DISSERTATIONES
MEDICINAE
UNIVERSITATIS
TARTUENSIS
350

LAGLE LEHES

The first study of voice and resonance related treatment outcomes of Estonian cleft palate children

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
350

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS
350

LAGLE LEHES

The first study of voice and resonance related treatment outcomes of Estonian cleft palate children

UNIVERSITY OF TARTU
Press
1632

Institute of Dentistry, Faculty of Medicine, University of Tartu, Tartu, Estonia

The dissertation is accepted for the commencement of the degree of Doctor of Philosophy in Medicine on 7th of July 2023 by the Council of the Faculty of Medicine, University of Tartu, Estonia.

Supervisors: Associate Professor Triin Jagomägi, DDS, PhD,
Institute of Dentistry, Faculty of Medicine,
University of Tartu, Estonia

Associate Professor Marika Padrik, PhD,
Institute of Education, Department of Special Education,
Faculty of Social Sciences, University of Tartu, Estonia

Priit Kasenõmm, MD, PhD,
Ear Clinic, Tartu University Hospital

Reviewers: Professor Arūnas Vasiliauskas, DDS, PhD,
Clinic of Orthodontics, Lithuanian University of Health Sciences, Lithuania

Vitali Vassiljev, MD, PhD,
Radiology Departement, Diagnostic Division,
The North Estonia Medical Centre, Estonia

Professor Mare Saag, PhD,
Institute of Dentistry, Faculty of Medicine,
University of Tartu, Estonia

Opponent: Senior Lecturer Karin Brunnegård, PhD,
Department of Clinical Sciences, Umeå University, Sweden

Commencement: 19th of October 2023

Publication of this dissertation is granted by the University of Tartu

ISSN 1024-395X (print)
ISBN 978-9916-27-325-8 (print)

ISSN 2806-240X (pdf)
ISBN 978-9916-27-326-5 (pdf)

University of Tartu Press
www.tyk.ee

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications referred to in the text by Roman numerals I–III as follows:

I Lehes, L., Horn, R., Lippus, P., Padrik, M., Kasenõmm, P., Jagomägi, T. (2018). Normative nasalance scores for Estonian children. Clinical Linguistics & Phonetics, 32 (11), 1054–1066. https://doi.org/10.1080/02699206.2018.1495767

II Lehes, L., Sõber, L., Padrik, M., Kasenõmm, P., Numa, J., Jagomägi, T. (2020). The effect of velopharyngeal insufficiency on voice quality in Estonian Children with Cleft Palate. Clinical Linguistics & Phonetics. https://doi.org/10.1080/02699206.2020.1780323

III Lehes, L.; Aria, C.; Padrik, M.; Kasenõmm, P.; Jagomägi, T. (2023). Pilot Study: Correlation between nasalance scores and cephalometric parameters in Estonian cleft palate children. Stomatologija [Accepted]

Author's contribution:
Papers I–III: conceptions and study designs; involvement with clinical examination; main lead in data acquisition and analysis, interpretation of the data, the writing of the articles.

LIST OF ABBREVIATIONS

BCLP	bilateral cleft lip and palate
CI	Confidence Intervals
CL	cleft lip
CP±L	cleft palate with or without cleft lip
CLP	cleft lip and palate
MDVP	Multidimensional Voice Program
VLS	videolaryngostroboscopy
VNE	videonasoendoscopy
OC	oral cleft
PAS	pharyngeal airway space
PVHI	Pediatric Voice Handicap Index
SMCP	submucous cleft palate
SPSS	Statistical Package for the Social Sciences
UCLP	unilateral cleft lip and palate
VPC	velopharyngeal closure
VPD	velopharyngeal dysfunction
VPI	velopharyngeal insufficiency

1 INTRODUCTION

Oral clefts (OC) are the second most common birth defect. OCs are divided based on the extent of the cleft, e.g., cleft lip (CL), cleft lip with or without cleft palate (CP±L), isolated cleft palate (CP), and submucous cleft palate (SMCP). Clefts may also be unilateral or bilateral. The prevalence of different types of CP±L varies according to ethnicity, gender and socioeconomic factors (Bender, 2000; Croen et al., 1998). In Europe, the combined birth prevalence of CP and CL with or without CP is approximately 1 per 700 live births (Leslie et al., 2016). Most cases of CP±L (approximately 70%) are non-syndromic, i.e. the clefts occur without any other anomalies (Manojlovic et al., 2023; Stanier & Moore, 2004).

Children born with any type of non-syndromic CP±L often demonstrate multiple problems such as early swallowing and feeding difficulties, abnormal articulation, resonance, voice disorders, craniofacial growth deviance and orthodontic abnormalities, hearing loss and poor language acquisition skills, psychosocial issues and learning difficulties at school. Patients often have to undergo multiple treatments starting at birth until young adulthood (Pasini et al., 2022; Stanier & Moore, 2004). Since the therapy may be long-term, it is a burden to the CP±L children and their families. Therefore, optimal care for these patients requires clear criteria and timely evaluation. A standard set of outcome measures for cleft care have been proposed; it contains eight major outcome domains: eating and drinking, dental and oral health, speech/communication, otologic health, breathing, appearance, psychosocial development, and burden of care (Allori, Kelley, et al., 2017). Research shows that lower satisfaction with appearance and speech seems to be mostly associated with increased emotional and social difficulties (S. Kelly & Shearer, 2020). Speech outcomes are affected by several pre- and postoperative factors, e.g., timing and techniques of surgical and orthodontic interventions, availability and quality of speech therapy, craniofacial growth and proportional development, other morphological and physiological factors (Nguyen, 2019). One of the primary treatment goals in CP±L therapy is to achieve normal speech.

Speech intelligibility is affected by articulation, nasality and voice quality. In cleft palate population, these characteristics are mainly impacted by velopharyngeal insufficiency (VPI) (Derakhshandeh et al., 2016). VPI results in excessive nasal resonance (hypernasality) on vowels and vocalic consonants (Kummer, 2013). Nasality is referred to as nasalization and is a linguistic category that can apply to vowels or consonants and is affected by coarticulation in a specific language (Kummer, 2013). Speech and language pathologists (SLP), who work with children with VPI, e.g. children with CP±L, consider nasality as one of the main impediments to intelligibility that requires multidisciplinary intervention.

Craniofacial morphology may also affect the severity of VPI in cleft-palate population (Denegri et al., 2021; Stellzig-Eisenhauer, 2001a). CP±L children have an increased risk for developing voice disorders (Fujiki & Thibeault, 2022).

Voice disorders are generally perceived as affecting speech quality and intelligibility. Laryngeal voice disorders often remain undetected in the population suffering from clefts. Still, many studies report a frequent presence of laryngeal voice disorders in the CP±L children's group, citing occurrence rates in the range of 5.5% to 60% (Hamming et al., 2009; Hocevar-Boltezar et al., 2006; Lehes et al., 2021; Robison & Otteson, 2011; Timmons et al., 2001). The extended range of results indicates that identification of voice problems is not an easy task. In this study, we have distinguished resonance disorders (resonance in voice) from laryngeal voice disordes.

In 2013, Ird and Suvi (Ird & Suvi, 2013) researched and described articulation errors in the Estonian CP±L group. Nasality and its relationship to craniofacial growth as well as to voice disorders are yet to be researched. Nasality results from a combination of different factors. One among the others that may affect nasality scores is Estonian quantity system. Estonian quantity system involves three contrastive prosodic patterns referred to short, long, and overlong. Therefore, in addition to the researched aspects in nasality in different language, we considered Estonian prosodic patterns as well.

The purpose of the present study is to evaluate and describe the resonance and voice related outcomes of CP±L children who received surgical treatment in Estonia.

All included children are treated accordingy to European guidelines.

2 REVIEW OF LITERATURE

2.1 Aetiology and epidemiology

CP±L arises as a result of pathologies in the development process during gestation. The aetiology of non-syndromic CP±L is not yet known. The described pathways associated with the development of CP±L show significant heterogeneity. Researchers agree that the aetiology of CP±L is multifactorial, i.e. genetic factors, environmental risk factors, and the interaction between them all play a role (Martinelli et al., 2020; Mossey et al., 2009; Phalke & Goldman, 2022). Different ethnic groups have unequal CP±L occurrence rates and different cleft types – relevant literature reports prevalence rates from 1 per 1,000 to 1 per 650 live births (IPDTOC Working Group, 2011; Salari et al., 2022; Ysunza et al., 2015). Among Caucasians, men have CP±L twice as frequently as women (Belcher et al., 2022; Calzolari et al., 2007; Salari et al., 2022; Wyszynski et al., 1996). In Estonia, the incidence of clefts is 1 per 777 live births (Jagomägi, 2012).

2.2 CP±L classification

Historically, researchers have suggested a number of different CP±L classifications. Mostly, these reflect anatomical and morphological, or embryological perspectives (Allori, Mulliken, et al., 2017). The different cleft types are usually divided based on their severity into unilateral or bilateral clefts of the lip, alveolus and palate, as well as isolated cleft palate. The extent of the cleft palate may range from a partial cleft in the soft palate to a complete cleft of both the hard and the soft palate. According to Inchingolo et al. (Inchingolo et al., 2022), the following main CP±L categories are distinguished: cleft lip with or without cleft palate (CP±L) and cleft palate (CP), uni- or bilateral. Submucosal clefts (SMCL) are reported less frequently. Submucous cleft palate is characterized by muscular diastasis of the velum in the presence of intact mucosa with variable combinations of bifid uvula and hard palatal defect (Khan et al., 2013). According to Klinto et al. (2022), the extent of speech impairment differs between girls and boys and between diagnoses – children born with BCLP have more severe speech problems compared to children born with unilateral cleft palate or SMCP.

2.3 Velopharyngeal (VP) function and nasality

According to Young & Spinner (2022), normal velopharyngeal closure (VPC) is accomplished by the coordinated action of the velum (soft palate), the lateral pharyngeal walls, and the posterior pharyngeal wall. Normal VPC is required for speech, for the production of oral sounds as well as for eating, to protect from nasal regurgitation of food or liquids. When VPC is needed, the middle third of the soft palate arcs upward and backward to contact the posterior pharyngeal wall at or above the level of the palatal plane. The lateral pharyngeal walls move

medially to contact the margins of the soft palate at or slightly below the level of the *torus tubarius*, and posterior pharyngeal wall advances to facilitate contact with the elevated soft palate (van Eeden, 2014). VPC affect nasality. Nasality refers to nasalization that is a linguistic category in normal speech and is related to VP function. Nasality is language specific, applies to vowels or consonants, and is affected by coarticulation. Speech nasalization is achieved primarily through the opening and closing of the VP port (Cler et al., 2021). Nasalized sounds are produced by lowering the velum, opening the mouth and ensuring simultaneous nasal and oral airflow. Appropriate nasalization is important for intelligible speech production and can be affected by a variety of disorders including hearing impairment, neurological diseases or structural issues such as CP (Cler et al., 2021). The degree of nasalance is determined mainly by the opening and closing of the VP passage between the oral and nasal vocal tract.

2.4 Velopharyngeal dysfunction in cleft-palate population

Velopharyngeal dysfunction (VPD) is a generic term that describes a disorder of the VP sphincter or valve, which functions to separate the nasal and oral cavities during activities that require increased intraoral pressure. When the soft palate and pharyngeal walls are unable to form an effective seal, the resulting abnormal connection between the nasal and oral cavities causes intraoral pressure to decrease. The term 'velopharyngeal insufficiency' (VPI) refers to a structurally caused VPD. Various forms of VPD have been described in literature (Young & Spinner, 2022). VPI is a form of VPD. VPI occurs most commonly in individuals with a history of CP±L (Sell et al., 2001; Witt et al., 1998; Young & Spinner, 2022). After CP surgery, the causes of VPI may be related to the shortened velum or to the irregularity of the movements needed to obtain a tight closure against the posterior pharyngeal wall during speech. The severity of VPI can vary from a very small pinhole-size opening to a very large opening that includes the entire VP port (Kummer, 2014). By interfering with the proper sealing of the oral from the nasal vocal tract, VPI affects speech resonance, causes speech sound errors and voice disorders. Resonance in speech is the result of the transfer and modification of the acoustic signal produced in the larynx through the vocal tract consisting of the pharynx, the oral and the nasal cavity. Hypernasality is a pathological form of resonance. Hypernasal resonance, excessive nasal resonance and articulation errors in speech are significant perceptual features of VPI (van Eeden, 2014). Researchers have pointed out that reliable assessment of hypernasality is difficult to achieve perceptually (Counihan & Cullinan, 1970a; Keuning et al., 1999; Persson et al., 2006; Yamashita et al., 2018). VPI results in hypernasal speech, nasal regurgitation, nasal emission, and decreased intraoral pressure during speech (A. Young & Spinner, 2022). The production of oral sounds, especially high-pressure oral consonants, is affected. The overall result is decreased speech intelligibility and significant functional and social impairment. VPD is described in approximately 20–30% of individuals who have received cleft palate

repair (Sell et al., 2001; Witt et al., 1998) and in 5–10% of patients with SMCP (Sullivan et al., 2011).

The Estonian language belongs to the Baltic-Finnic branch of Finno-Ugric languages. According to 2021 census data, Estonian is spoken by 84% of the population (Census Data, 2021). The language has roughly one million speakers.

Based on the use of the VP seal, Estonian phonemes are divided into two groups: (1) oral and (2) nasal phonemes (Asu & Teras, 2009a). Nasalized sounds are limited to consonant phonemes /m/, /n/, / ń/ and /ŋ/. Estonian vowel phonemes differ by tongue height, tongue frontness and lip rounding. Based on tongue height, Estonian vowels fall into three groups: (1) high vowels /i, ü, u/, (2) mid vowels /e, ö, õ, o/ and (3) low vowels /a, ä/. Studies suggest that vowel height affects their perceived nasality (Lewis et al., 2000; Watterson et al., 2007; L. H. Young et al., 2001). Estonian does not have any nasalized vowels (Eek et al., 2008a). There are three degrees of quantity on the foot level: short, long, and overlong. Quantity is realized by the lengthening of the stressed vowel or the intervocalic consonant, while the unstressed vowel is shortened in compensation (Lehiste, 2011; Lippus et al., 2013).

In English, (1) nasality (score, level, rating) usually refers to the perceptual assessment of speech, while (2) nasalance (score, level, rating) is a result of objective assessment that is often rendered as a numerical score. The corresponding Estonian terms are (1) nasaalsus(e) (aste) [(degree of) nasality] to describe the outcome of perceptual assessment, and (2) nasaleeritus(e) (aste) [(degree of) nasalance] to refer to the numerical results of objective measurements (Lehes et al., 2018). Estonian, the corresponding terms to describe nasality and nasalance are used. Estonian linguists suggested using two terms: ‘nasaalsus’ and ‘nasalisatsioon’. The term ‘nasaalsus’ refers to perceived pathological nasality: too high (hüpernasaalsus) or too low (hüponasaalsus) nasal resonance in speech. Whereas the term ‘nasalisatsioon’, is used to mark normal resonance in speech ((Eek et al., 2008b).

2.4.1 Speech sound errors

Cleft palate speech is a term that is widely used to describe the occurrence of atypical consonant production, abnormal nasal resonance and nasal airflow, disturbed laryngeal voice quality, and nasal or facial grimaces (Hanley et al., 2023; Phalke & Goldman, 2022). There are several possible causes for speech sound errors in individuals with CP±L, such as the abnormalities in oronasal structure and function, orofacial structure and growth, learned neuromotor patterns during early infancy, and/or disturbed psychosocial development (Hanley et al., 2023). According to Jones et al. (2003), even with early and timely surgical repair, a majority of pre-schoolers demonstrate delays in speech sound development and have typical CP speech.

Roughly, articulation errors characteristic of cleft palate speech are divided into two subtypes: obligatory and compensatory. Obligatory errors include sounds which are produced incorrectly before the surgical repair, also known as ‘passive

errors' (Nikhila, 2017). These errors cannot be corrected through speech therapy unless the underlying structural deformity is surgically repaired. Compensatory errors include those that occur due to maladaptive articulatory placements. Such errors can be corrected only through speech therapy (Riski, 2006). In order to choose the right treatment method it is important to identify the type of error that interferes with normal articulation.

In 2013, Ird and Suvi (2013) published the first version of their perceptual assessment protocol for Estonian CP±L speech. The preliminary version identifies and describes the types of articulation and resonance errors in Estonian. According to research underlying the protocol, the compensatory (e.g. glottal stops, backing) and obligatory (e.g. weak consonants, passive fricatives) speech sound errors observed in Estonian-speaking CP±L children are similar to those described in the literature for similar groups of speakers of other languages. Therefore, the author of the thesis did not analye speech sound errors but focused on resonance.

2.4.2 Craniofacial growth and resonance of speech

As stated earlier, one of the primary treatment goals in cleft palate repair is to obtain successful speech outcomes. The latter are influenced by several pre- and postoperative factors, e.g., the timing and techniques of surgical and orthodontic interventions and the availability of speech therapy, as well as by craniofacial growth and proportional development among other morphological and physiological factors. The literature on the subject suggests that there is no consensus regarding preferable surgical protocols (Peterson Falzone et al., 2010; Lohmander, 2011). Furthermore, Scandcleft Project Trial 2 concluded that poorer speech outcomes could not be attributed to a specific surgical protocol and suggested that improvements in speech quality tend to correlate with the number of speech therapy visits (Hammarström et al., 2020).

Still, establishing the links and determining the correlation between nasalance scores and cephalometric characteristics may help to explain how and to what extent craniofacial morphology impacts speech development and speech quality in the CP±L group. In CP±L patients, craniofacial growth is affected by genetic factors as well as by surgical interventions. Specialized literature suggests cleft type and cleft characteristics to be the main determining factors of long-term craniofacial growth alterations (Naqvi et al., 2015; Viñas et al., 2022).

2.4.3 Voice disorders

Children born with CP±L may also develop laryngeal dysphonia. It may go undetected and undiagnosed by clinicians because of many other accompanying problems, e.g., resonance disorders that may mask laryngeal voice disorders. Researchers report a wide range of (5.5% to 50%) voice disorder prevalence rates in CP±L population (Hamming et al., 2009; Hocevar-Boltezar et al., 2006; Lehes

et al., 2021; Robison & Otteson, 2011; Timmons et al., 2001). It stands to reason that altered voice quality along with other associated problems may significantly affect the intelligibility of speech and overall quality of life.

The underlying mechanisms of laryngeal dysphonia in CP±L group are still debated. The broadly shared conclusion and current hypothesis is that its underlying mechanism consists in increased adduction and hypertension in supralaryngeal structures (D'Antonio & Scherer, 2008; McWilliams et al., 1973; Robison & Otteson, 2011; Segura-Hernández et al., 2019; Villafuerte-Gonzalez et al., 2015). It is accepted that laryngeal hyperfunction may result in muscle tension dysphonia and cause morphological changes in the vocal folds (e.g., vocal nodules, inflammation, oedema). According to literature, vocal swelling and vocal nodules are the most common anatomical finding in CP and CP±L individuals (D'Antonio & Scherer, 2008; Dejonckere, 1999; A. W. Kummer, 2014b; Lehes et al., 2021; Van Lierde et al., 2004). Anatomical changes in vocal folds alter voice quality. Individuals with CP±L frequently exhibit chronic hoarseness as well as forced, soft, strangled or aspirated phonation (D'Antonio & Scherer, 2008; Henningsson et al., 2008; Kuehn & Henne, 2003; Lehes et al., 2021; Segura-Hernández et al., 2019).

2.5 Assessment of resonance and voice quality in CP±L children

Patients with VPD should be managed by a multidisciplinary team, using multimodal instruments to evaluate preoperative and postoperative speech outcomes (Paniagua et al., 2013). General guidelines and thorough assessment and examination of speech and voice disorders are key aspects for reliable treatment. Clinicians' need for evidence-based protocols and therapy tools to guarantee optimum outcomes in a reduced timeframe.

2.5.1 Evaluation of VP function

Despite advances in surgical management, it is estimated that 20–30% of children with repaired CP will continue to have hypernasal speech and require a second surgery to ensure normal VP function (Bicknell et al., 2002). The presence of hypernasality in repaired CP speech is a consequence of VPI (Dubey et al., 2019).

Clinicians and researchers have suggested different methods for evaluating VP function. The choice of the specific method is directly related to the focus of interest of the clinical investigation and to its need for accuracy (Paniagua et al., 2013). Research suggests that both auditory-perceptual assessment and instrumental assessment of VP function should be performed (Golding-Kushner et al., 1990). The combining of these measurement techniques is necessary to properly diagnose and treat resonance disorders (Bettens et al., 2014). Instrumental assessment of VP function includes videonasoendoscopy (VNE), videofluoroscopy (VF), magnetic resonance imaging (MRI), cephalometric radiographic analysis,

computed tomography (CT), ultrasound, acoustic and aerodynamic measurements. Not all of these methods are available for clinicians. Research suggests that at least one instrumental method should be used in addition to perceptual-auditory assessment (Golding-Kushner et al., 1990).

In Estonia, clinicians have access to all of the above-mentioned instrumental assessment methods. Still, they prefer using VNE – the diagnostic procedure used to examinate the nose, throat, and airway (Alvi & Harsha, 2022) that specifically allows direct visualisation of the soft palate, lateral pharyngeal walls, and posterior pharynx. The procedure may cause some discomfort for the patient but does not involve any exposure to radiation and can be performed on cooperating CP±L children (Alvi & Harsha, 2022; Golding-Kushner et al., 1990; Kobayashi et al., 2019). VNE helps to determine possible VPI during speech production. Direct visualisation demonstrates the severity of the VPI, its size and shape, the consistency of VP closure, the size of adenoids and tonsils and their potential role in VPC. These findings are crucial in providing clinical assessment input for comprehensive multidisciplinary team management of CP±L children.

2.5.2 Assessment of nasality

Nasality is measured perceptually and/or objectively. Perceptual assessment of nasality is usually the first tool that SLPs use, and is employed widely. Yet, studies report that perceptual assessment lacks reliability because it is influenced by a variety of factors such as the essence of the speech stimulus (Lehes et al., 2018; Mohd Ibrahim et al., 2020), the presence of articulation problems and audible nasal air emission/nasal turbulence, as well as loudness and pitch (Cler et al., 2021; Sundström & Oren, 2019; Zraick et al., 2000) and the experience and training of the listeners (Lewis et al., 2003; Scarmagnani et al., 2014). This has stimulated researchers and clinicians to take a growing interest in objective assessment of nasalance.

Similarly to perceived nasality, objective scores of nasalance can be influenced by many different factors: nasal obstruction, adenoidectomy, hearing impairment and cleft palate (Y. Liu et al., 2022; Watson et al., 2001). Although normative nasalance scores are language-specific, researchers have shown them to vary as a function of the speaker's dialect (Seaver et al., 1991; van Lierde, Wuyts, De Bodt, & Van Cauwenberge, 2001), the phonetic content of the speech stimulus (Lewis et al., 2000) as well as the speaker's age (Haapanen, 1991; Hirschberg et al., 2006; Van Lierde et al., 2003) and gender (van Lierde et al., 2001).

2.5.3 Assessment of voice quality

The four most common approaches taken by clinicians to assess the different parameters of voice production and quality include auditory-perceptual and acoustic assessment of voice quality, aerodynamic assessment of subglottal air pressure and nasoendoscopic evaluation of vocal fold movements (Villafuerte-Gonzalez et al., 2015). A combination of different assessment methods is vital in the CP±L

group since confining the examination exclusively to auditory-perceptual assessment may prove unreliable due to the influence exerted by the listeners' experience and preparation, by the speech stimuli used, and by the presence of articulation and resonance. Acoustic analysis is non-invasive, it provides an opportunity to assess voice quality and determine any susceptible underlying mechanisms of dysphonia. According to literature, several acoustic parameters are affected in CP±L population, whose condition may cause, e.g., alterations of fundamental frequency (F_0), pitch and amplitude perturbations (shimmer, jitter), variations in soft phonation index (SPI) may refer to incomplete vocal fold adduction, disturbed harmonics to noise ratio (HNR) (Segura-Hernández et al., 2019; Villafuerte-Gonzalez et al., 2015; Attuluri et al., 2017). Perturbation measures (jitter, shimmer) are regarded as indicators of abnormal vocal fold vibrations, which result in changes in the quality of voice.

Researches have not reached a common understanding of whether and to what extent VPI influences laryngeal voice quality. Leder and Lerman (1985) concluded that clinically significant hypernasality was related to inappropriate vocal fold adduction, whereas Hamming et al. (2009) did not report a correlation between the severity of VPI and hoarseness. In the CP±L group, VPI may cause the presence of dysphonia.

Surgical and orthodontic treatment may affect craniofacial, especially maxillary growth in the CP±L population. Maxillary development may affect speech quality, especially resonance in speech. In addition, based on the previously published articles (Nguyen, 2019; Schultes et al., 2000; Uslu-Akcam, 2017), we chose cephalometric landmarks and parameters that may affect speech quality.

2.6 Clinical management of CP±L children in Estonia

Patients with CP±L require complex and longitudinal care by a multidisciplinary cleft team. Multiple clinical practice guidelines (CPGs) have been proposed to provide a standardized framework for cleft care delivery (Yver et al., 2022).

In Estonia, there are two craniofacial centres that provide care for CP±L patients: one at Tartu University Hospital and the other at the North Estonia Medical Centre. The centres follow different surgical protocols: the former has opted for one-stage palate repair while the repair performed at the latter is two-stage. Other than the above-mentioned difference of protocol, the documentation and assessment of speech, maxillary growth and occlusion at the two centres follows standardized care procedures based on European guidelines (Shaw et al., 2001).

