Doctoral thesis for the Degree of Philosophy, Faculty of Medicine

Hearing and middle ear status in children and young adults with cleft palate

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For all children born with cleft palate

"I dream, I test my dreams against my beliefs,
I dare to take risks, and I execute my vision to make
those dreams come true."

Walt Disney, The Disney Way

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Abstract:

Objective: The overall aim of this thesis was to define the hearing and prevalence of abnormal middle ear status across childhood and into young adulthood and attempt to understand the effects of a higher prevalence of abnormal middle ear status on the auditory system. The prevalence of abnormal middle ear status is higher in children with cleft lip and palate or cleft palate (CP±L) than in children without CP±L. Little is known when or if the prevalence of abnormal middle ear status decreases as children age or the effects of this higher prevalence of abnormal middle ear status on hearing.

Methods: The studies examined audiological and otological data from children with CP±L and children without CP±L at 1, 1.5, 3 and 5 years of age, analysed audiological and otological data from adolescents with CP±L with and without additional malformations at 7, 10, 13 and 16 years of age, and presented hearing and speech recognition performance from a group of young adults with CP±L.

Results: The prevalence of abnormal middle ear status was higher in children with CP±L than in children without CP±L. This higher prevalence of abnormal middle ear status decreased significantly with age and normalized by 13 years. Individuals with CP±L also presented with worse hearing in the low and mid frequencies which also normalized by 13 years of age. However, the hearing thresholds in the higher frequencies did not improve. When abnormal middle ear status was present, children with CP±L presented with significantly higher hearing thresholds than children without CP±L. In young adults, poorer speech recognition performance existed in those with abnormal middle ear status on the day of testing as compared to those without abnormal middle ear status.

Conclusion: Higher prevalence of abnormal middle ear status is evident in individuals with CP±L. Also when a hearing loss is present, individuals with CP±L experience higher hearing thresholds than those without CP±L. This higher prevalence of abnormal middle ear status results in poorer high frequency hearing which could potentially lead to challenges in academics. It may also lead to difficulties understanding speech in social situations. Therefore, individuals with CP±L need regular audiolgical and otological follow-up to ensure management is appropriate and timely to ensure optimal speech, language, and auditory development as the presence of abnormal middle ear status effects hearing outcomes.

Key words: hearing, middle ear status, OME, cleft palate

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Abbreviations

ABR:	Auditory brainstem response
AOM:	Acute suppurative otitis media
ASSR:	Auditory steady state response
BCLP:	Bilateral cleft lip and palate
CP±L:	Cleft palate with or without cleft lip
dB HL:	DeciBel hearing level
GEE:	Generalized Estimating Equation
ICP:	Isolated cleft palate
ICP+:	Isolated cleft palate with additional malformations and/or identified syndromes
MLD:	Masking level difference
OAE:	Otoacoustic emissions
OM:	Otitis media
OME:	Otitis media with effusion
PTA:	Pure-tone average
PTA4:	Pure-tone average based on four frequencies (500 Hz, 1000 Hz, 2000 Hz, and 4000 HZ)
PTAHF:	Pure-tone average based on two high frequencies (6000 Hz and 8000 Hz)
UCLP:	Unilateral cleft lip and palate

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List of Publications

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I Flynn, T., Möller, C., Jönsson, R., Lohmander, A. (2009). The high prevalence of otitis media with effusion in children with cleft lip and palate as compared to children without clefts. *International Journal of Pediatric Otorhinolaryngology*, 73, 1441–1446.

II Flynn, T., Lohmander, A., Möller, C., Magnusson, L. (2012). A longitudinal study of hearing and abnormal middle ear status in adolescents with cleft lip and palate. *Laryngoscope*, Epub ahead of print.

III Flynn, T., Persson, C., Möller, C., Lohmander, A., Magnusson, L. (2013). A longitudinal study of hearing and middle ear status in individuals with cleft palate with and without additional malformations/syndromes. Submitted.

IV Flynn, T., Möller, C., Lohmander, A., Magnusson, L. (2012). Hearing and otitis media with effusion in young adults with cleft lip and palate. *Acta Oto-Laryngologica*, 132 (9), 959-966.

1 Introduction

A cleft lip and palate starts to be visible during the sixth to twelfth week of embryological development. This cleft palate leads to several challenges in development including feeding, maxillary growth and dentition, speech, and language, and hearing. Several studies have investigated the surgical techniques in regards to speech and language outcomes and to midfacial growth in children with cleft palate with or without cleft lip (CP±L), but few have examined the middle ear status and hearing.

There is need for further knowledge and definition of prevalence of abnormal middle ear status and hearing in children and adults with cleft palate, as children with CP±L exhibit an increased prevalence of abnormal middle ear status. However, this prevalence has not been systematically investigated. A limited number of studies have been performed retrospectively and prospectively. They have included few participants. Retrospective studies have been cross-sectional with a limited amount of data. A few prospective studies have been performed on young children (less than four years of age) or the data have been collected via a self-report questionnaire. There is a need for a longitudinal study to examine the prevalence of abnormal middle ear status and hearing in this population. There has been very little research linking abnormal middle ear status to hearing. Therefore, this thesis attempts to define the hearing and prevalence of abnormal middle ear status in children and young adults with CP±L. This is the first step towards a systematic investigation of abnormal middle ear status across childhood to find out the effects it may have on the development of speech, language, academic, and hearing skills.

2 Background

2.1 Auditory system and hearing

2.1.1 Embryological and fetal development of the ears, face, and palate

The embryological and fetal development of the ear, face, and palate are outlined in Table 1. Each structure is listed with the corresponding week of development (Northern & Downs, 2002; Zemlin, 1998). Lip closure occurs during the fifth and sixth week and the palate is formed between the fifth and twelfth week. The separation between the nasal and oral cavities begins during the sixth week (Coleman & Sykes, 2001).

The external ear is formed from the first and second branchial arches. From them, six hillocks form to give shape to the auricle. The tissue thickens and becomes cartilage. The external auditory canal originates from the first branchial groove and begins during the fourth to fifth week. Between the eighth and ninth week, the outer third of the external auditory canal is formed and consists of cartilage. It is not fully grown until 9 years of age.

The middle ear is formed from the first and second branchial arches and begins to develop during the third week. By the eighth week, the lower portion of the middle ear is present while the upper portion is still filled with mesenchyme. Of the ossicles, the malleus and incus are beginning to be formed, but are still in cartilaginous form. In the ninth week, the three layers of the tympanic membrane are starting to be developed. The stapes is formed during the fifteenth week in cartilage while the incus and malleus are ossified in the sixteenth week. The stapes ossifies during the eighteenth week and the middle ear cavity is pneumatized during the thirtieth week. All three ossicles are adult-sized.

The inner ear begins its development from the auditory pit in the third week. In the seventh week of development, one cochlear coil and the sensory cells in the utricle and saccule are formed. Two and a half turns of the cochlea is present in the eleventh week and the sensory cells are present in the cochlea in the twelfth week. The cochlea reaches adult size by week 19.

A schematic overview of tissues involved is CP±L is seen in Table 1.

Table 1. Embryological and fetal development of the ear, lip, and palate (Northern & Downs, 2002; Zemlin, 1998).

Fetal week	Inner Ear	Middle Ear	External Ear	Palate & Lip
3	Auditory pit	Tubotympanic recess begins (Eustachian tube and middle ear cavity)	Tissue thickenings begin to form	Mandibular arches, maxillary processes come out from the first brachial arch
6	Utricle and saccule present, semicircular canals begin		Auditory canal begins and 6 hillocks can be seen which form the auricle	Union of lateral nasal with maxillary processes creating a separation between nasal and oral cavity
8 and 9		Incus and malleus in cartilage; lower half of middle ear cavity formed and tympanic membrane has 2 layers of tissue	Outer third of auditory canal formed (cartilaginous)	Hard palate is fused and upper lip is fused and completed by week 10
12	2.5 turns in cochlea present and sensory cells in cochlea			Soft palatal muscles fuse
18		Stapes, malleus, and incus begin to ossify		
20	Maturation of inner ear to adult size		Aurical is adult shape, but still growing	
30		Pneumatization of tympanum	Auditory canal continues to grow	

2.1.2 Anatomy of the auditory system

The auditory system can be described in four components: (1) outer ear, (2) middle ear, (3) inner ear, and (4) central auditory pathways (See Figure 1). This thesis will focus on the anatomy of the middle ear with highlights of the inner ear. The central auditory pathways will not be discussed in detail.

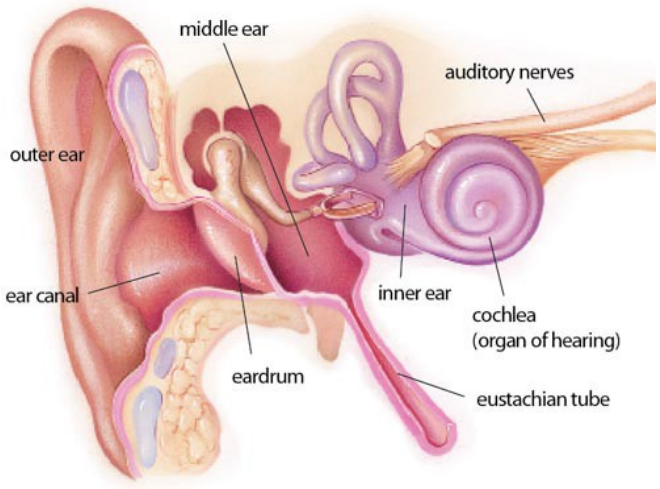

Figure 1. The auditory system. Reprinted with permission from Krames StayWell.

Outer ear

The outer ear is comprised by the pinna and the external auditory canal. The pinna or auricle is visible and fastened on the side of the head at an approximate angle of 30 degrees. There are several visible landmarks including the concha (deepest of several depressions), the helix (outer rim of the auricle), the tragus (small flap near the concha), and the earlobe (inferior extremity) (Zemlin, 1998).

The external auditory canal is a curved and irregularly shaped tube which is approximately 25 mm in length and ends at the tympanic membrane. The lateral one-third of the canal is supported by a cartilaginous skeleton and the remaining two-thirds of the canal is supported by osseous skeleton. The surrounding structure is fully cartilaginous until the end of the third year of life. The diameter is the largest at the auricular orifice (external) and gradually becomes narrower towards the isthmus (junction between the bony and cartilaginous portion) (Zemlin, 1998).

Middle ear

The middle ear begins at the tympanic membrane and encompasses the middle ear cavity, muscles, ossicles, and the opening of the Eustachian tube (auditory tube). See Figure 2. The middle ear cavity is an air-filled space which lies within the petrous portion of the temporal bone. It can be described by the anatomical landmarks on each of the six sides of the cavity. The lateral wall is formed by the tympanic membrane and the medial wall contains the oval and round windows and the promontory. The oval window is occupied by the footplate of the stapes while the round window opens into the basal turn of the cochlear. The promontory is where the lateral projection of the basal turn of the cochlea occurs. The superior wall is formed by the tegmental wall and separates the middle ear cavity from the cranium while the inferior wall is the tympanic plate of the temporal bone. The posterior wall is marked by the stapedius muscle and the anterior wall contains the tensor tympani muscle and the opening of the Eustachian tube (Zemlin, 1998).

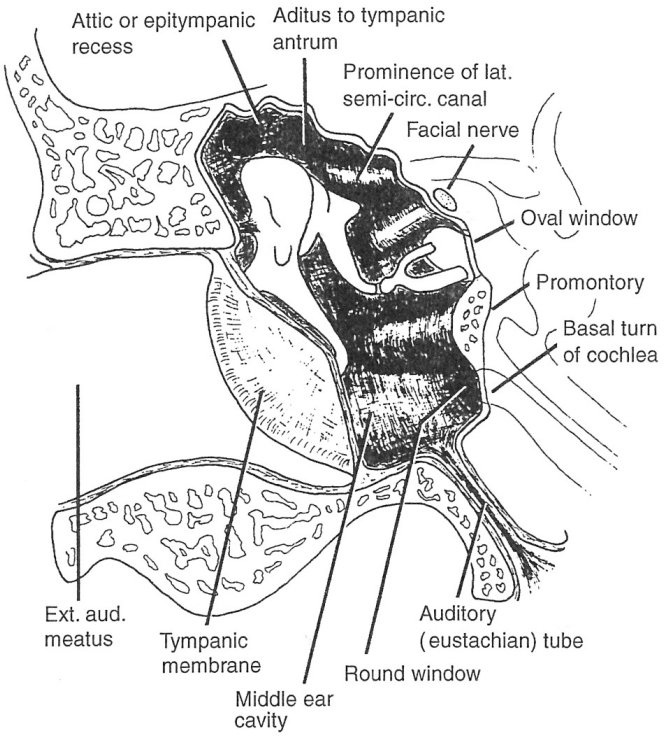

Figure 2. A schematic of the middle ear as seen from the front (Zemlin, 1998). Reprinted with permission from Pearson Education.

The external auditory canal ends at the tympanic membrane. The tympanic membrane forms the lateral wall of the middle ear cavity and is cone-shaped with the tip of the cone placed inward towards the middle ear cavity. The tympanic membrane consists of three layers of tissue: (1) thin outer cutaneous layer which is continuous with the lining of the external ear canal, (2) fibrous middle layer which is responsible for the compliance of the tympanic membrane and has an uneven distribution of fibers, and (3) internal layer of serious membrane which is continuous with the middle ear cavity. In the fibrous layer, the area that has the densest amount of fibers is called the pars tensa and the area with the least amount of fiber is called the pars flaccida. (Zemlin, 1998).

The middle ear contains two muscles: tensor veli tympani and the stapedius. The tensor veli tympani originates from the cartilaginous portion of the Eustachian tube and the great wing of the sphenoid and inserts into the malleus while the stapedius muscle originates from the bony canal in the posterior wall in the middle ear cavity and inserts into the neck of the stapes (Zemlin, 1998).

