Children with **acquired hearing loss** need special care, and this has major social and economic implications worldwide. The main cause is a common condition called **otitis media** with effusion, affecting eight out of every ten children in the Netherlands before age four. While an episode is generally self-limiting, it can lead to persistent hearing loss, which in turn could affect the child's behavior and linguistic development. To improve hearing, **ventilation tubes** are often surgically inserted into the eardrum.

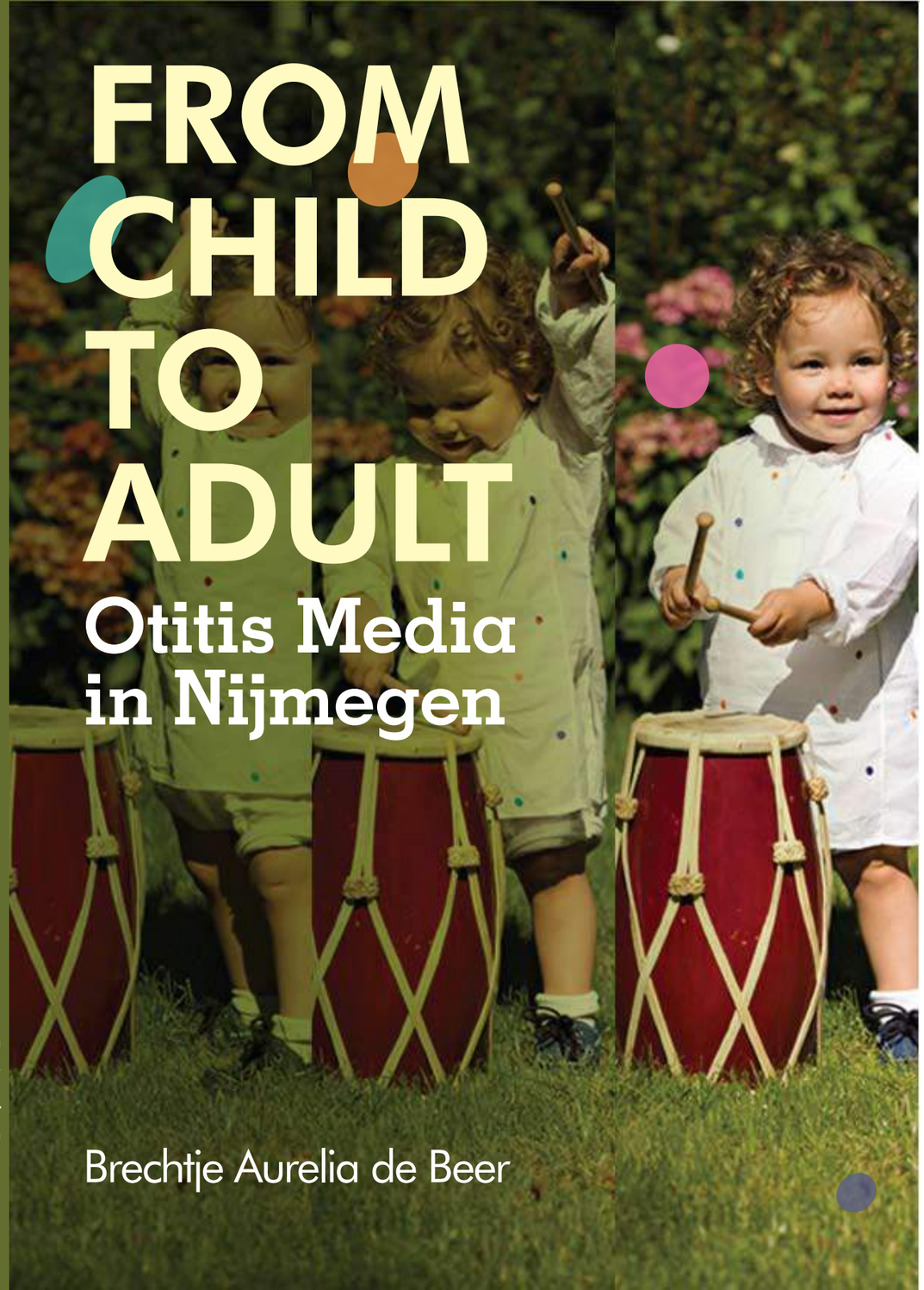
The research underpinning this thesis followed a Dutch birth cohort from **preschool age till adulthood** to gain insight into the late effects of otitis media and its surgical treatment. While the insertion of ventilation tubes did improve hearing immediately, the treatment induced a slight sensorineural hearing loss that seemed to worsen over time. This unintended **late adverse effect** highlights the need for modified options in otitis media management. Thus, the findings of this thesis pose a **challenge** to scientists and healthcare practitioners in ENT.

FROM CHILD TO ADULT; OTITIS MEDIA IN NIJMEGEN

B.A. de Beer

FROM CHILD TO ADULT

Otitis Media in Nijmegen



Brechtje Aurelia de Beer

UITNODIGING

Voor het bijwonen van de openbare verdediging van het proefschrift
From child to adult; otitis media in Nijmegen

Vrijdag 30 november 2007
10.30 uur
Aula Major
Radboud Universiteit
Comeniuslaan 2
6525 HP Nijmegen

Receptie ter plaatse na afloop van de promotie

Brechtje de Beer
Emmalaan 14
6571 AL Berg en Dal
b.debeer@kno.umcn.nl

Paranimfen

Klaartje de Beer
klaartje_debeer@hotmail.com
Tel: 06 228 003 75

Anne Petrie
acpetrie@hotmail.com.
Tel: 06 248 770 84

FROM CHILD TO ADULT
OTITIS MEDIA IN NIJMEGEN

Brechtje Aurelia de Beer

Print: Okimedia
Lay-out: Diny Helsper
Cover-design: Bas Ben Zineb; Jouri van Veen (foto)

Beer de, Brechtje
From child to adult; otitis media in Nijmegen

Thesis Radboud University Nijmegen Medical Centre
Nijmegen, the Netherlands.

ISBN/EAN: 978-90-9022253-0

From child to adult
Otitis Media in Nijmegen

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het College van Decanen
in het openbaar te verdedigen op
vrijdag 30 november 2007
om 10.30 uur precies

door

Brechtje Aurelia de Beer
geboren op 20 februari 1974
te Amsterdam

Promotores:	Prof. dr. K. Graamans
	Prof. dr. ir. G.A. Zielhuis
	Prof. dr. ir. A.F.M. Snik

Manuscriptcommissie:
Prof. dr. R. de Groot
Prof. dr. G.J. Hordijk
Dr. L.J.C. Anteunis

The study in this thesis was financially supported by Zon-MW projectnumber 21000053

Contents

1

Introduction

INTRODUCTION

Otitis media is a very common disorder in children. Acute otitis media (AOM) and otitis media with effusion (OME) are different stages on the otitis media continuum. AOM is defined as the presence of middle ear effusion in combination with rapid onset of one or more signs or symptoms of inflammation, such as fever, otalgia or otorrhea. OME is defined as middle ear effusion without signs or symptoms of an acute infectious process.[1] By the time they are 3 years old, 50-85% of all children have had AOM. The peak incidence is between ages 6 and 11 months.[2] The absence of symptoms with OME makes it difficult to estimate its prevalence, but the point prevalence of middle ear effusion on screening tests is about 20%. The peak incidence is at about 1 year of age. By age 3, nearly all children have had at least one episode of middle ear effusion (this includes both AOM and OME).[2] Its natural history and the subsequent likelihood of spontaneous resolution depend strongly on the type of OME. In general, about 75% of all newly detected OME cases resolve spontaneously in 6 months, with rates decreasing to 25% for preexisting OME of 3 months or longer duration.[3] The functional result of middle ear effusion is a mild conductive hearing loss of about 10 dB hearing level (HL).[4] However, a child with hearing loss complaints and middle ear effusion at otomicroscopy will have conductive hearing loss of about 25 to 30 dB HL. Just 5-10% of the children have hearing thresholds of 40-50 dB HL.[5] Both the high incidence and the high rate of spontaneous resolution suggest that the presence of middle ear effusion is a natural phenomenon, its presence at some stage in childhood being a normal finding. Notwithstanding this, some proportion of the children with persistent middle ear effusion (OME) and associated prolonged hearing loss will develop language delay and/or behavioral problems.[6-9]

The most common therapy for OME is surgery with insertion of a ventilation tube in one or both tympanic membranes. Each year about 20 of every 1000 children in the Netherlands under the age of 12 years undergo ventilation tube insertion.[10] The origin of this therapy goes back to Sir Astley Cooper, who observed around the turn of the 18th century that patients with tympanic membrane perforations experienced stabilization of their middle ear disease.[11] He was the first to report relief from deafness by incision of the tympanic membrane (myringotomy). However, middle ear fluid and consecutive hearing loss recurred soon, since these iatrogenic perforations of the tympanic membrane tend to close rapidly. Politzer realized that prolonged ventilation of the middle ear was needed. He attempted to prolong ventilation by inserting catgut, fish bones, lead wires, and gold rings into the myringotomy incision.[11] Because these attempts accomplish longstanding ventilation of the middle ear, stents were developed to keep the

perforation in the tympanic membrane open. From 1954 onwards Armstrong's method gained popularity for successful prolonged ventilation of the middle ear by insertion of polyethylene tubes.[12] These tubes remained in place for several weeks, just long enough to show some improvement, and were reinserted when the symptoms recurred. Armstrong cautioned that the tubes were not "a panacea in the management of secretory otitis media" and only appropriate in "chronic cases that have resisted management".[12] Nowadays, more than 50 years later, the appropriate use of ventilation tubes is still subject to debate, since opinions on the benefits and risks vary greatly.

Short- and long-term consequences

The traditional aims of treatment with ventilation tubes are (1) to improve hearing, (2) to reduce effusion prevalence and (3) to reduce infection incidence. Studies by the groups of Mandel[13,14] and Gates[15] show that both effusion prevalence and infection incidence are reduced by 50 to 75% in the year following ventilation tube insertion. Myringotomy with insertion of ventilation tubes implies drainage of middle ear effusion, which gives instant improvement of conductive hearing loss, with an individual variation of up to 50 dB.[5] The results of several randomized controlled trials[16-19] demonstrate that children who receive ventilation tubes perform on average 9 dB better than controls without ventilation tubes at 6 months (95% confidence interval (CI) 4-14 dB). By 12 months this mean effect has diminished to 6 dB (95% CI 3-9 dB). Two years after ventilation tube insertion the difference in mean hearing level is 4 dB (95% CI 2-6 dB), while by the 5-year follow-up at group level, the effect has disappeared.

Children who experience chronic or recurrent middle ear effusion and associated hearing loss may become delayed or impaired in their speech and behavioral development. It is difficult to conduct meta-analyses of the effect of ventilation tube insertion on language and cognitive development, since the studies on this topic have used different designs and outcome measures. For example, Rach et al.[20] found that at preschool age the hearing loss caused by middle ear effusion is responsible for lower levels of expressive language compared to children of the same age without OME. That study could not demonstrate any effect of treatment with ventilation tubes on speech capacity. In contrast, Maw et al.[21] found, after adjustment for baseline confounders, a marginally significant difference in expressive and comprehensive language 9 months after surgery, to the detriment of the children who had not received early ventilation tube insertion. But Rovers et al.[22] showed no difference in expressive and comprehensive language abilities at the age of 2 and 3 years between subjects treated with ventilation tubes and

children under a watchful waiting policy. A large study by Paradise et al.[23] showed that prompt ventilation tube insertion does not lead to more improvement of speech, language and cognition compared to insertion after 9 months of persisting middle ear effusion. A long-term follow-up of OME children who did or did not receive ventilation tubes before they were 4 years old found that at the age of 7-8 years, children with tubes did not perform better in terms of auditory perception, language ability and educational attainment compared to controls without tubes.[24] It should be noted that all of these clinical trials excluded children with speech and language delays, children with behavioral and learning problems, and children with specific clinical syndromes. They were excluded because ventilation tube insertion for recurrent or chronic OME is not a topic of controversy for these specific groups.

It is generally assumed that surgical treatment of middle ear effusion and subsequent reduction of infection risk will prevent long-term structural and functional damage of the middle ear. However, several studies suggest the opposite. It appears that ventilation tubes induce tympanic membrane abnormalities, such as tympanosclerosis and atrophy. Several studies mention prevalence rates of 50 to 80% of tympanosclerosis in ears that seem to have a history of ventilation tube insertion.[25-27] Although Tos has shown that the tympanic membrane is a dynamic structure and tympanic membrane abnormalities may improve or deteriorate over time, several studies demonstrated that tympano-sclerosis shows persistency in long-term follow up.[28-33] Persistent tympanic membrane abnormalities have been associated with conductive hearing loss. For instance, Schilder et al.[34] found that ears with tympanic membrane abnormalities had between 2.1 dB and 4.0 dB worse hearing levels compared with ears without tympanic membrane abnormalities at about age 8. Moreover, among the children with abnormal otomicroscopic findings, hearing levels in ears treated with ventilation tubes were 1.9 dB to 3.6 dB worse than in untreated ears.[34] In a six-year follow-up study, Hunter[35] showed significantly worse hearing thresholds in treated subjects. The same result was reported by Skinner.[36] This follow-up study demonstrated that hearing was worse 15 years after diagnosis in ears initially treated with ventilation tube insertion, although the difference was non-statistically significant compared to hearing in untreated ears.
Whether OME can be responsible for cochlear dysfunction is unclear. As Hunter[37] observed in her study, the number of insertions of ventilation tubes and the frequency of otitis media during follow-up were significantly and positively associated with poorer high frequency thresholds.

In conclusion, the short-term benefits of ventilation tubes for hearing, middle ear ventilation and infection risk may not match the long-term health benefits. It seems that the benefits of ventilation tubes in children with OME diminish over time. Whether the long-term adverse effects of ventilation tubes outweigh the long-term benefits is unclear. There is a need for better understanding of the long-term consequences, both structural and functional, of ventilation tube insertion. Structural consequences of VT insertion refer to changes in the conductive system of the middle ear, including the tympanic membrane. Hearing is taken as a primary functional consequence of childhood middle ear disease.

Objective

Follow-up of the original Radboud University Nijmegen Ear Research cohort, founded in 1984, offered the opportunity to investigate the long-term consequences of ventilation tube insertion as treatment for childhood otitis media. Subjects that had not been treated for childhood otitis media and subjects without a history of any middle ear problems served as controls.

The following specific research questions are addressed:

1. What are the long-term functional consequences of both treated and untreated otitis media in early childhood? Are subjects with a history of otitis media more susceptible to noise-induced hearing loss due to excessive personal stereo use?
2. What are the long-term structural consequences of both treated and untreated otitis media in terms of middle ear dynamics and of tympanic membrane morphology?

The availability of a control group of subjects without middle ear problems in their histories allowed us to document normal hearing levels in healthy young adults with a clean otologic history.

Outline of this thesis

In Chapter 2, hearing of young adults treated with ventilation tubes for childhood otitis media is compared to hearing of untreated subjects. Chapters 3, 4 and 5 describe changes in tympanic membrane appearance, dynamics of static admittance and the acoustic reflex from childhood to young adulthood as a consequence of treatment of otitis media with ventilation tube insertion. Whether a history of ventilation tube insertion leads to increased susceptibility to noise-induced hearing loss due to excessive personal stereo use is answered in Chapter 6. Since this study was designed with a control group of subjects without

a history of any middle ear problems, we were able to describe normal hearing of healthy young adults with a clean otologic history. Chapter 7 deals with this topic and compares the results with the reference levels produced by the ISO.
Finally, in Chapter 8, the overall conclusions of this thesis are discussed in light of present knowledge about long-term consequences of treated and untreated otitis media as therapy for otitis media. Some practical implications and proposals for future research are suggested in this last chapter as well.