2.7 Rationale for the included studies

Speech quality is a major factor to be considered when describing the effectiveness of the treatment received by CP±L children. Poor speech quality may affect their social interactions, their progress at school and, eventually, their overall quality of life. Kelly & Shearer (2020) stated that appearance and speech dissatisfaction may be ways in which to identify those at risk of psychosocial difficulties

within clinical settings. Therefore, we as the specialists should aim to the better subjective outcomes in speech and appearance in CP±L population. In order to achieve this target, we need evidence-based approach, and for this, in turn, objective thresholds. As stated above at 1.4.1, in 2013 Ird & Suvi (Ird & Suvi, 2013) developed test material for, and reported on, the Estonian-specific articulation errors in CP±L children. Nasalance and voice disorders in speakers of Estonian have not been described. In order to provide proper treatment, specific assessment protocols tailored to the Estonian language are needed. Establishing these and understanding the mechanisms of abnormal nasalance and voice disorders would considerably facilitate the work of multidisciplinary teams (including maxillofacial surgeons, SLPs, ear-nose-throat physicians, orthodontists) treating cleft patients.

3 AIMS OF THE STUDY

The general aim of the study was to develop specific assessment protocols tailored to the Estonian language to describe the voice and resonance related treatment outcomes in Estonian cleft palate children.

The specific aims were to:

(1) develop Estonian-specific optimised speech stimuli for Nasometer II and establish normative nasalance scores for Estonian (Paper I);

(2) develop Estonian specific optimised speech stimuli for videonasoendoscopy and analyse the correlation between the severity of VPI and the severity of voice disorders (Paper II);

(3) assess the voice quality and its impact on quality of life in Estonian children born with CP±L (Paper II);

(4) determine the cephalometric parameters that distinguish the healthy group from the cleft-palate one as well as the cephalometric parameters that predominantly relate to resonance disorders (Paper III).

4 MATERIALS AND METHODS

4.1 Participants

Based on the aims of the study, we recruited two groups of children: a control group of healthy preschool children and an another one of CP±L children of the same age. Healthy children were selected from nine different kindergartens from all over Estonia. All healthy children were screened by a qualified SLP for any possible articulation, resonance or voice disorders. If any of these problems were present or had occurred, the child was excluded from the study.

European minimum standard of care requires SLP consultation at the age of five to six for all CP±L children (Shaw et al., 2001). Therefore, all CP±L children have a regular clinical appointment with their cleft team at that age in the cleft centre of Tartu University Hospital or of the North Estonia Medical Centre. The opportunity to participate in the research project reported here was introduced to caregivers of non-syndromic CP±L patients, and data was collected during their regular clinical visits. There was no extra burden to the children or to the SLP. We did not include children who had any other congenital or acquired disease and we also excluded children with syndromic clefts, isolated cleft lip, delayed linguistic or psychomotor development and/or hearing loss. The mean age for all participating children was between five and seven years in both groups. This age was considered the most appropriate because most children have acquired pronunciation of all Estonian sounds by that age (Karlep, 1998).

As the general population of Estonia is small, the number of CP±L patients was also limited. We were unable to divide our CP±L group into subgroups based on the cleft type. We relied on the knowledge that there is considerable variation in how children with CP±L develop in terms of speech and that no direct relationship has been found between the severity of cleft palate and speech quality (Hardin-Jones & Jones, 2005). Similarly, no subdivision was undertaken based on the surgical protocol used in the case. Although the group included patients treated using different surgical methods (respectively, one-stage and two-stage palate repair), the small size and heterogeneity of the sample as well as previous findings (Hardin-Jones & Jones, 2005) concerning the effect of the surgical method on speech quality outcomes rendered subclassifications impractical.

Table 1. Number and distribution of subjects.

	CP±L group (n)					Healthy group (n)
	BLCP+CL	ULCP+CL	CPO	SMCP	TOTAL	
Study I	2	5	5	2	14	92
Study II	4	6	6	2	18	79
Study III	2	4	3	2	11	17

*n – number of participants, CPO – cleft palate only, SMCP – submucous cleft palate, BLCP+CL – bilateral cleft lip and palate; ULCP+CL – unilateral cleft lip and palate

4.2 Study design and methods

The study was designed as cross-sectional and comparative. The data were collected by a combination of objective (Multidimensional Voice Program (MDVP), Nasometer II, Dolphin Imaging Software) and subjective (Pediatric Voice Handicap Index (pVHI), GRBAS scale, videonasoendoscopy (VNE), videolaryngostroboscopy (VLS)) methods were performed by our multidisciplinary cleft teams.

Table 2. Subjects and methods

	Enrolment	Number of subjects	Methods and materials
Study I	March 2015 – February 2017	14 CP±L 92 healthy	Estonian stimuli for Nasometer II pilot study modification of speech stimuli normative nasalance scores test-retest reliability
Study II	October 2016 – February 2017	18 CP±L 79 healthy	Estonian stimuli for VNE acoustic analysis of voice (MDPV parameters) pVHI questionnaire auditory-perceptual analysis of voice (GRBAS) VNE VLS
Study III	September 2019 – March 2020	11 CP±L 17 heathy	Lateral cephalograms nasalance scores cephalometric parameters intra- and inter-rater reliability

4.2.1 Developing Estonian speech stimuli for Nasometer II and establishing normative nasalance for Estonian (Paper I)

First, in cooperation with the Institute of Estonian and General Linguistics and the Institute of Education of the University of Tartu, we developed unique Estonian-specific test material for Nasometer II. To ensure that the phonetic content of stimuli matches the distribution pattern of nasal and consonant phonemes as well as high and low vowel phonemes in Estonian speech, we verified our stimuli against phoneme distribution data taken from the Phonetic Corpus of Estonian Spontaneous Speech. The test material was developed such as to feature phonemes in all contrastive quantity degrees, and to be age-appropriate for five- to six-year-old children.

Prior to the actual investigation, we conducted a pilot study to assess the suitability of speech stimuli. We included ten healthy and three CP±L children (Estonian monolinguals) in the first trial. Speech samples were recorded individually

in a quiet room. Having explained the process, the examiner secured the Nasometer headset on the child's head according to the manufacturer's instructions. The child was then instructed to repeat the speech stimuli after the examiner. Each sentence was read to the child at a natural Estonian speech rate, loudness and pitch. There was a 2–3 second pause between each sentence. Nasometer II software was used to calculate the nasalance score for each sentence. All speech samples were recorded. Based on their analysis, we excluded two utterances that seemed to be too difficult to repeat *(Papa ei ole õhtul kodus* and *Kokk teeb ahjus kooki)*.

4.2.2 Methodology for voice assessment (Paper II)

Based on specialized literature (Attuluri, 2017; Aydınlı et al., 2016; Dejonckere, 1999) we combined subjective and objective assessment methods to achieve a detailed understanding of the underlying mechanism and the essence of dysphonia in CP±L children. The assessment consisted of:

(1) collecting data about parents' or caregivers' responses concerning their child's voice-related quality of life using the pVHI questionnaire (Appendix A);
(2) performing acoustic analysis of the child's voice using the MDVP;
(3) analyzing voice quality using auditory-perceptual assessment based on the GRBAS scale;
(4) performing videonasoendoscopy (VNE);
(5) performing videolaryngostroboscopy (VLS).

The pVHI is a paediatric version of voice handicap index (VHI). According to the literature, the pVHI is adapted into several languages, is reproducible and shows high clinical validity (Devadas et al., 2015; Oddon et al., 2018; Park et al., 2013; Sanz et al., 2015; Schneider et al., 2019a; Shoeib et al., 2012; Šimkienė et al., 2022; Veder et al., 2017; Özkan et al., 2015). It is linguistically validated in Estonian language. We trained all the parents or caregivers to differentiate resonance disorders from laryngeal voice disorders.

MDVP (Model 5105, version 3.1.7; KayPENTAX) is a software application commonly used for acoustic analysis of voice in clinical and research settings. For recordings, a dynamic microphone was positioned on a stand at approximately 10 cm from the child's mouth. Three samples of the sustained phonation of Estonian vowel /a/ ([ɑ]) were recorded. Four seconds of the utterance of the most stable trial was used for further analysis. Based on the literature about the possibly affected acoustic voice parameters, we chose six different markers to analyse: fundamental frequency (F_0), Shimmer (Shim), Jitter (Jitt), soft phonation index (SPI), noise-harmonic-ratio (NHR), voice turbulence index (VTI).

GRBAS scale is one of the most used auditory-perceptual assessment tools where 'G' stands for overall grade of hoarseness, 'R' – roughness, 'B' – breathiness, 'A' – asthenic, and 'S' – strained quality of the voice. These five components are

rated on four point Likert scale. First, we recorded speech samples (sustained vowel /a/ ([ɑ]) and continuous speech samples). Next, two raters were trained using GRBAS scale. Then the rates independently rated the speech samples on GRBAS scale. Inter- and intra-rater reliability was calculated.

VNE and VLS were performed. Flexible fibreoptic nasopharyngolaryngoscope (Kay Pentax model VNL 8-J10) was used for the procedures. First, the assessment protocol for VP function was followed, then the anatomy and functions of larynx were assessed. Both procedures were carried out together with our multidisciplinary cleft teams (included SLP, ENT-doctor, surgeon, orthodontist), were recorded and saved for later analysis. Prior to the VNE assessment, we developed Estonian test material for the best visualization of the VP function. The test material consists of verbal and non verbal (swallowing and blowing) tasks. Verbal stimuli include repetition of sustained high and low vowels and fricatives (/*s/, /h*/), strings of syllables (e.g /*pi-pi/, /ta-ta/*), words (e.g /*kõmmdi/, /patsi/)* and utterances loaded with pressure-sensitive phonemes (Appendix B). Based on the findings, VNE protocol was filled out by SLPs and ENT-doctors. Vocal fold vibration, its symmetry and regularity, and vocal fold closure during phonation and speech was specified by VLS. The purpose of VLS was to identify any morphological changes of focal folds. During the assessment, the child was asked to repeat sustained Estonian vowels /*i*/ ([i]) and /*e*/ ([ɛ]), repeat a sentence /*Juulikuus suur tuul.*/ and counting numbers from one to ten.

4.2.3 Cephalometric analysis (Paper III)

We assessed lateral cephalograms to measure craniofacial morphology and airway structures. Depending on gender, age and body type, the lateral cephalograms were taken using Galileos (Dentsply Sirona, Germany) at the suggested settings: 9.4 seconds, 60–84 kV, and 10–15 mA. The radiologist positioned the patient's head such that the Frankfort horizontal plane was parallel to the floor (Uslu-Akcam, 2017). The lateral cephalograms were traced, and Dolphin Imaging software (Dolphin Imaging & Management Solutions, USA) was used for digital analysis. Such digital analysis has been found reliable at the 95% level (method error) (Power et al., 2005). Omidkhoda et al. (2022) concluded that Dolphin Imaging software (version 11.8) can be used to reliably predict hard tissue as well as soft tissue, especially in the upper lip area. Two trained and calibrated examiners independently traced and measured the cephalometric parameters of all 28 included children. Inter-rater reliability was calculated. To assess the intra-rater reliability, 15 lateral cephalograms were randomly selected and presented to the rater to be assessed anew after three weeks.

Based on the aims of this study, as well as previous research by Ozge Uslu-Ackam (2017) and Van Thai Nguyen (2019), twelve different cephalometric landmarks were selected to identify skeletal morphology. Reference cephalometric landmarks and parameters are described in Figure 1 and Table 3.

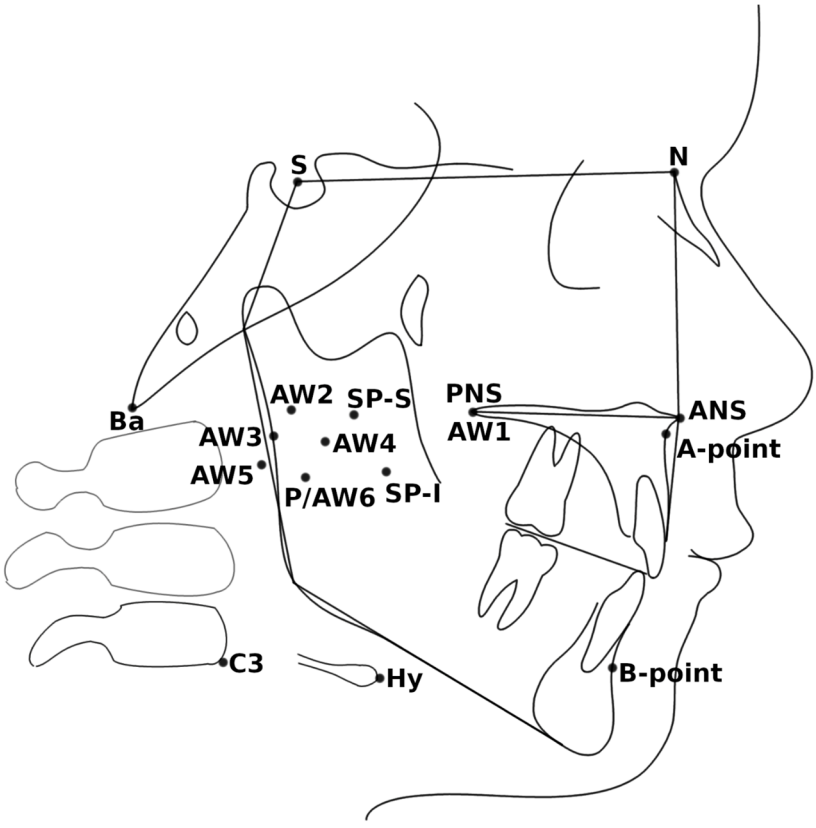

Figure 1. Cephalometric reference landmarks

Nasion (N): the intersection of the internasal suture with the nasofrontal suture in the midsagittal plane. **Sella (S):** the centre of the pituitary fossa of the sphenoid bone. **Basion (Ba):** the most inferior posterior point of the occipital bone at the anterior margin of the occipital foramen. **Anterior nasal spine (ANS):** the tip of the anterior nasal spine. **Posterior nasal spine (PNS)**: the tip of the posterior nasal spine. **A-point:** the deepest point on the curve of the maxilla. **B-point:** the most posterior point in the concavity along the anterior border of the symphysis. **Hyoid (Hy):** the most superior and anterior point on the body of hyoid bone**. C3:** the most anterior and inferior point on the corpus of the third cervical vertebra. **AW1** – airway anterior lower. **AW2** – airway posterior lower. **AW3** – middle posterior airway. **AW4** – middle anterior airway. **AW5** – inferior posterior airway **AW6** – inferior anterior airway. **P** – tip of the soft palate. **SP-S** – superior most point on the upper surface of the soft palate. **SP-I** – inferior most point on the lower surface of the soft palate (Illustration: Lehes (2022)).

Table 3. Cephalometric measurements

Measurements	Description
SNA (º)	The angle between the lines SN and NA
SNB (º)	The angle between the lines SN and NB
ANB (º)	The angle between the lines NA and NB
BA-S-N (º)	Cranial base angle
PNS-A (mm)	Distance from PNS to A
PNS-Ba (mm)	Distance from PNS to Ba
Hy-C3 (mm)	Distance from Hy to C3
PNS-P (mm)	The length of the soft palate
SP-S-SP-I (mm)	Maximum thickness of the soft palate
AW1-AW2 (mm)	The width of the nasopharyngeal airway
AW3-AW4 (mm)	The width of the upper oropharyngeal airway
AW5-AW6 (mm)	The width of the lower oropharyngeal airway

The threshold for oronasal stimuli (Paper I) was considered when correlating resonance disorders with cephalometric parameters.

4.3 Ethical considerations

Approval (no. 263/T2) for the study was obtained from the Ethics Review Committee on Human Research of the University of Tartu prior to beginning the research. The study was conducted in compliance with the Declaration of Helsinki concerning ethical principles for medical research involving human subjects. All participants were informed about the nature of and need for the study before commencing with the procedures. Consent was documented using an informed consent form signed by the parent/caregiver or the child when older than 7 years of age (Paper III), and physical copy of the signed consent form was handed out. After signing an informed consent form approved by the Ethics Committee, children and their parents were enrolled into the studies. All participants knew key aspects of the protocol. They could withdraw from the study at any given moment, without a reason.

5 RESULTS

5.1 Normative nasalance scores for Estonian children (Paper I)

5.1.1 Development of estonian speech stimuli for Nasometer II

Based on the data from Phonetic Corpus of Estonian Spontaneous Speech, we developed original Nasometer II test material for Estonian children. All developed and included utterances are semantically understandable as well as linguistically and phonetically age-appropriate for five-to-six-year-old children. The stimuli consist of 24 utterances divided into three groups: (1) oronasal stimuli (ONS) that include oral and nasal phonemes and represent the phoneme distribution encountered in spontaneous Estonian speech (10% of nasal phonemes), (2) oral stimuli (OS) that include only oral phonemes, and (3) nasal stimuli (NS) that are loaded with nasal phonemes (30% of nasal phonemes). Each stimulus group consists of eight utterances of at least six syllables each. The speech stimuli that were used are presented in Tables 4–6.

Table 4. Oronasal speech stimuli

Sentence	Translation
Isal on pikk habe.	Daddy has a long beard.
Lapsed mängivad palli.	Children play ball.
Väike naine loeb lehte.	A little woman is reading a paper.
Tüdruk sööb punast õuna.	A girl eats a red apple.
Saara ostis kommi.	Saara bought candy.
Tige tikker karjub.	Angry gooseberry screams.
Epu valge tutimüts.	Epp's white bobble beanie.
Ema punane mantel.	Mother's red coat.

Table 5. Nasal speech stimuli

Sentence	Translation
Emma mummuline kann.	Emma's polka-dotted jug.
Hani munes muna.	The goose laid an egg.
Mamma pani akna kinni.	Granny closed the window.
Naine kõnnib tänaval.	The woman walks in the street.
Inga tahab linna minna.	Inga wants to go to town.
Anna ei nuuska nina.	Anna doesn't blow her nose.
Ema annab homme kommi.	Mom will give candy tomorrow.
Inna pani nuku vanni.	Inna put the doll in the bath.

Table 6. Oral stimuli

Sentence	Translation
Lõbus papa sööb suppi.	Merry papa eats his soup.
Kaja pugib kooki.	Kaja munches on a cake.
Tädi otsib uut potti.	Auntie is looking for a new pot.
Harri veeretab vurri.	Harri spins the yoyo.
Kalle läheb külla.	Kalle goes on a visit.
Valli vaatab pilve.	Valli looks at the cloud.
Juta kukkus ojja.	Juta fell into the stream.
Sassi soojad sussid.	Sass's warm slippers.

5.2 Nasalance scores for Estonian healthy and CP±L children

Eleven children were retested. For test-retest reliability, Pearson's correlation was run to assess the stability of testing. There were high positive correlations between the first and second trials in all stimulus groups: oronasal – r=0.97, $p<0.05$; oral – r=0.99, $p<0.05$; nasal – r=0.93, $p<0.05$. Table 1 compares the mean nasalance scores obtained by the test-retest analysis for the different stimuli groups. The scores are presented as percentages.

Table 7. Test-retest comparison by speech stimuli groups

	ONS* (M)	**NS* (M*)**	**OS* (M*)**	**All** utterances **(M*)**
Trial 1	33.5	60.1	19.8	37.8
Trial 2	33.1	59.0	19.0	37.0

*ONS – oronasal utterances, NS – nasal utterances, OS – oral utterances, M – mean score

For internal consistency reliability, Cronbach's α was calculated for each stimuli group: oronasal – α=0.93; oral – α=0.97; nasal – α=0.92. The results showed that internal consistency was high in all groups.

The mean nasalance scores for oronasal stimuli for healthy non-cleft Estonian-speaking children were 30.5% and for those in the CP±L group, 47.1%, for nasal stimuli respectively 57.8% and 60.9, and for oral stimuli, 15.9% and 37.0%. Significant differences were found between the two groups in oronasal and oral utterances, but not in nasal one. No significant differences between genders were found ($p>0.05$). The normative nasalance scores for non-cleft Estonian-speaking children are presented in Table 8.

Table 8. Normative nasalance scores for Estonian.

Speech stimuli	N	M	SD	M +/– 2 SD*	Max*	Min*	CI* (95%)
ONS	92	30,5	5,8	18,9 – 42,1	56,3	19,5	29,2–31,6
NS	92	57,8	5,8	46,2 – 69,4	72,0	41,7	56,6–59,0
OS	92	15,9	6,0	3,9 – 27,9	45,9	6,8	14,6–17,1

*M +/– 2 – standard deviation from the mean, Max – maximum, Min – minimum, CI – confidence interval

5.3 The effect of VPI on voice quality (Paper II)

5.3.1 Voice-related quality of life

First, we gathered information about voice related quality of life from both study groups using the pVHI questionnaire. The mean pVHI total score for healthy children was 6.42 and, for cleft group, 17.33. The highest mean scores were calculated in both groups in the functional subscale. Total scores of pVHI and its subscales are presented in Table 9. Significant differences were found between healthy children and the CP±L group (p>0.05).

Table 9. Comparison of the pVHI scores between healthy children and children with CP±L

	Group	N	Mean	SD	p
Functional	CP±L	18	6.56	3.714	0.000
	Healthy	79	2.99	2.844	
Physical	CP±L	18	5.72	4.443	0.000
	Healthy	79	1.95	3.071	
Emotional	CP±L	18	5.06	4.820	0.000
	Healthy	79	1.48	2.297	
Total score	CP±L	18	17.33	11.209	0.000
	Healthy	79	6.42	6.725	

*SD – standard deviation, N – number of participants, p – statistical significance (>0.05)

5.3.2 Acoustic analysis of voice

The production of Estonian vowel /a/ ([ɑ]) by all the participants was recorded and analysed to obtain fundamental frequency (F_0), shimmer (Shim), jitter (Jitt), soft phonation index (SPI), noise-harmonic-ratio (NHR), and voice turbulence index (VTI) values. The results indicated the increased values of all parameters with the exceptioin of SPI. We found significant differences in the jitter, shimmer and NHR parameters between healthy children and the CP±L group (p<0.05).

Table 10. Comparison of acoustic parameters in healthy children and in children with CP±L

Ac. parameters	Group	Mean	SD	*p*
F_0	CP±L	285.09	55.51	0.314
	healthy	273.25	25.76	
Jitter	CP±L	1.37	0.72	0.000
	healthy	0.74	0.36	
Shimmer	CP±L	0.422	0.13	0.016
	healthy	0.345	0.08	
NHR	CP±L	0.13	0.04	0.009
	healthy	0.11	0.01	
VTI	CP±L	0.044	0.02	0.089
	healthy	0.035	0.02	
SPI	CP±L	10.8	6.34	0.201
	healthy	13.8	8.54	

We also checked for correlations between MDVP parameters and pVHI total scores in the CP±L group using Pearson's correlation coefficient. that the results showed the correlation between pVHI results and MDVP parameters were poor ($r<0.3$) and not significant ($p>0.05$).

5.3.3 Auditory-perceptual analysis of voice

Speech recordings of all CP±L children were graded on the GRBAS scale. A total of 18 speech samples was analysed by two trained independent listeners. Inter-rater reliability for GRBAS scale was high (κ=0.89).

The ratio between boys (13) and girls (5) was 2.6:1. Due to the small sample size, we only performed a descriptive analysis based on gender. The results are given in Table 11.

Table 11. Mean scores by the GRBAS scale.

	G (M)	**R (M)**	**B (M)**	**A (M)**	**S (M)**
F	1.00	.80	.60	.00	.40
M	.85	.85	.77	.23	.38
TOTAL	.89	.83	.72	.17	.39

*'G' – overall grade of hoarseness, 'R' – roughness, 'B' – breathiness, 'A' – asthenic, and 'S' – strained quality of the voice.

All mean scores were ≤ 1.0 – i.e., trained listeners did not notice considerable perceptually detectable voice disorders. Girls received a slightly higher score in the general category of hoarseness (‘G’). Boys graded higher for the asthenic aspect (‘A’) of voice.

We conducted a regression analysis to see whether there is a relationship between the scores of the GRBAS scale and the pVHI. We did not find strong correlations between pVHI scores and the GRBAS scale.

6 INSTRUMENTAL FINDINGS OF THE VELOPHARYNGEAL FUNCTION AND VOCAL FOLD FUNCTION

VNE as well as VLS were performed on all included CP±L children (N=18, 5 girls, 13 boys). All children tolerated the procedure relatively well. Nasoendoscopic videos were recorded and saved for later analysis. The size of the VP gap was graded on a five-point scale where '0' refers to normal VP function, '1' refers to a very small (pinhole) and five refers to a very large opening. Three children exhibited normal VP function, whereas in the others, the VP valve showed an opening: a minimal (pinhole) opening in six cases, a small one in five, a medium one in two and a large one also in two. The severity of the VP gap was measured by two raters: a clinical SLP and an ENT physician. VLS assessment revealed normal vocal fold morphology and vibrations in eight of the children (three of the five girls and five of the thirteen boys) and morphological changes in the remaining ten, of whom two presented bilateral vocal nodules and eight had oedema. Table 12 provides an overview of the findings of the VNE and VLS procedures and the total score of pVHI in the CP±L group. Based on descriptive statistics, the severity of the VPD did affect the pVHI score but was not related to altered vocal fold morphology or the dysfunction of the vocal fold closure.

Table 12. Overview of VPI, VLS, pVHI in the CP±L group

	F1	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	F2	M11	M12	F3	F4	F5	M13
VLS	0	2	2	0	1	1	1	0	1	1	1	0	0	0	0	1	1	0
VNE	4	1	4	2	3	2	1	0	1	2	2	2	1	3	0	1	0	1
pVHI	36	4	29	6	13	32	9	2	30	24	17	18	7	35	5	19	9	4

M – male, F – female; *VLS: '0' – normal vocal folds, '1' – oedema, '2' – nodules; *VNE – '0' – normal VPC, '1' – pinhole opening, '2' – small opening, '3' –medium opening, '4' – large opening

6.1 Cephalometric parameters and their relation to nasalance scores (Paper III)

Method error for the angular and linear analysis was not statistically significant, and did not exceed 1° and 1 mm (p<0.05), respectively. Intra- (α>0.7) and inter-rater (κ<0.6) reliability was sufficient. The analysis of craniofacial morphology of the CP±L group revealed a significant shortening of the hard (distance from posterior nasal spine to maxilla (PNS-A)) and the soft palate (distance from posterior nasal spine to the tip of soft palate (PNS-P)), as well the narrowing of the lower oropharyngeal airway (distance between AW5 and AW6). Descriptive statistics show that the CP±L group had a higher proportion of cases of class III skeletal malocclusion (ANB) and a more anterior positioning of the hyoid bone. We used the speech stimuli and normative nasalance scores presented in Paper I

(Lehes et al., 2018) and calculated the nasalance scores for both groups. Regression analysis of the data suggests that the shortening of the hard palate (PNS-A), anterior positioning of the hyoid bone (Hy-C3), and skeletal class III malocclusion (prognathic mandible, retrognathic maxilla (ANB) are related to higher nasalance scores (hypernasality). The flattening of the cranial base angle (Ba-S-N) resulted in higher risk for hyponasal resonance. Table 13 summarizes the results of Paper III.

