi: 10.1016/j.jpeds.2011.09.021.
59. Ji, Y., Garland, M. A., Sun, B., Zhang, S., Reynolds, K., McMahon, M., et al. (2020). Cellular and developmental basis of orofacial clefts. *Birth Defects Res* 112, 1558–1587. doi: 10.1002/bdr2.1768.
60. Jones, N. C., Lynn, M. L., Gaudenz, K., Sakai, D., Aoto, K., Rey, J.-P., et al. (2008). Prevention of the neurocristopathy Treacher Collins syndrome through inhibition of p53 function. *Nat Med* 14, 125–133. doi: 10.1038/nm1725.
61. Junaid, M., Slack-Smith, L., Wong, K., Bourke, J., Baynam, G., Calache, H., et al. (2022). Association between craniofacial anomalies, intellectual disability and autism spectrum disorder: Western Australian population-based study. *Pediatr Res* 92, 1795–1804. doi: 10.1038/s41390-022-02024-9.
62. Kaller, C. P., Unterrainer, J. M., Stefan, K., Weisbrod, M., Debelak, R., and Aschenbrenner, S. (2011). Tower of London- Freiburg Version (TOL-F).
63. Kessels, R. P. C., van Zandvoort, M. J. E., Postma, A., Kappelle, L. J., and de Haan, E. H. F. (2000). The Corsi Block-Tapping Task: Standardization and normative data. *Appl Neuropsychol* 7, 252–258. doi: 10.1207/S15324826AN0704_8.
64. Kocaaslan, F. N. D., Sendur, S., Koçak, I., and Çelebiler, Ö. (2020). The Comparison of Pierre Robin Sequence and Non-Syndromic Cleft Palate. *J Craniofac Surg* 31, 226–229. doi: 10.1097/SCS.0000000000005961.

65. Kondo, S., Schutte, B. C., Richardson, R. J., Bjork, B. C., Knight, A. S., Watanabe, Y., et al. (2002). Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. *Nat Genet* 32, 285–289. doi: 10.1038/ng985.
66. Kouskoura, T., Fragou, N., Alexiou, M., John, N., Sommer, L., Graf, D., et al. (2011). The genetic basis of craniofacial and dental abnormalities. *Schweiz Monatsschr Zahnmed* 121, 636–46.
67. Kucukguven, A., Calis, M., Topaloglu, H., and Ozgur, F. (2018). Assessment of Neurologic Disorders and Rare Intracranial Anomalies Associated With Cleft Lip and Palate. *Journal of Craniofacial Surgery* 29, 2195–2197. doi: 10.1097/SCS.0000000000004848.
68. Kummer, A. W., Lee, L., Stutz, L. S., Maroney, A., and Brandt, J. W. (2007). The prevalence of apraxia characteristics in patients with velocardiofacial syndrome as compared with other cleft populations. *Cleft Palate-Craniofacial Journal* 44. doi: 10.1597/05-170.1.
69. Lehtonen, V., Lithovius, R. H., Autio, T. J., Sándor, G. K., Ylikontiola, L. P., Harila, V., et al. (2016). Middle ear findings and need for ventilation tubes among pediatric cleft lip and palate patients in northern Finland. *Journal of Cranio-Maxillofacial Surgery* 44, 460–464. doi: 10.1016/j.jcms.2016.01.006.
70. LEI, T.-Y., WANG, H.-T., LI, F., CUI, Y.-Q., FU, F., LI, R., et al. (2016). Application of high resolution SNP arrays in patients with congenital oral clefts in south China. *J Genet* 95, 801–809. doi: 10.1007/s12041-016-0696-0.
71. Le Magueresse, C., and Monyer, H. (2013). GABAergic Interneurons Shape the Functional Maturation of the Cortex. *Neuron* 77, 388–405. doi: 10.1016/j.neuron.2013.01.011.
72. Leslie, E. J., Carlson, J. C., Shaffer, J. R., Butali, A., Buxó, C. J., Castilla, E. E., et al. (2017). Genome-wide meta-analyses of nonsyndromic orofacial clefts identify novel associations between FOXE1 and all orofacial clefts, and TP63 and cleft lip with or without cleft palate. *Hum Genet* 136, 275–286. doi: 10.1007/s00439-016-1754-7.
73. Li, C., Lan, Y., and Jiang, R. (2017). Molecular and Cellular Mechanisms of Palate Development. *J Dent Res* 96, 1184–1191. doi: 10.1177/0022034517703580.
74. Li, Z., Zhang, W., Li, C., Wang, M., Wang, S., Chen, R., et al. (2020). Articulation rehabilitation induces cortical plasticity in adults with non-syndromic cleft lip and palate. *Aging* 12, 13147–13159. doi: 10.18632/aging.103402.
75. Lithovius, R. H., Ylikontiola, L. P., Harila, V., and Sándor, G. K. (2014). A descriptive epidemiology study of cleft lip and palate in Northern Finland. *Acta Odontol Scand* 72, 372–375. doi: 10.3109/00016357.2013.840737.
76. Maarse, W., Rozendaal, A. M., Pajkrt, E., Vermeij-Keers, C., Mink van der Molen, A. B., and van den Boogaard, M.-J. H. (2012). A systematic review of associated structural and chromosomal defects in oral clefts: when is prenatal genetic analysis indicated? *J Med Genet* 49, 490–8. doi: 10.1136/jmedgenet-2012-101013.
77. Malvankar, D. D., Sacchidanand, S., and Mallikarjun, M. (2012). Ectrodactyly, ectodermal dysplasia, and cleft lip-palate (EEC) syndrome without clefting: a rare case report. *Dermatol Online J* 18, 5.
78. Marín, O. (2012). Interneuron dysfunction in psychiatric disorders. *Nat Rev Neurosci* 13, 107–120. doi: 10.1038/nrn3155.
79. McDonald-McGinn, D., Hain, H., Emanuel, B., and Zackai, E. (2020). *22q11.2 Deletion Syndrome*. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023.
80. Mossey, P. A., and Modell, B. (2012). "Epidemiology of oral clefts 2012: An international perspective," in *Cleft Lip and Palate: Epidemiology, Aetiology and Treatment* (S. Karger AG), 1–18. doi: 10.1159/000337464.

81. Mossey, P. A., Shaw, W. C., Munger, R. G., Murray, J. C., Murthy, J., and Little, J. (2011). Global Oral Health Inequalities: Challenges in the prevention and management of orofacial clefts and potential solutions. *Adv Dent Res* 23, 247–258. doi: 10.1177/0022034511402083.
82. Mueller, A. A., Sader, R., Honigmann, K., Zeilhofer, H. F., and Schwenzer-Zimmerer, K. (2007). Central nervous malformations in presence of clefts reflect developmental interplay. *Int J Oral Maxillofac Surg* 36. doi: 10.1016/j.ijom.2006.10.018.
83. Naidoo, R., Shuttleworth-Edwards, A. B., Botha, R., and Pienaar, I. (2019). The Tower of London-DX 2nd Edition test: Preliminary norms for educationally disadvantaged Xhosa-speaking individuals. *Journal of Psychology in Africa* 29, 60–66. doi: 10.1080/14330237.2019.1568074.
84. Nilsson, S., Merlo, J., Lyberg-Åhlander, V., and Psouni, E. (2015). Psychotropic drug use in adolescents born with an orofacial cleft: a population-based study. *BMJ Open* 5, e005306. doi: 10.1136/bmjopen-2014-005306.
85. Noble, K. G., Houston, S. M., Brito, N. H., Bartsch, H., Kan, E., Kuperman, J. M., et al. (2015). Family income, parental education and brain structure in children and adolescents. *Nat Neurosci* 18, 773–778. doi: 10.1038/nn.3983.
86. Nopoulos, P., Berg, S., Canady, J., Richman, L., Demark, D. Van, and Andreasen, N. C. (2000). Abnormal Brain Morphology in Patients With Isolated Cleft Lip, Cleft Palate, or Both: A Preliminary Analysis. *The Cleft Palate-Craniofacial Journal* 37, 441–446. doi: 10.1597/1545-1569(2000)037<0441:ABMIPW>2.0.CO;2.
87. Nopoulos, P., Berg, S., Canady, J., Richman, L., Van Demark, D., and Andreasen, N. C. (2002a). Structural brain abnormalities in adult males with clefts of the lip and/or palate. *Genetics in Medicine* 4, 1–9. doi: 10.1097/00125817-200201000-00001.
88. Nopoulos, P., Berg, S., VanDemark, D., Richman, L., Canady, J., and Andreasen, N. C. (2001). Increased incidence of a midline brain anomaly in patients with nonsyndromic clefts of the lip and/or palate. *Journal of Neuroimaging* 11. doi: 10.1111/j.1552-6569.2001.tb00072.x.
89. Nopoulos, P., Berg, S., VanDemark, D., Richman, L., Canady, J., and Andreasen, N. C. (2002b). Cognitive dysfunction in adult males with non-syndromic clefts of the lip and/or palate. *Neuropsychologia* 40, 2178–2184. doi: 10.1016/S0028-3932(02)00043-X.
90. Nopoulos, P., Boes, A. D., Jabines, A., Conrad, A. L., Canady, J., Richman, L., et al. (2010a). Hyperactivity, impulsivity, and inattention in boys with cleft lip and palate: relationship to ventromedial prefrontal cortex morphology. *J Neurodev Disord* 2, 235–242. doi: 10.1007/s11689-010-9060-5.
91. Nopoulos, P., Boes, A. D., Jabines, A., Conrad, A. L., Canady, J., Richman, L., et al. (2010b). Hyperactivity, impulsivity, and inattention in boys with cleft lip and palate: relationship to ventromedial prefrontal cortex morphology. *J Neurodev Disord* 2, 235–242. doi: 10.1007/s11689-010-9060-5.
92. Nopoulos, P., Choe, I., Berg, S., Van Demark, D., Canady, J., and Richman, L. (2005). Ventral Frontal Cortex Morphology in Adult Males with Isolated Orofacial Clefts: Relationship to Abnormalities in Social Function. *The Cleft Palate-Craniofacial Journal* 42, 138–144. doi: 10.1597/03-112.1.
93. Nopoulos, P., Langbehn, D. R., Canady, J., Magnotta, V., and Richman, L. (2007a). Abnormal Brain Structure in Children With Isolated Clefts of the Lip or Palate. *Arch Pediatr Adolesc Med* 161, 753. doi: 10.1001/archpedi.161.8.753.
94. Nopoulos, P., Richman, L., Andreasen, N., Murray, J. C., and Schutte, B. (2007b). Cognitive dysfunction in adults with Van der Woude syndrome. *Genetics in Medicine* 9, 213–218. doi: 10.1097/GIM.0b013e3180335abd.

95. Nopoulos, P., Richman, L., Andreasen, N., Murray, J., and Schutte, B. (2007c). Abnormal brain structure in adults with Van der Woude syndrome. *Clin Genet* 71, 511–517. doi: 10.1111/j.1399-0004.2007.00799.x.
96. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372, n71. doi: 10.1136/bmj.n71.
97. Parris, B. A. (2014). Task conflict in the Stroop task: When Stroop interference decreases as Stroop facilitation increases in a low task conflict context. *Front Psychol* 5. doi: 10.3389/fpsyg.2014.01182.
98. Pedersen, D. A., Wehby, G. L., Murray, J. C., and Christensen, K. (2016). Psychiatric Diagnoses in Individuals with Non-Syndromic Oral Clefts: A Danish Population-Based Cohort Study. *PLoS One* 11, e0156261. doi: 10.1371/journal.pone.0156261.
99. Pfisterer, U., Petukhov, V., Demharter, S., Meichsner, J., Thompson, J. J., Batiuk, M. Y., et al. (2020). Identification of epilepsy-associated neuronal subtypes and gene expression underlying epileptogenesis. *Nat Commun* 11, 5038. doi: 10.1038/s41467-020-18752-7.
100. Pool, S. M. W., der Lek, L. M. van, de Jong, K., Vermeij-Keers, C., and Mouës-Vink, C. M. (2021). Embryologically Based Classification Specifies Gender Differences in the Prevalence of Orofacial Cleft Subphenotypes. *The Cleft Palate-Craniofacial Journal* 58, 54–60. doi: 10.1177/1055665620935363.
101. PsyWay (2020). PsyWay Pszichológiai tesztek online kiértékelése. Available at: http://www.pszichotesztek.hu.
102. Rakesh, D., and Whittle, S. (2021). Socioeconomic status and the developing brain – A systematic review of neuroimaging findings in youth. *Neurosci Biobehav Rev* 130, 379–407. doi: 10.1016/J.NEUBIOREV.2021.08.027.
103. Richman, L. C., McCoy, T. E., Conrad, A. L., and Nopoulos, P. C. (2012). Neuropsychological, behavioral, and academic sequelae of cleft: Early developmental, school age, and adolescent/young adult outcomes. *Cleft Palate-Craniofacial Journal* 49. doi: 10.1597/10-237.
104. Richman, L. C., and Ryan, S. M. (2003). Do the Reading Disabilities of Children with Cleft Fit into Current Models of Developmental Dyslexia? *The Cleft Palate-Craniofacial Journal* 40, 154–157. doi: 10.1597/1545-1569_2003_040_0154_dtrdoc_2.0.co_2.
105. Rincic, M., Rados, M., Krsnik, Z., Gotovac, K., Borovecki, F., Liehr, T., et al. (2016). Complex intrachromosomal rearrangement in 1q leading to 1q32.2 microdeletion: a potential role of SRGAP2 in the gyrification of cerebral cortex. *Mol Cytogenet* 9, 19. doi: 10.1186/s13039-016-0221-4.
106. Roebuck, H., Freigang, C., and Barry, J. G. (2016). Continuous Performance Tasks: Not Just About Sustaining Attention. *Journal of Speech, Language, and Hearing Research* 59, 501–510. doi: 10.1044/2015_JSLHR-L-15-0068.
107. Rózsa S, Kő N, and Gádoros J (1999). A gyermekpszichiátriai zavarok kérdőíves mérése: Agyermekviselkedési kérdőív diagnosztikai megbízhatósága és a több információ forrásonalapuló jellemzések egyezése. *Psychiatria Hungarica* 4.
108. Salari, N., Darvishi, N., Heydari, M., Bokaee, S., Darvishi, F., and Mohammadi, M. (2022). Global prevalence of cleft palate, cleft lip and cleft palate and lip: A comprehensive systematic review and meta-analysis. *J Stomatol Oral Maxillofac Surg* 123, 110–120. doi: 10.1016/j.jormas.2021.05.008.
109. Saleem, K., Zaib, T., Sun, W., and Fu, S. (2019). Assessment of candidate genes and genetic heterogeneity in human non syndromic orofacial clefts specifically non syndromic cleft lip with or without palate. *Heliyon* 5, e03019. doi: 10.1016/j.heliyon.2019.e03019.
110. Sándor, G. K., Numminen, J., Wolff, J., Thesleff, T., Miettinen, A., Tuovinen, V. J., et al. (2014). Adipose stem cells used to reconstruct 13 cases with cranio-maxillofacial hard-tissue defects. *Stem Cells Transl Med* 3, 530–40. doi: 10.5966/sctm.2013-0173.

111. Sárközi, A., Wyszynski, D. F., and Czeizel, A. E. (2005). Oral clefts with associated anomalies: findings in the Hungarian Congenital Abnormality Registry. *BMC Oral Health* 5, 4. doi: 10.1186/1472-6831-5-4.
112. Scarpina, F., and Tagini, S. (2017). The stroop color and word test. *Front Psychol* 8. doi: 10.3389/fpsyg.2017.00557.
113. Schutte, B., Saal, H., Goudy, S., and Leslie, E. (2021). *IRF6-Related Disorders.* . GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023.
114. Scott, N. M., Weinberg, S. M., Neiswanger, K., Brandon, C. A., and Marazita, M. L. (2005). Hair whorls and handedness: Informative phenotypic markers in nonsyndromic cleft lip with or without cleft palate (NS CL/P) cases and their unaffected relatives. *Am J Med Genet* 136 A, 158–161. doi: 10.1002/ajmg.a.30806.
115. Shen, E. Y., and Huang, F. Y. (1996). Cleft lip and palate associated with malformation of the central nervous system: a prospective neurosonographic study. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 37.
116. Shriver, A. S., Canady, J., Richman, L., Andreasen, N. C., and Nopoulos, P. (2006). Structure and function of the superior temporal plane in adult males with cleft lip and palate: Pathologic enlargement with no relationship to childhood hearing deficits. *J Child Psychol Psychiatry* 47. doi: 10.1111/j.1469-7610.2006.01679.x.
117. Skorput, A. G. J., Gupta, V. P., Yeh, P. W. L., and Yeh, H. H. (2015). Persistent Interneuronopathy in the Prefrontal Cortex of Young Adult Offspring Exposed to Ethanol In Utero. *Journal of Neuroscience* 35, 10977–10988. doi: 10.1523/JNEUROSCI.1462-15.2015.
118. Speltz, M. L. (2000). Brief Report: Cognitive and Psychomotor Development of Infants With Orofacial Clefts. *J Pediatr Psychol* 25, 185–190. doi: 10.1093/jpepsy/25.3.185.
119. Stüssel, L. G., Hollstein, R., Laugsch, M., Hochfeld, L. M., Welzenbach, J., Schröder, J., et al. (2022). MiRNA-149 as a Candidate for Facial Clefting and Neural Crest Cell Migration. *J Dent Res* 101, 323–330. doi: 10.1177/00220345211038203.
120. Tan, T. Y., Kilpatrick, N., and Farlie, P. G. (2013). Developmental and genetic perspectives on Pierre Robin sequence. *Am J Med Genet C Semin Med Genet* 163, 295–305. doi: 10.1002/ajmg.c.31374.
121. Tillman, K. K., Hakelius, M., Höijer, J., Ramklint, M., Ekselius, L., Nowinski, D., et al. (2018). Increased Risk for Neurodevelopmental Disorders in Children With Orofacial Clefts. *J Am Acad Child Adolesc Psychiatry* 57, 876–883. doi: 10.1016/j.jaac.2018.06.024.
122. Tollefson, T. T., and Sykes, J. M. (2010). Differences in brain structure related to laterality of cleft lip. *Arch Facial Plast Surg* 12. doi: 10.1001/archfacial.2010.83.
123. Unterrainer, J. M., Rahm, B., Kaller, C. P., Leonhart, R., Quiske, K., Hoppe-Seyler, K., et al. (2004). Planning abilities and the Tower of London: Is this task measuring a discrete cognitive function? *J Clin Exp Neuropsychol* 26, 846–856. doi: 10.1080/13803390490509574.
124. Van Der Plas, E., Conrad, A., Canady, J., Richman, L., and Nopoulos, P. (2010). Effects of Unilateral Clefts on Brain Structure.
125. van Duin, E. D. A., Ceccarini, J., Booij, J., Kasanova, Z., Vingerhoets, C., van Huijstee, J., et al. (2020). "Lower [18F]fallypride binding to dopamine D2/3 receptors in frontal brain areas in adults with 22q11.2 deletion syndrome: a positron emission tomography study." . *Psychol Med* 50, 799–807. doi: 10.1017/S003329171900062X.
126. Venkatesh, R. (2009). Syndromes and anomalies associated with cleft. *Indian Journal of Plastic Surgery* 42, 51. doi: 10.4103/0970-0358.57187.
127. Watkins, S. E., Meyer, R. E., Aylsworth, A. S., Marcus, J. R., Allori, A. C., Pimenta, L., et al. (2018). Academic achievement among children with nonsyndromic orofacial clefts: A population-based study. *Cleft Palate-Craniofacial Journal* 55. doi: 10.1177/1055665617718823.

128. Weinberg, S. M., Andreasen, N. C., and Nopoulos, P. (2009). Three-dimensional morphometric analysis of brain shape in nonsyndromic orofacial clefting. *J. Anat* 214, 926–936. doi: 10.1111/j.1469-7580.2009.01084.x.
129. Weinberg, S. M., Parsons, T. E., Fogel, M. R., Walter, C. P., Conrad, A. L., and Nopoulos, P. (2013). Corpus Callosum Shape Is Altered in Individuals With Nonsyndromic Cleft Lip and Palate. *Am J Med Genet A* 161. doi: 10.1002/ajmg.a.35835.
130. Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., et al. (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Ottawa, ON: Ottawa Hospital Research Institute*.
131. World Health Organization. (2004). *ICD-10 : international statistical classification of diseases and related health problems. 10th revision.* 2nd edition.
132. Yang, F. F., McPherson, B., Shu, H., Xie, N., and Xiang, K. (2012). Structural abnormalities of the central auditory pathway in infants with nonsyndromic cleft lip and/or palate. *Cleft Palate-Craniofacial Journal* 49. doi: 10.1597/11-014.
133. Zheng, W., Li, B., Zou, Y., and Lou, F. (2019). The prenatal diagnosis and classification of cleft palate: the role and value of magnetic resonance imaging. *Eur Radiol* 29. doi: 10.1007/s00330-019-06089-9.
134. Zinkstok, J. R., Boot, E., Bassett, A. S., Hiroi, N., Butcher, N. J., Vingerhoets, C., et al. (2019). Neurobiological perspective of 22q11.2 deletion syndrome. *Lancet Psychiatry* 6, 951–960. doi: 10.1016/S2215-0366(19)30076-8.

# List of own publications

## Publications related to the Doctoral Thesis

**Total impact factor: 8,845**

1. **Sándor-Bajusz KA**, Dergez T, Molnár E, Hadzsiev K, Till Á, Zsigmond A, Vástyán A, Csábi G. *COGNITIVE FUNCTIONING AND CLINICAL CHARACTERISTICS OF CHILDREN WITH NON-SYNDROMIC OROFACIAL CLEFTS: A CASE-CONTROL STUDY*. Front Psychol 2023 Feb 28;14. doi: 10.3389/fpsyg.2023.1115304. **IF: 4,232**

2. **Sándor-Bajusz KA**, Sadi A, Varga E, Csábi G, Antonoglou G and Lohner Sz. *THE BRAIN IN ORAL CLEFTING: A SYSTEMATIC REVIEW WITH META-ANALYSES.* Front Neuroanat 2022 Jun 10;16:863900. doi: 10.3389/fnana.2022.863900. PMID: 35756498. **IF: 3,543**

*3.* **Sándor-Bajusz KA**, Maros T, Olasz L, Sándor G, Hadzsiev K and Vástyán A. *THE INFLUENCE OF GENETIC SYNDROMES ON THE ALGORITHM OF CLEFT LIP AND PALATE REPAIR – A RETROSPECTIVE STUDY.* Ann Maxillofac Surg. 2021 Nov 29. doi: 10.4103/ams.ams_77_21. Ahead of print. PMID: 35265497. PMID: 35833477. **IF: 1,07**

# Conference abstracts related to the Doctoral Thesis

**Total impact factor: 12,571**

1. **Sándor-Bajusz KA**, Molnár E, Dergez T, Hadzsiev K, Vástyán A, Csábi G. *EARLY LANGUAGE INTERVENTION AND IQ OF CHILDREN WITH NON-SYNDROMIC ORAL CLEFTS.* 6th Hungarian Neuroscience Meeting for Undergraduate Students, Graduate Students and young Post-Docs (HuNDoC 2023). Budapest, January 31, 2023.

2. **Sándor-Bajusz KA**, Dergez T, Vástyán A, Csábi G. *NEUROPSZICHIÁTRIAI ZAVAROK AJAK- ÉS SZÁJPADHASADÉKKAL SZÜLETETT GYERMEKEKBEN* [Neuropsychiatric disorders in children born with oral clefts]. Hungarian Paediatric Association, Annual National Paediatric Congress, Kecskemét, Hungary. September 15-17, 2022. GYERMEKGYÓGYÁSZAT 73 : 5 pp. 394-394. , 1 p.