REFERENCES

1. Bluestone CD. Definitions, terminology, and classification. In: Rosenfeld RM, Bluestone CD, eds. Evidence Based Otitis Media. 2nd ed. Hamilton, Canada: B.C. Decker Inc; 2003:120-135.
2. Casselbrant M, Mandel E.M. Epidemiology. In: Rosenfeld RM, Bluestone CD, eds. Evidence Based Otitis Media. 2nd ed. Hamilton, Canada: B.C. Decker Inc; 2003:147-162.
3. Rosenfeld R, Bluestone CD. Clinical pathway for otitis media with effusion. In: Rosenfeld RM, Bluestone CD, eds. Evidence Based Otitis Media. 2nd ed. Hamilton, Canada: B.C. Decker Inc; 2003:303-324.
4. Anteunis LJC, Engel JAM. Maastricht Otitis Media with Effusion Study. A prospective longitudinal study in infants from 0 to 2 years. Maastricht, The Netherlands: Datawyse B.V.; 2000.
5. Fria TJ, Cantekin EI, Eichler JA. Hearing acuity of children with otitis media with effusion. *Arch Otolaryngol* 1985;111:10-16.
6. Teele DW, Klein JO, Chase C, Menyuk P, Rosner BA, the Greater Boston Otitis Media Study Group. Otitis media in infancy and intellectual ability, school achievement, speech, and language at age 7 years. *The Journal of Infectious Diseases* 1990;162:685-694.
7. Chalmers D, Stewart I, Silva P, Mulvena A. Otitis Media with Effusion in Children: the Dunedin study. London, UK: Mac Keith Press; 1989.
8. Paradise JL. Otitis media and child development: should we worry? *Pediatr Infect Dis J* 1998;17:1076-1083.
9. Roberts J, Hunter L, Gravel J et al. Otitis media, hearing loss, and language learning: controversies and current research. *J Dev Behav Pediatr* 2004;25:110-122.
10. Engel JAM, Anteunis LJC, Hendriks JJT. Treatment with grommets in the Netherlands: incidence in children from birth to 12 years. In: Tos M, Thomsen J, Balle V, eds. Otitis Media Today.The Hague, The Netherlands: Kugler Publications; 1999:451-455.
11. Politzer A. History of Otology. Phoenix, USA: Columella Press; 1981.
12. Armstrong BW. A new treatment for chronic secretory otitis media. *Arch Otolaryngol* 1954;59:653-654.
13. Mandel EM, Rockette HE, Bluestone CD, Paradise JL, Nozza RJ. Myringotomy with and without tympanostomy tubes for chronic otitis media with effusion. *Arch Otolaryngol Head and Neck Surg* 1989;115:1217-1224.
14. Mandel EM, Rockette HE, Bluestone CD, Paradise JL, Nozza RJ. Efficacy of myringotomy with and without tympanostomy tubes for chronic otitis media with effusion. *Pediatr Infect Dis J* 1992;11:270-277.
15. Gates GA, Avery CA, Prihoda TJ, Cooper JC. Effectiveness of adenoidectomy and tympanostomy tubes in the treatment of chronic otitis media with effusion. *N Engl J Med* 1987; 317:1444-1451.
16. Black NA, Sanderson CFB, Freeland AP, Vessey MP. A randomised controlled trial of surgery for glue ear. *BMJ* 1990;300:1551-1556.
17. Dempster JH, Browning GG, Gatehouse SG. A randomized study of the surgical management of children with persistent otitis media with effusion associated with a hearing impairment. *J Laryngol Otol* 1993;107:284-289.
18. Maw R, Herod F. Otoscopic, impedance, and audiometric findings in glue ear treated by adenoidectomy and tonsillectomy. *Lancet* 1986;6:1399-1402.

19. Maw AR, Bawden R. The long-term outcome of secretory otitis media in children and the effects of surgical treatment: a ten year study. *Acta Otorhinolaryngol Belg* 1994;48:317-324.
20. Rach GH, Zielhuis GA, Baarle van PW, Broek van den P. The effect of treatment with ventilating tubes on language development in preschool children with otitis media with effusion. *Clin Otolaryngol* 1991;16:128-132.
21. Maw R, Wilks J, Harvey I, Peters TJ, Golding J. Early surgery compared with watchful waiting for glue ear and effect on language development in preschool children: a randomised trial. *Lancet* 1999;353:960-963.
22. Rovers MM, Straatman H, Ingels K, Wilt van der GJ, Broek van den P, Zielhuis GA. The effect of ventilation tubes on language development in infants with otitis media with effusion: a randomized trial. *Pediatrics* 2000;106:e42.
23. Paradise JL, Feldman HM, Campbell TF et al. Effect of early or delayed insertion of tympanostomy tubes for persistent otitis media on developmental outcomes at the age of three years. *N Eng J Med* 2001;344:1179-1187.
24. Grievink EH, Peters SAF. Developmental Consequences of Otitis Media with Effusion for Language Ability and Educational Attainment at Age Seven. Nijmegen, The Netherlands: WNO Grafisch Bedrijf; 1997.
25. Kay DJ, Nelson M, Rosenfeld RM. Meta-analysis of tympanostomy tube sequelae. *Otolaryngol Head Neck Surg* 2001;124:374-380.
26. Johnston LC, Feldman HM, Paradise JL et al. Tympanic membrane abnormalities and hearing levels at the ages of 5 and 6 years in relation to persistent otitis media and tympanostomy tube insertion in the first 3 years of life: a prospective study incorporating a randomized clinical trial. *Pediatrics* 2004;114:e58-e67.
27. Lous J, Fiellau-Nikolajsen M, Jeppesen AL. Secretory otitis media and language development: a six year follow-up study with case-control. *Int J of Pediatr Otorhinolaryngol* 1988;15:185-203.
28. Ben Ami M, Rosen G, Shlezinger T, Konack S, Ben Ami M. Otitis media with effusion--complications after treatment. *J Laryngol Otol* 1983;97:1091-1094.
29. Tos M, Stangerup SE, Holm-Jensen S, Sorensen CH. Spontaneous course of secretory otitis and changes of the eardrum. *Arch Otolaryngol* 1984;110:281-289.
30. Sederberg-Olsen JF, Sederberg-Olsen AE, Jensen AM. Late results of treatment with ventilation tubes for secretory otitis media in ENT practice. *Acta Otolaryngol* 1989; 108:448-455.
31. Tos M, Stangerup SE. Hearing loss in tympanosclerosis caused by grommets. *Arch Otolaryngol Head Neck Surg* 1989;115:931-935.
32. Maw AR, Bawden R. Tympanic membrane atrophy, scarring, atelectasis and attic retraction in persistent, untreated otitis media with effusion and following ventilation tube insertion. *Int J Pediatr Otorhinolaryngol* 1994;30:189-204.
33. Schilder AGM, Zielhuis GA, Haggard MP, van den Broek P. Long-term effects of otitis media with effusion: otomicroscopic findings. *Am J Otol* 1995;16:365-372.
34. Schilder AGM, Zielhuis GA, Straatman H, van den Broek P. Long-term effects of otitis media with effusion: auditory findings. In: Schilder AGM. Long-term Effects of Otitis Media with Effusion in Children. Nijmegen, The Netherlands: SSN Publishers; 1993:47-65.
35. Hunter LL, Margolis RH, Giebink GS, Schmitz JL, Le Chap T, Daly KA. Long-term prospective study of hearing loss in children after tympanostomy tube treatment of chronic otitis media with effusion. In: Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances in Otitis Media. Proceedings of the 6th International Symposium. Hamilton, Canada: BC Decker Inc, 1996:383-386.
36. Skinner DW, Lesser TH, Richards SH. A 15 year follow-up of a controlled trial of the use of grommets in glue ear. *Clin Otolaryngol* 1988;13:341-346.
37. Hunter LL, Margolis RH, Rykken JR, Le CT, Daly KA, Giebink GS. High frequency hearing loss associated with otitis media. *Ear Hear* 1996;17:1-11.

2

Hearing loss in young adults who had ventilation tube insertion in childhood

B.A. de Beer
A.G.M. Schilder
K. Ingels
A.F.M. Snik
G.A. Zielhuis
K. Graamans

Annals of Otology Rhinology Laryngology; 2004; 113: 438-444

ABSTRACT

Background: It is known that insertion of ventilation tubes can cause damage to the tympanic membrane and hearing deterioration in the long term.

Objective: To investigate long-term effects of recurrent otitis media and of ventilation tube insertion.

Methods: The study group (n=358 subjects), with/without a history of otitis media and/or ventilation tube insertion, was derived from a birth cohort that had been followed for 16 years. At 18 years of age, a standardized audiometric and otoscopic examination was performed.

Results: Ventilation tube insertion in childhood was associated with a mean persistent hearing loss in young adults of about 5 to 10 dB at the group level with a sensorineural component of 3 to 4 dB. This hearing loss could not be explained by the disease load of otitis media in childhood. Repeated insertions of ventilation tubes caused a greater deterioration of hearing than a single insertion. Structural changes of the tympanic membrane were a mediating factor in the causal relation between ventilation tube insertion and hearing loss.

Conclusion: Ventilation tube insertion in childhood may induce hearing deterioration in the long term.

INTRODUCTION

Insertion of ventilation tubes for treatment of otitis media has become one of the most common operative procedures in children since its introduction in 1954 by Armstrong.[1] In the last decade the procedure has faced criticism because of its limited effectiveness and adverse effects.[2] Some studies have reported an increased risk of audiological and anatomical sequelae associated with ventilation tube insertion. Ventilation tubes may cause structural changes to the tympanic membrane that persist for 10 years or longer after their extrusion.[3-10] Reports on the long-term consequences on hearing, based upon repeated objective audiometric measurements, have remained inconclusive so far. In the study by Skinner et al.,[5] 15 years after initial diagnosis, a small but non-significant difference in hearing was found between the surgically treated and non-treated ear to the disadvantage of the treated ear. Hunter et al.[11] showed in a 6-year follow-up study a significant decrease in hearing sensitivity in subjects treated with ventilation tubes for otitis media compared to subjects who had no history of otitis media or ventilation tube insertion. In contrast, Sederberg-Olsen et al.[6] did not observe any decrease in hearing sensitivity in subjects who had been followed for a mean period of 12 years after ventilation tube insertion.

In this study we intended to document the late effects of treatment with ventilation tubes for childhood otitis media. This study was performed in a birth cohort that had had repeated otoscopic examinations and audiometric measurements extending over an 18-year period. The following questions were addressed in this investigation: i) What is the relation between ventilation tube insertion in childhood and hearing sensitivity at young adult age? ii) What is the relationship between ventilation tube insertion in childhood and tympanic membrane appearance at young adult age? and iii) Does tympanic membrane pathology play a mediating role in the association between ventilation tube insertion in childhood and hearing sensitivity at young adult age?

POPULATION AND METHODS

Subjects of study

A birth cohort of 1439 subjects born in 1982-1983 formed the basis for this study; 1328 subjects from this group had participated in a study to evaluate the efficacy of preschool screening for otitis media with effusion (OME).[12] The latter study included tympanometry at 3-month intervals from 24 to 48 months of age. A detailed history, from birth onwards, had been taken at the first screening. This history was focused on middle-ear disease and its treatment. At the age of 8

years, 946 children from this cohort had been re-evaluated.[13,14] At that time otomicroscopy, tympanometry and pure-tone audiometry were performed to investigate the mid- to long-term effects of otitis media and its treatment on both hearing and the appearance of the tympanic membrane. Moreover, a detailed history of the occurrence of ear, nose and throat disorders and treatment in the period between the end of the screening (at 48 months) and 8 years had been taken. In 2001, at 18 years of age, those subjects most affected by otitis media or not affected at all in the period from birth to 8 years of age were invited for a re-evaluation. For the purpose of this selection a cumulative otitis media (OM) score was calculated for each subject. This personal OM score was based on the documented number of episodes of either OME (max score 100) or acute otitis media (AOM; max score 100). Adding the OME score and the AOM score formed the OM score (range 0 to 200). OME was considered present when either a type B tympanogram or presence of ventilation tubes had been observed before the screening (0 to 24 months), during the screening at 2 to 4 years of age, in the period between both studies (4 to 8 years), and/or at the examination at 8 years. AOM was considered present when the parents had reported events of otalgia with fever and/or otorrhea during the screening at 2 to 4 years of age, in the period between both studies (4 to 8 years), and/or at the examination at 8 years. The subjects in the highest and lowest tertiles of this OM score (n=528) formed the groups of subjects characterized as having either a positive (OM+) or a negative (OM–) otitis media history. Eventually, 358 subjects agreed to participate in this part of the follow-up study. The 716 ears of these subjects were categorized into three groups: 102 ears with a positive history of otitis media that had been treated by ventilation tubes in the period from birth until 8 years (OM+VT+); 264 ears with a positive history of otitis media that had not been surgically treated (OM+VT-); and 350 ears with a negative otitis media history (OM-), i.e. the reference group.

The effects of ventilation tube insertion on hearing have to be distinguished from the effects of otitis media. To that end, the disease load was assessed as well; both the severity and the persistence of otitis media before the insertion of ventilation tubes were determined. Disease load was defined as the number of type B tympanograms and the number of AOM episodes up to the first ventilation tube insertion or up to the subject's fourth year of life. This score was calculated for each ear.

Approval for the study was obtained from the Ethics Committee of the University Medical Center Nijmegen and an informed consent release was signed by the participants.

Outcome measurements

A standardized questionnaire was used to supplement the clinical information about the period between the previous evaluation at 8 years of age and this study at 18 years of age. Details on reported middle-ear disease were verified with data from the medical records.

Otomicroscopy was performed by a trained otolaryngology resident. Abnormalities of the tympanic membrane were classified as presence of atrophy, tympanosclerosis, retraction of the pars tensa, attic retraction, a perforation or cholesteatoma. Pure-tone audiometry was performed in an audiometric test booth using an Interacoustic Clinical Audiometer AC40 (Interacoustics, Assens, Denmark) and TDH 39P headphones (Telephonics, Huntington, New York) that were calibrated according to ISO 389 standards.[15] Air conduction thresholds were determined in both ears for octave and two half-octave frequencies from 0.25 to 8.0 kHz and bone conduction thresholds in one ear at 0.5, 1.0, 2.0, 3.0 and 4.0 kHz. If the air conduction thresholds exceeded +10 dB HL, bone conduction thresholds were measured in both ears with standard masking techniques. The pure-tone average (PTA) was defined as the mean air conduction level at the frequencies 0.5, 1.0 and 2.0 kHz. A Tymp87 impedance meter (Danplex, Odense, Denmark) was used for tympanometry. The audiometric data at 8 years of age had been obtained in the same exactly way, except the Interacoustic Clinical Audiometer that was used then was a previous model (AC5).[14]

Statistical methods

Hearing thresholds determined at 8 years and 18 years for the OM+VT+ group and the OM+VT- group were compared to the thresholds of the OM– group for left and right ears separately. Linear regression models were used for comparison of audiograms. This was done with the data obtained at 8 years of age as well as with those obtained at 18 years of age. Eight ears of 4 subjects were excluded from analysis of the audiological data obtained at 18 years of age for reasons of missing data, bilateral OME (n=2), or presence of neurofibromatosis (n=1). In three subjects with a unilateral congenital sensorineural deafness and in one subject who had been treated for cholesteatoma, only the healthy ear was included in the analyses. Middle-ear disease is likely to interfere with hearing acuity; therefore, we used only the audiological data for subjects who did not have OME, AOM, otorrhea or ventilation tubes in situ when they were evaluated at 8 years of age.

Random effect regression models were used to test the differences in PTA between the OM+VT+ and the OM+VT- group, taking into account the

dependency of ears within a subject. Several factors were included in these linear regression models (for different calculations): disease load until the first surgical intervention, age at first ventilation tube insertion, number of ventilation tube insertions, and prevalence of tympanic membrane abnormalities. The difference in disease load in the OM+VT+ and the OM+VT- group was tested with the Student *t* test. All analyses were performed with SAS statistical software (version 6.12; SAS, Cary, North Carolina).