Table 13. Comparison of measurements between the two groups and the correlation between nasalance scores and cephalometric parameters in the CP±L group.

Ceph. parameters	Participants	Difference in parameters (p<0.05)	Correlation between ceph.parameters and ONS (CP±L)		Correlation between ceph.parameters and NS (CP±L)		Correlation between ceph.parameters and OS (CP±L)	
			r	*p*	*r*	*p*	*r*	*p*
PNS-A (mm)	CP±L	0.03*	–0.52	0.05*	–0.45	0.08	–0.58	0.03*
	healthy							
PNS-Ba (mm)	CP±L	0.49	–0.32	0.17	–0.43	0.10	–0.19	0.29
	healthy							
Hy-C3 (mm)	CP±L	0.75	–0.64	0.02*	–0.45	0.08	–0.59	0.03*
	healthy							
SNA (º)	CP±L	0.58	–0.03	0.47	–0.04	0.45	–0.03	0.46
	healthy							
SNB (º)	CP±L	0.23	0.24	0.24	0.30	0.19	0.26	0.22
	healthy							
ANB (º)	CP±L	0.31	–0.50	0.06	–0.64	0.02*	–0.54	0.04*
	healthy							
Ba-S-N	CP±L	0.55	–0.36	0.14	–0.57	0.03*	–0.27	0.21
	healthy							
PNS-P	CP±L	0.01*	–0.38	0.13	–0.39	0.12	–0.27	0.22
	healthy							
SP-S-SP-I (mm)	CP±L	0.23	–0.10	0.38	–0.28	0.20	0.02	0.48
	healthy							
AW1-AW2 (mm)	CP±L	0.49	–0.08	0.41	0.03	0.46	0.02	0.47
	healthy							
AW3-AW4 (mm)	CP±L	0.68	0.17	0.31	0.06	0.43	0.20	0.28
	healthy							
AW5-AW6 (mm)	CP±L	0.04*	–0.04	0.45	0.06	0.43	–0.08	0.401
	healthy							

*ONS – oronasal utterances, NS – nasal utterances, OS – oral utterances

7 DISCUSSION

This is the first study that methodologically researches and describes voice and resonance disorders, as well as the related treatment outcomes, in Estonian surgically treated CP±L children. Based on the general aim, (1) we developed Estonian-specific speech stimuli for Nasometer II, (2) calculated normative nasalance scores for Estonian, (3) adjusted speech stimuli for VP assessment for Estonian, (4) investigated voice-related quality of life, (5) studied the underlying causes of laryngeal voice disorders in the CP±L group and (6) mapped the links between craniofacial morphology and resonance disorders. Estonian CP±L children exhibit significant incidence of hypernasality and laryngeal dysphonia, their voice-related quality of life is affected, and their craniofacial morphology affects the quality of their speech. We rejected the null hypothesis that speech related treatment outcomes are good or very good in Estonian surgically treated CP±L children, since the measured parameters were significantly poorer in that group compared to the group of healthy children.

7.1 Normative nasalance scores for Estonian children

The aim of the first study was to elaborate the Estonian stimuli for Nasometer II and establish normative nasalance scores. Setting the cut-off scores is crucial when applying nasalance scores in practice, especially when working with VPD patients. Based on the earlier studies by Brunnegård and van Doorn (2009) concerning Swedish speakers, and Sweeney, Sell, and O'Regan (2004) concerning Irish English ones, we developed three stimuli groups: (1) oronasal sentences, (2) oral sentences and (3) nasal sentences. This was the first study on nasalance in Estonian. Since specialized literature suggests that speech stimuli need to be at least 6 syllables long to validly assess nasalance (Watterson et al., 1999), single word repetition tasks were excluded.

Estonian-specific test material consists of nine six-syllable, ten seven-syllable and five eight-syllable sentences. The length of the sentences varies because of the need to maintain the phonetical balance of high and low vowels and high- and low-pressure consonants. In addition, the sentences had to be age appropriate for five-to-six-year-old children to repeat. The mean length of the stimuli was 6.8 syllables. The mean nasalance score for **oronasal stimuli** distinguish (p <0.05) the study group (30.4) from the CP±L group (47.1). Two sentences *Tige tikker karjub* (p=0.09) and *Ema punane mantel* (p=0.14) did not meet the criteria of set significance level. This is not surprising since the first sentence includes many high vowels while the second features five nasal phonemes. Both phenomena tend to raise the nasalance score. It is supported by earlier findings of Watterson, Hinton, and McFarlane (1996**),** who have shown that the higher the proportion of nasal sounds predicts higher nasalance scores**,** and of Kummer (2014) as well as of Lewis, Watterson, and Quint (2000) who conclude that high vowels have higher nasalance scores than low vowels. Since the internal consistency reliability

was high (α=0.93), these sentences were not excluded from the group of oronasal stimuli. In addition, these sentences are important in order to maintain phonetical balance for the whole sentence group. The mean for oral stimuli for the study group was 15.9 and for the CP±L group 37.0 (p<0.05). It may be explained by the effect that nasalance exerts on vocal loudness. Sadjadi, Ghorbani, Torabinezhad, Amiri, and Keyhani (2010) have found that nasalance decreases when vocal loudness increases. Six out of eight sentences had significantly lower nasalance scores in the study group compared to the CP±L group. Two sentences (*Kaja pugib kooki. (p*=0.08*), Tädi otsib uut potti*. (p=0.06)) did not statistically significantly distinguish healthy children from CP±L children, but there was a trend to difference. These two sentences can be classified as high-pressure consonant sentences. There are inconsistent findings regarding the impact of high-pressure consonants on nasalance scores. Karnell (1995) mentions the potential for higher scores due to nasal air emission or nasal turbulence, while others report no significant differences between high- and low-pressure consonants (Sweeney, Sell, & O'Regan, 2004). Matisoff (1975) has stated that the glottal stop is produced with a lowered velum which may not necessarily rise for the production of the following vowel. Therefore, the nasalance score may increase due to articulation errors. In our study, CP±L children's cleft-specific articulation errors were not analysed. Additionally, we may conclude that it is the complete combination of phonemes that influences the mean score (p<0.05). The absence of statistically significant difference between the two groups was an expected outcome. The reason for this is that nasal phonemes are produced with the velum lowered, allowing air to escape through the nasal cavity, which results in higher nasalance (Eek et al., 2008b). Therefore, nasal stimuli are not suitable to determine hypernasality. This finding is consistent with that of Kummer (2014) who concluded that oronasal as well as oral stimuli need to be used to assess the presence of hypernasality.

In Estonian, the mean nasalance of oronasal stimuli is 30.5, which is comparable to the scores for Swedish (Brunnegård & van Doorn, 2009), Hungarian (Hirschberg et al., 2006), Dutch (Van der Heijden et al., 2011), Flemish (van Lierde et al., 2001), Malay (Ibrahim et al., 2012) and Vietnamese (Nguyen et al., 2017). Oral stimuli had lower nasalance scores in Estonian compared to oronasal stimuli. The mean nasalance of oral stimuli was 15.9. The result supports Kummer (2014) who suggested nasalance scores below 20 for oral stimuli. As expected, the mean nasalance score is higher for nasal speech stimuli compared to oral and oronasal ones. The mean score is 57.8. The result is comparable to the findings for Swedish (Brunnegård & van Doorn, 2009) and for Australian English (van Doorn & Purcell, 1998).

One of the eligibility criteria for test material was the distinguishability between the study group and the CP±L group. The results of oronasal and oral stimuli revealed that the nasalance scores were significantly lower for the study group compared to the CP±L group. This suggests that the relevant groups of stimuli are suitable to identify the presence of resonance disorders.

When developing the test material, phonological quantity contrasts were considered. Thus, most phonemes occurred in three durations: short, long and overlong. The results warrant the conclusion that Estonian nasalance scores are comparable to those of many other languages and that phonological quantity contrast does not affect nasalance scores on the sentence level.

Although nasalance scores were higher for the girls compared to the boys in all three stimuli groups, the differences were not significant. Therefore, calculation of separate scores for boys and girls was forgone. The results reflect those of other studies who found no significant gender differences (Sweeney et al., 2004; van Doorn & Purcell, 1998).

The determination of cut-off values is essential for applying nasalance scores in clinical practice, e.g., for monitoring the improvement and dynamics of speech quality. Based on previous research, the clinical limit of abnormal nasal resonance was suggested to be +/–2 SDs from the mean scores (Van der Heijden et al., 2011; van Doorn & Purcell, 1998; van Lierde et al., 2001). Applying this to our results, the threshold for oronasal stimuli is 18.9–42.1, for oral stimuli 3.9–27.9, and for nasal stimuli 46.2–69.4. Children whose nasalance scores are higher than the above threshold could be considered hypernasal; children whose nasalance score falls below the lower cut-off value for oronasal and nasal stimuli could be considered hyponasal. A cautious interpretation of borderline scores is recommended because of individual variation and reliability issues (Whitehill, 2001).

Test-retest reliability was measured by two consecutive assessments of nasalance. The headset was removed and re-positioned on the child's head. There were high positive correlations between the first and second trials in all stimuli groups. Brunnegård and van Doorn (2009) suggest three sequential assessments of nasalance to reduce individual variation. Van der Heijden et al. (2011) argued that repetitive assessments are not age-appropriate for younger children. Since it takes approximately 15 minutes to assess nasalance for an Estonian-speaking patient, children tend to get tired in test-retest situations and their attention disperses. Based on our findings, as well as Nguyen et al.'s (2017) and Van der Heijden et al.'s (2011) suggestions, we found repetitive testing not to be of essential importance.

7.2 The effect of VPI on voice quality in Estonian cleft-palate children

Identification of voice problems is essential in clinical work with CP±L patients. Due to their complex health issues, dysphonia may go undetected, yet significantly affect their everyday communication and quality of life. During the author's second study, the author's cleft team used multi-dimensional voice programme (MDVP) to objectively analyze the acoustic parameters of voice, collected data on voice-related quality of life (pVHI), performed VNE for accurate assessment of VPD and used VLS to detect morphological changes in vocal folds.

Voice-related quality of life was assessed by submitting pVHI. pVHI is divided into three subscales – functional, physical and emotional – which aim to assess communication difficulties related to dysphonia, to voice perturbations such as hoarseness and to the psychological consequences of voice disorders (Schneider et al., 2019b). According to pVHI scores, we found that voice-related quality of life is significantly more affected in the CP±L group compared to the healthy group. Not only were the total scores higher in CP±L group, but also all three subscales indicated higher scores. The functional, emotional and physical aspects were all affected to a relatively similar degree. These results reflect those of Aydınlı et al. (2016) who also found considerable differences between the CP±L and the healthy group. Still, these results need to be interpreted with caution because, in the study, parents assessed their children's voice based exclusively on their subjective impression. Therefore, the results may be affected by resonance and articulation disorders that are difficult to distinguish from dysphonia for non-professional raters. Our explanation is similar to Boseley's and Hartnick's (2004) who suggest that pVHI does not distinguish resonance and articulation disorders from dysphonia.

MDVP parameters were calculated for acoustic analysis of voice. We found significant differences comparing the results of *Jitt, Shim* and *NHR* parameters between the healthy and the CP±L group. Jitter, shimmer and NHR were significantly higher in the CP±L group compared to the control group. The former group seems to show a higher relative standard deviation of the oscillations of fundamental frequency, higher variability of peak-to-peak amplitude between consecutive periods, higher variability in F_0 signal periodicity and higher ratio of energy of the inharmonic components. According to these parameters, CP±L children's voice appears pressed, hoarse and strained. These results support previous studies of (Aydınlı et al., 2016; Van Lierde et al., 2004; Varghese & Bhat, 2012; Villafuerte-Gonzalez et al., 2015). Jitter (frequency perturbation) showed the biggest difference between the two groups. In accordance with the results of this paper, previous studies have demonstrated that jitter is higher than the MDVP cut-off scores in children with VPI (Aydınlı et al., 2016; Zajac & Linville, 1989; Toran & Lal, 2009; Van Lierde et al., 2004). Niedzielska (2001) and Valadez et al. (2012) have suggested that jitter is related to the presence of vocal nodules. This is confirmed by our findings from video-laryngostroboscopy (VLS), which showed laryngeal pathologies and morphological changes of vocal folds in more than half of the CP±L group: two cases of bilateral vocal nodules and eight cases of inflammation of vocal folds. Although this result has not been reported previously, we conclude that vocal fold oedema affects jitter perturbation. Even if the results of the shimmer parameter were significantly different between the two groups, these did not exceed the cut-off limits stated in research reports (0.42–0.59dB) (Nicollas et al., 2008; Varghese & Bhat, 2012). Healthy children exhibited lower amplitude perturbation scores than CP±L children. These results are similar to those reported by Aydınlı et al. (2016), Varghese and Bhat (2012) and Villafuerte-Gonzalez et al. (2015). SInce we found that jitter and shimmer were significantly higher in the CP±L group, increased values of the NHR (which

is interpreted as increased spectral noise that could be due to amplitude and frequency variations (Di Nicola et al., 2006)) parameter were an expected outcome.

We did not find significant differences between SPI and VTI parameters in the two groups. This suggests that CP±L children did not have significantly more vocal fold adduction problems than healthy children. The fact that we found F_0 to be higher in the CP±L group is consistent with research reported by Aydınlı et al. (2016) and Villafuerte-Gonzalez et al. (2015) who also found higher F_0 in children with VPI compared to healthy children. These results need to be interpreted with caution given the exceptionally large standard deviation in our study group. Contrary to the expectations, we did not find any significant differences in SPI parameters (which show the adduction of vocal folds) between the CP±L and the healthy group. Even more, the SPI parameters were lower in the CP±L group compared to normal values. High SPI values have been suggested to correlate with incomplete focal fold adduction and breathy voice (Mathew & Bhat, 2009). Vocal folds in 10 out of 18 CP±L children who participated in our study presented morphological changes that affected normal adduction. Therefore, this is very intriguing finding needs to be verified in larger groups.

Furthermore, we investigated the relationship between pVHI scores and acoustic parameters to see whether the former correlates particularly strongly with a specific MDVP value. The correlation between the total score of the pVHI and the acoustic parameters of voice was generally poor. We concluded that parents were not able to distinguish dysphonia from other speech disorders (e.g., resonance disorders). Parents' answers appear to reflect their subjective feelings about the quality of their child's speech.

We did not find strong correlations between pVHI scores and the GRBAS scale values. Still, B (breathiness) tended to be significant. This suggests that parents notice the breathiness in their child's voice and consider that breathy voice has impact on the quality of life.

In addition to indirect assessments, all CP±L children were directly assessed by VNE and VLS. We did not perform VNE and VLS on healthy children for ethical considerations. Fifteen CP±L children out of 18 had some degree of VPI. Three had normal VPC but still exhibited some degree of hypernasality during their connected speech. We did not find severe VPI to cause greater voice disturbance. VLS assessment revealed normal vocal folds in eight children, while morphological changes were present in ten (60%). Changes in vocal fold function were caused by bilateral oedema (eight children out of 18) or nodules (two children out of 18). The percentage of morphological changes in our CP±L group was higher than the 32% previously reported by Van Lierde et al. (2004). Reported research shows the occurrence of vocal fold nodules to range from 15% to 35% in non-cleft children (Pannbacker, 2018). This suggests the conclusion that CP±L children on average are more susceptible to voice disorders.

7.3 Correlation between nasalance scores and cephalometric parameters in Estonian cleft-palate children

The author's third study aimed to find correlations between cephalometric parameters and resonance disorders. In order to do that, first, the author studied the cephalometric parameters to identify those that are statistically different in the two groups. The analysis showed statistically significant differences in the length of the hard (PNS-A) and soft palate (PNS-P), and in the width of the lower oropharyngeal airway (AW5-AW6). Our findings are in accordance with several previous studies (Gohilot et al., 2014; Wada et al., 1997; Wermker et al., 2012; Wu et al., 1996; Orr et al., 2016) that have highlighted the sagittal decrease of soft tissues and bone structures in cleft palate population because of the delayed and slower growth of the facial morphology complex due to early surgical interventions. In our study, we found that, in the CP±L group, the mean length of the hard palate was 3.7 mm less and of the soft palate 3.0 mm less than that of the corresponding measurements in the healthy group. However, due to small sample size, caution is suggested since the findings might not be applicable to the wider CP±L group. Another interesting and somewhat controversial finding that stood out was the increased width of the lower oropharyngeal airway in the CP±L group (its mean width was 1.9 mm larger). Here, the findings of the reported study do not support those of previous research. Nguyen (2019) and Tarawneh et al. (2019) have shown the lower oropharyngeal airway in the CP±L group to be narrower compared to that of healthy children. It is possible that our findings contradict those of earlier studies because of the small size of the study group, which may significantly affect the mean values computed for the group.

The second research question sought to determine which cephalometric parameters were most associated with hypernasal resonance in the CP±L paediatric population. In general, VPD and resonance problems – mainly hypernasality – are considered to be caused by functional and structural deviations or dynamic disturbances. Our analysis showed that hypernasal resonance is significantly related to (1) the length of the hard palate, (2) the distance between the hyoid bone and the third cervical vertebra, and (3) the angle formed by the lines NA and NB (ANB). Interestingly, the greater cranial base angle (Ba-S-N) was related to hyponasal resonance. There was no statistically significant association between cephalometric parameters and hypernasality. Several studies have suggested that resonance problems are due to the reduction – in the sagittal dimension – of the soft tissue and bone of the nasopharyngeal complex (Impieri et al., 2018; Jakhi & Karjodkar, 1990; Stellzig-Eisenhauer, 2001b; Wada et al., 1997; Wu et al., 1996). Our study supports these findings – our analysis showed that the shortening of the hard palate in the sagittal plane was significantly associated with hypernasality.

Kummer (2014) and Impieri et al. (2018) conclude that VP disturbance often results from anatomically deviant hard and soft palate measurements. This supports the need to objectively measure cephalometric parameters to determine whether VPC can be achieved at all without surgical intervention. According to

Kaduk et al. (2003) the hyoid bone is considered important for the openness of the upper respiratory tract. As noted earlier, the distance between the hyoid bone and the third cervical vertebra is related to hypernasal resonance. We found the CP±L group to present a more anterior positioning of the hyoid. This finding is consistent with studies by Kaduk et al. (2003), Nguyen (2019) and Wermker et al. (2012) who also reported that CP±L children's hyoid bone might be dislocated to a more anterior position. Kaduk et al. (2003) added that even a small change in hyoid placement may affect resonance and pronunciation. The explanation they offered is that that the anterior position of the bone may reflect a compensation mechanism to facilitate swallowing and/or compensate VPD. Laitinen et al. (2001) suggest that the anterior position of the hyoid and the position of the tongue have an impact on the development of the bite that, in turn, may affect the quality of speech. The third cephalometric parameter that was associated with hypernasal resonance was ANB. The CP±L group showed an increased ANB (3.5°) compared to controls (2.3°). While it was once commonly believed that an ANB angle of 2°±3° was normal (Holdaway, 1956), Hussels & Nanda (1984) observed that the calculated values of the angle vary widely following changes based on four ANB-controlling factors. These factors are growth pattern, teeth position, soft tissue, orthodontic treatment. Today, according to many different researches (Di Blasio et al., 2017; Emral et al., 2012; Macrì & Festa, 2022), ANB of 2 ± 2° is considered within a normal range. Our study showed the ANB angle to be in normal range in both groups. Therefore, we may assume that skeletal growth is roughly in normal range in the CP±L group. Hypernasal resonance cannot be directly related to the length of hard palate. Abnormal resonance may be partly due to soft tissue problems, e.g., the decreased length of the soft palate. Still, as stated earlier, the slightest changes in facial morphology may cause speech problems. Thus, we may assume that even where the ANB degree within normal limits but slightly on the high side, it may still affect speech quality.

Last, we found that the parameter of the cranial base angle (Ba-S-N) was related to resonance. Growth of the midface is generally impeded in CP±L patients who have undergone surgical repair. On the other hand, untreated CP±L patients exhibit unrestricted midfacial growth similar to that of healthy children (Khanna et al., 2020). In our study, Ba-S-N angle was 3° greater in CP±L group compared to healthy children. This finding was also reported by Gopinath et al. (2017). We may suggest that the significantly higher Ba-S-N angle is caused by surgical procedures that affect the anteroposterior growth and development of the maxilla in CP±L children. In contrast, several studies disagree with this finding and report no differences in the cranial base angle (X. Liu & Chen, 2018; Tinano et al., 2015). In our study, the higher Ba-S-N angle was related to the higher nasalance scores that were measured in the nasal sentences group. This means that the higher Ba-S-N angle was related to hyponasal resonance. We suggest that the posterior position of the maxilla may (over)compensate for the increased Ba-S-N angle and wider upper nasopharyngeal airway. Sales et al. (2021) also concluded in their meta-analysis that the effect of maxillary advancement on speech and VP function remains controversial in CP±L patients.

In contrast to Stellzig-Eisenhauer (2001), our study does not warrant the conclusion that increased distance from the tip of the posterior nasal spine (PNS) to the most inferior posterior point of the occipital bone at the anterior margin of the occipital foramen (Ba) was related to resonance problems. This was not an unexpected outcome because it also agrees with our earlier observations, which showed that there are no differences in PNS-Ba parameters between the two groups. In addition, our finding is supported by the work of Wu et al. (1996) who found PNS-Ba parameters not to be related to hypernasal resonance. Soft palate function and length play an important role in balancing resonance in speech. According to specialized literature, soft palate thickness does not influence resonance in contrast to soft palate length that has significant impact on resonance (Kim et al. 2001). Several authors have reported a relationship between shortened soft palate and the presence of hypernasality in speech (Impieri et al., 2018; Jakhi & Karjodkar, 1990; Stellzig-Eisenhauer, 2001b; Wu et al., 1996). In contrast to these reports, we did not find the correlation significant. Still, the the mean length of soft palate in the CP±L group was 3 mm shorter than in the control group, yet this significant difference did not show up in resonance analysis. To explain this contradictory result, we analysed every CP±L child independently. The analysis revealed that the length of the soft palate for one CP±L child was 38.1 mm (mean length 25.2 mm). Thus, it appears that one significantly different measurement considerably affected the mean result of the group, and for this reason, we cannot generalize these results to the whole group. In future studies, we should exclude data that may significantly affect mean scores. Surprisingly, there were no correlations between the width of the upper and lower nasopharyngeal or of the oropharyngeal airway and the hypernasality of speech. In 1996, Wu et al. and, in 2001, Stellzig-Eisenhauer, described the relationship between oropharyngeal and nasopharyngeal airway width. Stellzig-Eisenhauer (2001) added that even when the nasopharyngeal airway was wider, it was possible for the length and mobility of the soft palate to compensate for the deficiency and prevent hypernasality. Thus, the problem is much more complicated and complex than just the measured numbers showed. Clinicians and researches need to see a bigger picture and consider different aspects of craniofacial growth of CP±L children.

7.4 Clinical implications

In Estonia, national statistics about the prevalence and types of CP±L are not compiled and no regular monitoring of the condition takes place, which means that the data are not readily availabe. There are two different cleft centres in the country that do not share a information about their patients and their timing of surgeries, the regularity of speech therapy, orthodontic treatment, etc. To ensure a proper follow-up and recall system, a national cleft register is urgently required. In addition, it is important to establish standards of record-taking with a minimum list of required particulars and of additional, recommended ones. The minimum particulars are models, lateral cephalograms, photos, speech, audiometry, and

patient/parent satisfaction surveys (American Cleft Palate-Craniofacial Association, 2017).

Our study is the first attempt to systematically and methodologically research and describe resonance and voice disordes in the Estonian CP±L population, and to set measurable standards for treatment outcomes for Estonian-speaking patients. Firstly, determination of cut-off scores is essential for applying nasalance scores in clinical practice. Among other things, knowing the cut-off scores helps to evaluate the effectiveness of speech therapy. Not the least, the results are also important for research, e.g., for linguists who investigating cross-linguistic nasalance scores. According to Watterson et al. (2007), for clinical purposes (e.g., pre- and postoperative assessments) it is recommended to collect nasalance scores for each stimuli group at least twice. The same research project also found that, for patients with hypernasal speech, the variation in nasalance may be as high as 10 points. Second, based on the findings, laryngeal dysphonia is relevant in CP±L children and these should not be ignored. Due to a combination of different speech-related comorbidities, voice disorders may go undetected and worsen the overall speech and life quality. Therefore, the identification of voice disorders is essential in clinical practice, and SLP should include voice therapy in their everyday practice. Third, the author's last study revealed that morphological changes in the velopharyngeal and oropharyngeal region may affect speech quality. We concluded that the length of the hard and the soft palate, as well as the narrower lower oropharyngeal airway, were related to hypernasal speech. These results are of practical use to multidisciplinary CP±L teams, especially orthodontists and surgeons.

7.5 Research limitation

The principal limitation was sample size. Based on Long et al., (2011), a sample size of 30 to 40 is recommended based on a 0.05 significance level and 80% power to enable significant power for sensitive and important outcome measures. In Estonia, about 20 CP±L children are born every year. To meet this recommendation, we would have had to include 30–40 CP±L patients whose age was appropriate during the time of data collection. Despite all efforts, fewer than 20 CP±L children were found who met the inclusion criteria. First, the potential sample was significantly reduced due to the fact that one third of Estonia's population is Russian-speaking or Russian-Estonian bilingual, ruling out the inclusion of children with the corresponding linguistic background. The second factor that had an impact on sample size was the need to exclude children with articulation disorders, which may themselves affect voice and resonance. Although the sample size of our study was small, it may still be considered reliable in the Estonian context.

