

Follow-up of childhood hearing disorders: hearing loss, tinnitus and dizziness in adulthood

A population-based cohort study

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2 List of papers

1. Aarhus L, Tambs K, Kvestad E, Engdahl B. Childhood otitis media: A cohort study with 30 year follow-up of hearing (the HUNT study). *Ear and Hearing* 2015;36(3):302-8 .
2. Aarhus L, Tambs K, Nafstad P, Bjørgan E, Engdahl B. Childhood sensorineural hearing loss: Effects of combined exposure with aging or noise exposure later in life. *European Archives of otolaryngology and Head and Neck Surgery* 2015. Online first. doi:10.1007/s00405-015-3649-y.
3. Aarhus L, Engdahl B, Tambs K, Hoffman H. The association between childhood hearing disorders and tinnitus in adulthood: Results from a cohort study (HUNT). *JAMA Otolaryngology - Head & Neck Surgery*. Accepted / in press.
4. Aarhus L, Tambs K, Hoffman H, Engdahl B. Childhood otitis media is associated with increased risk of dizziness in adulthood: The HUNT cohort study. Submitted.

3 Abbreviations

SHINT: School Hearing Investigation in Nord-Trøndelag

NTHLS: Nord-Trøndelag Hearing Loss Study

HUNT: Nord-Trøndelag Health Study

CSOM: chronic suppurative otitis media

rAOM: recurrent acute otitis media

OME: otitis media with effusion

SNHL: sensorineural hearing loss

BPPV: benign paroxysmal position vertigo

ARHL: age-related hearing loss

NIHL: noise-induced hearing loss

dB HL: decibel hearing level

PTA: puretone average

HF: high frequency

OR: odds ratio

CI: confidence intervals

4 Summary

This project aimed to assess the associations between various hearing disorders in childhood and hearing loss, tinnitus and dizziness in adulthood. Especially, we examined childhood otitis media and childhood sensorineural hearing loss (SNHL). Knowledge about these long-term outcomes is scarce, and important when considering level of intervention and for patient information.

The data were obtained from a population-based cohort study of 32,786 adults (aged 20-59 years, mean 40 years) who underwent puretone audiometry and completed a health questionnaire in the Nord-Trøndelag Hearing loss study (1996-1998). As children, the same persons underwent audiometry in a longitudinal school hearing investigation (at 7, 10 and 13 years of age). Children found with hearing loss underwent an ear, nose and throat specialist examination (3066 children), in which they were diagnosed with various hearing disorders.

In conclusion, our study indicates that childhood chronic suppurative otitis media (CSOM) and childhood hearing loss after recurrent acute otitis media (rAOM) are associated with significant hearing loss, tinnitus and dizziness in adulthood. This stresses the importance of appropriate prevention, treatment and follow-up of these otitis media conditions.

The common condition childhood otitis media with effusion, both with and without eardrum pathology, is associated with marginally increased adult hearing thresholds. This can safely be communicated to worried patients.

The childhood hearing disorders SNHL, CSOM and hearing loss after rAOM are associated with a faster deterioration of hearing throughout adulthood. This “faster aging” may reflect that an already impaired cochlea is more susceptible to age-related degeneration. The faster aging effect is moderate and hardly necessitates more frequent follow-up. The finding should be confirmed by a study with repeated audiometries in adulthood.

Finally, our large study could not reveal significantly altered susceptibility to noise induced hearing loss associated with childhood SNHL or childhood otitis media. Although

it still is important with protection against harmful noise, this is valuable information for people with a childhood-onset hearing loss.

5 Background

5.1 Basic knowledge

5.1.1 Hearing loss

Definition. Sound is mechanical airborne waves. The term sound *frequency* (measured in hertz) refers to the frequency of the wave vibration and is perceived as the pitch of the sound. Sound *intensity* (measured in decibel) refers to the power transferred by the wave (energy per second) and is perceived as the loudness of the sound. Clinicians measure sound intensity in decibel hearing level (dB HL). The lowest sound intensity of a puretone stimulus a person detect 50% of the time, is defined as the hearing *threshold*. For young, healthy persons, this is at 0 dB HL. The puretone stimulus is produced by an audiometer and the results are printed in an audiogram (Figure 1). Hearing loss can be classified as mild, moderate, severe or profound. The World Health Organisation (WHO) defines the hearing loss categories by the puretone average (PTA) of 0.5-1-2-4 kHz in the better hearing ear as follows: mild 26-40 dB HL, moderate 41-60 dB HL, severe 61-80 dB HL and profound ≥ 81 dB HL. Disabling hearing loss is defined as >40 dB HL in adults and >30 dB HL in children (WHO, 2015).

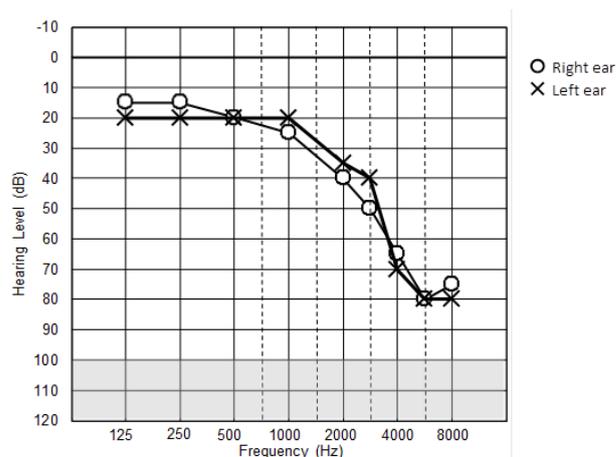


Figure 1. Audiogram showing puretone thresholds as a function of frequency. Classic age-related hearing loss with bilateral, high frequency hearing loss.

Prevalence. Hearing loss prevalence is a measure of how many people in a defined population that have hearing loss at any given time or over a time interval. According to WHO, more than 5% of the world's population has *disabling* hearing loss: 328 million adults and 32 million children (WHO, 2015). A detailed description of hearing loss prevalences is found later (“hearing across the lifespan”).

Etiology. Hearing loss can be divided into conductive or sensorineural, a combination is called a mixed hearing loss. Conductive hearing loss is due to pathology of the outer ear (the auricle and the external auditory canal) or the middle ear (the eardrum and the cavity behind it), so that sound does not pass freely to the inner ear. Generally, the overall sound volume is reduced. SNHL is due to pathology of the inner ear (the cochlea), the auditory nerve or the central nervous system. The hearing loss is permanent because the hair cells and the nerve cannot regenerate or be repaired. SNHL is congenital or acquired, and the causes can broadly be divided into genetic and environmental (like noise exposure, infections, trauma, birth asphyxia, ototoxic drugs and others). The most common cause of SNHL is age-related hearing loss (ARHL). SNHL often results in a reduced dynamic range and loudness recruitment.

Impact: The impact of hearing loss is described later (“hearing across the lifespan”).

Management. Early identification of the hearing loss and appropriate management help many persons. Conductive hearing loss is often temporary or corrected with surgical or medical treatments. Treatments of SNHL and long-term conductive hearing loss include use of various types of hearing aids, assistive devices, adjustment to hearing loss and managing communication. The functional benefits of hearing aid are well described (Mulrow et al., 1990). Cochlear implants, a surgically implanted electronic device that convert sound waves to electrical impulses, can be used for severe or profound hearing loss.

Hearing across the lifespan. At least one child in 1000 is born with bilateral SNHL of at least 40 dB HL. While about 50% of congenital SNHL is due to genetic disorders (about 1/3 syndromic), about 50% has environmental causes, such as intrauterine infections (Smith et al., 2005) (review). In genetic SNHL, the hearing loss (phenotype) may develop

later in life (“late-onset hearing loss”). The developing auditory cortex is highly plastic. Studies of cochlear implanted children show that early intervention with adequate stimulation of the cortex increases the likelihood of normal auditory cortical development in children with congenital deafness (Cardon et al., 2012) (review). Accordingly, cochlear implants are used increasingly within the first year of life.

The majority of hearing loss in preschool and school-aged children is surely minimal or mild, temporary, conductive hearing loss due to otitis media, especially otitis media with effusion (OME, defined later).

A study of 1281 children in 3rd, 6th, and 9th grades showed a prevalence of 11% of all types of hearing loss (temporary or permanent), including *minimal* hearing loss (>15 dB HL) (Bess et al., 1998). Another study, of 6166 school children aged 6-19 years, showed a prevalence of 15% (PTA of 0.5-2 kHz or PTA of 3-6 kHz >15 dB HL in the worse hearing ear) (Niskar et al., 1998). A review based on the average of comparable audiometric screening studies in the United States reported a prevalence of 3.1 % (PTA of 0.5-2 kHz >20 dB HL in the worse hearing ear) (Mehra et al., 2009).

Childhood hearing loss presents a substantial disability worldwide. Even minimal hearing loss has been shown to affect speech, academic and psychosocial development (Bess et al., 1998) (Davis et al., 1986).

The great majority of hearing loss in *adults* is SNHL due to age-related degeneration of the cochlear hair cells. ARHL often starts in the high frequency (HF) range in the 30-40thies, and is more pronounced in males. Although hearing normally declines with age, there is great individual variation in the age of onset and severity. While only a small part of this variation seems to be explained by noise exposure, ear diseases or other exposure, ARHL is to a large extent heritable (Kvestad et al., 2012).

The Nord-Trøndelag Hearing Loss Study (NTHLS) showed a weighted hearing loss prevalence of 19% (PTA of 0.5-4 kHz \geq 25 dB HL in the better hearing ear) for the total sample (n=50,723, age 20-101, mean age=50 years). The prevalence was 0.8% in 20-24 year old females and 51% in 65-69 year old males (Borchgrevink et al., 2005).

Hearing loss affects communication. About 10% of the adult population report bilateral hearing difficulty in hearing speech in a quiet environment (Davis, 1989). Also, hearing loss has been associated with poorer health-related quality of life (Chia et al., 2007), reduced mental health (Tambs, 2004), low educational attainment, underemployment and economic impairments (Emmett and Francis, 2014).

5.1.2 Tinnitus

Definition. Tinnitus can be defined as the perception of sound in the absence of a corresponding external acoustic stimulus (Langguth et al., 2013) (review).

Prevalence. Most studies show tinnitus prevalences between 10% and 15% in the adult population (Baguely et al., 2013) (review). The NTHLS study showed tinnitus prevalences (“bothered by ringing in the ears”) from 9.6% (30-39 years) to 24% (70-79 years), with an overall prevalence of 15% (n=47,410) (Hoffman, 2004).

Etiology. The most important risk factor of tinnitus is hearing loss. This association is well described in both children (Nodar, 1972, Coelho et al., 2007,) and adults (Sindhusake et al., 2003, Hoffman, 2004, Nondahl et al., 2011), but the etiology is complex. Tinnitus is reported in apparently normal hearing persons, and far from all persons with hearing loss report tinnitus. A prominent theory of tinnitus generation states that hearing loss (temporary or permanent) is the initial source of tinnitus, but that subsequent neural changes in the central auditory system maintain the condition (Langguth et al., 2013) (review). In addition to hearing loss, other risk factors (like male sex, increasing age, low income, ear infections and occupational noise exposure) have been associated with tinnitus (Hoffman, 2004). The heritability of tinnitus has been estimated to be low (Kvestad et al., 2010).

Impact. An English study reported that tinnitus was described as moderately annoying by 2.8%, severely annoying by 1.6%, and at a level that severely affected ability to lead a normal life by 0.5% (n= 48,313) (Davis A, 2000). In the HUNT study, participants with tinnitus scored moderately higher on anxiety and depression and lower on self-esteem and well-being than those without tinnitus (Krog et al., 2010).

Management. In addition to eventual treatment of underlying or co-occurring pathology, treatment often includes counselling, cognitive behavioural therapy and sound therapy.

5.1.3 Dizziness

Definition. Dizziness can be defined as the sum of vertigo (illusion of movement of oneself or the environment), disequilibrium (a sensation of imbalance and/or postural instability), presyncope (feeling faint or light-headed) and “other” types of dizziness (Sloane et al., 2001).