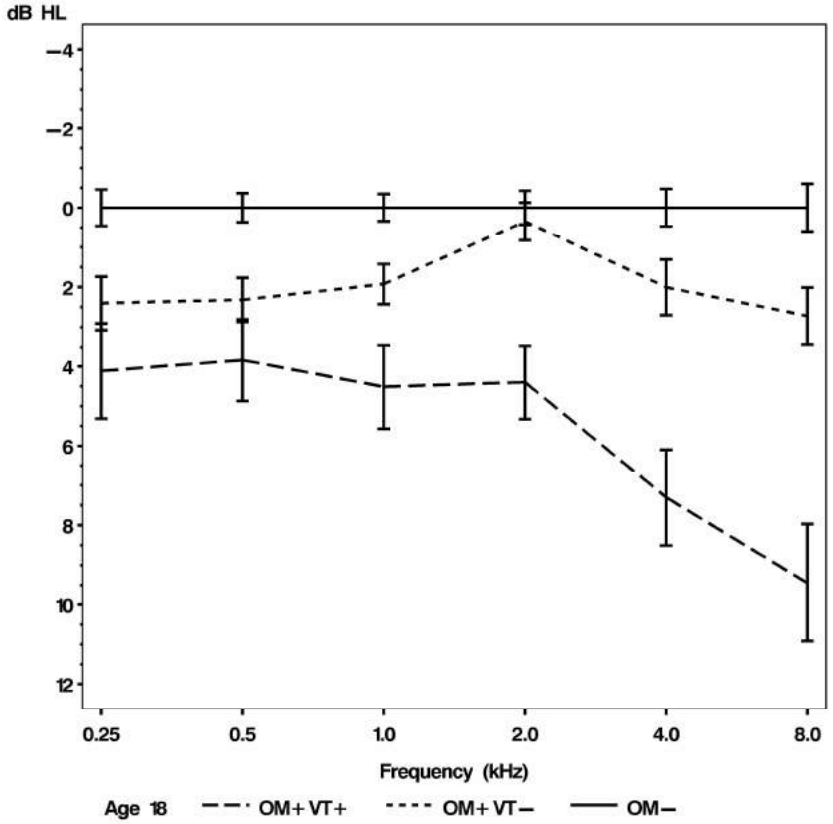
RESULTS

In accordance with the design of this study, all subjects were of the same age at the time of evaluation. The distribution of gender was comparable in the treated (OM+VT+) and untreated (OM+VT-) otitis media groups and in the OM– reference group (Table 1). OM+VT+ ears had a substantially higher disease load than the OM+VT- ears (Table 1). Within the OM+VT+ group, 43 percent of the right ears had undergone insertion more than once and the majority of the ears had got their first ventilation tube before the age of 4 years. Note that in Table 1 the results of only the right ears are shown because results for both ears were similar.

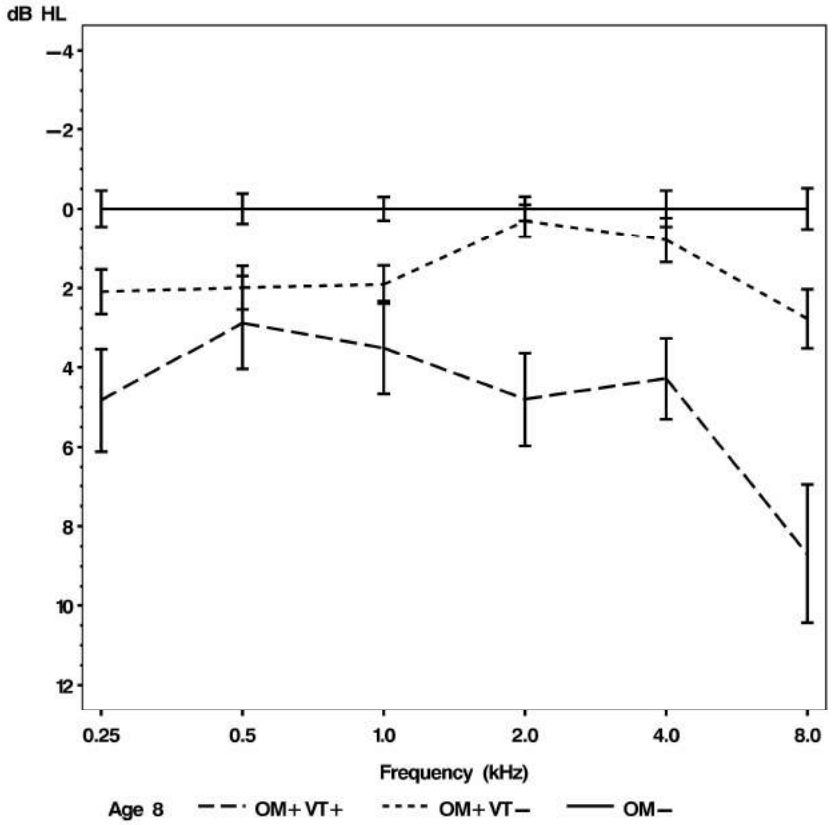
Table 1. Basic characteristics of the three study groups. Results for right ears

	OM+VT+	**OM+VT-**	**OM–**
Number	51	132	174
Male	47%	48%	43%
Median disease load* (P_{25}, P_{75})	77 (60,95)	60 (45,76)	10 (0,11)
Number of VT insertions			
0	-	132	-
1	29	-	-
≥ 2	22	-	-
Age at first VT insertion			
0 - 2 yr.	1	-	-
2 - 4 yr.	40	-	-
> 4 yr.	10	-	-

Abbreviations: OM, otitis media; VT, ventilation tubes; +, positive history; - negative history.
*Sum of proportion of type B tympanograms and of AOM episodes up to the first ventilation tube insertion or up to 4 years of age (range 0-200).



1a



1b

Figure 1. Mean air conduction thresholds of right ears of OM+VT- and OM+VT+ group relative to the hearing level of the OM- group at age 18 years (1a) and 8 years (1b).

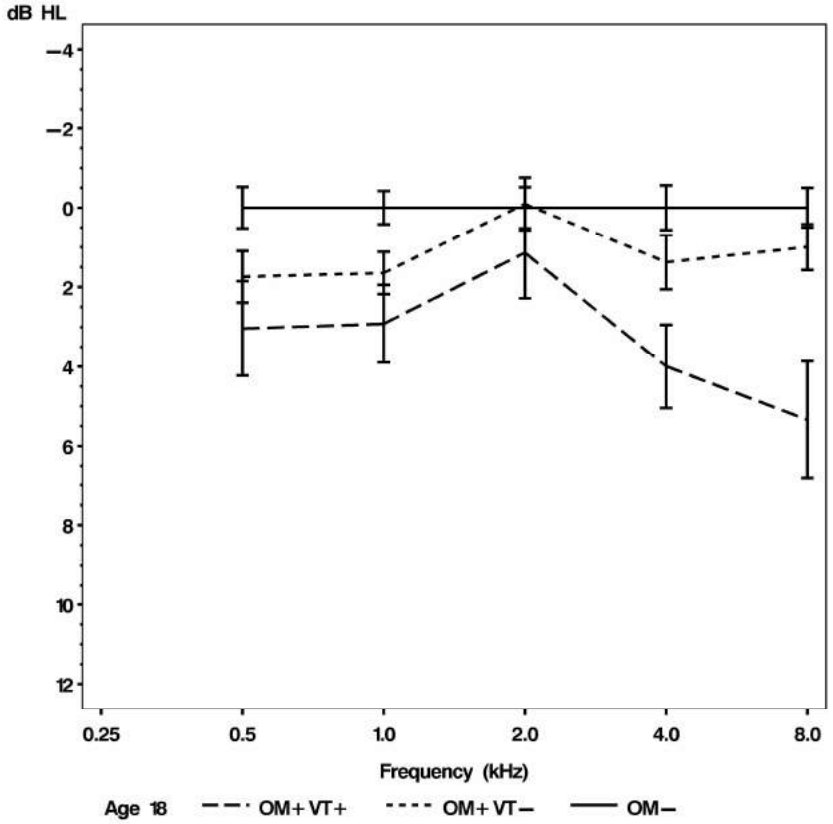
Ventilation tubes and hearing sensitivity

The results of pure-tone audiometry in the frequency range from 0.25 to 8.0 kHz are presented in Figure 1. At 18 years of age, the mean air conduction thresholds in the OM+VT+ group as well as the OM+VT- group were significantly poorer than in the OM- reference group (p<0.05). Differences between the OM+VT+ group and OM- references ranged from 4 dB HL to 9 dB HL; those between the OM+VT- group and the OM- references were about 2 dB HL. The difference in mean thresholds between the OM+VT+ and the OM+VT- group was significant (p<0.05, Figure 1a). At 8 years of age, a similar pattern was observed for mean air conduction thresholds in the two otitis media groups, OM+VT- and OM+VT+, compared to the reference group. Also at that age, there was a significant difference between the OM+VT+ and the OM+VT- group (p<0.05, Figure 1b).

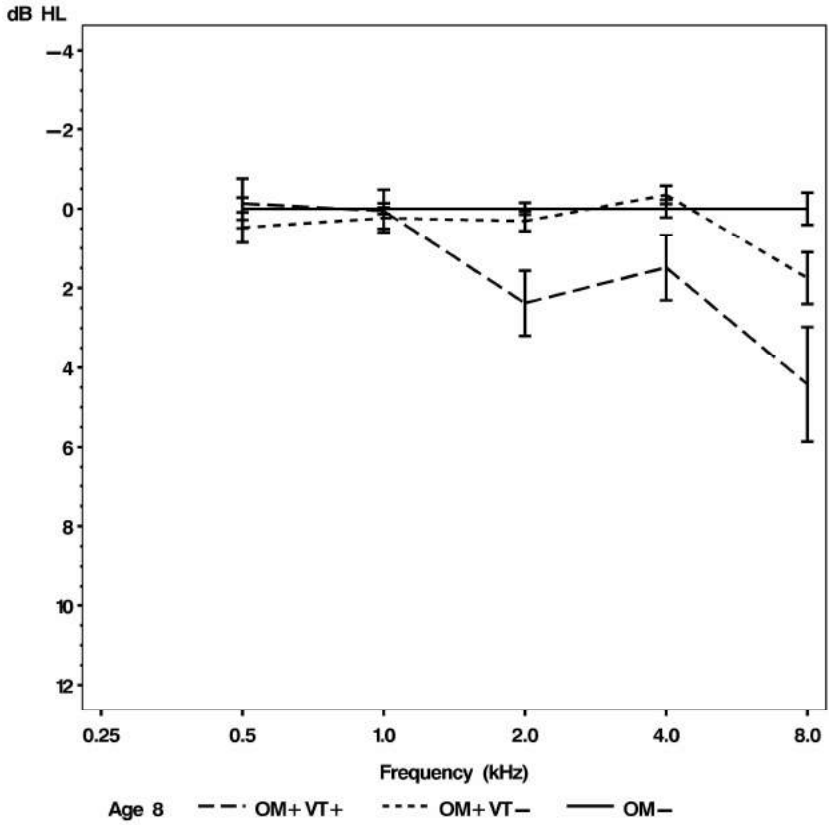
The mean bone conduction thresholds at 18 years of age were also significantly poorer in the OM+VT+ and the OM+VT- group than in the OM- reference group (p<0.05, Figure 2a). Differences between the OM+VT+ group and OM- references ranged from 1 to 4 dB HL; differences between the OM+VT- group and the OM- references were about 1 dB HL. Also here, the difference in thresholds between the OM+VT+ group and the OM+VT- group was significant (p<0.05; 1 to 2.5 dB). The latter significant difference could not be demonstrated at 8 years. However, we found a significant difference in bone conduction thresholds between the OM+VT+ group and the OM- references at 8 years (p<0.05, Figure 2b). At that age, the mean bone conduction thresholds in the OM+VT- group and the OM- group were similar. Figures 2a and 2b represent bone conduction thresholds.

We investigated the individual correlation between mean PTA at 18 years and 8 years within the subjects. The expected effect of ventilation tube insertion on hearing in individuals appeared to be less reproducible than the effect that could be expected at the group level. However, in 75% of the subjects, the difference between the PTA at 18 and 8 years of age was 7 dB HL or less. It has to be emphasized, however, that in individuals a shift of the PTA of more than 7 dB HL in consecutive measurements represents a real deterioration (or improvement), whereas 7 dB HL or less may be the result of measurement errors.[16]

Our statistical analysis with random effect regression models revealed that disease load could not explain the effect of tubes on the mean PTA at 18 years of age. Ears with a history of ventilation tubes had a 3.2 dB HL poorer mean PTA than similar ears without tubes (p<0.001).



2a



2b

Figure 2. Mean bone conduction thresholds of worst ears of OM+VT- and OM+VT+ group relative to the hearing level of the OM- reference group at age 18 years (2a) and 8 years (2b).

The PTA of ears in which ventilation tubes had been inserted more than once was 3.0 dB HL poorer than those that had been treated with tubes only once (p<0.05). There was no correlation between the age of the subject at insertion of the first ventilation tubes and the mean hearing level at 18 years.

Ventilation tubes and tympanic membrane appearance

The presence of tympanic membrane abnormalities at 18 years appeared to be strongly associated with a history of ventilation tube insertion (Table 2). The proportion of tympanic membranes with tympanosclerosis, atrophy, attic retraction, pars tensa retraction or perforation was significantly larger in the OM+VT+ group than in the OM+VT- group. Three out of 4 ears that had been treated by inserting ventilation tubes in childhood showed at least one type of a tympanic membrane abnormality at 18 years. Thirty-seven percent of the ears had different types of tympanic membraneabnormality. Concomitant presence of atrophy and pars tensa retraction was the most frequently observedabnormality.

The mediating role of tympanic membrane appearance in the association between ventilation tubes and hearing sensitivity

Tympanic membrane abnormalities were significantly associated with hearing at 18 years of age; i.e., hearing tended to be worse in ears with tympanosclerosis, atrophy, attic retraction, pars tensa retraction or perforation. The mean PTA was 3.4 dB HL worse in ears with one or more types of tympanic membrane abnormality compared to those with normal tympanic membranes (p<0.001).

Table 2. Prevalence of tympanic membrane abnormalities at age 18 years; n (%)

	OM+VT+	**OM+VT-**	***P* value***	**OM-**
Number of ears	101	258		345
Any tympanic membrane abnormality	76 (75)	46 (18)	<0.001	5 (1)
Tympanosclerosis	65 (64)	23 (9)	<0.001	5 (1)
Atrophy	22 (22)	16 (6)	<0.001	-
Attic retraction	21 (21)	22 (9)	0.002	-
Pars tensa retraction	16 (16)	8 (3)	<0.001	-
Perforation	6 (6)	3 (1)	0.02	-

Abbreviations: OM, otitis media; VT, ventilation tubes; +, positive history; - negative history.
*Comparison between OM+VT+ and OM+VT- ears.

Table 3. Effect of ventilation tubes and tympanic membrane abnormalities on hearing sensitivity.*

Tympanic Membrane Abnormalities	OM+VT+ and TMA+	OM+VT+ and TMA-	OM+VT- and TMA+	OM+VT- and TMA-	P value^ OM+VT vs OM+VT-	P value^ TMA+ vs TMA-
Any TMA	6.8	4.0	5.3	2.5	0.08	<0.001
Tympanosclerosis	6.8	4.8	4.8	2.7	0.02	<0.01
Atrophy	7.9	5.6	5.1	2.8	<0.001	0.02
Attic retraction	9.1	5.2	6.5	2.6	<0.001	<0.001
Pars tensa retraction	8.4	5.7	5.5	2.9	<0.001	0.03
Perforation	11.6	5.8	8.6	2.9	<0.001	<0.001

Abbreviations: OM, otitis media; VT, ventilation tubes; TMA, tympanic membrane abnormalities; +, positive history; - negative history.
* The mean of pure tone average was used. All values are reported in decibel Hearing Level.
^ Comparison between OM+VT+ and OM+VT- or between TMA+ and TMA-.