The ossicles are a chain of bones comprising the malleus, incus, and stapes. The malleus consists of a manubrium, head, neck and lateral and anterior processes. The lateral process of the malleus attaches to the tympanic membrane and pulls the tympanic membrane in which gives it a concave shape. The next ossicle, the incus, is comprised of a body and a short and long process. The body of the incus rests on the head of the malleus. The final ossicle, the stapes is constituted of a head, footplate, and two crura. The head of the stapes connects to the long process of the incus while the footplate is fastened to the oval window by the annular ligament (Zemlin, 1998).

The Eustachian tube connects the middle ear and the nasopharynx and is approximately 35 to 38 mm in length. In an adult, the Eustachian tube is directed downward, forward, and medially. In a child, the Eustachian tube is directed horizontally and about half the length with very little osseous portion. There is an osseous and cartilaginous portion of the tube with the osseous portion beginning at the anterior wall of the middle ear cavity and extending approximately 12 mm. The cartilaginous portion is approximately 18 to 24 mm in length and ends in soft connective tissue in the nasopharynx. The Eustachian tube has three muscles originating from it: salpingopalatini, levator veli palatini, and the tensor veli palatini. The salgpingopalatini originates from the cartilaginous portion of the tube and inserts into the soft palate while the levator

veli palatini originates from the temporal bone at the junction of the cartilaginous and osseous intersection of the tube and inserts into the soft palate.The tensor veli palatini originates from the cartilaginous and osseous portions of the tube and inserts into the palatal aponeurosis (Zemlin, 1998).

Inner ear

The inner ear is divided into two sections: organs of hearing and organs of balance. The organs of balance will not be discussed in this thesis as they were not investigated. The organs of hearing include the cochlea which contains the scala vestibuli, scala tympani, scala media, with the Organ of Corti. The cochlea is a bony canal and is approximately 35 mm in length and coils around two and five-eighths turn. It is divided into the scala vestibuli and the scala tympani by the spiral lamina and is filled with perilymph. The cochlea is also divided by the scala media, a tube approximately 34 mm in length filled with endolymph. In the inferior portion of the scala media is the basilar membrane, which attaches to the spiral lamina. Within the scala media lays the Organ of Corti, inner hair cells, outer hair cells, and the tectorial membrane. The basal end of the scala tympani and scala media communicate with the round window. The high frequency inner hair cells are located in the basal end and the low frequency inner hair cells are located in the apical end. Therefore, the high frequency region is located closest to the middle ear cavity (see Figure 3). (*Audiology: Diagnosis*, 2007; Zemlin, 1998).

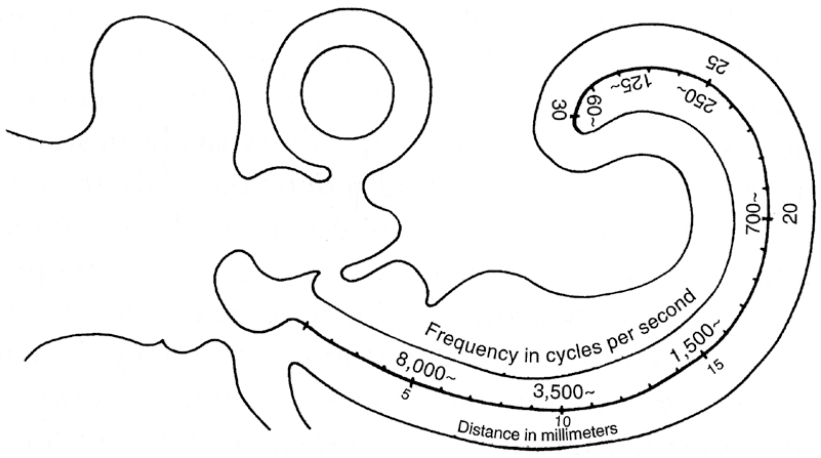

Figure 3. Frequency location along the basilar membrane (Zemlin, 1998). Reprinted with permission from Pearson Education.

2.1.2 Physiology of the auditory system

The physiology of the middle ear is the focus on this thesis and will be the center of this discussion of physiology. The other components of the auditory system will not be discussed in detail.

The function of the outer ear is to collect and direct acoustical sound energy. The middle ear transforms the acoustical energy to mechanical energy and performs impedance matching. The inner ear transforms the mechanical energy to hydrodynamic wave energy and encodes the energy into nerve impulses (Zemlin, 1998) .

The air-filled middle ear cavity needs to have the same pressure as the atmospheric pressure in order to efficiently transfer and transform sound. The tympanic membrane moves best when the atmospheric and middle ear cavity pressures are equal. Slight pressure differences result in the elevation of hearing thresholds, affecting more the low than the high frequencies. This may be due to the stiffening of the tympanic membrane. In order to maintain equal pressure, the Eustachian tube opens. It is normally closed, but opens approximately every fifth swallow. Eustachian tube has three functions: protection from nasopharyngeal secretions, equalization of pressure between the middle ear cavity, and the atmosphere and clearance of the middle ear secretions (Fireman, 1997; Zemlin, 1998).

Pressure equalization occurs when the Eustachian tube opens frequently and equates the atmospheric pressure and the pressure in the middle ear cavity. The Eustachian tube opens by the contraction of the tensor veli palatini which pulls the lateral wall away from the more stationary medial wall. The levator veli palatini may also aid in the opening of the Eustachian tube by elevating the cartilage of the tube when the muscle contracts. The tensor tympani and salpingopalatini may play a role in the opening of the Eustachian tube (Fireman, 1997; Zemlin, 1998). See Figure 4 for an illustration of the Eustachian tube and muscles.

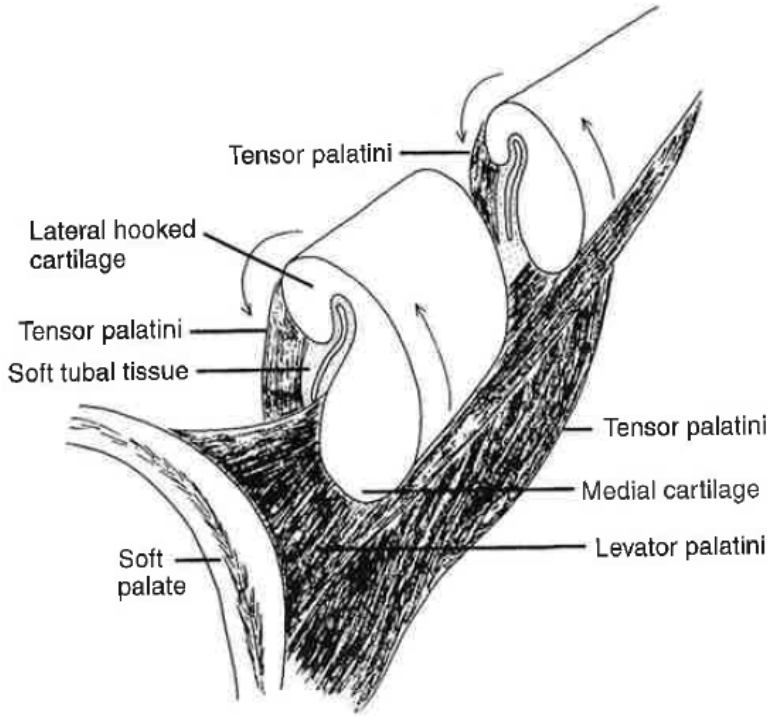

Figure 4. Dilation of the Eustachian tube (Zemlin, 1998). Reprinted with permission from Pearson Education.

The third function of the Eustachian tube is to drain secretions from the middle ear and again allowing the middle ear cavity to be air-filled. The mucous drains from the middle ear cavity to the nasopharynx (Fireman, 1997; Zemlin, 1998).

The inner ear transforms hydrodynamic energy to nerve impulses. This begins by the stapes' footplate moving the oval window. The oval window displaces and moves the perilymph in the scala vestibuli and scala tympani. This motion in turn moves the basilar membrane. The basilar membrane moves and the inner hair cells are excited as they shear the tectorial membrane and transmit a neural impulse up the auditory nerve. The high frequency excitation is located at the basal end and the low frequency excitation is located at the apical end of the cochlea (*Audiology: Diagnosis*, 2007; Zemlin, 1998).

The sound, now re-encoded, is transmitted up to the central auditory system via the spiral ganglion neurons which are the beginning of the auditory nerve. The auditory signal travels through the cochlear nucleus, superior olivary complex, lateral lemniscus, inferior colliculus, and the medial geniculate body to the

auditory cortex in the right and left temporal lobes. During the path to the auditory cortex, the auditory signal is divided for the right and left sides. At the cochlear nucleus, a synapse occurs and the sound is divided with half of the nerve fibers traveling up on the right side and other half of the nerve fibers ascending on the left side. Another synapse for some of the fibers occurs at the lateral lemniscus while others remain uninterrupted and synapse at the inferior colliculus. The final point of synapse for the sound before ending at the auditory cortex takes place at the medial geniculate body. The tonotopographical arrangement is maintained throughout this pathway (*Audiology: Diagnosis,* 2007; Zemlin, 1998).

In normal hearing, sound is primarily transmitted via air to the external ear. However, sound is also conducted through the bone. This occurs when there is direct contact between the skull and the sound source or the sounds are intense enough to produce vibrations within the skull. In turn, the skull vibrates the ossicular chain and the inner ear. The movements in the skull cause a difference in pressures between the scala tympani and scala vestibuli. This pressure differentiation results in the displacement of the basilar membrane (*Audiology: Diagnosis*, 2007; Zemlin, 1998).

2.1.3 Types of hearing loss

On average, normal hearing is 0 decibel hearing level (dB HL) with thresholds falling in the range of -10 dB HL to 20 dB HL. Hearing loss is commonly considered when thresholds are greater than 20 dB HL (Tharpe & Sladen, 2008). Individuals with normal hearing thresholds have little difficulty hearing normal conversational speech. By measuring and comparing air conduction and bone conduction thresholds, the hearing loss can be defined. The main types of hearing loss include: (1) sensorineural, (2) conductive, and (3) mixed. Other hearing losses can include auditory processing disorders, pseudohypoacucis, or auditory neuropathy spectrum disorder. Conductive hearing loss occurs when the sound is not conducted efficiently through the outer and/or middle ear. Pure-tone bone conduction thresholds are within normal range, but air conduction thresholds exceed 20 dB HL. Sensorineural hearing loss implies air and bone conduction thresholds exceed the normal range and are within 10 dB of each other. A mixed hearing loss is a combined sensorineural and conductive hearing loss involving the outer ear, middle ear, inner ear, and/or central pathways. Air

and bone thresholds exceed the normal range, but the bone thresholds are better than the air conduction thresholds. The difference between the bone and air conduction thresholds is referred to as the air-bone gap. This gap needs to be greater than 10 dB to be considered a mixed loss (*Audiology: Diagnosis,* 2007). See Figure 5 for audiograms representing the different types of hearing loss.

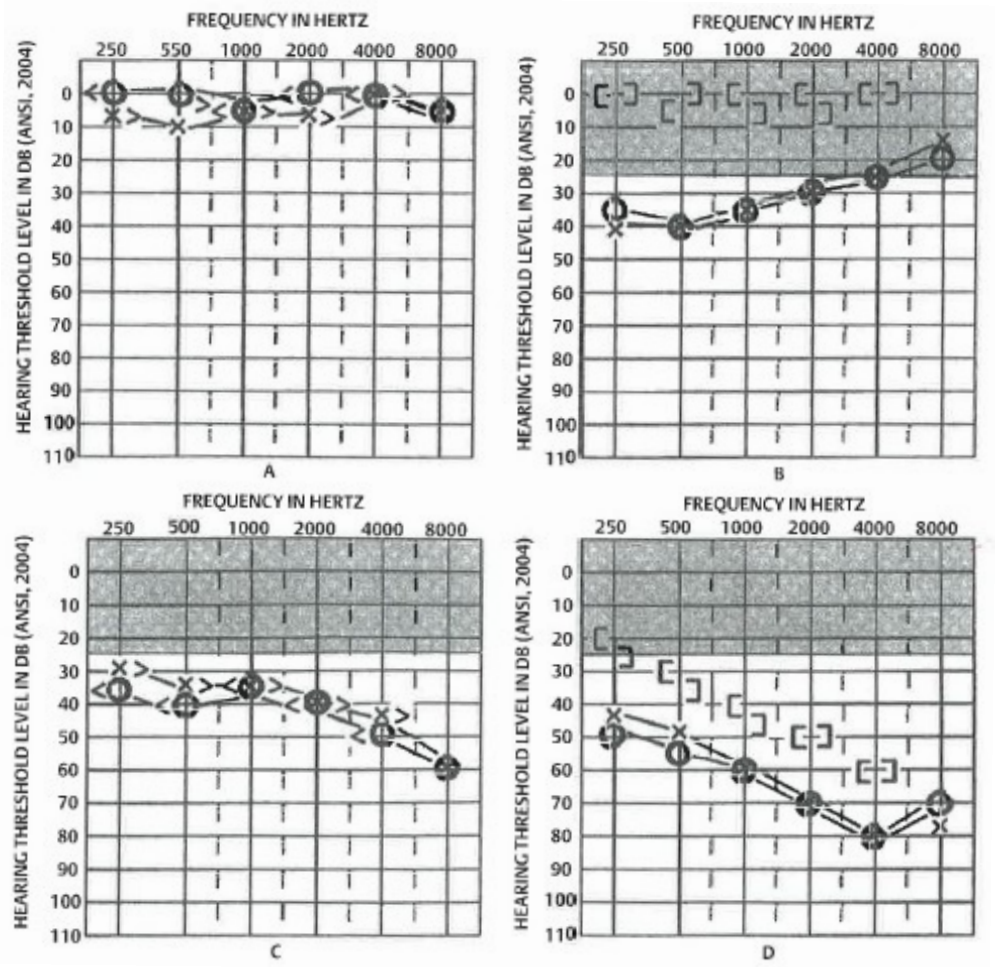

Figure 5: Audiometric results showing (a) normal hearing, (b) conductive hearing loss, (c) sensorineural hearing loss, and (d) mixed hearing loss, (*Audiology: Diagnosis*, 2007). Reprinted with permission from Thieme Publishers.