8 CONCLUSION AND FUTURE RESEARCH

1. Speech quality is the main treatment outcome of CP±L patients. Resonance in speech affects significantly speech intelligibility. Voice disordes frequently accompany resonance disorders. Most Estonian CP±L children exhibit both resonance and voice disorders quite expressively. The conclusion is based on our main findings in CP±L group, (1) nasalization is significantly higher compared to what is shown by healthy children, (2) laryngeal voice disorders and morphological changes of vocal folds are common, and (3) craniofacial morphology differed compared to the norms.
2. We developed Estonian-specific optimized speech stimuli and calculated normative nasalance scores. These normative scores can be used for diagnosis, evaluation of speech therapy effectiveness and follow-up treatment of patients with resonance disorders, especially patients with cleft palate.
3. Laryngeal dysphonia is frequent among CP±L children. Due to a combination of many speech-related comorbidities, voice disorders may go undetected and worsen the overall speech and life quality.
4. Changes in craniofacial morphology may have an impact on speech quality. Based on our findings, we may conclude that changes in the length of soft and hard palate, the distance between the hyoid bone and the third cervical vertebra, and the angle formed by the NA line and the NB line (ANB) are more sensitive to resonance. Therefore, speech and language therapists should work closely with orthodontists.
5. Parents' evaluation – that voice (and speech in general) significantly affects the quality of life of CP±L children – did not correlate with objective findings. This suggests that it is important to combine subjective and objective evaluation methods.
6. The severity of VPI does not directly correlate with the severity of voice disorders.

Further studies are needed to evaluate the effectiveness of speech therapy and of orthodontic and surgical intervention. Longitudinal study and large sample size are required to evaluate long-term outcomes of cleft treatment.

REFERENCES

Allori, A. C., Kelley, T., Meara, J. G., Albert, A., Bonanthaya, K., Chapman, K., Cunningham, M., Daskalogiannakis, J., de Gier, H., Heggie, A. A., Hernandez, C., Jackson, O., Jones, Y., Kangesu, L., Koudstaal, M. J., Kuchhal, R., Lohmander, A., Long, R. E., Magee, L., … Wong, K. W. (2017). A Standard Set of Outcome Measures for the Comprehensive Appraisal of Cleft Care. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *54*(5), 540–554. https://doi.org/10.1597/15-292

Allori, A. C., Mulliken, J. B., Meara, J. G., Shusterman, S., & Marcus, J. R. (2017). Classification of Cleft Lip/Palate: Then and Now. *The Cleft Palate Craniofacial Journal*, *54*(2), 175–188. https://doi.org/10.1597/14-080

Alvi, S., & Harsha, P. (2022). Flexible Nasopharyngoscopy. *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK539740/

Andreassen, M. L., Leeper, H. A., MacRae, D. L., & Nicholson, I. R. (1994). Aerodynamic, acoustic, and perceptual changes following adenoidectomy. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *31*(4), 263–270. https://doi.org/10.1597/1545-1569(1994)031<0263:AAAPCF>2.3.CO;2

Asu, E. L., & Teras, P. (2009a). Estonian. *Journal of the International Phonetic Association*, *39*(3), 367–372. https://doi.org/10.1017/S002510030999017X

Asu, E. L., & Teras, P. (2009b). Estonian. *Journal of the International Phonetic Association*, *39*(3), 367–372. https://doi.org/10.1017/S002510030999017X

Attuluri, N. (2017). Voice Perturbations in Repaired Cleft Lip and Palate. *Global Journal of Otolaryngology*, *8*(1). https://doi.org/10.19080/GJO.2017.08.555729

Aydınlı, F. E., Özcebe, E., Kulak Kayıkçı, M. E., Yılmaz, T., & Özgür, F. F. (2016). Investigating the Effects of Glottal Stop Productions on Voice in Children With Cleft Palate Using Multidimensional Voice Assessment Methods. *Journal of Voice*, *30*(6), 763.e9-763.e15. https://doi.org/10.1016/j.jvoice.2015.10.007

Belcher, R. H., Patel, S. A., Kynes, M., Carlucci, J. G., Hodson, E., Zhao, S., Lipscomb, B., & Heimburger, D. C. (2022). Demographics and trends of cleft lip and palate patients born in Tennessee from 2000 to 2017. *International Journal of Pediatric Otorhinolaryngology*, *163*, 111312. https://doi.org/10.1016/j.ijporl.2022.111312

Bender, P. L. (2000). Genetics of cleft lip and palate. *Journal of Pediatric Nursing*, *15*(4), 242–249. https://doi.org/10.1053/jpdn.2000.8148

Bettens, K., Wuyts, F., & Lierde, K. (2014). Instrumental assessment of velopharyngeal function and resonance: A review. *Journal of communication disorders*, *52*. https://doi.org/10.1016/j.jcomdis.2014.05.004

Bicknell, S., McFadden, L. R., & Curran, J. B. (2002). Frequency of pharyngoplasty after primary repair of cleft palate. *Journal (Canadian Dental Association)*, *68*(11), 688–692.

Boseley, M. E., & Hartnick, C. J. (2004). Assessing the outcome of surgery to correct velopharyngeal insufficiency with the pediatric voice outcomes survey. *International Journal of Pediatric Otorhinolaryngology*, *68*(11), 1429–1433. https://doi.org/10.1016/j.ijporl.2004.06.002

Bradford, L. J., Brooks, A. R., & Shelton, R. L. (1964). Clinical judgment of hypernasality in cleft palate children. *The Cleft Palate Journal*, *35*, 329–335.

Brunnegård, K., & van Doorn, J. (2009). Normative data on nasalance scores for Swedish as measured on the Nasometer: Influence of dialect, gender, and age. *Clinical Linguistics & Phonetics*, *23*(1), 58–69. https://doi.org/10.1080/02699200802491074

Calzolari, E., Pierini, A., Astolfi, G., Bianchi, F., Neville, A. J., & Rivieri, F. (2007). Associated anomalies in multi-malformed infants with cleft lip and palate: An epidemiologic study of nearly 6 million births in 23 EUROCAT registries. *American Journal of Medical Genetics. Part A*, *143A*(6), 528–537. https://doi.org/10.1002/ajmg.a.31447

Cler, G. J., Perkell, J. S., & Stepp, C. E. (2021). Oral configurations during vowel nasalization in English. *Speech communication*, *129*, 17–24. https://doi.org/10.1016/j.specom.2021.02.005

Counihan, D. T., & Cullinan, W. L. (1970a). Reliability and dispersion of nasality ratings. *The Cleft Palate Journal*, *7*, 261–270.

Counihan, D. T., & Cullinan, W. L. (1970b). Reliability and dispersion of nasality ratings. *The Cleft Palate Journal*, *7*, 261–270.

Croen, L. A., Shaw, G. M., Wasserman, C. R., & Tolarová, M. M. (1998). Racial and ethnic variations in the prevalence of orofacial clefts in California, 1983–1992. *American Journal of Medical Genetics*, *79*(1), 42–47. https://doi.org/10.1002/(sici)1096-8628(19980827)79:1<42::aid-ajmg11>3.0.co;2-m

D'Antonio, L. L., & Scherer, N. J. (2008). *Communication Disorders Associated with Cleft Palate*. 20.

Dejonckere, P. H. (1999). Voice problems in children: Pathogenesis and diagnosis. *International Journal of Pediatric Otorhinolaryngology*, *49*, S311–S314. https://doi.org/10.1016/S0165-5876(99)00230-X

Denegri, M. A., Silva, P. P., Pegoraro-Krook, M. I., Ozawa, T. O., Yaedu, R. Y. F., & Dutka, J. de C. R. (2021). Cephalometric predictors of hypernasality and nasal air emission. *Journal of Applied Oral Science*, *29*, e20210320. https://doi.org/10.1590/1678-7757-2021-0320

Derakhshandeh, F., Nikmaram, M., Hosseinabad, H. H., Memarzadeh, M., Taheri, M., Omrani, M., Jalaie, S., Bijankhan, M., & Sell, D. (2016). Speech characteristics after articulation therapy in children with cleft palate and velopharyngeal dysfunction—A single case experimental design. *International Journal of Pediatric Otorhinolaryngology*, *86*, 104–113. https://doi.org/10.1016/j.ijporl.2016.04.025

Devadas, U., Dhanya, M., & Gunjawate, D. (2015). Adaptation and validation of the Malayalam pediatric voice handicap index. *International Journal of Pediatric Otorhinolaryngology*, *79*(9), 1425–1428. https://doi.org/10.1016/j.ijporl.2015.06.018

Di Nicola, V., Fiorella, M., Spinelli, D., & Fiorella, R. (2006). Acoustic analysis of voice in patients treated by reconstructive subtotal laryngectomy. Evaluation and critical review. *Acta Otorhinolaryngologica Italica*, *26*(2), 59–68.

Dubey, A. K., Prasanna, S. R. M., & Dandapat, S. (2019). Detection and assessment of hypernasality in repaired cleft palate speech using vocal tract and residual features. *The Journal of the Acoustical Society of America*, *146*(6), 4211–4223. https://doi.org/10.1121/1.5134433

Eek, A., Teras, P., & Gornischeff, A. (2008a). *Eesti keele foneetika. I*. Tallinna Tehnikaülikooli Kirjastus.

Eek, A., Teras, P., & Gornischeff, A. (2008b). *Eesti keele foneetika. I*. Tallinna Tehnikaülikooli Kirjastus.

Fairbanks, G. (1960). *Voice and Articulation Drillbook* (2nd edition). Harper & Row.

Fletcher, S. G. (1972). Contingencies for Bioelectronic Modification of Nasality. *Journal of Speech and Hearing Disorders*, *37*(3), 329–346. https://doi.org/10.1044/jshd.3703.329

Fletcher, S. G. (1978). *Diagnosing speech disorders from cleft palate*. Grune and Stratton.

Fletcher, S. G., & Higgins, J. M. (1980). Performance of Children with Severe to Profound Auditory Impairment in Instrumentally Guided Reduction of Nasal Resonance. *Journal of Speech and Hearing Disorders*, *45*(2), 181–194. https://doi.org/10.1044/jshd.4502.181

Fujiki, R. B., & Thibeault, S. L. (2022). Are Children with Cleft Palate at Increased Risk for Laryngeal Pathology? *The Cleft Palate Craniofacial Journal*, 1055665622 1104028. https://doi.org/10.1177/10556656221104027

Godino-Llorente, J. I., Osma-Ruiz, V., Sáenz-Lechón, N., Cobeta-Marco, I., González-Herranz, R., & Ramírez-Calvo, C. (2008). Acoustic analysis of voice using WPCVox: A comparative study with Multi Dimensional Voice Program. *European Archives of Oto-Rhino-Laryngology: Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): Affiliated with the German Society for Oto-Rhino-Laryngology – Head and Neck Surgery*, *265*(4), 465–476. https://doi.org/10.1007/s00405-007-0467-x

Gohilot, A., Pradhan, T., & Keluskar, K. M. (2014). Cephalometric evaluation of adenoids, upper airway, maxilla, velum length, need ratio for determining velopharyngeal incompetency in subjects with unilateral cleft lip and palate. *Journal of the Indian Society of Pedodontics and Preventive Dentistry*, *32*(4), 297–303. https://doi.org/10.4103/0970-4388.140950

Golding-Kushner, K., Argamaso, R., Cotton, R., Grames, L., Henningsson, G., Jones, D. L., Karnell, M., Klaiman, P., Lewin, M., & Marsh, J. (1990). Standardization for the reporting of nasopharyngoscopy and multiview videofluoroscopy: A report from an International Working Group. *The Cleft Palate Journal*. https://www.semanticscholar.org/paper/Standardization-for-the-reporting-of-and-multiview-Golding-Kushner-Argamaso/ab03121884ee75ef69d68a5ee6f991986900e8b3

Gopinath, V. K., Samsudin, A. R., Noor, S. N. F. M., & Sharab, H. Y. M. (2017). Facial profile and maxillary arch dimensions in unilateral cleft lip and palate children in the mixed dentition stage. *European Journal of Dentistry*, *11*(1), 76–82. https://doi.org/10.4103/ejd.ejd_238_16

Haapanen, M. L. (1991). Nasalance scores in normal Finnish speech. *Folia Phoniatrica*, *43*(4), 197–203.

Hammarström, I. L., Nyberg, J., Alaluusua, S., Rautio, J., Neovius, E., Berggren, A., Persson, C., Willadsen, E., & Lohmander, A. (2020). Scandcleft Project Trial 2—Comparison of Speech Outcome in 1- and 2-Stage Palatal Closure in 5-Year-Olds With UCLP. *The Cleft Palate-Craniofacial Journal*, *57*(4), 458–469. https://doi.org/10.1177/1055665619888316

Hamming, K. K., Finkelstein, M., & Sidman, J. D. (2009). Hoarseness in children with cleft palate. *Otolaryngology--Head and Neck Surgery: Official Journal of American Academy of Otolaryngology-Head and Neck Surgery*, *140*(6), 902–906. https://doi.org/10.1016/j.otohns.2009.01.036

Hanley, L., Ballard, K. J., Dickson, A., & Purcell, A. (2023). Speech Intervention for Children With Cleft Palate Using Principles of Motor Learning. *American Journal of Speech-Language Pathology*, *32*(1), 169–189. https://doi.org/10.1044/2022_AJSLP-22-00007

Harding-Bell, A., & Grunwell, P. (1996). Characteristics of cleft palate speech. *European journal of disorders of communication : the journal of the College of Speech and Language Therapists, London*, *31*, 331–357. https://doi.org/10.3109/13682829609031326

Hardin-Jones, M. A., & Jones, D. L. (2005). Speech Production of Preschoolers with Cleft Palate. *The Cleft Palate Craniofacial Journal*, *42*(1), 7–13. https://doi.org/10.1597/03-134.1

Henningsson, G., Kuehn, D. P., Sell, D., Sweeney, T., Trost-Cardamone, J. E., Whitehill, T. L., & Speech Parameters Group. (2008). Universal parameters for reporting speech outcomes in individuals with cleft palate. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *45*(1), 1–17. https://doi.org/10.1597/06-086.1

Hirschberg, J., Bók, S., Juhász, M., Trenovszki, Z., Votisky, P., & Hirschberg, A. (2006). Adaptation of nasometry to Hungarian language and experiences with its clinical application. *International Journal of Pediatric Otorhinolaryngology*, *70*(5), 785–798. https://doi.org/10.1016/j.ijporl.2005.09.017

Hocevar-Boltezar, I., Jarc, A., & Kozelj, V. (2006). Ear, nose and voice problems in children with orofacial clefts. *The Journal of Laryngology and Otology*, *120*(4), 276–281. https://doi.org/10.1017/S0022215106000454

Holdaway, R. A. (1956). Changes in relationship of points A and B during orthodontic treatment. *American Journal of Orthodontics*, *42*(3), 176–193. https://doi.org/10.1016/0002-9416(56)90112-9

Hussels, W., & Nanda, R. S. (1984). Analysis of factors affecting angle ANB. *American Journal of Orthodontics*, *85*(5), 411–423. https://doi.org/10.1016/0002-9416(84)90162-3

Härtel, J., Gundlach, K. K. H., & Ruickoldt, K. (1994). Incidence of velopharyngoplasty following various techniques of palatoplasty. *Journal of Cranio-Maxillofacial Surgery*, *22*(5), 272–275. https://doi.org/10.1016/S1010-5182(05)80075-7

Ibrahim, H. M., Reilly, S., & Kilpatrick, N. (2012). Normative nasalance scores for the Malay language. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *49*(5), e61–63. https://doi.org/10.1597/11-001

Impieri, D., Tønseth, K. A., Hide, Ø., Brinck, E. L., Høgevold, H. E., & Filip, C. (2018). Impact of orthognathic surgery on velopharyngeal function by evaluating speech and cephalometric radiographs. *Journal of Plastic, Reconstructive & Aesthetic Surgery: JPRAS*, *71*(12), 1786–1795. https://doi.org/10.1016/j.bjps.2018.07.018

Inchingolo, A. M., Fatone, M., Malcangi, G., Avantario, P., Piras, F., Patano, A., Pede, C., Netti, A., Ciocia, A., Ruvo, E., Viapiano, F., Palmieri, G., Campanelli, M., Mancini, A., Settanni, V., Carpentiere, V., Marinelli, G., Latini, G., Rapone, B., & Dipalma, G. (2022). Modifiable Risk Factors of Non-Syndromic Orofacial Clefts: A Systematic Review. *Children*, *9*, 1846. https://doi.org/10.3390/children9121846

IPDTOC Working Group. (2011). Prevalence at birth of cleft lip with or without cleft palate: Data from the International Perinatal Database of Typical Oral Clefts (IPDTOC). *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *48*(1), 66–81. https://doi.org/10.1597/09-217

Ird, K., & Suvi, T. (2013). *Huule- ja/või suulaelõhega laste kõnekvaliteedi hindamine* [Thesis, Tartu Ülikool]. https://dspace.ut.ee/handle/10062/31844

Jagomägi, T. (2012). *A study of the genetic etiology of nonsyndromic cleft lip and palate.*

Jakhi, S. A., & Karjodkar, F. R. (1990). Use of cephalometry in diagnosing resonance disorders. *American Journal of Orthodontics and Dentofacial Orthopedics*, *98*(4), 323–332. https://doi.org/10.1016/S0889-5406(05)81489-1

Jones, C. E., Chapman, K. L., & Hardin-Jones, M. A. (2003). Speech development of children with cleft palate before and after palatal surgery. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *40*(1), 19–31. https://doi.org/10.1597/1545-1569_2003_040_0019_sdocwc_2.0.co_2

Kaduk, W. M. H., Grabowski, R., & Gundlach, K. K. H. (2003). Position of the hyoid bone in cleft lip, alveolus, and palate: Variation of normal anatomy or sign accompanying the malformation? *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *40*(1), 1–5. https://doi.org/10.1597/1545-1569_2003_040_0001_pothbi_2.0.co_2

Karlep, K. (1998). *Psühholingvistika ja emakeeleõpetus: [Õpik]*. Tartu : Tartu Ülikooli Kirjastus. http://dspace.ut.ee/handle/10062/51214

Kelly, S. N., & Shearer, J. (2020). Appearance and Speech Satisfaction and Their Associations With Psychosocial Difficulties Among Young People With Cleft Lip and/or Palate. *The Cleft Palate-Craniofacial Journal*, *57*(8), 1008–1017. https://doi.org/10.1177/1055665620926083

Kelly, S., & Shearer, J. (2020). Appearance and Speech Satisfaction and Their Associations With Psychosocial Difficulties Among Young People With Cleft Lip and/or Palate. *The Cleft Palate-Craniofacial Journal*, *57*, 105566562092608. https://doi.org/10.1177/1055665620926083

Keuning, K. H., Wieneke, G. H., & Dejonckere, P. H. (1999). The intrajudge reliability of the perceptual rating of cleft palate speech before and after pharyngeal flap surgery: The effect of judges and speech samples. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *36*(4), 328–333. https://doi.org/10.1597/1545-1569_1999_036_0328_tirotp_2.3.co_2

Khan, M., Ullah, H., Naz, S., Iqbal, T., Ullah, T., Tahir, M., & Ullah, O. (2013). A revised classification of the cleft lip and palate. *The Canadian Journal of Plastic Surgery*, *21*(1), 48–50.

Khanna, R., Tikku, T., Verma, S., Verma, G., & Dwivedi, S. (2020). Comparison of maxillofacial growth characteristics in patients with and without cleft lip and palate. *Journal of Cleft Lip Palate and Craniofacial Anomalies*, *7*, 30. https://doi.org/10.4103/jclpca.jclpca_22_19

Klintö, K., Eriksson, M., Abdiu, A., Brunnegård, K., Cajander, J., Hagberg, E., Hakelius, M., Havstam, C., Mark, H., Okhiria, Å., Peterson, P., Svensson, K., & Becker, M. (2022). Inter-centre comparison of data on surgery and speech outcomes at 5 years of age based on the Swedish quality registry for patients born with cleft palate with or without cleft lip. *BMC Pediatrics*, *22*(1), 303. https://doi.org/10.1186/s12887-022-03367-2

Kobayashi, Y., Kanamori, D., Fujii, N., Kataoka, Y., Hirai, E., Yoshioka, S., Satoh, K., Toyama, H., Naito, K., & Matsuo, K. (2019). Velopharyngeal closure analysis using four-dimensional computed tomography: A pilot study of healthy volunteers and adult patients with cleft palate. *BMC Medical Imaging*, *19*, 54. https://doi.org/10.1186/s12880-019-0350-4

Kuehn, D. P., & Henne, L. J. (2003). Speech evaluation and treatment for patients with cleft palate. *American Journal of Speech-Language Pathology*, *12*(1), 103–109. https://doi.org/10.1044/1058-0360(2003/056)

Kumar, S., & Babu, M. R. (2015). *Short Term Phonatory Stability Analysis in the Voice of Children With Cleft Lip And Palate*. 3.

Kummer, A. (2014). Speech Evaluation for Patients with Cleft Palate. *Clinics in plastic surgery*, *41*, 241–251. https://doi.org/10.1016/j.cps.2013.12.004

Kummer, A. W. (2013). *Cleft Palate & Craniofacial Anomalies: Effects on Speech and Resonance* (3rd edition). Delmar Cengage Learning.

Kummer, A. W. (2014a). *Cleft palate and craniofacial anomalies: Effects on speech and resonance* (Third edition). Delmar, Cengage Learning.

Kummer, A. W. (2014b). Speech and Resonance Disorders Related to Cleft Palate and Velopharyngeal Dysfunction: A Guide to Evaluation and Treatment. *Perspectives on School-Based Issues*, *15*(2), 57. edb.

Kummer, A. W. (2014c). Speech and Resonance Disorders Related to Cleft Palate and Velopharyngeal Dysfunction: A Guide to Evaluation and Treatment. *Perspectives on School-Based Issues*, *15*(2), 57. edb.

Laitinen, J., Hurmerinta, K., Ranta, R., Sarmas, R., & Haapanen, M. L. (2001). Comparisons of speech aerodynamics and lateral craniofacial cephalometrics in cleft lip and palate patients with and without Finnish /r/-sound distortion. *Folia Phoniatrica et Logopaedica: Official Organ of the International Association of Logopedics and Phoniatrics (IALP)*, *53*(2), 85–92. https://doi.org/10.1159/000052658

Leder, S. B., & Lerman, J. W. (1985). Some acoustic evidence for vocal abuse in adult speakers with repaired cleft palate. *The Laryngoscope*, *95*(7 Pt 1), 837–840.

Lehes, L., Horn, R., Lippus, P., Padrik, M., Kasenõmm, P., & Jagomägi, T. (2018). Normative nasalance scores for Estonian children. *Clinical Linguistics & Phonetics*, *32*(11), 1054–1066. https://doi.org/10.1080/02699206.2018.1495767

Lehes, L., Numa, J., Sõber, L., Padrik, M., Kasenõmm, P., & Jagomägi, T. (2021). The effect of velopharyngeal insufficiency on voice quality in Estonian Children with Cleft Palate. *Clinical Linguistics & Phonetics*, *35*(5), 393–404. https://doi.org/10.1080/02699206.2020.1780323

Lehiste, I. (2011). Prosodic change in progress: From quantity language to accent language. *Prosodic change in progress: From quantity language to accent language* (lk 47–66). De Gruyter Mouton. https://doi.org/10.1515/9783110894530.47

Leslie, E. J., Carlson, J. C., Shaffer, J. R., Feingold, E., Wehby, G., Laurie, C. A., Jain, D., Laurie, C. C., Doheny, K. F., McHenry, T., Resick, J., Sanchez, C., Jacobs, J., Emanuele, B., Vieira, A. R., Neiswanger, K., Lidral, A. C., Valencia-Ramirez, L. C., Lopez-Palacio, A. M., … Marazita, M. L. (2016). A multi-ethnic genome-wide association study identifies novel loci for non-syndromic cleft lip with or without cleft palate on 2p24.2, 17q23 and 19q13. *Human Molecular Genetics*, *25*(13), 2862–2872. https://doi.org/10.1093/hmg/ddw104

Lewis, K. E., Watterson, T. L., & Houghton, S. M. (2003). The influence of listener experience and academic training on ratings of nasality. *Journal of Communication Disorders*, *36*(1), 49–58.