Table 3 show the mean PTA for combinations of a history of ventilation tube insertion (yes/no) and presence of some type of tympanic membrane abnormality (yes/no).

The combination of a history of ventilation tube insertion and the presence of (some type of) tympanic membrane abnormality affected the mean PTA more seriously than a positive history of ventilation tube insertion or presence of tympanic membrane abnormality alone.

DISCUSSION

This study shows that young adults with a history of otitis media and insertion of ventilation tubes in childhood (OM+VT+) have poorer hearing than those not treated surgically for otitis media (OM+VT-). The difference in air conduction thresholds between the OM+VT+ and the OM+VT- group remained stable over the period between 8 and 18 years of age (Figure 1). In contrast, bone conduction thresholds appeared to deteriorate over time (Figure 2), suggesting an intrinsic progression of cochlear damage after cessation of middle-ear disease and extrusion of ventilation tubes. This phenomenon has not been previously reported in the literature. A plausible explanation is that noxious agents associated with otitis media have the ability to cross the round window membrane[17-19] and may have a protracted influence on the hair cells in the cochlea. We compared our figures to those of the OM- group. There is no doubt that the values reported for

the latter group are the most appropriate references, since our study is focused on the long-term effects of otitis media.

Differences in mean hearing sensitivity between the OM+VT+ and OM+VT- group could not be explained by the disease load of otitis media in childhood. As a consequence it should be concluded that the insertion of ventilation tubes must be responsible for the hearing loss in the OM+VT+ group. Moreover, mean hearing loss increased with the number of ventilation tube insertions. Our results concur with those of previous studies based on a smaller series of subjects and/or shorter follow-up. Daly et al.[20] reported an increased prevalence of hearing loss in adolescents and young adults 9 to 23 years after ventilation tube insertion. They suggested that this hearing loss was progressive. Hunter et al.[21] reported poorer hearing in older children (aged 7-11 years) than in younger children (3-6 years) treated by ventilation tubes. This observation also suggests that the effect of otitis media on hearing thresholds might be progressive. In Hunter's study the older children had mean air conduction thresholds of 3 and 5 dB HL at 0.25 to 4.0 kHz and 8.8 dB HL at 8.0 kHz, which is worse than the thresholds of controls in the same age range. Their figures are similar to ours. Furthermore, similar to our results, they showed that hearing loss is more pronounced at higher frequencies, that is from 3.0 to 8.0 kHz.

Our study confirms that after ventilation tube insertion, tympanic membrane abnormalities are frequently found at long-term follow-up; in this study, it occurs in 75% of the subjects. In the literature, the rates of tympanic membrane abnormalities resulting from ventilation tube insertion were found after long-term follow-up (11-18 years) to vary from 60% to 80%.[5,8,22] Likewise, the proportion of ears with tympanosclerosis, atrophy, attic retraction and pars tensa retraction corresponds with prevalence figures reported by others.[4-9,22] The prevalence of perforation of the tympanic membrane (6%) is higher than expected.[5,6,22]

Because of the high correlation of ventilation tube insertion and tympanic membrane abnormalities on the one hand and the correlation between ventilation tube insertion and hearing loss on the other, we investigated whether the effect of ventilation tube insertion on hearing was mediated by tympanic membrane abnormalities. We found an independent detrimental effect on air conduction thresholds of both tympanic membrane abnormalities and a history of ventilation tube insertion. This meant that tympanic membrane abnormalities were not a prerequisite for the development of hearing deficits at young adult age after ventilation tube insertion in childhood. However, most hearing losses were found in subjects who had a combination of tympanic membrane abnormalities and a history of ventilation tube insertion.

Our study group differs considerably from the series reported previously; our group is unique with respect to its size, small age range, length of follow-up and design. The study group comprises 358 subjects (i.e., 716 ears) from a birth cohort with a prospective follow-up of 18 years. Subjects with a negative and a positive history of otitis media, treated and untreated, underwent standardized examinations at regular intervals. This design allowed us to investigate and document the effects of the disease and the effects of its treatment on hearing separately. While the analyses made adjustments for disease load, it could be questioned whether these adjustments were valid. In view of the fluctuating character of otitis media, repeated measurements are required for a reliable judgment on the degree of the disease load. In our study population, 9 tympanometric measurements of both ears were carried out at 3-month intervals between the subject's second and fourth birthday. This procedure was continued with thorough documentation of the otitis media history before and after that screening. Therefore, we believe that our figures give a reliable representation of the otitis media disease load in childhood.

This study allows us to draw the following conclusions:

1. Treatment of otitis media with ventilation tube insertion in childhood results in an average hearing loss of 4 to 9 dB HL at young adult age (range 0.25 to 8.0 kHz).
2. This hearing loss is more severe in subjects who have had repeated tube insertions.
3. This hearing loss consists of a conductive and a sensorineural component, and the latter may be progressive.
4. Tympanic membrane abnormalities are not necessarily involved but it are frequently prevalent as a mediating factor in the causal chain between ventilation tube insertion in childhood and hearing loss in young adulthood.

REFERENCES

1. Armstrong BW. A new treatment for chronic secretory otitis media. *Arch Otolaryngol* 1954;59:653-654.
2. Schilder AGM. Assessment of complications of the condition and of the treatment of otitis media with effusion. *Int J Pediatr Otorhinolaryngol* 1999;49 Suppl 1:S247-S251.
3. Ben Ami M, Rosen G, Shlezinger T, Konack S, Ben Ami M. Otitis media with effusion--complications after treatment. *J Laryngol Otol* 1983;97:1091-1094.
4. Tos M, Stangerup SE, Larsen P. Dynamics of eardrum changes following secretory otitis. A prospective study. *Arch Otolaryngol Head Neck Surg* 1987;113:380-385.
5. Skinner DW, Lesser TH, Richards SH. A 15 year follow-up of a controlled trial of the use of grommets in glue ear. *Clin Otolaryngol* 1988;13:341-346.

6. Sederberg-Olsen JF, Sederberg-Olsen AE, Jensen AM. Late sequelae related to treatment with ventilation tubes for secretory otitis media in ENT practice. In: Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances in Otitis Media. Proceedings of the 5th International Symposium. Hamilton, Canada: BC Decker Inc, 1993: 843-846.
7. Maw AR, Bawden R. Tympanic membrane atrophy, scarring, atelectasis and attic retraction in persistent, untreated otitis media with effusion and following ventilation tube insertion. *Int J Pediatr Otorhinolaryngol* 1994;30:189-204.
8. Stangerup SE, Tos M, Arnesen R, Larsen P. A cohort study of point prevalence of eardrum pathology in children and teenagers from age 5 to age 16. *Eur Arch Otorhinolaryngol* 1994;251:399-403.
9. Levine SC, Daly KA, Lindgren BR, Giebink GS. Tympanic membrane pathology in adolescents and young adults 12 to 16 years after tympanostomy tube insertion for chronic OME. In: Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances in Otitis Media. Proceedings of the 6th International Symposium. Hamilton, Canada: BC Decker Inc, 1996: 376-379.
10. Riley DN, Herberger S, McBride G, Law K. Myringotomy and ventilation tube insertion: a ten-year follow-up. *J Laryngol Otol* 1997;111:257-261.
11. Hunter LL, Margolis RH, Giebink GS, Schmitz JL, Le Chap T, Daly KA. Long-term prospective study of hearing loss in children after tympanostomy tube treatment of chronic otitis media with effusion. In: Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances in Otitis Media. Proceedings of the 6th International Symposium. Hamilton, Canada: BC Decker Inc, 1996: 383-386.
12. Zielhuis GA, Rach GH, van den Broek P. Screening for otitis media with effusion in preschool children. *Lancet* 1989;1:311-314.
13. Schilder AGM, Zielhuis GA, Haggard MP, van den Broek P. Long-term effects of otitis media with effusion: otomicroscopic findings. *Am J Otol* 1995;16:365-372.
14. Schilder AGM. Long-term effects of otitis media with effusion in children. Nijmegen, the Netherlands: SSN Publishers; 1993.
15. ISO 389. Acoustics. Standard reference zero for the calibration of pure-tone audiometers. Geneva, Switzerland: International Organization of Standardization 1998.
16. Dreschler WA, Plomp R. Relation between psychophysical data and speech perception for hearing-impaired subjects.I. *Journal of the Acoustical Society of America* 1980;68:1608-1615.
17. Huang M, Dulon D, Schacht J. Outer hair cells as potential targets of inflammatory mediators. *Ann Otol Rhinol Laryngol Suppl* 1990;148:35-38.
18. Lim DJ, Kawauchi H, DeMaria TF. Role of middle ear endotoxin in inner ear inflammatory response and hydrops: long-term study. *Ann Otol Rhinol Laryngol Suppl* 1990;148:33-34.
19. Schachern PA, Paparella MM, Goycoolea MV, Duvall AJ, III, Choo YB. The permeability of the round window membrane during otitis media. *Arch Otolaryngol Head Neck Surg* 1987;113:625-629.
20. Daly KA, Hunter LL, Levine SC, Lindgren BR, Giebink GS. Relationships between otitis media sequelae and age. *Laryngoscope* 1998;108:1306-1310.
21. Hunter LL, Margolis RH, Rykken JR, Le CT, Daly KA, Giebink GS. High frequency hearing loss associated with otitis media. *Ear Hear* 1996;17:1-11.
22. Larsen P, Tos M, Stangerup SE. Progression of drum pathology following secretory otitis media. In: Lim D, Bluestone CD, Klein J, Nelson J.D., eds. Recent Advances in Otitis Media. Proceedings of the 4th International Symposium. Toronto, Canada: B.C. Decker Inc, 1987: 34-38.

3

Natural course of tympanic membrane pathology related to otitis media and ventilation tubes between ages 8 and 18 years

B.A. de Beer
A.G.M. Schilder
G.A. Zielhuis
K. Graamans

Otology & Neurotology 2005; 26: 1016-1021

ABSTRACT

Objective: To present the course of tympanic membrane pathology in childhood and young adulthood following otitis media in early life.

Study design: Prospective follow-up study.

Setting: Community study of a birth cohort.

Patients: 358 subjects with a positive and negative history of otitis media (OM+ or OM-) and/or ventilation tube insertion (VT+ or VT-) derived from a birth cohort that had been followed from preschool to adult age.

Methods: Standardized otomicroscopic examination performed at ages 8 and 18 years.

Main outcome measures: Tympanic membrane abnormalities, i.e. tympano-sclerosis, atrophy, atelectasis and retraction pockets of the pars tensa and retraction of the pars flaccida.

Results: At the age of 8 years, tympanic membrane abnormalities was highly prevalent in the both otitis media positive sub cohorts (OM+VT+, 92% and OM+VT-, 46%), while in the OM negative ears (11%) tympanic membrane abnormalities were rare. In the subsequent ten-year period many tympanic membrane abnormalities disappeared spontaneously, although the prevalence of tympanosclerosis remained substantial in the OM+VT+ cohort.

Conclusion: The natural course of most tympanic membrane abnormalities associated with otitis media in early life is favorable over time, suggesting an intrinsic repair capacity of the tympanic membrane. Tympanosclerosis, the most prevalent sequelae of otitis media and treatment with ventilation tubes, however, shows little tendency of resolution.

INTRODUCTION

Structural changes of the tympanic membrane have been reported as a consequence of otitis media experienced early in life.[1-3] Because otitis media is often managed with ventilation tubes, such tympanic membrane pathology may result from both the disease and its treatment. Potential abnormalities affecting the tympanic membrane include tympanosclerosis, atrophy, retraction, atelectasis and perforation of the pars tensa, and retraction of the pars flaccida. Some of these become apparent only after extrusion of the ventilation tube. Tympanosclerosis seems to be particularly related to tube insertion,[4] whereas the other types of eardrum pathology occur in (formerly) tubed as well as non-tubed ears.[5] Little is known about how these abnormalities of the tympanic membrane evolve in time and how they affect middle ear function and hearing later in life.

The aim of the present study is to document tympanic membrane pathology in a birth cohort that has been followed from ages 2 to 18 years.[6-8] Repeated otomicroscopy and careful documentation of ventilation tube insertions over these years allowed us to study both the dynamics of these abnormalities as well as to separate the effects of otitis media from those of its treatment.

POPULATION AND METHODS

Subjects

This study involved 358 individuals (716 ears) selected from a birth cohort followed from the age of 2 years.[6-8] At that age a detailed history regarding otitis media (and its treatment) in the first two years of life was taken. Between the ages of 2 to 4 years a tympanogram was made every three months. At the age of 8 years otomicroscopy was performed and the occurrence and treatment of otitis media between 4 and 8 years of age was documented. Parental information was checked in the medical records of these individuals.[7,9] For details on numbers of participants and examinations see Figure 1.

For the purpose of selection of subjects for the present study a cumulative otitis media (OM) score was calculated for each subject. Details on this score have been reported previously.[10] In short, the OM score was based on the documented number of episodes of either otitis media with effusion (OME; diagnosed by tympanometry) or acute otitis media (AOM; parental report) experienced from birth to 8 years of age. The sum of the OME score and the AOM score formed the OM score. Out of the subjects still living in Nijmegen and of whom a complete OM score could be calculated, the subjects in the highest and lowest third part of the OM score (n=528) formed the (sub)cohorts of subjects characterized as having

either a positive (OM+) or a negative (OM-) otitis media history. Of these about 400 subjects were contacted in order to achieve the first sample of 358 (183 OM+ and 175 OM-) who agreed to participate in the present follow-up study at age 18 years. Non-participants had similar childhood characteristics as participants. The OM+ cohort was then categorized into subjects treated with ventilation tubes (OM+VT+, n=51) and subjects managed non-surgically (OM+VT-, n=132). In numbers of ears that is: 102 OM+VT+, 264 OM+VT-, and 350 OM-.

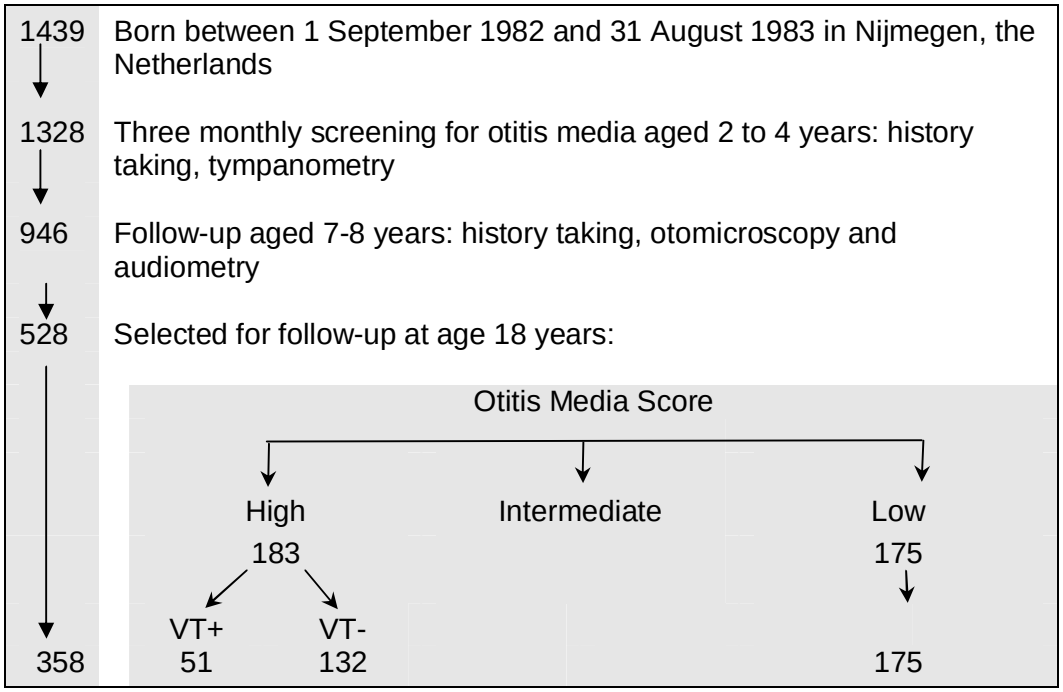


Figure 1. Composition of study population. All numbers represent numbers of subjects. Abbreviations: VT, ventilation tubes; +, positive history; -, negative history.