Hearing loss can also be categorized by degree. Mild hearing loss is considered 21-40 dB HL, moderate hearing loss 41-70 dB HL, severe hearing loss 71-90, and profound hearing loss from 91 dB HL (*Audiology: Diagnosis*, 2007; Northern & Downs, 2002; Tharpe & Sladen, 2008).

2.1.4 Methods to assess middle ear status and hearing

Otomicroscopy

Otomicroscopy involves a visual examination of the external auditory canal and tympanic membrane. The examination is not complete until the entire tympanic membrane is visualized. See figure 6 for a normal tympanic membrane.

Cerumen is often seen in the external auditory canal and removed if necessary. The anatomy seen and the color of the tympanic membrane can provide information on the status of the middle ear (*Audiology: Diagnosis*, 2007) (see Table 2).

Table 2. Color and anatomy of the tympanic membrane and possible reasons (*Audiology: Diagnosis*, 2007; Lee & Yeo, 2004).

Color	
	Translucent: healthy
	White masses: cholesteatoma, tympanosclerosis, middle ear osteoma
	Dark blue masses: venous vascular structures
	Dark red masses: highly vascular tumors or granulation tissue
	Opaque or yellow: otitis media with effusion (OME)
Anatomy	
	Long and short processes of the malleus: healthy
	Long process of the incus: healthy
	Head of the malleus: erosion of the superior auditory canal and lateral wall of the middle ear cavity
	Body of the incus: erosion of the superior auditory canal and lateral wall of the middle ear cavity
	Perforation or deep retraction of the pars flaccida: cholesteatoma
	Fluid, bubbles: otitis media with effusion (OME)
	Retracted tympanic membrane: otitis media with effusion (OME)

A pneumatic otoscope is also commonly used to examine the middle ear. The degree of mobility of the tympanic membrane is measured. The otoscope produces a negative or positive pressure in the ear canal which typically leads to normal movement of the ear drum. However, if the tympanic membrane is sluggish, it may be due to otitis media with effusion (OME). If the tympanic membrane moves rapidly, the tympanic membrane may be perforated (*Audiology: Diagnosis*, 2007).

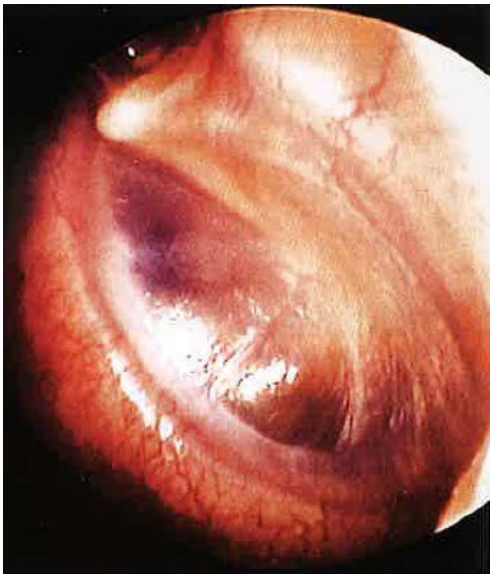

Figure 6: Normal tympanic membrane (*Audiology: Diagnosis*, 2007). Reprinted with permission from Thieme Publishers.

Tympanometry

Tympanometry can be used to evaluate the function of the middle ear. The results provide a graphic representation of eardrum mobility as a function of mechanically varying air pressure. The mobility is represented by the middle ear admittance or compliance and is often expressed as an equivalent volume in cubic centimeters. Other measures generated by tympanometry include the width, static admittance or tympanogram height, and ear canal volume (*Audiology: Diagnosis*, 2007).

In tympanometry, the ear canal is sealed and the pressure is gradually changed from a positive (200 daPa) to a negative (-200 to -300 daPa). A probe tube transfers a pure tone which is sent into the external auditory canal. The amount of sound or energy reflected is measured through another probe tube and the resulting compliance is displayed in graphic form as a function of ear canal pressure (*Audiology: Diagnosis*, 2007). This is depicted in Figure 7.

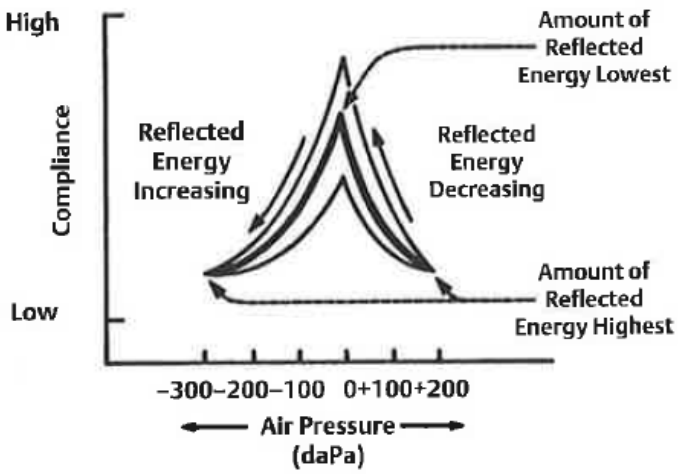

Figure 7: Schematic representation of how varying air pressure in the external ear canal affects the stiffness of the tympanic membrane and the reflected energy of the probe tube (*Audiology: Diagnosis*, 2007). Reprinted with permission from Thieme Publishers.

The amount of reflected energy is at the lowest when the middle ear cavity and the external ear canal have the same pressure. In a normal ear, this occurs at atmospheric pressure. The amount of energy absorbed by the tympanic membrane is the highest and the amount of energy reflected by the tympanic membrane is the lowest. This signifies high compliance. However, when there is a pressure difference between the external auditory canal and the middle ear cavity, the tympanic membrane stiffens the amount of reflected energy increases as less is absorbed by the tympanic membrane. This implies low compliance (*Audiology: Diagnosis*, 2007).

Different types of tympanograms can be classified by the shape of the curve. The classification system described by Lidén (1969) and Jerger (1970) is the most commonly used and categorizes the amount of compliance and static admittance into three types of tympanograms: A, B, and C (J. Jerger, 1970).

Type A suggests normal tympanic membrane mobility. It can be further classified into Type A_d and A_s. Type A_d represents abnormally high static admittance and Type A_s represents abnormally low static admittance. Type B represent little or no static admittance while Type C represents normal static admittance, but with negative pressure in the middle ear cavity. Type C can also be further classified into C1 and C2, with CI corresponding to a middle ear pressure of -100 to -199 daPa and C2 corresponding to -200 to -400 daPa (Fiellau-Nikolajsen, 1983). See Figure 8 for examples of the differing types of tympanograms (*Audiology: Diagnosis*, 2007; J. Jerger, 1970; Liden, 1969).

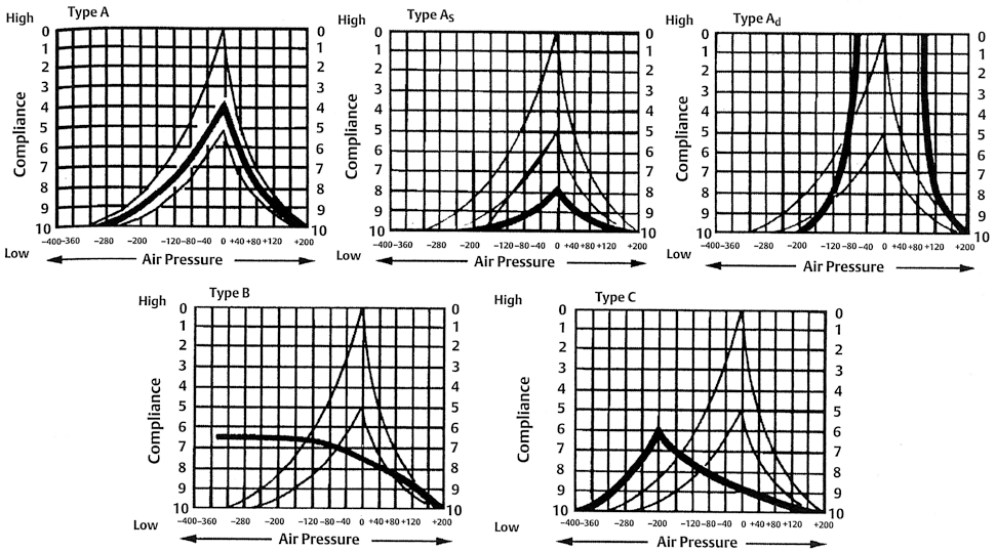

Figure 8: The classic classification of tympanograms (*Audiology: Diagnosis*, 2007; J. Jerger, 1970). Reprinted with permission from Thieme Publishers.

Pure-tone audiometry

Pure-tone audiometry measures the lowest intensity of tone to which a person responds across the audiometric frequencies. The pure-tone audiogram depicts intensity as a function of frequency. The frequencies tested typically include, 250 Hz to 8000 Hz. The intensity refers to the amount of sound presented to the individual. The range of intensity for the audiometer includes -10 dB HL to 110 dB HL. It is measured in decibel hearing level (dB HL). A threshold of 0 dB HL is the reference to average normal hearing at each of the frequencies (*Audiology: Diagnosis*, 2007).

When performing audiometry, a sound is presented and a response is given if the sound is heard. Air conduction thresholds are obtained by delivering the sound under headphones, insert earphones, or loudspeaker in a sound-field. Bone conduction thresholds are obtained by delivering sound via a bone conduction oscillator placed on the individual's mastoid, the skull bone behind the ear. Air conduction and bone conduction thresholds are assessed in order to understand what type of hearing loss may be present.

Adults and older children cooperate and give an active response such as pushing a button or raising a hand when a sound is heard. However, children may not be able to participate in the same manner. Therefore, there are different behavioral and electrophysiological methods of testing children. For behavioral testing, there are three methods commonly used (See Table 3). The first method is utilized with children from 0 to 6 months of age. The child is observed for different responses to sound which can include eye blinking, eye widening, cessation of an activity, initiation of an activity, or arousal from sleep. This type of behavioral auditory is called behavioral observation audiometry (BOA). From 6 months to approximately 30 months, the response may be a conditioned to a head turn. This response is conditioned with a visual reinforcement. The visual reinforcement may be a light-up puppet/toy or a segment from a DVD. This is called visual reinforcement audiometry (VRA). From approximately 30 to 48 months of age, children can be reinforced to respond to a sound with an action (eg., putting a block on a tower). This is called conditioned play audiometry (CPA). From age 4 to 5 years, adult responses such as finger tapping or pushing a button can be reliably elicited (*Audiology: Diagnosis*, 2007; Cone-Wesson, 2003).

Table 3. Behavioral audiometry techniques used with children from 0-48 months (*Audiology: Diagnosis*, 2007).

Test	Technique	Developmental age range
Behavioral observation audiometry	Observe response to sound	0-6 months
Visual reinforcement audiometry	Head turn conditioning and reinforced with animated toy and/or DVD	6-30 months
Conditioned play audiometry	Play activity conditioning and reinforced with activity of the game	30 months to 48 months

Another way of assessing children is the use of electroacoustical and electrophysiological tests. These include otoacoustic emissions (OAE), auditory brainstem response (ABR), and auditory steady-state response (ASSR). These assessments do not require a behavioral response from the child as they elicit a sound in response to a sound or evoke a change in brain potentials. OAEs test the integrity of the outer hair cells while ABR and ASSR assess the functioning of the brainstem (Cone-Wesson, 2003).

Speech recognition testing

Speech recognition tests assess how much speech an individual can recognize in various conditions with differing stimuli. Speech recognition testing is used for two reasons. Firstly, speech recognition testing can confirm pure-tone audiometry results. Secondly, they can provide insight into the sight of lesion within the auditory system as speech recognition scores are obtained at suprathreshold levels. Different assessments, conditions, and procedures can be utilized (See Table 4). The assessments can vary by using consonants and/or vowels, words or sentences. These different stimuli can be presented in a noisy or quiet condition. Various procedures are used to attempt to describe how a person recognizes speech. This can be done either with a fixed amount of noise and speech or by adaptively adjusting noise or speech depending on the person's response (*Audiology: Diagnosis*, 2007).

Table 4. Different conditions and stimuli for speech recognition testing.

Noise condition	• Noise • Quiet
Speech stimuli	• Consonants and/or vowels • Word level • Sentence level
Procedure for noise conditions	• Adaptive: Adaptive noise with fixed speech or Adaptive speech with fixed noise • Fixed: Fixed noise and speech level
Scoring procedures	• Percent correct • Speech level or speech-to-noise ratio for a given percentage correct (often 50%)

Masking level difference

Masking level difference assesses binaural processing, or the ability of listeners to use the difference in sounds at two ears to segregate sounds sources. This allows the auditory system to improve in discriminating separate sound sources in interfering noise. The detection of a signal in noise is improved when the phase of the signal is different than the phase of the noise at the two ears. The signal and noise appear to originate from different locations in space. This is often referred to as the "cocktail party effect". The masked threshold of a signal can sometimes be lower when listening with two ears instead of one ear.

2.2 Otitis media with effusion (OME)

Otitis media (OM) is a broad term used to describe a continuum of related disease conditions of the middle ear (Klein et al., 1989). This thesis investigates otitis media with effusion (OME), which is when fluid exists in the middle ear and is not accompanied by signs or symptoms of an acute infection (See Figure 9). Another kind of OM is acute otitis media (AOM), which is a bacterial infection of the middle ear characterized by sudden onset and short duration (Lous et al., 2008).