Prevalence. A study of 1287 persons aged 14-90 years which used the “Vertigo Symptom Scale” reported a dizziness prevalence of 15% (Wiltink et al., 2009). In another study, also using the Vertigo Symptom Scale (n=2064, age 18-64 years), 10% reported some degree of dizziness-related handicap (Yardley et al., 1998). Neuhauser et al. found a prevalence of vestibular vertigo of 4.9% in the last 12 months (n=4869, age >18 years). Their definition of vestibular vertigo included at least one of the following 1) rotational vertigo; 2) positional vertigo; 3) dizziness with nausea and either oscillopsia or imbalance (Neuhauser et al., 2008).

Etiology. The causes of dizziness can broadly be divided into vestibular (mostly associated with vertigo) and non-vestibular (mostly associated with disequilibrium, presyncope or “other” types of dizziness). The vestibular system is divided into the *peripheral* system (the vestibular labyrinth/the “balance organ” in the inner ear) and the *central* system (the parts of the central nervous system that process the information, along with proprioceptive and ocular input). Peripheral vestibular disorders, like benign paroxysmal position vertigo (BPPV), vestibularis neuritis and Meniere disease, are by far most common. Non-vestibular risk factors include medical, psychiatric and neurological dizziness (Timothy, 2014) (review).

Impact. Dizziness is associated with extensive handicap and psychological morbidity (Yardley et al., 1998). Vestibular dysfunction significantly increases the likelihood of falls, which are among the most morbid and costly health conditions affecting older individuals (Agrawal et al., 2009).

Management. In addition to eventual treatment of underlying or co-occurring pathology, treatment often includes various vertigo-habituation exercises (Cohen, 2006) (review).

5.1.4 Otitis media

Otitis media is an inflammation of the middle ear (the eardrum or the cavity behind it) without reference to etiology or pathogenesis (Gates et al., 2002). This complex disease occurs as related clinical subtypes.

Otitis media with effusion (OME) is a chronic inflammation of the middle ear, often due to eustachian tube dysfunction. A non-purulent middle ear effusion is present (a collection of sterile liquid in the cavity behind the eardrum). There are no signs and symptoms of acute infection (Gates et al., 2002). Generally OME is found in small children (small eustachian tubes), with a prevalence of about 20% at 2 years of age and a prevalence of about 6% at 10 years of age (Zielhuis et al., 1990) (review). The rates of spontaneous resolution are high. Longstanding disease with documented hearing loss (such as >6-9 months) is mostly treated with ear tubes.

Acute otitis media (AOM) is an acute inflammation of the middle ear caused by a viral or bacterial infection, often in connection with upper airway infections. A purulent middle ear effusion is present, and there are symptoms and signs of acute infection such as otalgia, otorrhoea, fever or irritability (Gates et al., 2002). AOM is the most common cause of pediatrician visits, and by age 3 years, 50-85% of children have had AOM (Casselbrant ML, 1999). The rate of spontaneous resolution is high and the treatment is mostly symptomatic, such as analgesic or antipyretics.

Recurrent (r) acute otitis media can be defined as ≥ 3 episodes of AOM in a 6 month period or ≥ 4 episodes the prior year. It is also referred to as *complicated* otitis media, and affects 10-20% of children by age 1 year (Casselbrant ML, 1999). RAOM is often referred to an ear, nose and throat (ENT) department to assure correct treatment, like antibiotics and hearing controls. Late attendance to day-care as well as a day-care with few children (less infections) (Rovers et al., 1999) (review), and breastfeeding (Duffy et

al., 1997) have been associated with reduced risk of acute otitis media. There is ongoing research on otitis media preventing vaccines (Pelton et al., 2013).

Chronic suppurative otitis media (CSOM) is a chronic infection of the middle ear and the mastoid cells, including a chronic perforation of the eardrum and intermittent otorrhoea (Gates et al. 2002). Global estimated CSOM incidence rate is 4.8 per thousand people, with a higher prevalence in developing countries (Monasta et al., 2012) (review). CSOM can present with a cholesteatoma: A destructive and expanding growth consisting of keratinizing squamous epithelium in the middle ear and/or mastoid process.

Cholesteatoma can destruct the ossicles and spread through the base of the skull into the brain. Treatments of CSOM include prevention of infections, antibiotics and various types of middle ear surgery, like tympanoplastics, ossicular plastics and cholesteatoma removal.

5.2 Childhood hearing disorders: hearing loss, tinnitus and dizziness later in life

This project aimed to assess the associations between various hearing disorders in childhood and hearing loss, tinnitus and dizziness in adulthood. Especially, we examined childhood otitis media and childhood SNHL. Informative data on these long-term outcomes are scarce, and the knowledge about them is important when planning level of intervention and for patient information. Also, such epidemiologic data can help generate new pathophysiologic hypotheses and may ultimately help improve therapy.

5.2.1 Childhood otitis media

Knowledge about possible long-term outcomes after childhood otitis media is important in considerations of interventions, such as prevention (like attendance to daycare, hygiene management and vaccine research), treatment (like antibiotics and surgery) and follow-up (like ENT- and hearing controls). Knowledge about altered susceptibility to noise induced hearing loss (NIHL) is important to clear out for possible increased protection against harmful noise. The next section describes the literature that is relevant regarding otitis media and *subsequent* hearing loss, tinnitus and dizziness.

In *ongoing* otitis media, the middle ear fluid (or the eardrum perforation in CSOM) causes a conductive hearing loss, sometimes accompanied by tinnitus. Overwhelming evidence from human temporal bone studies and experimental studies in animals (basic research) suggests that toxins or inflammatory mediators from otitis media enter and affect the labyrinth (the cochlea and the vestibular apparatus) by crossing the round window membrane (Cureoglu et al., 2005) (review). In acute serous labyrinthitis, one of the most common complications occurring during otitis media, invasion by bacterial or viral toxins inflames the labyrinth. This acute inflammation is usually associated with temporary vertigo (vestibular affection) and sometimes mild SNHL (cochlear affection), implying preservation of viable hair cells. Treatment mostly includes antibiotics and sometimes middle ear surgery. However, once toxic substances enter the inner ear, various long-term impairments can occur:

Hearing loss. A large number of studies have shown impaired bone-conduction thresholds (implying SNHL) in adults with otitis media, mostly CSOM (Hulka, 1941, English et al., 1973, Paparella et al., 1984, Cusimano et al., 1989, El-Sayed, 1998, Redaelli de Zinis et al., 2005, Yoshida et al., 2013, Luntz et al., 2013). Recently, a study showed SNHL in children with CSOM (Yehudai et al., 2015). Risk factors for SNHL include duration of CSOM (Cusimano et al., 1989, Redaelli de Zinis et al., 2005, Luntz et al., 2013), a smaller mastoid area (Yoshida et al., 2013) and of course the presence of cholesteatome (Luntz et al., 2013), which may expand and destruct the labyrinth.

Also, many studies have shown hearing loss in children with a *history* of various types of otitis media. Repeated findings of high or extended high frequency hearing loss in children with a history of otitis media (Ahonen and McDermott, 1984, McDermott et al., 1986, Margolis et al., 1993, Sorri et al., 1995, Hunter et al., 1996, Laitila et al., 1997, Margolis et al., 2000), strongly indicates structural damage of the basal turn of the cochlea. A few studies have shown an association between otitis media in childhood and hearing loss in *adulthood* (De Beer et al., 2003, Tambs et al., 2004, Jensen et al., 2013,). In the study of Yilmaz et al., young adults with a history of childhood otitis media had fewer otoacoustic emissions detected (Yilmaz et al., 2006).

Longstanding hearing loss after otitis media can also be due to *middle ear* impairments, such as pathology of the eardrum (tympanosclerosis, atrophy, retraction, adhesion, perforation), of the ossicular chain (fixation, discontinuity or resorption) or of the middle ear mucosa (hyperplasia, hypertrophia) (Jung et al., 2013) (review). Middle ear impairments needing treatments are often associated with CSOM, in which various types of middle ear surgery (tympanoplastics, ossicular chain plastics, cholesteatoma removal) has been done for decades.

Tinnitus. As described, hearing loss is the most important risk factor for tinnitus. As such, it is reasonable to expect an association between a history of otitis media and tinnitus, in that otitis media influences later hearing threshold, which in turn influences the occurrence of tinnitus. Another reason to expect such an association is because animal studies have suggested that *temporary* conductive hearing loss in early life may alter the functional properties of the auditory cortex on a permanent basis, which could increase the risk of later tinnitus (Sun et al., 2014). A few cross-sectional studies (Sindhusake et al., 2003, Hoffman, 2004, Nondahl et al., 2011) and a cohort study (Dawes and Welch, 2010) have shown an association between otitis media in childhood and tinnitus in adulthood.

Dizziness. Although the vestibule is relatively far from the round window, it has been shown that endotoxin can penetrate the inner ear via various routes, such as the round window, blood vessels or lymphatics, and/or interscala exchange, resulting in a disturbance not only of the cochlea but also of the *vestibular* end organs (Takumida and Anniko, 2004). A few cohort studies have shown an association between a *history* of recurrent childhood otitis media and vestibular dysfunction (Schaaf, 1985, Denning and Mayberry, 1987, Casselbrant et al., 2000), but only in preschool children.

Interactions: aging and noise exposure. Possibly, a pre-existing cochlear impairment caused by childhood otitis media could increase the susceptibility to cochlear affection caused by aging or noise exposure. Increased susceptibility to NIHL has been found among young adults with self-reported, recurrent childhood ear infections (Job et al., 1999) and the effect of childhood ear infections on adult hearing seems to increase with

age (Tambs et al., 2004). Yet, these effects are reported from cross-sectional studies only.

The rationale of this study. Evidence about the extent to which various types of childhood otitis media are associated with permanent hearing loss, tinnitus or dizziness is scarce. Also, the association between otitis media and susceptibility to NIHL or ARHL is unclear. Thus, we aimed to assess the association between various types of otitis media in childhood and hearing loss, tinnitus and dizziness in adulthood, and whether these associations were influenced by aging or noise exposure.

Table 1. Cohort studies examining hearing thresholds, tinnitus or dizziness *after* childhood otitis media.

Study, year	Exposure (childhood otitis media)	Outcome measure (time at measure)	Result
Ahonen and McDermott, 1984	Cleft palate and rOM ¹	Puretone audiometry (childhood)	Extended high frequency hearing loss
McDermott et al., 1986	rOM	Puretone audiometry (childhood)	Extended high frequency hearing loss
Margolis et al., 1993	rAOM ²	Puretone audiometry (childhood)	Extended high frequency hearing loss
Sorri et al., 1995	rAOM	Puretone audiometry (childhood)	High frequency hearing loss
Hunter et al., 1996	rOM	Puretone audiometry (childhood)	High frequency hearing loss
Laitila et al., 1997	rAOM	Puretone audiometry (childhood)	Extended high frequency hearing loss
Margolis et al., 2000	rOM	Puretone audiometry (childhood)	Extended high frequency hearing loss
de Beer et al., 2003	rAOM or rOME	Puretone audiometry (18 years)	Extended high frequency hearing loss
Augustsson et al., 2006	“Mostly rOME”	Puretone audiometry (18 years)	4dB increased hearing thresholds, PTA 0.5-4 kHz
Jensen et al., 2013	CSOM ³	Puretone audiometry (18-24 years)	Normal hearing thresholds
			PTA >15 dB HL at low or high frequency area
Dawes et al., 2010	OME <i>before</i> 11 years + hearing loss at 11 years	Tinnitus questionnaire (mean age 32 years)	Increased risk of tinnitus
Casselbrant et al., 2000	Recurrent or persistent MEE ⁴ (preschool)	Vestibular tests (preschool)	Poorer performance on rotational test
Schaaf et al., 1985	>6 episodes of AOM (preschool)	Vestibular tests (preschool)	Poorer performance on vestibulospinal tests

¹ Otitis media with effusion

² Recurrent acute otitis media

³ Chronic suppurative otitis media

⁴ Middle ear effusion (a collection of purulent or non-purulent liquid in the space behind the eardrum)

5.2.2 Childhood sensorineural hearing loss

Since childhood SNHL is permanent, it is of course associated with both hearing loss and tinnitus in adulthood. The exact nature of these associations and how SNHL develops through life is however uncertain. Regarding childhood SNHL, this project examined 1) the effects of childhood SNHL combined with aging or noise exposure later in life (paper 2); 2) whether adults with childhood-onset SNHL experience a higher degree of tinnitus than adults with a correspondingly strong, but adult-onset hearing loss (paper 3). The association between childhood SNHL and dizziness in adulthood was not examined.