Lewis, K. E., Watterson, T., & Quint, T. (2000). The effect of vowels on nasalance scores. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *37*(6), 584–589. https://doi.org/10.1597/1545-1569(2000)037<0584:TEOVON>2.0.CO;2

Lippus, P., Asu, E. L., Teras, P., & Tuisk, T. (2013a). Quantity-related variation of duration, pitch and vowel quality in spontaneous Estonian. *Journal of Phonetics*, *41*(1), 17–28. https://doi.org/10.1016/j.wocn.2012.09.005

Lippus, P., Asu, E. L., Teras, P., & Tuisk, T. (2013b). Quantity-related variation of duration, pitch and vowel quality in spontaneous Estonian. *Journal of Phonetics*, *41*(1), 17–28. https://doi.org/10.1016/j.wocn.2012.09.005

Liu, X., & Chen, Z. (2018). Effects of Palate Repair on Cranial Base and Maxillary Morphology in Patients With Unilateral Complete Cleft Lip and Palate. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *55*(10), 1367–1374. https://doi.org/10.1177/1055665618768544

Liu, Y., Lee, S. A. S., & Chen, W. (2022). The Correlation Between Perceptual Ratings and Nasalance Scores in Resonance Disorders: A Systematic Review. *Journal of Speech, Language, and Hearing Research: JSLHR*, *65*(6), 2215–2234. https://doi.org/10.1044/2022_JSLHR-21-00588

Long, R. E., Hathaway, R., Daskalogiannakis, J., Mercado, A., Russell, K., Cohen, M., Semb, G., & Shaw, W. (2011). The Americleft study: An inter-center study of treatment outcomes for patients with unilateral cleft lip and palate part 1. Principles and study design. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *48*(3), 239–243. https://doi.org/10.1597/09-180.1

Manojlovic, Z., Auslander, A., Jin, Y., Schmidt, R. J., Xu, Y., Chang, S., Song, R., Ingles, S. A., Nunes, A., Vavra, K. C., Feigelson, D., Rakotoarison, S., DiBona, M., Magee, K., Smile, O., Ramamonjisoa, A., & Magee III, W. (2023). Genome Analysis Using Whole-Exome Sequencing of Non-Syndromic Cleft Lip and/or Palate from Malagasy Trios Identifies Variants Associated with Cilium-Related Pathways and Asian Genetic Ancestry. *Genes*, *14*(3), 3. https://doi.org/10.3390/genes14030665

Martinelli, M., Palmieri, A., Carinci, F., & Scapoli, L. (2020). Non-syndromic Cleft Palate: An Overview on Human Genetic and Environmental Risk Factors. *Frontiers in Cell and Developmental Biology*, *8*. https://www.frontiersin.org/articles/10.3389/fcell.2020.592271

Mathew, M. M., & Bhat, J. S. (2009). Soft phonation index—A sensitive parameter? *Indian Journal of Otolaryngology and Head & Neck Surgery*, *61*(2), 127–130. https://doi.org/10.1007/s12070-009-0050-4

Matisoff, J. A. (1975). Rhinoglottophilia: The Mysterious Connection between Nasality and Glottality. *Nasàlfest* (lk 265–288). Language Universals Project, Department of Linguistics, Stanford University.

McWilliams, B. J., Lavorato, A. S., & Bluestone, C. D. (1973). Vocal cord abnormalities in children with velopharyngeal valving problems. *The Laryngoscope*, *83*(11), 1745–1753.

Mehta, D. D., & Hillman, R. E. (2008). Voice assessment: Updates on perceptual, acoustic, aerodynamic, and endoscopic imaging methods. *Current opinion in otolaryngology & head and neck surgery*, *16*(3), 211–215. https://doi.org/10.1097/MOO.0b013e3282fe96ce

Mohd Ibrahim, H., Lim, H. W., Ahmad Rusli, Y., & Lim, C. T. (2020). Speech stimuli and nasalance scores for the assessment of resonance in in Mandarin speaking Malaysian children. *Clinical Linguistics & Phonetics*, *34*(6), 554–565. https://doi.org/10.1080/02699206.2019.1668480

Mossey, P. A., Little, J., Munger, R. G., Dixon, M. J., & Shaw, W. C. (2009). Cleft lip and palate. *Lancet (London, England)*, *374*(9703), 1773–1785. https://doi.org/10.1016/S0140-6736(09)60695-4

Naqvi, Z. A., Shivalinga, B., Ravi, S., & Munawwar, S. S. (2015). Effect of cleft lip palate repair on craniofacial growth. *Journal of Orthodontic Science*, *4*(3), 59–64. https://doi.org/10.4103/2278-0203.160236

Nguyen, V. T. (2019). *The first study of the treatment outcomes of patients with cleft lip and palate in Central Vietnam* [Thesis]. https://dspace.ut.ee/handle/10062/64820

Nguyen, V. T., Lehes, L., Truong, T. T. H., Hoang, T. V. A., & Jagomägi, T. (2017). Normative nasalance scores for Vietnamese-speaking children. *Logopedics, Phoniatrics, Vocology*, 1–7. https://doi.org/10.1080/14015439.2017.1389985

Nicollas, R., Garrel, R., Ouaknine, M., Giovanni, A., Nazarian, B., & Triglia, J.-M. (2008). Normal voice in children between 6 and 12 years of age: Database and nonlinear analysis. *Journal of Voice: Official Journal of the Voice Foundation*, *22*(6), 671–675. https://doi.org/10.1016/j.jvoice.2007.01.009

Niedzielska, G. (2001). Acoustic analysis in the diagnosis of voice disorders in children. *International Journal of Pediatric Otorhinolaryngology*, *57*(3), 189–193. https://doi.org/10.1016/s0165-5876(00)00411-0

Nikhila, K. G. (2017). A Study on Patterns of Compensatory Articulation Errors with Reference to Age of Surgery in Children with Repaired Cleft Lip and Palate. *Global Journal of Otolaryngology*, *7*(2). https://doi.org/10.19080/GJO.2017.07.555706

Oddon, P. A., Boucekine, M., Boyer, L., Triglia, J. M., & Nicollas, R. (2018). Health-related quality of life in children with dysphonia and validation of the French Pediatric Voice Handicap Index. *International Journal of Pediatric Otorhinolaryngology*, *104*, 205–209. https://doi.org/10.1016/j.ijporl.2017.09.026

Omidkhoda, M., Heravi, F., Shahrestani, F., & Noori, M. (2022). The Accuracy of Dolphin Software in Predicting Soft Tissue Changes after Orthognathic Surgery. *Iranian Journal of Orthodontics*, *17*(2), 1–9. https://doi.org/10.22034/ijo.2022.553491.1065

Omori, K. (2011). *Diagnosis of Voice Disorders*. *54*(4), 6.

Orr, D. J. A., Teeling, E. C., Puechmaille, S. J., & Finarelli, J. A. (2016). Patterns of orofacial clefting in the facial morphology of bats: A possible naturally occurring model of cleft palate. *Journal of Anatomy*, *229*(5), 657–672. https://doi.org/10.1111/joa.12510

Padrik, M., Hallap, M., Aid, M., Mäll, R., Helekivi, T., Aavik-Vadi, V., Tartu Ülikool, & Eesti Logopeedide Ühing (Toim). (2013). *5–6-aastaste laste kõne test*. Studium.

Paniagua, L. M., Signorini, A. V., Costa, S. S. da, Collares, M. V. M., & Dornelles, S. (2013). Velopharyngeal dysfunction: A systematic review of major instrumental and auditory-perceptual assessments. *International Archives of Otorhinolaryngology*, *17*(3), 251–256. https://doi.org/10.7162/S1809-97772013000300004

Pannbacker, M. (2018). Treatment of Vocal Nodules. *American Journal of Speech-Language Pathology*. https://pubs.asha.org/doi/pdf/10.1044/1058-0360.0803.209

Park, S. S., Kwon, T.-K., Choi, S. H., Lee, W. Y., Hong, Y. H., Jeong, N. G., Sung, M. W., & Kim, K. H. (2013). Reliability and validity of the Korean version of Pediatric Voice Handicap Index: In school age children. *International Journal of Pediatric Otorhinolaryngology*, *77*(1), 107–112. https://doi.org/10.1016/j.ijporl.2012.10.006

Pasini, M., Cagidiaco, I., Fambrini, E., Miceli, M., & Carli, E. (2022). Life Quality of Children Affected by Cleft Lip Palate and Alveolus (CLPA). *Children*, *9*(5), 757. https://doi.org/10.3390/children9050757

Persson, C., Lohmander, A., & Elander, A. (2006). Speech in children with an isolated cleft palate: A longitudinal perspective. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *43*(3), 295–309. https://doi.org/10.1597/04-071.1

Phalke, N., & Goldman, J. J. (2022). Cleft Palate. *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK563128/

Power, G., Breckon, J., Sherriff, M., & McDonald, F. (2005). Dolphin Imaging Software: An analysis of the accuracy of cephalometric digitization and orthognathic prediction. *International Journal of Oral and Maxillofacial Surgery*, *34*(6), 619–626. https://doi.org/10.1016/j.ijom.2005.04.003

Riski, J. E. (2006). Speech, Language, and Velopharyngeal Dysfunction: Management Throughout the Life of an Individual with Cleft Palate. S. Berkowitz (Toim), *Cleft Lip and Palate* (lk 705–718). Springer. https://doi.org/10.1007/3-540-30020-1_46

Robison, J. G., & Otteson, T. D. (2011). Prevalence of Hoarseness in the Cleft Palate Population. *Archives of Otolaryngology–Head & Neck Surgery*, *137*(1), 74–77. https://doi.org/10.1001/archoto.2010.225

Sadjadi, V., Ghorbani, A., Torabinezhad, F., Amiri, Y., & Keyhani, M. R. (2010). The Effect of Vocal Loudness on Nasalance of Vowels in Persian Adults. *Iranian Rehabilitation Journal*, *8*(2), 31–35.

Salari, N., Darvishi, N., Heydari, M., Bokaee, S., Darvishi, F., & Mohammadi, M. (2022). Global prevalence of cleft palate, cleft lip and cleft palate and lip: A comprehensive systematic review and meta-analysis. *Journal of Stomatology, Oral and Maxillofacial Surgery*, *123*(2), 110–120. https://doi.org/10.1016/j.jormas.2021.05.008

Sales, P. H. H., Costa, F. W. G., Cetira Filho, E. L., Silva, P. G. B., Albuquerque, A. F. M., & Leão, J. C. (2021). Effect of maxillary advancement on speech and velopharyngeal function of patients with cleft palate: Systematic Review and Meta-Analysis. *International Journal of Oral and Maxillofacial Surgery*, *50*(1), 64–74. https://doi.org/10.1016/j.ijom.2020.07.030

Sanz, L., Bau, P., Arribas, I., & Rivera, T. (2015). Adaptation and validation of Spanish version of the pediatric Voice Handicap Index (P-VHI). *International Journal of Pediatric Otorhinolaryngology*, *79*(9), 1439–1443. https://doi.org/10.1016/j.ijporl.2015.06.021

Scarmagnani, R. H., Oliveira, A. C. de A. S. F. de, Fukushiro, A. P., Salgado, M. H., Trindade, I. E. K., & Yamashita, R. P. (2014). Impact of inter-judge agreement on perceptual judgment of nasality. *CoDAS*, *26*(5), 357–359.

Schneider, K., Mehlum, C. S., Grønhøj, C., Kjærgaard, T., Møller, C. L., von Buchwald, C., & Hjuler, T. (2019a). Reliability and validity of The Danish pediatric voice handicap index. *International Journal of Pediatric Otorhinolaryngology*, *125*, 11–14. https://doi.org/10.1016/j.ijporl.2019.06.020

Schneider, K., Mehlum, C. S., Grønhøj, C., Kjærgaard, T., Møller, C. L., von Buchwald, C., & Hjuler, T. (2019b). Reliability and validity of The Danish pediatric voice handicap index. *International Journal of Pediatric Otorhinolaryngology*, *125*, 11–14. https://doi.org/10.1016/j.ijporl.2019.06.020

Schultes, G., Gaggl, A., & Kärcher, H. (2000). A comparison of growth impairment and orthodontic results in adult patients with clefts of palate and unilateral clefts of lip, palate and alveolus. *The British Journal of Oral & Maxillofacial Surgery*, *38*(1), 26–32. https://doi.org/10.1054/bjom.1999.0132

Seaver, E. J., Dalston, R. M., Leeper, H. A., & Adams, L. E. (1991). A study of nasometric values for normal nasal resonance. *Journal of Speech and Hearing Research*, *34*(4), 715–721.

Segura-Hernández, M., Valadez-Jiménez, V. M., Ysunza, P. A., Sánchez-Valerio, A. P., Arch-Tirado, E., Lino-González, A. L., & Hernández-López, X. (2019). Acoustic analysis of voice in children with cleft lip and palate following vocal rehabilitation.

Preliminary report. *International Journal of Pediatric Otorhinolaryngology*, *126*, 109618. https://doi.org/10.1016/j.ijporl.2019.109618

Sell, D. (2005). Issues in perceptual speech analysis in cleft palate and related disorders: A review. *International Journal of Language & Communication Disorders*, *40*(2), 103–121.

Sell, D., Grunwell, P., Mildinhall, S., Murphy, T., Cornish, T. A., Bearn, D., Shaw, W. C., Murray, J. J., Williams, A. C., & Sandy, J. R. (2001). Cleft lip and palate care in the United Kingdom--the Clinical Standards Advisory Group (CSAG) Study. Part 3: Speech outcomes. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *38*(1), 30–37. https://doi.org/10.1597/1545-1569_2001_038_0030_clapci_2.0.co_2

Shaw, W. C., Semb, G., Nelson, P., Brattström, V., Mølsted, K., Prahl-Andersen, B., & Gundlach, K. K. (2001). The Eurocleft project 1996–2000: Overview. *Journal of Cranio-Maxillo-Facial Surgery: Official Publication of the European Association for Cranio-Maxillo-Facial Surgery*, *29*(3), 131–140; discussion 141–142. https://doi.org/10.1054/jcms.2001.0217

Shaw, W., Semb, G., Nelson, P., Brattström, V., Mølsted, K., Prahl-Andersen, B., & Gundlach, K. (2001). The Eurocleft Project 1996–2000: Overview. *Journal of maxillofacial surgery*, *29*, 131–140. https://doi.org/10.1054/jcms.2001.0217

Shoeib, R. M., Malki, K. H., Mesallam, T. A., Farahat, M., & Shehata, Y. A. (2012). Development and validation of the Arabic pediatric voice handicap index. *International Journal of Pediatric Otorhinolaryngology*, *76*(9), 1297–1303. https://doi.org/10.1016/j.ijporl.2012.05.023

Stanier, P., & Moore, G. E. (2004). Genetics of cleft lip and palate: Syndromic genes contribute to the incidence of non-syndromic clefts. *Human Molecular Genetics*, *13 Spec No 1*, R73-81. https://doi.org/10.1093/hmg/ddh052

Stellzig-Eisenhauer, A. (2001a). The influence of cephalometric parameters on resonance of speech in cleft lip and palate patients. An interdisciplinary study. *Journal of Orofacial Orthopedics = Fortschritte Der Kieferorthopadie: Organ/Official Journal Deutsche Gesellschaft Fur Kieferorthopadie*, *62*(3), 202–223. https://doi.org/10.1007/pl00001929

Stellzig-Eisenhauer, A. (2001b). The influence of cephalometric parameters on resonance of speech in cleft lip and palate patients. An interdisciplinary study. *Journal of Orofacial Orthopedics = Fortschritte Der Kieferorthopadie: Organ/Official Journal Deutsche Gesellschaft Fur Kieferorthopadie*, *62*(3), 202–223. https://doi.org/10.1007/pl00001929

Sullivan, S. R., Vasudavan, S., Marrinan, E. M., & Mulliken, J. B. (2011). Submucous cleft palate and velopharyngeal insufficiency: Comparison of speech outcomes using three operative techniques by one surgeon. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *48*(5), 561–570. https://doi.org/10.1597/09-127

Sundström, E., & Oren, L. (2019). Sound production mechanisms of audible nasal emission during the sibilant /s/. *The Journal of the Acoustical Society of America*, *146*(6), 4199–4210. https://doi.org/10.1121/1.5135566

Sweeney, T., & Sell, D. (2008). Relationship between perceptual ratings of nasality and nasometry in children/adolescents with cleft palate and/or velopharyngeal dysfunction. *International Journal of Language & Communication Disorders*, *43*(3), 265–282. https://doi.org/10.1080/13682820701438177

Sweeney, T., Sell, D., & O'Regan, M. (2004). Nasalance scores for normal-speaking Irish children. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *41*(2), 168–174. https://doi.org/10.1597/02-094

Šimkienė, R., Šiupšinskienė, N., Purlys, P., Žvirblis, T., & Lesinskas, E. (2022). Adaptation and Validation of the Lithuanian Version of the Pediatric Voice Handicap Index. *Journal of Voice*. https://doi.org/10.1016/j.jvoice.2022.02.012

Zajac, D. J., & Linville, R. N. (1989). Voice perturbations of children with perceived nasality and hoarseness. *The Cleft Palate Journal*, *26*(3), 226–231; discussion 231–232.

Zraick, R. I., Liss, J. M., Dorman, M. F., Case, J. L., LaPointe, L. L., & Beals, S. P. (2000). Multidimensional scaling of nasal voice quality. *Journal of Speech, Language, and Hearing Research: JSLHR*, *43*(4), 989–996. https://doi.org/10.1044/jslhr.4304.989

Zur, K. B., Cotton, S., Kelchner, L., Baker, S., Weinrich, B., & Lee, L. (2007). Pediatric Voice Handicap Index (pVHI): A new tool for evaluating pediatric dysphonia. *International Journal of Pediatric Otorhinolaryngology*, *71*(1), 77–82. https://doi.org/10.1016/j.ijporl.2006.09.004

Tarawneh, A., Ali, A. A., & Alazm, K. F. (2019). *Evaluation of Pharyngeal Airway Dimensions in a Sample of Jordanian Preadolescent Cleft Lip and Palate Patients before Orthognathic Surgery*. https://www.semanticscholar.org/paper/Evaluation-of-Pharyngeal-Airway-Dimensions-in-a-of-Tarawneh-Ali/d1267193dd3e0dcf113d1264e34cdcac10532cf3

Timmons, M. J., Wyatt, R. A., & Murphy, T. (2001). Speech after repair of isolated cleft palate and cleft lip and palate. *British Journal of Plastic Surgery*, *54*(5), 377–384. https://doi.org/10.1054/bjps.2000.3599

Tinano, M. M., Martins, M. A. T. S., Bendo, C. B., & Mazzieiro, Ê. (2015). Base of the skull morphology and Class III malocclusion in patients with unilateral cleft lip and palate. *Dental Press Journal of Orthodontics*, *20*(1), 79–84. https://doi.org/10.1590/2176-9451.20.1.079-084.oar

Toran, K. C., & Lal, B. K. (2009). Objective analysis of voice in normal young adults. *Kathmandu University Medical Journal (KUMJ)*, *7*(28), 374–377. https://doi.org/10.3126/kumj.v7i4.2757

Uslu-Akcam, O. (2017). Pharyngeal airway dimensions in skeletal class II: A cephalometric growth study. *Imaging Science in Dentistry*, *47*(1), 1–9. https://doi.org/10.5624/isd.2017.47.1.1

Vaivads, M., Balode, E., & Pilmane, M. (2020). Factors affecting facial development and formation of cleft lip and palate: A literature review. *Papers on Anthropology*, *29*(2), 2. https://doi.org/10.12697/poa.2020.29.2.02

Valadez, V., Ysunza, A., Ocharan-Hernandez, E., Garrido-Bustamante, N., Sanchez-Valerio, A., & Pamplona, M. C. (2012). Voice parameters and videonasolaryngoscopy in children with vocal nodules: A longitudinal study, before and after voice therapy. *International Journal of Pediatric Otorhinolaryngology*, *76*(9), 1361–1365. https://doi.org/10.1016/j.ijporl.2012.06.007

Van der Heijden, P., Hobbel, H. H. F., Van der Laan, B. F. a. M., Korsten-Meijer, A. G. W., & Goorhuis-Brouwer, S. M. (2011). Nasometry normative data for young Dutch children. *International Journal of Pediatric Otorhinolaryngology*, *75*(3), 420–424. https://doi.org/10.1016/j.ijporl.2010.12.020

van Doorn, J., & Purcell, A. (1998). Nasalance levels in the speech of normal Australian children. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *35*(4), 287–292. https://doi.org/10.1597/1545-1569(1998)035<0287:NLITSO>2.3.CO;2

van Eeden, S. (2014). Speech Therapy in Cleft Palate and Velopharyngeal Dysfunction Edited by The Spires Cleft Centre Speech and Language Therapy (SLT) Team, Ginette Phippen (ed.) (Guildford: J&R Press, 2014) [Pp. 401.] ISBN 978-1-907826-14-6, £29.99. *International Journal of Language & Communication Disorders*, *50*. https://doi.org/10.1111/1460-6984.12110

Van Lierde, K. M., Claeys, S., De Bodt, M., & Van Cauwenberge, P. (2004). Vocal quality characteristics in children with cleft palate: A multiparameter approach. *Journal of Voice*, *18*(3), 354–362. https://doi.org/10.1016/j.jvoice.2003.12.006

Van Lierde, K. M., Wuyts, F. L., De Bodt, M., & Van Cauwenberge, P. (2001). Nasometric values for normal nasal resonance in the speech of young Flemish adults. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *38*(2), 112–118. https://doi.org/10.1597/1545-1569(2001)038<0112:NVFNNR>2.0.CO;2

Van Lierde, K. M., Wuyts, F. L., De Bodt, M., & Van Cauwenberge, P. (2003). Age-related patterns of nasal resonance in normal Flemish children and young adults. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery*, *37*(6), 344–350.

Varghese, A. L., & Bhat, D. J. S. (2012). Perturbation In Voice Of Children With Cleft Lip And /Or Palate. *Advances in Life Science and Technology*, *6*(0), 52-56–56.

Veder, L., Pullens, B., Timmerman, M., Hoeve, H., Joosten, K., & Hakkesteegt, M. (2017). Reliability and validity of the Dutch pediatric Voice Handicap Index. *International Journal of Pediatric Otorhinolaryngology*, *96*, 15–20. https://doi.org/10.1016/j.ijporl.2017.02.023

Villafuerte-Gonzalez, R., Valadez-Jimenez, V. M., Hernandez-Lopez, X., & Ysunza, P. A. (2015). Acoustic analysis of voice in children with cleft palate and velopharyngeal insufficiency. *International Journal of Pediatric Otorhinolaryngology*, *79*(7), 1073–1076. https://doi.org/10.1016/j.ijporl.2015.04.030

Viñas, M. J., Galiotto-Barba, F., Cortez-Lede, M. G., Rodríguez-González, M. Á., Moral, I., Delso, E., González-Meli, B., Lobo, F., López-Cedrún, J. L., Neagu, D., Garatea, J., Garatea, A., Berenguer, B., Lorca-García, C., Delgado, M. D., Martí, E., Gutiérrez, J. M., Hernández, C., Murillo-González, J., … Martínez-Sanz, E. (2022). Craniofacial and three-dimensional palatal analysis in cleft lip and palate patients treated in Spain. *Scientific Reports*, *12*(1), 1. https://doi.org/10.1038/s41598-022-23584-0

Wada, T., Satoh, K., Tachimura, T., & Tatsuta, U. (1997). Comparison of nasopharyngeal growth between patients with clefts and noncleft controls. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *34*(5), 405–409. https://doi.org/10.1597/1545-1569_1997_034_0405_congbp_2.3.co_2

Watson, A., Sell, D., & Grunwell, P. (2001). *Management of Cleft Lip and Palate*. Wiley.