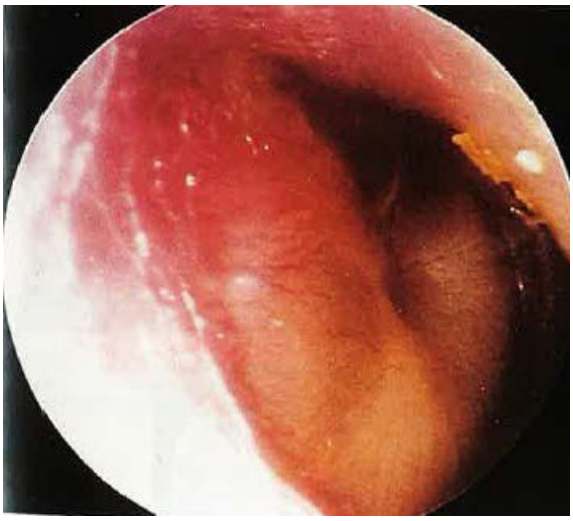

Figure 9: Fluid behind tympanic membrane exhibiting OME (*Audiology: Diagnosis*, 2007). Reprinted with permission from Thieme Publishers.

There are several possible causes of OME. These include Eustachian tube dysfunction, defects in the immune system, allergies, upper respiratory infections, sequelae after AOM, and/or structural anomalies in the middle ear and/or Eustachian tube (Fireman, 1997; Sheahan & Blayney, 2003). Although the causes may be different, they lead to low pressure in the middle ear cavity.

Due to the Eustachian tube not opening to equalize pressure, low pressure exists in the middle ear cavity. Negative pressure results in a retracted tympanic membrane and secretion of mucous from the tissues through osmosis into the middle ear cavity (Broen et al., 1996). This lower pressure can be a result of an AOM, Eustachian tube dysfunction, and/or structural anomalies (Browning, Rovers, Williamson, Lous, & Burton, 2010; Lous et al., 2008; Sheahan & Blayney, 2003).

Defects in the immune system, upper respiratory infections, and allergies may lead to swelling in the Eustachian tube or membranes around the tube. Another cause is enlarged adenoids which may block the opening of the Eustachian tube. The swelling may also close or obstruct the opening of the Eustachian tube. This can cause the fluids to be trapped in the middle ear cavity. However, if there are no fluids present, the obstruction may result in the middle ear cavity absorbing the gases and resulting in negative pressure (Fireman, 1997; van den Aardweg, Schilder, Herkert, Boonacker, & Rovers, 2010; Zemlin, 1998).

In children the fluid may become trapped easier as the Eustachian tube is shorter, more horizontal, and composed of more cartilage than the adult tube. This flaccidity and positioning of the Eustachian tube allows for increased risk of nasopharngeal secretions entering the middle ear cavity from retrograde reflux (Zemlin, 1998).

2.2.1 Prevalence and Duration of OME

Prevalence

Prevalence rates of OME in children from 1 to 8 years of age vary among studies reported in the literature, from four to 50% (Mandel, Doyle, Winther, & Alper, 2008). This is possibly due to: (1) the population included in the study (eg., age, development, socio-economic status, maternal education), or to (2) the definition of OME (which signs and symptoms were used to diagnose the presence of the disease and duration of episode) (Browning et al., 2010; Mandel

et al., 2008). OME can be indirectly diagnosed through using microtoscopy, pneumatic otoscopy, and/or tympanometry and directly through myringotomy.

OME has two peaks in prevalence. The first and largest peak of 20 to 32% is at 2 years of age and relates to episodes of OME following AOM (Mandel et al., 2008; Zielhuis, Rach, van den Bosch, & van den Broek, 1990). The initial peak at 2 years of age may be due to the position of the Eustachian tube compared to the nasopharynx. The Eustachian tube is more horizontal and shorter at younger ages. This can lead to the inability to equalize pressure between the middle ear cavity and outside the ear which may result in negative pressure. Negative pressure results in a retracted tympanic membrane and secretion of mucous from the tissues through osmosis into the middle ear cavity (Broen et al., 1996). The second peak of 16 to 18% around 5 years of age relates to an increase in upper respiratory tract infections. This close connection may be due to closer contact with other children at school (Mandel et al., 2008; Williamson, Dunleavey, Bain, & Robinson, 1994; Zielhuis et al., 1990). By 7 to 8 years of age, the prevalence is approximately 6 to 7% (Tos, 1983; Williamson et al., 1994).

Several risk factors for OM have been identified (K. A. Daly et al., 2010; Hoffman, Park, Losonczy, & Chiu, 2007; Mandel et al., 2008; Teele, Klein, & Rosner, 1989; Williamson et al., 1994). These include cold-like illnesses, increased number of days at daycare, bottle-feeding, low birth-weight, time of the year (autumn and winter), or recurrent OM.

Duration

The duration of OME has been investigated. The number of days with fluid present decreases as children becomes older (Mandel et al., 2008; Paradise et al., 1997; Teele et al., 1989). During the first year of life, a child may have fluid present between 17- 44 days and 23 - 52 days in the second year (K.A. Daly, 1997; Teele et al., 1989). In 25% of children aged between 2 to 4 years, bilateral OME resolves within 3 months, and in 30% of older children with bilateral OME, spontaneous resolution occurs after 6 to 12 months(American Academy of Family Physicians, American Academy of Otolaryngology-Head and Neck Surgery, & American Academy of Pediatrics Subcommittee on Otitis Media with Effusion, 2004; Tos, 1983; Williamson et al., 1994). In more recent investigation of children 1 to 8 years of age, 70 to 90% of the OME episodes lasted between one to four weeks (Mandel et al., 2008).

2.2.2 Management and Treatment

Following diagnosis of OME, children are treated and managed differently depending if the child is at risk for further episodes of OME. Treatment and management is either medical or surgical in nature. Currently, there is no proven medical management of OME and surgical treatment remains controversial (Browning et al., 2010).

A common management of children who are not at risk for OME is "watchful waiting" (Paradise et al., 2007). Watchful waiting is when a child is watched for 6 months from the date of bilateral OME onset or 9 months for unilateral OME. The child is re-examined every 3 to 6 months until effusion is no longer present, significant hearing loss is identified, or structural abnormalities in the middle ear or eardrum are suspected. Following persistent OME or significant hearing loss, surgical intervention may be an option. The surgical insertion of a pressure equalizing tube can provide aeration and equalization of pressure to the middle ear cavity and thus allow the fluid drain and decrease secretion from the mucosa (American Academy of Family Physicians et al., 2004; Paradise et al., 2007) (See Figure 10). Another surgical treatment can be adenoidectomy in order to open the entrance to the Eustachian tube (van den Aardweg et al., 2010).

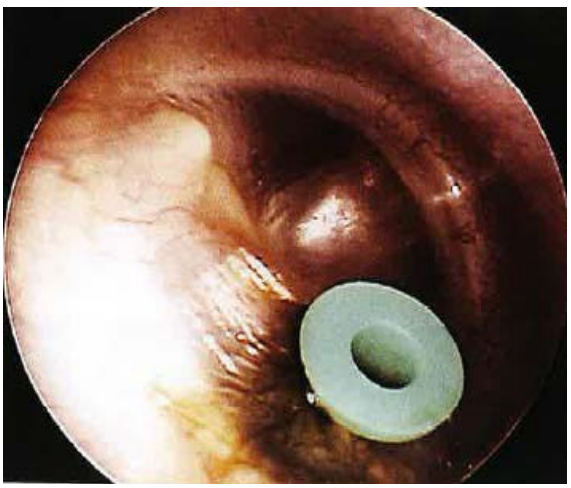

Figure 10: Placement of a pressure equalizing tube in the tympanic membrane (*Audiology: Diagnosis*, 2007). Reprinted with permission from Thieme Publishers.

2.2.3 Association with hearing loss

OME is associated with a mild-to-moderate conductive hearing loss with levels fluctuating between 0 to 55 HL dB across the speech frequencies (Gravel & Wallace, 2000). Approximately 60% of children with OME presented with a threshold of > 20 dB HL at one or more frequencies (Paradise et al., 2000). The configuration of the hearing loss may be flat or better hearing in the mid frequencies. This variation may reflect the amount of fluid within the middle ear cavity or the viscosity of the fluid, as well as the possible addition of ossicular chain or tympanic membrane conditions (eg., retracted tympanic membrane). Hearing loss associated with OME is distinctly different than permanent conductive or sensorineural hearing loss as it is temporary, variable in degree, frequently recurrent, and often asymmetric (Gravel & Ellis, 1995). This associated hearing loss has been examined through the use of the auditory brainstem response (ABR). In a study by Gravel and Wallace (1995), a click ABR in the first year of life revealed elevated thresholds (37.8 dB nHL) in a group of infants with an average of 4 episodes of bilateral OME as compared to a group of infants (20.3 dB nHL) with an average of under 1 episode of OME.

Behavioral audiometry (visually reinforced audiometry or conditioned play audiometry) has also been used to assess hearing loss in children with OME. Several studies have demonstrated poorer hearing thresholds in children with a history of OME compared to children without a history of OME (Davie & Frank, 1999; Gravel et al., 2006; Gravel & Wallace, 2000; Roberts et al., 1995; Sabo, Paradise, Kurs-Lasky, & Smith, 2003). These poorer hearing thresholds exist in infants and young children when OME is not present. Young children with a history of bilateral OME demonstrated poorer hearing thresholds (3-6 dB increase) than young children with unilateral OME (Gravel & Wallace, 2000; Sabo et al., 2003). When OME is present in young children with chronic OME, a 25 dB elevation of hearing thresholds has been noted (Davie & Frank, 1999).

This type of hearing loss seems to normalize with age. In school-aged children with a history of OME, hearing loss is not demonstrated across the typical audiometric frequencies (250 Hz to 8000 Hz) (Gravel et al., 2006; Hunter et al., 1996). However, when OME is present, elevated thresholds are seen (Hunter et al., 1996).

Extended high frequency hearing loss might persist following resolution of OME in children with a history of OME (Gravel et al., 2006; Hunter et al., 1996). Elevated thresholds are present throughout the extended high frequencies from 9 kHz to 20 kHz (Gravel et al., 2006; Hunter et al., 1996). A difference of 9 dB at 9 kHz, 15 dB at 12.5 kHz, 10 dB at 14 kHz, and 22 dB at 18 and 20 kHz has been presented in studies between children with a history of OME and children without a history of OME (Gravel et al., 2006; Hunter et al., 1996). Factors predicting this high frequency hearing loss include (1) a greater number of pressure equalizing tube insertions, (2) a higher number of episodes of OME, and (3) more hearing loss early in life (Gravel et al., 2006; Hunter et al., 1996)

2.3 Cleft lip and palate

2.3.1 Incidence

CP±L is among the most common anomalies affecting between 0.9 to 2 in 1000 births (Coleman & Sykes, 2001; Group, 2011; Hagberg, Larson, & Milerad, 1998; Milerad, Larson, Ph, Hagberg, & Ideberg, 1997; Mossey, Little, Munger, Dixon, & Shaw, 2009; Schutte & Murray, 1999). The reported incidence of CP±L differs due to methodological differences including sample source (hospital verses population based), method of collection, inclusion criteria, sampling fluctuation, and variability of clinical expression of facial morphology and associated anomalies (Mossey et al., 2009; Wyszynski, Sarkozi, & Czeizel, 2006). See Table 5 for incidence of CP±L.

The cleft can affect the lip, lip and palate, or only the palate. The lip can be uni- or bilaterally involved. Clefts are typically categorized into four categories: (1) cleft lip, (2) unilateral cleft lip and palate (UCLP), (3) isolated cleft palate (ICP), and (4) bilateral cleft lip and palate (BCLP) (See Figure 11). The cleft lip will not be discussed in this project as there has been no evidence linking cleft of the lip to an increase in OME.

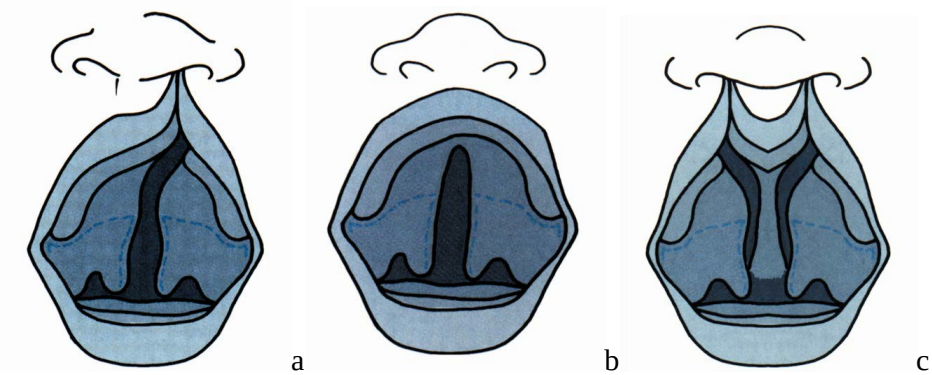

Figure 11. Cleft categories: (a) UCLP, (b), ICP, and (c) BCLP. Reprinted with permission from May Johansson.

Table 5. Incidence figures of CP±L worldwide and in Sweden by cleft type.

Type of cleft	Incidence worldwide	Incidence in Sweden
Unilateral cleft lip and palate	0.7/1000 births(Group, 2011), including BCLP	0.4/1000 births(Hagberg et al., 1998)
Isolated cleft palate	0.5/1000 births(Coleman & Sykes, 2001)	0.6-0.7/1000 births(Hagberg et al., 1998) (Chetpakdeechit, Mohlin, Persson, & Hagberg, 2010)
Bilateral cleft lip and palate	0.7/1000 births(Group, 2011), including UCLP	0.3/1000 births(Hagberg et al., 1998)
Cleft Lip	0.3/1000 births(Group, 2011)	0.6/1000 births(Hagberg et al., 1998)

Unilateral cleft lip and palate

A unilateral cleft lip and palate (UCLP) occurs when there is a cleft in the lip, and the primary and secondary palate. The primary palate involves the portion of the maxilla anterior to the incisive foramen (pre-maxilla), while the secondary palate involves the palatal shelves posterior to the incisive foramen (Coleman & Sykes, 2001). The lip and primary palate involvement is unilateral. In Sweden, the incidence is 0.4 per 1000 births (Hagberg et al., 1998).