3. **Sándor-Bajusz KA**, Sadi A, Varga E, Csábi G, Antonoglou G, Lohner S. *THE BRAIN IN ORAL CLEFTING: PRELIMINARY RESULTS OF A SYSTEMATIC REVIEW WITH META-ANALYSES.* EPA 30th European Congress of Psychiatry, Budapest. June 4-7, 2022. EUROPEAN PSYCHIATRY 65(S1):S641-S641. doi: 10.1192/j.eurpsy.2022.1644. **IF: 7,156**

4. **Sándor-Bajusz KA**, Molnár E, Dergez T, Hadzsiev K, Vástyán A, Csábi G. *EXECUTIVE FUNCTIONS OF CHILDREN WITH ORAL CLEFTS: A PILOT STUDY.* 19th International Congress of ESCAP, Maastricht, The Netherlands. June 19-21, 2022.

5. **Sándor-Bajusz KA**, Varga E, Antonoglou GA, Lohner S. *BRAIN STRUCTURE OF INDIVIDUALS WITH ORAL CLEFTS: FIRST RESULTS OF A SYSTEMATIC REVIEW WITH META-ANALYSES.* 34th ECNP Congress, Lisbon, Portugal. October 2-5, 2021. EUROPEAN NEUROPSYCHOPHARMACOLOGY 53(S1): S147. doi: 10.1016/j.euroneuro.2021.10.194. **IF: 5,415**

6. **Sándor-Bajusz KA**, Molnár E, Dergez T, Hadzsiev K, Vástyán A, Csábi G. *KOGNITÍV FUNKCIÓK VIZSGÁLATA AJAK- ÉS SZÁJPADHASADÉKKAL SZÜLETETT GYERMEKEKBEN: ELŐZETES EREDMÉNYEK* (*COGNITIVE FUNCTION OF CHILDREN WITH ORAL CLEFTS: A PILOT STUDY).* Hungarian Paediatric Association, Annual National Paediatric Congress, Pécs, Hungary. May 24-26, 2021.

7. **Sándor-Bajusz KA**, Molnár E, Dergez T, Hadzsiev K, Vástyán A, Csábi G. *COGNITIVE FUNCTION OF CHILDREN WITH ORAL CLEFTS: A PILOT STUDY.* MedPECS (Medical Conference for PhD Students and Experts of Clinical Sciences), Pécs, Hungary. May 15, 2021

# Other publications

**Total impact factor: 21,164**

1. **Sándor-Bajusz KA**, Kraut Andrea, Baasan O, Máarovics G, Berényi K and Lohner S. *PUBLICATION OF CLINICAL TRIALS ON MEDICINAL PRODUCTS: A FOLLOW-UP STUDY*. Trials. 2022 Apr 21;23(1):330. doi: 10.1186/s13063-022-06268-y. PMID: 35449017. **IF: 2,754**

2. Nagy D, **Sándor-Bajusz KA**, Bódy B, Decsi T, van Harsselaar J, Theis S, Lohner S (2021). *EFFECT OF CHICORY-DERIVED INULIN-TYPE FRUCTANS ON ABUNDANCE OF BIFIDOBACTERIUM AND ON BOWEL FUNCTION: A SYSTEMATIC REVIEW WITH META-ANALYSES.* Crit Rev Food Sci Nutr. 2022 Jul 14:1-18. doi: 10.1080/10408398.2022.2098246. **IF: 11,208**

**3.** Mendez-Echevarria A, **Sándor-Bajusz KA**, Calvo C. *SEVERE SINUS BRADYCARDIA ASSOCIATED WITH REMDESIVIR IN A CHILD WITH SEVERE SARS-COV-2 INFECTION-REPLY*. Eur J Pediatr. 2021 Jan 19:1–2. doi: 10.1007/s00431-021-03952-0. PMID: 33464367. **IF: 3,601**

4. Méndez-Echevarría A, Pérez-Martínez A, Gonzalez Del Valle L, Ara MF, Melendo S, Ruiz de Valbuena M, Vazquez-Martinez JL, Morales-Martínez A, Remesal A, **Sándor-Bajusz KA**, Cabañas F, Calvo C. *COMPASSIONATE USE OF REMDESIVIR IN CHILDREN WITH COVID-19*. Eur J Pediatr. 2020 Nov 16:1–6. doi: 10.1007/s00431-020-03876-1. PMID: 33200304. **IF: 3,601**

# Appendix

Parental Questionnaire generated for the study (original version in Hungarian)

1

PTE KK GYERMEKGYÓGYÁSZATI KLINIKA

## Szülői Kérdőív

Ajak- és szájpadhasadékos kutatásban résztvevő gyermekek szülei részére

**GYERMEKÉT ILLETŐ KÉRDÉSEK:**

**Terhesség alatti időszak:**

1. Ikerterhességnek indult?
   - Nem
   - Igen
2. Terhesség alatt történt-e:
   - Dohányzás
   - Alkohol fogyasztás
   - Egyéb drog, kábítószer fogyasztás
   - Az alábbi gyógyszerek szedése:
     - Antiepileptikum: Phenytoin, Carbamazepine
     - Antiemetikum: Thietylperazine
     - Antibiotikum: Oxytetracycline
   - Egyéb:_____
3. Ha igen, a terhesség melyik szakaszában történt?
   - 1. trimeszter (1-3 hónap)
   - 2. trimeszter (4-7 hónap)
   - 3. trimeszter (7-9 hónap)
   - A terhesség alatt mindvégig

4. Terhesség alatt történt-e:
    - Magas vérnyomás
    - Diabetes (magas vércukor)
    - Fertőzés (Toxoplasma gondii, (egyéb mikrobák), Rubeola vírus, Cytomegalovírus, Herpes simplex vírusok)
    - Egyéb

5. Ha az "egyéb" opciót választotta, kérjük részletezze:

_____

6. Hányadik terhesség volt? _____

7. Történt-e megelőző művi/ spontán abortusz (vetélés)?
    - Spontán
    - Művi (mütét)
    - Művi (gyógyszer)
    - Nem történt

**Gyermeke születése:**

8. Gyermeke melyik terhességi héten született?
9. Milyen APGAR pontszámmal?
10. Milyen testsúllyal, testhosszal, fejkörfogattal?
11. Milyen úton született?
    - Természetes
    - Császár
12. Milyen ajak- és/vagy szájpadhasadékkal született (tipus, oldal)?

    _____

13. Születését követően hány napig kellett kórházban tartózkodni?

    _____

14. Születését követően, gyermekének szüksége volt-e:
    - Légzéstámogatás
    - Antibiotikum terápia
    - Kékfény
    - Egyéb
    - Nem volt szükség
15. Ha az "egyéb" opciót választotta, kérjük részletezze:

_____

**Gyermeke fejlődése:**

16. Mikor (hány hónaposan) kezdett el gyermeke:
    - forogni:
    - ülni:
    - kúszni:
    - mászni:
    - járni:
    - Normál ütemben, vagy voltak kihagyások?
17. Mikor mondta első szavait?

_____

18. Mikor beszélt tő- majd összefüggő mondatokban?

_____

19. Szobatisztasága hány hónap-éves korban alakult ki?

_____

20. Visszaesések voltak?

_____

21. Táplálással voltak-e nehézségek?

_____

**Gyermeke hallása:**

22. Hallásával gondok voltak?

_____

23. Hallókészüléket visel vagy viselt korábban?

_____

24. Hallókészülékkel/Cochleáris implantátummal rendelkezik?

_____

25. Grommet (dobüregi tubus) behelyezés megtörtént?

_____

**Egyéb ismert:**

26. Gyermekének egyéb ismert testi, testre való betegsége? Ha igen:
    - Milyen jellegű? _____
27. Gyermekének egyéb ismert pszichiátriai (lelki, pszichére vonatkozó) betegség? Ha igen:
    - Milyen jellegű? _____

**Gyermeke iskolai teljesitménye:**

28. Óvodáskorában beilleszkedése, szabálytartása rendben zajlott?
    - Igen
    - Nem
29. Óvodában évet kellett ismételnie?

_____

30. Jelenlegi óvoda, általános iskola: Gyermeke hányadik osztályba jár?

_____

31. Mi az össztanulmányi átlaga?

_____

32. Szakértői Bizottság vizsgálta? Ha igen, megálapítottak valamit gyermekénél?

_____

33. Különleges bánásmódot, tantervet igényel vagy igényelt korábban?

- Speciális iskola?
- SNI (sajátos nevelési igényű) tanuló?
- BTM (beilleszkedési, tanulási, magatartási nehézséggel küzdő) tanuló?
- Felmentett tárgyak?
- Egyik sem

34. Magán tanuló volt-e valaha?

- Igen
- Nem

35. Évet kellett ismételnie?

- Igen
- Nem

36. Gyógypedagógiai fejlesztést kap/kapott? Ha igen, milyet?

_____

37. Gyermeke hány nyelven beszél?

_____

**Gyógyszerszedés:**

38. Rendszeres gyógyszert szed? Ha igen:
    - Gyógyszer neve: _____
    - Mennyiség (dózis, mg), adagolás:_____

## CSALÁD ÉS SZÜLŐKET ILLETŐ KÉRDÉSEK:

39. Gyermekének hány testvére van? _____

40. Testvérei egészségesek? Van olyan, aki ajak-és vagy szájpadhasadékkal született?

_____

41. Száj- és szájpadhasadék előfordult a családba?
    - Igen
    - Nem

42. Családban előforduló szomatikus betegségek? Ha igen, milyen jellegű?

_____

43. Előfordult vérrokonsági házasság?
    - Igen
    - Nem

44. Családban előforduló pszichiátriai betegségek (pld. depresszió, szorongás, kényszerbetegség, bipoláris betegség, autizmus)?

_____

**Családi állapot:**

45. Ön:

- házas
- élettárs
- elváltak
- külön élnek
- özvegy
- Egyéb:_____

46. Ha elváltak, külön élnek:

- A gyermek kivel él? _____
- Milyen a jelenlegi családi felállás? (féltestvérek, nevelőapa/anya)
  _____

**Szülői adatok:**

47. Szülők életkora:

- Apa: _____
- Anya: _____

48. Szülők foglalkozása:

- Apa:
    - Alkalmazott, beosztott
    - Köztiszviselő (közalkalmazott)
    - Fizikai dolgozó
    - Háztartásbeli
    - Nyugdíjas
    - Rokkant nyugdíjas
    - Vállalkozó
    - Egyéb:_____
- Anya:
    - Alkalmazott, beosztott
    - Köztiszviselő (közalkalmazott)
    - Fizikai dolgozó
    - Háztartásbeli
    - Nyugdíjas
    - Rokkant nyugdíjas
    - Válalkozó
    - Egyéb:_____

49. Legmagasabb iskolai végzettség:
    - Apa:
        - Általános iskola/ befejezett 8 általános
        - Szakmunkásképző/ OKJ képző
        - Gimnázium, szakközépiskola
        - Felsőfokú: Egyetem, főiskola
    - Anya:
        - Általános iskola/ befejezett 8 általános
        - Szakmunkásképző/ OKJ képző
        - Gimnázium, szakközépiskola
        - Felsőfokú: Egyetem, főiskola

**Családi milieu:**

50. Otthoni környezetük mostanában harmonikus vagy konfliktusos?
    - Ha vannak konfliktusok, milyen fajta? Mi váltja ki, mi okozza őket?

_____

Parental Questionnaire generated for the study (English version)

1

DEPARTMENT OF PEDIATRICS
UNIVERSITY OF PÉCS

# Parent Questionnaire

For parents of children participating in cleft lip and palate research

## QUESTIONS ABOUT YOUR CHILD:

**During pregnancy:**

1. Was it initially a twin pregnancy?
   - o No
   - o Yes
2. Was any of the following agents used during pregnancy:
   - o Smoking, tobbaco use
   - o Alcohol
   - o Other drug use
   - o Any of the following medications:
     - o Antiepileptic drugs: Phenytoin, Carbamazepine
     - o Antiemetic: Thietylperazine
     - o Antibiotic: Oxytetracycline
   - o Other:_____
3. If yes, please indicate at what stage of pregnancy it occured:
   - o 1st trimester (1-3 months)
   - o 2nd trimester (4-7 months)
   - o 3rd trimester (7-9 months)
   - o Throughout the pregnancy

4. Did any of the following occur during pregnancy:

   o High blood pressure

   o Diabetes (high blood sugar)

   o Infection (Toxoplasma gondii, (other microbes), Rubeola virus, Cytomegalovirus, Herpes simplex viruses)

   o Other

5. If you selected "other", please specify:

_____

6. Was this child your first pregnancy? If no, please explain the order:

_____

7. Did you have a previous abortion (miscarriage)?

   o Spontaneous

   o Artificial (surgical)

   o Artificial (drug-induced)

   o None

**Childbirth:**

8. In which week of pregnancy was your child delivered?

_____

9. What was the APGAR score?

_____

10. What was your child's body weight, body length, head circumference?

_____

11. How was your child delivered?

o Natural (vaginal)

o Caesarean (C-section)

12. What type of cleft lip and/or palate was your child born with (affected side)?

_____

13. How many days after birth did you have to stay in the hospital?

_____

14. After birth, did your child require any of the following:

o Respiratory support

o Antibiotic therapy

o Blue light (for jaundice)

o Other

o None

15. If you selected "other", please specify:

_____

**Your child's development:**

16. When (months) did your child start to:

o Turn over:

o Sit:

o Crawl:

o Creep:

o Walk:

o Did these occur at a normal pace, or were there lapses?

_____

17. When did your child speak their first words?

_____

18. When did your child speak in coherent sentences?

_____

19. At how many months was your child potty-trained?

_____

20. Were there any relapses?

_____

21. Did your child have feeding difficulties?

_____

**Your child's hearing development:**

22. Were there difficulties with your child's hearing?

_____

23. Does your child wear or have they worn hearing aids previously?

_____

24. Does your child have a hearing aid/cochlear implant?

_____

25. Has a grommet (eardrum tube) been inserted?

_____

**Other known medical conditions:**

26. Does your child have any other known physical, bodily illness? If yes, please describe:

_____

27. Does your child have any other known psychiatric (mental, psychological) illness? If yes, please describe:

_____

**Academic performance and learning:**

28. Did your child settle in well at school?

o Yes

o No

29. Did your child have to repeat a year in kindergarten?

_____

30. Current kindergarten, primary or high school: what grade is your child in?

_____

31. What is your child's overall grade point average?

_____

32. Has your child been assessed by a Review Committee for special education? If yes, has the assessment revealed a special need?

_____

33. Does your child need or has previously needed a special education plan or services?

o Designated Special Education School?

o IEP (individualized education plan)?

o BIP (behavioral intervention plan)?

o Exempted subjects?

o None of the above

34. Has your child ever been home-schooled?

    o Yes

    o No

35. Did your child have to repeat an academic year?

    o Yes

    o No

36. Is your child currently receiving/has your child received special education services? If yes, what kind?

    _____

37. How many languages does your child speak?

    _____

**Medication:**

38. Does your child take any medication? If yes:

    o Name of medication: _____

    o Quantity (dose, mg), frequency:_____

## FAMILY AND PARENTING:

**Family:**

39. How many siblings does your child have?

    _____

40. Are the siblings healthy? Were any of the siblings born with cleft lip and/or palate?

    _____

41. Is their a history of cleft lip and/or palate in your family?

    o Yes

    o No

42. Is there a family history of somatic diseases in your family? If yes, what type?

    _____

43. Have consanguineous marriages occured in your family?

    o Yes

    o No

44. Do you have a family history of psychiatric illness (e.g. depression, anxiety, OCD, bipolar disorder, autism)?

    _____

**Marital status:**

45. Please indicate your current status:

    o Married

    o partner

    o divorced

    o separated

    o widowed

    o Other:_____

46. If you are divorced or separated:

    o Who does the child live with?_____

    o What is the current family situation (half siblings, foster father/mother)?

    _____

**Parental details:**

47. Parents' age:
    - o Father: _____
    - o Mother: _____
48. Parents' occupation:
    - o Father:
        - o Employed
        - o Civil servant (public employee)
        - o Physical worker
        - o Domestic worker
        - o Pensioner
        - o Disabled pensioner
        - o Self-employed
        - o Other:_____
    - o Mother:
        - o Employed, salaried
        - o Public employee (civil servant)
        - o Physical worker
        - o Domestic worker
        - o Pensioner
        - o Disabled pensioner
        - o Divorcer
        - o Other:_____

49. Highest level of education:

    o Father:

        o Primary school/ completed 8 primary

        o Vocational school/ OKJ training

        o Secondary school, vocational school

        o Higher education: university, college

    o Mother:

        o Primary school/ completed 8 primary

        o Vocational school/ OKJ training

        o Secondary school, vocational school

        o Higher education: university, college

**Family environment:**

50. Has your home environment been harmonious or conflictual lately? If there are conflicts, what kind? What triggers them, what causes them?

    _____

Published supporting PDFs (3)

Original Article - Retrospective Study

# The Influence of Genetic Syndromes on the Algorithm of Cleft Lip and Palate Repair – A Retrospective Study

**Kinga Amália Sándor-Bajusz[1], Teodor Barna Maros[2], Lajos Olasz[3], George Kálmán Sándor[4], Kinga Hadzsiev[5], Attila Mihály Vástyán[1,6]**

Departments of [1]Paediatrics, [3]Dentistry, Oral and Maxillofacial Surgery and [5]Medical Genetics, University of Pécs, Pécs, [2]Department of Otorhinolaryngology, Ferenc Flór County Hospital, Kistarcsa, [6]Paediatric Surgery, Department of Paediatrics, University of Pécs, Pécs, Hungary, [4]Department of Oral and Maxillofacial Surgery, Medical Research Centre, University of Oulu, Oulu University Hospital, Oulu, Finland

## Abstract

**Introduction:** This study aimed to determine if the treatment algorithm used for nonsyndromic cleft patients required alteration to manage syndromic cleft lip and/or palate patients. **Methods:** The records of patients managed by the Pécs Cleft Team between January 1999 and December 2015 were analyzed retrospectively. The sources of the data included clinical and genetic records. **Results:** A total of 607 patients were managed by the cleft team during the study. Sixteen patients (2.6%) were noted to be afflicted with a particular identifiable syndrome. Seven different genetic syndromes and one sequence were present in the study. The Pierre Robin sequence occurred most often, comprising 50% of the cohort. The treatment algorithm used in managing nonsyndromic clefts required modification in 13 of the 16 syndromic patients. **Discussion:** The presence of a genetic syndrome may notably affect the treatment algorithm in children born with cleft lip and/or palate. The surgical treatment of certain associated anomalies has by necessity, priority over the timing of the reconstruction of the cleft lip and/or cleft palate in syndromic patients.

**Keywords:** Child, cleft lip, cleft palate, syndrome, treatment timing

## Introduction

Cleft lip and/or cleft palate (CLP) are common developmental anomalies.[1] In general, the worldwide incidence of clefts is estimated to be between 1 and 2.21 cases per 1000 live births.[1] In most cases, CLP occurs as an isolated anomaly. However, the association of CLP with genetic syndromes, the so-called syndromic cleft lip and palate (SCLP), has been described previously in the seventies.[2] At that time, only 154 cleft-related syndromes were known in contrast to the well over 500 syndromes recognized in the literature today.[3] SCLP patients represent between 10% and 30% of CLP cases, according to past and current publications.[3-5]

The aim of this clinical study was to identify syndromic cleft patients and evaluate how their genetic syndrome influenced the timing of the algorithm in the treatment of CLP. The study was conducted on patients managed by the Pécs Cleft Team (PCT) between January 1999 and December 2015.

Access this article online

Quick Response Code:

Website: www.amsjournal.com

DOI: 10.4103/ams.ams_77_21

## Methods

A study of nonsyndromic and syndromic cleft patients managed and followed by the PCT was conducted over the 16 years between January 1999 and December 2015. Detailed clinical documentation of all patients, including genetic and epidemiological data, was required for inclusion in the study. The data were collected retrospectively without personal identifying details. At the time of the data collection, permission from the regional ethical committee was not deemed to be obligatory because of the retrospective nature of the study. Special permission was obtained and granted for data collection from the Hungarian Congenital Abnormality Registry (HCAR). The

**Address for correspondence:** Dr. Kinga Amália Sándor-Bajusz, School of Clinical Neurosciences, University of Pécs, Pécs, Hungary. E-mail: sandor.kinga@pte.hu

**Received:** 27-03-2021 **Last Revised:** 08-04-2021
**Accepted:** 31-08-2021 **Published:** 29-11-2021



**How to cite this article:** Sándor-Bajusz KA, Maros TB, Olasz L, Sándor GK, Hadzsiev K, Vástyán AM. The influence of genetic syndromes on the algorithm of cleft lip and palate repair – A retrospective study. Ann Maxillofac Surg 2021;11:270-3.

Ethics Committee of the University of Pécs waived the need for ethics approval and the need to obtain consent for the collection, analysis and publication of the retrospectively obtained and anonymized data for this study. The reason for this waiver was the retrospective nature of this study and the anonymized nature of the data used in the study. All procedures performed in the study were conducted in accordance with the ethics standards given in the 1964 Declaration of Helsinki, as revised in 2013.

Special emphasis was placed on the syndromic features of the patients and their associated anomalies. The type and timing of the surgeries or interventions unrelated to the clefts were listed and categorized. The timing of the cleft lip and/or cleft palate repair was recorded as well, and was compared with the algorithm used for nonsyndromic cleft patients. The Online Mendelian Inheritance in Man database[6] was used to identify the genetic syndromes. Epidemiological data were obtained from the HCAR. The study used descriptive statistics consisting of means and percentages of the presenting syndromes and participants of the study, which were calculated and used along with standard deviations in the data analysis.

## Results

Among the 607 CLP patients, 25 children (4.1%) had associated anomalies noted during the study period. Sixteen (2.6%) of the 607 CLP patients were found to be SCLP cases. A total of seven different genetic syndromes and one sequence were identified in this cohort [Figure 1a and b].

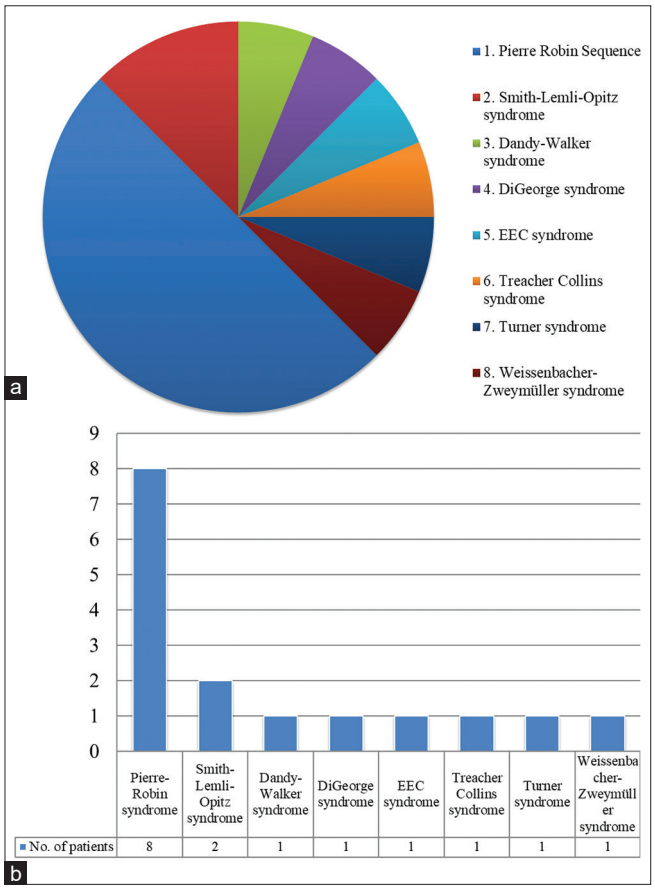


**Figure 1:** (a) The distribution of the seven genetic syndromes and one sequence present in the cohort. (b) Number of individuals in each group

Pierre Robin sequence (PRS) comprised 50% of all cases. Ten patients (60%) were boys and six (40%) were girls of the SCLP group. The majority of the SCLP patients had cleft palate only, $n = 13$ (81%) [Figure 2]. The other syndromes observed in the cohort included: Smith-Lemli Opitz syndrome, Dandy–Walker syndrome, DiGeorge syndrome, Ectrodactyly-ectodermal dysplasia-clefting syndrome, Treacher Collins syndrome, Turner syndrome, and Weissenbacher–Zweymüller syndrome.