Watterson, T., Hinton, J., & McFarlane, S. (1996). Novel stimuli for obtaining nasalance measures from young children. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *33*(1), 67–73. https://doi.org/10.1597/1545-1569(1996)033<0067:NSFONM>2.3.CO;2

Watterson, T., Lewis, K., Allord, M., Sulprizio, S., & O'Neill, P. (2007). Effect of vowel type on reliability of nasality ratings. *Journal of Communication Disorders*, *40*(6), 503–512. https://doi.org/10.1016/j.jcomdis.2007.02.002

Watterson, T., Lewis, K. E., & Foley-Homan, N. (1999). Effect of stimulus length on nasalance scores. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *36*(3), 243–247. https://doi.org/10.1597/1545-1569(1999)036<0243:EOSLON>2.3.CO;2

Wermker, K., Jung, S., Joos, U., & Kleinheinz, J. (2012). Nasopharyngeal development in patients with cleft lip and palate: A retrospective case-control study. *International Journal of Otolaryngology*, *2012*, 458507. https://doi.org/10.1155/2012/458507

Whitehill, T. L. (2001). Nasalance measures in Cantonese-speaking women. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *38*(2), 119–125. https://doi.org/10.1597/1545-1569(2001)038<0119:NMICSW>2.0.CO;2

Witt, P. D., Wahlen, J. C., Marsh, J. L., Grames, L. M., & Pilgram, T. K. (1998). The effect of surgeon experience on velopharyngeal functional outcome following palatoplasty: Is there a learning curve? *Plastic and Reconstructive Surgery*, *102*(5), 1375–1384. https://doi.org/10.1097/00006534-199810000-00009

Wu, J. T., Huang, G. F., Huang, C. S., & Noordhoff, M. S. (1996). Nasopharyngoscopic evaluation and cephalometric analysis of velopharynx in normal and cleft palate patients. *Annals of Plastic Surgery*, *36*(2), 117–122; discussion 122–123. https://doi.org/10.1097/00000637-199602000-00002

Wyatt, R., Sell, D., Russell, J., Harding, A., Harland, K., & Albery, L. (1996). Cleft palate speech dissected: A review of current knowledge and analysis. *British Journal of Plastic Surgery*, *49*(3), 143–149. https://doi.org/10.1016/S0007-1226(96)90216-7

Wyszynski, D. F., Beaty, T. H., & Maestri, N. E. (1996). Genetics of nonsyndromic oral clefts revisited. *The Cleft Palate-Craniofacial Journal: Official Publication of the American Cleft Palate-Craniofacial Association*, *33*(5), 406–417. https://doi.org/10.1597/1545-1569_1996_033_0406_gonocr_2.3.co_2

Özkan, E. T., Tüzüner, A., Demirhan, E., & Topbaş, S. (2015). Reliability and validity of the Turkish pediatric Voice Handicap index. *International Journal of Pediatric Otorhinolaryngology*, *79*(5), 680–684. https://doi.org/10.1016/j.ijporl.2015.02.014

Yamashita, R. P., Borg, E., Granqvist, S., & Lohmander, A. (2018). Reliability of Hypernasality Rating: Comparison of 3 Different Methods for Perceptual Assessment. *The Cleft Palate Craniofacial Journal*, *55*(8), 1060–1071. https://doi.org/10.1177/1055665618767116

Young, A., & Spinner, A. (2022). Velopharyngeal Insufficiency. *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK563149/

Young, L. H., Zajac, D. J., Mayo, R., & Hooper, C. R. (2001). Effects of vowel height and vocal intensity on anticipatory nasal airflow in individuals with normal speech. *Journal of Speech, Language, and Hearing Research: JSLHR*, *44*(1), 52–60. https://doi.org/10.1044/1092-4388(2001/005)

Ysunza, P. A., Pamplona, M. C., & Repetto, G. (2015). Cleft Palate, Interdisciplinary Diagnosis, and Treatment. *BioMed Research International*, *2015*, 701850. https://doi.org/10.1155/2015/701850

Yver, C. M., Chorath, K. T., Connolly, J., Shah, M., Majmudar, T., Moreira, A. G., & Rajasekaran, K. (2022). Clinical Practice Guidelines for the Management of Patients With Cleft Lip and Palate: A Systematic Quality Appraisal Using the Appraisal of Guidelines for Research and Evaluation II Instrument. *Journal of Craniofacial Surgery*, *33*(2), 449. https://doi.org/10.1097/SCS.0000000000008155

APPENDICES

APPENDIX A:
Laste häälehäire küsimustik

Lapse nimi: ..... Vanus:.....a.....k

Ma hindan oma lapse jutukust järgnevalt (ringita vastus)

1	2	3	4	5	6	7
Vaikne kuulaja			keskmine rääkija			väga jutukas

Juhised: need on väited, mida kasutatakse hääle ja hääle mõju kirjeldamisel. Ringita vastus, mis näitab, kui tihti on Su lapsel olnud sama kogemus:
0 – mitte kunagi 1 – väga harva 2 – mõnikord 3 – sageli 4 – alati

I osa: funktsionaalsust hindav alltest
1. Mu lapse häält on teistel raske kuulda 0 1 2 3 4
2. Inimestel on raske minu lapsest mürarikkas ruumis aru saada 0 1 2 3 4
3. Meil on kodus last raske kuulda, kui ta hüüab teisest toast 0 1 2 3 4
4. Minu laps kaldub suhtlemist oma hääle tõttu vältima 0 1 2 3 4
5. Mu laps suhtleb sõprade, naabrite või sugulastega oma hääle tõttu vähem 0 1 2 3 4
6. Inimesed paluvad lapsel öeldut korrata, kui nad räägivad näost näkku 0 1 2 3 4
7. Minu lapse hääleprobleem piirab tema isiklikku, hariduslikku ja sotsiaalset aktiivsust 0 1 2 3 4

II osa: füüsilisust hindav alltest
1. Mu lapsel saab rääkides õhk otsa 0 1 2 3 4
2. Mu lapse hääl muutub päeva jooksul 0 1 2 3 4
3. Inimesed küsivad: “Mis mu lapse häälel viga on?” 0 1 2 3 4
4. Minu lapse hääl on kuiv, kriipiv ja/või kähe 0 1 2 3 4
5. Minu lapse häälekvaliteet on ettearvamatu 0 1 2 3 4
6. Minu laps peab rääkimisel kõvasti pingutama 0 1 2 3 4
7. Minu lapse hääl on halvem õhtuti 0 1 2 3 4
8. Minu lapse hääl katkeb /”ütleb üles” rääkides 0 1 2 3 4
9. Minu laps peab karjuma, et teised teda kuuleksid 0 1 2 3 4

III osa: emotsionaalsust hindav alltest
1. Minu laps on teistega rääkides oma hääle tõttu pinges 0 1 2 3 4
2. Minu lapse hääl äratab inimeste tähelepanu 0 1 2 3 4
3. Leian, et teised inimesed ei mõista mu lapse hääleprobleemi 0 1 2 3 4
4. Minu laps on oma hääleprobleemist häiritud/ frustreeritud 0 1 2 3 4
5. Minu laps seltsib teistega oma hääle tõttu vähem 0 1 2 3 4
6. Minu laps on pahane, kui inimesed paluvad tal öeldut korrata 0 1 2 3 4
7. Minu lapsele valmistab piinlikkust, kui tal palutakse öeldut korrata 0 1 2 3 4

APPENDIX B: Stimuli for videonasoendoscopic assessment of velopharyngeal function

1. Non-speech stimuli: swallowing (3 times), blowing (3 times)

2. Fonation of sustained sounds /a/, /i/, /s/, /h/

3. Repetitions of strings of syllables
   a. /pa-pa-pa-pa-pa-pa/
   b. /pi-pi-pi-pi-pi-pi/
   c. /ka-ka-ka-ka-ka-ka/
   d. /ki-ki-ki-ki-ki-ki/

4. Repetition of words:
   a. /akna/
   b. /lampi/
   c. /hambad/
   d. /kinki/
   e. /pinges/
   f. /kimpu/
   g. /kõmmdi/
   h. /patsi/

5. Repetition of sentences:
   a. /Piibe paneb poti kappi/
   b. /Teet väntab rattaga poodi/
   c. /Kase ladvas kukkus kägu/
   d. /Sass silitab kassi/

SUMMARY IN ESTONIAN

Esimene suulaelõhega sündinud patsientide hääle ja resonantsiga seotud ravitulemuste uuring Eestis

Sissejuhatus

Huule- ja/või suulaelõhe (HSL) on üks sagedasemaid kaasasündinud väärarenguid, esinemissagedusega 1/700 elussünni kohta, sõltuvalt geograafilistest ja etnilistest variatsioonidest. Suulaelõhega sündinud lastel esineb sageli mitmeid kaasuvaid probleeme, sh neelamis- ja söömisraskused, probleemid kõnearenguga, mille peamiseks põhjuseks on velofarüngeaalsest düsfunktsioonist tingitud resonantsiprobleemid, häälehäired, kolju- ja näopiirkonna kasvu ning arengu kõrvalekalded, ortodontilised probleemid, kuulmislangus, keelelise arengu probleemid ning õpiraskused. Uuringud näitavad, et kõige enam mõjutavad HSL-iga lapse psühhosotsiaalset toimetulekut tema välimus ja kõne kvaliteet. Seega on ravitöös vajalik nendele aspektidele erilist tähelepanu pöörata.

Logopeedilise tegevuse ning kirurgilise ja ortodontilise sekkumise efektiivsuse kindlaks määramiseks on oluline täpselt fikseerida HSL-laste kõnes ilmnevad iseärasused. Oluline on leida seosed suulaelõhega sündinud laste kõnekvaliteedi ja seda mõjutada võivate tegurite vahel. HSL-laste kõne arusaadavust mõjutavad nii resonantsi- kui ka häälepuuded. Uuringud on leidnud, et HSL-iga sündinud laste kraniofatsiaalne kasv erineb eakohase arenguga eakaaslastega võrreldes. Kraniofatsiaalse kasvu proportsionaalsust on võimalik hinnata tsefalomeetriaga. Tsefalomeetriliste parameetrite disproportsionaalsus võib mõjutada hääles avalduvat resonantsi. Selline resonantsipuue avaldub tavaliselt hüpernasaalsusena. Oluline on teha kindlaks, millised tsefalomeetrilised parameetrid mõjutavad kõnekvaliteeti enam.

Uurimistöö eesmärgiks oli kirjeldada HSL-laste kõnes esinevaid häälehäireid ja resonantsipuudeid. Lähtuvalt uurimistöö eesmärgist püstitati alljärgnevad uurimisküsimused:

1. Milliste näitajatega peab arvestama eestikeelse testmaterjali välja töötamisel nasomeetriliseks uuringuks? Millised on eakohase arenguga eesti keelt emakeelena rääkivate laste nasalaerituse piirväärtused?
2. Millise etioloogiaga on HSL-iga sündinud laste häälehäired? Kas ja mil määral mõjutab HSL-iga sündinud lastel esinev düsfoonia nende elukvaliteeti?
3. Kas ja mil määral erineb Eesti HSL-iga sündinud laste kraniofatsiaalne kasv eakaaslaste kraniofatsiaalsest kasvust? Millised näokolju parameetrid mõjutavad HSL-iga sündinud laste kõnes esinevaid resonantsipuudeid?

Uurimistöö käigus alustati HSL-diagnooside spetsiifilise riikliku andmebaasi loomisega, mis võimaldab HSL-iga sündinud laste ravitulemuste jälgimist.

Uuringu metoodika

Valim

Uuringusse kaasati 92 eakohase arenguga tervet last ning 18 HSL-last. Kõigi uuringus osalenud laste emakeeleks oli eesti keel. HSL-gruppi kuuluvatel lastel

oli eakohane psühhomotoorne areng ja ühe- või kahepoolne läbistav huule-suulaelõhe, isoleeritud suulaelõhe või limaskestaalune suulaelõhe. Valimist jäeti välja lapsed, kellel esines lõhe sündroomi koosseisus, isoleeritud huulelõhe, tunnetustegevuse mahajäämus, kuulmislangus või keelepuue. Valim koosnes eelkooliealistest lastest vanuses 4a6k – 6a11k. Tabelis 1 on esitatud uuringus osalenud laste arvud ja HSL-iga sündinud laste diagnoosid.

Tabel 1. Valimis osalenud laste arvud ja jaotuvus.

	HSL-grupp (n*)					Tervete laste grupp (n*)
	Kahepoolne läbistav huule-suulaelõhe	Ühepoolne läbistav huule-suulaelõhe	Iso-leeritud suulaelõhe	Limas-kesta alune suulaelõhe	KOKKU	
Uuring I	2	5	5	2	14	92
Uuring II	4	6	6	2	18	79
Uuring III	2	4	3	2	11	17

*n – osalejate arv

Metoodika

Tegemist oli läbilõike uuringuga. Andmete kogumisel kasutati nii objektiivseid (*Multidimensional Voice Program* (MDVP), *Nasometer II*, *Dolphin Imaging Software*) kui subjektiivseid (laste häälepuude küsimustik (pVHI), GRBAS-skaala, videonasoendoskoopia (VNE), videolarüngostroboskoopia (VLS)) hindamisvahendeid. Tabelis 2 on toodud välja uurimistöö ajakava ja metoodika.

Tabel 2. Uurimistöö ajakava ja metoodika.

	Teostamine	Valim	Metoodika ja materjalid
Uuring I	märts 2015 – veebruar 2017	14 HSL 92 eakohase arenguga	– pilootuuring: eestikeelse stiimulmaterjali koos-tamine ja nasaleerituse normide välja töötamine – stiimulmaterjali kohandamine – nasaleerituse piirväärtuste arvutamine
Uuring II	oktoober 2016 – veebruar 2017	18 HSL 79 eakohase arenguga	– eestikeelsete stiimulmaterjali koostamine VNE-uuringu teostamiseks – hääle akustiline analüüs (MDVP) – pVHI küsimustiku täitmine – auditiiv-pertseptiivne häälekvaliteedi hindamine (GRBAS) – VNE-uuring – VLS-uuring
Uuring III	september 2019 – märts 2020	11 HSL 17 eakohase arenguga	– lateraalsete koljuülesvõtete analüüs – tsefalomeetriliste parameetrite leidmine – tsefalomeetriliste parameetrite analüüs

Tulemused

Nasaleerituse normide (uuring I) kogumiseks eesti keeles koostati unikaalne eesti keele spetsiifikat arvestav stiimulite kogum. Stiimulite välja töötamisel ja häälikute distributsiooni arvestamisel lähtuti Tartu Ülikooli Eesti keele spontaanse kõne foneetilise korpuse andmetest. Testmaterjali koostamisel arvestati (1) oraalsete ja nasaalsete häälikute esinemissagedusega eesti keeles, (2) kõrgete ja madalate vokaalide mõjuga nasaalsusele ning (3) eesti keele keerulise prosoodilise süsteemiga. Nasaleerituse hindamiseks töötati välja kolm erinevat stiimulite gruppi: (1) nii oraalseid kui nasaalseid häälikuid sisaldavad lausungid; (2) rohkelt nasaalseid häälikuid sisaldavad lausungid ja (3) ainult oraalseid häälikuid sisaldavad lausungid. Nasomeetri tarkvara abil leiti iga lapse nasaleerituse aste. Seejärel arvutati iga lausungi keskmine tulemus ning iga lausungigrupi keskmine tulemus. Tulemused näitasid, et sugude vahelisi statistiliselt olulisi erinevusi nasaleerituse piirväärtustes ei esinenud ühegi lausungigrupi puhul. Rohkelt nasaale sisaldavate lausungite nasaleerituse astmete vahel ei esinenud statistiliselt olulist erinevust HSL-iga ja tervete laste gruppide vahel. Statistiline erinevus esines oraalseid häälikuid ja nii oraalseid kui nasaalseid häälikuid sisaldavate lausungite nasaleerituse astmete võrdlemisel HSL-iga ja tervete laste gruppide vahel. Oraalseid ja nasaalseid häälikuid sisaldavate lausungite nasaleerituse keskmiseks astmeks kujunes 30,5, mis on lähedane tulemus nii rootsi (29,5) kui ka ungari (31,7) keele tulemustele. Rohkelt nasaale sisaldavate lausungite keskmine aste eesti keeles on 57,8, mis samuti võrreldav rootsi (56,5) ja austraalia inglise keele (59,6) tulemustega. Ainult oraale sisaladavate lausungite nasaleerituse keskmine aste oli eesti keeles 15,9, mis on sarnane nii rootsi, flaami, inglise (Iirimaa), inglise (Austraalia), ungari, korea ja soome keele tulemustega.

Hääle kvaliteet (uuring II) mõjutab oluliselt eesti HSL-laste elukvaliteeti. HSL-iga sündinud laste vanemate subjektiivsed hinnangud oma laste häälekvaliteedile ja häälega seotud heaolule erinesid oluliselt kõigis hääleaspektides (funktsionaalsus, füüsilisus, emotsionaalsus) tavaarenguga laste vanemate hinnangutest. Hääle akustiliste parameetrite objektiivsel hindamisel leiti, et kahe grupi vahel esinevad olulised erinevused hääle põhisageduse variatiivsuse (vF0) ja hääle kõheduse indeksi tulemustes (NHR) ning sagedus- (*jitter*) ja intensiivsusperturbatsiooni (*shimmer*) näitajates. Muutused eelnimetatud parameetrites avalduvad hääles kähedusena, pingena või pressitusena. Häälehäirete etioloogia välja selgitamiseks teostati VSL-uuring ning leiti, et 44%-l lastest ei esinenud häälepaelte morfoloogilisi muutuseid, 12%-l esinesid bilateraalsed häälepaelte nupukesed ja 44%-l bilateraalne häälepaelte turse. Velofarüngeaalse funktsiooni hindamiseks kasutati VNE-uuringut. 83%-l lastest avaldus velofarüngeaalne düsfunktsioon (VFD). Uuringus leiti, et VFD raskusaste ei ole otseses seoses häälepaelte morfoloogiliste muutustega, küll aga on seotud madalamate hinnangutega häälega seostud elukvaliteedile. Kõikide uuringus osalenud HSL-laste eelsalvestatud häälenäidiseid hinnati ka auditiiv-pertseptiivselt. Hindamine toimus neljapunktilisel häälekvaliteedi raskusastme määramise (GRBAS) skaalal ja selle viisid läbi kaks teineteisest sõltumatut hindajat. HSL-laste skoorid GRBAS skaalal olid

kõrgemad poistel 'A' – parameetri (jõuetus) ja tüdrukutel 'G' – parameetri (üldine häälehäire raskusaste) osas.

Näokolju parameetreid (uuring III) mõõdeti kahe teineteisest sõltumatu hindaja poolt. Lateraalseid tsefalogramme analüüsiti digitaalselt *Dolphin Imaging* tarkvaraga. Hindajate vaheline ($\alpha>0.7$) ja hindajate sisemine ($\kappa<0.6$) reliaablus olid piisavad uuringu usaldusväärsuse tagamiseks. Kraniofatsiaalse morfoloogia analüüsist selgus, et HSL-iga sündinud laste kõvasuulae pikkus sagitaaltasapinnas (PNS-A) ja pehmesuulae pikkus (PNS-P) on oluliselt ($p<0.05$) lühemad ning orofarüngeaalne hingamistee (AW5–AW6) oluliselt kitsam võrreldes kontrollgrupiga. Samuti esines HSL-lastel sagedamini tagumise asetusega ülalõug, skeletaalset klass III hambumust (ANB) ning keeleluu eespoolsemat asetust (Hy-C3). Hüpernasaalse resonantsiga on oluliselt seotud ($p<0.05$) kõvasuulae pikkus sagitaaltasapinnas (PNS-A), orofarüngeaalse hingamistee sügavus (AW5–AW6), keeleluu eespoolsem asetus (Hy-C3) ning skeletaalne klass III suhe.

Järeldused

1. Kõne kvaliteet on üks peamisi ravikvaliteedi näitajaid HSL-laste ravis. Kõige sagedamini esineb HSL-lastel resonantsiprobleeme tingituna VFD-st. Lisaks, esineb HSL-lastel ka häälehäireid. Resonantsipuuded ja häälehäired mõjutavad oluliselt kõne arusaadavust. Eesti HSL-lastel avalduvad nii resonantsikui häälehäired üsna ilmekalt: (1) nasaleerituse aste on oluliselt kõrgem võrreldes kontrollgrupiga; (2) häälehäireid ja häälepealte morfoloogilisi muutuseid esineb rohkem kui pooltel HSL-lastel; (3) kraniofatsiaalsed parameetrid erinevad HSL- ja tervete laste gruppides.

2. Me töötasime välja eesti keele spetsiifilised unikaalsed testmaterjalid ja stiimulid nasaalsuse ja velofarüngeaalse funktsiooni hindamiseks. Nasaleerituse piirväärtusi saavad kasutada praktikud oma igapäevases kliinilises töös resonantsipuuete diagnoosimiseks, teraapia efektiivsuse hindamiseks ja kõne kvaliteedi dünaamiliseks hindamiseks.

3. Düsfoonia esinemissagedus on oluliselt kõrgem HSL-laste grupis võrreldes kontrollgrupiga. Kuna HSL-laste kõne arusaadavust mõjutavad mitmed tegurid, siis võivad häälehäired jääda märkamatuks. Häälehäirete õigeaegne diagnostika ja ravi parandavad kõne üldist arusaadavust.

4. Kõne kvaliteeti mõjutavad ka muutused kraniofatsiaalses arengus. Lähtuvalt meie uuringust mõjutavad HSL-laste kõnekvaliteeti peamiselt pehme- ja/või kõvasuulae lühenemine, eesmise asetusega keeleluu ning üla- ja alalõualuu asetus. Seega on HSL-laste ravis oluline roll ravimeeskonna tihedal koostöö eesmärgiga tagada nendele lastele parim võimalik kõne kvaliteet.

5. HSL-laste vanemad hindasid laste häälekvaliteeti oluliselt madalamalt võrreldes kontrollgrupi tulemustega. HSL-laste vanemate hinnanguil mõjutab HSL-laste häälekvaliteet oluliselt nende laste elukvaliteeti. PHVI tulemused aga ei korreleerunud hääle akustiliste parameetrite tulemustega. Seetõttu on häälehäire diagnoosimisel oluline kombineerida erinevad (objektiivseid ja subjektiivseid) hindamismeetodeid.

6. Velofarüngeaalse düsfunktsiooni raskusaste ei ole otseses seoses häälehäire raskusastme ega morfoloogiliste muutustega häälepaeltel.

ACKNOWLEDGEMENTS

All studies published in the thesis are based on teamwork with the contribution of many persons, and I am delighted to express my sincerest gratitude and appreciation to everybody who has taken part in these studies and supported me with the present thesis:

Associate professor Dr. Triin Jagomägi, my principal supervisor, for her true mentorship, valuable advice and constant support. Her encouragement has kept me working. In addition, I would like to thank her for the immeasurable contribution to the cleft community, and all the patient-related work she has done at Stomatology Clinic of Tartu University Hospital.

Associate professor Marika Padrik, my supervisor, for her quick reading, expert advice, listening skills, fruitful conversations and clear mind, for maintaining optimism and devoting her valuable time during all these years.

Associate professor Dr. Priit Kasenõmm, my supervisor, for his valuable guidance and scientific advice, for his quick and constructive feedback for my papers. His teaching skills are excellent in scientific writing.

Dr. Linda Sõber, my dear colleague and friend, for her thoroughness, her innovative thinking, her dedication and commitment to medicine. *Thank you for all the oranges and hearthy laughs*.

My co-authotrs, professor Pärt Lippus, for his expert advice on Estonian phonetics, and my master's students at the Institute of Education in the University of Tartu: Reet Horn, Jette Numa and Carina Aria, for their dedication, collaboration and enthusiasm.

My organizational supporters, Mari Pärn, Evekai Usar and Anne Suluste, for their adaptability and for always being there with good thoughts. My advisor, Dr. Van Thai Nguyen, for his time for discussions. My language reviewer, Meelis Leesik, for his thorough proofreading and exerpet advice, questions and suggestions.

My reviewers, prof. Arūnas Vasiliauskas, Dr. Vitali Vassiljev, prof. Mare Saag, for their time, attentive listening skills and invaluable insights.

The staff members of the Cleft Team in North Estonia Medical Centre, in Unimed United Clinics, in Ear Clinic of Tartu University Hospital, and in Rehabilitation Clinic of Tartu University for their valuable scientific advice and inspiration.

All included children and their parents, for devoting their time and energy to make this thesis possible.

Merje Viigand, my dear colleague and friend, for her productive dialogues, for creating a sense of calm amidst uncertainty.

My dear friends, Piret, Pirkko, Karli, and Hardi, for keeping up my spirit, taking care of my social well-being, getting me through the rough times, and always believing in me.

Thank you, my beloved family, my mother Lea, my sister Egle, my children Erik Johannes and Ott Oskar, for your never-ending support, for your understanding, encouragement and faith. Thank you Leho, for being my biggest supporter.

Dedicated to the memory of my father

PUBLICATIONS

CURRICULUM VITAE

Name: Lagle Lehes
Date and place of birth: November 5th, 1978, Pärnu, Estonia
Citizenship: Estonian
Phone: +372 5561 6054
E-mail: lagle.lehes@ut.ee

Education:

2016–...	University of Tartu, Faculty of Medicine, PhD Student
2007–2009	University of Tartu, Department of Special Education, Speech and Language Pathology, MA
1998–2002	University of Tartu, Department of Special Education, BA
1994–1997	Pärnu Sütevaka Humanitarian Gymnasium

Professional employment:

01.06.2012 – …	Tartu University Hospital, clinical speech and language pathologist
01.02.2018 – …	University of Tartu, Faculty of Social Sciences, Institute of Education, Junior Lecturer in Speech Therapy

Scientific work: My principal research interests lie between scientific basis of speech and voice therapy, therapy outcomes and its relation to stomatology and otorinolaryngology.

Publications in international peer-reviewed journals:

Lehes, Lagle; Aria, Carina; Padrik, Marika; Kasenõmm, Priit; Jagomägi, Triin (2023). Correlation between nasalance scores and cephalometric parameters in Estonian cleft palate children. Stomatologija [forthcoming].

Lehes, L., Sõber, L., Padrik, M., Kasenõmm, P., Numa, J., Jagomägi, T. (2020). The effect of velopharyngeal insufficiency on voice quality in Estonian Children with Cleft Palate. Clinical Linguistics & Phonetics. DOI: 10.1080/02699206.2020.1780323.

Lagle, Lehes; Thi Thuy Hang, Truong; Thi Van Anh, Hoang; Triin, Jagomägi (2020). Nasalance scores for Vietnamese-speaking children with oral clefts. Stomatologija, 22, 80–85.

Nguyen, Van Thai; Lehes, Lagle; Truong, Thi Thuy Hang; Hoang, Thi Van Anh; Jagomägi, Triin (2019). Normative nasalance scores for Vietnamese-speaking children. Logopedics Phoniatrics Vocology, 44 (2), 51–57. DOI: 10.1080/14015439.2017.1389985.

Lehes, L., Horn, R., Lippus, P., Padrik, M., Kasenõmm, P., Jagomägi, T. (2018). Normative nasalance scores for Estonian children. Clinical Linguistics & Phonetics, 32 (11), 1054–1066. DOI: 10.1080/02699206.2018.1495767.

ELULOOKIRJELDUS

Nimi: Lagle Lehes
Sünniaeg ja -koht: 05.11.1978, Pärnu, Eesti
Kodakondus: Eesti
Telefon: +372 5561 6054
E-post: lagle.lehes@ut.ee

Haridus:

2016–...	Tartu Ülikool, Meditsiiniteaduste valdkond, doktorant
2007–2009	Tartu Ülikool, eripedagoogika osakond, logopeedia õppetool, MA
1998–2002	Tartu Ülikool, eripedagoogika osakond, BA
1994–1997	Pärnu Sütevaka Humanitaargümnaasium

Erialane teenistuskäik:

01.06.2012 – …	SA Tartu Ülikooli Kliinikum, kliiniline logopeed
01.02.2018 – …	Tartu Ülikool, Sotsiaalteaduste valdkond, haridusteaduste instituut, logopeedia nooremlektor

Teadustöö põhisuunad: Teadustöös keskendun teaduspõhiste logopeediliste teraapiasuundade välja töötamisele ja kohandamisele eesti keelele, logopeediliste teraapiate efektiivsuse mõõtmisele ning tulemuste võimalikele seostele stomatoloogiliste ja otorinolarüngoloogiliste probleemidega.

Artiklid rahvusvahelistes eelretsenseeritavates ajakirjades:

Lehes, Lagle; Aria, Carina; Padrik, Marika; Kasenõmm, Priit; Jagomägi, Triin (2023). Pilot study: Correlation between nasalance scores and cephalometric parameters in Estonian cleft palate children. Stomatologija [forthcoming].

Lehes, L., Sõber, L., Padrik, M., Kasenõmm, P., Numa, J., Jagomägi, T. (2020). The effect of velopharyngeal insufficiency on voice quality in Estonian Children with Cleft Palate. Clinical Linguistics & Phonetics. DOI: 10.1080/02699206.2020.1780323

Lagle, Lehes; Thi Thuy Hang, Truong; Thi Van Anh, Hoang; Triin, Jagomägi (2020). Nasalance scores for Vietnamese-speaking children with oral clefts. Stomatologija, 22, 80–85.