The effects of childhood SNHL combined with aging or noise exposure later in life.

Knowledge about altered susceptibility to NIHL is important to determine for possible increased protection against harmful noise. The expected change of hearing through adulthood is important to clear out to develop an appropriate follow-up plan (hearing aid adjustments, counselling, information).

A priori, many possible underlying mechanisms make it reasonable to expect interaction effects when SNHL of different etiologies, such as childhood SNHL (due to genetic disorders, infections, other), ARHL and NIHL coexist in the same ear and at the same frequency area. A possible *super-additive* interaction follows the idea that an already impaired cochlea is more susceptible to further damage by other factors. Another explanation could be a common genetic susceptibility to childhood SNHL, NIHL and ARHL. In contrast, a *less than additive effect* follows from the idea that when a number of hair cells are previously damaged by one factor, there is less chance for the other factor to cause further damage. In other words, hair cells lost from one cause cannot be «re-lost» from another cause.

Another possible explanation of “faster aging” through adulthood could be late progression of childhood SNHL itself (“progressive childhood SNHL”). Longitudinal studies of children with SNHL have shown that between 4% and 30% of these children have a progressive hearing loss during *childhood*, depending on age, observation time and definition of progression (Parving, 1988, Brookhouser et al., 1994, Berrettini et al., 1999, Pittman and Stelmachowicz, 2003, Johansen et al., 2004,). The underlying

mechanism behind this hearing loss progression is unknown, but genetic factors are probably important (Johansen et al., 2004).

The effects associated with combinations of different SNHL etiologies (like aging or noise exposure) have been difficult to determine, often because the time and magnitude of each exposure has been unclear. For example, numerous studies have investigated possible interaction effects between NIHL and ARHL (Rosenhall, 2003) (review), but they have been difficult to assess. In our study, the participants were tested for childhood SNHL, *before* the potential onset of ARHL and NIHL. This provided a unique opportunity to study possible interactions effects when SNHL of different etiologies coexist in the same ear and at the same frequency area.

Tinnitus in adulthood: Does time of hearing loss onset matter? There are large differences in susceptibility to tinnitus among adults with correspondingly strong hearing loss. Knowledge about which factors that influence the risk of having tinnitus is important to identify high-risk groups needing a more structured follow-up.

Many possible explanations make it reasonable to believe that adults with childhood-onset hearing loss experience *less* tinnitus than adult with correspondingly strong, but adult-onset hearing loss. The auditory cortex is plastic in early life (Cardon et al., 2012) (review). Small children could be more adapted to cope with their hearing loss-related tinnitus, and maintain this trait throughout life. Alternatively, one could imagine an increasing ability to successfully cope with tinnitus with duration of time living with this condition. Furthermore, adult-onset hearing loss (often noise- or age-related) could be associated with certain types of cochlear damage, with a larger effect on tinnitus than the etiologies of childhood-onset hearing loss (such as genetic or infectious).

On the other hand, adults with childhood-onset SNHL could experience *more* tinnitus than those with adult-onset hearing loss, in that long-term exposure to tinnitus result in a vicious circle and accumulated problems.

To our knowledge, no study has investigated whether adults with childhood-onset SNHL experience an altered degree of tinnitus than do adults with a correspondingly strong, but adult-onset hearing loss. Hence, this was one of the aims in the present project.

6 Aims

The overall aims of this thesis were to assess:

1. To what extent various types of otitis media in childhood are associated with hearing loss, tinnitus and dizziness in adulthood, and whether these associations depend on age or noise exposure;
2. The effects of childhood SNHL combined with aging or noise exposure later in life.

7 Materials and methods

7.1 Participants

This project linked two large, prior hearing investigations: The school hearing investigation in Nord-Trøndelag (SHINT) and the Nord-Trøndelag Hearing Loss Study (NTHLS).

The baseline childhood study. SHINT (1954-1986) was an audiometric screening of nearly all 7, 10 and 13 year old school children in the entire Nord-Trøndelag County, conducted by the late Norwegian ENT – specialist, H. F. Fabritius, and his colleagues (Fabritius, 1968). The study did not record information confirming the participation of children with *normal* hearing, so the exact number of participants is unknown. The number of children born between 1941 and 1977 in Nord-Trøndelag, about 78,000, may serve as a crude approximation (vital statistics and migration statistics published yearly for 1941-1977 by Statistics Norway). Children found with hearing loss at screening were invited to a later ENT specialist examination. From 1954 to 1962, average attendance at the ENT examinations for children with positive screening was 97% (Fabritius, 1968), and we have no reason to believe that this high level of attendance changed later. Altogether, 10,269 children took part in the ENT specialist examination.

The follow-up adult study. NTHLS (1996-1998) was a part of The Nord-Trøndelag Health Study (HUNT 2, 1995-97). HUNT 2 was a general, population-based study where all residents in the county of Nord-Trøndelag, Norway, aged ≥ 20 years were invited. Out of 93,898 invited persons, 65,237 participated (69%). HUNT 2 included several types of examinations and health questionnaires. Detailed information about HUNT 2 is found elsewhere (Holmen et al., 2003). NTHLS included a puretone audiometry and hearing questionnaires. The total adult population (≥ 20 years) from 17 of the 23 municipalities in Nord-Trøndelag was invited. Valid audiometric data were collected from 50,723 participants. Among persons born between 1941 and 1977 (the population of this study), 87% of the county population was invited with an overall participation rate of 59%.

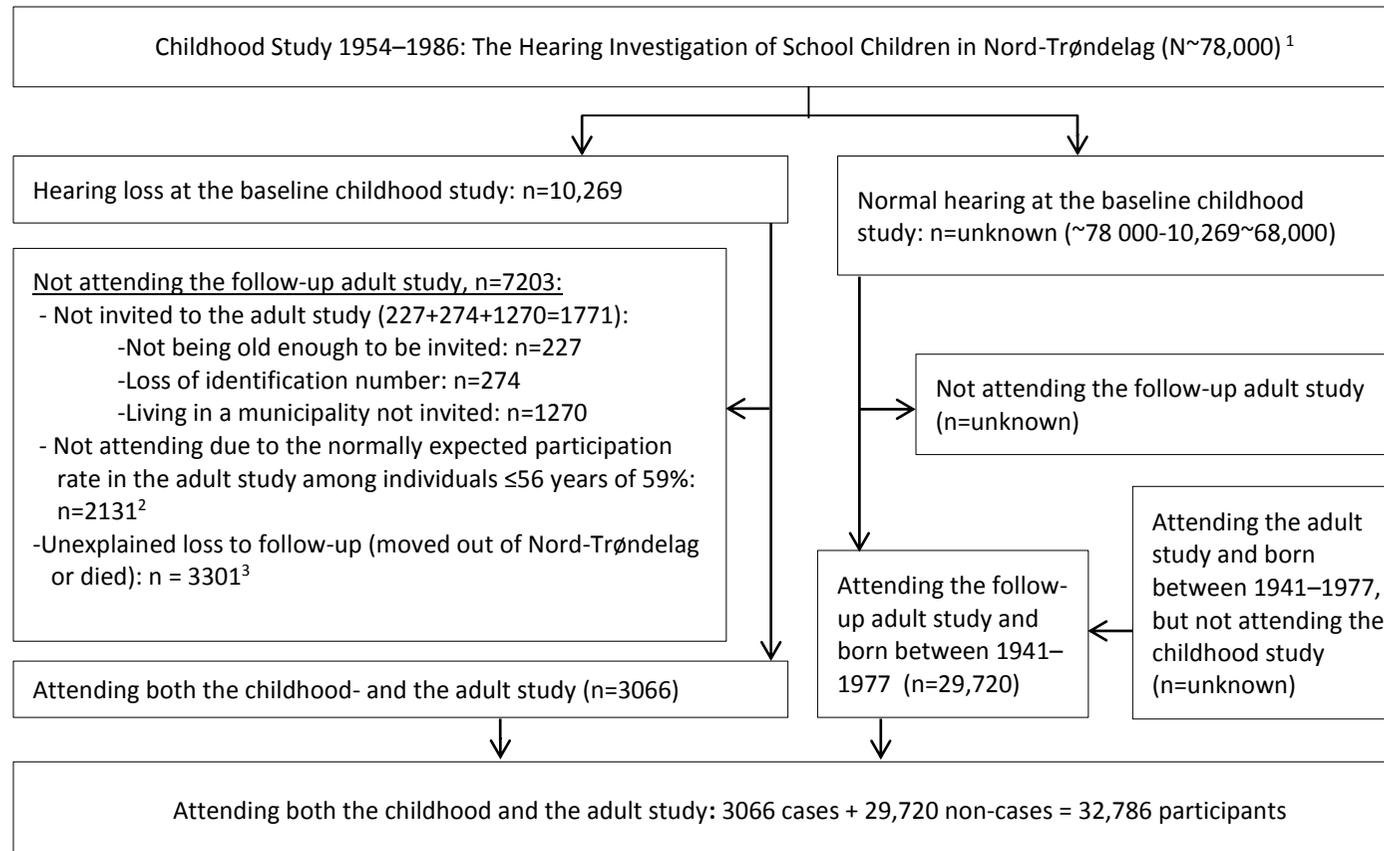
After linkage. This project included participants of the follow-up adult study who were born between 1941 and 1977 (primary school age during the baseline childhood study), n=32,786:

Childhood hearing loss cases: Among the 10,269 children diagnosed with various types of hearing disorders in the childhood study, 3066 attended the adult study.

Non-cases (reference group): As previously described, the childhood study did not register the children with *normal* hearing. Thus, as a reference group, we included all participants of the adult study who were in primary school age during the childhood study (born between 1941 and 1977) and who were not registered with hearing loss in the childhood study, n=29,720. (This weakness is discussed later: “information bias”).

Out of this “basis” cohort (n=32,786), the papers included various groups of participants. The exact inclusion/exclusion criteria of each paper will not be repeated. A flow chart, showing the general “loss to follow-up” from the childhood study to the adult study, is presented in Figure 1. (The “loss to follow-up” is discussed later: “selection bias”).

Figure 1. The flow of participants from the baseline childhood study to the follow-up adult study.



¹ Children born in Nord Trøndelag between 1954-1986 = 78,524

² Reasoning: Number of cases in the adult study=3066. Assuming normally expected participation rate of 59%, number of invited (x) should be $3066=0.59x$, $x=5197$ ($5197 \times 0.59=3066$). Accordingly, normally expected number of *not* participating= $5197-3066=2131$ (5197×0.41)

³ Unexplained loss to follow-up: $7203 - (1771+2131)=3301$

7.2 Measurement of the variables

The childhood study included an audiometric screening at school, and for the children with hearing loss at the screening, a later ENT specialist examination with a new audiometry. The following variables were measured: childhood hearing threshold and childhood hearing disorder (diagnosis).

Childhood hearing threshold. The audiometric *screening* was performed by a trained hearing assistant or a district health nurse in a quiet location within the school, obtaining air-conduction thresholds by puretone audiometry at 0.25, 0.5, 1, 2, 4 and 8 kHz. Hearing loss for the screening was defined by thresholds 20 dB HL or greater at 3 or more frequencies (in the same ear) or a 30 dB HL or greater threshold at one or more frequencies. The audiometers were Amplivox audiometers type 70, later Model 51 and model 81 calibrated according to the Norwegian standard at the time (BS 2497, 1954; ISO R389, 1964; ISO 389, 1975)

All children with hearing loss at the screening were invited to a later *ENT specialist examination* at one of 14 different out-patient clinics in Nord-Trøndelag. Also, their parents completed a questionnaire about their child's ear problems. The medical examination included a new puretone audiometry with both air- and bone-conduction thresholds. Unfortunately, Dr. Fabritius did not describe the audiometric conditions or the equipment that were used at the outpatient clinics. Depending on the diagnosis, the children had one or more examinations. We used the audiograms from the last ENT examination (not the audiograms from the screening) to represent the childhood hearing threshold. Missing values: Mostly, hearing thresholds <20 dB HL were not registered in the childhood audiograms, so values for many single frequencies were "missing". These missing values were replaced by the mean value of those values <20 dB HL registered in the total case group (n=10,269). For instance for 1000 Hz, right ear, there were 2855 cases with values ≥ 20 dB HL, 1535 cases with registered values <20 dB HL, and 5879 cases with missing values (hearing thresholds <20 dB HL). Mean values for the cases with registered values <20 dB HL was 12 dB (95% confidence interval [CI]: 11-13), and missing values in the case group were replaced by this mean value. In paper 4

(childhood SNHL), the missing values were replaced by the mean value of those values <20 dB HL registered in the total SNHL group (n=1489).