The algorithm used by the PCT had to be modified for most of the SCLP patients ($n = 13$, 81%). The modifications were necessary due to the nature and needs of the given syndrome. This was true in all SCLP cases, except for one patient. The timing of the cleft repair procedure in the SCLP cohort is illustrated in Figure 3.

The authors observed notable delays in the timing of the palate repair in SCLP patients. In two SCLP patients, the palatoplasty procedure was completed much later, at 4 years of age. In addition, 15 patients underwent additional surgeries due to the presence of the syndromes and associated medical conditions [Figure 4]. These operations had of necessity priority over the repair of the CLP deformities. Tracheostomies were needed in three patients with PRS.

Secondary operations for CLP were required in six patients (37.5%). Speech improvement operations or pharyngoplasty and tympanostomy tube placements were the most common secondary operations. These procedures were mainly required in patients with PRS [Figure 5].

## Discussion

Treating SCLP patients is by nature, more complex than treating nonsyndromic cleft patients. Syndromic patients require more attention and support for their multiple potential special needs from both the family and the health care facility, including the cleft teams.[1,7-11]

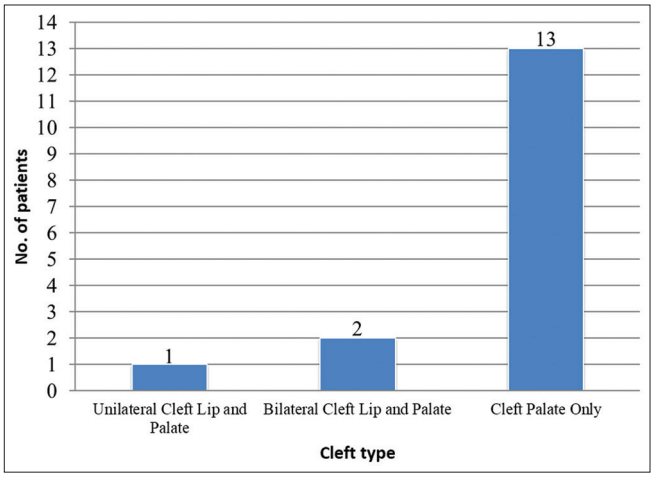


**Figure 2:** The distribution of cleft type in syndromic patients

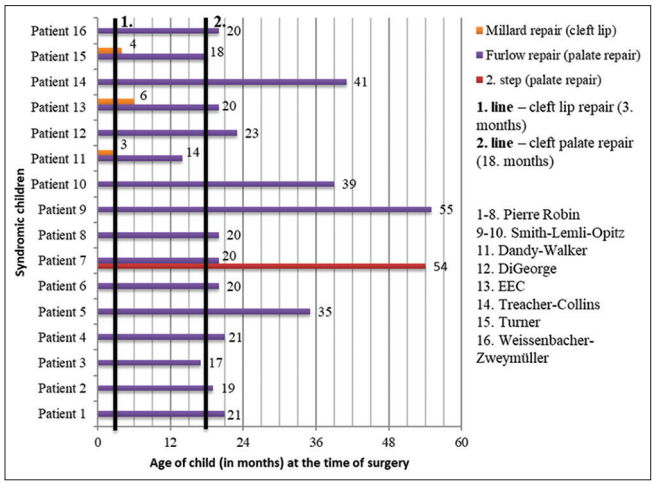


**Figure 3:** The timing of the cleft repair surgery for syndromic patients. Vertical lines in bold (1 and 2) represent the usual timing of the cleft repair surgeries carried out by the Pécs Cleft Team. Patients 1–16 are grouped according to the types of syndromes

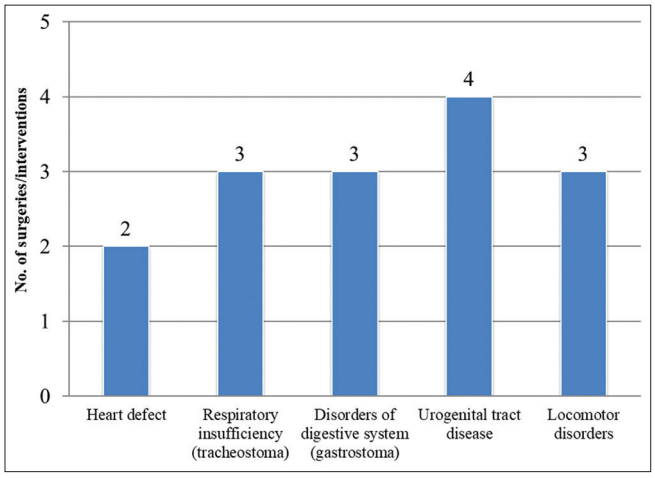


**Figure 4:** The distribution of additional surgeries for the affected organ system (s) for syndromic patients

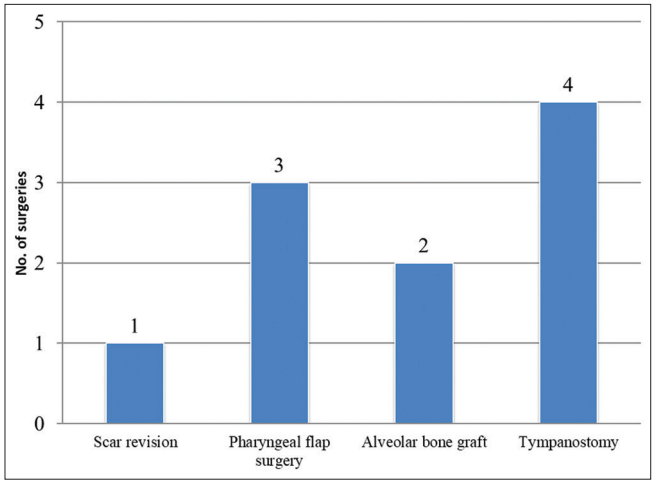


**Figure 5:** Types of secondary ancillary operations carried out on syndromic cleft patients

The percentage of the SCLP patients managed by the PCT was 2.6% during the study. This number is below the 10% and 30% prevalence described in the literature.[3-5,12,13] On the other hand, the prevalence of PRS in the SCLP cohort was similar to the literature, according to the data obtained from the HCAR. In contrast, Smith-Lemli-Opitz, Dandy–Walker syndrome, and Turner syndrome were underrepresented in this SCLP cohort. The under-diagnosis and/or reporting of cases could be responsible for their low prevalence.

Interestingly, two very rare syndromes both Ectrodactyly-ectodermal dysplasia-clefting syndrome and Weissenbacher–Zweymüller syndrome were present in the syndromic cohort.[14-16] A center for rare congenital diseases was subsequently established in Pécs during the latter half of the study period, in 2009, which may explain the more current appearance and reporting of these rare syndromes.

The cleft team needed to modify the treatment algorithm for CLP in the majority (81%) of the SCLP patients. One example of these alterations is the delay of the primary cleft repair operations. The main causes of the delay in palatoplasty for PRS patients were airway issues and feeding problems. In other patients, cardiorespiratory and urogenital interventions had priority over the cleft surgeries. Upper respiratory infections also caused a delay in the timing of the primary cleft operations in some cases [Figures 3 and 4].

The high rate (37.5%) of the secondary operations such as speech improvement surgery and ancillary procedures such as placement of tympanostomy tubes for the SCLP patients is in accordance with the literature.[7,11,17-19]

The authors have noted velopharyngeal insufficiency and speech problems as more common conditions in SCLP patients, especially those patients with PRS. This explains the high rate of pharyngoplasties and tympanostomies in these patients.[7,17-19] The author's findings support these observations. In some previous studies, however, no differences were found between the secondary operations for nonsyndromic patients and patients with PRS.[20]

## Conclusion

The presence of a genetic syndrome noticeably altered the treatment algorithm of the PCT in the majority of children born with SCLP (81%) compared to nonsyndromic CLP patients. The surgical treatment of the associated anomalies has priority over the timing of the reconstruction of the cleft lip and palate in a number of syndromic patients. Cleft palate only and velopharyngeal insufficiency were more common in the syndromic group. Secondary operations for clefts were needed in greater numbers in SCLP patients than in nonsyndromic patients. With improvements in pediatric care and better recognition of the milder phenotypes, the number of future SCLP patients is likely to increase. Syndromic patients

will likely require further flexible modifications of the cleft treatment timing algorithm.

## Financial support and sponsorship

Nil.

## Conflicts of interest

Dr. George Kalman Sandor was associated as a section editor of this journal and this manuscript was subject to this journal's standard review procedures, with this peer review handled independently of this section editor and their research group.

## References

1. Corcoran M, Karki S, Harila V, Luoto A, Ylikontiola L, Sándor GK, *et al.* Dental fear among adolescents with cleft. Int J Paediatr Dent 2021. p. 1-8.
2. Cohen MM Jr. Syndromes with cleft lip and cleft palate. Cleft Palate J 1978;15:306-28.
3. Venkatesh R. Syndromes and anomalies associated with cleft. Indian J Plast Surg 2009;42 Suppl: S51-5.
4. Saleem K, Zaib T, Sun W, Fu S. Assessment of candidate genes and genetic heterogeneity in human non syndromic orofacial clefts specifically non syndromic cleft lip with or without palate. Heliyon 2019;5:e03019.
5. Irfanulla Khan AN, Prashanth CS, Srinath N. Genetic etiology of cleft lip and cleft palate. AIMS Mol Sci 2020;7:328-48.
6. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University, Baltimore, MD. Available from: https://omim.org/. [Last Accessed on 2020 Sep 29].
7. Godbout A, Leclerc JE, Arteau-Gauthier I, Leclerc LD. Isolated versus Pierre Robin sequence cleft palates: Are they different? Cleft Palate Craniofac J 2014;51:406-11.
8. Cladis F, Kumar A, Grunwaldt L, Otteson T, Ford M, Losee JE. Pierre Robin sequence: A perioperative review. Anesth Analg 2014;119:400-12.
9. Karki S, Horváth J, Laitala ML, Vástyán A, Nagy Á, Sándor GK, *et al.* Validating and assessing the oral health-related quality of life among Hungarian children with cleft lip and palate using Child-OIDP scale. Eur Arch Paediatr Dent 2021;22:57-65.
10. Corcoran M, Karki S, Harila V, Kyngäs H, Luoto A, Ylikontiola LP, *et al.* Oral health-related quality of life among young adults with cleft in northern Finland. Clin Exp Dent Res 2020;6:305-10.
11. Lehtonen V, Lithovius RH, Autio TJ, Sándor GK, Ylikontiola LP, Harila V, *et al.* Middle ear findings and need for ventilation tubes among pediatric cleft lip and palate patients in northern Finland. J Craniomaxillofac Surg 2016;44:460-4.
12. Sárközi A, Wyszynski DF, Czeizel AE. Oral clefts with associated anomalies: Findings in the Hungarian Congenital Abnormality Registry. BMC Oral Health 2005;5:4.
13. Doray B, Badila-Timbolschi D, Schaefer E, Fattori D, Monga B, Dott B, *et al.* Epidemiology of orofacial clefts (1995-2006) in France (Congenital Malformations of Alsace Registry). Arch Pediatr 2012;19:1021-9.
14. Galil A, Carmi R, Goldstein E, Porter B, Bar Ziv J, Chemke J. Weissenbacher-Zweymuller syndrome: Long-term follow-up of growth and psychomotor development. Dev Med Child Neurol 1991;33:1104-9.
15. Bigatà X, Bielsa I, Artigas M, Azón A, Ribera M, Ferrándiz C. The ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC): Report of five cases. Pediatr Dermatol 2003;20:113-8.
16. Malvankar DD, Sacchidanand S, Mallikarjun M. Ectrodactyly, ectodermal dysplasia, and cleft lip-palate (EEC) syndrome without clefting: A rare case report. Dermatol Online J 2012;18:5.
17. Hardwicke JT, Richards H, Cafferky L, Underwood I, Horst BT, Slator R. Outcomes of cleft palate repair in patients with Pierre Robin sequence: A matched case-control study. Plast Reconstr Surg 2016;137:927-35.
18. Kocaaslan FN, Sendur S, Koçak I, Çelebiler Ö. The comparison of Pierre Robin sequence and non-syndromic cleft palate. J Craniofac Surg 2020;31:226-9.
19. Gustafsson C, Vuola P, Leikola J, Heliövaara A. Pierre Robin sequence: Incidence of speech-correcting surgeries and fistula formation. Cleft Palate Craniofac J 2020;57:344-51.
20. Stransky C, Basta M, Solot C, Cohen M, Low DW, Larossa D, *et al.* Do patients with Pierre Robin sequence have worse outcomes after cleft palate surgery? Ann Plast Surg 2013;71:292-6.

frontiers | Frontiers in Psychology

TYPE Original Research
PUBLISHED 28 February 2023
DOI 10.3389/fpsyg.2023.1115304



OPEN ACCESS

EDITED BY
Fabrizio Stasolla,
Giustino Fortunato University,
Italy

REVIEWED BY
Jonathan Fries,
University of Vienna,
Austria
Virpi Harila,
University of Oulu,
Finland

*CORRESPONDENCE
Kinga Amália Sándor-Bajusz
✉ sandor.kinga@pte.hu

SPECIALTY SECTION
This article was submitted to Neuropsychology, a section of the journal Frontiers in Psychology

RECEIVED 03 December 2022
ACCEPTED 08 February 2023
PUBLISHED 28 February 2023

CITATION
Sándor-Bajusz KA, Dergez T, Molnár E, Hadzsiev K, Till Á, Zsigmond A, Vástyán A and Csábi G (2023) Cognitive functioning and clinical characteristics of children with non-syndromic orofacial clefts: A case-control study.
*Front. Psychol.* 14:1115304.
doi: 10.3389/fpsyg.2023.1115304



# Cognitive functioning and clinical characteristics of children with non-syndromic orofacial clefts: A case-control study

Kinga Amália Sándor-Bajusz[1]*, Tímea Dergez[2], Edit Molnár[1], Kinga Hadzsiev[3], Ágnes Till[3], Anna Zsigmond[3], Attila Vástyán[4] and Györgyi Csábi[1]

[1]Division of Child and Adolescent Psychiatry, Department of Pediatrics, Medical School and Clinical Center, University of Pécs, Pécs, Hungary, [2]Institute of Bioanalysis, Medical School and Clinical Center, University of Pécs, Pécs, Hungary, [3]Department of Medical Genetics, Medical School and Clinical Center, University of Pécs, Pécs, Hungary, [4]Division of Pediatric Surgery, Department of Pediatrics, Medical School and Clinical Center, University of Pécs, Pécs, Hungary

**Introduction:** The higher rate of neuropsychiatric disorders in individuals with non-syndromic orofacial clefts has been well documented by previous studies. Our goal was to identify children with non-syndromic orofacial clefts that are at risk for abnormal neurodevelopment by assessing their developmental history and present cognitive functioning.

**Materials and methods:** A single-center, case-controlled study was carried out at the Department of Pediatrics of the University of Pécs in Hungary. The study consisted of three phases including questionnaires to collect retrospective clinical data and psychometric tools to assess IQ and executive functioning.

**Results:** Forty children with non-syndromic oral clefts and 44 age-matched controls participated in the study. Apgar score at 5min was lower for the cleft group, in addition to delays observed for potty-training and speech development. Psychiatric disorders were more common in the cleft group (15%) than in controls (4.5%), although not statistically significant with small effect size. The cleft group scored lower on the Continuous Performance Test. Subgroup analysis revealed significant associations between higher parental socio-economic status, academic, and cognitive performance in children with non-syndromic orofacial clefts. Analyzes additionally revealed significant associations between early speech and language interventions and higher scores on the Verbal Comprehension Index of the WISC-IV in these children.

**Discussion:** Children with non-syndromic orofacial clefts seem to be at risk for deficits involving the attention domain of the executive system. These children additionally present with difficulties that affect cognitive and speech development. Children with non-syndromic orofacial clefts show significant skill development and present with similar cognitive strengths as their peers. Longitudinal studies with larger sample sizes are needed to provide more conclusive evidence on cognitive deficits in children with non-syndromic orofacial clefts at risk for neurodevelopmental difficulties.

KEYWORDS

**cleft lip, cleft palate, neurodevelopment, executive function, developmental outcomes**

# 1. Introduction

Orofacial clefts are the most common craniofacial anomalies that affect the lip, palate and/or both structures (Harila et al., 2013; Li et al., 2019). Approximately 30% of oral clefts are associated with a known genetic syndrome (syndromic clefts), however, the remaining 70% occur without a known identified syndrome (non-syndromic clefts; Mossey and Modell, 2012; Saleem et al., 2019). Orofacial clefts (OFCs) are divided into three different subtypes on an anatomically basis; cleft lip (CL), cleft lip and palate (CLP) and cleft palate only (CPO; Lithovius et al., 2014). The higher risk of mental disorders in individuals born with non-syndromic OFCs is well documented in the literature (Richman and Ryan, 2003; Nopoulos et al., 2005, 2010; Boes et al., 2007; Richman et al., 2012; Pedersen et al., 2016; Tillman et al., 2018; Gallagher and Collett, 2019). These children are disproportionately afflicted by psychiatric disorders including schizophrenia, intellectual disability, autism spectrum disorder, anxiety disorders and ADHD (Pedersen et al., 2016; Ansen-Wilson et al., 2018; Tillman et al., 2018). Children with non-syndromic OFCs are also at high risk for learning disabilities (Richman and Ryan, 2003; Tillman et al., 2018; Gallagher and Collett, 2019). Multiple stress factors including repetitive cleft repair surgeries, aesthetics, and functional consequences such as speech difficulty were believed to be the basis of such deficits (Gallagher and Collett, 2019). However, the underlying mechanisms for these deficits have not been clarified (Yang et al., 2012; Gallagher and Collett, 2019). A unified maldevelopment of the brain and facial structures is a possible etiology behind the observed neuropsychiatric disorders in this patient population (Speltz, 2000; Nopoulos et al., 2005; Boes et al., 2007; Weinberg et al., 2009; Yang et al., 2012; Adamson et al., 2014; Ansen-Wilson et al., 2018; Gallagher and Collett, 2019).

Executive dysfunction occurs when cognitive skills responsible for organizing and self-regulating behaviors are impaired (Shaheen, 2014; Zelazo, 2015). Executive functions are interconnected with the maturation of the prefrontal cortex, and their dysfunctions are common in neurodevelopmental and psychiatric disorders (Shaheen, 2014; Zelazo, 2015; Bausela-Herreras et al., 2019; Faedda et al., 2019). Specific patterns of executive dysfunction manifest according to different types of neurodevelopmental disorder and may even be a precursor before the diagnosis of these conditions (Zelazo, 2015; Bausela-Herreras et al., 2019; Otterman et al., 2019). Neuroimaging studies and the underlying cognitive deficits suggest that frontal and prefrontal cortical function may be impaired in children with non-syndromic OFCs (Nopoulos et al., 2010; Adamson et al., 2014; Chollet et al., 2014), and recommend further examination of executive functioning during follow-up (Tillman et al., 2018). Previous studies have examined the executive system in children with non-syndromic OFCs (Nopoulos et al., 2002; Laasonen et al., 2004; Conrad et al., 2009; Lemos and Feniman, 2010; Bodoni et al., 2021), but screened only one or two of its dimensions. It is often unclear whether syndromic participants were excluded from these studies (Gallagher and Collett, 2019), and may include a mixed population of both syndromic and non-syndromic forms (Nopoulos et al., 2000, 2002). Underlying genetic abnormalities—which are present in syndromic oral clefts—often affect proper brain development and function (McDonald-McGinn et al., 2015; Berg et al., 2016) and may therefore misrepresent the non-syndromic population (Rincic et al., 2016; Sándor-Bajusz et al., 2022).

The primary goal of our study was to screen cognitive deficits in children with non-syndromic OFCs to identify an at-risk subpopulation for neurodevelopmental disorders. We further aimed to identify risk factors that may additionally affect the overall neurodevelopmental course of these children. We hypothesized that children with non-syndromic OFCs would present with more cognitive difficulties compared to their non-cleft peers.

# 2. Materials and methods

## 2.1. Design

A single-center, case-controlled study was carried out at the Department of Pediatrics of the University of Pécs in Hungary. The study was approved by the Regional Ethics Committee of the University of Pécs (approval number: 7967-PTE 2020) and was performed in line with the principles of the Declaration of Helsinki. Permission to utilize the materials in the study was granted by the copyright holders (PsyWay, 2020).

## 2.2. Participants

All participating children with non-syndromic OFCs (further mentioned as the cleft group) are patients of the Cleft Team of the Pediatric Surgery Unit, Department of Pediatrics of the University of Pécs. The inclusion criteria consisted of the following: children with non-syndromic OFCs, 6–16 years old and an IQ ≥ 70. An OFC was considered non-syndromic when the cleft was the only single malformation without additional physical or developmental anomalies (Bjørnland et al., 2021). Controls were recruited from the community of Baranya County, specifically from public elementary, high schools, and post advertisements on social media. The inclusion criteria of the controls included the following: healthy children born without oral clefts, 6–16 years old and IQ ≥ 70. Medical geneticists examined all participants of the cleft group to rule out the presence of additional congenital malformations and/or underlying syndromes. The study was carried out between July 2020 and March 2022 in the Department of Pediatrics of the University of Pécs, Hungary. Informed consent was obtained from the parents and participants in the study.

## 2.3. Materials

Initially all psychometric tests were completed on site. Due to the ongoing COVID-19 pandemic, parts of the study were completed online; this included the questionnaires and the four cognitive tests (Stroop, TOL, CPT, and Corsi). Measurements that required in-person completion (IQ test) were postponed onto a later period once the pandemic situation improved.

### 2.3.1. Questionnaires

A parental questionnaire was developed for the study to collect demographic data. This included prenatal and postnatal history, birth, motor and language development, education, previous psychiatric treatment, and history of somatic and neuropsychiatric disorders. Parental socio-economic data were additionally collected, including

parental age, education, and employment status. Parents were also asked regarding family history of neuropsychiatric disorders and/or any previous psychiatric treatment. The Hungarian version of the Child Behavior Checklist (CBCL) was used to screen for behavioral and emotional problems in children and adolescents during the previous 6 months (Achenbach, 1991; Rózsa et al., 1999).

#### 2.3.2. Computer-based cognitive tests

Four computer-based tests were used to assess the main domains of executive functioning. All tests were provided by the Psyway Hungarian psychometric website and all tests are standardized and norm-referenced (PsyWay, 2020). Each cognitive test is summarized in Table 1.

#### 2.3.3. Intelligence test: WISC-IV (Wechsler intelligence scale for children—Fourth edition)

We used the official Hungarian version of the WISC-IV (Nagyné Réz et al., 2007) to measure full-scale IQ, important for the assessment of executive functioning (Grizzle, 2011; Ardila, 2018).