Nguyen, Van Thai; Lehes, Lagle; Truong, Thi Thuy Hang; Hoang, Thi Van Anh; Jagomägi, Triin (2019). Normative nasalance scores for Vietnamese-speaking children. Logopedics Phoniatrics Vocology, 44 (2), 51–57. DOI: 10.1080/14015439.2017.1389985

Lehes, L., Horn, R., Lippus, P., Padrik, M., Kasenõmm, P., Jagomägi, T. (2018). Normative nasalance scores for Estonian children. Clinical Linguistics & Phonetics, 32 (11), 1054–1066. DOI: 10.1080/02699206.2018.1495767

DISSERTATIONES MEDICINAE UNIVERSITATIS TARTUENSIS

1. **Heidi-Ingrid Maaroos**. The natural course of gastric ulcer in connection with chronic gastritis and *Helicobacter pylori*. Tartu, 1991.
2. **Mihkel Zilmer**. Na-pump in normal and tumorous brain tissues: Structural, functional and tumorigenesis aspects. Tartu, 1991.
3. **Eero Vasar**. Role of cholecystokinin receptors in the regulation of behaviour and in the action of haloperidol and diazepam. Tartu, 1992.
4. **Tiina Talvik**. Hypoxic-ischaemic brain damage in neonates (clinical, biochemical and brain computed tomographical investigation). Tartu, 1992.
5. **Ants Peetsalu**. Vagotomy in duodenal ulcer disease: A study of gastric acidity, serum pepsinogen I, gastric mucosal histology and *Helicobacter pylori*. Tartu, 1992.
6. **Marika Mikelsaar**. Evaluation of the gastrointestinal microbial ecosystem in health and disease. Tartu, 1992.
7. **Hele Everaus**. Immuno-hormonal interactions in chronic lymphocytic leukaemia and multiple myeloma. Tartu, 1993.
8. **Ruth Mikelsaar**. Etiological factors of diseases in genetically consulted children and newborn screening: dissertation for the commencement of the degree of doctor of medical sciences. Tartu, 1993.
9. **Agu Tamm**. On metabolic action of intestinal microflora: clinical aspects. Tartu, 1993.
10. **Katrin Gross**. Multiple sclerosis in South-Estonia (epidemiological and computed tomographical investigations). Tartu, 1993.
11. **Oivi Uibo**. Childhood coeliac disease in Estonia: occurrence, screening, diagnosis and clinical characterization. Tartu, 1994.
12. **Viiu Tuulik**. The functional disorders of central nervous system of chemistry workers. Tartu, 1994.
13. **Margus Viigimaa**. Primary haemostasis, antiaggregative and anticoagulant treatment of acute myocardial infarction. Tartu, 1994.
14. **Rein Kolk**. Atrial versus ventricular pacing in patients with sick sinus syndrome. Tartu, 1994.
15. **Toomas Podar**. Incidence of childhood onset type 1 diabetes mellitus in Estonia. Tartu, 1994.
16. **Kiira Subi**. The laboratory surveillance of the acute respiratory viral infections in Estonia. Tartu, 1995.
17. **Irja Lutsar**. Infections of the central nervous system in children (epidemiologic, diagnostic and therapeutic aspects, long term outcome). Tartu, 1995.
18. **Aavo Lang**. The role of dopamine, 5-hydroxytryptamine, sigma and NMDA receptors in the action of antipsychotic drugs. Tartu, 1995.
19. **Andrus Arak**. Factors influencing the survival of patients after radical surgery for gastric cancer. Tartu, 1996.

20. **Tõnis Karki**. Quantitative composition of the human lactoflora and method for its examination. Tartu, 1996.
21. **Reet Mändar**. Vaginal microflora during pregnancy and its transmission to newborn. Tartu, 1996.
22. **Triin Remmel**. Primary biliary cirrhosis in Estonia: epidemiology, clinical characterization and prognostication of the course of the disease. Tartu, 1996.
23. **Toomas Kivastik**. Mechanisms of drug addiction: focus on positive reinforcing properties of morphine. Tartu, 1996.
24. **Paavo Pokk**. Stress due to sleep deprivation: focus on $GABA_A$ receptor-chloride ionophore complex. Tartu, 1996.
25. **Kristina Allikmets**. Renin system activity in essential hypertension. Associations with atherothrombogenic cardiovascular risk factors and with the efficacy of calcium antagonist treatment. Tartu, 1996.
26. **Triin Parik**. Oxidative stress in essential hypertension: Associations with metabolic disturbances and the effects of calcium antagonist treatment. Tartu, 1996.
27. **Svetlana Päi**. Factors promoting heterogeneity of the course of rheumatoid arthritis. Tartu, 1997.
28. **Maarike Sallo**. Studies on habitual physical activity and aerobic fitness in 4 to 10 years old children. Tartu, 1997.
29. **Paul Naaber**. *Clostridium difficile* infection and intestinal microbial ecology. Tartu, 1997.
30. **Rein Pähkla**. Studies in pinoline pharmacology. Tartu, 1997.
31. **Andrus Juhan Voitk**. Outpatient laparoscopic cholecystectomy. Tartu, 1997.
32. **Joel Starkopf**. Oxidative stress and ischaemia-reperfusion of the heart. Tartu, 1997.
33. **Janika Kõrv**. Incidence, case-fatality and outcome of stroke. Tartu, 1998.
34. **Ülla Linnamägi**. Changes in local cerebral blood flow and lipid peroxidation following lead exposure in experiment. Tartu, 1998.
35. **Ave Minajeva**. Sarcoplasmic reticulum function: comparison of atrial and ventricular myocardium. Tartu, 1998.
36. **Oleg Milenin**. Reconstruction of cervical part of esophagus by revascularised ileal autografts in dogs. A new complex multistage method. Tartu, 1998.
37. **Sergei Pakriev**. Prevalence of depression, harmful use of alcohol and alcohol dependence among rural population in Udmurtia. Tartu, 1998.
38. **Allen Kaasik**. Thyroid hormone control over β-adrenergic signalling system in rat atria. Tartu, 1998.
39. **Vallo Matto**. Pharmacological studies on anxiogenic and antiaggressive properties of antidepressants. Tartu, 1998.
40. **Maire Vasar**. Allergic diseases and bronchial hyperreactivity in Estonian children in relation to environmental influences. Tartu, 1998.
41. **Kaja Julge**. Humoral immune responses to allergens in early childhood. Tartu, 1998.

42. **Heli Grünberg**. The cardiovascular risk of Estonian schoolchildren. A cross-sectional study of 9-, 12- and 15-year-old children. Tartu, 1998.
43. **Epp Sepp**. Formation of intestinal microbial ecosystem in children. Tartu, 1998.
44. **Mai Ots**. Characteristics of the progression of human and experimental glomerulopathies. Tartu, 1998.
45. **Tiina Ristimäe**. Heart rate variability in patients with coronary artery disease. Tartu, 1998.
46. **Leho Kõiv**. Reaction of the sympatho-adrenal and hypothalamo-pituitary-adrenocortical system in the acute stage of head injury. Tartu, 1998.
47. **Bela Adojaan**. Immune and genetic factors of childhood onset IDDM in Estonia. An epidemiological study. Tartu, 1999.
48. **Jakov Shlik**. Psychophysiological effects of cholecystokinin in humans. Tartu, 1999.
49. **Kai Kisand**. Autoantibodies against dehydrogenases of α-ketoacids. Tartu, 1999.
50. **Toomas Marandi**. Drug treatment of depression in Estonia. Tartu, 1999.
51. **Ants Kask**. Behavioural studies on neuropeptide Y. Tartu, 1999.
52. **Ello-Rahel Karelson**. Modulation of adenylate cyclase activity in the rat hippocampus by neuropeptide galanin and its chimeric analogs. Tartu, 1999.
53. **Tanel Laisaar**. Treatment of pleural empyema — special reference to intrapleural therapy with streptokinase and surgical treatment modalities. Tartu, 1999.
54. **Eve Pihl**. Cardiovascular risk factors in middle-aged former athletes. Tartu, 1999.
55. **Katrin Õunap**. Phenylketonuria in Estonia: incidence, newborn screening, diagnosis, clinical characterization and genotype/phenotype correlation. Tartu, 1999.
56. **Siiri Kõljalg**. *Acinetobacter* – an important nosocomial pathogen. Tartu, 1999.
57. **Helle Karro**. Reproductive health and pregnancy outcome in Estonia: association with different factors. Tartu, 1999.
58. **Heili Varendi**. Behavioral effects observed in human newborns during exposure to naturally occurring odors. Tartu, 1999.
59. **Anneli Beilmann**. Epidemiology of epilepsy in children and adolescents in Estonia. Prevalence, incidence, and clinical characteristics. Tartu, 1999.
60. **Vallo Volke**. Pharmacological and biochemical studies on nitric oxide in the regulation of behaviour. Tartu, 1999.
61. **Pilvi Ilves**. Hypoxic-ischaemic encephalopathy in asphyxiated term infants. A prospective clinical, biochemical, ultrasonographical study. Tartu, 1999.
62. **Anti Kalda**. Oxygen-glucose deprivation-induced neuronal death and its pharmacological prevention in cerebellar granule cells. Tartu, 1999.
63. **Eve-Irene Lepist**. Oral peptide prodrugs – studies on stability and absorption. Tartu, 2000.

64. **Jana Kivastik**. Lung function in Estonian schoolchildren: relationship with anthropometric indices and respiratory symptomas, reference values for dynamic spirometry. Tartu, 2000.
65. **Karin Kull**. Inflammatory bowel disease: an immunogenetic study. Tartu, 2000.
66. **Kaire Innos**. Epidemiological resources in Estonia: data sources, their quality and feasibility of cohort studies. Tartu, 2000.
67. **Tamara Vorobjova**. Immune response to *Helicobacter pylori* and its association with dynamics of chronic gastritis and epithelial cell turnover in antrum and corpus. Tartu, 2001.
68. **Ruth Kalda**. Structure and outcome of family practice quality in the changing health care system of Estonia. Tartu, 2001.
69. **Annika Krüüner**. *Mycobacterium tuberculosis* – spread and drug resistance in Estonia. Tartu, 2001.
70. **Marlit Veldi**. Obstructive Sleep Apnoea: Computerized Endopharyngeal Myotonometry of the Soft Palate and Lingual Musculature. Tartu, 2001.
71. **Anneli Uusküla**. Epidemiology of sexually transmitted diseases in Estonia in 1990–2000. Tartu, 2001.
72. **Ade Kallas**. Characterization of antibodies to coagulation factor VIII. Tartu, 2002.
73. **Heidi Annuk**. Selection of medicinal plants and intestinal lactobacilli as antimicrobil components for functional foods. Tartu, 2002.
74. **Aet Lukmann**. Early rehabilitation of patients with ischaemic heart disease after surgical revascularization of the myocardium: assessment of health-related quality of life, cardiopulmonary reserve and oxidative stress. A clinical study. Tartu, 2002.
75. **Maigi Eisen**. Pathogenesis of Contact Dermatitis: participation of Oxidative Stress. A clinical – biochemical study. Tartu, 2002.
76. **Piret Hussar**. Histology of the post-traumatic bone repair in rats. Elaboration and use of a new standardized experimental model – bicortical perforation of tibia compared to internal fracture and resection osteotomy. Tartu, 2002.
77. **Tõnu Rätsep**. Aneurysmal subarachnoid haemorrhage: Noninvasive monitoring of cerebral haemodynamics. Tartu, 2002.
78. **Marju Herodes**. Quality of life of people with epilepsy in Estonia. Tartu, 2003.
79. **Katre Maasalu**. Changes in bone quality due to age and genetic disorders and their clinical expressions in Estonia. Tartu, 2003.
80. **Toomas Sillakivi**. Perforated peptic ulcer in Estonia: epidemiology, risk factors and relations with *Helicobacter pylori*. Tartu, 2003.
81. **Leena Puksa**. Late responses in motor nerve conduction studies. F and A waves in normal subjects and patients with neuropathies. Tartu, 2003.
82. **Krista Lõivukene**. *Helicobacter pylori* in gastric microbial ecology and its antimicrobial susceptibility pattern. Tartu, 2003.

83. **Helgi Kolk**. Dyspepsia and *Helicobacter pylori* infection: the diagnostic value of symptoms, treatment and follow-up of patients referred for upper gastrointestinal endoscopy by family physicians. Tartu, 2003.
84. **Helena Soomer**. Validation of identification and age estimation methods in forensic odontology. Tartu, 2003.
85. **Kersti Oselin**. Studies on the human MDR1, MRP1, and MRP2 ABC transporters: functional relevance of the genetic polymorphisms in the *MDR1* and *MRP1* gene. Tartu, 2003.
86. **Jaan Soplepmann**. Peptic ulcer haemorrhage in Estonia: epidemiology, prognostic factors, treatment and outcome. Tartu, 2003.
87. **Margot Peetsalu**. Long-term follow-up after vagotomy in duodenal ulcer disease: recurrent ulcer, changes in the function, morphology and *Helicobacter pylori* colonisation of the gastric mucosa. Tartu, 2003.
88. **Kersti Klaamas**. Humoral immune response to *Helicobacter pylori* a study of host-dependent and microbial factors. Tartu, 2003.
89. **Pille Taba**. Epidemiology of Parkinson's disease in Tartu, Estonia. Prevalence, incidence, clinical characteristics, and pharmacoepidemiology. Tartu, 2003.
90. **Alar Veraksitš**. Characterization of behavioural and biochemical phenotype of cholecystokinin-2 receptor deficient mice: changes in the function of the dopamine and endopioidergic system. Tartu, 2003.
91. **Ingrid Kalev**. CC-chemokine receptor 5 (CCR5) gene polymorphism in Estonians and in patients with Type I and Type II diabetes mellitus. Tartu, 2003.
92. **Lumme Kadaja**. Molecular approach to the regulation of mitochondrial function in oxidative muscle cells. Tartu, 2003.
93. **Aive Liigant**. Epidemiology of primary central nervous system tumours in Estonia from 1986 to 1996. Clinical characteristics, incidence, survival and prognostic factors. Tartu, 2004.
94. **Andres, Kulla**. Molecular characteristics of mesenchymal stroma in human astrocytic gliomas. Tartu, 2004.
95. **Mari Järvelaid**. Health damaging risk behaviours in adolescence. Tartu, 2004.
96. **Ülle Pechter**. Progression prevention strategies in chronic renal failure and hypertension. An experimental and clinical study. Tartu, 2004.
97. **Gunnar Tasa**. Polymorphic glutathione S-transferases – biology and role in modifying genetic susceptibility to senile cataract and primary open angle glaucoma. Tartu, 2004.
98. **Tuuli Käämbre**. Intracellular energetic unit: structural and functional aspects. Tartu, 2004.
99. **Vitali Vassiljev**. Influence of nitric oxide syntase inhibitors on the effects of ethanol after acute and chronic ethanol administration and withdrawal. Tartu, 2004.

100. **Aune Rehema**. Assessment of nonhaem ferrous iron and glutathione redox ratio as markers of pathogeneticity of oxidative stress in different clinical groups. Tartu, 2004.
101. **Evelin Seppet**. Interaction of mitochondria and ATPases in oxidative muscle cells in normal and pathological conditions. Tartu, 2004.
102. **Eduard Maron**. Serotonin function in panic disorder: from clinical experiments to brain imaging and genetics. Tartu, 2004.
103. **Marje Oona**. *Helicobacter pylori* infection in children: epidemiological and therapeutic aspects. Tartu, 2004.
104. **Kersti Kokk**. Regulation of active and passive molecular transport in the testis. Tartu, 2005.
105. **Vladimir Järv**. Cross-sectional imaging for pretreatment evaluation and follow-up of pelvic malignant tumours. Tartu, 2005.
106. **Andre Õun**. Epidemiology of adult epilepsy in Tartu, Estonia. Incidence, prevalence and medical treatment. Tartu, 2005.
107. **Piibe Muda**. Homocysteine and hypertension: associations between homocysteine and essential hypertension in treated and untreated hypertensive patients with and without coronary artery disease. Tartu, 2005.
108. **Külli Kingo**. The interleukin-10 family cytokines gene polymorphisms in plaque psoriasis. Tartu, 2005.
109. **Mati Merila**. Anatomy and clinical relevance of the glenohumeral joint capsule and ligaments. Tartu, 2005.
110. **Epp Songisepp**. Evaluation of technological and functional properties of the new probiotic *Lactobacillus fermentum* ME-3. Tartu, 2005.
111. **Tiia Ainla**. Acute myocardial infarction in Estonia: clinical characteristics, management and outcome. Tartu, 2005.
112. **Andres Sell**. Determining the minimum local anaesthetic requirements for hip replacement surgery under spinal anaesthesia – a study employing a spinal catheter. Tartu, 2005.
113. **Tiia Tamme**. Epidemiology of odontogenic tumours in Estonia. Pathogenesis and clinical behaviour of ameloblastoma. Tartu, 2005.
114. **Triine Annus**. Allergy in Estonian schoolchildren: time trends and characteristics. Tartu, 2005.
115. **Tiia Voor**. Microorganisms in infancy and development of allergy: comparison of Estonian and Swedish children. Tartu, 2005.
116. **Priit Kasenõmm**. Indicators for tonsillectomy in adults with recurrent tonsillitis – clinical, microbiological and pathomorphological investigations. Tartu, 2005.
117. **Eva Zusinaite**. Hepatitis C virus: genotype identification and interactions between viral proteases. Tartu, 2005.
118. **Piret Kõll**. Oral lactoflora in chronic periodontitis and periodontal health. Tartu, 2006.
119. **Tiina Stelmach**. Epidemiology of cerebral palsy and unfavourable neurodevelopmental outcome in child population of Tartu city and county, Estonia Prevalence, clinical features and risk factors. Tartu, 2006.

120. **Katrin Pudersell**. Tropane alkaloid production and riboflavine excretion in the field and tissue cultures of henbane (*Hyoscyamus niger* L.). Tartu, 2006.
121. **Külli Jaako**. Studies on the role of neurogenesis in brain plasticity. Tartu, 2006.
122. **Aare Märtson**. Lower limb lengthening: experimental studies of bone regeneration and long-term clinical results. Tartu, 2006.
123. **Heli Tähepõld**. Patient consultation in family medicine. Tartu, 2006.
124. **Stanislav Liskmann**. Peri-implant disease: pathogenesis, diagnosis and treatment in view of both inflammation and oxidative stress profiling. Tartu, 2006.
125. **Ruth Rudissaar**. Neuropharmacology of atypical antipsychotics and an animal model of psychosis. Tartu, 2006.
126. **Helena Andreson**. Diversity of *Helicobacter pylori* genotypes in Estonian patients with chronic inflammatory gastric diseases. Tartu, 2006.
127. **Katrin Pruus**. Mechanism of action of antidepressants: aspects of serotoninergic system and its interaction with glutamate. Tartu, 2006.
128. **Priit Põder**. Clinical and experimental investigation: relationship of ischaemia/reperfusion injury with oxidative stress in abdominal aortic aneurysm repair and in extracranial brain artery endarterectomy and possibilities of protection against ischaemia using a glutathione analogue in a rat model of global brain ischaemia. Tartu, 2006.
129. **Marika Tammaru**. Patient-reported outcome measurement in rheumatoid arthritis. Tartu, 2006.
130. **Tiia Reimand**. Down syndrome in Estonia. Tartu, 2006.
131. **Diva Eensoo**. Risk-taking in traffic and Markers of Risk-Taking Behaviour in Schoolchildren and Car Drivers. Tartu, 2007.
132. **Riina Vibo**. The third stroke registry in Tartu, Estonia from 2001 to 2003: incidence, case-fatality, risk factors and long-term outcome. Tartu, 2007.
133. **Chris Pruunsild**. Juvenile idiopathic arthritis in children in Estonia. Tartu, 2007.
134. **Eve Õiglane-Šlik**. Angelman and Prader-Willi syndromes in Estonia. Tartu, 2007.
135. **Kadri Haller**. Antibodies to follicle stimulating hormone. Significance in female infertility. Tartu, 2007.
136. **Pille Ööpik**. Management of depression in family medicine. Tartu, 2007.
137. **Jaak Kals**. Endothelial function and arterial stiffness in patients with atherosclerosis and in healthy subjects. Tartu, 2007.
138. **Priit Kampus**. Impact of inflammation, oxidative stress and age on arterial stiffness and carotid artery intima-media thickness. Tartu, 2007.
139. **Margus Punab**. Male fertility and its risk factors in Estonia. Tartu, 2007.
140. **Alar Toom**. Heterotopic ossification after total hip arthroplasty: clinical and pathogenetic investigation. Tartu, 2007.

141. **Lea Pehme**. Epidemiology of tuberculosis in Estonia 1991–2003 with special regard to extrapulmonary tuberculosis and delay in diagnosis of pulmonary tuberculosis. Tartu, 2007.
142. **Juri Karjagin**. The pharmacokinetics of metronidazole and meropenem in septic shock. Tartu, 2007.
143. **Inga Talvik**. Inflicted traumatic brain injury shaken baby syndrome in Estonia – epidemiology and outcome. Tartu, 2007.
144. **Tarvo Rajasalu**. Autoimmune diabetes: an immunological study of type 1 diabetes in humans and in a model of experimental diabetes (in RIP-B7.1 mice). Tartu, 2007.
145. **Inga Karu**. Ischaemia-reperfusion injury of the heart during coronary surgery: a clinical study investigating the effect of hyperoxia. Tartu, 2007.
146. **Peeter Padrik**. Renal cell carcinoma: Changes in natural history and treatment of metastatic disease. Tartu, 2007.
147. **Neve Vendt**. Iron deficiency and iron deficiency anaemia in infants aged 9 to 12 months in Estonia. Tartu, 2008.
148. **Lenne-Triin Heidmets**. The effects of neurotoxins on brain plasticity: focus on neural Cell Adhesion Molecule. Tartu, 2008.
149. **Paul Korrovits**. Asymptomatic inflammatory prostatitis: prevalence, etiological factors, diagnostic tools. Tartu, 2008.
150. **Annika Reintam**. Gastrointestinal failure in intensive care patients. Tartu, 2008.
151. **Kristiina Roots**. Cationic regulation of Na-pump in the normal, Alzheimer's and CCK_2 receptor-deficient brain. Tartu, 2008.
152. **Helen Puusepp**. The genetic causes of mental retardation in Estonia: fragile X syndrome and creatine transporter defect. Tartu, 2009.
153. **Kristiina Rull**. Human chorionic gonadotropin beta genes and recurrent miscarriage: expression and variation study. Tartu, 2009.
154. **Margus Eimre**. Organization of energy transfer and feedback regulation in oxidative muscle cells. Tartu, 2009.
155. **Maire Link**. Transcription factors FoxP3 and AIRE: autoantibody associations. Tartu, 2009.
156. **Kai Haldre**. Sexual health and behaviour of young women in Estonia. Tartu, 2009.
157. **Kaur Liivak**. Classical form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in Estonia: incidence, genotype and phenotype with special attention to short-term growth and 24-hour blood pressure. Tartu, 2009.
158. **Kersti Ehrlich**. Antioxidative glutathione analogues (UPF peptides) – molecular design, structure-activity relationships and testing the protective properties. Tartu, 2009.
159. **Anneli Rätsep**. Type 2 diabetes care in family medicine. Tartu, 2009.
160. **Silver Türk**. Etiopathogenetic aspects of chronic prostatitis: role of mycoplasmas, coryneform bacteria and oxidative stress. Tartu, 2009.

161. **Kaire Heilman**. Risk markers for cardiovascular disease and low bone mineral density in children with type 1 diabetes. Tartu, 2009.
162. **Kristi Rüütel**. HIV-epidemic in Estonia: injecting drug use and quality of life of people living with HIV. Tartu, 2009.
163. **Triin Eller**. Immune markers in major depression and in antidepressive treatment. Tartu, 2009.
164. **Siim Suutre**. The role of TGF-β isoforms and osteoprogenitor cells in the pathogenesis of heterotopic ossification. An experimental and clinical study of hip arthroplasty. Tartu, 2010.
165. **Kai Kliiman**. Highly drug-resistant tuberculosis in Estonia: Risk factors and predictors of poor treatment outcome. Tartu, 2010.
166. **Inga Villa**. Cardiovascular health-related nutrition, physical activity and fitness in Estonia. Tartu, 2010.
167. **Tõnis Org**. Molecular function of the first PHD finger domain of Autoimmune Regulator protein. Tartu, 2010.
168. **Tuuli Metsvaht**. Optimal antibacterial therapy of neonates at risk of early onset sepsis. Tartu, 2010.
169. **Jaanus Kahu**. Kidney transplantation: Studies on donor risk factors and mycophenolate mofetil. Tartu, 2010.
170. **Koit Reimand**. Autoimmunity in reproductive failure: A study on associated autoantibodies and autoantigens. Tartu, 2010.
171. **Mart Kull**. Impact of vitamin D and hypolactasia on bone mineral density: a population based study in Estonia. Tartu, 2010.
172. **Rael Laugesaar**. Stroke in children – epidemiology and risk factors. Tartu, 2010.
173. **Mark Braschinsky**. Epidemiology and quality of life issues of hereditary spastic paraplegia in Estonia and implemention of genetic analysis in everyday neurologic practice. Tartu, 2010.
174. **Kadri Suija**. Major depression in family medicine: associated factors, recurrence and possible intervention. Tartu, 2010.
175. **Jarno Habicht**. Health care utilisation in Estonia: socioeconomic determinants and financial burden of out-of-pocket payments. Tartu, 2010.
176. **Kristi Abram**. The prevalence and risk factors of rosacea. Subjective disease perception of rosacea patients. Tartu, 2010.
177. **Malle Kuum**. Mitochondrial and endoplasmic reticulum cation fluxes: Novel roles in cellular physiology. Tartu, 2010.
178. **Rita Teek**. The genetic causes of early onset hearing loss in Estonian children. Tartu, 2010.
179. **Daisy Volmer**. The development of community pharmacy services in Estonia – public and professional perceptions 1993–2006. Tartu, 2010.
180. **Jelena Lissitsina**. Cytogenetic causes in male infertility. Tartu, 2011.
181. **Delia Lepik**. Comparison of gunshot injuries caused from Tokarev, Makarov and Glock 19 pistols at different firing distances. Tartu, 2011.
182. **Ene-Renate Pähkla**. Factors related to the efficiency of treatment of advanced periodontitis. Tartu, 2011.