Childhood hearing disorder (main predictor variable). In addition to the audiometric measurements, the ENT examination included family and medical history and a complete ENT examination. The doctor recorded the history, findings, diagnoses (the presumed etiology of the hearing loss) and the treatments. Some children had more than one diagnosis (e.g., SNHL and excessive cerumen). In this study, only the diagnosis considered most severe was registered according to the following hierarchy, (definitions by dr. Fabritius): (1) SNHL: air-conduction thresholds in agreement with the bone-conduction thresholds. Unfortunately, Dr. Fabritius did not define the maximum accepted air-bone gap; (2) anomalies of the outer or middle ear; (3) otosclerosis; (4) CSOM: chronic infection of the middle ear including eardrum perforation (duration unfortunately not specified) and intermittent secretion, conductive or mixed hearing loss; (5) hearing loss after rAOM: no middle ear effusion at the examination but a history of preschool rAOM, sometimes also occurring during school years. Mostly including eardrum pathology, conductive or mixed hearing loss; (6) OME: chronic middle ear effusion, reduced mobility of the eardrum tested by Brüning`s magnifying glass, no signs or symptoms of acute infection; (7) AOM: middle ear effusion with signs and symptoms of acute infection; (8) otitis externa; (9) foreign body; (10) excessive cerumen; (11) other diagnoses: intellectual disability, unknown etiology or no registered etiology.

The adult study, NTHLS, included an audiometry and two questionnaires. This project used questionnaire 1 (Q1), which was completed by all participants while staying in the waiting room. To the extent permitted by a strict schedule, the team checked that the questionnaire was fully answered and helped explain when necessary. The following variables were measured in the NTHLS: adult hearing threshold (audiometry), tinnitus, dizziness and noise exposure (all by Q1).

Adult hearing threshold (outcome variable) was assessed by puretone audiometry. Two teams travelled around Nord-Trøndelag county as part of the HUNT, administering the hearing examination. Each team consisted of one trained audiologist and one or, on busy days, two trained assistants. Hearing thresholds were obtained with five

Interacoustics AD25 automatic audiometers with TDH-39P earphones and MX 41/AR cushions linked to a personal computer. These inter-linked instruments were self-administered, permitting five subjects to be examined simultaneously. The thresholds were determined in accordance with ISO 8253-1 (International Organization for Standardization, 2010) with fixed frequencies, using an automatic procedure. A maximum threshold shift of 120 dB was recorded, and threshold shifts exceeding this value (no response to the maximum sound signal) were treated as a 120 dB loss. Masking was not used. Bone conduction thresholds were not measured. The audiometry included the standard frequencies .25, .5, 1, 2, 3, 4, 6, and 8 kHz. Semi-portable, dismantable sound attenuation booths were used in rooms specially selected to avoid background noise. The audiometers were re-calibrated (ISO 389-1) (International Organization for Standardization, 1994) every six months.

This project treated hearing thresholds >100 dB HL as a 100 dB hearing loss. The PTA of various frequency areas was used, such as the PTA at 0.5-4 kHz in the tinnitus paper (paper 3), or the PTA at 3-8 kHz in the SNHL paper (paper 2). Missing values: Only participants with valid audiometric data were included in the project.

Noise exposure (covariate). Occupational noise exposure was measured by items on Q1 about loud noise at work in general (scored 0–3) and specific sources of noise from: staple gun/hammering, metal hammering/riveting, circular saw/machine planing, chainsaw operation, tractor/construction machines, sledge hammer operation, blasting, and machine-room and other factory noise. These items were individually answered and scored as “yes” or “no”. Non-occupational noise exposure was assessed by items about impulse noise (i.e., explosions, shootings) and playing in a band or going to discotheques, rock concerts, or similar loud events. These items were scored “no” = 0, “Don’t know, may be” = 1, and “yes” = 2. A general index based on all the noise scores was computed to estimate the overall impact of noise, similar to the one described by Tambs et al. (Tambs et al., 2006). The scores for each separate item were weighted by the respective regression coefficients in an initial regression analysis predicting the defined adult hearing threshold outcome variable and summed. Missing values were treated as no noise exposure.

Tinnitus (outcome variable). Participants answered “yes/no/don’t know,may be”, to the question (Q1), “Are you bothered by ringing in the ears?”. The variable was dichotomized using “don’t know” and “no” as the reference category. Missing values: Participants with non-valid Q1 (*no* completed items) were excluded from the tinnitus study. Valid Q1 but missing on the tinnitus item were treated as no tinnitus (numbers are presented in paper 3).

Dizziness (outcome variable): Participants answered “yes/maybe/no” to the question (Q1) “Are you bothered by dizziness”. The variable was dichotomized using “no” as the reference category. Missing values: The relatively few participants with missing values were excluded from the dizziness study (numbers are presented in paper 4).

Socio-economic status (covariate): We obtained information on these covariates from national registries and from questionnaires in *HUNT 2* (not the NTHLS). From national registries we used information on highest level of completed education (primary and secondary school, vocational school, high school, undergraduate and graduate school) and income in 1998. There were no missing values for income. The few missing values for education were imputed as graduate school.

7.3 Statistical analyses

The principal predictor variable was diagnosis, measured in the childhood study (categorical, with normal hearing at the childhood study as the reference category). The covariates were: noise exposure (continuous or binary), sex, age (in years) and socio-economic status (continuous). The outcome variables were: hearing threshold (continuous), tinnitus (binary) and dizziness (binary). All covariates and outcomes were measured in the adult study.

We used multiple linear or logistic regression analyses, specifying the significance level to 0.05, to estimate the associations between the various diagnoses and the outcome variables (SPSS version 20), with and without adjustments. Interaction effects were tested to examine whether some of the associations were moderated by age, sex or noise exposure.

In the multiple regression analyses with adult hearing threshold as the outcome variable (paper 1 and paper 2), the residual plot revealed clear signs of heteroscedasticity: the residual variance increased with increasing values for predicted adult hearing threshold. To produce maximally correct standard errors, a bootstrap method with 1000 samples was used to estimate the confidence intervals.

Descriptive statistics. To compare the baseline risk factors in childhood hearing loss cases (n=10,269) who did (n=3066) or did not (n=7203) attend the adult study (to reveal possible selection bias) we used a chi-square test for sex and diagnosis, and an independent t-test for childhood hearing threshold.

8 Summary of the papers

All papers were based on the previously described cohort study of 32,786 adults (aged 20-56 years, mean 40 years) who underwent a puretone audiometry and completed a health questionnaire in the Nord Trøndelag Hearing Loss Study. As children, the same persons underwent screening audiometry in a longitudinal school hearing investigation (at 7, 10 and 13 years of age). Children with hearing loss at the school screening underwent an ENT examination in which they were diagnosed with various hearing disorders (n=3066).

Paper 1. Childhood otitis media: A cohort study with 30 year follow-up of hearing (The HUNT study)

We aimed to assess to what extent various types of otitis media in childhood were associated with hearing loss in adulthood, and whether these associations were influenced by age, sex or noise exposure in adulthood. The sample included 23,483 adults: 21,507 with normal hearing at the school investigation and no self-reported history of recurrent otitis media (the reference group), and 1976 diagnosed with various types of childhood otitis media.

Compared to the reference group, adults diagnosed with childhood hearing loss together with OME (n=1255), CSOM (n=108) or after rAOM (n=613) had significantly increased hearing thresholds in the low/mid/high frequency range: 2-2-2 / 17-17-20 / 7-7-10 dB, respectively. The effects were adjusted for age, sex and noise exposure in adulthood. Children diagnosed with hearing loss after rAOM had on average somewhat improved hearing thresholds as adults. The effects of childhood CSOM and childhood hearing loss after rAOM on adult hearing thresholds were larger in middle-aged than in younger adults. Eardrum pathology marginally increased the adult hearing loss (1-3 dB) in children with OME or hearing loss after rAOM. Our study could not reveal significant differences in the effect of self-reported noise exposure on adult hearing thresholds between the otitis media groups and the reference group.

Our study concluded that childhood CSOM and childhood hearing loss after rAOM are associated with a significant adult hearing loss. Apparently, these conditions are associated with a moderately faster deterioration of hearing through adulthood, yet this finding should be confirmed by a study with repeated audiometries throughout adulthood.

Paper 2. Childhood sensorineural hearing loss: Effects of combined exposure with aging or noise exposure later in life.

We aimed to examine the effects of childhood SNHL combined with aging or noise exposure on hearing thresholds later in life. The sample included 30,003 adults: 29,720 with normal hearing thresholds at the school investigation (the reference group) and 283 diagnosed with childhood HF-SNHL (PTA 3-8 kHz \geq 25 dB HL, worse hearing ear).

Age stratified analyses showed that the difference in HF hearing thresholds between adults with and without childhood HF-SNHL was 33 dB (95% CI: 31-34) in young adults (n=173, aged 20-39 years) and 37 dB (95% CI: 34-39) in middle-aged adults (n=110, aged 40-56 years). The effect of childhood HF-SNHL combined with noise exposure was a simple additive effect.

In conclusion it appears to be a super-additive effect of childhood-onset HF-SNHL and aging on adult HF hearing thresholds. The finding should be confirmed by a study with repeated audiometries throughout adulthood. No altered susceptibility to NIHL associated with childhood SNHL was revealed.

Paper 3. The association between hearing disorders in childhood and tinnitus in adulthood: Results from a cohort study (HUNT)

We aimed to assess the associations between various types of hearing disorders in childhood and tinnitus in adulthood. The sample included 32,430 adults: 29,404 with

normal hearing at the school investigation (the reference group), and 3026 diagnosed with various childhood hearing disorders.

Adults who had hearing loss at the school investigation reported more tinnitus than the reference group (OR = 1.4, 95% CI: 1.3-1.6). Childhood hearing disorders associated with tinnitus in adulthood included: SNHL (OR = 2.4, CI: 1.9-3.0), CSOM (OR = 2.4, CI: 1.5-3.9), and childhood hearing loss after rAOM (OR = 1.6, CI: 1.3-2.0). The effects were adjusted for age, sex, and noise exposure in adulthood. In further analyses that included adjustment for adult hearing threshold, only childhood SNHL was associated with tinnitus, now with a lower risk (OR=0.7, CI: 0.6-0.9).

We concluded that childhood hearing disorders associated with increased risk of tinnitus in adulthood include SNHL, CSOM and hearing loss after rAOM. It appears that these significant associations are mediated by or transmitted through adult hearing loss.

Paper 4. Childhood otitis media is associated with increased risk of dizziness in adulthood: Results from the HUNT cohort study

We aimed to assess the association between otitis media in childhood and dizziness in adulthood. The sample included 21,962 adults: 21,270 with normal hearing at the school investigation and a negative history of recurrent otitis media (the reference group), and 692 diagnosed with childhood otitis media.

Adults with childhood CSOM (n=102) or childhood hearing loss after rAOM (n=590) were at significantly increased risk of reported dizziness when compared to adults with normal hearing at the school investigation and no self-reported history of recurrent otitis media. After adjusting for adult age, sex and socio-economic status, the OR were 2.1 (95% CI: 1.4-3.3) and 1.3 (95% CI: 1.0-1.5), respectively.

We concluded that childhood CSOM and childhood hearing loss after rAOM are associated with increased risk of dizziness in adulthood.

9 Discussion

9.1 Results

9.1.1 Descriptive statistics of the cohort

Table 1 shows the descriptive statistics of the total, basis cohort (n=32,786). Out of this cohort, the papers included various groups of participants. The final samples are presented in the papers.