### 2.4. Procedure

The study was divided into three phases, which begun by completing two online questionnaires (Phase 1) followed by online cognitive tasks (Phase 2) and an in-person IQ test (Phase 3, see Figure 1).

### 2.5. Statistics

Statistical analysis was carried out using IBM SPSS Statistics 28 Software. A descriptive statistical analysis was performed. The primary aim of the analysis was to compare the differences in the results of cognitive tests (London Tower, Stroop, Corsi, and Continuous Performance Test), IQ (WISC-IV), CBCL (Child Behavior Checklist) and the demographic parameters between the two study groups. Occupational statuses of the parents were classified as follows: employed, not employed, or retired. Academic levels of the parents were initially grouped into basic (elementary, lower secondary education), intermediate (upper secondary) and advanced (college or university). We later grouped these levels as either higher education (upper secondary education, college, or university) or lower education (elementary, lower secondary education) to increase statistical power.

The raw score is an untransformed score from a measurement of the above listed cognitive tests and the CBCL questionnaire. The raw scores were converted into a scale called *T*-score scale, which assumes a normal distribution with the mean = 50 and the standard deviation = 10. The *T*-scores of all psychometric tests were expressed as means ± standard deviations. The categorical data of the cleft and control groups were analyzed using contingency tables and the chi-squared or Fischer's test, as appropriate. For quantitative variables, two-sided independent samples Student's *t*-test were used. The Welch test was applied in cases when the variance was not homogenous. Analysis of variance (ANOVA) was used to test the difference among more than two groups (e.g., in case of analysis based on the type of cleft). These variables follow a normal distribution. Statistical significance was established as a value of $p$ of <0.05. Effect sizes were defined as Cohen's $d$ value in case of two independent groups, $\eta^2$ in case of ANOVA test, and $\phi$ value in case of Chi-square test (Coe, 2002).

## 3. Results

### 3.1. Participants

We recruited 43 children with non-syndromic OFCsand 44 controls for the study. Past medical history revealed two syndromic OFCs and these participants were excluded from the study. One participant of the cleft group was lost to follow up. The data of 84 study participants were analyzed (see Figure 1).

### 3.2. Cognitive functioning

The CPT revealed differences between the two groups: the cleft group scored lower on detectability (%) than controls ($p = 0.022$, $d = 0.55$, see Table 2). They also missed more targets than controls ($p = 0.058$, $d = 0.46$, see Table 2). We did not observed differences for the remaining cognitive test results (see Supplementary Tables 1–3). None of the participants scored below average in any of the dimensions of the WISC-IV, however controls scored higher on the PRI and WMI subtests (see Supplementary Table 4).

### 3.3. Questionnaires

#### 3.3.1. CBCL questionnaire

##### 3.3.1.1. Children (self-report)

Two dimensions of the CBCL showed significant differences between the groups: controls reported higher symptoms of

TABLE 1 Cognitive tests used in the study to measure executive functioning.

| Cognitive test | EF domain(s) measured | Main outcome measures used in the study |
|---|---|---|
| Stroop test | Cognitive flexibility (Diamond, 2013; Parris, 2014; Scarpina and Tagini, 2017) | Inhibition of cognitive interference: speed and accuracy of the response |
| Tower of London | Planning ability and working memory (Bull et al., 2004; Unterrainer et al., 2004; Kaller et al., 2011; Naidoo et al., 2019) | Total correctly solved trials, total rule violation, mean execution time, average number of trials and weighted performance score |
| Corsi block-tapping test | Visuo-spatial working memory (Kessels et al., 2000; Brunetti et al., 2014) | Block-span |
| Continuous performance task | Attention (Conners, 2014; Roebuck et al., 2016) | Detectability (%), omissions (%) and commissions (%) |

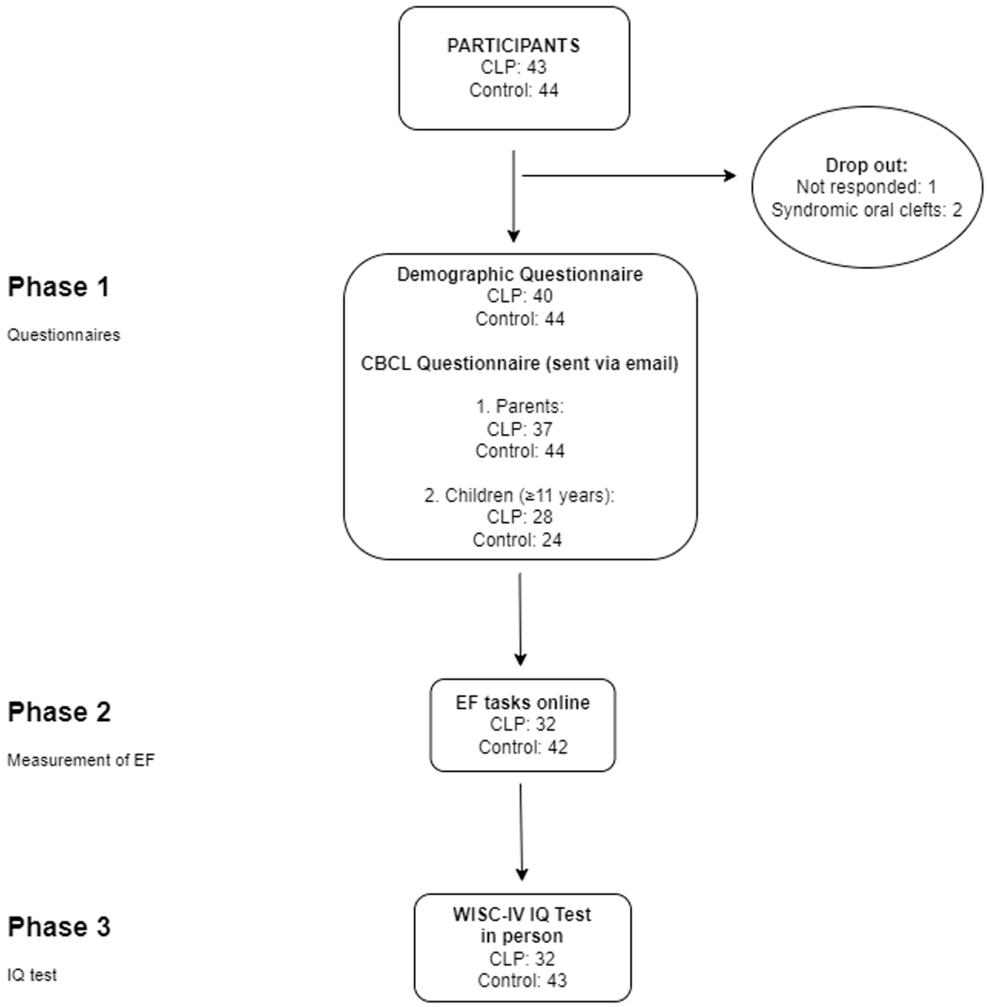


FIGURE 1
Study flow. The analyzes were divided into three phases. The number of the participants are provided for each phase (CLP, cleft lip and/or palate group; EF, executive function; IQ, intelligence quotient).

TABLE 2 Results of the CPT (continuous performance task).

| Performance measures | Group | *n* | Mean±SD | *p*-Value | Cohen's *d* |
|---|---|---|---|---|---|
| Detectability (%) | Control | 41 | 59.46 ± 14.90 | 0.022* | 0.55 |
| | Cleft | 32 | 51.03 ± 15.66 | | |
| Omission errors (%) (missed targets) | Control | 41 | 59.54 ± 13.00 | 0.058 | 0.46 |
| | Cleft | 32 | 53.84 ± 11.84 | | |
| Commission errors (%) (false response without target) | Control | 41 | 52.00 ± 12.21 | 0.47 | 0.17 |
| | Cleft | 32 | 54.28 ± 14.49 | | |

*Statistical significance. Data are presented as means and standard deviations (SD).

externalization, somatic, attention, oppositional, and behavioral problems than clefts. Clefts reported higher symptoms of affective problems (see Table 3).

#### 3.3.1.2. Parental report

Parents of the controls reported higher symptoms across all scales of the CBCL compared to parents of the cleft group, with small effect sizes (see Supplementary Table 5).

### 3.3.2. Demographic measures

#### 3.3.2.1. Children

##### 3.3.2.1.1. Cleft status

There were no significant differences between the age of cleft versus controls (see Table 4). More than half of the cleft group was represented by boys (56.6%), while controls had more girl participants

10.3389/fpsyg.2023.1115304

TABLE 3 Results of the CBCL self-report.

| Scales | Group | *n* | Mean±SD | *p*-Value | Cohen's *d* |
|---|---|---|---|---|---|
| Internalization | Control | 28 | 52.57 ± 10.57 | 0.64 | 0.13 |
| | Cleft | 24 | 54.17 ± 14.00 | | |
| Externalization | Control | 28 | 53.29 ± 8.68 | 0.024* | 0.65 |
| | Cleft | 24 | 47.83 ± 8.05 | | |
| Affective problems | Control | 28 | 50.39 ± 8.42 | 0.39 | 0.24 |
| | Cleft | 24 | 53.08 ± 13.10 | | |
| Anxiety | Control | 28 | 49.50 ± 10.16 | 0.69 | 0.11 |
| | Cleft | 24 | 50.71 ± 11.75 | | |
| Somatic problems | Control | 28 | 51.60 ± 11.54 | 0.46 | 0.21 |
| | Cleft | 24 | 49.42 ± 9.37 | | |
| Attention deficit/ hyperactivity | Control | 28 | 54.89 ± 10.83 | 0.24 | 0.33 |
| | Cleft | 24 | 51.67 ± 8.29 | | |
| Oppositional defiance | Control | 28 | 54.25 ± 10.60 | 0.048* | 0.56 |
| | Cleft | 24 | 48.13 ± 11.15 | | |
| Behavioral problems | Control | 28 | 51.32 ± 7.61 | 0.19 | 0.37 |
| | Cleft | 24 | 48.46 ± 7.90 | | |

*Statistical significance. Data are presented as means and standard deviations (SD).

(67.7%, $p = 0.031$, $\phi = 0.24$). Three subtypes of OFCs were present in the cleft group: 45% with cleft lip and palate (CLP), 37.5% with cleft lip (CL) and 17.5% with cleft palate only (CPO). Left-sided (32.5%) and bilateral (32.5%) OFCs were the most common. Overall, 29.16% of the cleft group reported their repaired OFCs as a current medical condition. All participants of the cleft group had repaired clefts, and none of these children had persistent hearing deficiency.

#### 3.3.2.1.2. Academic performance and past psychiatric history

We observed no differences in the overall academic score; both clefts and controls achieved a good overall score in the current academic year (see Table 4). Preschool integration was significantly more difficult for the cleft group compared to controls ($p = 0.025$, $\phi = 0.26$). Both study groups did well later in preschool without requiring grade repetition ($p = 0.96$, $\phi = 0.005$). Children of the cleft group were examined by pedagogical professional services more often than controls ($p < 0.001$, $\phi = 0.49$). Participants in the cleft group required special education plans more often than controls ($p = 0.016$, $\phi = 0.29$). There were no differences in the rate of elementary grade repetition between clefts and controls ($p = 0.60$, $\phi = 0.073$). We observed a higher proportion of psychiatric disorders in the cleft group (15%) compared to controls (4.5%; $p = 0.14$, $\phi = 0.18$). The cleft group received previous psychiatric therapy more often (15%) than controls (0%; $p = 0.009$, $\phi = 0.29$). The reported psychiatric diagnoses were ADHD (50%), borderline personality disorder (12.5%), learning disability (12.5%), depression (12.5%) and anxiety disorder (12.5%). Children in the cleft group required additional support for learning, psychological and physical well-being during their education more often than controls ($p < 0.001$, $\phi = 0.49$), specifically speech and language therapy ($p < 0.001$, $\phi = 0.51$). Overall, 4.5% of controls reported having a psychiatric comorbidity, which included dyslexia (50%) and ADHD (50%).

#### 3.3.2.1.3. Pregnancy and developmental history

All participating children were born full-term *via* uncomplicated births. No differences were observed in the total number of pregnancies, and natural and caesarian delivery ($p = 0.63$, $\phi = 0.05$). Apgar score at 5 min was lower in the cleft group ($p = 0.031$, $d = 0.48$, see Table 4). No differences were observed in the week of delivery, head circumference and birthweight between the two study groups (see Table 4). The need for postnatal supportive care did not differ between clefts and controls (respiratory support, surfactant therapy, phototherapy, antibiotics, and transfusions; $p = 0.23$, $\phi = 0.13$). Mothers of the cleft group reported feeding ($p = 0.007$, $\phi = 0.29$) and hearing ($p < 0.001$, $\phi = 0.51$) difficulties more often than mothers of controls. The cleft group developed motor skills (roll over, sitting) later than controls, however the effect sizes were small (see Table 4). The cleft group was potty trained at an older age than controls ($p = 0.008$, $d = 0.53$, see Table 4). Parents of the cleft group reported that their children were able to form two-word sentences at a later age compared to reports of parents of controls ($p = 0.039$, $d = 0,60$, see Table 4). First words and coherent sentences were also spoken later by children in the cleft group (See Table 4).

### 3.3.2.2. Parents

#### 3.3.2.2.1. Age, marital and employment status

Parents of the control group were older at the time of assessment than those of the cleft group (see Table 4). Mothers of the cleft group gave birth to their child at an older age than mothers of controls ($p = 0.50$, $d = 0.05$). Most parents of clefts (70.0%) and controls (69.8%) were married, and no differences were observed between the relationship statuses of parents of both groups ($p = 0.47$, $\phi = 0.08$). The employment statuses of fathers ($p = 0.42$, $\phi = 0.25$) and mothers ($p = 0.86$, $\phi = 0.19$) did not differ between the two groups.

#### 3.3.2.2.2. Past psychiatric and academic history

History of psychiatric disorders was more often reported by parents of controls (27.3%) compared to clefts (7.5%; $p = 0.010$, $\phi = 0.39$). One parent of the control group reported to have history of anxiety, but most parents did not further specify these conditions. The majority of reported psychiatric diagnoses in the family of the cleft group were depression (75%) or anxiety disorders (25%). Most parents completed high school and/or had a university degree. Significant differences were not observed in the mother's level of education between the two study groups ($p = 0.29$, $\phi = 0.12$). Fathers of the control group achieved a higher degree of education than fathers of the cleft group who had lower secondary education ($p = 0.024$, $\phi = 0.25$).

## 3.4. Subgroup analysis of the cleft group

Following data collection and analyzes, we hypothesized that the more complex cleft subtypes would obtain lower scores on the IQ test, and present with a history of atypical neurodevelopment, academic difficulties, and psychiatric disorders. We further assumed that early interventions for speech and language would positively impact cognitive development, and the later would be reflected in the IQ score of these children.

A total of 10 girls and 30 boys were tested in the cleft group (see Table 5): Boys became potty-trained earlier (2.39 years) than girls

TABLE 4 Demographic data of the study groups.

| Variable | Cleft group (mean±SD) | *n* | Control group (mean±SD) | *n* | *p*-Value | Cohen's *d* |
|---|---|---|---|---|---|---|
| Age | 12.00 ± 2.62 | 39 | 11.77 ± 2.63 | 44 | 0.69 | 0.09 |
| Education | | | | | | |
| Academic year | 6.17 ± 2.38 | 39 | 6.06 ± 2.75 | 44 | 0.99 | 0.04 |
| Overall academic score | 4.45 ± 0.51 | 38 | 4.46 ± 0.58 | 43 | 0.95 | 0.02 |
| Birth | | | | | | |
| Week of delivery | 38.97 ± 2.19 | 39 | 39.20 ± 1.62 | 44 | 0.59 | 0.12 |
| APGAR score 1 | 8.88 ± 0.62 | 36 | 8.97 ± 0.52 | 41 | 0.58 | 0.16 |
| APGAR score 2 | 9.77 ± 0.59 | 36 | 9.97 ± 0.15 | 41 | 0.031* | 0.48 |
| Birth weight (g) | 3414.87 ± 614.58 | 39 | 3488.31 ± 618.23 | 44 | 0.59 | 0.12 |
| Birth height (cm) | 51.76 ± 4.08 | 38 | 50.43 ± 3.32 | 44 | 0.11 | 0.36 |
| Head circumference (cm) | 34.75 ± 1.51 | 16 | 34.43 ± 1.90 | 30 | 0.57 | 0.19 |
| Motor development | | | | | | |
| Rolls over (months) | 3.97 ± 0.93 | 39 | 4.17 ± 1.02 | 40 | 0.37 | 0.20 |
| Sits (months) | 6.50 ± 1.55 | 38 | 7.29 ± 2.00 | 41 | 0.06 | 0.44 |
| Crawls (months) | 8.61 ± 1.74 | 38 | 8.47 ± 1.80 | 41 | 0.73 | 0.08 |
| Walks (months) | 11.88 ± 1.38 | 39 | 12.02 ± 1.64 | 43 | 0.68 | 0.09 |
| Potty-trained (years) | 2.71 ± 0.84 | 39 | 2.34 ± 0.54 | 42 | 0.008* | 0.53 |
| Language development | | | | | | |
| First words (months) | 15.00 ± 7.65 | 39 | 13.50 ± 4.83 | 37 | 0.53 | 0.23 |
| Two-word phrases (months) | 24.43 ± 9.77 | 38 | 19.52 ± 6.11 | 34 | 0.039* | 0.60 |
| Coherent sentences (year) | 2.50 ± 0.75 | 38 | 2.22 ± 0.59 | 38 | 0.055 | 0.41 |
| Parental SES | | | | | | |
| Gravidity of mother | 2.44 ± 1.37 | 39 | 2.66 ± 1.94 | 44 | 0.99 | 0.13 |
| Mother's age | 42.79 ± 4.43 | 39 | 44.67 ± 4.57 | 43 | 0.063 | 0.42 |
| Father's age | 45.71 ± 5.06 | 39 | 48.13 ± 5.24 | 43 | 0.037* | 0.47 |

Data are presented as means and standard deviations (SD). The number of participants is provided for each variable (*n*). Units are provided for each measurement. Overall academic score was provided according to the 5-point grade system used in Hungary, which defines 1 as insufficient, 2 as sufficient, 3 as satisfactory, 4 as good and 5 as excellent.

(3.50 years; $p = 0.037$, $d = 0.79$). Hearing difficulties were in highest proportion for CPO (57.1%) than for CL (13.3%) and CPL (44.4%) however with small effect size ($p = 0$ 0.063, $d = 0.36$). In the analysis according to types of clefts, CLP was the subtype that was most often referred to special education services: CL in 40%, CPO in 14% and CLP in 72% of the cases ($p = 0.023$, $d = 0.29$). CLP subtype was diagnosed with psychiatric comorbidities in highest proportion (22.2%) compared to CL (13.3%) and CPO (0%) ($p = 0.53$, $d = 0.22$). CLP subtype had additionally received previous psychiatric care in highest proportion (22.2%) compared to the rest of the cleft subtypes ($p = 0.61$, $d = 0.23$). Left (15.4%) and bilateral (30.8%) sided clefts presented the highest proportion of psychiatric diagnoses ($p = 0.27$, $d = 0.35$). The relationship between parental socioeconomic status (SES) and children's cognitive performance.

We aimed to explore variables of parental SES that may influence the outcome of academic and cognitive performance. Fathers with a high academic background reached a higher overall academic average compared to children with fathers of low academic background ($p = 0.005$, $d = 0.79$). Children with mothers of a high academic background reached a higher overall academic average compared to children with mothers of a low academic background (see Table 6). The same pattern was observed for the IQ scores: children who scored higher on almost all indexes of the IQ had parents with a higher academic background (see Supplementary Tables 6, 7). A total of 44.4% of cleft children with single parents had a psychiatric condition(s), while only 6.5% had psychiatric condition(s) when raised by married parents ($p = 0.016$, $d = 0.44$).

### 3.4.1. The relationship between speech/language therapy and the IQ score

We explored the effect of speech and language therapy on IQ scores and overall academic average. FS-IQ and VCI scores were

TABLE 5 Demographical data of the orofacial cleft group.

| Variable | *n* |
|---|---|
| Age | |
| Younger group (6–11 years) | 18 |
| Older group (12–16 years) | 22 |
| Sex | |
| Male | 30 |
| Female | 10 |
| Type of orofacial cleft | |
| CLP | 18 |
| CPO | 7 |
| CL | 15 |
| Side of orofacial cleft | |
| Right | 8 |
| Left | 13 |
| Bilateral | 13 |
| Midline | 6 |

CLP, cleft lip and palate; CPO, cleft palate only; CL, cleft lip.

TABLE 6 Parental level of education in relation to overall academic average of the cleft group.

| Level of education | | *n* | Mean±SD | *p*-Value | Cohen's *d* |
|---|---|---|---|---|---|
| Father | High | 25 | 4.60 ± 0.42 | 0.005* | 1,02 |
| | Low | 14 | 4.11 ± 0.57 | | |
| Mother | High | 29 | 4.62 ± 0.42 | <0.001* | 1.88 |
| | Low | 10 | 3.85 ± 0.38 | | |

*Statistical significance.

higher for children who received therapy (see Table 7). Overall academic average was higher for cleft participants who did not undergo therapy, although with small effect size (see Table 7). A one-way ANOVA was performed to compare the effect of the affected side of the cleft (left, right, bilateral and midline) on IQ scores. We observed differences for continuous variables in WMI when tested by the affected side ($p = 0.037$, $\eta^2 = 0.27$, see Supplementary Table 8).

## 4. Discussion

We analyzed the cognitive functioning and clinical characteristics of 40 children with non-syndromic OFCs and 44 age-matched controls. All participants performed well on the executive function tasks, except for the CPT; children with non-syndromic OFCs scored lower and missed targets more often than controls (omission errors, see Table 4). The results raise the possibility of an underlying attention deficit in these children described previously by other studies (Nopoulos et al., 2010; Pedersen et al., 2016). The two groups scored within normal ranges on the IQ test, however controls scored higher on the PRI and WMI subtests. Subgroup analysis of the cleft group revealed significant relationships between parental SES and IQ scores: children of parents with a higher educational background scored significantly higher on the IQ test, specifically reflected in perceptual reasoning and the full-scare IQ score. We also observed a significant association between early intervention and IQ: children who received speech and language therapy achieved higher scores specifically reflected in the verbal component (VCI) of the WISC-IV (see Table 7). We further observed the influence of family structure on mental health outcomes: children raised by single parents were diagnosed with psychiatric conditions more often than children raised by married parents.

Children of the control group reported more symptoms of externalizing disorders (attention, oppositional, behavioral), while children with non-syndromic OFCs reported symptoms of internalizing disorders (affective, anxiety) more than controls (Table 3). Parents of the control group reported higher symptoms across all scales of the CBCL. However, retrospective analysis of past medical history revealed that children with non-syndromic OFCs were clinically diagnosed with psychiatric disorders at a higher proportion and received psychiatric support more often than controls. Larger cohort studies have previously described this observation (Pedersen et al., 2016; Tillman et al., 2018). While there is a clear difference in the proportion of psychiatric disorders between our two study groups, this is not statistically detectable, and the effect size is small. A larger sample may provide conclusive evidence of this observation.