183. **Maarja Krass**. L-Arginine pathways and antidepressant action. Tartu, 2011.
184. **Taavi Lai**. Population health measures to support evidence-based health policy in Estonia. Tartu, 2011.
185. **Tiit Salum**. Similarity and difference of temperature-dependence of the brain sodium pump in normal, different neuropathological, and aberrant conditions and its possible reasons. Tartu, 2011.
186. **Tõnu Vooder**. Molecular differences and similarities between histological subtypes of non-small cell lung cancer. Tartu, 2011.
187. **Jelena Štšepetova**. The characterisation of intestinal lactic acid bacteria using bacteriological, biochemical and molecular approaches. Tartu, 2011.
188. **Radko Avi**. Natural polymorphisms and transmitted drug resistance in Estonian HIV-1 CRF06_cpx and its recombinant viruses. Tartu, 2011, 116 p.
189. **Edward Laane**. Multiparameter flow cytometry in haematological malignancies. Tartu, 2011, 152 p.
190. **Triin Jagomägi**. A study of the genetic etiology of nonsyndromic cleft lip and palate. Tartu, 2011, 158 p.
191. **Ivo Laidmäe**. Fibrin glue of fish (*Salmo salar*) origin: immunological study and development of new pharmaceutical preparation. Tartu, 2012, 150 p.
192. **Ülle Parm**. Early mucosal colonisation and its role in prediction of invasive infection in neonates at risk of early onset sepsis. Tartu, 2012, 168 p.
193. **Kaupo Teesalu**. Autoantibodies against desmin and transglutaminase 2 in celiac disease: diagnostic and functional significance. Tartu, 2012, 142 p.
194. **Maksim Zagura**. Biochemical, functional and structural profiling of arterial damage in atherosclerosis. Tartu, 2012, 162 p.
195. **Vivian Kont**. Autoimmune regulator: characterization of thymic gene regulation and promoter methylation. Tartu, 2012, 134 p.
196. **Pirje Hütt**. Functional properties, persistence, safety and efficacy of potential probiotic lactobacilli. Tartu, 2012, 246 p.
197. **Innar Tõru**. Serotonergic modulation of CCK-4- induced panic. Tartu, 2012, 132 p.
198. **Sigrid Vorobjov**. Drug use, related risk behaviour and harm reduction interventions utilization among injecting drug users in Estonia: implications for drug policy. Tartu, 2012, 120 p.
199. **Martin Serg**. Therapeutic aspects of central haemodynamics, arterial stiffness and oxidative stress in hypertension. Tartu, 2012, 156 p.
200. **Jaanika Kumm**. Molecular markers of articular tissues in early knee osteoarthritis: a population-based longitudinal study in middle-aged subjects. Tartu, 2012, 159 p.
201. **Kertu Rünkorg**. Functional changes of dopamine, endopioid and endocannabinoid systems in CCK2 receptor deficient mice. Tartu, 2012, 125 p.
202. **Mai Blöndal**. Changes in the baseline characteristics, management and outcomes of acute myocardial infarction in Estonia. Tartu, 2012, 127 p.

203. **Jana Lass**. Epidemiological and clinical aspects of medicines use in children in Estonia. Tartu, 2012, 170 p.
204. **Kai Truusalu**. Probiotic lactobacilli in experimental persistent *Salmonella* infection. Tartu, 2013, 139 p.
205. **Oksana Jagur**. Temporomandibular joint diagnostic imaging in relation to pain and bone characteristics. Long-term results of arthroscopic treatment. Tartu, 2013, 126 p.
206. **Katrin Sikk**. Manganese-ephedrone intoxication – pathogenesis of neurological damage and clinical symptomatology. Tartu, 2013, 125 p.
207. **Kai Blöndal**. Tuberculosis in Estonia with special emphasis on drug-resistant tuberculosis: Notification rate, disease recurrence and mortality. Tartu, 2013, 151 p.
208. **Marju Puurand**. Oxidative phosphorylation in different diseases of gastric mucosa. Tartu, 2013, 123 p.
209. **Aili Tagoma**. Immune activation in female infertility: Significance of autoantibodies and inflammatory mediators. Tartu, 2013, 135 p.
210. **Liis Sabre**. Epidemiology of traumatic spinal cord injury in Estonia. Brain activation in the acute phase of traumatic spinal cord injury. Tartu, 2013, 135 p.
211. **Merit Lamp**. Genetic susceptibility factors in endometriosis. Tartu, 2013, 125 p.
212. **Erik Salum**. Beneficial effects of vitamin D and angiotensin II receptor blocker on arterial damage. Tartu, 2013, 167 p.
213. **Maire Karelson**. Vitiligo: clinical aspects, quality of life and the role of melanocortin system in pathogenesis. Tartu, 2013, 153 p.
214. **Kuldar Kaljurand**. Prevalence of exfoliation syndrome in Estonia and its clinical significance. Tartu, 2013, 113 p.
215. **Raido Paasma**. Clinical study of methanol poisoning: handling large outbreaks, treatment with antidotes, and long-term outcomes. Tartu, 2013, 96 p.
216. **Anne Kleinberg**. Major depression in Estonia: prevalence, associated factors, and use of health services. Tartu, 2013, 129 p.
217. **Triin Eglit**. Obesity, impaired glucose regulation, metabolic syndrome and their associations with high-molecular-weight adiponectin levels. Tartu, 2014, 115 p.
218. **Kristo Ausmees**. Reproductive function in middle-aged males: Associations with prostate, lifestyle and couple infertility status. Tartu, 2014, 125 p.
219. **Kristi Huik**. The influence of host genetic factors on the susceptibility to HIV and HCV infections among intravenous drug users. Tartu, 2014, 144 p.
220. **Liina Tserel**. Epigenetic profiles of monocytes, monocyte-derived macrophages and dendritic cells. Tartu, 2014, 143 p.
221. **Irina Kerna**. The contribution of *ADAM12* and *CILP* genes to the development of knee osteoarthritis. Tartu, 2014, 152 p.

222. **Ingrid Liiv**. Autoimmune regulator protein interaction with DNA-dependent protein kinase and its role in apoptosis. Tartu, 2014, 143 p.
223. **Liivi Maddison**. Tissue perfusion and metabolism during intra-abdominal hypertension. Tartu, 2014, 103 p.
224. **Krista Ress**. Childhood coeliac disease in Estonia, prevalence in atopic dermatitis and immunological characterisation of coexistence. Tartu, 2014, 124 p.
225. **Kai Muru**. Prenatal screening strategies, long-term outcome of children with marked changes in maternal screening tests and the most common syndromic heart anomalies in Estonia. Tartu, 2014, 189 p.
226. **Kaja Rahu**. Morbidity and mortality among Baltic Chernobyl cleanup workers: a register-based cohort study. Tartu, 2014, 155 p.
227. **Klari Noormets**. The development of diabetes mellitus, fertility and energy metabolism disturbances in a Wfs1-deficient mouse model of Wolfram syndrome. Tartu, 2014, 132 p.
228. **Liis Toome**. Very low gestational age infants in Estonia. Tartu, 2014, 183 p.
229. **Ceith Nikkolo**. Impact of different mesh parameters on chronic pain and foreign body feeling after open inguinal hernia repair. Tartu, 2014, 132 p.
230. **Vadim Brjalin**. Chronic hepatitis C: predictors of treatment response in Estonian patients. Tartu, 2014, 122 p.
231. **Vahur Metsna**. Anterior knee pain in patients following total knee arthroplasty: the prevalence, correlation with patellar cartilage impairment and aspects of patellofemoral congruence. Tartu, 2014, 130 p.
232. **Marju Kase**. Glioblastoma multiforme: possibilities to improve treatment efficacy. Tartu, 2015, 137 p.
233. **Riina Runnel**. Oral health among elementary school children and the effects of polyol candies on the prevention of dental caries. Tartu, 2015, 112 p.
234. **Made Laanpere**. Factors influencing women's sexual health and reproductive choices in Estonia. Tartu, 2015, 176 p.
235. **Andres Lust**. Water mediated solid state transformations of a polymorphic drug – effect on pharmaceutical product performance. Tartu, 2015, 134 p.
236. **Anna Klugman**. Functionality related characterization of pretreated wood lignin, cellulose and polyvinylpyrrolidone for pharmaceutical applications. Tartu, 2015, 156 p.
237. **Triin Laisk-Podar**. Genetic variation as a modulator of susceptibility to female infertility and a source for potential biomarkers. Tartu, 2015, 155 p.
238. **Mailis Tõnisson**. Clinical picture and biochemical changes in blood in children with acute alcohol intoxication. Tartu, 2015, 100 p.
239. **Kadri Tamme**. High volume haemodiafiltration in treatment of severe sepsis – impact on pharmacokinetics of antibiotics and inflammatory response. Tartu, 2015, 133 p.

240. **Kai Part**. Sexual health of young people in Estonia in a social context: the role of school-based sexuality education and youth-friendly counseling services. Tartu, 2015, 203 p.
241. **Urve Paaver**. New perspectives for the amorphization and physical stabilization of poorly water-soluble drugs and understanding their dissolution behavior. Tartu, 2015, 139 p.
242. **Aleksandr Peet**. Intrauterine and postnatal growth in children with HLA-conferred susceptibility to type 1 diabetes. Tartu. 2015, 146 p.
243. **Piret Mitt**. Healthcare-associated infections in Estonia – epidemiology and surveillance of bloodstream and surgical site infections. Tartu, 2015, 145 p.
244. **Merli Saare**. Molecular Profiling of Endometriotic Lesions and Endometria of Endometriosis Patients. Tartu, 2016, 129 p.
245. **Kaja-Triin Laisaar**. People living with HIV in Estonia: Engagement in medical care and methods of increasing adherence to antiretroviral therapy and safe sexual behavior. Tartu, 2016, 132 p.
246. **Eero Merilind**. Primary health care performance: impact of payment and practice-based characteristics. Tartu, 2016, 120 p.
247. **Jaanika Kärner**. Cytokine-specific autoantibodies in AIRE deficiency. Tartu, 2016, 182 p.
248. **Kaido Paapstel**. Metabolomic profile of arterial stiffness and early biomarkers of renal damage in atherosclerosis. Tartu, 2016, 173 p.
249. **Liidia Kiisk**. Long-term nutritional study: anthropometrical and clinico-laboratory assessments in renal replacement therapy patients after intensive nutritional counselling. Tartu, 2016, 207 p.
250. **Georgi Nellis**. The use of excipients in medicines administered to neonates in Europe. Tartu, 2017, 159 p.
251. **Aleksei Rakitin**. Metabolic effects of acute and chronic treatment with valproic acid in people with epilepsy. Tartu, 2017, 125 p.
252. **Eveli Kallas**. The influence of immunological markers to susceptibility to HIV, HBV, and HCV infections among persons who inject drugs. Tartu, 2017, 138 p.
253. **Tiina Freimann**. Musculoskeletal pain among nurses: prevalence, risk factors, and intervention. Tartu, 2017, 125 p.
254. **Evelyn Aaviksoo**. Sickness absence in Estonia: determinants and influence of the sick-pay cut reform. Tartu, 2017, 121 p.
255. **Kalev Nõupuu**. Autosomal-recessive Stargardt disease: phenotypic heterogeneity and genotype-phenotype associations. Tartu, 2017, 131 p.
256. **Ho Duy Binh**. Osteogenesis imperfecta in Vietnam. Tartu, 2017, 125 p.
257. **Uku Haljasorg**. Transcriptional mechanisms in thymic central tolerance. Tartu, 2017, 147 p.
258. **Živile Riispere**. IgA Nephropathy study according to the Oxford Classification: IgA Nephropathy clinical-morphological correlations, disease progression and the effect of renoprotective therapy. Tartu, 2017, 129 p.
259. **Hiie Soeorg**. Coagulase-negative staphylococci in gut of preterm neonates and in breast milk of their mothers. Tartu, 2017, 216 p.

260. **Anne-Mari Anton Willmore**. Silver nanoparticles for cancer research. Tartu, 2017, 132 p.
261. **Ott Laius**. Utilization of osteoporosis medicines, medication adherence and the trend in osteoporosis related hip fractures in Estonia. Tartu, 2017, 134 p.
262. **Alar Aab**. Insights into molecular mechanisms of asthma and atopic dermatitis. Tartu, 2017, 164 p.
263. **Sander Pajusalu**. Genome-wide diagnostics of Mendelian disorders: from chromosomal microarrays to next-generation sequencing. Tartu, 2017, 146 p.
264. **Mikk Jürisson**. Health and economic impact of hip fracture in Estonia. Tartu, 2017, 164 p.
265. **Kaspar Tootsi**. Cardiovascular and metabolomic profiling of osteoarthritis. Tartu, 2017, 150 p.
266. **Mario Saare**. The influence of AIRE on gene expression – studies of transcriptional regulatory mechanisms in cell culture systems. Tartu, 2017, 172 p.
267. **Piia Jõgi**. Epidemiological and clinical characteristics of pertussis in Estonia. Tartu, 2018, 168 p.
268. **Elle Põldoja**. Structure and blood supply of the superior part of the shoulder joint capsule. Tartu, 2018, 116 p.
269. **Minh Son Nguyen**. Oral health status and prevalence of temporomandibular disorders in 65–74-year-olds in Vietnam. Tartu, 2018, 182 p.
270. **Kristian Semjonov**. Development of pharmaceutical quench-cooled molten and melt-electrospun solid dispersions for poorly water-soluble indomethacin. Tartu, 2018, 125 p.
271. **Janne Tiigimäe-Saar**. Botulinum neurotoxin type A treatment for sialorrhea in central nervous system diseases. Tartu, 2018, 109 p.
272. **Veiko Vengerfeldt**. Apical periodontitis: prevalence and etiopathogenetic aspects. Tartu, 2018, 150 p.
273. **Rudolf Bichele**. TNF superfamily and AIRE at the crossroads of thymic differentiation and host protection against *Candida albicans* infection. Tartu, 2018, 153 p.
274. **Olga Tšuiko**. Unravelling Chromosomal Instability in Mammalian Preimplantation Embryos Using Single-Cell Genomics. Tartu, 2018, 169 p.
275. **Kärt Kriisa**. Profile of acylcarnitines, inflammation and oxidative stress in first-episode psychosis before and after antipsychotic treatment. Tartu, 2018, 145 p.
276. **Xuan Dung Ho**. Characterization of the genomic profile of osteosarcoma. Tartu, 2018, 144 p.
277. **Karit Reinson**. New Diagnostic Methods for Early Detection of Inborn Errors of Metabolism in Estonia. Tartu, 2018, 201 p.
278. **Mari-Anne Vals**. Congenital N-glycosylation Disorders in Estonia. Tartu, 2019, 148 p.

279. **Liis Kadastik-Eerme**. Parkinson's disease in Estonia: epidemiology, quality of life, clinical characteristics and pharmacotherapy. Tartu, 2019, 202 p.
280. **Hedi Hunt**. Precision targeting of intraperitoneal tumors with peptide-guided nanocarriers. Tartu, 2019, 179 p.
281. **Rando Porosk**. The role of oxidative stress in Wolfram syndrome 1 and hypothermia. Tartu, 2019, 123 p.
282. **Ene-Ly Jõgeda**. The influence of coinfections and host genetic factor on the susceptibility to HIV infection among people who inject drugs. Tartu, 2019, 126 p.
283. **Kristel Ehala-Aleksejev**. The associations between body composition, obesity and obesity-related health and lifestyle conditions with male reproductive function. Tartu, 2019, 138 p.
284. **Aigar Ottas**. The metabolomic profiling of psoriasis, atopic dermatitis and atherosclerosis. Tartu, 2019, 136 p.
285. **Elmira Gurbanova**. Specific characteristics of tuberculosis in low default, but high multidrug–resistance prison setting. Tartu, 2019, 129 p.
286. **Van Thai Nguyeni**. The first study of the treatment outcomes of patients with cleft lip and palate in Central Vietnam. Tartu, 2019, 144 p.
287. **Maria Yakoreva**. Imprinting Disorders in Estonia. Tartu, 2019, 187 p.
288. **Kadri Rekker**. The putative role of microRNAs in endometriosis pathogenesis and potential in diagnostics. Tartu, 2019, 140 p.
289. **Ülle Võhma**. Association between personality traits, clinical characteristics and pharmacological treatment response in panic disorder. Tartu, 2019, 121 p.
290. **Aet Saar**. Acute myocardial infarction in Estonia 2001–2014: towards risk-based prevention and management. Tartu, 2019, 124 p.
291. **Toomas Toomsoo**. Transcranial brain sonography in the Estonian cohort of Parkinson's disease. Tartu, 2019, 114 p.
292. **Lidiia Zhytnik**. Inter- and intrafamilial diversity based on genotype and phenotype correlations of Osteogenesis Imperfecta. Tartu, 2019, 224 p.
293. **Pilleriin Soodla**. Newly HIV-infected people in Estonia: estimation of incidence and transmitted drug resistance. Tartu, 2019, 194 p.
294. **Kristiina Ojamaa**. Epidemiology of gynecological cancer in Estonia. Tartu, 2020, 133 p.
295. **Marianne Saard**. Modern Cognitive and Social Intervention Techniques in Paediatric Neurorehabilitation for Children with Acquired Brain Injury. Tartu, 2020, 168 p.
296. **Julia Maslovskaja**. The importance of DNA binding and DNA breaks for AIRE-mediated transcriptional activation. Tartu, 2020, 162 p.
297. **Natalia Lobanovskaya**. The role of PSA-NCAM in the survival of retinal ganglion cells. Tartu, 2020, 105 p.
298. **Madis Rahu**. Structure and blood supply of the postero-superior part of the shoulder joint capsule with implementation of surgical treatment after anterior traumatic dislocation. Tartu, 2020, 104 p.

299. **Helen Zirnask**. Luteinizing hormone (LH) receptor expression in the penis and its possible role in pathogenesis of erectile disturbances. Tartu, 2020, 87 p.
300. **Kadri Toome**. Homing peptides for targeting of brain diseases. Tartu, 2020, 152 p.
301. **Maarja Hallik**. Pharmacokinetics and pharmacodynamics of inotropic drugs in neonates. Tartu, 2020, 172 p.
302. **Raili Müller**. Cardiometabolic risk profile and body composition in early rheumatoid arthritis. Tartu, 2020, 133 p.
303. **Sergo Kasvandik**. The role of proteomic changes in endometrial cells – from the perspective of fertility and endometriosis. Tartu, 2020, 191 p.
304. **Epp Kaleviste**. Genetic variants revealing the role of STAT1/STAT3 signaling cytokines in immune protection and pathology. Tartu, 2020, 189 p.
305. **Sten Saar**. Epidemiology of severe injuries in Estonia. Tartu, 2020, 104 p.
306. **Kati Braschinsky**. Epidemiology of primary headaches in Estonia and applicability of web-based solutions in headache epidemiology research. Tartu, 2020, 129 p.
307. **Helen Vaher**. MicroRNAs in the regulation of keratinocyte responses in *psoriasis vulgaris* and atopic dermatitis. Tartu, 2020, 242 p.
308. **Liisi Raam**. Molecular Alterations in the Pathogenesis of Two Chronic Dermatoses – Vitiligo and Psoriasis. Tartu, 2020, 164 p.
309. **Artur Vetkas**. Long-term quality of life, emotional health, and associated factors in patients after aneurysmal subarachnoid haemorrhage. Tartu, 2020, 127 p.
310. **Teele Kasepalu**. Effects of remote ischaemic preconditioning on organ damage and acylcarnitines' metabolism in vascular surgery. Tartu, 2020, 130 p.
311. **Prakash Lingasamy**. Development of multitargeted tumor penetrating peptides. Tartu, 2020, 246 p.
312. **Lille Kurvits.** Parkinson's disease as a multisystem disorder: whole transcriptome study in Parkinson's disease patients' skin and blood. Tartu, 2021, 142 p.
313. **Mariliis Põld.** Smoking, attitudes towards smoking behaviour, and nicotine dependence among physicians in Estonia: cross-sectional surveys 1982–2014. Tartu, 2021, 172 p.
314. **Triin Kikas**. Single nucleotide variants affecting placental gene expression and pregnancy outcome. Tartu, 2021, 160 p.
315. **Hedda Lippus-Metsaots**. Interpersonal violence in Estonia: prevalence, impact on health and health behaviour. Tartu, 2021, 172 p.

316. **Georgi Dzaparidze.** Quantification and evaluation of the diagnostic significance of adenocarcinoma-associated microenvironmental changes in the prostate using modern digital pathology solutions. Tartu, 2021, 132 p.
317. **Tuuli Sedman.** New avenues for GLP1 receptor agonists in the treatment of diabetes. Tartu, 2021, 118 p.

318. **Martin Padar.** Enteral nutrition, gastrointestinal dysfunction and intestinal biomarkers in critically ill patients. Tartu, 2021, 189 p.
319. **Siim Schneider.** Risk factors, etiology and long-term outcome in young ischemic stroke patients in Estonia. Tartu, 2021, 131 p.
320. **Konstantin Ridnõi.** Implementation and effectiveness of new prenatal diagnostic strategies in Estonia. Tartu, 2021, 191 p.
321. **Risto Vaikjärv.** Etiopathogenetic and clinical aspects of peritonsillar abscess. Tartu, 2021, 115 p.
322. **Liis Preem.** Design and characterization of antibacterial electrospun drug delivery systems for wound infections. Tartu, 2022, 220 p.
323. **Keerthie Dissanayake.** Preimplantation embryo-derived extracellular vesicles: potential as an embryo quality marker and their role during the embryo-maternal communication. Tartu, 2022, 203 p.
324. **Laura Viidik.** 3D printing in pharmaceutics: a new avenue for fabricating therapeutic drug delivery systems. Tartu, 2022, 139 p.
325. **Kasun Godakumara.** Extracellular vesicle mediated embryo-maternal communication – A tool for evaluating functional competency of pre-implantation embryos. Tartu, 2022, 176 p.
326. **Hindrek Teder.** Developing computational methods and workflows for targeted and whole-genome sequencing based non-invasive prenatal testing. Tartu, 2022, 138 p.
327. **Jana Tuusov.** Deaths caused by alcohol, psychotropic and other substances in Estonia: evidence based on forensic autopsies. Tartu, 2022, 157 p.
328. **Heigo Reima.** Colorectal cancer care and outcomes – evaluation and possibilities for improvement in Estonia. Tartu, 2022, 146 p.
329. **Liisa Kuhi.** A contribution of biomarker collagen type II neoepitope C2C in urine to the diagnosis and prognosis of knee osteoarthritis. Tartu, 2022, 157 p.
330. **Reeli Tamme.** Associations between pubertal hormones and physical activity levels, and subsequent bone mineral characteristics: a longitudinal study of boys aged 12–18. Tartu, 2022, 118 p.
331. **Deniss Sõritsa.** The impact of endometriosis and physical activity on female reproduction. Tartu, 2022, 152 p.
332. **Mohammad Mehedi Hasan.** Characterization of follicular fluid-derived extracellular vesicles and their contribution to periconception environment. Tartu, 2022, 194 p.
333. **Priya Kulkarni.** Osteoarthritis pathogenesis: an immunological passage through synovium-synovial fluid axis. Tartu, 2022, 268 p.
334. **Nigul Ilves.** Brain plasticity and network reorganization in children with perinatal stroke: a functional magnetic resonance imaging study. Tartu, 2022, 169 p.
335. **Marko Murruste.** Short- and long-term outcomes of surgical management of chronic pancreatitis. Tartu, 2022, 180 p.
336. **Marilin Ivask.** Transcriptomic and metabolic changes in the WFS1-deficient mouse model. Tartu, 2022, 158 p.

337. **Jüri Lieberg.** Results of surgical treatment and role of biomarkers in pathogenesis and risk prediction in patients with abdominal aortic aneurysm and peripheral artery disease. Tartu, 2022, 160 p.
338. **Sanna Puusepp.** Comparison of molecular genetics and morphological findings of childhood-onset neuromuscular disorders. Tartu, 2022, 216 p.
339. **Khan Nguyen Viet.** Chemical composition and bioactivity of extracts and constituents isolated from the medicinal plants in Vietnam and their nanotechnology-based delivery systems. Tartu, 2023, 172 p.
340. **Getnet Balcha Midekessa.** Towards understanding the colloidal stability and detection of Extracellular Vesicles. Tartu, 2023, 172 p.
341. **Kristiina Sepp.** Competency-based and person-centred community pharmacy practice – development and implementation in Estonia. Tartu, 2023, 242 p.
342. **Linda Sõber.** Impact of thyroid disease and surgery on patient's quality of voice and swallowing. Tartu, 2023, 114 p.
343. **Anni Lepland.** Precision targeting of tumour-associated macrophages in triple negative breast cancer. Tartu, 2023, 160 p.
344. **Sirje Sammul.** Prevalence and risk factors of arterial hypertension and cardiovascular mortality: 13-year longitudinal study among 35- and 55-year-old adults in Estonia and Sweden. Tartu, 2023, 158 p.
345. **Maarjaliis Paavo**. Short-Wavelength and Near-Infrared Autofluorescence Imaging in Recessive Stargardt Disease, Choroideremia, *PROM1*-Macular Dystrophy and Ocular Albinism. Tartu, 2023, 202 p.
346. **Kaspar Ratnik.** development of predictive multimarker test for preeclampsia in early and late pregnancy. Tartu, 2023, 134 p.
347. **Kärt Simre.** Development of coeliac disease in two populations with different environmental backgrounds. Tartu, 2023, 161 p.
348. **Qurat Ul Ain Reshi.** Characterization of the maternal reproductive tract and spermatozoa communication during periconception period via extracellular vesicles. Tartu, 2023, 182 p.
349. **Stanislav Tjagur.** *Mycoplasma genitalium* and other sexually transmitted infections causing urethritis – their prevalence, impact on male fertility parameters and prostate health. Tartu, 2023, 225 p.