Because the study was observational in design subjects were treated for otitis media according current guidelines (Dutch GP and ORL guidelines). It was expected that the subjects treated with ventilation tubes had more serious disease compared to subjects not surgically treated. In fact, with a created disease load score, this was not confirmed.[10] Both groups, OM+VT+ and OM+VT-, had comparable disease load. To compare the appearance of the tympanic membrane at 18 and 8 years we decided that ears had to be free of OME, AOM, otorrhea and ventilation tubes at both ages. All but 4 ears was due to pathology at 8 years. This left 59 OM+VT+ ears and 224 OM+VT- ears available for analysis.

Approval for the study was obtained from the Ethics Committee of the University Medical Center Nijmegen; the participants signed for informed consent.

Outcome measurements

Otomicroscopy at 18 years of age was performed by the first author (B.B.) in all subjects. Tympanic membrane abnormalities were documented according to the same classification as used by the second author (A.S.) at age 7-8 years.[7] The pars tensa of tympanic membrane was divided into three parts; for each of these parts the presence or absence of tympanosclerosis, atrophy, atelectasis, retraction pocket or perforation was recorded. The severity of the pars tensa conditions referred to the number of affected third parts. For grading of retraction or atelectasis of the pars tensa Sadé's classification was used.[11] Pars flaccida retraction was classified according to Tos[12] in grades 0 (no retraction) to 4 (erosion of the bony annulus and retraction may extend to the head of the malleus).

RESULTS

The prevalence of tympanic membrane pathology was high in OM+ ears at 8 years of age: 92% in OM+VT+ ears and 46% in OM+VT- ears. At 18 years of age, prevalences had dropped to 72% in OM+VT+ ears and to17% in OM+VT- ears. In ears with a negative history of otitis media tympanic membrane pathology was rare at 18 years of age (1%); ten years earlier the prevalence was 11%.

Figures 2 to 7 show prevalences of specific abnormalities at 8 and 18 years of age for each of the three sub cohorts (OM+VT+, OM+VT- and OM- ears). Table 1 shows, for OM+VT+ and OM+VT- ears separately, the prevalence and degree of concordance at ages 8 and 18 years for each of the specific tympanic membrane abnormalities and thus provide information about the probability of persistence or recovery of these conditions.

Tympanosclerosis was the most persistent tympanic membrane abnormality, afflicting 56% of OM+VT+ ears and 9% of OM+VT- ears at 18 years of age. In the OM- ears tympanosclerosis was rare (1% at ages 8 and 18 years). The high percentages of persistence on an individual level are illustrated in Table 1. One in three formerly tubed ears developed tympanosclerosis after having been free of tympanosclerosis at 8 years of age.

Prevalence of *atrophy* decreased from ages 8 to 18 years, particularly in OM+VT+ ears (from 63% to 20%). On an individual level, atrophy had persisted at age 18 years in one in four OM+VT+ ears, compared to one in seven OM+VT- ears.

Table 1. Concordance of tympanic membrane abnormality at ages 8 and 18 years in ears of treated and untreated subjects

Subject Age at Measurement, y		Change in Tympanic Membrane Abnormality from Age 8 to 18 y, n (%)	
8	**18**	**OM+VT+**	**OM+VT-**
		Tympanosclerosis	
+	+	25 (71)	8 (67)
+	-	10 (29)	4 (33)
-	+	8 (33)	12 (6)
-	-	16 (67)	200 (94)
		Atrophy	
+	+	9 (24)	8 (13)
+	-	28 (76)	54 (87)
-	+	3 (14)	7 (4)
-	-	19 (86)	155 (98)
		Atelectasis	
+	+	3 (15)	4 (8)
+	-	17 (85)	44 (92)
-	+	1 (3)	3 (2)
-	-	38 (97)	173 (98)
		Retraction pocket	
+	+	NA	NA
+	-	2 (100)	NA
-	+	3 (5)	1 (0.4)
-	-	54 (95)	223 (99.6)
		Retraction pars flaccida	
+	+	12 (35)	8 (11)
+	-	22 (65)	66 (89)
-	+	NA	9 (6)
-	-	25 (100)	144 (94)
		Perforation	
+	+	1 (50)	NA
+	-	1 (50)	NA
-	+	3 (5)	3 (1)
-	-	54 (95)	221 (99)

Abbreviations: OM, otitis media; VT, ventilation tubes; +, positive history; - negative history; NA, not applicable.

Atelectasis was frequently observed at 8-year evaluation: in 34% of OM+VT+ ears and 21% of OM+VT- ears. In most ears atelectasis disappeared between ages 8 and 18 years; at 18 years of age it was found in only 7% of OM+VT+ ears and 3% of OM+VT- ears. At age 8 years atelectasis was even observed in the OM- ears (4%). Table 1 shows that atelectasis rarely developed after the age of 8 years.

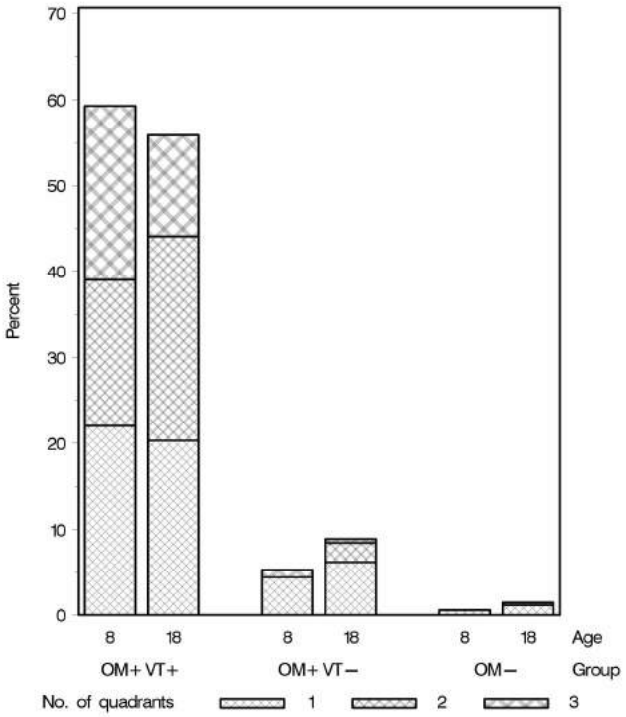


Figure 2: Tympanosclerose

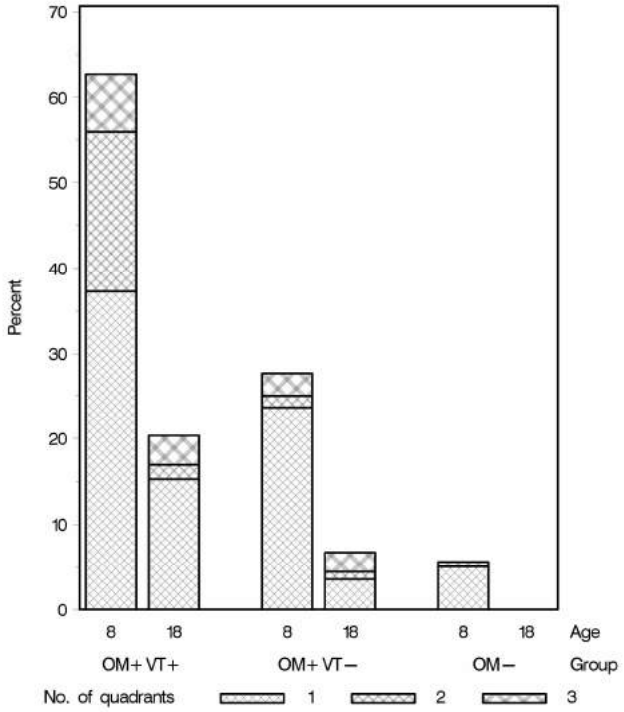


Figure 3: Atrophy

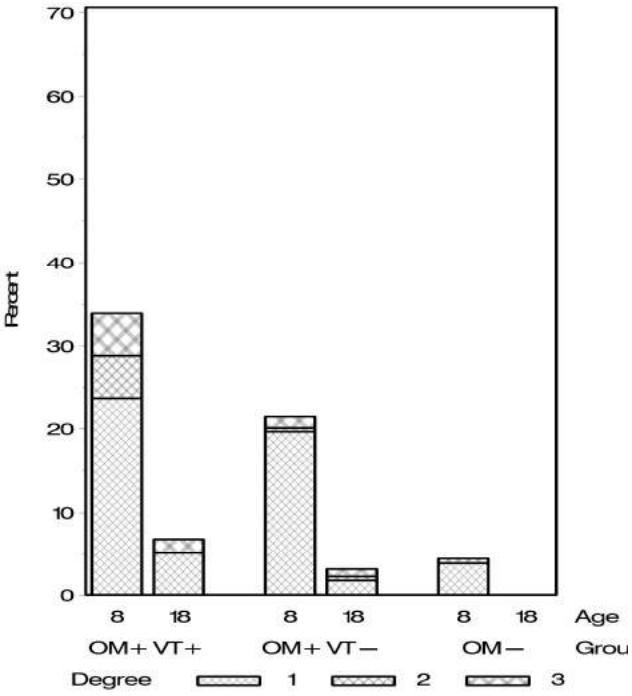


Figure 4: Atelectasis

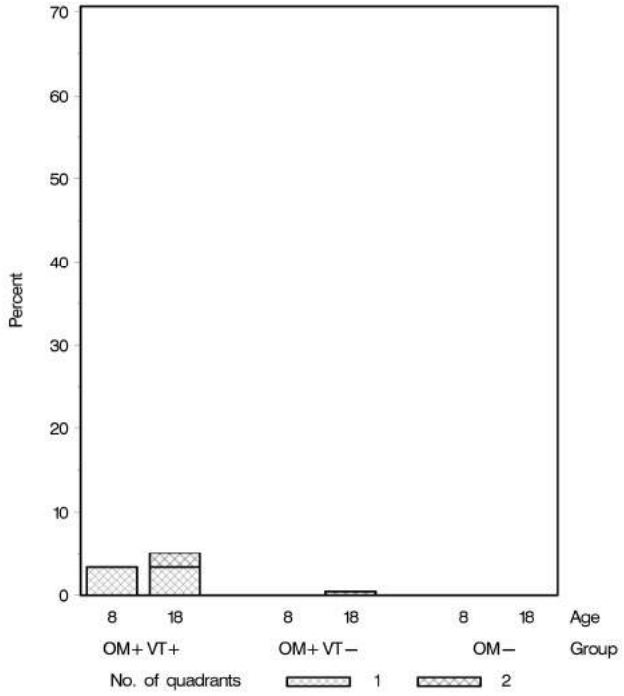


Figure 5: Retraction pocket

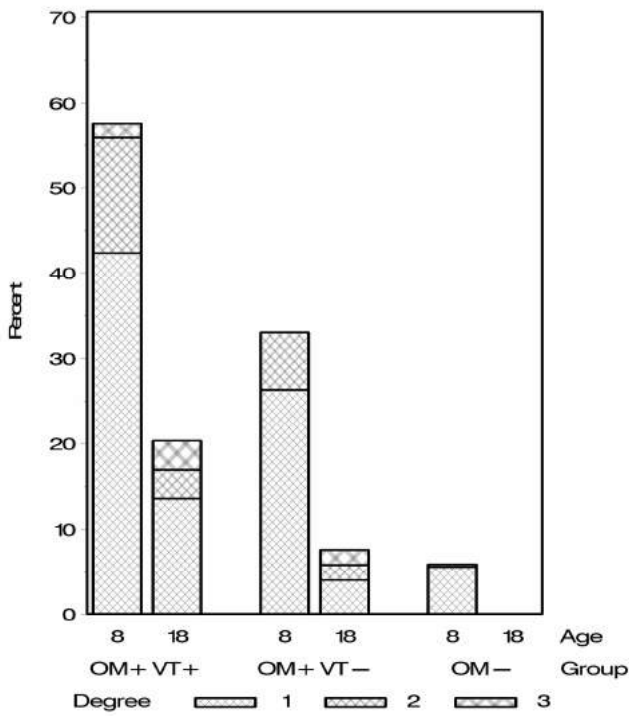


Figure 6: Retraction pars flaccida

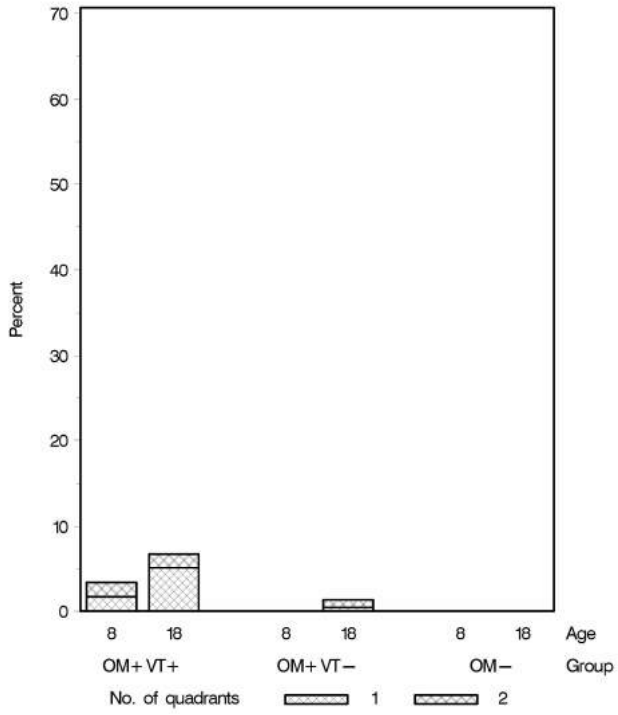


Figure 7: Perforation

Figures 2-7. Histograms of specific types of tympanic membrane abnormalities. Number of affected pars tensa quadrants for tympanosclerosis, atrophy, retraction pocket and perforation. Degree of severity for atelectasis (Sadé classification) and retraction of the pars flaccida (Tos classification). Abbreviations: OM, otitis media; VT, ventilation tubes; TMA, tympanic membrane abnormalities; +, positive history; - negative history.

Localized *retraction pockets* of the pars tensa were infrequent both at 8 and at 18 years of age: 3% and 5% in OM+VT+ and <1% in OM+VT- ears, respectively. Remarkably, all ears showing a retraction pocket at 8 years of age had healed by the age of 18 years, while some new cases had formed between 8 and 18 years of age.

Prevalences of *retraction of the pars flaccida* decreased from 48% and 33% in the OM+VT+ and OM+VT- ears at 8 years of age to 20% and 8% at 18 years of age. In the OM- ears retraction of the pars flaccida was observed in 6% at age 8 years; at age 18 years all these had resolved. Table 1 shows that attic retraction persisted in one out of three OM+VT+ ears and in one out of nine OM+VT- ears.

Perforations of the tympanic membrane were very rare. Table 1 shows that in one ear the perforation had healed spontaneously between ages 8 and 18 years, while

in another OM+VT+ ear the perforation had persisted. In three ears of the OM+VT- sub cohort, a perforation had developed between 8 and 18 years.

One OM+VT- ear had been treated for *cholesteatoma* between 8 and 18 years, no other cases of cholesteatoma were observed.