Bilateral cleft lip and palate

A bilateral cleft lip and palate (BCLP) occurs when there is bilateral involvement of the lip and primary palate together with the secondary palate (Coleman & Sykes, 2001). In Sweden, the incidence is 0.3 per 1000 births (Hagberg et al., 1998).

Isolated cleft palate

An isolated cleft palate (ICP) involves the entire or part of the secondary palate (Coleman & Sykes, 2001). The secondary palate can be divided into the hard and soft palate. ICP involves a cleft of the soft palate only or also extending into the hard palate of different degrees. In Sweden, the incidence is 0.6 to 0.7 per 1,000 in Sweden (Chetpakdeechit, Mohlin, et al., 2010; Hagberg et al., 1998).

Cleft palate and additional malformations and/or syndromes

A CP±L can be commonly associated with additional malformations or syndromes. More than 300 named syndromes involve a cleft (Coleman & Sykes, 2001). The ICP is the cleft type most commonly associated with additional malformations or syndromes. Twenty-two to 55% of all children born with an ICP have an associated syndrome or malformation (Coleman & Sykes, 2001; Hagberg et al., 1998; Milerad et al., 1997; Schutte & Murray, 1999; Stoll, Alembik, Dott, & Roth, 2000). In Sweden, 22 to 34% of children born with ICP presented with additional malformations with Pierre Robin sequence being the most common (Chetpakdeechit, Mohlin, et al., 2010; Hagberg et al., 1998; Milerad et al., 1997).

2.3.2 Treatment and management

In Sweden, six centers treat the children born with a CP±L. Treatment includes surgical closure of the cleft, orthodontic care, speech and language therapy, and otological and audiological assessment and surgery. Typically involved professions are plastic surgeons, orthodontists, speech-language pathologists, otolaryngologists, and audiologists.

In Sweden, there are two main procedures for surgical repair. The procedures differ on timing of closure and surgical technique. One procedure includes a one-stage closure at 12 to 18 months of age and the other procedure includes a two-stage closure with early soft palate repair at around 6 months of age and closure of the hard palate cleft at 24 months of age. In Gothenburg, the two-stage procedure is utilized. However, the age for hard palate closure at the Gothenburg center has changed throughout the years. In the mid 90s, the hard palate was closed around 8 years of age. Since then, the age for hard palate closure was gradually lowered to the current 2 years of age. See Table 6 for surgical procedures of individuals included in this thesis.

Table 6. Surgical protocol of individuals included in this thesis by study (I-IV).

Study	I	II	III	IV
Primary lip closure	3-4 months	3 months		6 weeks
Soft palate closure	5 months	7 months	8 months	8 months
Hard palate closure	12 or 36 months*	55 months	46 months	7 years, 9 months

* According to the procedure in the randomized clinical trial Scandcleft project (Lohmander et al., 2009).

The children born with a CP±L are seen at regular intervals at the cleft clinics. Speech and language development, ears and hearing, maxillary growth and occlusion are carefully followed. In Gothenburg, these intervals include the ages of 1, 1½, 3, 5, 7, 10, 13, 16, and 19 years.

Due to the cleft of the palate, difficulties may arise with feeding, development of speech, language, dentition, facial structures, and hearing. This project focuses on the challenges with auditory development and hearing.

2.3.3 Cleft palate and speech and language development

Speech and language development in children with CP±L is deviant from early childhood and often during pre-school and early school ages with reported prevalence of around 20 to 50 %. For some individuals the deviances can continue into adulthood. Infants and toddlers with CP±L present with delayed

babbling and a lower frequency of dentals/alveolar consonant placements and particularly oral stops than in children without CP±L (Jones, Chapman, & Hardin-Jones, 2003; Lohmander, Olsson, & Flynn, 2011; Scherer, Williams, & Proctor-Williams, 2008; Willadsen & Albrechtsen, 2006). They also acquire words at an approximate three month delay as compared to children without CP±L (Broen, Devers, Doyle, Prouty, & Moller, 1998; Scherer et al., 2008).

The deviant speech production in children with CP±L is characterized by retracted articulation and hypernasality (Lohmander, Friede, & Lilja, 2012; Lohmander & Persson, 2008). Children with CP±L also exhibit poorer consonant production, as measured by percent correct consonants, as compared to children without CP±L (Lohmander & Persson, 2008). This is seen from 3 years to 5 years of age (Lohmander et al., 2012; Lohmander & Persson, 2008). These characteristics of speech decline in prevalence with perceived normal articulation, nasality and intelligibility in the absolute majority of the individuals at 16 and 19 years, respectively (Lohmander et al., 2012).

Children with CP±L and additional malformation and/or syndromes exhibit worse speech than children with CP±L and no additional malformation and/or syndromes (Persson, Elander, Lohmander-Agerskov, & Soderpalm, 2002). Deviances that were poorer in the CP±L with additional malformations and/or syndromes include velopharyngeal impairment, hypernasality, nasal emission, weak pressure consonants, retracted oral consonants, and glottal articulation (Persson et al., 2002).

2.3.4 Cleft palate and OME

The epidemiology of OME is different in children with CP±L than in children without cleft. There are two main differences: (1) children with CP±L present with a higher prevalence of OME as compared to children without cleft and (2) OME is present at earlier ages with children with CP±L exhibiting OME at birth (Sheahan & Blayney, 2003).

For children with CP±L, OME is universally present and often within the first six months of life (Dhillon, 1988; Paradise, Bluestone, & Felder, 1969; Robinson, Lodge, Jones, Walker, & Grant, 1992; Stool & Randall, 1967). The high prevalence of OME in children and adults with CP±L is most likely due to Eustachian tube dysfunction (See Table 7). The muscles responsible for dilating

and opening the Eustachian tube are not able to contract properly and open the Eustachian tube (Arnold, Nohadani, & Koch, 2005; Bluestone, Wittel, & Paradise, 1972; Huang, Lee, & Rajendran, 1997; Matsune, Sando, & Takahashi, 1991a, 1991b; Sheahan & Blayney, 2003). Also the Eustachian tube is hypercompliant and collapses easily, is floppy, and the opening is obstructed (Sheahan & Blayney, 2003; Takahashi, Honjo, & Fujita, 1994). Therefore, the Eustachian tube is unable to equalize pressure and drain secretions. This causes negative pressure inside the middle ear with tympanic membrane retractions. This leads to secretions being formed which become trapped inside the middle ear cavity and results in OME.

Table 7. Eustachian tube dysfunction in individuals with CP±L (Arnold et al., 2005; Bluestone et al., 1972; Huang et al., 1997; Matsune et al., 1991a, 1991b; Sheahan & Blayney, 2003; Takahashi et al., 1994).

Opening failure	
	Lack of insertion of the tensor veli palatini and levator veli palatini into the palatine aponeurosis
	Lack of insertion at origin of tensor veli palatini in Eustachian tube
	Fewer tendons and muscle fibers in the tensor veli palatini
	Hypoplastic levator veli palatine
Hypercompliance of Eustachian tube	
	Easy collapsibility
	Increased floppiness
	Functional obstruction

When young children with CP±L were compared to young children without cleft, the children with CP±L demonstrated a higher prevalence of OME (Broen et al., 1996). This could continue throughout childhood and into adolescence (Ovesen & Blegvad-Andersen, 1992). Studies have demonstrated a decrease in OME as children become older (Bardach et al., 1992; Moller, 1975; Sheahan, Miller, Sheahan, Earley, & Blayney, 2003). Nevertheless, the prevalence of OME is still high with 13 to 49% of adolescent's with CP±L to still present with OME (Gordon, Jean-Louis, & Morton, 1988; Timmermans, Vander Poorten, Desloovere, & Debruyne, 2006). However, these studies have been performed cross-sectionally. No previous longitudinal studies have been performed to validate these findings in children with CP±L from childhood into adolescence.

Another consideration to investigate is prevalence of OME by cleft type. Three studies have examined children with CP±L and prevalence of OME by cleft type and age (Bardach et al., 1992; Handzic-Cuk, Cuk, Gluhinic, Risavi, & Stajner-Katusic, 2001; Moller, 1975). Overall, the prevalence of OME decreases with increasing age. Children with BCLP exhibited a decrease of OME following the age of 7 to 10 years (Bardach et al., 1992; Handzic-Cuk, Cuk, Risavi, Katusic, & Stajner-Katusic, 1996). Children with ICP exhibited a decrease in the prevalence of OME a little older, following the age of 15 years (Handzic-Cuk et al., 1996; Moller, 1975). For children with UCLP, there has been conflicting evidence. Handzic-Cuk et al. (1996) noted a slow decrease in the prevalence of OME following 7 years of age. In contrast, for children with UCLP, an increase in prevalence of OME between 6 and 15 years of age has been demonstrated (Moller, 1975).

2.3.5 Cleft palate and hearing

In young children with CP±L, a study has demonstrated a prevalence of 90 to 93 percent with OME with a conductive hearing loss (Fria, Paradise, Sabo, & Elster, 1987). Hearing thresholds were more elevated in children with CP±L than children without CP±L (Broen et al., 1998; Broen et al., 1996). Also, approximately 50 to 60 % of individuals with OME and CP±L present with a conductive hearing loss that is fluctuating and mild to moderate in nature (Bennett, 1972; Ovesen & Blegvad-Andersen, 1992; Sheahan, Blayney, Sheahan, & Earley, 2002).

This hearing loss may continue to exist into adolescence with 20 to 39 % of adolescences with CP±L presenting with a conductive hearing loss (Gordon et al., 1988; Gould, 1990; Ovesen & Blegvad-Andersen, 1992; Timmermans et al., 2006). However, other studies have exhibited lower rates of hearing loss, between two and 13 % (Bardach et al., 1992; Moller, 1975; Valtonen, Dietz, & Qvarnberg, 2005). These differences may have been related to the type of cleft examined and the definition of hearing loss. There have been two studies which compared hearing loss and cleft type cross-sectionally across different age groups (Handzic-Cuk et al., 1996; Moller, 1975). The prevalence of hearing loss decreased with age with normal hearing achieved between 10 to 15 years in all cleft types (Handzic-Cuk et al., 1996; Moller, 1975).

When considering the definition of hearing loss, most studies have defined hearing loss as a pure-tone average (PTA) of 500, 1000, and 2000 Hz (Gordon et al., 1988; Gould, 1990; Handzic-Cuk et al., 1996; Moller, 1975; Ovesen & Blegvad-Andersen, 1992; Timmermans et al., 2006; Valtonen et al., 2005). This did not include the higher frequencies that may have been affected by long-term exposure to OME. Research investigating high-frequency hearing loss in children without CP±L has documented extended high frequency hearing loss following resolution of OME in children with a history of OME (Gravel et al., 2006; Hunter et al., 1996). Elevated thresholds were present throughout the extended high frequencies from 9000 Hz to 20,000 Hz. In people with CP±L, two studies have documented hearing in the extended high frequencies (Ahonen & McDermott, 1984; Handzic-Cuk et al., 1996). When compared to hearing thresholds at 250 and 4000 Hz, thresholds at 6000 Hz and 8000 Hz were elevated (Ahonen & McDermott, 1984; Bennett, 1972; Handzic-Cuk et al., 1996). Ahonen and McDermott (1984) further documented an elevation in thresholds in children with CP±L as compared to children without CP±L between 10,000 to 20,000 Hz. These studies examined children's and adults' hearing on one day of testing and did not consider hearing loss longitudinally across childhood into adulthood.

Speech recognition and binaural auditory processing may also be delayed in children with a positive history of OME. The hearing loss associated with OME may lead to difficulties in recognizing speech in noise and processing sound binaurally. Several studies have documented poorer speech recognition in noise in children with a positive history of early life OME (Brown, 1994; S. Jerger, Jerger, Alford, & Abrams, 1983; Schilder, Snik, Straatman, & van den Broek, 1994). The ability to categorize phonemes has also been degraded in children with a positive history of early life OME (Groenen, Crul, Maassen, & van Bon, 1996; Zumach, Chenault, Anteunis, & Gerrits, 2011). Binaural processing may also be poorer due to previous episodes of OME (J. W. Hall, 3rd, Grose, Dev, & Ghiassi, 1998; Hogan & Moore, 2003; Moore, Hutchings, & Meyer, 1991).

The previous literature examining the effects of OME on speech recognition and auditory development has involved children without additional malformations and/or syndromes. The comparison of this research to children with CP±L needs to be taken with consideration. When the CP±L is added, the situation changes, as it has been clearly documented, children with CP±L experience

higher prevalence of abnormal middle ear status (Broen et al., 1996; Ovesen & Blegvad-Andersen, 1992). When children with CP±L experience abnormal middle ear status, the associated hearing loss may be worse than in children without CP±L. Since children with CP±L demonstrate a higher prevalence of OME (Broen et al., 1996; Ovesen & Blegvad-Andersen, 1992). They may experience more time with a mild to moderate hearing loss than children without CP±L. Therefore, children with CP±L may experience some of the same challenges as children with a permanent mild sensorineural hearing loss. Children with a mild sensorineural hearing loss show greater difficulties academically and experience increased stress, need for social support, and lower self-esteem (Bess, Dodd-Murphy, & Parker, 1998; Blair, Peterson, & Viehweg, 1985). Children with mild to moderate hearing loss also perform poorer on speech in noise tests (Beattie, 1989; Crandell, 1993) and require more effort to listen (Hick & Tharpe, 2002). Furthermore, children with mild hearing loss experience worse phonological short-term memory and phonological discrimination than children without hearing loss (Wake et al., 2006). These consequences may lead to poorer performance in school and lower academic skills.