Table 1. Descriptive statistics of the cohort in the project, n=32,786.

	Number	Sex male (%)	Age at the follow- up adult study Mean (95% CI)	Hearing threshold at the baseline childhood study ¹ Mean (95% CI)	Hearing threshold at the follow-up adult study ¹ Mean (95% CI)	Occurrence of tinnitus at the follow-up adult study (%) ²	Occurrence of dizziness at the follow-up adult study (%) ²
<i>Reference group³</i>	29,720	47	40 (40-40)	<i>Normal</i>	10 (10-10)	11	8
All types of hearing loss	3,066	51	40 (39-40)	19 (19-20)	16 (16-17)	15	10
Sensorineural hearing loss	462	36	36 (36-37)	31 (29-33)	32 (30-34)	22	10
Outer/middle ear anomalies	7	57	38 (27-49)	44 (22-67)	46 (25-66)	29	14
Otosclerosis	5	0	48 (41-55)	27 (19-36)	35 (30-39)	100	20
Otitis Media, Total	2,061	49	41 (40-41)	17 (17-17)	(14 (14-15)	14	10
CSOM	108	44	41 (39-42)	24 (22-26)	28 (24-32)	22	10
Hearing loss after rAOM	613	51	41 (40-41)	19 (18-20)	18 (17-19)	17	11
Otitis Media with Effusion	1,255	49	41 (41-42)	16 (15-16)	11 (11-12)	12	9
Acute Otitis Media	85	45	35 (33-37)	18 (15-20)	10 (7-12)	11	4
Otitis externa	13	31	37 (33-42)	17 (11-23)	9 (6-11)	15	0
Foreign body	7	43	43 (37-50)	20 (7-32)	7 (1-12)	29	0
Cerumen	162	45	39 (38-41)	18 (17-19)	10 (9-12)	9	9
Unknown / other diagnosis	349	50	38 (37-39)	16 (16-17)	12 (11-13)	12	11

¹ PTA 0.5-4 kHz, in the ear defined as the worse hearing ear in the baseline childhood study (defined by PTA 0.5-4 kHz). Reference group: Random ear.

² Missing values, “no” and “maybe” are treated as no tinnitus or no dizziness

³ Normal hearing at the baseline childhood study (hearing loss defined as thresholds 20 dB HL or greater at 3 or more frequencies in the same ear or a 30 dB HL or greater threshold at one or more frequencies).

9.1.2 Childhood otitis media: hearing loss, tinnitus and dizziness in adulthood.

We examined the extent to which various types of otitis media in childhood were associated with hearing loss, tinnitus and dizziness in adulthood. Our study showed that compared to the reference group (defined previously), childhood CSOM and childhood hearing loss after rAOM were statistically significantly ($p < 0.05$) associated with increased adult hearing thresholds (17-17-20 dB and 7-7-10 dB, in the low/mid/high frequency range); tinnitus (OR=2.4 and OR=1.6) and dizziness (OR=2.1 and OR=1.3). Childhood OME was associated with marginally increased adult hearing thresholds, both with (2-2-2 dB) and without (1-1-1 dB) eardrum pathology, and no increased risk of adult tinnitus. The associations with hearing thresholds and tinnitus were adjusted for age, sex and noise exposure in adulthood. The associations with dizziness were adjusted for age, sex and socio-economic status in adulthood.

Hearing loss. Cross-sectional studies have found that a self-reported history of recurrent otitis media (unknown type) in childhood is associated with increased adult hearing thresholds (Tambs et al., 2004) and self-reported auditory disabilities in adulthood (Stephenson et al., 1995). In a cohort study from Greenland, 214 children aged 3-8 years with CSOM (defined as an eardrum perforation >14 days with or without ear discharge) underwent audiometry at ages 18-24 years. At follow-up, 55% showed an unilateral or bilateral hearing loss at either low (PTA at 0.5-2 kHz) or high frequencies (PTA at 4-6 kHz) of >15 dB HL (Jensen et al., 2013). In another study, 121 children <8 years old were diagnosed with rOME or rAOM. At 18 years of age, these participants had 4 dB increased hearing threshold (PTA 0.5-4 kHz) compared to those without such a history (de Beer et al., 2003).

Regarding childhood OME, a cohort study followed-up 173 boys <14 years of age who were referred to an ENT-department from screening or from other doctors because of ear disease, "usually OME". At 18 years of age, there were no differences in hearing thresholds between this childhood OME group and boys without such a history (Augustsson and Engstrand, 2006). Considering eardrum pathology, a cohort study compared hearing thresholds between adults with *surgical* treated childhood OME and an age- and gender-matched normative data set. The study found that the hearing loss

associated with eardrum pathology was of limited magnitude (Khodaverdi et al., 2013). Our study did not have enough power to separate between different types of eardrum pathology (tympanosclerosis, total/segmental atrophy, atelectasis, retraction). Probably, for example retraction has a better prognosis than atelectasis.

Since our adult study did not include bone-conduction thresholds, we could not conclude whether the effects on adult hearing thresholds were due to middle- or inner ear pathology. We speculate, however, that a major part of the adult hearing loss is SNHL due to the effects of inflammatory mediators or toxins from otitis media on the cochlea.

Tinnitus. Cross-sectional studies have found that a self-reported history of recurrent otitis media in childhood is associated with tinnitus in adulthood (Nondahl et al., 2011, Sindhusake et al., 2003, Hoffman, 2004), showing OR=1.7 in men (Nondahl et al., 2011) and relative risk=1.5 (Sindhusake et al., 2003). A cohort study found that the combination of a history of childhood OME (before 11 years of age) and hearing loss at 11 years of age was associated with an increased risk of tinnitus at 32 years of age. Neither childhood OME alone or elevated thresholds at 11 years of age alone predicted adult tinnitus (Dawes and Welch, 2010). The study did not provide adult hearing thresholds or information about noise exposure, so it could not conclude whether the association was mediated by adult hearing loss or confounded by unevenly distributed noise exposure.

Hearing loss is the main risk factor of tinnitus. Hence, it is reasonable that childhood CSOM and childhood hearing loss after rAOM, being associated with adult hearing loss, are also associated with adult tinnitus. After including adjustment for adult hearing threshold, the significant association disappeared. We suggest that adult hearing loss plays an important role in mediating the positive association with adult tinnitus, in that childhood otitis media influences the adult hearing threshold, which again influences the occurrence of tinnitus. If so, only otitis media associated with a subsequent hearing loss is associated with subsequent tinnitus. This interpretation is perhaps in some disagreement with animal studies suggesting that temporary conductive hearing loss in early life can alter the functional properties of the auditory cortex on a permanent basis,

which could increase the risk of later tinnitus (Sun et al., 2014). Since our study only included otitis media with hearing loss occurring between 7 and 13 years of age, it is unclear to what extent our results can be generalized to otitis media in younger children. For younger children, the auditory pathway shows greater plasticity (Cardon et al., 2012) (review) and may not lead to similar outcomes.

Dizziness. A cohort study reported, that preschool children with a history of recurrent or persistent middle ear effusion (n=40) had lower gain to a rotational stimulus compared to children without a history of significant middle ear effusion (Casselbrant et al., 2000). Another cohort study of preschool children, with a history of >6 episodes of otitis media (n=18), revealed lower scores on vestibulospinal function tests compared to children without previous episodes of otitis media (Denning and Mayberry, 1987). To our knowledge, no study has evaluated dizziness in adulthood after a history of childhood otitis media.

We can only speculate about the underlying mechanisms. Our result could reflect a permanent effect of inflammatory mediators or toxins from otitis media on the vestibular apparatus. Although the vestibule is relatively far from the round window, it has been shown that endotoxin can penetrate the inner ear via various routes, such as the round window, blood vessels or lymphatics, and/or interscala exchange, resulting in a disturbance not only of the cochlea but also of vestibular end organs (Takumida and Anniko, 2004). Otitis media could be associated with an accelerated age-related cellular loss in the vestibular apparatus (presbystatis). Also, otitis media could predispose to later vestibulopathies. The recurrent nature, and also some shared histopathological characteristics, of BPPV vestibularis nevrilis, or Ménière's (the three most common vestibulopathies), suggest a recurrent cause (Gacek, 2013), and a viral etiology is suggested. Knowledge about possible influence due to a history of recurrent otitis media is scarce. Paparella et al. (1983) suggested that childhood chronic otitis media may be associated with Ménière's later in life, and BPPV has been related to previous inner ear disease (Riga et al., 2011) (review).

We did not include childhood OME in the dizziness paper. This very common condition, which is probably also prevalent in the diagnostic groups not classified as childhood

OME (due to OME without the screening dates), was not associated with either a relevant hearing loss or tinnitus in adulthood. Analyses (not presented in the paper) revealed that after adjustment for age, sex, socio-economic status and self-reported recurrent ear infections, childhood OME was not associated with dizziness in adulthood.

Interaction with aging or noise exposure later in life. We examined whether the association between childhood otitis media and adult hearing thresholds were influenced by aging or noise exposure in adulthood. These interaction analyses were also performed for the childhood SNHL group, and because of similarities, the results are discussed in the next section.

9.1.3 Childhood sensorineural hearing loss

The effects of childhood SNHL combined with aging or noise exposure later in life.

Aging. Our study showed that the association between childhood HF-SNHL and adult HF hearing threshold, and between CSOM and adult HF hearing threshold, was stronger for middle-aged than for younger adults.

A cross-sectional study of self-reported, recurrent otitis media in the NTHLS data material found that the effects on adult hearing thresholds varied from 2 dB among younger adults to 5-6 dB among older adults (Tambs et al., 2004). A study of a Dutch cohort (aged 24-81 years, N=1721) observed for an average of 12 years with repeated audiometries, reported an association between poorer baseline hearing threshold and faster deterioration of hearing (Linssen et al., 2014). Gates et al. described “faster aging” in ears with pre-existing noise damage (Gates et al., 2000).

Our finding of “faster aging” (accelerated deterioration of hearing thresholds throughout adulthood) in ears with pre-existing childhood SNHL or childhood CSOM could possibly reflect that an already impaired cochlea is more susceptible to age-related degeneration. Regarding childhood SNHL, another explanation might be late progression of childhood SNHL *itself* (“progressive childhood SNHL”). Given the very long observations-time, we find the latter explanation less likely.

However, this apparently increasing effect with age could also represent a *birth-cohort effect*. Each participant had only one hearing test in adulthood, so the subcohort tested in late adulthood was not the same as the subcohort tested in young adulthood. The subcohort born in the 40-50thies could have had a more serious and poorer treated childhood disease resulting in more severe adult hearing loss compared to the subcohort born in the 60-70thies. Considering the course and treatment of otitis media in the 50 thies, antibiotics were prescribed, and all types of middle ear surgery were performed at the Namsos hospital. With regard to SNHL at that time, our data did not provide very systematic data on possible etiological factors (like infection, noise exposure, genetic disorders etc.). However, our study did evaluate possible birth-cohort effects regarding childhood hearing threshold, which we think is the most important source of such confounding. There was no correlation between childhood hearing threshold and birth-year. Thus, we believe our finding reflects “faster aging” and not a birth-cohort effect. Still, the result should be confirmed by a study with at least two audiometries in adulthood.

Noise exposure. Our study showed that there was no statistically significant interaction effect between any childhood hearing disorder (SNHL, CSOM, childhood hearing loss after rAOM) and noise exposure on adult hearing thresholds.

A cross-sectional study found that the combination of a history of recurrent otitis media in childhood and exposure to personal stereos > 1 hours per day was associated with hearing loss at 18-24 years of age. In contrast, hearing loss was not associated with a history of otitis media without frequent personal stereo exposure, or to frequent personal stereo exposure without a history of otitis media. The author suggested that persons with and without a history of otitis media in childhood have different susceptibility to hearing damage from personal stereo exposure (Job et al., 1999). Their study was criticized because of its explorative nature and the retrospective assessment of otitis media. A cohort study of 18 year old adults with a documented history of rOME or rAOM (n=121) showed no altered susceptibility to hearing loss from personal stereo use (de Beer et al., 2003). To our knowledge, there are no studies of possible interactions between childhood SNHL and noise exposure.