DISCUSSION

This is the first prospective follow-up study on tympanic membrane pathology related to otitis media covering the period from preschool to adult age. Although tympanic membrane abnormalities were common at the age of 8 years in both subcohorts with a positive otitis media history, i.e. children treated with ventilation tubes (OM+VT+; 92%) and those managed non-surgically (OM+VT-; 46%), many resolved in the period between ages 8 and 18 years (prevalences 71% and 17%, respectively). In the ears of subjects that had not experienced otitis media in childhood, the prevalence of tympanic membrane abnormalities was low both at 8 (11%) and at 18 years of age (2%). Only one ear developed cholesteatoma (i.e. 0.005%) of those with otitis media in childhood. Development of new tympanic membrane abnormalities in the period between 8 and 18 years of age was rare, although more common in the OM+VT+ than in the OM+VT- cohort. Tympanosclerosis was the most persistent tympanic membrane abnormality and observed predominantly in the OM+VT+ ears (56%). Ears that were excluded because of OME, AOM, otorrhea and/or ventilation tubes present at time of one of the evaluations at 8 or 18 years, showed the same tendency of repair of tympanic membrane abnormalities. However, the prevalence of tympanosclerosis at 18 years of age was higher than in the ears included in the present study (68% versus 56%), as was the persistence rate on the individual level (87% versus 71%).

Previous studies have also shown that tympanic membrane abnormalities is related to otitis media experienced earlier in life, especially in ears treated with ventilation tubes.[5,13-16] Accordingly the tendency of tympanosclerosis to persist has been demonstrated before.[15,17-20] The present study shows that, except for tympanosclerosis, most pars tensa abnormalities and retraction of the pars flaccida resolve in the period between 8 and 18 years of age. Most likely the tympanic membrane is capable of repair itself over time, after otitis media has resolved and/or ventilation tubes have been extruded. Maturation of the middle ear system and the consequent improvement of ventilation could also contribute to the reversibility of tympanic membrane abnormalities.

With regard to atrophy it is not yet clear whether this is a reversible condition. We found a decline in the prevalence of atrophy over the period from 8 to 18 years of age. Several studies, however, have reported an increasing prevalence of atrophy with age.[5,14,15,21,22] Skinner et al.[15] have reported an increase in the prevalence of atrophy in formerly tubed ears as well as non-tubed ears 5 and 15 years after surgical treatment or non-surgical treatment. Likewise, Sederberg-Olsen et al.[3,22] observed an increase in the prevalence of atrophy 7,5 and 12 years after treatment with ventilation tubes, although it should be emphasized that their data concern the combined prevalence of atrophy and/or incudopexy. In our study, the latter was defined as a degree of atelectasis and therefore the two studies are difficult to compare. The groups of subjects followed by Stangerup et al.[14] and Maw and Bawden[5] diverge over the course of time: the number of subjects in follow-up decreased annually, possibly leaving only severe cases to complete full follow-up periods. Another explanation for the conflicting results of our and previous studies could be differences in definition, and the fact that atrophy, out of all pathologic tympanic membrane conditions, seems to be most susceptible to interobserver variation and misclassification during otomicroscopic assessment.
It should be emphasized that although most tympanic membrane abnormalities are mild in nature, associated with marginal hearing loss on the individual level,[4,23,24] such effects may have substantial impact on hearing acuity at the population level.[10]
The strength of this study is its prospective design with subjects selected from a birth cohort. The history of otitis media in early childhood was carefully documented without any bias towards group classification and/or extension at later age. Since only part of the subjects with otitis media were treated with ventilation tubes, the effects of otitis media itself could be separated from the effects of its treatment.

We conclude that the natural course of most tympanic membrane abnormalities associated with otitis media in early life is favorable over time, suggesting an intrinsic repair capacity of the tympanic membrane. Tympanosclerosis, the most prevalent sequelae of OM and treatment with ventilation tubes, however, shows little tendency of repair.

REFERENCES

1. Ben Ami M, Rosen G, Shlezinger T, Konack S, Ben Ami M. Otitis media with effusion--complications after treatment. *J Laryngol Otol* 1983;97:1091-1094.
2. Tos M, Stangerup SE, Holm-Jensen S, Sorensen CH. Spontaneous course of secretory otitis and changes of the eardrum. *Arch Otolaryngol* 1984;110:281-289.
3. Sederberg-Olsen JF, Sederberg-Olsen AE, Jensen AM. Late results of treatment with ventilation tubes for secretory otitis media in ENT practice. *Acta Otolaryngol* 1989;108:448-455.
4. Tos M, Stangerup SE. Hearing loss in tympanosclerosis caused by grommets. *Arch Otolaryngol Head Neck Surg* 1989;115:931-935.
5. Maw AR, Bawden R. Tympanic membrane atrophy, scarring, atelectasis and attic retraction in persistent, untreated otitis media with effusion and following ventilation tube insertion. *Int J Pediatr Otorhinolaryngol* 1994;30:189-204.
6. Zielhuis GA, Rach GH, van den Broek P. Screening for otitis media with effusion in preschool children. *Lancet* 1989;1:311-314.
7. Schilder AGM, Zielhuis GA, Haggard MP, van den Broek P. Long-term effects of otitis media with effusion: otomicroscopic findings. *Am J Otol* 1995;16:365-372.
8. de Beer BA, Graamans K, Snik AF, Ingels K, Zielhuis GA. Hearing deficits in young adults who had a history of otitis media in childhood: use of personal stereos had no effect on hearing. *Pediatrics* 2003;111:e304-e308.
9. Schilder AGM. Long-term effects of otitis media with effusion in children. Nijmegen, the Netherlands: SSN Publishers: 1993.
10. de Beer BA, Schilder AG, Ingels K, Snik AF, Zielhuis GA, Graamans K. Hearing loss in young adults who had ventilation tube insertion in childhood. *Ann Otol Rhinol Laryngol* 2004;113:438-444.
11. Sade J, Berco E. Atelectasis and secretory otitis media. *Ann Otol Rhinol Laryngol* 1976;85:66-72.
12. Tos M, Poulsen G. Attic retractions following secretory otitis. *Acta Otolaryngol* 1980;89:479-486.
13. Ryding M, White P, Kalm O. Eustachian tube function and tympanic membrane findings after chronic secretory otitis media. *Int J Pediatr Otorhinolaryngol* 2004;68:197-204.
14. Stangerup SE, Tos M, Arnesen R, Larsen P. A cohort study of point prevalence of eardrum pathology in children and teenagers from age 5 to age 16. *Eur Arch Otorhinolaryngol* 1994;251:399-403.
15. Skinner DW, Lesser TH, Richards SH. A 15 year follow-up of a controlled trial of the use of grommets in glue ear. *Clin Otolaryngol* 1988;13:341-346.
16. Larsen P, Tos M, Stangerup SE. Progression of drum pathology following secretory otitis media. In Lim D, Bluestone CD, Klein J, Nelson JD eds. Recent Advances in Otitis Media. Proceedings of the 4th International Symposium. Toronto, Canada: B.C. Decker Inc, 1987: 34-38.
17. Rosenfeld RM, Isaacson G.C. Tympanotomy Tube Care and Consequences. In Rosenfeld RM, Bluestone CD, eds. Evidence Based Otitis Media 2nd edition. Hamilton, Canada: B.C. Decker Inc; 2003: 460-481.
18. Daly KA, Hunter LL, Levine SC, Lindgren BR, Giebink GS. Relationships between otitis media sequelae and age. *Laryngoscope* 1998;108:1306-1310.
19. Maw AR. Development of tympanosclerosis in children with otitis media with effusion and ventilation tubes. *J Laryngol Otol* 1991;105:614-617.
20. Tos M, Stangerup SE, Larsen P. Dynamics of eardrum changes following secretory otitis. A prospective study. *Arch Otolaryngol Head Neck Surg* 1987;113:380-385.
21. Levine SC, Daly KA, Lindgren BR, Giebink GS. Tympanic membrane pathology in adolescents and young adults 12 to 16 years after tympanostomy tube insertion for chronic OME. In Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances in Otitis Media. Proceedings of the 6th International Symposium. Hamilton, Canada: BC Decker Inc, 1996: 376-379.
22. Sederberg-Olsen JF, Sederberg-Olsen AE, Jensen AM. Late sequelae related to treatment with ventilation tubes for secretory otitis media in ENT practice. In Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances in Otitis Media. Proceedings of the 5th International Symposium. Hamilton, Canada: BC Decker Inc, 1993: 843-846.

23. Hunter LL, Margolis RH. Effects of tympanic membrane abnormalities on auditory function. *J Am Acad Audiol* 1997;8:431-446.
24. Stenstrom RJ, Bernard PAM, Feldman W, Durieux-Smith A, Pless IB, Beauregard Y. Long-term sequelae of ventilation tube insertion for the treatment of otitis media with effusion and recurrent acute otitis media. In Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances of Otitis Media. Proceedings of the 6th International Symposium. Hamilton, Canada: BC Decker Inc, 1996: 373-375.

4

The effect of otitis media in childhood on the development of middle ear admittance upon reaching adulthood

B.A. de Beer
A.F.M. Snik
A.G.M. Schilder
K. Graamans
G.A. Zielhuis

Archives of Otolaryngology Head and Neck Surgery 2005; 131: 777-781

ABSTRACT

Objective: To determine the long-term change in static admittance after a positive or negative history of otitis media and ventilation tube insertion; and to investigate the association between static admittance and tympanic membrane abnormalities.
Design: Prospective follow-up study.

Subjects: A total of 358 subjects with or without a history of otitis media (OM+ or OM-) and ventilation tube insertion (VT+ or VT-) derived from a birth cohort that had been observed from preschool to adult age.
Main outcome measures: Otomicroscopic and tympanometric data obtained at subject ages 8 and 18 years.

Results: Static admittance values generally increased with age. At 8 years of age static admittance was highest in OM+VT+ ears and lowest in OM- ears. At 18 years of age the difference between OM+VT+ and OM+VT- ears was larger, while the difference in static admittance between OM+VT- and OM- ears had disappeared. In the group of OM+VT+ subjects the proportion of extreme static admittance values increased from 16% to 35% between age 8 and 18. Correlations of individual static admittance values at 8 and 18 years were high in all groups and ranged from 0.61 to 0.85. We could not demonstrate an intermediate role of tympanic membrane abnormalities in the relation between ventilation tubes and static admittance at young adult age, except for atrophy.

Conclusion: The static admittance value at age 8 years was a strong predictor for the value at age 18 years. A OM+VT+ status was associated with a larger increase in static admittance than can be expected on the basis of age alone.

INTRODUCTION

Acoustic middle ear admittance, as assessed by tympanometry, is a measure of the ease with which acoustic energy flows into the middle ear. Usually, this is assessed with a probe tone of 226 Hz; at this frequency the admittance is dominated by stiffness of the middle ear system.[1] Although incorrect, the term *compliance* has been used interchangeably with admittance. An obvious example of a condition leading to values above the reference range of admittance is discontinuity of the ossicles; an example of a condition associated with values below the reference range is otitis media with effusion. Tympanic membrane abnormalities also seem to affect admittance. While atrophy is associated with increased admittance[2], tympanosclerosis tends to be associated with decreased middle ear admittance.[3]

Gaihede et al.[3] compared static admittance values of ears with and without a history of ventilation tubes. More tympanic membrane pathology was observed in previously tubed ears, but the static admittance values were normal. The reason might be that tympanosclerosis and atrophy in previously tubed ears have opposite effects on static admittance.

It is not yet known how static admittance develops over time in subjects who had otitis media as children, whether it was treated with ventilation tubes or left untreated. Tympanic membrane abnormalities seem to be dynamic in that atrophy tends to increase over time.[4-8] Tympanosclerosis, however, tends to be a more stable condition after the extrusion of ventilation tubes.[8-11] The objective of this study is to report on the dynamics of static admittance and to study the association between static admittance and tympanic membrane abnormalities. A birth cohort that had been followed with repeated otomicroscopy and tympanometry from the age of 2 years was an ideal study population for a follow-up examination at age 18 years.

Four questions are addressed in this study:

1. Are the observed differences in static admittance related to otitis media and/or ventilation tube insertion in childhood?
2. How does static admittance at age 8 years correlate with that at age 18 years?
3. Are the higher static admittance values found for ears with a history of otitis media associated with tympanic membrane abnormalities?
4. Are changes in static admittance between age 8 and 18 associated with changes in tympanic membrane pathology over that same period?

POPULATION AND METHODS

Subjects

This study is based on data derived from 358 individuals (716 ears) who were selected from a birth cohort that had been followed since the age of 2 years.[12-14] At that age a detailed history regarding otitis media (and its treatment) in the first 2 years of life was recorded. Between the ages of 2 to 4 years, a tympanogram was made every 3 months. At the age of 8 years, otomicroscopy was performed, and the occurrence and treatment of otitis media between 4 and 8 years of age were documented. Parental information was checked in the medical records of these individuals.[13,15] Figure 1 graphically illustrates details about this cohort.

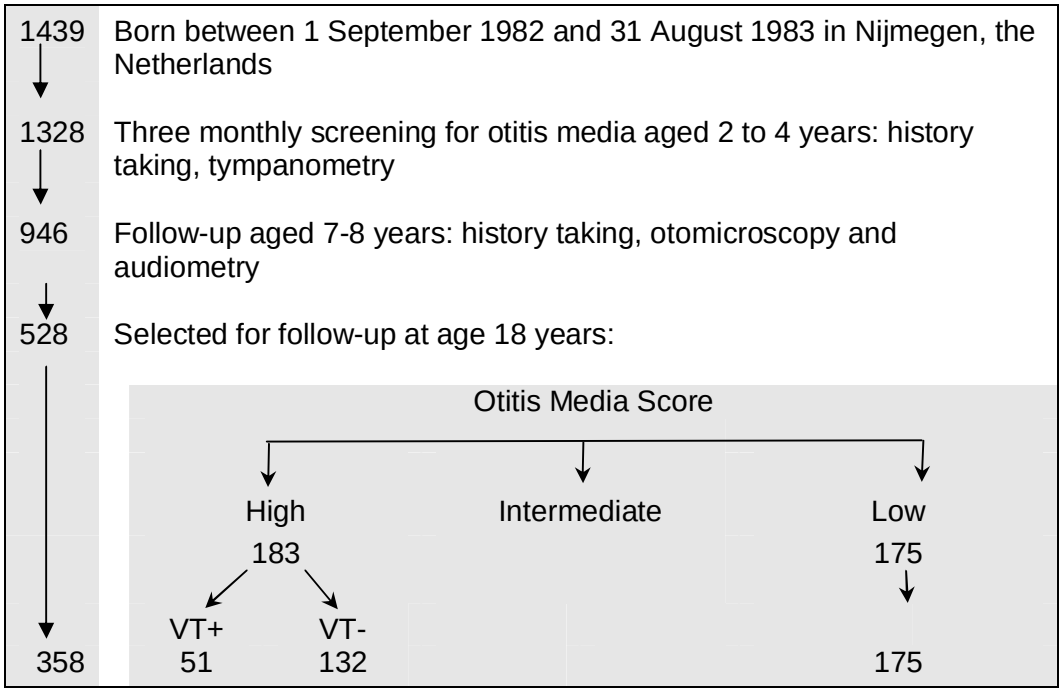


Figure 1. Composition of study population. All numbers represent numbers of subjects. Abbreviations: VT, ventilation tubes; +, positive history; -, negative history.

To select the subjects for the present study, a cumulative otitis media (OM) score was calculated for each individual. Details on calculating this score have been reported previously.[16] In short, the OM score is based on the documented number of episodes of either otitis media with effusion (OME; diagnosed by tympanometry) or acute otitis media (AOM; parental report) experienced from birth to 8 years of age. The sum of the OME score and the AOM score forms the OM score. The subjects in the highest and lowest third of the OM score (n=528) form the groups with either a positive (OM+) or a negative (OM-) history of otitis media. Of

these 528 subjects, 358 (183 OM+ and 175 OM-) agreed to participate in the present follow-up study at age 18 years. The OM+ group was then divided into subjects who had been treated with ventilation tubes (OM+VT+, n=51) and subjects who had been managed non-surgically (OM+VT-, n=132). In terms of the number of ears, that is 102 OM+VT+, 264 OM+VT-, and 350 OM-.
To compare middle ear admittance at age 8 and 18 years, ears with OME, AOM, otorrhea, perforations, or ventilation tubes at the time of either examination were excluded from the analyses. As a result, this part of the study included 54 OM+VT+ ears of 31 subjects, 224 OM+VT- ears of 119 subjects, and 342 OM- ears of 172 subjects.
Approval for the study was obtained from the Ethics Committee of the University Medical Center Nijmegen; the participants signed for informed consent.