Another area to consider with a focus on the addition of CP±L is the research on OME and speech and language development. Although the research indicates delays in speech and language skills in children with positive histories of early life OME are resolved by age 7 (Zumach, Gerrits, Chenault, & Anteunis, 2010), this does not take into account children with CP±L. As mentioned earlier, children with CP±L exhibit poorer consonant production, as measured by percent correct consonant, as compared to children without CP±L (Jones et al., 2003; Lohmander et al., 2012; Lohmander & Persson, 2008; Scherer et al., 2008). With more time with abnormal middle ear status and higher thresholds when a hearing loss is present, speech and language development in children with CP±L may be delayed. Hearing needs to be examined more carefully in this group when investigating speech and language outcomes in order to fully understand the effect of abnormal middle ear status and its associated hearing loss on speech and language development in this population.

As mentioned above, there are considerations to the current research on OME with regards to the addition of a CP±L. Furthermore, if children with CP±L present with additional malformations and/or syndromes, there is yet another

consideration. Children with CP±L and additional malformations and/or syndromes may also be at an increased risk for hearing difficulties. This may be due to increased prevalence of hearing losses in children with additional malformations and/or syndromes (Matheny, Hall, & Manaligod, 2000; Ott & Issing, 2008; Szymko-Bennett et al., 2001; van der Burgt, 2007).

3 Aims

3.1 General aims

The general aims of this thesis were to:

- Define the prevalence of OME in young children, adolescents and adults born with cleft palate.
- Describe the hearing in young children, adolescents and adults born with cleft palate.

3.2 Specific aims

The specific aims of each study were to:

- Study I: Compare the audiological characteristics and prevalence of abnormal middle ear status longitudinally in young children born with and without cleft lip and palate.
- Study II: Define the audiological outcomes and prevalence of abnormal middle ear status of children born with cleft lip and palate and isolated cleft palate as a cohort from school-age to adolescence.
- Study III: Describe the audiological outcomes and prevalence of abnormal middle ear status of children born with cleft palate with additional malformations and/or identified syndrome as a cohort from school-age to adolescence.
- Study IV: Examine the long-term effects of abnormal middle ear status on hearing sensitivity, speech recognition, MLD in adults with repaired cleft lip and palate.

4 Materials and Methods

4.1 Participants

A total of 195 participants were included in the studies. There were 151 children, adolescents, and young adults with CP±L and 44 children and young adults without cleft (See Table 8).

Table 8. Participant characteristics

	I	II	III	IV	Total (195)
Control group	21			23	41
Unilateral cleft lip and palate (UCLP)	22	24		26	72
Isolated cleft palate (ICP)		23	64*		68
Bilateral cleft lip and palate (BCLP)		11			11
Gender (m/f)	23/20	32/26	25/39	33/16	105/90
Age	1-5 years	7-16 years	7-16 years	20-31 years	

*19 of the same individuals in study II

4.1.1 Study I

Two groups of children were followed prospectively and longitudinally from 1 year of age to 5 years of age. There were 22 children with UCLP (cleft group) and 21 children without CP±L (control group). The children in the UCLP were a consecutive series and were treated by the Gothenburg Cleft Palate Team. The cleft group was born between 1997 and 2002 in the western region of Sweden. The children in the control group were born in 2001 in the western region of Sweden and were randomly recruited from three well-baby clinics in Gothenburg.

4.1.2 Study II

In study II, a consecutive series of 87 children born between 1991 and 1993 in the Västra Götaland Region of Sweden were eligible. They presented with a UCLP, ICP, and BCLP and were treated by the Gothenburg Cleft Palate Team, Sweden. Twenty-nine children were excluded due to the presence of additional malformations and/or identified syndromes.

The remaining group of 58 children was divided into three groups based on type of cleft. There were 24 children with UCLP, 23 children with ICP, and 11 children with BCLP. Of the children in the ICP group, 11 had cleft of the soft palate and 12 had cleft of the hard and soft palate.

4.1.3 Study III

In study III, 64 participants with ICP were born over four years in the Västra Götaland Region of Sweden. The participants were a consecutive series which presented with an ICP and were treated by the Gothenburg Cleft Palate Team, Sweden. They were divided into two groups: ICP (n=27) and ICP plus additional malformations and/or identified syndromes (ICP+) (n=37).

4.1.4 Study IV

Two groups of young adults aged 20 to 31 years were seen at one visit at the audiological clinic. There were 26 adults with surgically repaired UCLP (cleft group) ranging in age from 20 to 31 years and 23adults without CP±L (control group) ranging in age from 21 to 31 years (mean= 26 y).

4.1.5 Ethical approval

Ethical approval was obtained by the Gothenburg Regional Ethical Board:

- Study I (R 256-97)
- Study II and III (R 456-12)
- Study IV (R 132-09).

4.2 Methods

Records were examined longitudinally and prospectively for study I and retrospectively for studies II and III. Data were collected at four data points (study I: 1, 1.5, 3, and 5 years of age; studies II and III: 7, 10, 13, and 16 years of age) during a clinical visit. Assessments included otomicroscopy, tympanometry, and pure-tone audiometry. Data were missing if there was no audiologist or otolaryngologist present on the day of the visit to conduct the assessments, or the adolescent did not attend the appointment (Table X).

In study IV, data were collected prospectively for a case-control study. The data were collected during one clinical visit and included otoscopy, tympanometry, pure-tone audiometry, speech-recognition testing, and masking level difference (Table 9).

Table 9. The methods for each of the studies with measurements, data points, and type of clefts included.

	Measurements	**Data points**	**Design**	**Type of clefts included**
Study I	Otomicroscopy Tympanometry Pure-tone audiometry	1, 1.5, 3, and 5 years of age	Prospective, Case-controlled Longitudinal	UCLP and non-cleft
Study II	Otomicroscopy Tympanometry Pure-tone audiometry	7, 10, 13, and 16 years of age	Retrospective Longitudinal	UCLP, ICP, BCLP
Study III	Otomicroscopy Tympanometry Pure-tone audiometry	7, 10, 13, and 16 years of age	Retrospective Longitudinal	ICP and ICP+
Study IV	Otoscopy Tympanometry Pure-tone audiometry Speech recognition Masking level difference	1 point (participants were 20-31 years old)	Prospective Case-controlled	UCLP and non-cleft

4.2.1 Otomicroscopy (Studies I, II, III)

Otolaryngologists performed otomicroscopy and were specialists in seeing children with CP±L. Results from otomicroscopy were classified as normal or abnormal (fluid-filled middle ear cavity, retracted tympanic membrane, or pressure equalising tubes-in-situ).

4.2.2 Tympanometry (Studies I-IV)

Tympanometry was completed with standard equipment to evaluate the status of the middle ear. A 226-Hz probe frequency was utilized. Tympanograms were classified as normal (type A and C1), abnormal (type B; no discernable peak, and C2), or if the adolescent had pressure-equalising tubes in-situ (Ovesen & Blegvad-Andersen, 1992).

4.2.3 Pure Tone Audiometry (Studies I, II, III, IV)

Pure Tone Audiometry was conducted under head-phones with standard equipment. Ear specific thresholds were obtained for 500, 1000, 2000, 4000, 6000, and 8000 Hz. A four frequency pure-tone average (PTA4) and a high frequency average (PTA HF) of 6000 and 8000 Hz were calculated for each ear. Normal hearing was considered to be ≤20 dB HL, mild hearing loss 21-40 dB HL, and moderate hearing loss 41-60 dB HL (*Audiology: Diagnosis*, 2007). A conductive loss was determined to be present when air-conduction thresholds exceeded 20 dB HL and there was an air-bone gap of 10 dB or more (*Audiology: Diagnosis*, 2007). A sensorineural hearing loss was determined to be present when air-conduction thresholds exceeded 20 dB HL with an air-bone gap of less than 10 dB. Finally, a mixed hearing loss was determined to be present when air- and bone-conduction thresholds were more than 20 dB HL with an air-bone gap of more than 10 dB.

For study IV, bone conduction thresholds were obtained for each participant. However, for studies I-III, bone conduction thresholds were not always tested.

4.2.4 Middle ear status (Studies I-IV)

In this study, otomicroscopy, tympanometry, and hearing sensitivity assessments were used in evaluating middle ear status. Abnormal middle ear status was deemed to be present if one of the following conditions were met: (a) fluid was present or tympanic membrane was retracted, (b) tympanostomy tubes in-situ, or (c) perforated tympanic membrane. All data were jointly examined by two of the authors.

4.2.5 Speech recognition testing (Study IV)

Testing was conducted at the word and sentence level in a soundproof booth. The participant was seated one meter from the loudspeaker placed at 0º in front of them. A standard audiometer was utilized to deliver the speech and noise materials through the same speaker in a sound-field condition.

Word Level

The Swedish Phonemically Balanced words in Noise (SPBN) which is comprised of Phonemically Balanced (PB) monosyllabic words was administered (Magnusson, 1995). The premixed speech materials (speech with steady-state, speech-weighted noise at a fixed speech-to-noise ratio of +4 dB) were delivered to each participant with noise at 61 dB SPL and speech at 65 dB SPL at the ear.

Each participant listened to one list of 10 words for training and one list of 50 words for testing. They were asked to repeat the word they heard. Whole word scoring was utilized.

Sentence Level

The Swedish Hearing in Noise Test (HINT) (Hallgren, Larsby, & Arlinger, 2006) was administered. This test consists of everyday sentences. Speech and noise were presented from the same speaker with the noise routed through channel 1 of the standard audiometer and speech routed through channel 2 of the same audiometer. Noise was held constant at 65 dB SPL and speech was initially set at 63 dB SPL at the ear (i.e., -2 dB signal-to-noise ratio, SNR). An adaptive procedure was utilized to determine a 50% recognition threshold. Whole sentence scoring was utilized. The intensity of the speech was decreased

by 2 dB when the participant repeated the whole sentence correctly and increased by 2 dB when the participant repeated any part of the sentence incorrectly. Three lists were administered (list 1, 2, and 3), each containing 10 sentences. The first list was a training list. Participants were asked to repeat the sentence they heard. The mean SNR was calculated for the two test lists (list 2 and 3), excluding the SNRs for the first four sentences and the hypothetical 21st sentence (Flynn, Moller, Lohmander, & Magnusson, 2012).

4.2.6 Masking Level Difference (Study IV)

To assess binaural processing, MLDs for pure-tones in noise were obtained. Two interaural phase conditions were compared: (1) noise in phase and signal in phase, N_0S_0, and (2) noise in phase and signal 180º out of phase, $N_0S\pi$. MLD was defined as the difference between the signal in phase (N_0 S_0) and the signal out of phase ($N_0S\pi$) conditions. Testing was completed through a standard audiometer. The signal was a 500 Hz pulsing tone and the masker was a one-half octave band of noise centered at 500 Hz (i.e., the audiometer's standard masking noise). Noise was continuously presented with the signal ($S\pi$ or S_0) increasing and decreasing in intensity. The participants were asked to indicate when they heard the pulsing tone with in noise by pushing a button.

Noise was presented at the attenuator setting of 50 dB (i.e., the effective masking level related to 50 dB HL), and the pulsing tone was initially presented at 60 dB HL. Each participant was asked if the signal was audible and the noise tolerable. The stimuli were presented binaurally through headphones. When the participant heard the tone, the audiologist decreased the intensity of the tone by 3 dB until the participant could no longer hear the tone. When the participant ceased hearing the tone, the audiologist increased the signal by 1 dB. Three reversals were completed to establish a threshold. This was completed for two conditions: (1) the signal (S_0) in phase and (2) the signal 180º out of phase ($S\pi$). Signal in phase (S_0) was conducted first and signal 180º out of phase ($S\pi$) was conducted second. The difference was calculated to obtain the MLD for each participant.

4.3 Statistical description and analysis

Statistical analysis of the results was performed using the Generalized Estimating Equation (GEE), as data were repeated measures taken at four discrete time points for studies I, II, and III. The GEE accounts for the dependency between the ears over time. Results from the analysis are reported in mean differences. Data were analyzed between groups and within groups over time. Study I also included the use of the Chi square analysis and an odds ratio. For study IV, an independent samples t-test to compare group means and a bivariate correlation were performed using SPSS for Windows (Versions 17.0, 19.0, and 20.0).

5 Results

5.1 Middle ear status

5.1.1 Main results

Overall, children and adults with UCLP demonstrated a decrease in the prevalence of OME over time (See Figure 11). This figure includes children from study I (aged 1-5 years), adolescents from study II (aged 7-16 years), and young adults from study IV (aged 20-31 years). This gradual decrease was different from children without CP±L. Children without CP±L had a peak in the prevalence of OME at about 6 to 15 months of age (Klein, 1989) and then normalized by 7 years of age (Sheahan & Blayney, 2003). The children with UCLP presented with OME into young adulthood.