Accordingly, our results indicate an unchanged susceptibility to later NIHL but a moderately increased susceptibility to later ARHL. This difference might reflect differences in the cochlear mechanisms underlying age- and noise-related hearing loss. However, accurate measurements of noise exposure are difficult to achieve (in contrast to age), and mostly they are retrospective and self-reported, like in our study. The negative interaction effect with noise exposure could reflect lack of validity or precision. This issue is discussed later (“methodological consideration”). In short, we do not suspect serious information bias or a type 2 error, so we believe our finding indicates that there is no important altered susceptibility to noise associated with these childhood conditions.

Childhood SNHL and tinnitus in adulthood. Our study showed that compared to the reference group (normal hearing at the school investigation) childhood SNHL was, as hypothesized, associated with a statistically significantly increased risk of tinnitus in adulthood: OR=2.4. After including adjustment for adult hearing thresholds, childhood SNHL was associated with a decreased risk: OR= 0.7.

To our knowledge, there are no similar studies. There are several possible explanations of why adults with childhood-onset SNHL could have lower risk of tinnitus than adults with a correspondingly strong, but later-onset hearing loss (described in “background”). In short, children, with more cognitive flexibility than adults, may cope better with their hearing loss-related-tinnitus and maintain this capacity throughout life. Eventually, they could learn to cope better with tinnitus with time, resulting in a lower prevalence of reported tinnitus in adulthood compared to those who have had less time for tinnitus habituation. Another explanation could be that the etiologies of childhood SNHL (like genetic and infectious) are less frequently associated with tinnitus than the etiologies of adult-onset hearing loss, such as noise exposure and aging.

9.2 Methodological considerations

The overall goal of an epidemiologic study is to obtain a both valid (lack of systematic error) and precise (lack of random error) estimate of the effect size or measure of disease occurrence in the source population of the study. Often, a further objective is to

obtain an estimate that is also valid to the target population outside the study (Rothman et al., 2008).

We believe the main strengths of this project were the thoroughly medical examinations at baseline and the extremely long observation-time, whereas the main weaknesses were the lack of baseline data for non-cases and the large loss to follow-up.

The following chapters discuss the accuracy of the present study in detail: the internal validity, the precision and the generalizability (external validity).

9.2.1 Internal validity

The main threats of internal validity are selection bias, information bias and confounding.

Selection bias. Selection bias results from procedures used to select subjects and from factors that influence study participation. The common element of such bias is that the relation between exposure and disease is different for those who participate and for all those who should have been theoretically eligible for study, including those who do not participate (Rothman et al., 2008).

Selection bias occurs at the stage of recruitment of participants or during the process of retaining them in the study. Since all schools in Nord-Trøndelag county were included in the childhood study, we do not suspect a selection bias at this stage. However, there was certainly a *loss to follow-up* from the baseline childhood study to the follow-up adult study, since only 3066 (30%) out of 10,269 childhood hearing loss cases attended the adult study. Figure 1 presents some explanations of this loss to follow-up. The remaining loss to follow-up ($n \sim 3300$) is difficult to explain, but emigration out of Nord-Trøndelag after the childhood study or death (about 2% according to information provided by Statistics Norway) are undoubtedly parts of the explanation. To reveal possible *selective* loss to follow-up, we performed descriptive statistics comparing risk factors (etiology, sex, childhood hearing thresholds) between childhood hearing loss cases who did or did not follow-up. The analyses revealed no important differences between the two groups (there were a slightly lower prevalence of AOM, unknown

etiology and females among cases who followed-up. Also, they were slightly older: mean birthyear 1956 versus 1959). Regarding the adult study, this was not only a hearing investigation but a part of a very large general health screening examination (HUNT 2), so we do not think the occurrence of eventual hearing loss, tinnitus or dizziness affected the likelihood to participate. Altogether, we do not suspect serious selection bias in our study.

Information bias. Information bias is caused by measurement errors in the needed information. For discrete variables, measurement error is usually called misclassification. Classification error that depend or do not depend on the actual values of other variables is called differential or non-differential misclassification, respectively (Rothman., 2008).

Information bias: diagnosis. We suspect few *false-positives* (that someone who is truly non-exposed will be classified as exposed), since the diagnoses were determined by an ENT specialist after at least one thoroughly examination including repeated audiometries. Although most otitis media cases showed a conductive hearing loss (*viz.*, normal bone-conduction thresholds indicating a normal inner ear function), some of these children also had impaired bone-conduction thresholds (a mixed hearing loss), indicating some degree of SNHL. This SNHL component is probably due to inner ear damage by otitis media, but other etiologies (like noise exposure) cannot be excluded. Yet, it is unlikely that these children should be more exposed to noise than other children. Concerning the diagnosis "*childhood CSOM*", our adult study did not confirm curation at the time of follow-up. CSOM can heal and years later re-rupture due to a new infection, which could again deteriorate the hearing. Considering the long observation-time (mean 31 years) and the access to middle ear surgery and antibiotic treatment at that time, we expect curation to be likely. Finally, it is important to point out, that we examined childhood hearing loss after rAOM (defined previously), not the common condition rAOM (or the very common condition AOM).

The probability of *false-negatives* (that someone who is truly exposed will be classified as non-exposed) is an important weakness of the project. Since there were three separate hearing examinations (at 7, 10 and 13 years of age), most of the long-standing childhood hearing loss (like SNHL, CSOM and hearing loss after rAOM) were probably

detected. Yet, we lacked information confirming that non-cases (“normal hearing at the school investigation”) actually took part in the childhood study. By including all participants of the adult study who were in primary school age during the childhood study, we assumed that: 1) They lived in Nord-Trøndelag between 1954 and 1986. To the extent that migration explains some of the loss to follow-up, there must also have been an immigration to Nord-Trøndelag, since the number of inhabitants has slightly increased during the last fifty years (Holmen et al., 2003). Assuming that this migration was not much different for hearing impaired people than for the remaining population, it means that some NTHLS participants, possibly more than a thousand, are false negatives regarding childhood hearing problem; 2) all children in Nord-Trøndelag between 1954 and 1986 attended primary school. According to Statistics Norway, the number of pupils that attended first class at primary school during the childhood study period was nearly equal to the number of individuals born 7 years earlier; 3) The childhood study included all children at primary school between 1954 and 1986. A great effort was made to include all school children, like those living at small places who only attended school every other week, children at special schools and so on (Fabritius, 1968). This situation: that some participants categorized as non-cases had undetected childhood hearing loss because they did not participate in the childhood study (false negatives), has probably caused a very small underestimation of the associations, since the false negative true negative ratio will remain very low because of the low prevalence of the childhood conditions SNHL, CSOM and childhood hearing loss after rAOM.

Finally, regarding false negatives, we do suspect that many childhood hearing loss cases with *short-term* hearing loss (like OME, otitis externa, cerumen or AOM) were classified as non-cases. A large part of these very common conditions were probably not detected, because non-cases had them without the school screening dates. In addition, AOM and OME are most common in preschool children. Since these diagnoses have marginal effects on the employed outcomes, this misclassification has probably resulted in a marginal underestimation of the effects.

Information bias: adult hearing threshold. Puretone audiometry is regarded a highly valid measure of hearing loss. Regarding the *reliability* (the consistency of the measurement), the test-retest correlation for 0.25-8 kHz among randomly drawn

subjects examined twice, were, for the right ear, 0.88,0.91,0.95,0.97,0.96, 0.98,0.97,0.95,0.97, and, for the left ear, 0.68,0.79,0.94,0.97,0.98,0.97,0.97,0.97. This indicates a very high reliability for mid- and high-frequencies. The effect of intermittent background noise is likely to have affected the low frequency results, yet this study did not use 0.25 kHz.

Information bias: childhood hearing threshold. The imputation of missing childhood hearing thresholds probably introduced some inaccuracy. However, childhood hearing threshold was used to reveal possible selection bias (due to differences between childhood hearing loss cases who did or did not attend the follow-up adult study) and to reveal possible bias by birth-cohort effects. Since we can think of no reason why an inaccuracy by imputation should be unevenly distributed across these subgroups, we do not believe the imputation has biased the results. The variable was also used to identify the childhood-SNHL group with PTA 3-8 kHz ≥ 25 dB HL, and a possible inaccuracy may have introduced a minor misclassification of cases.

Information bias: noise exposure. This information was obtained retrospectively. A non-differential misclassification could have caused a weaker association between noise exposure and adult hearing threshold. Yet, the questionnaire in NTHLS contained detailed data about both non-occupational and occupational noise exposure, showing a significant effect on adult hearing threshold. A differential misclassification, for example if persons with hearing loss more often remember or falsely recall noise exposure than those with normal hearing, generally tends to exaggerate associations. On the other hand, persons with hearing loss who know the cause (such as a childhood hearing disorder) could falsely remember less exposure to noise. Yet, we have no reason to suspect such systematic differences to be large. Finally, previous research indicates that self-report is a valid measure of occupational noise (Schlaefer et al., 2009).

Information bias: tinnitus. We believe the simple question, “Are you bothered by tinnitus?” to be valid in terms of face validity as we believe it measures whether a person is bothered by tinnitus or not. Potential differences in tinnitus prevalence might result from differences in how the question is phrased. Whereas a restrictive definition of tinnitus results in a lower tinnitus prevalence, a more liberal definition results in a

higher prevalence. Hence, the association between childhood hearing disorders and tinnitus might have been weaker for a more liberal tinnitus definition (viz., “experienced tinnitus” rather than “bothered by tinnitus”). On the other hand, the use of the term “bothered” may imply that the content of the item is conflated with tolerance to tinnitus, that is, with a psychological component. The consequence of this wording might then have been an attenuated association between reported tinnitus and hearing. Concerning the reliability, approximately half the sample completed a new questionnaire with a similar question about tinnitus (“are you bothered by tinnitus”) a few months after they participated in NTHLS. The test-retest polychoric correlation was calculated to be 0.65 (95% CI: 0.63-0.67) (Kvestad et al., 2010), implying that the reliability is satisfactory.

Information bias: dizziness This outcome variable was based on a single, self-reported answer to the question: “Are you bothered by dizziness”. However, another large study, which used the established and validated “Vertigo Symptom Scale”, found a dizziness prevalence of 15% (Wiltink et al., 2009), which is quite similar to our finding (17%). The causes of dizziness are multifactorial. It has been suggested that vestibular vertigo (defined previously) accounts for about 1/3 of dizziness symptoms in the general adult population (Neuhauser et al., 2008). Probably, the observed effect of otitis media had been much larger using a more specific measure of vestibular vertigo as an outcome variable instead of “dizziness”.

Concerning noise exposure, tinnitus and dizziness, we have no reason to believe that the treatment of the relatively few missing values (by imputation or exclusion) has biased the results.

Confounding. In statistics, a confounding variable is an extraneous variable in a statistical model that correlates (directly or inversely) with both the explanatory variable and the outcome variable. The confounders may be unequally distributed among exposed and unexposed persons. We evaluated all available variables with a potential to confound. Nevertheless, it is impossible to measure *all* variables that may have confounding potential, and it is always a controversy whether there exist unmeasured potential confounders that may influence the estimated associations.

9.2.2 Precision

Random error is defined as the error that remains after systematic errors are eliminated, and is the variation in a measurement or estimation process that cannot be explained. Variance is a common measure of random variation, and precision is often taken to be the inverse of the variance, and hence the opposite of random error (Rothman et al., 2008). In statistics, significance testing (p-values) is a common tool to decide whether random error could have produced an association. Statistical significance testing usually focuses on the null hypothesis (no association between two variables in a superpopulation). Whereas an incorrect rejection of the null hypothesis is called a type 1 error, the incorrect decision not to reject is called a type 2 error. Yet, the use of significance testing has been criticised, and a common tool to estimate the magnitude of the association and the precision is the confidence interval.

Statistical precision in estimation depends on the study size and the study efficiency. We evaluated a large number of participants, including childhood hearing loss cases.