Outcome measurements

The first author (B.B.) performed otomicroscopy and tympanometry in all subjects at age 18 years. At that time, tympanic membrane abnormalities were documented according to the same classification that the third author (A.S.) had used to study these subjects when they were between 7 and 8 years old.[13] Pars tensa pathologic features such as tympanosclerosis, atrophy, atelectasis, retraction pocket, perforation, and pars flaccida retraction were recorded. At age 18, tympanometry was performed with a Tymp87 Middle Ear Analyzer (Danplex, Copenhagen, Denmark), whereas at age 8 it was performed with a GSI-27 Middle Ear Analyzer (Grason Stadler Inc., Madison, Wisconsin). With both tympanometers, a 226 Hz probe tone and a pump speed of 200 daPa/sec were applied. The measure of interest for this study was static admittance expressed in cubic centimeters. The static admittance value is defined as the peak admittance value (when pressure on both sides of the tympanic membrane is equal) minus the admittance value of the ear canal at +200 daPa (at the start of tympanometry when the tympanic membrane is stiffened).[17]
To account for the interdependence of the two ears in one subject, either the mean of both ears was calculated, or both ears were included in a fixed effect regression model. The contribution of tympanic membrane abnormalities to the variation in static admittance was analyzed by comparing multiple regression models with and without explanatory variables. All analyses were performed using SAS statistical software (version 6.12; SAS, Cary, North Carolina).

Table 1. Distribution of static admittance values*

Subject Age at Measurement	Subjects No.	5th Percentile	Median	95th Percentile
8				
OM+VT+	31	0.4	0.7	1.9
OM+VT-	119	0.2	0.5	1.8
OM-	172	0.3	0.6	1.3
18				
OM+VT+	49	0.5	1.2	2.8
OM+VT-	131	0.2	0.7	2.0
OM-	174	0.4	0.7	1.7

Abbreviations: OM, otitis media; VT, ventilation tubes; +, positive history; - negative history.
* The mean of both ears of each subject was used. All static admittance values are reported in cubic centimeters.

RESULTS

Distributions of static admittance for the study groups at ages 8 and 18 years are listed in Table 1. At age 8 years, the median static admittance values were 0.7 cm^3 in OM+VT+ ears, 0.5 cm^3 in OM+VT-, and 0.6 cm^3 in OM- ears. There were small but statistically significant differences in 90% ranges (from the 5^{th} to the 95^{th} percentile) between the OM+VT+ and OM+VT- groups and between the OM+VT- and OM- groups (Wilcoxon, $p<0.05$). At age 18 years, the median static admittance values were 1.2 cm^3 in OM+VT+ ears, 0.7 cm^3 in OM+VT- ears, and 0.7 cm^3 in OM- ears. Apparently, the difference in static admittance between OM+VT+ and OM+VT- ears had become larger, while the difference in static admittance between OM+VT- and OM- ears had disappeared by the time the subjects reached age 18 years.

In general, static admittance values increased with age. Extreme values can be separated from normal values by using an age-specific reference, namely the 95^{th} percentile static admittance value of the OM- ears. The extreme values at age 8 years were defined as values above 1.3 cm^3. Accordingly, 9% of the OM+VT- ears and 16% of the OM+VT+ ears had extreme static admittance values. At age 18 years, 11% of the OM+VT- ears and 35% of the OM+VT+ ears had an extreme static admittance value above the 95^{th} percentile of the reference group, i.e. a value above 1.7 cm^3.

Figures 2 to 4 are scatter plots of the (log-transformed) individual static admittance values at ages 8 and 18 for the OM+VT+, OM+VT- and OM- ears,

respectively. The diagrams show that static admittance values at ages 8 and 18 years were very well correlated for all study groups. The correlation coefficient for OM+VT+ ears was 0.61. For the OM+VT- and OM- groups, the correlation coefficients were even higher: 0.83 and 0.85 respectively.

Tympanic membrane abnormalities are strongly associated with otitis media, and some abnormalities seem to be the direct result of previous ventilation tube insertions. We therefore investigated the contribution of tympanic membrane abnormalities to static admittance at age 18 years in the whole otitis media study group (OM+VT+ and OM+VT- combined) using multiple linear regression models. Tympanosclerosis, atrophy, atelectasis, retraction, and retraction of the pars flaccida were all included in this model as covariates. They were used to test the hypothesis that tympanic membrane abnormalities of whatever nature explain the effect of previous ventilation tube insertion on static admittance at age 18 years. Comparison of two models (not shown), one with and one without these tympanic membrane abnormalities, by no means supported this hypothesis. The effect of previous ventilation tube insertion remained unchanged after introducing tympanic membrane abnormalities into this model. Of the latter, only atrophy contributed significantly to the model.

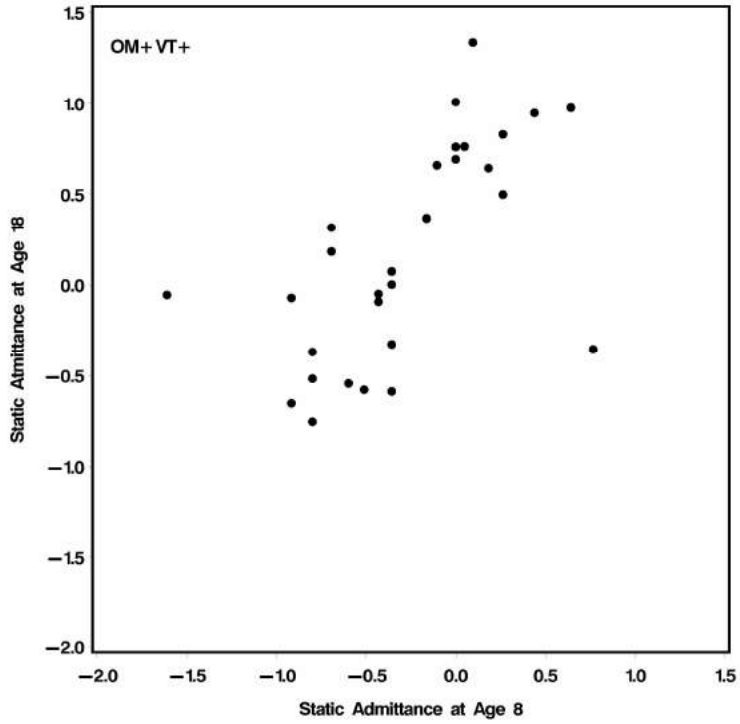


Figure 2. Association of static admittance values at ages 8 and 18 years for ears with a history of both otitis media and insertion of ventilation tubes. All static admittance values are reported in cubic meters. The mean values of both ears of a subject have been log transformed.

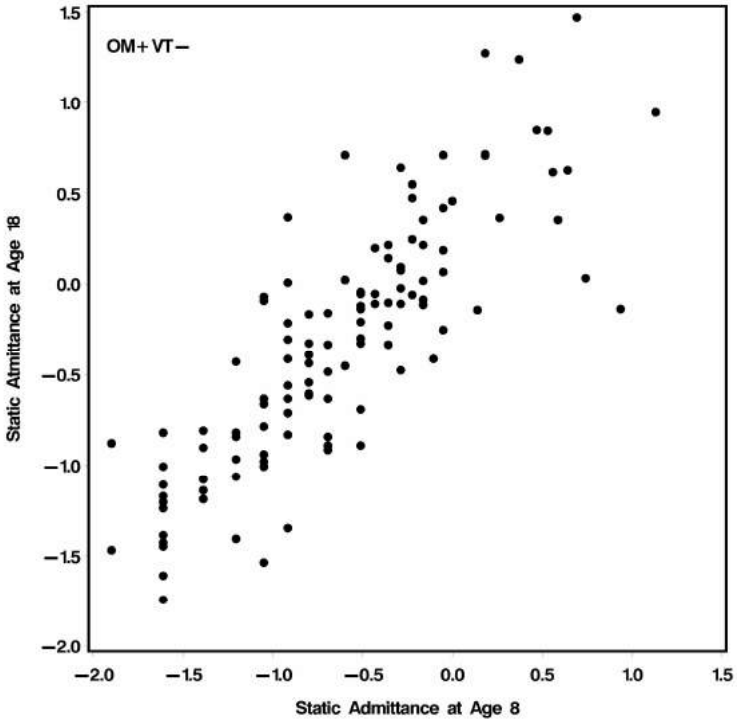


Figure 3. Association of static admittance values at ages 8 and 18 years for ears with a history of otitis media but no insertion of ventilation tubes. All static admittance values are reported in cubic meters. The mean values of both ears of a subject have been log transformed.

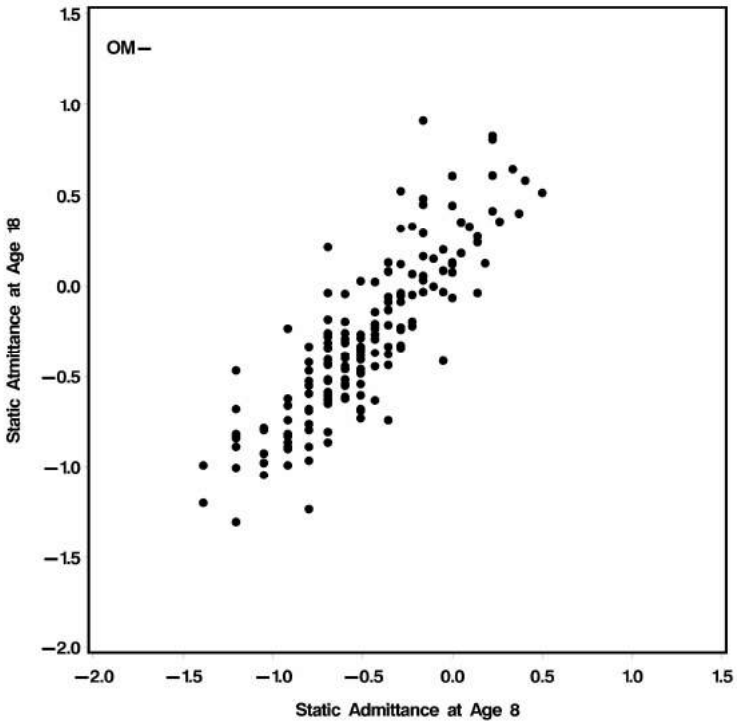


Figure 4. Association of static admittance values at ages 8 and 18 years for ears with no history of otitis media. All static admittance values are reported in cubic meters. The mean values of both ears of a subject have been log transformed.

Table 2. Effect of tympanic membrane abnormalities in ears on the change in static admittance values.

Subject Age at Measurement, y		Change in Admittance from Age 8 to 18 y, cm^3	*P value* (t Test)
8	**18**		
		Tympanosclerosis	
+	+	0.54	0.29
+	-	0.81	
-	+	0.55	0.30
-	-	0.37	
		Atrophy	
+	+	0.74	0.67
+	-	0.66	
-	+	0.75	0.05
-	-	0.31	
		Atelectasis	
+	+	1.05	0.17
+	-	0.64	
-	+	0.77	0.16
-	-	0.32	
		Retraction pocket	
+	+	?	NA
+	-	0.75	
-	+	1.74	0.04
-	-	0.41	
		Retraction pars flaccida	
+	+	0.78	0.14
+	-	0.51	
-	+	0.19	0.61
-	-	0.33	

Abbreviations: NA, not applicable; +, abnormality present; -, abnormality absent; ?, unknown.
All static admittance values are reported in cubic centimeters.

Table 2 lists, for each tympanic membrane abnormality separately, the change in static admittance (the value at age 18 years minus the value at age 8 years) related to the change in status of each abnormality. Static admittance values tended to increase from age 8 to 18 years when atrophy, atelectasis, retraction pocket, or retraction of the pars flaccida persisted or appeared in this period. Likewise, an increase in static admittance value was noted when abnormalities were absent or resolved in this period, although this increase was smaller. In contrast to expectation, persistent or newly developed tympanosclerosis was not associated with a smaller (or negative) increase in static admittance between age

8 and 18 years. As expected, newly developed atrophy coincides with a significantly higher increase in static admittance (p=0.05) compared to ears free of atrophy at both ages. The same result was found for newly developed retraction pockets (p<0.05).

DISCUSSION

This prospective follow-up study is unique in that it observed subjects with and without otitis media from preschool age to adult age and thereby documented long-term changes in middle ear mobility, specifically static admittance values, in relation to otitis media and its treatment. The difference in static admittance between OM+VT+ and OM+VT- ears was not as distinct at age 8 years as it was at 18 years of age. The highest values for static admittance at both ages were observed in the OM+VT+ group. At age 18 years, the difference in static admittance between the OM+VT- and OM- ears had disappeared. This suggests that treatment with ventilation tubes accelerates the increase of static admittance values. While there was hardly any change in the proportion of ears that had extreme static admittance values between age 8 and 18 years in the OM+VT- group, a dramatic increase of this proportion was observed in the OM+VT+ group. Specifically, 1 out of 3 OM+VT+ ears had a static admittance value above the 95th percentile of the reference group (OM-) at age 18 years.

This study demonstrated remarkably high correlations in all study groups between static admittances measured at ages 8 and 18 years. Despite a fairly large variation in static admittance, the individual position in the distribution appears to be stable over the teenage years, making the value at age 8 years a good predictor of the value at age 18 years.

The static admittance values of ears of the OM- group, the otologically normal values, were in the same range as those used in the literature as reference values. For instance, Haapaniemi[18] studied otologically normal school-aged children and found a 90% range of 0.2 to 1.0 cm^3 and a median of 0.5 cm^3 for 7-year-olds. This is comparable to the 90% range of static admittance values that we found in our nonotitis group at age 8 years: 0.3 to 1.3 cm^3, median 0.6 cm^3. At age 18 years, the 90% range of static admittance in this group was 0.4 cm^3 to 1.7 cm^3, with a median of 0.7 cm^3. The data are in accordance with the values mentioned in studies by Wiley[19] and Margolis and Goycoolea[20] for 20- to 30-year-old subjects: a 90% range of 0.4 to 1.7 cm^3, with a median and mean, respectively of 0.8 cm^3. Wiley et al.[21] showed that static admittance increased with age, a finding also reported for static admittance at school age.[18] The present study also

found a marked increase in median static admittance from ages 8 to 18 years. It is not likely that this increase is due to a difference in the instruments used at both examinations, because well-calibrated equipment was used in accordance with strict measurement procedures. Interestingly, De Chicchis and Nozza[22] showed that the static admittance data obtained with commercially available tympanometers were consistent, independent of the device used.

In the OM+VT+ group, we found a considerably higher median static admittance value than in the OM+VT- group. Abundant studies have demonstrated the close relation between tympanic membrane abnormalities and a history of ventilation tube insertion.[5,6,8,23,24] Yet we could not demonstrate an intermediate role of tympanic membrane abnormalities in the relation between ventilation tubes and static admittance. Only for atrophy could we find a statistically significant positive correlation with static admittance. Consequently, tympanic membrane abnormalities do not explain the effect of ventilation tubes on static admittance at age 18 years. Furthermore, changes in tympanic membrane abnormalities did not appear to be related to changes in the static admittance value over time. Only newly developed atrophy or retraction pocket of the pars tensa increased static admittance value significantly in the period from ages 8 to 18 years.