Psychiatric diagnoses varied across cleft subtypes and the affected side: the highest proportion of psychiatric diagnoses were observed in CLP, and bilateral-sided clefts. These observations may suggest that the more complicated clefts more likely present with psychiatric comorbidities (Pedersen et al., 2016; Gallagher et al., 2018). We did not observe psychiatric comorbidities in CPO children, which is in contrast with previous observations (Nilsson et al., 2015; Pedersen et al., 2016; Tillman et al., 2018; Gallagher and Collett, 2019). Interestingly, less than half (29.16%) of the cleft group participants recognized their repaired OFC as a disease or medical condition. This may indicate that the causative stressor is in fact something other than the physical awareness of the defect itself (Aleksieva et al., 2021). Apgar score at 5 min was lower for the cleft group than for controls, but clinically within the normal range. We observed no further complications in the postnatal period between the two study groups. There was a tendency of a slower onset of developmental milestones in children with OFCs; potty-training and the use of two-word phrases presented at a later age compared to controls, also within clinical ranges. Children with OFCs experienced difficulties integrating into preschool, and most required additional support for learning, psychological and physical well-being throughout their education. Difficulties with speech and language development are known to be a consequence related to the primary defect; however, studies highlight the possibility of a central auditory dysfunction, which may cause developmental issues that affect these skills (Čeponien et al., 1999; Yang et al., 2012; Conrad et al., 2021). Based on our results, children with non-syndromic OFCs initially have a slower development and experience difficulties integrating into preschool; however, it seems that they go through a "catch-up phase" around school age and perform well—almost equal to their peers—throughout elementary and high school.

TABLE 7 Effect of speech and language therapy on IQ scores and overall academic average.

| Cognitive performance | Speech and language therapy | *n* | Mean±SD | *p*-Value | Cohen's *d* |
|---|---|---|---|---|---|
| FS-IQ | No | 16 | 107.06 ± 10.77 | 0.077 | 0.66 |
| | Received | 15 | 114.13 ± 10.68 | | |
| VCI | No | 16 | 109.44 ± 10.73 | 0.005* | 1.10 |
| | Received | 15 | 121.20 ± 10.63 | | |
| PRI | No | 16 | 104.50 ± 10.67 | 0.24 | 0.43 |
| | Received | 15 | 108.67 ± 8.44 | | |
| WMI | No | 16 | 102.38 ± 13.88 | 0.55 | 0.22 |
| | Received | 15 | 105.13 ± 11.54 | | |
| PSI | No | 16 | 103.63 ± 9.02 | 0.83 | 0.07 |
| | Received | 15 | 104.53 ± 14.22 | | |
| Overall academic average | No | 18 | 4.54 ± 0.48 | 0.22 | 0.40 |
| | Received | 21 | 4.33 ± 0.56 | | |

FS-IQ, full-scale IQ; VCI, verbal comprehension index; PRI, perceptual reasoning index; WMI, working memory index; PSI, processing speed index.

Our study has important limitations. The small sample size of the study, limited us to further explore relationships within gender, cleft subtype and affected side. The sample size varied across the different phases of the study. Most of the children in the cleft group were represented by males. The retrospective nature of the questionnaires may have created bias in the data provided. We could not assess the baseline level of executive functioning prior to the interventional programs (speech and language therapy), and we may observe an overall "corrected" level of cognitive functioning. However, this study has several strengths. Our study is the first to provide data on cognitive performance and clinical characteristics of Hungarian children with non-syndromic OFCs across a wide age-range. We were able to provide data on neurodevelopmental differences in children with non-syndromic OFCs in early infancy and the preschool period. We further demonstrated how these children, despite having previous difficulties during early infancy, can "catch-up" to their peers and perform well. Early intervention, additional help in school and proper parental support seem to have a strong effect on proper cognitive development for this patient population. Our observations suggest the presence of attention deficit in children with non-syndromic OFCs in support of the higher proportion of ADHD diagnosis seen in this population compared to controls. Assessing the executive system at an earlier stage of development, prior to interventional programs, may be useful to screen and identify individuals within the cleft population who are at risk for atypical neurodevelopment.

Children with non-syndromic OFCs seem to be at risk for atypical cognitive and speech development. This may be explained by a unified brain and facial maldevelopment *in utero*. Future studies with large sample sizes are needed to further explore this underlying etiology to identify this subpopulation, since not all children with non-syndromic OFCs present with such difficulties. Longitudinal studies are needed to provide more evidence of baseline cognitive functioning to study early signs of atypical neurodevelopment and the effect of early interventions. Under the right environment, these children present with similar cognitive strengths as their peers and show significant skill development. A good multidisciplinary team, early interventions, special education programs, and proper parental support allow most children with non-syndromic OFCs to perform just as well as other children.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Regional Ethics Committee of the University of Pécs (approval number: 7967-PTE 2020). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## Author contributions

KS-B, GC, AV, and KH contributed to conception and design of the study. KS-B, ÁT, AZ, KH, EM, and AV collected the data and organized the database. GC supervised the study. TD performed the statistical analysis. KS-B wrote the first draft of the manuscript. GC and TD wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

## Funding

The authors received financial support from the University of Pécs for the open-access publication of this manuscript.

## Acknowledgments

We would like to acknowledge George K.B. Sándor who has dedicated his professional career for the significant advancements in cleft repair surgery, by which he has contributed to improvements in quality of life for both orofacial cleft patients and their families. His work has greatly inspired the current research, equally dedicated to improving the clinical care of children born with orofacial clefts. GC was supported by the FIKP-IV and the TNIL Projects.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2023.1115304/full#supplementary-material

## References

Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist/4–18 and 1991 Profile*. Burlington: University of Vermont, Department of Psychiatry

Adamson, C. L., Anderson, V. A., Nopoulos, P., Seal, M. L., and da Costa, A. C. (2014). Regional brain morphometric characteristics of nonsyndromic cleft lip and palate. *Dev. Neurosci.* 36, 490–498. doi: 10.1159/000365389

Aleksieva, A., Begnoni, G., Verdonck, A., Laenen, A., Willems, G., and Cadenas de Llano-Pérula, M. (2021). Self-esteem and oral health-related quality of life within a cleft lip and/or palate population: a prospective cohort study. *Int. J. Environ. Res. Public Health* 18:6078. doi: 10.3390/ijerph18116078

Ansen-Wilson, L. J., Everson, J. L., Fink, D. M., Kietzman, H. W., Sullivan, R., and Lipinski, R. J. (2018). Common basis for orofacial clefting and cortical interneuronopathy. *Transl. Psychiatry* 8:8. doi: 10.1038/s41398-017-0057-7

Ardila, A. (2018). Is intelligence equivalent to executive functions? *Psicothema* 30, 159–164. doi: 10.7334/psicothema2017.329

Bausela-Herreras, E., Tirapu-Ustárroz, J., and Cordero-Andrés, P. (2019). Executive function deficits and neurodevelopmental disorders in childhood and adolescence. *Rev. Neurol.* 69, 461–469. doi: 10.33588/rn.6911.2019133

Berg, E., Haaland, Ø. A., Feragen, K. B., Filip, C., Vindenes, H. A., Moster, D., et al. (2016). Health status among adults born with an Oral cleft in Norway. *JAMA Pediatr.* 170, 1063–1070. doi: 10.1001/jamapediatrics.2016.1925

Bjørnland, T., Nørholt, S. E., Rasmusson, L., and Sándor, G. K. (2021). *Nordic Textbook of Oral and Maxillofacial Surgery Munksgaard*. Available online at: https://books.google.hu/books?id=aR1rzgEACAAJ (Accessed January 26, 2022).

Bodoni, P. S. B., Leoni, R. F., do Vale, A. B., da Silva, P. H. R., Meira Junior, S. G., Richieri Costa, A., et al. (2021). Neuropsychological functioning and its relationship with brain anatomical measures of children and adolescents with non-syndromic cleft lip and palate. *Child Neuropsychol.* 27, 2–16. doi: 10.1080/09297049.2020.1776240

Boes, A. D., Murko, V., Wood, J. L., Langbehn, D. R., Canady, J., Richman, L., et al. (2007). Social function in boys with cleft lip and palate: relationship to ventral frontal cortex morphology. *Behav. Brain Res.* 181, 224–231. doi: 10.1016/J.BBR.2007.04.009

Brunetti, R., del Gatto, C., and Delogu, F. (2014). eCorsi: Implementation and testing of the Corsi block-tapping task for digital tablets. *Front. Psychol.* 5:939. doi: 10.3389/fpsyg.2014.00939

Bull, R., Espy, K. A., and Senn, T. E. (2004). A comparison of performance on the towers of London and Hanoi in young children. *J. Child Psychol. Psychiatry* 45, 743–754. doi: 10.1111/j.1469-7610.2004.00268.x

Čeponien, R., Hukki, J., Cheour, M., Haapanen, M. L., Ranta, R., and Näätänen, R. (1999). Cortical auditory dysfunction in children with oral clefts: relation with cleft type. *Clin. Neurophysiol.* 110, 1921–1926. doi: 10.1016/S1388-2457(99)00152-2

Chollet, M. B., DeLeon, V. B., Conrad, A. L., and Nopoulos, P. (2014). Morphometric analysis of brain shape in children with nonsyndromic cleft lip and/or palate. *J. Child Neurol.* 29, 1616–1625. doi: 10.1177/0883073813510603

Coe, R. (2002). "It's the effect size, stupid: what '"effect size"' is and why it is important" in *Paper presented at the British Educational Research Association Annual Conference*. ed. R. Coe (Exeter: University of Exeter)

Conners, C. K.. (2014). *Conners CPT3, Continuous Performance Test. 3rd*. Toronto: Multi-Health Systems

Conrad, A. L., Richman, L., Nopoulos, P., and Dailey, S. (2009). Neuropsychological functioning in children with non-Syndromic cleft of the lip and/or palate. *Child Neuropsychol.* 15, 471–484. doi: 10.1080/09297040802691120

Conrad, A. L., Wermke, K., Eisenmann, M., Kuhlmann, E., Benavides, A., Koscik, T., et al. (2021). Preliminary evaluation of pre-speech and neurodevelopmental measures in 7–11-week-old infants with isolated oral clefts. *Pediatr. Res.* 89, 85–90. doi: 10.1038/s41390-020-0887-5

Diamond, A. (2013). Executive functions. *Annu. Rev. Psychol.* 64, 135–168. doi: 10.1146/annurev-psych-113011-143750

Faedda, N., Romani, M., Rossetti, S., Vigliante, M., Pezzuti, L., Cardona, F., et al. (2019). Intellectual functioning and executive functions in children and adolescents with attention deficit hyperactivity disorder (ADHD) and specific learning disorder (SLD). *Scand. J. Psychol.* 60, 440–446. doi: 10.1111/sjop.12562

Gallagher, E. R., and Collett, B. R. (2019). Neurodevelopmental and academic outcomes in children with Orofacial clefts: a systematic review. *Pediatrics* 144, 1–10. doi: 10.1542/peds.2018-4027

Gallagher, E. R., Siebold, B., Collett, B. R., Cox, T. C., Aziz, V., and Cunningham, M. L. (2018). Associations between laterality of orofacial clefts and medical and academic outcomes. *Am. J. Med. Genet. A* 176, 267–276. doi: 10.1002/ajmg.a.38567

Grizzle, R. (2011). "Wechsler intelligence scale for children, fourth edition" in *Encyclopedia of Child Behavior and Development*. eds. S. Goldstein and J. A. Naglieri (Boston, MA: Springer US), 1553–1555.

Harila, V., Ylikontiola, L. P., Palola, R., and Sándor, G. K. (2013). Maxillary arch dimensions in cleft infants in northern Finland. *Acta Odontol. Scand.* 71, 930–936. doi: 10.3109/00016357.2012.734420

Kaller, C. P., Unterrainer, J. M., Stefan, K., Weisbrod, M., Debelak, R., and Aschenbrenner, S. (2011). *Tower of London-Freiburg Version (TOL-F)*. Mödling: Schuhfried

Kessels, R. P. C., van Zandvoort, M. J. E., Postma, A., Kappelle, L. J., and de Haan, E. H. F. (2000). The Corsi block-tapping task: standardization and normative data. *Appl. Neuropsychol.* 7, 252–258. doi: 10.1207/S15324826AN0704_8

Laasonen, M., Haapanen, M.-L., Mäenpää, P., Pulkkinen, J., Ranta, R., and Virsu, V. (2004). Visual, auditory, and tactile temporal processing in children with Oral clefts. *J. Craniofacial Surg.* 15, 510–518. doi: 10.1097/00001665-200405000-00033

Lemos, I. C. C., and Feniman, M. R. (2010). Teste de Habilidade de Atenção Auditiva Sustentada (THAAS) em crianças de sete anos com fissura labiopalatina. *Braz. J. Otorhinolaryngol.* 76, 199–205. doi: 10.1590/S1808-86942010000200009

Li, J., Rodriguez, G., Han, X., Janečková, E., Kahng, S., Song, B., et al. (2019). Regulatory mechanisms of soft palate development and malformations. *J. Dent. Res.* 98, 959–967. doi: 10.1177/0022034519851786

Lithovius, R. H., Ylikontiola, L. P., Harila, V., and Sándor, G. K. (2014). A descriptive epidemiology study of cleft lip and palate in northern Finland. *Acta Odontol. Scand.* 72, 372–375. doi: 10.3109/00016357.2013.840737

McDonald-McGinn, D. M., Sullivan, K. E., Marino, B., Philip, N., Swillen, A., Vorstman, J. A. S., et al. (2015). 22q11.2 deletion syndrome. *Nat. Rev. Dis. Primers.* 1:15071. doi: 10.1038/nrdp.2015.71

Mossey, P. A., and Modell, B. (2012). Epidemiology of oral clefts 2012: an international perspective. *Front. Oral. Biol.* 16, 1–18. doi: 10.1159/000337464

Nagyné Réz, I., Lányiné Engelmayer, A., and Kuncz, E. (2007). *WISC-IV: Wechsler Gyermek Intelligenciateszt-Negyedik kiadás. 4th* Edn. Budapest (Hungary): OS Hungary Tesztfejlesztő Kft.

Naidoo, R., Shuttleworth-Edwards, A. B., Botha, R., and Pienaar, I. (2019). The tower of London-DX 2nd edition test: preliminary norms for educationally disadvantaged Xhosa-speaking individuals. *J. Psychol. Afr.* 29, 60–66. doi: 10.1080/14330237.2019.1568074

Nilsson, S., Merlo, J., Lyberg-Åhlander, V., and Psouni, E. (2015). Psychotropic drug use in adolescents born with an orofacial cleft: a population-based study. *BMJ Open* 5:e005306. doi: 10.1136/bmjopen-2014-005306

Nopoulos, P., Berg, S., Canady, J., Richman, L., van Demark, D., and Andreasen, N. C. (2000). Abnormal brain morphology in patients with isolated cleft lip, cleft palate, or both: a preliminary analysis. *Cleft Palate Craniofac. J.* 37, 441–446. doi: 10.1597/1545-1569_2000_037_0441_abmipw_2.0.co_2

Nopoulos, P., Berg, S., Van Demark, D., Richman, L., Canady, J., and Andreasen, N. C. (2002). Cognitive dysfunction in adult males with non-syndromic clefts of the lip and/or palate. *Neuropsychologia* 40, 2178–2184. doi: 10.1016/S0028-3932(02)00043-X

Nopoulos, P., Boes, A. D., Jabines, A., Conrad, A. L., Canady, J., Richman, L., et al. (2010). Hyperactivity, impulsivity, and inattention in boys with cleft lip and palate: relationship to ventromedial prefrontal cortex morphology. *J. Neurodev. Disord.* 2, 235–242. doi: 10.1007/s11689-010-9060-5

Nopoulos, P., Choe, I., Berg, S., van Demark, D., Canady, J., and Richman, L. (2005). Ventral frontal cortex morphology in adult males with isolated Orofacial clefts: relationship to abnormalities in social function. *Cleft Palate Craniofac. J.* 42, 138–144. doi: 10.1597/03-112.1

Otterman, D. L., Koopman-Verhoeff, M. E., White, T. J., Tiemeier, H., Bolhuis, K., and Jansen, P. W. (2019). Executive functioning and neurodevelopmental disorders in early childhood: a prospective population-based study. *Child Adolesc. Psychiatry Ment. Health* 13:38. doi: 10.1186/s13034-019-0299-7

Parris, B. A. (2014). Task conflict in the Stroop task: when Stroop interference decreases as Stroop facilitation increases in a low task conflict context. *Front. Psychol.* 5:1182. doi: 10.3389/fpsyg.2014.01182

Pedersen, D. A., Wehby, G. L., Murray, J. C., and Christensen, K. (2016). Psychiatric diagnoses in individuals with non-Syndromic Oral clefts: a Danish population-based cohort study. *PLoS One* 11:e0156261. doi: 10.1371/journal.pone.0156261

PsyWay (2020). PsyWay Pszichológiai tesztek online kiértékelése. Available at: http://www.pszichotesztek.hu

Richman, L. C., McCoy, T. E., Conrad, A. L., and Nopoulos, P. C. (2012). Neuropsychological, behavioral, and academic sequelae of cleft: early developmental, school age, and adolescent/young adult outcomes. *Cleft Palate Craniofac. J.* 49, 387–396. doi: 10.1597/10-237

Richman, L. C., and Ryan, S. M. (2003). Do the reading disabilities of children with cleft fit into current models of developmental dyslexia? *Cleft Palate Craniofac. J.* 40, 154–157. doi: 10.1597/1545-1569_2003_040_0154_dtrdoc_2.0.co_2

Rincic, M., Rados, M., Krsnik, Z., Gotovac, K., Borovecki, F., Liehr, T., et al. (2016). Complex intrachromosomal rearrangement in 1q leading to 1q32.2 microdeletion: a potential role of SRGAP2 in the gyrification of cerebral cortex. *Mol. Cytogenet.* 9:19. doi: 10.1186/s13039-016-0221-4

Roebuck, H., Freigang, C., and Barry, J. G. (2016). Continuous performance tasks: not just about sustaining attention. *J. Speech Lang. Hear. Res.* 59, 501–510. doi: 10.1044/2015_JSLHR-L-15-0068

Rózsa, S., Kő, N., and Gádoros, J. (1999). A gyermekpszichiátriai zavarok kérdőíves mérése: Agyermekviselkedési kérdőív diagnosztikai megbízhatósága és a több információ forrásonalapuló jellemzések egyezése. *Psychiatr. Hung.* 4, 375–392.

Saleem, K., Zaib, T., Sun, W., and Fu, S. (2019). Assessment of candidate genes and genetic heterogeneity in human non syndromic orofacial clefts specifically non syndromic cleft lip with or without palate. *Heliyon* 5:e03019. doi: 10.1016/j.heliyon.2019.e03019

Sándor-Bajusz, K. A., Sadi, A., Varga, E., Csábi, G., Antonoglou, G. N., and Lohner, S. (2022). The brain in Oral Clefting: a systematic review with meta-analyses. *Front. Neuroanat.* 16:863900. doi: 10.3389/FNANA.2022.863900

Scarpina, F., and Tagini, S. (2017). The stroop color and word test. *Front. Psychol.* 8:00557. doi: 10.3389/fpsyg.2017.00557

Shaheen, S. (2014). How Child's play impacts executive function–related behaviors. *Appl. Neuropsychol. Child* 3, 182–187. doi: 10.1080/21622965.2013.839612

Speltz, M. L. (2000). Brief report: cognitive and psychomotor development of infants with orofacial clefts. *J. Pediatr. Psychol.* 25, 185–190. doi: 10.1093/jpepsy/25.3.185

Tillman, K. K., Hakelius, M., Höijer, J., Ramklint, M., Ekselius, L., Nowinski, D., et al. (2018). Increased risk for neurodevelopmental disorders in children with orofacial clefts. *J. Am. Acad. Child Adolesc. Psychiatry* 57, 876–883. doi: 10.1016/j.jaac.2018.06.024

Unterrainer, J. M., Rahm, B., Kaller, C. P., Leonhart, R., Quiske, K., Hoppe-Seyler, K., et al. (2004). Planning abilities and the tower of London: is this task measuring a discrete cognitive function? *J. Clin. Exp. Neuropsychol.* 26, 846–856. doi: 10.1080/13803390490509574

Weinberg, S. M., Andreasen, N. C., and Nopoulos, P. (2009). Three-dimensional morphometric analysis of brain shape in nonsyndromic orofacial clefting. *J. Anat.* 214, 926–936. doi: 10.1111/j.1469-7580.2009.01084.x

Yang, F. F., McPherson, B., Shu, H., Xie, N., and Xiang, K. (2012). Structural abnormalities of the central auditory pathway in infants with nonsyndromic cleft lip and/or palate. *Cleft Palate Craniofac. J.* 49, 137–145. doi: 10.1597/11-014

Zelazo, P. D. (2015). Executive function: reflection, iterative reprocessing, complexity, and the developing brain. *Dev. Rev.* 38, 55–68. doi: 10.1016/j.dr.2015.07.001

frontiers | Frontiers in Neuroanatomy

SYSTEMATIC REVIEW
published: 10 June 2022
doi: 10.3389/fnana.2022.863900

# The Brain in Oral Clefting: A Systematic Review With Meta-Analyses

*Kinga A. Sándor-Bajusz[1,2]*, Asaad Sadi[3], Eszter Varga[1], Györgyi Csábi[1], Georgios N. Antonoglou[4] and Szimonetta Lohner[5,6]*

[1] Department of Pediatrics, University of Pécs, Pécs, Hungary, [2] Doctoral School of Clinical Neurosciences, University of Pécs, Pécs, Hungary, [3] Adult Psychiatric Division, Borlänge Specialist Clinic, Borlänge, Sweden, [4] Periodontology Unit, Faculty of Dentistry, Centre for Host Microbiome Interactions, Oral and Craniofacial Sciences, King's College London, London, United Kingdom, [5] Cochrane Hungary, Clinical Centre of the University of Pécs, Medical School, University of Pécs, Pécs, Hungary, [6] Department of Public Health Medicine, Medical School, University of Pécs, Pécs, Hungary

**Background:** Neuroimaging of individuals with non-syndromic oral clefts have revealed subtle brain structural differences compared to matched controls. Previous studies strongly suggest a unified primary dysfunction of normal brain and face development which could explain these neuroanatomical differences and the neuropsychiatric issues frequently observed in these individuals. Currently there are no studies that have assessed the overall empirical evidence of the association between oral clefts and brain structure. Our aim was to summarize the available evidence on potential brain structural differences in individuals with non-syndromic oral clefts and their matched controls.

**Methods:** MEDLINE, Scopus, Cochrane Central Register of Controlled Trials, Web of Science and Embase were systematically searched in September 2020 for case-control studies that reported structural brain MRI in individuals with non-syndromic oral clefts and healthy controls. Studies of syndromic oral clefts were excluded. Two review authors independently screened studies for eligibility, extracted data and assessed risk of bias with the Newcastle-Ottawa Scale. Random effects meta-analyses of mean differences (MDs) and their 95% confidence intervals (95% CI) were performed in order to compare global and regional brain MRI volumes.

**Results:** Ten studies from 18 records were included in the review. A total of 741 participants were analyzed. A moderate to high risk of bias was determined for the included studies. The cerebellum (MD: −12.46 $cm^3$, 95% CI: −18.26, −6.67, $n$ = 3 studies, 354 participants), occipital lobes (MD: −7.39, 95% CI: −12.80, −1.99, $n$ = 2 studies, 120 participants), temporal lobes (MD: −10.53 $cm^3$, 95% CI: −18.23, −2.82, $n$ = 2 studies, 120 participants) and total gray matter (MD: −41.14 $cm^3$; 95% CI: −57.36 to −24.92, $n$ = 2 studies, 172 participants) were significantly smaller in the cleft group compared to controls.