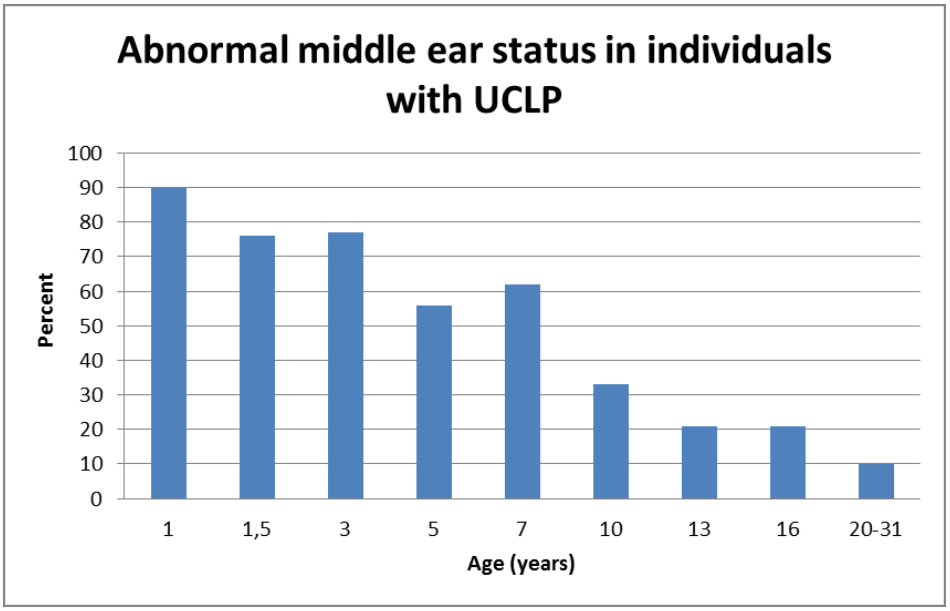

Figure 12. Percentage of ears with abnormal middle ear status at different ages in individuals with UCLP. Data are from studies I, II, and IV.

5.1.2 Study I

Children with UCLP presented with a significantly higher prevalence of abnormal middle ear status than children without cleft. This was evident at each of the data points (1, 1.5, 3, and 5 years of age).

5.1.3 Study II

All cleft groups (UCLP, ICP, and BCLP) demonstrated a decrease in the prevalence of abnormal middle ear status over time. More specifically, the ICP group had significantly less abnormal middle ear status than the BCLP and UCLP groups at 7 and 16 years of age. Within the groups, the UCLP group exhibited significantly less abnormal middle ear status step-wise between 7 and 13 years of age, the ICP group had significantly less abnormal middle ear status at 13 years of age then 10 years of age, and the BCLP presented with significantly less middle ear status at 10 years of age then 7 years of age.

5.1.4 Study III

Children and adolescents with ICP+ presented with a higher prevalence of abnormal middle ear status than children with an ICP.

When the ICP+ group was classified into six subgroups, the subgroup with an ICP and a sequence exhibited the highest prevalence of abnormal middle ear status. This subgroup was also the largest subgroup within the ICP+ group.

5.2 Hearing sensitivity

5.2.1 Main results

Overall, the mean dB HL for each of the audiometric frequencies of children from study I (aged 1-5 years), adolescents from study II (aged 7-16 years), and young adults from study IV (aged 20-31 years) is presented (Figure 13). The data are longitudinal from 1 to 5 years of age and 7 to 16 years of age respectively. There was a gradual improvement in hearing from age 1 year to 16 years of age in the low and mid frequencies. This is in line with normal auditory development in children without hearing loss (Werner & Marean, 1996).

However, at 10 years of age, there was an elevation of thresholds in the high frequencies. This elevation is larger than the typical one seen in children without hearing loss(Werner & Marean, 1996). The mean hearing thresholds at 6000 Hz and 8000 Hz were significantly elevated as compared to the low and mid frequencies. This elevation of thresholds was present at 10, 16, and 20-31 years of age.

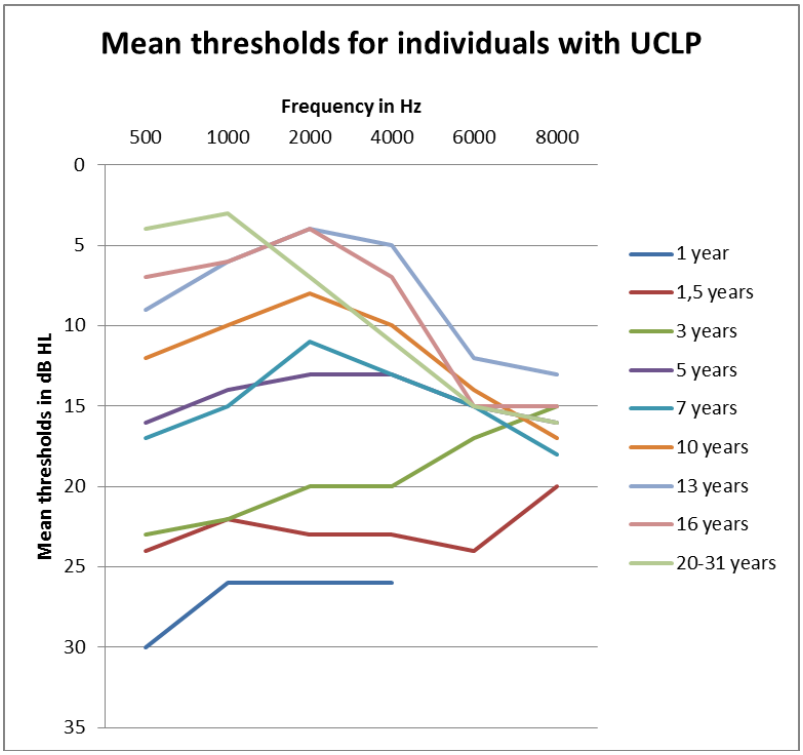

Figure 13. Mean thresholds for ears in individuals with UCLP from studies I, II, and IV.

5.2.2 Study I

When children presented with abnormal middle ear status and a hearing loss, children with UCLP exhibited a significantly higher hearing threshold (PTA4) than children without cleft.

5.2.3 Study II

Hearing statistically improved as children with CP±L became older for the low and mid-frequencies up to 13 years of age for all cleft types (UCLP, ICP, and BCLP). However, the hearing did not significantly improve for the high frequencies. The BCLP group had significantly worse hearing at 4000 Hz, 6000 Hz, 8000 Hz, and PTA HF from 7 to 13 years of age.

5.2.4 Study III

When the hearing was analyzed, the ICP+ group presented with significantly poorer hearing than the ICP group across frequencies. Within the ICP+ group, the hearing significantly became worse for 6000 Hz between 13 and 16 years of age and did not improve for 8000 Hz.

Within in the ICP+ group, the subgroup with monogenic syndromes demonstrated with the highest percentage of ears with hearing loss.

5.3 Speech recognition and MLD (study IV)

Young adults with UCLP presented with elevated hearing thresholds as compared with young adults without CP±L. No significant differences were observed between young adults with UCLP and young adults without on speech recognition in noise or binaural processing. However, there was poorer speech recognition performance in those adults with UCLP and abnormal middle ear status on the day of testing as compared with young adults with UCLP without abnormal middle ear status on the day of testing.

6 Discussion

This thesis describes the prevalence of abnormal middle ear status and hearing in children and adolescents with CP±L. The studies completed investigated these outcomes in a longitudinal methodology to attempt to ensure a more accurate picture from age 1 year to 20 to 31 years.

6.1 Middle ear status

For children with CP±L, OME is universally present at birth (Paradise et al., 1969; Stool & Randall, 1967) and is frequent throughout childhood (Flynn, Moller, Jonsson, & Lohmander, 2009; Gordon et al., 1988; Handzic-Cuk et al., 2001; Moller, 1975; Ovesen & Blegvad-Andersen, 1992; Sheahan et al., 2003; Timmermans et al., 2006). When comparing children with CP±L to children without cleft, they present with a higher prevalence of abnormal middle ear status (Broen et al., 1996; Flynn, Lohmander, Moller, & Magnusson, 2012; Flynn et al., 2009; Ovesen & Blegvad-Andersen, 1992). This higher prevalence may be due to Eustachian tube dysfunction (Arnold et al., 2005; Bluestone et al., 1972; Huang et al., 1997; Matsune et al., 1991a; Sheahan & Blayney, 2003). However, it is unknown when this higher prevalence decreases. The peak in the prevalence of abnormal middle ear status has not been systemically investigated in children with CP±L. This thesis examined the prevalence of abnormal middle ear status from age 1 to 16 years. The peak in the prevalence of abnormal middle ear status is following 7 years of age (Flynn, Lohmander, et al., 2012; Flynn et al., 2009; Handzic-Cuk et al., 2001). Even though the number of ears included in the data from this thesis at 7 years is smaller compared to 10, 13, and 16 years, there is still a larger number of ears than previously reported in the literature (Handzic-Cuk et al., 2001; Sheahan et al., 2003). Since the number of ears is half as many as at 10, 13, and 16 years of age, there may be not “peak” at 7 years of age. Therefore, a gradual decline in the presence of abnormal middle ear status may exist which is different than in children without CP±L. In children without CP±L, there are two peaks in the prevalence of OME. One is at 2 years of age and the other at 5 years of age. The reason for the two peaks is due to episodes of OME following AOM and upper respiratory infections and Eustachian tube position (Mandel et al., 2008; Zielhuis et al., 1990). Children with CP±L’s structural anomalies disguise these two peaks. Both peaks in

prevalence in children without CP±L are lower than children with CP±L at 2 and 5 years of age.

In this thesis, children and adolescents with ICP present with the lowest amount of abnormal middle ear status as compared to UCLP and BCLP. Two studies present with different conclusions (Handzic-Cuk et al., 2001; Moller, 1975). The ICP group presented with the most amount of abnormal middle ear status, as compared to UCLP (Handzic-Cuk et al., 2001; Moller, 1975) and BCLP (Handzic-Cuk et al., 2001). This may be due to the inclusion criteria. Handzic-Cuk et al. (2001) and Moller (1975) did not specify if children with additional malformations and/or identified syndromes were included in their studies. In the study comparing cleft types and abnormal middle ear status, children were excluded if they presented with additional malformations and/or syndromes (Flynn, Lohmander, et al., 2012). Twenty-two to 55% of individuals with ICP present with additional malformations and/or identified syndromes (Chetpakdeechit, Stavropoulos, & Hagberg, 2010; Coleman & Sykes, 2001; Hagberg et al., 1998; Milerad et al., 1997; Schutte & Murray, 1999; Stoll, 2000). These additional malformations and/or syndromes may affect the middle ear status (Flynn, Persson, Möller, Lohmander, & Magnusson, 2013). This thesis demonstrated children and adolescents with ICP+ presented with a significantly higher prevalence of abnormal middle ear status than individuals with ICP. The ICP+ group presented with a higher prevalence of abnormal middle ear status at 10 and 13 years of age as compared to individuals with UCLP and BCLP and a similar prevalence at 16 years of age. If children with additional malformations and/or syndromes were included in the other studies, this could elevate the number of ears with abnormal middle ear status.

6.2 Hearing sensitivity

The hearing of children, adolescents, and young adults was described in this thesis. It is important to consider hearing when investigating middle ear status; since, 60percent of individuals with OME present with a conductive hearing loss that is fluctuating and mild to moderate in nature (Bennett, 1972; Ovesen & Blegvad-Andersen, 1992; Paradise et al., 2000; Sheahan et al., 2002). There is a high correlation between abnormal tympanic membrane appearance and/or tympanometry and audiometry in individuals with CP±L (Bennett, 1972; Broen et al., 1996; Gordon et al., 1988; Ovesen & Blegvad-Andersen, 1992; Sheahan

et al., 2002). When children with and without CP±L presented with abnormal middle ear status, the hearing averages PTA4 for children with cleft were significantly higher than for those without cleft. This could be due to several reasons. Firstly, the viscosity of the fluid in the middle ear may have been thicker in children with UCLP when OME was present. This thicker fluid would not allow sound to be transferred as efficiently and result in a higher threshold. The fluid may have higher adhesiveness as shown in children requiring multiple sets of pressure-equalizing tubes (Dodson, Cohen, & Rubin, 2012). Secondly, children with cleft may present with a sensori-neural hearing loss. Because bone conduction was not consistently assessed, it is unknown what type of hearing loss exists. Studies have reported a small prevalence of sensori-neural hearing loss in children with cleft palate (Moller, 1975; Rohrich et al., 1996; Sheahan et al., 2002).

Another association between OME and hearing is a possible high frequency hearing loss from repeated exposure to OME. Continued episodes of OME have been shown to lead to an extended high frequency hearing loss in children and adults with a positive history of OME without cleft (Gravel et al., 2006; Hunter et al., 1996; Margolis, Saly, & Hunter, 2000) and with cleft (Ahonen & McDermott, 1984; Bennett, 1972; McDermott, Fausti, & Frey, 1986). This high frequency hearing loss is not likely due to middle ear involvement or a mechanical dysfunction. Normal wideband middle ear impedance (Margolis et al., 2000) and distortion product OAEs (Gravel et al., 2006) were shown when the extended high frequency hearing loss was present. The hearing loss in 6000 Hz and 8000 Hz in the present thesis was also not likely due to the cleft. When children with CP±L were compared to children without CP±L and positive OME histories and to children without CP±L and minimal history of OME, children with CP±L and children without CP±L and positive OME histories demonstrated similar thresholds in the high frequencies (McDermott et al., 1986).

The notion of the cleft causing abnormal auditory outcomes has been proposed (Ceponiene et al., 1999; Nopoulos et al., 2002; Yang & McPherson, 2007). Nopoulos et al. (2002) compared adult males with clefts and matched healthy males. Adults with clefts demonstrated abnormalities in the left temporal lobe where the auditory cortex is. Ceponiene et al. (1999) examined children with and without clefts. Children with complete UCLP were less able to identify a change in auditory input on the central processing level. However, these studies

did not consider OME. Perhaps the children and adults tested demonstrated a long-standing history of OME, but this was not stated in either study.

6.3 Speech recognition and MLD

Previous research and this thesis showed a decrease in speech recognition in children without CP±L and with positive histories of OME early in life and in young adults with CP±L (Brown, 1994; Flynn, Moller, et al., 2012; S. Jerger et al., 1983; Schilder et al., 1994). When the duration of OME was examined, the children with more episodes of OME performed significantly worse than those with less OME (Schilder et al., 1994). In another study including children of the same age at testing, showed no difference on speech recognition performance in noise for children with a positive history of OME and those without a positive history of OME (Gravel et al., 2006). However, the children with a positive history of OME only experienced episodes of OME in the first 3 years of their lives. Some of the children in the Schilder et al. (1994) study presented with OME until time of testing. In this thesis, examination of the effect of duration of OME was not able to be performed as full medical history was not accessible for the group of young adults with CP±L. However, when asking the individuals participating, two groups could be formed: those with short-term and those with long-term abnormal middle ear status. This grouping is based on the person's account of their experience with episodes of OME and pressure equalizing tubes being placed. When speech recognition was analyzed with these groupings, differences existed at the word level, but not the sentence level. This is in line with previous research on children with a positive history of OME (Brown, 1994; S. Jerger et al., 1983; Schilder et al., 1994).