Regarding the expected effect size, childhood CSOM and childhood hearing loss after rAOM are conditions in which an inner ear affection and hence subsequent hearing loss, tinnitus, dizziness or altered susceptibility to NIHL or ARHL, are reasonable to expect. Due to heteroscedasticity (the residual variance increased with increasing values for predicted adult hearing threshold), we used a bootstrap method in some of the analyses to produce maximally correct confidence intervals. In the tinnitus paper, in which multiple interaction terms were tested, we specified the significance level to 0.01 in the interaction analyses (to avoid type 1 error).

9.2.3 Generalizability

In addition to obtain valid and precise inferences as they apply to the source population, a further objective is often to obtain valid inferences as they apply to the target population outside the study (Rothman et al., 2008).

Place. This survey was based on the population of the Nord-Trøndelag, a large administrative area of 22,463 square kilometres. The adult population is around 95,000. The population is stable, with a net out migration of 0.3% per year (1996-2000); and

homogenous (less than 3% non-Caucasian). In many respects, Nord-Trøndelag is representative of Norway in terms of geography, economy, industry and income sources, age distribution, morbidity and mortality. However, the county has no large cities, and the mean levels of education are slightly lower than the national averages. In developing countries, in which childhood CSOM and complicated AOM are undertreated, the associations with adult hearing thresholds, tinnitus and dizziness might be even stronger.

Time. Although the childhood study took place between 1954 and 1986, we believe the diagnostic procedures and the classification of the hearing disorders were not very different from today. The classifications of the various types of otitis media at that time (Fabritius, 1968) correspond well with the classifications used today (Gates et al., 2002). Also, we believe the course and treatment of the studied conditions were not very different from today. Altogether, we believe our findings can be generalized to present time. If some of the association for otitis media reflect a poorer course and treatment at that time, this would only further underline the importance of optimal treatment in more adverse conditions.

Population. Our study included children between 7 and 13 years of age. Tambs et al. found that early age (<2 years of age) at onset for otitis media was associated with poorer adult hearing thresholds than later onset (Tambs et al., 2004). Since we examined hearing loss after recurrent *preschool* AOM, we cannot safely conclude that the long-term outcomes of RAOM in older children or adults are similar.

9.2.4 Design

This historical cohort study was conceived after the exposure and outcome assessments had occurred. Limitation due to use of *secondary* data were: 1) SHINT: lack of registrations of hearing thresholds <20 dB HL; 2) SHINT: no confirmation of participation (identity) for the children with normal hearing thresholds. In spite of this, we used the whole HUNT cohort of subjects except the SHINT cases as reference group; 3) possible differences in audiometric measurement conditions between SHINT and NTHLS, which may have affected the estimated change in hearing from childhood to adulthood for the

“sequeale AOM group”, (paper 1); 4) NTHLS: Hearing thresholds in adulthood were only measured cross-sectionally. A better design to examine the change of hearing throughout adulthood had included repeated audiometries in adulthood. With such a design, it had been possible to compare the average change of hearing in adulthood between cases and non-cases instead of testing for possible interaction effects with age (and so avoid possible birth-cohort effects). Possible bias due to all these weaknesses are discussed previously.

9.2.5 Causality

Causal inference may be viewed as a special case of the more general process of scientific reasoning. The cause of a specific disease occurrence can be defined as an antecedent event, condition or characteristic that was necessary for the occurrence of the disease at the moment it occurred, given that other conditions are fixed (Rothman et al.,2008). There are several models of causation, such as the sufficient component cause theory, the counter to fact causality and criteria based causality. Yet, epidemiologists have not agreed on a set of causal criteria and how to apply them. In short, our correlational study cannot safely establish cause and effect, only associations. However, since this is a longitudinal study, it seems unlikely that hearing loss, tinnitus or dizziness in adulthood could affect childhood ear diseases; therefore, we think it is reasonable to assume this directionality.

10 Conclusions and implications

Our study indicates that childhood chronic suppurative otitis media (CSOM) and childhood hearing loss after recurrent acute otitis media (rAOM) are associated with significant hearing loss, tinnitus and dizziness in adulthood. This stresses the importance of appropriate prevention, treatment and follow-up of these otitis media conditions.

The common condition childhood otitis media with effusion, both with and without eardrum scarring, is associated with minimally increased adult hearing thresholds. This can safely be communicated to worried patients.

The childhood hearing disorders SNHL, CSOM and hearing loss after rAOM are associated with a faster deterioration of hearing throughout adulthood. This “faster aging” may reflect that an already impaired cochlea is more susceptible to age-related degeneration. The faster aging effect is moderate and hardly necessitates more frequent follow-up. The finding should be confirmed by a study with repeated audiometries in adulthood.

Finally, our large study could not reveal significantly altered susceptibility to noise induced hearing loss associated with childhood SNHL or childhood otitis media. Although it still is important with protection against harmful noise, this is valuable information for people with a childhood onset hearing loss.

References

- AGRAWAL, Y., CAREY, J. P., DELLA SANTINA, C. C., SCHUBERT, M. C. & MINOR, L. B. 2009. Disorders of balance and vestibular function in US adults: data from the National Health and Nutrition Examination Survey, 2001-2004. *Arch Intern Med*, 169, 938-44.
- AHONEN, J. E. & MCDERMOTT, J. C. 1984. Extended high-frequency hearing loss in children with cleft palate. *Audiology*, 23, 467-76.
- AUGUSTSSON, I. & ENGSTRAND, I. 2006. Hearing loss as a sequel of secretory and acute otitis media as reflected by audiometric screening of Swedish conscripts. *Int J Pediatr Otorhinolaryngol*, 70, 703-10.
- BAGULEY, D., MCFERRAN, D. & HALL, D. 2013. Tinnitus. *Lancet*, 382, 1600-7.
- BERRETTINI, S., RAVECCA, F., SELLARI-FRANCESCHINI, S., MATTEUCCI, F., SICILIANO, G. & URSINO, F. 1999. Progressive sensorineural hearing loss in childhood. *Pediatr Neurol*, 20, 130-6.
- BESS, F. H., DODD-MURPHY, J. & PARKER, R. A. 1998. Children with minimal sensorineural hearing loss: prevalence, educational performance, and functional status. *Ear Hear*, 19, 339-54.
- BORCHGREVINK, H. M., TAMBS, K. & HOFFMAN, H. J. 2005. The Nord-Trondelag Norway Audiometric Survey 1996-98: unscreened thresholds and prevalence of hearing impairment for adults > 20 years. *Noise Health*, 7, 1-15.
- BROOKHOUSER, P. E., WORTHINGTON, D. W. & KELLY, W. J. 1994. Fluctuating and/or progressive sensorineural hearing loss in children. *Laryngoscope*, 104, 958-64.
- CARDON, G., CAMPBELL, J. & SHARMA, A. 2012. Plasticity in the developing auditory cortex: evidence from children with sensorineural hearing loss and auditory neuropathy spectrum disorder. *J Am Acad Audiol*, 23, 396-411; quiz 495.
- CASSELBRANT, M. L., FURMAN, J. M., MANDEL, E. M., FALL, P. A., KURS-LASKY, M. & ROCKETTE, H. E. 2000. Past history of otitis media and balance in four-year-old children. *Laryngoscope*, 110, 773-8.
- CASSELBRANT, M. L., MANDEL, EM. 1999. Evidence-based otitis media. CD Bluestone (Eds.), *Epidemiology*. Hamilton: BC Decker, (1999); 117-136
- CHIA, E. M., WANG, J. J., ROCHTCHINA, E., CUMMING, R. R., NEWALL, P. & MITCHELL, P. 2007. Hearing impairment and health-related quality of life: the Blue Mountains Hearing Study. *Ear Hear*, 28, 187-95.

- COELHO, C. B., SANCHEZ, T. G. & TYLER, R. S. 2007. Tinnitus in children and associated risk factors. *Prog Brain Res*, 166, 179-91.
- COHEN, H. S. 2006. Disability and rehabilitation in the dizzy patient. *Curr Opin Neurol*, 19, 49-54.
- CUREOGLU, S., SCHACHERN, P. A., RINALDO, A., TSUPRUN, V., FERLITO, A. & PAPARELLA, M. M. 2005. Round window membrane and labyrinthine pathological changes: an overview. *Acta Otolaryngol*, 125, 9-15.
- CUSIMANO, F., COCITA, V. C. & D'AMICO, A. 1989. Sensorineural hearing loss in chronic otitis media. *J Laryngol Otol*, 103, 158-63.
- DAVIS, A., RAFAIE A EI. 2000. Epidemiology of tinnitus. RS Tyler (Ed.), Tinnitus handbook, Singular, Thomson Learning, San Diego, CA (2000), pp. 1-23
- DAVIS, A. C. 1989. The prevalence of hearing impairment and reported hearing disability among adults in Great Britain. *Int J Epidemiol*, 18, 911-7.
- DAVIS, J. M., ELFENBEIN, J., SCHUM, R. & BENTLER, R. A. 1986. Effects of mild and moderate hearing impairments on language, educational, and psychosocial behavior of children. *J Speech Hear Disord*, 51, 53-62.
- DAWES, P. J. & WELCH, D. 2010. Childhood hearing and its relationship with tinnitus at thirty-two years of age. *Ann Otol Rhinol Laryngol*, 119, 672-6.
- DE BEER, B. A., GRAAMANS, K., SNIK, A. F., INGELS, K. & ZIELHUIS, G. A. 2003. Hearing deficits in young adults who had a history of otitis media in childhood: use of personal stereos had no effect on hearing. *Pediatrics*, 111, e304-8.
- DENNING, J. & MAYBERRY, W. 1987. VESTIBULAR DYSFUNCTION IN PRESCHOOL-CHILDREN WITH A HISTORY OF OTITIS-MEDIA. *Occupational Therapy Journal of Research*, 7, 335-348.
- DUFFY, L. C., FADEN, H., WASIELEWSKI, R., WOLF, J. & KRISTOFIK, D. 1997. Exclusive breastfeeding protects against bacterial colonization and day care exposure to otitis media. *Pediatrics*, 100, E7.
- EL-SAYED, Y. 1998. Bone conduction impairment in uncomplicated chronic suppurative otitis media. *Am J Otolaryngol*, 19, 149-53.
- EMMETT, S. D. & FRANCIS, H. W. 2014. The Socioeconomic Impact of Hearing Loss in U.S. Adults. *Otol Neurotol*.
- ENGLISH, G. M., NORTHERN, J. L. & FRIA, T. J. 1973. Chronic otitis media as a cause of sensorineural hearing loss. *Archives of Otolaryngology*, 98, 18-22.