OPEN ACCESS

**Edited by:**
*Salvador Martinez, Miguel Hernández University of Elche, Spain*

**Reviewed by:**
*Lana Vasung, Harvard Medical School, United States*
*Ziliang Zhu, University of North Carolina at Chapel Hill, United States*
*Fernando Navarro-Mateu, Servicio Murciano de Salud, Spain*

***Correspondence:**
*Kinga A. Sándor-Bajusz*
*sandor.kinga@pte.hu*

**Received:** *14 February 2022*
**Accepted:** *11 April 2022*
**Published:** *10 June 2022*

**Citation:**
*Sándor-Bajusz KA, Sadi A, Varga E, Csábi G, Antonoglou GN and Lohner S (2022) The Brain in Oral Clefting: A Systematic Review With Meta-Analyses. Front. Neuroanat. 16:863900. doi: 10.3389/fnana.2022.863900*

**Discussion:** There may be structural brain differences between individuals with non-syndromic oral clefts and controls based on the available evidence. Improvement in study design, size, methodology and participant selection could allow a more thorough analysis and decrease study heterogeneity.

**Keywords: cleft lip, cleft palate, neurodevelopment, brain, neuroimaging**

## INTRODUCTION

Oral clefts are one of the most common birth defects with a worldwide incidence of 1:700 births (Mossey and Modell, 2012). Oral clefts can be syndromic or non-syndromic, the latter occurring as a single anomaly in the absence of other physical and developmental disorders (Mossey and Modell, 2012; Bjørnland et al., 2021). The etiology of oral clefts is multifactorial, including gene-environmental interactions, hereditary causes, antenatal nutrition, and drug exposure (Lithovius et al., 2014; Bjørnland et al., 2021). Oral clefts can be anatomically classified as cleft lip (CL), cleft palate (CP), and combined cleft lip and palate (CLP) (Lithovius et al., 2014; Bjørnland et al., 2021).

Syndromic oral clefts are predisposed to more complex treatment due to the underlying genetic disorder and other associated health complications (Sándor-Bajusz et al., 2021). Syndromic individuals often have mental comorbidities including intellectual disability and learning disorders (Hardin-Jones and Chapman, 2011; Diaz-Stransky and Tierney, 2012; Feragen et al., 2014; McDonald-McGinn et al., 2015; Zinkstok et al., 2019). Decades of research revealed the presence of neuropsychiatric and neurodevelopmental disorders in individuals with non-syndromic oral clefts (Broder et al., 1998; Richman and Ryan, 2003; Conrad et al., 2008; Pedersen et al., 2016; Ansen-Wilson et al., 2018; Tillman et al., 2018). Children with oral clefts are associated with a significant agglomeration of psychiatry disorders including intellectual disability, autism spectrum disorder, ADHD and learning disorders (Pedersen et al., 2016; Ansen-Wilson et al., 2018; Tillman et al., 2018). Neurodevelopmental delays have been documented in younger children including fine motor, gross motor and both expressive and receptive language development (Conrad et al., 2008; Hardin-Jones and Chapman, 2011; Gallagher and Collett, 2019). These observations were suggested to be the consequence of multiple stressors including social stigma, frequent anesthesia exposure and/or cleft-related airway obstruction impairing proper neurodevelopment (Gallagher and Collett, 2019).

New advances in oral cleft research have strongly suggested a unified primary dysfunction of normal brain and face development, that could explain the neurodevelopmental-related deficits observed in these children (Conrad et al., 2021). This primary dysfunction seems to affect a crucial developmental stage of a physiological migration of cells that will later form the face and parts of the brain and the central nervous system (Ansen-Wilson et al., 2018; Ornoy, 2020). Neuroimaging studies have additionally revealed significant differences in the brain structure of individuals with non-syndromic oral clefts compared to matched controls. However, a definitive statement cannot be made due to the heterogeneity among the studies including quality, sample size, methodology and outcomes (Yang et al., 2012; Gallagher and Collett, 2019).

The aim of the present systematic review was to assess the overall empirical evidence of the association between of non-syndromic oral clefts and the brain.

## METHODS

The current meta-analysis was registered in PROSPERO (International Prospective Register of Systematic Reviews[1]; RRID:SCR_019061, identifier CRD42020167773), and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020, RRID:SCR_018721) guideline (Page et al., 2021).

### Search Strategy

Searches of the following databases were conducted until 7 September 2020: MEDLINE (Ovid; RRID:SCR_002185), Scopus, Cochrane Central Register of Controlled Trials (CENTRAL; RRID:SCR_006576), Web of Science and Embase (RRID:SCR_001650). Clinicaltrials.gov (RRID:SCR_002309) was searched to identify ongoing/completed studies and unpublished SRs (see **Supplementary Table 1** for the full search strategy used in each of the databases).

### Selection of Studies

#### Inclusion Criteria

The following criteria had to be met for inclusion into the study: (1) Case-control studies with humans; (2) Individuals with non-syndromic (isolated) oral clefts, without restriction to age; (3) Healthy controls; (4) Structural brain differences of individuals with non-syndromic oral clefts vs. their controls as a relevant outcome: structural differences had to be explored with brain MRI. No restrictions were applied for language.

#### Exclusion Criteria

The publication was excluded if it had any of the following: (1) Animal studies (2) Individuals with syndromes (syndromic forms of oral clefts, such as Pierre-Robin sequence or Velocardiofacial syndrome).

The selection process was performed with the Covidence systematic review software (RRID:SCR_016484) (Veritas Health Innovation, 2017).

Two review authors (KSB and EV) screened the titles and/or abstracts of studies retrieved from the searches. Additional sources were also screened (hand searching, reference/citation

[1]https://www.crd.york.ac.uk/prospero/

lists) to identify articles that may potentially meet the inclusion criteria. Full texts of these potentially eligible records were retrieved and assessed by one review author (KSB), while a second checked the decisions (EV). Any differences between the two reviewers were settled by consensus after consulting a third author (GA or SL).

## Data Extraction

Data was extracted independently by three authors (KSB, AS, and EV). Discrepancies were resolved the same way as stated above.

Study setting (design, institution, country), patient demographics (number, age, sex, ethnicity, gender, type of oral cleft, brain imaging details, data processing) and outcome measurement details (general and regional brain MRI measurements) were collected. Any data that were not described in the article were calculated from existing data, or were obtained by contacting the authors.

The primary outcome measures were structural differences of the brain of individuals with oral clefts vs. individuals without oral clefts (controls) investigated *via* MRI. Other sought outcomes included the correlation between observed structural differences in the brain of individuals with oral clefts and alterations in neurological and/or mental functioning compared to controls.

## Risk of Bias Assessment

The Newcastle-Ottawa Scale (NOS) (Wells et al., 2000) was used for all outcomes to assess the quality of non-randomized case-control studies included in the systematic review. Assessment was completed by two authors (KSB, AS) and independently checked by a third (SL) the same way to resolve discrepancies.

## Statistical Analysis and Data Synthesis Methods

Review Manager Software Version 5.4 was used for data synthesis (RRID:SCR_003581) (Cochrane, 2020). The random-effects model was chosen *a priori* as the primary method to estimate all pooled estimates for studies that were comparable in design, exposure and outcomes. This model was used to account for the differences within study populations such as age, sex, and type of oral clefts. Mean Differences (MDs) and their corresponding 95% confidence intervals (CI 95%) were used for continuous outcomes.

The extent and impact of between-study heterogeneity was assessed by inspecting the forest plots and by calculating the tau-squared and the I-squared statistics, respectively. The I-squared thresholds represented heterogeneity that may not be important (0–40%), moderate (30–60%), substantial (50–90%), or considerable (75–100%). Possible sources of heterogeneity in meta-analyses were sought through pre-specified mixed-effects subgroup analyses if at least two studies were included for a comparison (same intervention/outcome). Pre-defined subgroup analyses included: (i) age; (ii) sex; (iii) ethnicity; (iv) cleft form (non-syndromic vs. syndromic).

### Additional Analyses

Assessment of reporting biases (small-study effects or publication bias) was planned through the inspection of a contour-enhanced funnel plot and with the Egger's weighted regression test if a sufficient number of trials were identified ($n > 10$).

# RESULTS

## Study Selection (Systematic Literature Search)

A total of 257 records were identified following the database searches. Overall, 245 records underwent title and abstract screening following duplicate removal. Thirty-two records were retrieved and assessed for eligibility. Two records were additionally identified by handsearching, and only one met the inclusion criteria (Yang et al., 2012). A total of 10 studies from 18 records met the inclusion criteria. Three records included individuals diagnosed with Van der Woude syndrome, a syndromic form of oral clefts (Nopoulos et al., 2000, 2002, 2005). These records were included in the current systematic review as none of the syndromic individuals exceeded 15% of total cleft participants.

The study selection process is shown in the flow diagram of **Figure 1**.

Fifteen records seemed to meet the inclusion criteria, however, they were excluded during the full-text screening process. The reasons for exclusion were as follows: absence of a control group ($n = 3$ Shen and Huang, 1996; Mueller et al., 2007; Zheng et al., 2019), conference abstracts or commentaries ($n = 4$ Chollet et al., 2010; Tollefson and Sykes, 2010; DeVolder et al., 2014, 2015), wrong study population that only included syndromic cases of oral clefts ($n = 2$ Nopoulos et al., 2007a,b), absence of neuroimaging ($n = 5$ Čeponiene et al., 1999; Scott et al., 2005; Kummer et al., 2007; Conrad et al., 2008; Watkins et al., 2018), or neuroimaging other than brain MRI ($n = 1$ Becker et al., 2008).

### Study Characteristics

The study characteristics are presented in **Tables 1A,B**. The majority were conducted in the US. Other countries included Australia (Adamson et al., 2014), Brazil (Bodoni et al., 2021), and China (Yang et al., 2012; Li et al., 2020). Study size ranged between 24 and 234 participants. The majority of the participants were males of Caucasian ethnicity. Most of the participants were children.

## Risk of Bias of Included Studies

The risk of bias assessment of included studies are shown in **Table 2**. The overall risk of bias ranged from medium to high. Selection of cleft participants, their comparators and the assessment of exposure were described in half of the studies. Information on recruitment and reasons for dropout were not available in most studies. Only one study reported blinding personnel of group status during MRI scanning (Nopoulos et al., 2007c).

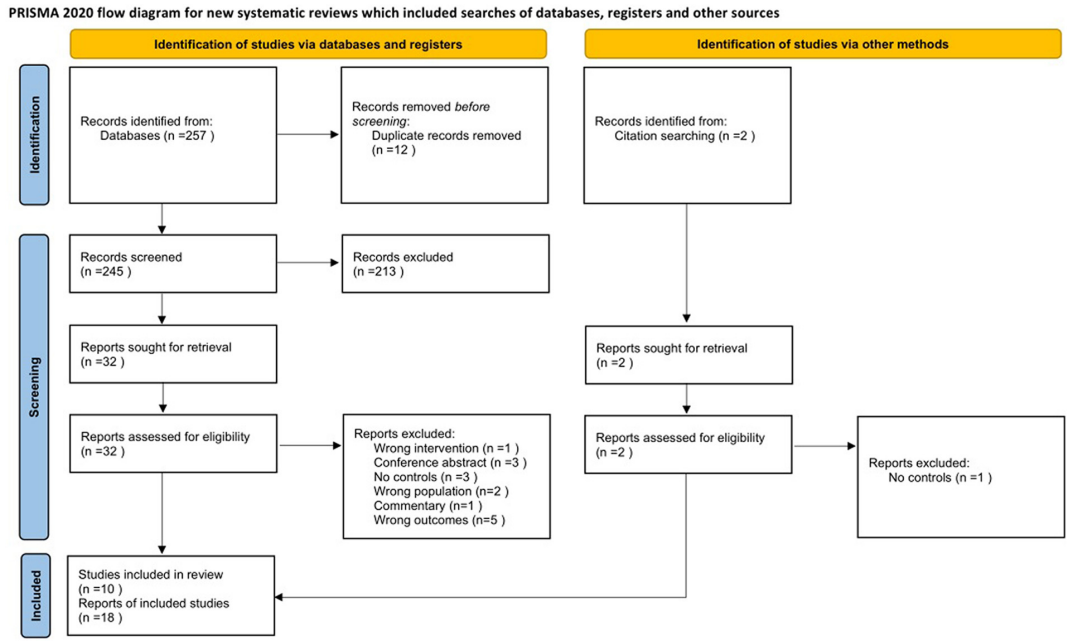


**FIGURE 1 |** Flow diagram of the study selection process.

## Results

Five studies were comparable in terms of study design, exposure and outcome. Studies were pooled using a random-effect meta-analysis.

All five studies segmented the brain according to all or one of the following: intracranial volume was divided into total brain tissue and cerebrospinal fluid; the brain tissue was divided into the cerebrum and cerebellum; the cerebrum was subdivided into the frontal, parietal, temporal, and occipital lobes. The majority of the studies used the Talairach Atlas-based method for measures of general and regional brain tissue. Most studies used three different sequences (T1-weighted, T2-weighted, and/or proton density images) with comparable parameters to classify tissue into gray matter, white matter, and cerebrospinal fluid. Additional details of MRI analysis are presented in **Supplementary Table 2**.

### Primary Outcome

#### *Studies Investigating Global Measurements*

Global measurements were anatomically grouped into three groups: total brain volumes (including MRI volumes of the cerebrum and cerebellum), cerebral volumes (only MRI volumes of the cerebrum), and cerebellar volumes (only MRI volumes of the cerebellum).

*Total Brain Volumes.* The cleft group had lower total gray matter volume compared to controls (MD: −41.14 $cm^3$; 95% CI: −57.36 to −24.92; $n$ = 2; 172 participants; $I^2$: 0%) (**Figure 2**). There were no differences in brain size of oral cleft subjects compared to controls (MD: −38.86 $cm^3$; 95% CI: −83.88 to 6.16; $n$ = 4;322 participants; $I^2$: 48%) (**Figure 3**). No differences were found in white matter volume of oral cleft subjects and their controls (MD: −21.93 $cm^3$; 95% CI: −64.20 to 20.33; $n$ = 2; 172 participants; $I^2$: 69%) (see **Supplementary Figure 1**).

*Cerebral Volume.* Total volume of the cerebrum in the oral cleft group did not differ from the control group (MD: −22.42 $cm^3$; 95% CI: −66.40 to 21.56; $n$ = 3; 268 participants; $I^2$: 58%) (**Figure 4**). There were no differences in gray matter volume of the cerebrum between oral clefts and controls (MD: −6.45 $cm^3$; 95% CI: −25.17 to 12.27; $n$ = 2; 202 participants; $I^2$: 0%) (see **Supplementary Figure 2**). An included study found a significantly lower gray matter volume on the left side of the cerebrum in individuals with oral cleft (Yang et al., 2012, $P$ = 0.033). However, the study could not be included in the meta-analysis due to incomplete data (missing SD values). No differences were observed in cerebral white matter volume between oral clefts and controls (MD: −5.08 cm3; 95% CI: −20.19 to 10.03; $n$ = 2; 146 participants; $I^2$:0%) (**Supplementary Figure 3**).

*Cerebellar Volume.* The cerebellum was significantly smaller in oral clefts compared to controls (MD: −12.46 $cm^3$; 95% CI: −18.26, −6.67; $n$ = 3; 354 participants; $I^2$: 0%, $n$ = 3) (**Figure 5**).

#### *Studies Investigating Regional Measurements*

*Frontal Lobe Volume.* The size of the frontal lobe did not differ between the cleft group and controls (MD: 18.27 $cm^3$; 95% CI: −12.62 to 49.16; $n$ = 2; 120 participants $I^2$: 0%) (**Supplementary Figure 4**). There were no differences in frontal gray matter volume between oral clefts and controls (MD: 4.77 $cm^3$; 95% CI: −7.84 to 17.38; $n$ = 2; 165 participants; $I^2$: 0%) (**Supplementary Figure 5**). There were no differences in the two components of the ventrofrontal cortex; the straight gyrus (MD: −0.17 $cm^3$; 95% CI: −1.35 to 1.00; $n$ = 2; 165

**TABLE 1A |** Characteristics of included studies.

| References | Country | Study participants present in another reference? | Inclusion | Exclusion | N |
|---|---|---|---|---|---|
| Nopoulos et al. (2000) | United States | No | Adult males (18 +) with non-syndromic oral clefts | Congenital syndromes | 28 |
| Nopoulos et al. (2001) | United States | No | Adult males with non-syndromic oral clefts | Congenital syndromes | 124 |
| Nopoulos et al. (2002) | United States | No | Non-syndromic oral clefts | Congenital syndromes | 92 |
| Nopoulos et al. (2005) (Nopoulos, 2002A) | United States | Same study cohort as (Nopoulos et al., 2002) | Adult males (18 +) with non-syndromic clefts | Congenital syndromes | 92 |
| Shriver et al. (2006) (Nopoulos, 2002B) | United States | Same patient population as (Nopoulos et al., 2002) | Adult males (18 +) with non-syndromic oral clefts | Genetic syndrome, serious, active medical or neurologic disease or active substance abuse/dependence, psychiatric disorders | 89 |
| Nopoulos et al. (2007c) | United States | No | Children with non-syndromic oral clefts | Braces (artifact in MRI scan), IQ < 70, genetic syndrome | 148 |
| Boes et al. (2007) (Nopoulos, 2007A) | United States | Subset of cleft participants from Nopoulos et al. (2007c) | Boys with non-syndromic oral clefts | Genetic syndromes, serious medical or neurological disease | 73 |
| Weinberg et al. (2009) | United States | No | Adult males (18 +) | N/A | 86 |
| van der Plas et al. (2010) (Nopoulos, 2007E) | United States | Participants of both groups were part of another study (Nopoulos et al., 2007c) | Children with unilateral CLP or CL only | CP, bilateral CLP or CL, genetic syndromes, serious medical and neurological disease | 90 |
| Nopoulos et al. (2010) (Nopoulos, 2007B) | United States | Subset of cleft participants from Nopoulos et al. (2007c) | Boys with non-syndromic oral clefts | Braces (creates artifact in MRI scan), IQ < 70, genetic syndrome | 110 |
| Conrad et al. (2010) (Nopoulos, 2007C) | United States | Cleft MRI results from Nopoulos et al. (2007c) | Children with non-syndromic oral clefts | Genetic syndromes, significant hearing loss (requiring a hearing aid), braces, history of head trauma, brain tumor or epilepsy. | 86 |
| DeVolder et al. (2013) (Nopoulos, 2007D) | United States | Subset of participants of two previous studies from Nopoulos et al. (2007c) and Conrad et al. (2010) | Children with non-syndromic oral clefts | Braces (artifact in MRI scan), IQ < 70 | 234 |
| Yang et al. (2012) | China | No | Full-term birth, uncomplicated delivery, non-syndromic oral cleft | Congenital syndromes, other chronic health disorders | 54 |
| Weinberg et al. (2013) | United States | No | Males, non-syndromic oral clefts, limited to 18–50 year old | Congenital syndromes | 64 |
| Adamson et al. (2014) | Australia | No | Children with non-syndromic oral clefts | Genetic syndromes | 52 |
| Chollet et al. (2014) (Nopoulos, 2007F) | United States | MRI data from previous study by Nopoulos et al. (2007c) | Children with non-syndromic oral clefts | Braces, FSIQ < 70, genetic syndromes | 96 |
| Bodoni et al. (2021) | Brazil | No | Children with non-syndromic oral clefts | Sensory or motor problems, psychiatric disorders, claustrophobia, contraindications to MRI | 24 |
| Li et al. (2020) | China | No | N/A | Brain structural abnormalities, neurological or psychiatric disorders, and MRI contraindications | 69 |

*N, population size; CLP, Cleft lip and palate; CP, Cleft palate; CL, Cleft lip.*

participants; $I^2$: 90%) and orbitofrontal cortex (MD: −0.99 $cm^3$; 95% CI: −2.69 to 0.71; $n$ = 2; 165 participants; $I^2$: 0%) (see **Supplementary Figures 6**, **7**).

*Parietal Lobe Volume.* There were no differences in the size of the parietal lobe between the cleft group and controls (MD: 4.91 $cm^3$; 95% CI: −4.29 to 14.10; $n$ = 2; 120 participants; $I^2$: 0%) (see **Supplementary Figure 8**).

*Temporal Lobe Volume.* Smaller temporal lobes were found for the cleft group compared to controls (MD: −10.53 $cm^3$; 95% CI: −18.23 to −2.82; $n$ = 2; 120 participants; $I^2$: 0%) (**Figure 6**). No differences were found on any side of the Superior temporal plane (STP) (left side MD: −0.37 cm3; −1.78 to 1.04; $n$ = 2; 143 participants; $I^2$: 66%. Right side MD: 0.20 cm3; 95% CI: −0.21 to 0.60; $n$ = 2; 143 participants; $I^2$: 0%) (**Supplementary Figures 9**, **10**).