Another area to consider when examining abnormal middle ear status, is binaural processing. The mild to moderate, fluctuating hearing loss associated with OME may lead to disruptions in the development of the auditory system in regards to binaural processing. Research indicates the MLD in children with positive OME is significantly smaller (J. W. Hall, 3rd et al., 1998; Hogan & Moore, 2003; Moore et al., 1991), but slowly "recovers" to normal range in approximately four years following resolution of OME (J. W. Hall & Grose, 1993).

The smaller MLDs seen in previous studies were in children with pressure equalizing tubes placed shortly before testing (J. W. Hall, 3rd et al., 1998; J. W. Hall, 3rd, Grose, & Pillsbury, 1995; J. W. Hall & Grose, 1993). It can be concluded those children who received pressure equalizing tubes presented with OME before the pressure equalizing tubes were inserted. Therefore, the testing occurred very close in time to the presence of OME and the effects of the OME on the auditory system were still present. This is in accordance with four adults presenting with OME on the day of testing (one had pressure equalizing tubes in-situ) in the current study.

Furthermore, in the present study, smaller MLDs did not disappear but were still present for six of the participants who demonstrated abnormal middle ear status into adolescence. Conversely, the Hall and Grose (1993) study followed children for four years following the placement of pressure equalizing tubes. The difference between the children with pressure equalizing tubes placed and those without pressure equalizing tubes disappeared by the third year following the placement of pressure equalizing tubes. This is a relatively slow recovery for children without CP±L. With the addition of CP±L with a higher prevalence of OME and increased hearing thresholds with OME, the recovery time may be slower. This is demonstrated in this thesis with some of the adults' auditory system not recovering.

6.4 Methodology discussion

Two of the studies (study II and study III) in this thesis are retrospective. Being retrospective causes some challenges in data collection. Although the number of ears included in study II and III are high, there were quite a few ears missing at age 7. The missing data at age 7 is due to a change in clinical routines. Appointments at Sahlgrenska University Hospital Otolaryngology and Audiological clinics for children born with CP±L were not routine until 1998, after most of the individuals in study II and III were 7 years old. Also, many individuals did not come at 16 years of age or requested not to see the Otolaryngologist or the Audiologist as they felt it was not needed.

Another challenge in this thesis was the definition of OME and abnormal middle ear status. In study I and IV, OME was defined as one of three conditions: (a) fluid was present or tympanic membrane was retracted, (b) tympanostomy tubes in-situ, or (c) perforated tympanic membrane. This definition was chosen due to

data collection points. Data was collected at set ages that were more than 6 months apart and/or on one day. The fluctuating nature of OME makes it a challenge to capture all episodes in this manner of data collection. Individuals with pressure-equalizing tubes in-situ or a perforated tympanic membrane would have had OME prior to the insertion of the tube and the day the data was collected; therefore, they were included in the group with OME. If these groups were not included in the OME group, how would these children have been categorized a month later when the pressure-equalizing tube had fallen out or the eardrum mended? Their pathologies would not have been reflected in the data collected. The pressure-equalizing tube in-situ reflects the treatment and management for OME in Sweden. This care functions well for children with CP±L, as evidenced in study I with the prevalence of pressure-equalizing tubes increasing between 12 and 18 months of age. Once OME was detected, pressure-equalizing tubes were placed. This leads to another example in study I, where the prevalence of pressure equalizing tubes was illustrated separately in an attempt to demonstrate those ears with tubes were different than those with fluid in the middle ear or a retracted tympanic membrane. During the review of study IV, one reviewer commented on this definition or categorization of OME:

> *Reviewer: I don't fully understand why OME is supposed to be present with a dry and patent pressure equalizing tube in situ. OME is rather more likely to recur when the tube is blocked. Classifying cleft patients with an open and dry tube as OME patients may skew the results!*
>
> *Response: The participant with the pressure equalizing tube in situ was classified as having OME, as the participant would have previously had OME in order to receive the pressure equalizing tube. Since the testing only occurred on one day, the participant with a pressure equalizing tube was considered to have OME in order to accurately describe the participant's short-term OME history.*

The reviewer accepted the response and the definition of OME was kept. However, for study II, the definition and categorization of OME was also questioned by both reviewers and changed:

> *Reviewer: It is illogical and incorrect to label patients with either a perforated tympanic membrane or in situ PE tubes as having OME. Perhaps the authors should reconsider this definition (e.g. label as "abnormal ears") or re-analyze*

the data by stratifying by OME, perforation, or PE tubes. Indeed, just because a patient has a PE tube in situ does not mean they are necessarily continuing to have middle ear pathology since the tubes may take several years to extrude during which time the pathology of the Eustachian tube may have resolved.

Response: The reviewer is correct. The definition has been changed and labeled "abnormal ears". This definition has been used throughout the paper.

Reviewer: The OME definition includes presence of myringotomy tubes or TM perforation, and this is not really correct. This should be teased out in the analysis.

Response: The reviewer is correct. The definition has been changed to be "abnormal middle ear status". This includes the presence of myringotomy tubes, TM performation, fluid-filled middle ear, or retracted TM.

The definition was changed for study II and III because the categorization of OME used in study I and IV is not accurate, as OME is a condition that exists when fluid is in the middle ear and is not accompanied by signs of a bacterial infection (Lous et al., 2008). Consequently, the title for middle ear pathologies was changed for studies II and III to abnormal middle ear status to be more accurate and attempt to capture all conditions of middle ear pathologies. The new title of abnormal middle ear pathologies is in line with the literature. Other studies have classified middle ear pathologies as normal or abnormal tympanic membrane appearance (Bennett, 1972; Lous et al., 2008; Sheahan et al., 2002; Timmermans et al., 2006; Valtonen et al., 2005). Abnormal tympanic membrane appearance included OME, a perforation, or retraction (Bennett, 1972; Ovesen & Blegvad-Andersen, 1992; Timmermans et al., 2006; Valtonen et al., 2005).

Even though it was a challenge to capture all episodes of OME, the methodology to define OME/abnormal middle ear status was rigorous and consistent through the thesis. Otomicroscopy, tympanometry, and hearing sensitivity were used to define the status of the middle ear. This has not been the case in previous literature. Different methods of assessment have been utilized to define the appearance of the tympanic membrane and status of the middle ear: otomicroscopy, pneumatic otoscopy, myringotomy with effusion, and tympanometry. However, not all measures have been used simultaneously

(See Table 10). There have been a few studies which used one type of assessment to define the status of the middle ear: visualization of the tympanic membrane (Paradise et al., 1969; Stool & Randall, 1967) or tympanometry (Handzic-Cuk et al., 2001). One study utilized two methods of assessment including visualization of the tympanic membrane and tympanometry (Dhillon, 1988). A couple of studies combined assessments of middle ear status and reported audiometry, but did not reflect upon the audiometry and middle ear status results (Rynnel-Dagoo, Lindberg, Bagger-Sjoback, & Larson, 1992; Timmermans et al., 2006); while other studies did reflect upon the audiometric results in light of the middle ear status (Bennett, 1972; Broen et al., 1996; Gordon et al., 1988; Hubbard, Paradise, McWilliams, Elster, & Taylor, 1985; Moller, 1975; Ovesen & Blegvad-Andersen, 1992; Sheahan et al., 2002; Valtonen et al., 2005).

Another consideration when examining the definition of OME and the measurements used is the inconsistency of parameters of tympanometry. Tympanometry has been calculated using differing parameters in interpreting tympanograms. The borders of Type A, Type C1 and Type C2 tympanograms have been altered, depending on the author of the study.

Also, the definition of hearing loss has been also inconsistent and needs to be considered. When considering the definition of hearing loss, most studies have defined hearing loss as a three frequency PTA (500 Hz, 1000 Hz, and 2000 Hz) (Gordon et al., 1988; Gould, 1990; Handzic-Cuk et al., 1996; Moller, 1975; Ovesen & Blegvad-Andersen, 1992; Timmermans et al., 2006; Valtonen et al., 2005). Currently, a four frequency PTA is standard, which was used in this thesis. In addition the high frequencies were analyzed.

Finally, studies I and IV also utilized a control group. This allows for a direct comparison to individuals without cleft palate. This is critical when investigating the effects of OME on individuals with cleft in order to examine the possibilities of the results being due to the presence of the cleft or the repeated exposure to episodes of OME.

The Gothenburg cleft palate team is one of six centers in Sweden for treating children and adults with cleft palate. The cleft palate in Gothenburg consists of several professions including surgeons, orthodontists, speech-language pathologists, otolaryngologists, and audiologists. This team is unique in Sweden as the otolaryngologist and audiologist are active members on the team.

Children and adolescents also see the otolaryngologist and audiologist at all routine clinical checks. It is because of these regular appointments studies II and III were able to be performed.

Table 10. Overview of assessments utilized in studies investigating individuals with CP±L.

Study	Otomicrocopy	Myringotomy with effusion	Pneumatic otoscopy	Tympanometry	Audiometry
Stool and Randall, 1967	X	X			
Paradise, Bluestone et al., 1969	X	X			
Bennett, 1972	X				X
Moller, 1975		X			X
Hubbard, Paradise et al., 1985		X	X	X	X
Dhillon, 1988	X			X	
Gordon, Jean-Louis et al., 1988	X			X	X
Ovesen and Blegvad-Andersen, 1992	X			X	X
Rynnel-Dagoo, Lindberg et al., 1992	X		X		X
Broen, Moller et al., 1996				X	X
Handzic-Cuk, Cuk et al., 2001				X	
Sheahan, Blayney et al., 2002	X				X
Valtonen, Dietz et al., 2005			X		X
Timmermans, Vander Poorten et al., 2006	X			X	X

7 Summary

This thesis expands the current knowledge base on the prevalence of abnormal middle ear status with longitudinal data investigating children, adolescents, and young adults born with a cleft palate. It also examines hearing and attempts to define the effects of a higher prevalence of abnormal middle ear status on hearing. Few other longitudinal studies have been performed and have only focused on middle ear status. This thesis also includes hearing and has been able to investigate what occurs over time as children age.

7.1 Middle ear status

Children with CP±L exhibit a higher prevalence of abnormal middle ear status than those without CP±L. This higher prevalence of abnormal middle ear status continues to stay relatively high until seven years of age. Following seven years of age, there is a significant decrease in the amount of abnormal middle ear status and it continues to decrease with age. This pattern is evident across all three cleft groups studied (UCLP, ICP, and BCLP). Individuals with ICP present with a significantly lower prevalence of abnormal middle ear status than those with UCLP or BCLP. However, individuals within the ICP+ group present with a significantly higher prevalence of abnormal middle ear status than those in the ICP group. In comparison to individuals with UCLP and BCLP, the ICP+ group exhibited a lower prevalence of abnormal middle ear status at 7 years of age, a higher prevalence at 10 and 13 years of age and a similar prevalence at 16 years of age.

7.2 Hearing sensitivity

Individuals with CP±L present with elevated hearing thresholds at 6000 Hz and 8000 Hz. The group with BCLP exhibited with significantly higher thresholds than those individuals in the ICP and UCLP groups. This elevation in the high frequencies was also noted in the young adults with UCLP. Also, the ICP+ group of individuals demonstrated with significantly higher thresholds than those in the ICP group. The ICP+ group and the BCLP group demonstrated similar hearing thresholds at 16 years of age at 6000 Hz and 8000 Hz. The

increased hearing thresholds in the high frequencies may be due to the increased episodes of OME.

Another interesting result revealed when OME and a hearing loss was present, children with UCLP demonstrated higher thresholds than children without CP±L. These increased thresholds may be due to a thicker viscosity of the effusion in children with CP±L.

7.3 Speech recognition and MLD

When young adults presented with abnormal middle ear status, they performed significantly worse on speech recognition measures at the word and sentence level than young adults with CP±L. This was noted at the sentence and word level speech recognition materials. Furthermore, within the cleft group, participants with long-standing abnormal middle ear status exhibited smaller MLDs than those with short-term abnormal middle ear status.

8 Conclusion and clinical implications

As others have indicated, children and young adults with CP±L need regular audiological and otological clinical examinations to ensure that they are free from OME, and that hearing is managed appropriately and in a timely manner. It is even more imperative to closely follow these individuals with CP±L, as they present with a higher prevalence of abnormal middle ear status, elevated hearing thresholds when OME and a hearing loss are present, a possible acquired high frequency hearing loss, and poorer performance on speech recognition measures. Even though many studies have investigated the effects of OME on hearing, speech, language, and academic performance, the results cannot be transferred to individuals with CP±L. They are a subgroup of individuals which require examination with special consideration of anatomical structures. The increased prevalence of abnormal middle ear status experienced in children with CP±L may lead to increased hearing thresholds in the high-frequencies (4000, 6000, and 8000 Hz), which may negatively affect their abilities to communicate in noisy situations. For children this may lead to difficulties in the classroom and for adults this may lead to difficulties at work. Also, the presence of smaller MLDs may lead to challenges in localizing sound and hearing in noisy.

9 Future Research

Further research is needed to fully examine the effects of prolonged abnormal middle ear status on the development of the auditory cortex and hearing. Also, investigations exploring when individuals with CP±L require audiological management and what type is best suited are needed. A first step in this endeavor would be to conduct speech recognition testing at the word and sentence level on a routine basis to ensure individuals with CP±L are recognizing speech in noisy conditions.

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