- FABRITIUS, H. F. 1968. Hearing investigations of school children in North Trondelag County. *J Oslo City Hosp*, 18, 5-44.
- GACEK, R. R. 2013. A perspective on recurrent vertigo. *ORL J Otorhinolaryngol Relat Spec*, 75, 91-107.
- GATES, G. A., KLEIN, J. O., LIM, D. J., MOGI, G., OGRA, P. L., PARARELLA, M. M., PARADISE, J. L. & TOS, M. 2002. Recent advances in otitis media. 1. Definitions, terminology, and classification of otitis media. *Ann Otol Rhinol Laryngol Suppl*, 188, 8-18.
- GATES, G. A., SCHMID, P., KUJAWA, S. G., NAM, B. & D'AGOSTINO, R. 2000. Longitudinal threshold changes in older men with audiometric notches. *Hear Res*, 141, 220-8.
- HOFFMAN, H. J., REED GW 2004. Epidemiology of tinnitus. I: SNOW, JB Jr, ed. *Tinnitus: Theory and Management*. Hamilton, Ontario: B.C. Decker, Inc. 2004; 16-41.
- HOLMEN, J., MIDTHJELL, K., KRÜGER, Ø., LANGHAMMER, A., HOLMEN, T. L., BRATBERG, G. H., VATTEN, L. & LUND-LARSEN, P. G. 2003. The Nord-Trøndelag Health Study 1995–97 (HUNT 2): objectives, contents, methods and participation. *Norsk epidemiologi*, 13, 19-32.
- HULKA, JH. 1941. Bone-conduction changes in acute otitis meida. *Arch Otolaryngol*; 333: 333-50.
- HUNTER, L. L., MARGOLIS, R. H., RYKKEN, J. R., LE, C. T., DALY, K. A. & GIEBINK, G. S. 1996. High frequency hearing loss associated with otitis media. *Ear Hear*, 17, 1-11.
- JENSEN, R. G., KOCH, A. & HOMOE, P. 2013. The risk of hearing loss in a population with a high prevalence of chronic suppurative otitis media. *Int J Pediatr Otorhinolaryngol*, 77, 1530-5.
- JOB, A., RAYNAL, M. & RONDET, P. 1999. Hearing loss and use of personal stereos in young adults with antecedents of otitis media. *Lancet*, 353, 35.
- JOHANSEN, I. R., HAUCH, A. M., CHRISTENSEN, B. & PARVING, A. 2004. Longitudinal study of hearing impairment in children. *Int J Pediatr Otorhinolaryngol*, 68, 1157-65.
- JUNG, T. T., ALPER, C. M., HELLSTROM, S. O., HUNTER, L. L., CASSELBRANT, M. L., GROTH, A., KEMALOGLU, Y. K., KIM, S. G., LIM, D., NITTROUER, S., PARK, K. H., SABO, D. & SPRATLEY, J. 2013. Panel 8: Complications and sequelae. *Otolaryngol Head Neck Surg*, 148, E122-43.
- KHODAVERDI, M., JORGENSEN, G., LANGE, T., STANGERUP, S. E., DROZDZIEWICZ, D., TOS, M., BONDING, P. & CAYE-THOMASEN, P. 2013. Hearing 25 years after

- surgical treatment of otitis media with effusion in early childhood. *Int J Pediatr Otorhinolaryngol*, 77, 241-7.
- KROG, N. H., ENGDAHL, B. & TAMBS, K. 2010. The association between tinnitus and mental health in a general population sample: results from the HUNT Study. *J Psychosom Res*, 69, 289-98.
- KVESTAD, E., CZAJKOWSKI, N., ENGDAHL, B., HOFFMAN, H. J. & TAMBS, K. 2010. Low heritability of tinnitus: results from the second Nord-Trøndelag health study. *Arch Otolaryngol Head Neck Surg*, 136, 178-82.
- KVESTAD, E., CZAJKOWSKI, N., KROG, N. H., ENGDAHL, B. & TAMBS, K. 2012. Heritability of hearing loss. *Epidemiology*, 23, 328-31.
- LAITILA, P., KARMA, P., SIPILA, M., MANNINEN, M. & RAKHO, T. 1997. Extended high frequency hearing and history of acute otitis media in 14-year-old children in Finland. *Acta Otolaryngol Suppl*, 529, 27-9.
- LANGGUTH, B., KREUZER, P. M., KLEINJUNG, T. & DE RIDDER, D. 2013. Tinnitus: causes and clinical management. *Lancet Neurol*, 12, 920-30.
- LINSSEN, A. M., VAN BOXTEL, M. P., JOORE, M. A. & ANTEUNIS, L. J. 2014. Predictors of hearing acuity: cross-sectional and longitudinal analysis. *J Gerontol A Biol Sci Med Sci*, 69, 759-65.
- LUNTZ, M., YEHUDAI, N., HAIFLER, M., SIGAL, G. & MOST, T. 2013. Risk factors for sensorineural hearing loss in chronic otitis media. *Acta Otolaryngol*, 133, 1173-80.
- MARGOLIS, R. H., HUNTER, L. L., RYKKEN, J. R. & GIEBINK, G. S. 1993. Effects of otitis media on extended high-frequency hearing in children. *Ann Otol Rhinol Laryngol*, 102, 1-5.
- MARGOLIS, R. H., SALY, G. L. & HUNTER, L. L. 2000. High-frequency hearing loss and wideband middle ear impedance in children with otitis media histories. *Ear Hear*, 21, 206-11.
- MCDERMOTT, J. C., FAUSTI, S. A. & FREY, R. H. 1986. Effects of middle-ear disease and cleft palate on high-frequency hearing in children. *Audiology*, 25, 136-48.
- MEHRA, S., EAVEY, R. D. & KEAMY, D. G., JR. 2009. The epidemiology of hearing impairment in the United States: newborns, children, and adolescents. *Otolaryngol Head Neck Surg*, 140, 461-72.
- MONASTA, L., RONFANI, L., MARCHETTI, F., MONTICO, M., VECCHI BRUMATTI, L., BAVCAR, A., GRASSO, D., BARBIERO, C. & TAMBURLINI, G. 2012. Burden of disease caused by otitis media: systematic review and global estimates. *PLoS One*, 7, e36226.

- MULROW, C. D., AGUILAR, C., ENDICOTT, J. E., TULEY, M. R., VELEZ, R., CHARLIP, W. S., RHODES, M. C., HILL, J. A. & DENINO, L. A. 1990. Quality-of-life changes and hearing impairment. A randomized trial. *Ann Intern Med*, 113, 188-94.
- NEUHAUSER, H. K., RADTKE, A., VON BREVERN, M., LEZIUS, F., FELDMANN, M. & LEMPERT, T. 2008. Burden of dizziness and vertigo in the community. *Arch Intern Med*, 168, 2118-24.
- NISKAR, A. S., KIESZAK, S. M., HOLMES, A., ESTEBAN, E., RUBIN, C. & BRODY, D. J. 1998. Prevalence of hearing loss among children 6 to 19 years of age: the Third National Health and Nutrition Examination Survey. *JAMA*, 279, 1071-5.
- NODAR, R. H. 1972. Tinnitus aurium in school age children. *Journal of Auditory Research*, vol. 12, pp. 133-135.
- NONDAHL, D. M., CRUICKSHANKS, K. J., HUANG, G. H., KLEIN, B. E., KLEIN, R., NIETO, F. J. & TWEED, T. S. 2011. Tinnitus and its risk factors in the Beaver Dam offspring study. *Int J Audiol*, 50, 313-20.
- PAPARELLA, M. M., DE SOUSA, L. C. & MANCINI, F. 1983. Meniere's syndrome and otitis media. *Laryngoscope*, 93, 1408-15.
- PAPARELLA, M. M., MORIZONO, T., LE, C. T., MANCINI, F., SIPILA, P., CHOO, Y. B., LIDEN, G. & KIM, C. S. 1984. Sensorineural hearing loss in otitis media. *Ann Otol Rhinol Laryngol*, 93, 623-9.
- PARVING, A. 1988. Longitudinal study of hearing-disabled children. A follow-up investigation. *Int J Pediatr Otorhinolaryngol*, 15, 233-44.
- PELTON, S. I., PETTIGREW, M. M., BARENKAMP, S. J., GODFROID, F., GRIJALVA, C. G., LEACH, A., PATEL, J., MURPHY, T. F., SELAK, S. & BAKALETZ, L. O. 2013. Panel 6: Vaccines. *Otolaryngol Head Neck Surg*, 148, E90-101.
- PITTMAN, A. L. & STELMACHOWICZ, P. G. 2003. Hearing loss in children and adults: audiometric configuration, asymmetry, and progression. *Ear Hear*, 24, 198-205.
- REDAELLI DE ZINIS, L. O., CAMPOVECCHI, C., PARRINELLO, G. & ANTONELLI, A. R. 2005. Predisposing factors for inner ear hearing loss association with chronic otitis media. *Int J Audiol*, 44, 593-8.
- RIGA, M., BIBAS, A., XENELLIS, J. & KORRES, S. 2011. Inner ear disease and benign paroxysmal positional vertigo: a critical review of incidence, clinical characteristics, and management. *Int J Otolaryngol*, 2011, 709469.
- ROSENHALL, U. 2003. The influence of ageing on noise-induced hearing loss. *Noise Health*, 5, 47-53.

- ROTHMAN, K.J., GREENLAND, S., & LASH, T.L. 2008. Modern Epidemiology, 3rd Edition. *Philadelphia, PA: Lippincott, Williams & Wilkins.*
- ROVERS, M. M., ZIELHUIS, G. A., INGELS, K. & VAN DER WILT, G. J. 1999. Day-care and otitis media in young children: a critical overview. *Eur J Pediatr*, 158, 1-6.
- SCHAAF, R. C. 1985. The frequency of vestibular disorders in developmentally delayed preschoolers with otitis media. *Am J Occup Ther*, 39, 247-52.
- SCHLAEFER, K., SCHLEHOFER, B. & SCHUZ, J. 2009. Validity of self-reported occupational noise exposure. *Eur J Epidemiol*, 24, 469-75.
- SINDHUSAKE, D., GOLDING, M., NEWALL, P., RUBIN, G., JAKOBSEN, K. & MITCHELL, P. 2003. Risk factors for tinnitus in a population of older adults: the blue mountains hearing study. *Ear Hear*, 24, 501-7.
- SLOANE, P. D., COEYTAUX, R. R., BECK, R. S. & DALLARA, J. 2001. Dizziness: state of the science. *Ann Intern Med*, 134, 823-32.
- SMITH, R. J., BALE, J. F., JR. & WHITE, K. R. 2005. Sensorineural hearing loss in children. *Lancet*, 365, 879-90.
- SORRI, M., MAKI-TORKKO, E. & ALHO, O. P. 1995. Otitis media and long-term follow-up of hearing. *Acta Otolaryngol*, 115, 193-5.
- STEPHENSON, H., HIGSON, J. & HAGGARD, M. 1995. Binaural hearing in adults with histories of otitis media in childhood. *Audiology*, 34, 113-23.
- SUN, W., FU, Q., ZHANG, C., MANOHAR, S., KUMARAGURU, A. & LI, J. 2014. Loudness Perception Affected by Early Age Hearing Loss. *Hear Res*.
- TAKUMIDA, M. & ANNIKO, M. 2004. Localization of endotoxin in the inner ear following inoculation into the middle ear. *Acta Otolaryngol*, 124, 772-7.
- TAMBS, K. 2004. Moderate effects of hearing loss on mental health and subjective well-being: results from the Nord-Trondelag Hearing Loss Study. *Psychosom Med*, 66, 776-82.
- TAMBS, K., HOFFMAN, H. J., BORCHGREVINK, H. M., HOLMEN, J. & ENGDAHL, B. 2006. Hearing loss induced by occupational and impulse noise: results on threshold shifts by frequencies, age and gender from the Nord-Trondelag Hearing Loss Study. *Int J Audiol*, 45, 309-17.
- TAMBS, K., HOFFMAN, H. J., ENGDAHL, B. & BORCHGREVINK, H. M. 2004. Hearing loss associated with ear infections in Nord-Trondelag, Norway. *Ear Hear*, 25, 388-96.

- TIMOTHY, C. HAIN. 2014. Epidemiology of dizziness. http://dizziness-and-balance.com/disorders/dizzy_epi.html. Accessed: 24.06.15.
- WORLD HEALTH ORGANIZATION, Deafness and hearing loss, 2015. <http://www.who.int/mediacentre/factsheets/fs300/en/>. Accessed: 24.06.16.
- WILTINK, J., TSCHAN, R., MICHAL, M., SUBIC-WRANA, C., ECKHARDT-HENN, A., DIETERICH, M. & BEUTEL, M. E. 2009. Dizziness: anxiety, health care utilization and health behavior--results from a representative German community survey. *J Psychosom Res*, 66, 417-24.
- YARDLEY, L., OWEN, N., NAZARETH, I. & LUXON, L. 1998. Prevalence and presentation of dizziness in a general practice community sample of working age people. *Br J Gen Pract*, 48, 1131-5.
- YEHUDAI, N., MOST, T. & LUNTZ, M. 2015. Risk factors for sensorineural hearing loss in pediatric chronic otitis media. *Int J Pediatr Otorhinolaryngol*, 79, 26-30.
- YILMAZ, S., KARASALIHOGU, A. R., TAS, A., YAGIZ, R. & TAS, M. 2006. Otoacoustic emissions in young adults with a history of otitis media. *J Laryngol Otol*, 120, 103-7.
- YOSHIDA, H., MIYAMOTO, I. & TAKAHASHI, H. 2013. Relationship between CT findings and sensorineural hearing loss in chronic otitis media. *Auris Nasus Larynx*.
- ZIELHUIS, G. A., RACH, G. H., VAN DEN BOSCH, A. & VAN DEN BROEK, P. 1990. The prevalence of otitis media with effusion: a critical review of the literature. *Clin Otolaryngol Allied Sci*, 15, 283-8.