**TABLE 1B |** Demographic data of included studies.

| References | Demographic measures of clefts | | | | Demographic measures of controls | | |
|---|---|---|---|---|---|---|---|
| | Age: mean (SD) | Gender (%) | Ethnicity (%) | Cleft subtype (N) | Age: mean (SD) | Gender (%) | Ethnicity (%) |
| Nopoulos et al. (2000) | 33.7 (7.3) | Male (100%) | Caucasian (100%) | CL (1), CPO (5, one is syndromic), CLP (8, one is syndromic) | 33.1 (7.7) | Male (100%) | Caucasian (100%) |
| Nopoulos et al. (2001) | 30.3 (N/A) | Male (100%) | Caucasian (100%) | CPO (15), CLP (34, three are syndromic) | 27.3 (N/A) | Male (52%), female (48%) | N/A |
| Nopoulos et al. (2002) | 30.1 (7.04) | Male (100%) | Caucasian (100%) | CPO (14), CLP (32, three are syndromic) | 28.8 (7.60) | Male (100%) | Caucasian (100%) |
| Nopoulos et al. (2005) (Nopoulos, 2002A) | 30.1 (7.04) | Male (100%) | Caucasian (100%) | CPO (14), CLP (32, three are syndromic | 28.8 (7.60) | Male (100%) | Caucasian (100%) |
| Shriver et al. (2006) (Nopoulos, 2002B) | 30.1 (7.04) | Male (100%) | Caucasian (100%) | CPO (14), CLP (32, three are syndromic) | 28,8 (7.60) | Male (100%) | Caucasian (100%) |
| Nopoulos et al. (2007c) | 12.1 (3.26) | Male (67.57%), female (33.33%) | White (90.5%), Asian American (8, 1%), Hispanic (1.4%) | CL (18), CPO (23), CLP (33) | 12.3 (3.08) | Male (67.57%), female (33, 33%) | White (87.8%), Asian American (5.4%), Hispanic (6.8) |
| Boes et al. (2007) (Nopoulos, 2007A) | 9.98 (1.64) | Male (100%) | Provided for both study groups: African (1.37%), Asian (1.37%), Asian American (4.11%), Caucasian (89.04%), Hispanic (1,37%), and mixed (2.74%). | CL (8), CPO (7), CLP (15) | 10.68 (1.45) | All male | See oral cleft group |
| Weinberg et al. (2009) | 30.1 (7.1) | Male (100%) | Caucasian (100%) | CPO (14), CLP (31) | 28.8 (7.5) | All male | Caucasian (100%) |
| van der Plas et al. (2010) (Nopoulos, 2007E) | Separated by cleft side: Right, 13 (2.68); left cleft, 11.7 (2.80) | Male (100%) | N/A | CL (9), CLP (24) | 12,2 (3.01) | All males | N/A |
| Nopoulos et al. (2010) (Nopoulos, 2007B) | 11.9 (3.3) | Male (100%) | Caucasian (95%; detailed info N/A) | CL (11), CPO (13), CLP (26) | 12.1 (2.7) | All males | See oral cleft group |
| Conrad et al. (2010) (Nopoulos, 2007C) | 13.27 (3.28) | Male, (59%) female (41%) | White (70%) Asian American (9%), Hispanic (5%), multiracial (7%) unknown (9%) | CL (7), CPO (11), CLP (25) | 13.28 (3.27) | Males (59%), females, (41%) | White: 37 (86%), multiracial: 1 (2%), unknown: 5 (12%) |
| DeVolder et al. (2013) (Nopoulos, 2007D) | Male: 13.44 (4.61), female: 14.11 (3.80) | Male: (61.68%). female: (38.31%) | N/A | CL (22), CP (31), CLP (52) | Male: 13.04 (3.92), female: 13.65 (3.82) | Males (50.39%), females: 63 (49.60%) | N/A |
| Yang et al. (2012) | 15.6 months (5.7 months) | Male: 24 (88.9%), female: 3 (11.1%) | Han Chinese (100%) | CL (2), CP (6), CLP (19) | 15.6 months (5.7 months) | Same as oral cleft group | Han Chinese (100%) |
| Weinberg et al. (2013) | 32.3 (7.4) | All male | N/A | N/A | 29.1 (7.9) | All male | N/A |
| Adamson et al. (2014) | 10.40 (2.57) | Males: 11 (42.31%) Females: 15 (57.69%) | N/A | N/A | 10, 52 (1.72) | Male (61, 54%), female (38.46%) | N/A |

*(Continued)*

**TABLE 1B |** (Continued)

| References | Demographic measures of clefts | | | | Demographic measures of controls | | |
|---|---|---|---|---|---|---|---|
| | Age: mean (SD) | Gender (%) | Ethnicity (%) | Cleft subtype (N) | Age: mean (SD) | Gender (%) | Ethnicity (%) |
| Chollet et al. (2014) (Nopoulos, 2007F) | CP: 11.7 (± 3.2), CLP: 12.7 (± 3.1) | Male (66, 67%), female (33, 33%) | Caucasian (82%), Asian American (8%), African American (1%), Hispanic/Latino (2%), Native Hawaiian/Pacific Islander (1%), biracial (4%), N/A (1%) | CP (22), CLP (35) | 12.5 (3.0) | Male (69.23%) female (30.77%) | See oral cleft group |
| Bodoni et al. (2021) | 13 (1) | Male (58, 33%), female (41, 67%) | N/A | CLP (12) | 13 (2) | Male (58.33%), female (41.67%) | N/A |
| Li et al. (2020) | Group B before therapy: 24 (4.92)*, group A after therapy 22.8 (5.4)* | Male: 26 (57.78%) female:19 (42.22%) | N/A | N/A | 22 (1.58)* | Male: 15 (62.50%), female: 9 (37.50%) | N/A |

*N, population size; CLP, Cleft lip and palate; CP, Cleft palate; CL, Cleft lip.*
**Data were calculated from median (IQR) values with statistical tool developed by Wan et al. (2014) and Luo et al. (2018).*

**TABLE 2 |** Risk of bias (RoB) assessment using the Newcastle-Ottawa Scale.

| Studies | Selection | | | | Comparability | Outcome | | | Total quality score |
|---|---|---|---|---|---|---|---|---|---|
| Author, year | Is the case definition adequate? | Representativeness of the cases | Selection of controls | Definition of controls | Comparability of cases and controls on the basis of design or analysis | Ascertainment of outcome | Same method of ascertainment for cases and controls | Non-response rate | 9 = Low RoB; 7–8 = Medium RoB; < 6 = High RoB |
| Nopoulos et al. (2000) | * | * | * | * | ** | * | * | * | **6** |
| Nopoulos et al. (2001) | * | * | * | * | ** | * | * | * | **5** |
| Nopoulos et al. (2002) | * | * | * | * | ** | * | * | * | **7** |
| Nopoulos et al. (2007c) | * | * | * | * | ** | * | * | * | **8** |
| Weinberg et al. (2009) | * | * | * | * | ** | * | * | * | **5** |
| Yang et al. (2012) | * | * | * | * | ** | * | * | * | **7** |
| Weinberg et al. (2013) | * | * | * | * | ** | * | * | * | **6** |
| Adamson et al. (2014) | * | * | * | * | ** | * | * | * | **8** |
| Bodoni et al. (2021) | * | * | * | * | ** | * | * | * | **7** |
| Li et al. (2020) | * | * | * | * | ** | * | * | * | **4** |

*Total quality score of 9 indicates low RoB, 7–8 medium RoB and ≤ 6 high RoB (Wells et al., 2000; Muka et al., 2020). The asterisks represent the scores under each dimension of the Newcastle-Ottawa Scale.*

*Occipital Lobe Volume.* The cleft group had significantly smaller occipital lobes compared to controls (MD: −7.39 $cm^3$; 95% CI: −12.80 to −1.99; $n = 2$; 120 participants; $I^2$: 0%) (**Figure 7**).

**Tables 3**, **4** summarize studies that were not included in the meta-analyses due to the variability in either methods or outcome.

## Secondary Outcome

### *Studies Investigating Mental and Social Functioning*

Heterogeneity of methods and outcomes prevented statistical pooling for meta-analyses for most secondary outcomes, with the exception of IQ scores. These secondary outcomes are illustrated in **Table 5**.

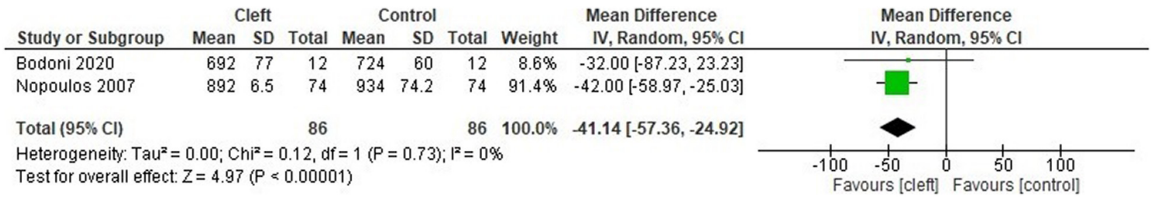


**FIGURE 2 |** Forest plot for total brain gray matter volume ($cm^3$).

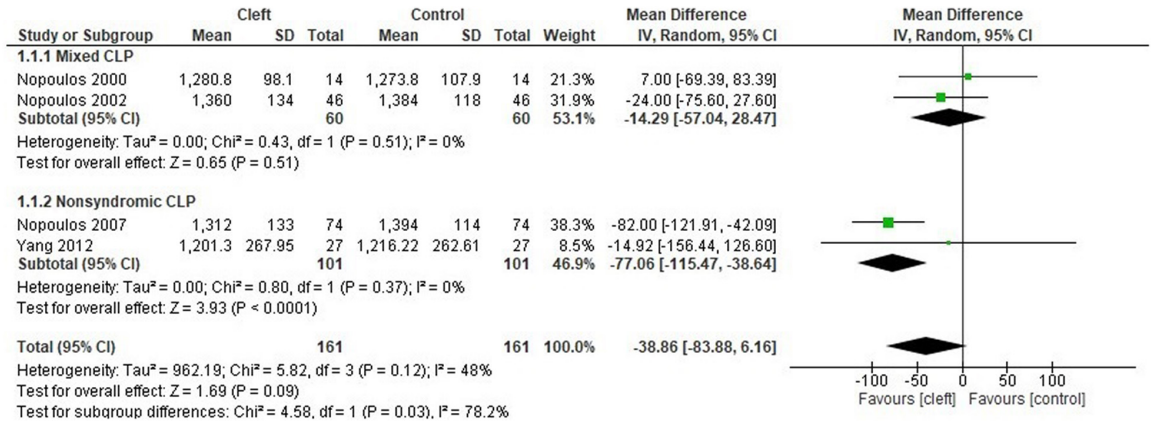


**FIGURE 3 |** Forest plot for total brain volume ($cm^3$) with subgroup analysis (non-syndromic vs. mixed).

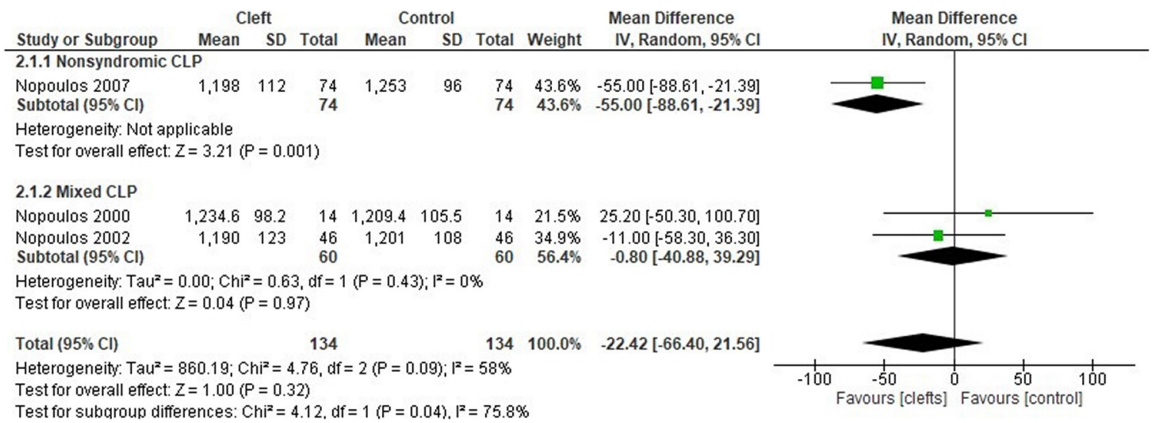


**FIGURE 4 |** Forest plot for total volume of the cerebrum ($cm^3$) with subgroup analysis (non-syndromic vs. mixed).

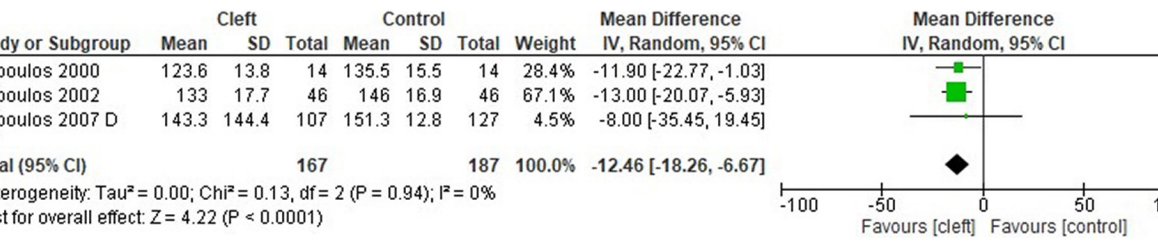


**FIGURE 5 |** Forest plot for total volume of the cerebellum ($cm^3$).

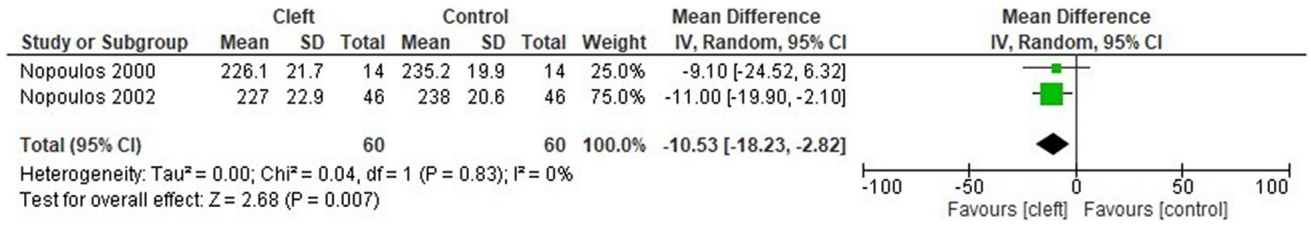


**FIGURE 6 |** Forest plot for temporal lobe volume ($cm^3$).

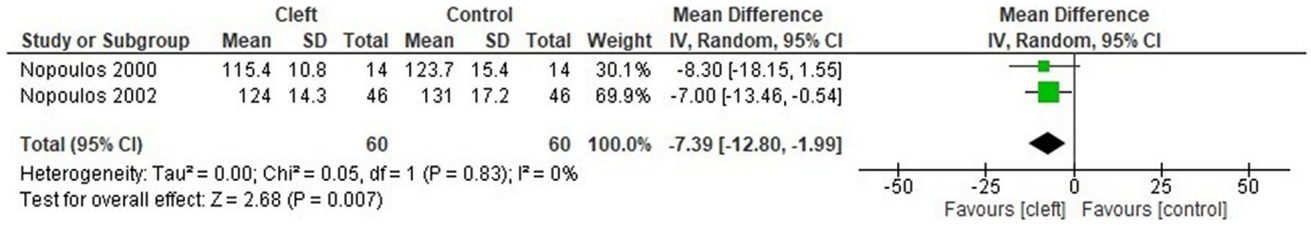


**FIGURE 7 |** Forest plot for occipital lobe volume ($cm^3$).

**TABLE 3 |** Regional measurements.

| Study | Outcome | Results (mean, SD) |
|---|---|---|
| Nopoulos et al. (2000) | Total lobar volumes: frontal, parietal, temporal and occipital | Significantly larger frontal lobes for clefts (440.4, 39.1) than controls (421.4, 46.0; $P = 0.02$). Smaller temporal and occipital lobes for clefts (226.1, 21.7) vs. controls (235.2, 19.9; $P = 0.02$); clefts (115.4, 10.8) vs. control (123.7,15.4; $P = 0.009$), respectfully. No significant differences between parietal lobe volumes. |
| Nopoulos et al. (2002) and Nopoulos (2002A,B) | Total lobar volumes, gray and white matter volumes provided separately: frontal (and VFC), parietal, temporal (and STP) and occipital | Significantly smaller volumes observed in clefts for all the following: total frontal lobe (463, 55.9) vs. controls (460, 49.7; $P = 0.029$); frontal gray matter (275, 32.3) vs. controls (270, 30.0; $P = 0.028$); parietal lobe (264, 28.0) compared to controls (260, 26.7; $P = 0.001$); parietal gray matter (143, 15.6) vs. controls (139, 15.3; $P = 0.006$); smaller temporal lobe (227, 22.9) vs. controls (238, 20.6; $P \leq 0.0001$); temporal gray matter (153, 14.4) vs. controls (159, 12.9), $P = 0.002$; temporal white matter (74,0, 10.3) vs. controls (78,9, 10.8; $P = 0.005$); smaller occipital lobe (124, 14.3) vs. controls (131, 17.2; $P = 0.007$); and occipital white matter (Kummer et al., 2007; Mueller et al., 2007; Luo et al., 2018) vs. controls (61.6, 7.39; $P \leq 0.0001$). The volume of SG (of the VFC) was smaller in clefts (5.876, 1.184) than controls (6.733, 1.533; $P = 0.02$). Total volume of STP greater in clefts (11.96, 1.807) vs. controls (11.61, 1.776; $P = 0.034$), but no significant differences when two sides were compared separately. |
| Nopoulos et al. (2007c) and Nopoulos (2007A,E) | Lobar gray and white matter volumes separately: frontal (and VFC), parietal, temporal and occipital | *Only means were provided:* Frontal white matter was significantly lower in boys with right clefts (156.0) compared with boys with left clefts (166.3; $P = 0.01$), and healthy boys (164.5; $P = 0.01$). Same was observed occipital white matter in right cleft (35.1), left cleft (39.5) and controls (38.6; $P = 0.004$). The VFC, parietal, temporal lobes, and gray matter of frontal and occipital lobe did not differ between the two groups. |
| Yang et al. (2012) | STP, thalamus | Total volume of the STP on the left side significantly smaller for cleft subjects (7.42, 2.91) vs. controls (8.77, 3.38; $P = 0.0006$). Thalamus on the left side significantly smaller for cleft (4.98, 0.66) than controls (5.59, 1.06; $P < 0.001$). |
| Li et al. (2020) | Left postcentral gyrus, right inferior frontal gyrus | *Only narrative data available:* before articulation therapy group had an increased gray matter volume in left postcentral gyrus compared to controls ($P < 0.001$) and after therapy group ($P < 0.05$). Increased gray matter volume in right inferior frontal gyrus in the before therapy group compared to controls ($P < 0.05$). |
| Weinberg et al. (2013) | Eight corpus callosum landmarks assessed. | Mean corpus callosum shape of cleft subjects was significantly different from controls (Procrustes distance = 0.049; $P = 0.029$). There was a decrease in overall antero-posterior length of the corpus callosum with an increase in convexity of the body in cleft subjects compared to controls. |
| Nopoulos et al. (2001) | Enlargement of CSP analyzed by a rating scale designed for the study. | One individual out of the 75 controls had an enlarged CSP. Four out of the 49 cleft subjects had enlarged CSP. The incidence of enlarged CSP was significantly different between the two groups ($P = 0.039$). |

*VFC, Ventrofrontal cortex; STP, Superior temporal plane; CSP, Cavum septum pellucidum.*

**TABLE 4 |** 3D morphometric analysis of brain shape.

| Study | Outcome | Results |
|---|---|---|
| Nopoulos (2007F) | 3D brain shape analyzed with EDMA (interlandmark distances) | *Narrative data:* Major differences in cleft subjects included posterior expansion of the occipital lobe, reorientation of the cerebellum, heightened callosal midbody, and posterior displacement of the caudate nucleus and thalamus. The magnitude of expansion of the occipital lobe was greatest in children with CP. |
| Weinberg et al. (2009) | 3D brain shape analyzed with EDMA (interlandmark distances) and CVA (shape coordinates) | *Narrative data:* Major brain shape changes associated with clefting were observed with CVA and EDMA: this included selective enlargement of the anterior cerebrum coupled with a relative reduction in posterior and/or inferior cerebral portions, changes in the medio-lateral position of the cerebral poles, posterior displacement of the corpus callosum, and reorientation of the cerebellum. |

*EDMA, Euclidean distance matrix analysis; CVA, canonical variates analysis; CP, Cleft palate.*

**TABLE 5 |** Psychometric tools used to measure psychosocial functioning.

| Study | Outcome | Results | Validated |
|---|---|---|---|
| Nopoulos (2002A) | Social function measured with the Psychiatric Symptoms You Currently have-Baseline tool (PSYCH-base), and the relationship to brain volumes. | Social function was measured only for cleft subjects (recreational interests and activities; relationship with friends and peers; relationship with family members). Twenty-six percent of oral cleft subjects rated relationship with friends as poor. Thirteen percent of oral cleft subjects rated their relationship with family members as poor. Six percent of subjects rated recreational participation as poor. No significant differences of social function between CLP and CP subtypes. Significant correlation was observed between smaller surface of the OF and social dysfunction in cleft subjects ($P = 0.003$). | Yes |
| Nopoulos (2007B) | Pediatric Behavior Scale derived hyperactivity/impulsivity/inattention (HII) scores and its relationship to the volume of the vmPFC. | The cleft group showed significantly elevated scores in HII compared to controls ($P = 0.021$). Boys of the control group with the lowest right vmPFC volume scored the highest on the HII ($P = 0.041$). In the cleft group, boys with the highest volume of the right vmPFC achieved the highest HII scores ($P = 0.005$). | Yes |
| Noppulos (2002B) | Boston Naming Test, Rey Auditory-Verbal Learning Test, Rey–Osterreith Complex Figure Test, Stroop Test. Relationship of test performance and brain volumes. | Lower test performance on the Boston Naming Task correlated with greater STP volume for oral cleft subjects, but not significant ($P = 0.074$). No correlations observed in the other tests. | Yes |
| Bodoni et al. (2021) | RAVEN, Rey Complex Figure, Wisconsin. Relationship between test performance and brain volumes. | Cleft group performed significantly worse on the Raven test compared to controls, and had non-verbal intelligence scores below average ($P = 0.006$). Raven test correlated positively with decreased cortical thickness of right pars orbitalis in oral clefts. Rey Complex Figure Test—Memory scores in oral cleft subjects showed significant positive correlation to decreased cortical thickness in: left supramarginal gyrus, right supramarginal gyrus, left superior parietal lobule, left inferior parietal lobule, right inferior parietal lobule, right middle temporal gyrus, right pars orbitalis, right superior temporal gyrus, and right rostral middle frontal gyrus ($P \leq 0.05$). | Yes |
| Nopoulos (2007A) | Self-Description Questionnaire: SDQ-1 and relationship to brain volumes. | Boys with oral clefts had significantly poorer peer relations in the self-reported SDQ-1 score ($P = 0.002$). Significant correlation between small SG measures and self-reported low peer relation scores was observed ($P \leq 0.05$). | Yes |
| Nopoulos (2007C) | Speech measured by hypernasality, articulation proficiency, and nasalance. Relationship between performance and brain volumes. | Boys had greater impaired speech than girls in all three domains. These differences reached significance only for the hypernasality rating ($P = 0.003$). Speech and structure correlations for boys with oral clefts were significant for cerebellar volume and articulation ($P = 0.015$), and those with worse articulations had smaller cerebellar volumes. | N/A |

*CLP, Cleft lip and palate; CP, Cleft palate; OFC, orbitofrontal cortex; vmPFC, Ventro-medial prefrontal cortex.*

*Full-Scale IQ.* Significantly lower FSIQ scores were as observed in individuals with oral clefts compared to controls (MD: −12.58; FSIQ; 95% CI: −21.98 to -3.17; $n = 2$; 234 participants; $I^2 = 84\%$) (**Figure 8**). All of the studies used the Wechsler Intelligence Scale of different editions.

## Subgroup Analysis

Four meta-analyses demonstrated moderate to considerable levels of heterogeneity. Subgroup analysis was feasible for only two of the four meta-analyses (**Figures 3**, **4**). Subgroup analyses were performed for age, sex, ethnicity, non-syndromic, and mixed (syndromic and non-syndromic) oral clefts.

### Total Brain Volume

The non-syndromic subgroup had significantly smaller total brain volume compared to controls. However, this significant difference was not seen in the mixed subgroup (syndromic and non-syndromic cases) (MD: −77.06 $cm^3$; 95% CI: −115.47 to −38.64; $n = 2$; 202 participants; $I^2 = 0\%$; **Figure 3**). The same phenomenon was observed for age (children vs. adults),

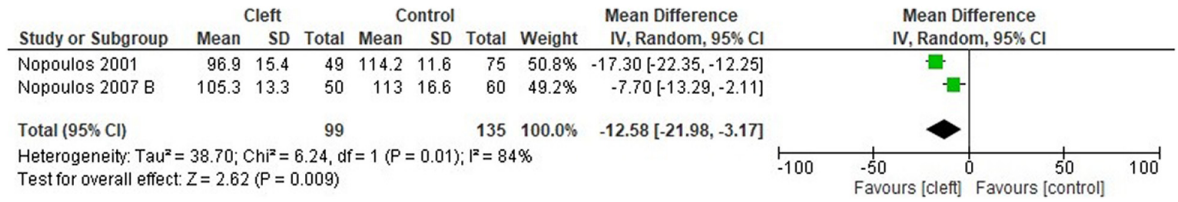


**FIGURE 8 |** Forest plot for full-scale IQ scores.

sex (male only vs. mixed) and ethnicity (Caucasian vs. mixed) (**Supplementary Figures 11A–C**). These factors may be possible sources of the heterogeneity seen in the main analysis.

### Total Cerebral Volume

A decrease in heterogeneity was found in the subgroup analysis of mixed oral clefts (MD: −0.80 $cm^3$; 95%CI: −40.88 to 39.29; $n = 2$; 120 participants; $I^2 = 0\%$; **Figure 4**). The same phenomenon was observed for age (children vs. adults) and sex (male vs. male and female) (**Supplementary Figures 12A,B**).

## Reporting Bias

Tests for funnel plot asymmetry could not be used to detect reporting bias due to the few studies included in the meta-analysis ($n \leq 10$) (Higgins et al., 2019).

# DISCUSSION

The aim of this review was to analyze the empirical evidence of the association between non-syndromic oral clefts and the brain. Overall, oral cleft subjects had smaller cerebral gray matter, cerebellum, temporal lobes, and occipital lobes compared to controls. Individuals with oral clefts had lower FSIQ scores compared to matched controls. Most of the studies controlled for confounders such as age and/or sex to control for brain growth and development; however, only half of the studies for subjects and/or parent's sociodemographic level (Nopoulos et al., 2000, 2002, 2007c; Li et al., 2020; Bodoni et al., 2021). The risk of bias for the included studies was moderate to high. Most included studies did not analyze cleft subtypes separately which was likely due to the small sample size across subgroups.

Some effects of oral clefts may have remained hidden as a consequence to the small number of studies for most outcomes. A few studies have included syndromic cases of oral cleft, notably Van der Woude syndrome. Van der Woude is a dominantly inherited syndrome caused by the deletion of a gene encoding the interferon regulatory factor-6 (IRF6) on chromosome 1q32 (Johns Hopkins University, 2022). The authors state that the oral cleft occurs in an isolated matter without any other significant developmental issues and allow these individuals to be a part of the non-syndromic group. However, there have been documented cases of cognitive deficits and brain structural abnormalities of Van der Woude syndrome (Nopoulos et al., 2007a; Rincic et al., 2016). Including individuals with Van der Woude syndrome may have an impact on the results of the non-syndromic cleft population.

The total gray matter volume was significantly smaller in the cleft group, an interesting outcome as the total brain and cerebral volume did not significantly differ between the two groups. We hypothesize the following to explain this observation: (1) Shifts in brain tissue distribution in individuals with non-syndromic oral clefts have been shown previously (Nopoulos et al., 2007c). This phenomenon was suggested to occur due to a "compensatory overgrowth" of either brain tissue component unaffecting total brain size (Nopoulos et al., 2002). The cerebellum was significantly smaller in the cleft group; however, the gray or white matter volumes of the cerebellum could not be analyzed separately due to the lack of data in studies. This may indicate the presence of a smaller cerebellar cortex in the oral cleft group (i.e., gray matter), a difference which may not affect the overall tissue size of the "compensated" brain. (2) Subgroup analysis revealed a significantly smaller brain and cerebrum in studies with exclusively non-syndromic oral cleft participants. These differences were not observed in studies with mixed syndromic participants (**Figures 3**, **4**). Total brain gray matter volume was analyzed in studies with non-syndromic individuals exclusively (**Figure 2**). Non-syndromic oral clefts may have smaller total brain and cerebrum, but the presence of syndromic individuals might have influenced this outcome.

There is supportive evidence regarding a primary unified maldevelopment of the brain during clefting; this might be an underlying etiology for the high risk of neuropsychiatric and neurodevelopmental issues seen in this patient population (Ansen-Wilson et al., 2018). Previous systematic reviews have shown an increased risk of neurodevelopmental and academic difficulties in individuals with non-syndromic oral clefts (Hunt et al., 2005; Al-Namankany and Alhubaishi, 2018; Gallagher and Collett, 2019). These studies, however, highlight the difficulty of summarizing the available evidence due to the lack of uniformity and consistency across studies. It has been proposed that syndromes and additional conditions related to the cleft should be analyzed in a separate group in order to observe if the additional condition is of any way a confounding variable affecting cognitive functioning (Feragen et al., 2014). Future studies should consider the assessment of brain structural data in reference to the subtype of oral clefts, the side affected, additional congenital malformations or comorbidities, anamnestic data on neurodevelopment, age and gender.

Our study has several important limitations. The majority of participants were Caucasian and originated from one register (University of Iowa Cleft Lip and Palate Registry). The clinic-based recruitment and the absence of blinding during the MRI

procedures may have introduced bias. Most studies did not report participation rate or investigate the differences between participants and dropouts. We could not analyze structural brain differences across the subtypes of oral cleft and gender due to the small sample sizes. It was not possible to isolate data of the syndromic cases from the overall data of respective studies. Furthermore, the impact of surgical interventions on the developing brain could not be analyzed due to lack of data regarding the timing of the surgery, age of the patient, type of cleft repair surgery and anesthesia exposure. Only one study included the cleft repair status of its participants (Yang et al., 2012). Demographic factors, such as age and/or sex of the participants were provided by most of the included studies; however, there was a lack of detailed information of parental socio-economic factors including education and financial backgrounds. Parental socio-economic factors are known to strongly relate to the child's neurodevelopment (Noble et al., 2015; Rakesh and Whittle, 2021) and may be a crucial factor in the developing brain of children with oral clefts. It is unclear how brain structural differences affect psychosocial functioning due to the variable assessment tools used in the included studies.

The meta-analyses combined data across studies in order to estimate the effect of oral clefts on brain structure. The main limitations of these meta-analyses are the incomplete reporting of study designs and the variable definition of the patient population across the studies. The interpretation and synthesis of the included studies may have been influenced by these factors. Applicability of our results may be affected due to the limited data for certain subgroups, such as cleft type and gender.

The current review has a number of strengths. To the best of our knowledge, this is the first study to have assessed the overall empirical evidence of brain imaging studies in oral clefts carried out for over two decades. We were able to highlight possible sources of heterogeneity including sex, ethnicity, age and syndromic cases of oral clefts.

There may be structural brain differences between individuals with non-syndromic oral clefts and controls based on the available evidence. Structural brain MRI studies may provide evidence on how the type and degree of clefting plays a role with later cognitive development and functioning. Improvement in study design, size, methodology, and participant selection may allow a more thorough analysis and decrease study heterogeneity. Future studies may greatly benefit the clinical field in establishing timely therapeutic interventions for the necessary cognitive domains as a part of the complex therapy applied to these patients.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

KS-B: review design, protocol drafting, search strategy, screening against eligibility criteria, data extraction, data analysis and interpretation, risk of bias assessment, and manuscript drafting. AS: data extraction, data analysis, risk of bias assessment, and manuscript drafting. EV: screening against eligibility criteria, data extraction, and data analysis. GC: search strategy, protocol drafting, data interpretation, and manuscript drafting. GA: review design, protocol drafting, screening against eligibility criteria, data extraction, data analysis, and interpretation. SL: review design, protocol drafting, search strategy, duplicate removals, data analysis and interpretation, risk of bias assessment, and manuscript drafting. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnana.2022.863900/full#supplementary-material

## REFERENCES


Adamson, C. L., Anderson, V. A., Nopoulos, P., Seal, M. L., and Da Costa, A. C. (2014). Regional brain morphometric characteristics of nonsyndromic cleft lip and palate. *Dev. Neurosci.* 36, 490–498. doi: 10.1159/000365389

Al-Namankany, A., and Alhubaishi, A. (2018). Effects of cleft lip and palate on children's psychological health: a systematic review. *J. Taibah. Univ. Med. Sci.* 13, 311–318. doi: 10.1016/j.jtumed.2018.04.007

Ansen-Wilson, L. J., Everson, J. L., Fink, D. M., Kietzman, H. W., Sullivan, R., and Lipinski, R. J. (2018). Common basis for orofacial clefting and cortical interneuronopathy. *Transl. Psychiatry* 8:8. doi: 10.1038/s41398-017-0057-7

Becker, D. B., Coalson, R. S., Sachanandani, N. S., Fair, D., Lugar, H. M., Kirchner, L. E., et al. (2008). Functional neuroanatomy of lexical processing in children with cleft lip and palate. *Plast. Reconstr. Surg.* 122, 1371–1382. doi: 10.1097/PRS.0b013e3181881f54

Bjørnland, T., Nørholt, S. E., Rasmusson, L., and Sándor, G. K. (2021). *Nordic Textbook of Oral and Maxillofacial Surgery Munksgaard*. Available online at: https://books.google.hu/books?id=aR1rzgEACAAJ (accessed January 26, 2022).

Boes, A. D., Murko, V., Wood, J. L., Langbehn, D. R., Canady, J., Richman, L., et al. (2007). Social function in boys with cleft lip and palate: relationship to ventral frontal cortex morphology. *Behav. Brain Res.* 181, 224–231. doi: 10.1016/j.bbr.2007.04.009

Bodoni, P. S. B., Leoni, R. F., do Vale, A. B., da Silva, P. H. R., Meira Junior, S. G., Richieri Costa, A., et al. (2021). Neuropsychological functioning and its relationship with brain anatomical measures of children and adolescents with non-syndromic cleft lip and palate. *Child Neuropsychol.* 27, 2–16. doi: 10.1080/09297049.2020.1776240

Broder, H. L., Richman, L. C., and Matheson, P. B. (1998). Learning disability, school achievement, and grade retention among children with cleft: a two-center study. *Cleft Palate Craniofac. J.* 35, 127–131. doi: 10.1597/1545-15691998035<0127:LDSAAG<2.3.CO;2

Čeponiene, R., Hukki, J., Cheour, M., Haapanen, M. L., Ranta, R., and Näätänen, R. (1999). Cortical auditory dysfunction in children with oral clefts: relation with cleft type. *Clin. Neurophysiol.* 110, 1921–1926.

Chollet, M. B., Nopoulos, P., Conrad, A., and DeLeon, V. (2010). Brain morphology of children with cleft lip and/or palate. *FASEB J.* 24, 1369–1370.

Chollet, M. B., DeLeon, V. B., Conrad, A. L., and Nopoulos, P. (2014). Morphometric analysis of brain shape in children with nonsyndromic cleft lip and/or palate. *J. Child Neurol.* 29, 1616–1625. doi: 10.1177/0883073813510603

Cochrane (2020). *Review Manager (RevMan) [Computer program]. Version 5.4*. London: The Cochrane Collaboration.

Conrad, A. L., Canady, J., Richman, L., and Nopoulos, P. (2008). Incidence of neurological soft signs in children with isolated cleft of the lip or palate. *Percept. Mot. Skills* 106, 197–206. doi: 10.2466/pms.106.1.197-206

Conrad, A. L., Dailey, S., Richman, L., Canady, J., Karnell, M. P., Axelson, E., et al. (2010). Cerebellum structure differences and relationship to speech in boys and girls with nonsyndromic cleft of the lip and/or palate. *Cleft Palate Craniofac. J.* 47, 469–475. doi: 10.1597/08-228

Conrad, A. L., Wermke, K., Eisenmann, M., Kuhlmann, E., Benavides, A., Koscik, T., et al. (2021). Preliminary evaluation of pre-speech and neurodevelopmental measures in 7–11-week-old infants with isolated oral clefts. *Pediatr. Res.* 89, 85–90. doi: 10.1038/s41390-020-0887-5

DeVolder, I., Conrad, A., Magnotta, V., and Nopoulos, P. (2015). Difficulties in timing perception related to abnormal brain structure in children and adolescents with nonsyndromic cleft lip and/or cleft palate. *Cleft Palate Craniofac. J.* 52:e110.

DeVolder, I., Conrad, A., Richman, L., Magnotta, V., and Nopoulos, P. C. (2014). White matter structure in individuals with isolated cleft lip and/or palate: a diffusion tensor imaging study. *Cleft Palate Craniofac. J.* 51.

DeVolder, I., Richman, L., Conrad, A. L., Magnotta, V., and Nopoulos, P. (2013). Abnormal cerebellar structure is dependent on phenotype of isolated cleft of the lip and/or palate. *Cerebellum* 12, 236–244. doi: 10.1007/s12311-012-0418-y

Diaz-Stransky, A., and Tierney, E. (2012). Cognitive and behavioral aspects of Smith-Lemli-Opitz syndrome. *Am. J. Med. Genet. Part C Semin. Med. Genet.* 160C, 295–300. doi: 10.1002/ajmg.c.31342

Feragen, K. B., Stock, N. M., and Rumsey, N. (2014). Toward a reconsideration of inclusion and exclusion criteria in cleft lip and palate: implications for psychological research. *Cleft Palate Craniofac. J.* 51, 569–578. doi: 10.1597/12-326

Gallagher, E. R., and Collett, B. R. (2019). Neurodevelopmental and academic outcomes in children with orofacial clefts: a systematic review. *Pediatrics* 144:e20184027. doi: 10.1542/peds.2018-4027

Hardin-Jones, M., and Chapman, K. (2011). Cognitive and language issues associated with cleft lip and palate. *Semin. Speech Lang.* 32, 127–140. doi: 10.1055/s-0031-1277715

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., et al. (2019). "Cochrane handbook for systematic reviews of interventions," in *Cochrane Handbook for Systematic Reviews of Interventions*, eds J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. J. Page, et al. (Hoboken, NJ: Wiley).

Hunt, O., Burden, D., Hepper, P., and Johnston, C. (2005). The psychosocial effects of cleft lip and palate: a systematic review. *Eur. J. Orthod.* 27, 274–285. doi: 10.1093/ejo/cji004

Johns Hopkins University (2022). *Online Mendelian Inheritance in Man, OMIM*. Baltimore, MD: Johns Hopkins University.

Kummer, A. W., Lee, L., Stutz, L. S., Maroney, A., and Brandt, J. W. (2007). The prevalence of apraxia characteristics in patients with velocardiofacial syndrome as compared with other cleft populations. *Cleft Palate Craniofac. J.* 44, 175–181. doi: 10.1597/05-170.1

Li, Z., Zhang, W., Li, C., Wang, M., Wang, S., Chen, R., et al. (2020). Articulation rehabilitation induces cortical plasticity in adults with non-syndromic cleft lip and palate. *Aging (Albany NY)* 12, 13147–13159. doi: 10.18632/aging.103402

Lithovius, R. H., Ylikontiola, L. P., Harila, V., and Sándor, G. K. (2014). A descriptive epidemiology study of cleft lip and palate in Northern Finland. *Acta Odontol. Scand.* 72, 372–375. doi: 10.3109/00016357.2013.840737

Luo, D., Wan, X., Liu, J., and Tong, T. (2018). Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat. Methods Med. Res.* 27, 1785–1805. doi: 10.1177/0962280216669183

McDonald-McGinn, D. M., Sullivan, K. E., Marino, B., Philip, N., Swillen, A., Vorstman, J. A. S., et al. (2015). 22q11.2 deletion syndrome. *Nat. Rev. Dis. Prim.* 1:15071.

Mossey, P. A., and Modell, B. (2012). "Epidemiology of oral clefts 2012: an international perspective," in *Cleft Lip and Palate: Epidemiology, Aetiology and Treatment*, ed. M. T. Cobourne (Basel: S. Karger AG), 1–18. doi: 10.1159/000337464

Mueller, A. A., Sader, R., Honigmann, K., Zeilhofer, H. F., and Schwenzer-Zimmerer, K. (2007). Central nervous malformations in presence of clefts reflect developmental interplay. *Int. J. Oral Maxillofac. Surg.* 36, 289–295. doi: 10.1016/j.ijom.2006.10.018

Muka, T., Glisic, M., Milic, J., Verhoog, S., Bohlius, J., Bramer, W., et al. (2020). A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research. *Eur. J. Epidemiol.* 35, 49–60. doi: 10.1007/s10654-019-00576-5

Noble, K. G., Houston, S. M., Brito, N. H., Bartsch, H., Kan, E., Kuperman, J. M., et al. (2015). Family income, parental education and brain structure in children and adolescents. *Nat. Neurosci.* 18, 773–778. doi: 10.1038/nn.3983

Nopoulos, P., Berg, S., Canady, J., Richman, L., Van Demark, D., and Andreasen, N. C. (2000). Abnormal brain morphology in patients with isolated cleft lip, cleft palate, or both: a preliminary analysis. *Cleft Palate Craniofac. J.* 37, 441–446. doi: 10.1597/1545-15692000037<0441:ABMIPW<2.0.CO;2

Nopoulos, P., Berg, S., Canady, J., Richman, L., Van Demark, D., and Andreasen, N. C. (2002). Structural brain abnormalities in adult males with clefts of the lip and/or palate. *Genet. Med.* 4, 1–9. doi: 10.1097/00125817-200201000-00001

Nopoulos, P., Boes, A. D., Jabines, A., Conrad, A. L., Canady, J., Richman, L., et al. (2010). Hyperactivity, impulsivity, and inattention in boys with cleft lip and palate: relationship to ventromedial prefrontal cortex morphology. *J. Neurodev. Disord.* 2, 235–242. doi: 10.1007/s11689-010-9060-5

Nopoulos, P., Choe, I., Berg, S., Van Demark, D., Canady, J., and Richman, L. (2005). Ventral frontal cortex morphology in adult males with isolated orofacial clefts: relationship to abnormalities in social function. *Cleft Palate Craniofac. J.* 42, 138–144. doi: 10.1597/03-112.1

Nopoulos, P., Richman, L., Andreasen, N., Murray, J., and Schutte, B. (2007a). Abnormal brain structure in adults with Van der Woude syndrome. *Clin. Genet.* 71, 511–517. doi: 10.1111/j.1399-0004.2007.00799.x

Nopoulos, P., Richman, L., Andreasen, N., Murray, J. C., and Schutte, B. (2007b). Cognitive dysfunction in adults with Van der Woude syndrome. *Genet. Med.* 9, 213–218. doi: 10.1097/GIM.0b013e3180335abd

Nopoulos, P., Langbehn, D. R., Canady, J., Magnotta, V., and Richman, L. (2007c). Abnormal brain structure in children with isolated clefts of the lip or palate. *Arch. Pediatr. Adolesc. Med.* 161, 753. doi: 10.1001/archpedi.161.8.753

Nopoulos, P., Berg, S., VanDemark, D., Richman, L., Canady, J., and Andreasen, N. C. (2001). Increased incidence of a midline brain anomaly in patients with nonsyndromic clefts of the lip and/or palate. *J. Neuroimaging* 11, 418–424. doi: 10.1111/j.1552-6569.2001.tb00072.x

Ornoy, A. (2020). Craniofacial malformations and their association with brain development: the importance of a multidisciplinary approach for treatment. *Odontology* 108, 1–15. doi: 10.1007/s10266-019-00433-7

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 372:n71. doi: 10.1136/bmj.n71

Pedersen, D. A., Wehby, G. L., Murray, J. C., and Christensen, K. (2016). Psychiatric diagnoses in individuals with non-syndromic oral clefts: a danish population-based cohort study Maher B, editor. *PLoS One* 11:e0156261. doi: 10.1371/journal.pone.0156261

Rakesh, D., and Whittle, S. (2021). Socioeconomic status and the developing brain – a systematic review of neuroimaging findings in youth. *Neurosci. Biobehav. Rev.* 130, 379–407. doi: 10.1016/j.neubiorev.2021.08.027

Richman, L. C., and Ryan, S. M. (2003). Do the reading disabilities of children with cleft fit into current models of developmental dyslexia? *Cleft Palate Craniofac. J.* 40, 154–157. doi: 10.1597/1545-1569_2003_040_0154_dtrdoc_2.0.co_2

Rincic, M., Rados, M., Krsnik, Z., Gotovac, K., Borovecki, F., Liehr, T., et al. (2016). Complex intrachromosomal rearrangement in 1q leading to 1q32.2 microdeletion: a potential role of SRGAP2 in the gyrification of cerebral cortex. *Mol. Cytogenet.* 9:19. doi: 10.1186/s13039-016-0221-4

Sándor-Bajusz, K., Maros, T., Olasz, L., Sándor, G., Hadzsiev, K., and Vástyán, A. (2021). The influence of genetic syndromes on the algorithm of cleft lip and palate repair – a retrospective study. *Ann. Maxillofac. Surg.* 11, 270–273. doi: 10.4103/ams.ams_77_21

Scott, N. M., Weinberg, S. M., Neiswanger, K., Brandon, C. A., and Marazita, M. L. (2005). Hair whorls and handedness: informative phenotypic markers

in nonsyndromic cleft lip with or without cleft palate (NS CL/P) cases and their unaffected relatives. *Am. J. Med. Genet.* 136, 158–161. doi: 10.1002/ajmg.a.30806

Shen, E. Y., and Huang, F. Y. (1996). Cleft lip and palate associated with malformation of the central nervous system: a prospective neurosonographic study. *Zhonghua Min. Guo Xiao Er Ke Yi Xue Hui Za Zhi* 37, 39–44.

Shriver, A. S., Canady, J., Richman, L., Andreasen, N. C., and Nopoulos, P. (2006). Structure and function of the superior temporal plane in adult males with cleft lip and palate: pathologic enlargement with no relationship to childhood hearing deficits. *J. Child Psychol. Psychiatry* 47, 994–1002. doi: 10.1111/j.1469-7610.2006.01679.x

Tillman, K. K., Hakelius, M., Höijer, J., Ramklint, M., Ekselius, L., Nowinski, D., et al. (2018). Increased risk for neurodevelopmental disorders in children with orofacial clefts. *J. Am. Acad. Child Adolesc. Psychiatry* 57, 876–883. doi: 10.1016/j.jaac.2018.06.024

Tollefson, T. T., and Sykes, J. M. (2010). Differences in brain structure related to laterality of cleft lip. *Arch. Fac. Plast. Surg.* 12, 431–432. doi: 10.1001/archfacial.2010.83

van der Plas, E., Conrad, A., Canady, J., Richman, L., and Nopoulos, P. (2010). Effects of unilateral clefts on brain structure. *Arch. Pediatr. Adolesc. Med.* 164, 763–768. doi: 10.1001/archpediatrics.2010.123

Veritas Health Innovation (2017). *Covidence Systematic Review Sofware*. Melbourne, VIC: Covidence.

Wan, X., Wang, W., Liu, J., and Tong, T. (2014). Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* . 14:135. doi: 10.1186/1471-2288-14-135

Watkins, S. E., Meyer, R. E., Aylsworth, A. S., Marcus, J. R., Allori, A. C., Pimenta, L., et al. (2018). Academic achievement among children with nonsyndromic orofacial clefts: a population-based study. *Cleft Palate Craniofac. J.* 55, 12–20. doi: 10.1177/1055665617718823

Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., et al. (2000). *The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. Ottawa, ON: Ottawa Hospital Research Institute.

Weinberg, S. M., Andreasen, N. C., and Nopoulos, P. (2009). Three-dimensional morphometric analysis of brain shape in nonsyndromic orofacial clefting. *J. Anat.* 214, 926–936. doi: 10.1111/j.1469-7580.2009.01084.x

Weinberg, S. M., Parsons, T. E., Fogel, M. R., Walter, C. P., Conrad, A. L., and Nopoulos, P. (2013). Corpus callosum shape is altered in individuals with nonsyndromic cleft lip and palate. *Am. J. Med. Genet. A* 161A, 1002–1007. doi: 10.1002/ajmg.a.35835

Yang, F. F., McPherson, B., Shu, H., Xie, N., and Xiang, K. (2012). Structural abnormalities of the central auditory pathway in infants with nonsyndromic cleft lip and/or palate. *Cleft Palate Craniofac. J.* 49, 137–145. doi: 10.1597/11-014

Zheng, W., Li, B., Zou, Y., and Lou, F. (2019). The prenatal diagnosis and classification of cleft palate: the role and value of magnetic resonance imaging. *Eur. Radiol.* 29, 5600–5606. doi: 10.1007/s00330-019-06089-9

Zinkstok, J. R., Boot, E., Bassett, A. S., Hiroi, N., Butcher, N. J., Vingerhoets, C., et al. (2019). Neurobiological perspective of 22q11.2 deletion syndrome. *Lancet Psychiatry* 6, 951–960. doi: 10.1016/S2215-0366(19)30076-8

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.