It should be emphasized that the number of subjects in the OM+VT+ group was rather small. Therefore, it is hard to draw conclusions about various combinations of tympanic membrane abnormalities. The association between atrophy and static admittance is in line with the data in the literature.[2,7] For instance, in a follow-up study on ventilation tube insertion in 165 ears, Daly et al.[25] found an association of high static admittance with atrophy. However, 40% of the ears with high static admittance did not show atrophy in that study. Apparently, other factors as yet unknown contribute to the pronounced difference in static admittance between OM+VT+ and OM+VT- ears. Changes in middle-ear structures resulting in an increased mobility might play a role. Our observation allows us to speculate on factors that mediate an increased mobility of the middle-ear system. Sheer stress from the weight of the ventilation tubes on the tympanic membrane could negatively affect the quality of the tympanic membrane permanently.[26] Atrophy of the lenticular process of the incus is frequently seen during surgery on ears with a history of otitis media.[27] This could result in laxity of the incudostapedial joint and consequently in an increased static admittance.

The clinical importance of increased static admittance depends on its relation to hearing acuity. To our knowledge, there are no studies showing that increased static admittance results in or plays a mediating role in hearing loss, but associations have been found between a history of ventilation tube insertion and

hearing loss.[25, 28] Our group reported this in a previous study.[14] The present study shows a relation between a history of ventilation tube insertion and increased static admittance value. However, we could not demonstrate a statistically significant relationship between increased static admittance value and hearing loss. Presumably, this resulted from limitations of our study and the relatively low number of subjects included. Given the changes in physiologic characteristics of the middle-ear system associated with an increased static admittance value, it seems likely that hearing is affected as well.

We can conclude that the static admittance value at age 8 years is predictive of the value at age 18 years. It has been demonstrated that static admittance values increases with age. Indeed, a history of ventilation tube insertion is associated with a higher increase of static admittance than can be expected on the basis of age alone. Moreover, this study shows that, during follow-up, the proportion of extreme static admittance values increases in ears previously treated with ventilation tube insertion. Tympanic membrane abnormalities do not seem to play an important role in increasing static admittance values. This does not hold true for atrophy, however.

REFERENCES

1. Shanks J, Shelton C. Basic principles and clinical applications of tympanometry. *Otolaryngol Clin North Am* 1991;24:299-328.
2. Feldman AS. Eardrum abnormality and the measurement of middle ear function. *Arch Otolaryngol* 1974;99:211-217.
3. Gaihede M, Lildholdt T, Lunding J. Sequelae of secretory otitis media: changes in middle ear biomechanics. *Acta Otolaryngol* 1997;117:382-389.
4. Haapaniemi JJ. Immittance findings in school-aged children. *Ear Hear* 1996;17:19-27.
5. Levine SC, Daly KA, Lindgren BR, Giebink GS. Tympanic membrane pathology in adolescents and young adults 12 to 16 years after tympanostomy tube insertion for chronic OME. In: Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances in Otitis Media. Proceedings of the 6th International Symposium. Hamilton, Canada: BC Decker Inc, 1996: 376-379.
6. Stangerup SE, Tos M, Arnesen R, Larsen P. A cohort study of point prevalence of eardrum pathology in children and teenagers from age 5 to age 16. *Eur Arch Otorhinolaryngol* 1994;251:399-403.
7. Maw AR, Bawden R. Tympanic membrane atrophy, scarring, atelectasis and attic retraction in persistent, untreated otitis media with effusion and following ventilation tube insertion. *Int J Pediatr Otorhinolaryngol* 1994;30:189-204.
8. Sederberg-Olsen JF, Sederberg-Olsen AE, Jensen AM. Late sequelae related to treatment with ventilation tubes for secretory otitis media in ENT practice. In: Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances in Otitis Media. Proceedings of the 5th International Symposium. Hamilton, Canada: BC Decker Inc, 1993: 843-846.
9. Skinner DW, Lesser TH, Richards SH. A 15 year follow-up of a controlled trial of the use of grommets in glue ear. *Clin Otolaryngol* 1988;13:341-346.
10. Rosenfeld RM, Isaacson G.C. Tympanotomy Tube Care and Consequences. In: Rosenfeld RM, Bluestone CD, eds. Evidence Based Otitis Media, 2nd ed. Hamilton, Canada: B.C. Decker Inc; 2003: 460-481.

11. Daly KA, Hunter LL, Levine SC, Lindgren BR, Giebink GS. Relationships between otitis media sequelae and age. *Laryngoscope* 1998;108:1306-1310.
12. Tos M, Stangerup SE, Larsen P. Dynamics of eardrum changes following secretory otitis. A prospective study. *Arch Otolaryngol Head Neck Surg* 1987;113:380-385.
13. Zielhuis GA, Rach GH, van den Broek P. Screening for otitis media with effusion in preschool children. *Lancet* 1989;1:311-314.
14. Schilder AGM, Zielhuis GA, Haggard MP, van den Broek P. Long-term effects of otitis media with effusion: otomicroscopic findings. *Am J Otol* 1995;16:365-372.
15. De Beer BA, Graamans K, Snik AF, Ingels K, Zielhuis GA. Hearing deficits in young adults who had a history of otitis media in childhood: use of personal stereos had no effect on hearing. *Pediatrics* 2003;111:e304-e308.
16. Schilder AGM. Long-term effects of otitis media with effusion in children. Nijmegen, the Netherlands: SSN Publishers; 1993.
17. De Beer BA, Schilder AG, Ingels K, Snik AF, Zielhuis GA, Graamans K. Hearing loss in young adults who had ventilation tube insertion in childhood. *Ann Otol Rhinol Laryngol* 2004;113:438-444.
18. Gelfand SA. Acoustic immitance assessment. In: Gelfand SA, ed. Essentials of Audiology. New York, USA: Thieme; 1997: 217-252.
19. Wiley TL. Static acoustic-admittance measures in normal ears: a combined analysis for ears with and without notched tympanograms. *J Speech Hear Res* 1989;32:688.
20. Margolis RH, Goycoolea HG. Multifrequency tympanometry in normal adults. *Ear Hear* 1993;14:408-413.
21. Wiley TL, Cruickshanks KJ, Nondahl DM, Tweed TS, Klein R, Klein BE. Tympanometric measures in older adults. *J Am Acad Audiol* 1996;7:260-268.
22. De Chicchis AR, Nozza RJ. Comparison of acoustic immittance measures obtained with different commercial instruments. *J Am Acad Audiol* 1996;7:120-124.
23. Ryding M, White P, Kalm O. Eustachian tube function and tympanic membrane findings after chronic secretory otitis media. *Int J Pediatr Otorhinolaryngol* 2004;68:197-204.
24. Larsen P, Tos M, Stangerup SE. Progression of drum pathology following secretory otitis media. In: Lim D, Bluestone CD, Klein J, Nelson J.D., eds. Recent Advances in Otitis Media. Proceedings of the 4th International Symposium. Toronto, Canada: B.C. Decker Inc, 1987: 34-38.
25. Daly KA, Hunter LL, Lindgren BR, Margolis R, Giebink GS. Chronic otitis media with effusion sequelae in children treated with tubes. *Arch Otolaryngol Head Neck Surg* 2003;129:517-522.
26. Prendergast PJ, Kelly DJ, Rafferty M, Blayney AW. The effect of ventilation tubes on stresses and vibration motion in the tympanic membrane: a finite element analysis. *Clin Otolaryngol* 1999;24:542-548.
27. Tos M, Stangerup SE, Larsen P. Incidence and progression of myringo-incudo-pexy after secretory otitis. *Acta Otolaryngol* 1992;112:512-517.
28. Stenstrom RJ, Bernard PAM, Feldman W, Durieux-Smith A, Pless IB, Beauregard Y. Long-term sequelae of ventilation tube insertion for the treatment of otitis media with effusion and recurrent acute otitis media. In: Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances of Otitis Media. Proceedings of the 6th International Symposium. Hamilton, Canada: BC Decker Inc, 1996; 373-375.

5

Non-measurable acoustic reflex in normal-hearing adults with a history of otitis media and ventilation tube insertion

B.A. de Beer
K. Graamans
G.A. Zielhuis
A.F.M. Snik

International Journal of Audiology 2007, accepted

ABSTRACT

Objective: To assess the effect of childhood otitis media and its treatment on the acoustic reflex.

Setting: Follow-up study of a Dutch birth cohort from age 2 to 18 years (n=358). Otological examination data, including measurement of the acoustic reflex, was recorded prospectively. All subjects had normal hearing, viz. hearing thresholds better than 15 dB HL at 0.25 Hz to 8.0 kHz.

Outcome measures:Three groups were defined according to their history of otitis media (OM) and ventilation tube insertion (VT): OM-, OM+VT-, OM+VT+. The contralateral acoustic reflex (CAR) threshold was measured for both ears at age 18 years.

Results: The median CAR threshold for the OM-, OM+VT-, and OM+VT+ groups was 90, 95, and 95 dB SPL respectively after correction for air-bone gap in the stimulus ear. For 46% of the ears in the OM+VT+ group, the acoustic reflex was not measurable. Presence of tympanic membrane abnormalities as well as air-bone gap in the probe ear (ear in which the activating stimulus was measured) increased the risk of a non-measurable CAR. In a multivariate regression analyses we demonstrated that the effect of a history of ventilation tube insertion on CAR response is partly independent, though is enhanced by the intercorrelated status of the middle ear, viz. presence of tympanic membrane abnormalities and air-bone gap.

Conclusions: Childhood otitis media is associated with a non-measurable CAR. This association is strongest in ears treated with ventilation tubes and is partly, though importantly, explained by the presence of tympanic membrane abnormalities.

INTRODUCTION

Contraction of the stapedius muscle dampens vibrations in the middle-ear conductive system. This results in an attenuation of the sound signal on its way towards the cochlea. The stapedius muscle is part of a reflex arc; this arc is activated by loud sounds, typically 90 dB SPL or louder. It has been suggested that this reflex, often referred to as the acoustic reflex, prevents loud, low-frequency sounds from reaching the cochlea. In addition, the stapedius muscle is activated just before vocalization, probably to attenuate the subject's own relatively loud voice.[1]

Measurements of the acoustic reflex are used clinically in the assessment of middle-ear function. The reflex response depends on the mobility of the tympanic membrane and middle-ear ossicles. Together with audiometric data, reflex measurements provide important clinical information about middle-ear status.

It has been suggested that otitis media and/or its treatment might lead to poor acoustic reflexes or elevated reflex thresholds. A small study by Ryding et al.[2] showed that ten-year-old normal-hearing children with a history of recurrent otitis media in early childhood had elevated contralateral acoustic reflex thresholds as compared to a control group. Also Stephenson et al.[3] suggested that elevated contralateral acoustic reflex thresholds were the result of childhood otitis media. It was argued that the acoustic reflex response was affected by the peripheral sequelae of otitis media, namely slightly higher hearing thresholds and minor tympanic membrane abnormalities. Welsch and Dawes[4] recently reported that the presence of tympanic membrane abnormalities in both the stimulus and the probe ear compromised the acoustic reflex, a relation found to exist independently of audiometric thresholds. An inverse relation between otitis media and the quality of the acoustic reflex has been suggested. In that light, the present study was designed to investigate and refine this relation.

POPULATION AND METHODS

Subjects

This study involved 358 normal-hearing individuals (<15 dB HL from 0.25 to 8.0 kHz) selected from a birth cohort that had been followed from the age of 2 years.[5-7] A detailed history of otitis media (and its treatment) in the first two years of life had been taken at the outset. Between the ages of 2 and 4 years, a tympanogram was made every three months. At age 8, otomicroscopy had been performed, and the data on occurrence and treatment of otitis media between 4

and 8 years of age was documented. Parental information was validated with the medical records of these individuals.[6-8]

To select a population for the present study, a cumulative otitis media (OM) score was calculated for each subject in the original cohort. Details on this score have been reported previously.[8] In short, the OM score was based on the documented number of episodes of either otitis media with effusion (OME; diagnosed by tympanometry) or acute otitis media (AOM; parental report) experienced from birth to 8 years of age. The sum of the OME score and the AOM score was taken as the OM score. The subjects in the highest and lowest third of the OM scoring range (n=528) formed the (sub-) cohorts of subjects characterized as having either a positive (OM+) or a negative (OM-) otitis media history (see Table 1). Of these 528 subjects, 358 (183 OM+ and 175 OM-) agreed to participate and took part in the present study when they were 18 years old. The OM+ cohort was then divided into subjects treated with ventilation tubes (OM+VT+, n=51) and subjects managed conservatively (OM+VT-, n=132). Expressed as the number of ears, that is: 102 OM+VT+, 264 OM+VT-, and 350 OM-. The analyses excluded ears of subjects with OME, AOM, otorrhea, perforations, or ventilation tubes present at a previous evaluation (at age 8) and at the present evaluation (at age 18).

Approval for the study was obtained from the Ethics Committee of the Radboud University Nijmegen Medical Centre; the participants signed for informed consent.

METHODS

The first author (B.B.) performed otomicroscopy and tympanometry on all subjects, and any tympanic membrane abnormalities were documented according to the classification used by Schilder et al.[6]. Pure-tone audiometry was performed in an audiometric test booth using an Interacoustic Clinical Audiometer AC40 (Interacoustics, Assens, Denmark) and TDH 39P headphones (Telephonics, Huntington, New York) that were calibrated according to ISO 389 standards.[9] Air conduction thresholds in dB hearing levels (HL) were determined for both ears at octave frequencies ranging from 0.25 to 8.0 kHz. Bone conduction thresholds were determined for one ear at 0.5, 1.0, 2.0, and 4.0 kHz. If the air conduction thresholds exceeded 10 dB HL, bone conduction thresholds were measured in both ears with standard masking techniques. Air-bone gaps were calculated for both ears, presuming that the bone conduction threshold of the one ear was equal to that of the contralateral ear in cases where just one side was measured.

Tympanometric measures of the middle ear were obtained using a Tymp87 Middle Ear Analyzer (Danplex, Copenhagen, Denmark). A 226 Hz probe tone was

employed in the tympanometer. The speed of the air-pressure pump was 200 daPa/s and the pressure was swept from +200 daPa to -400 daPa. Acoustic reflex measurement was performed at the subject's peak middle-ear pressure, commonly at atmospheric pressure. The measure of interest was the threshold of the contralateral acoustic reflex (CAR). Thus, the CAR of the right ear is determined by positioning the probe in the right ear and presenting the stimulus to the left ear. CAR thresholds were assessed at intensities between 70 and 110 dB in sound pressure level (SPL) with steps of 5 dB. Besides the CAR threshold at 1.0 kHz, the CAR thresholds at 0.5, 2.0, and 4.0 kHz were assessed as well.

Statistical methods

All analyses were performed using SAS statistical software 6.12 (SAS, Cary, North Carolina). Distributions of reflex thresholds in the three subgroups (OM-, OM+VT-, OM+VT+) were skewed and thus characterized by medians. For each subject and each ear, the bone conduction threshold was subtracted from the air conduction threshold, both as measured at three frequencies, 0.5, 1.0, and 2.0 kHz. The three measurements were averaged for each person/ear. The mean for all subjects was then calculated. Multivariate regression models using fixed effects to account for dependency of ears within subjects (PROC GENMOD) were used to assess the relative contribution of ventilation tubes, air-bone gap, and tympanic membrane abnormalities to the acoustic reflex threshold.

RESULTS

The basic characteristics of the three study groups are shown in Table 1. Figure 1a is a histogram showing the distribution of the CAR at 1.0 kHz for each of the three subgroups separately. The median CAR threshold at 1.0 kHz was 95 dB SPL in the OM- group. In OM+VT- and OM+VT+ ears, the median CAR thresholds at 1.0 kHz were 100 dB SPL, respectively 105 dB SPL. The proportion of non-measurable CAR thresholds was significantly larger for OM+VT+ ears than for OM+VT- ears (47% versus 15%; $p<0.01$). For 3% of OM- ears, the CAR was non-measurable. Figure 1b is a histogram showing the distribution of measurable CAR thresholds after subtracting the air-bone gap in the stimulus ear as well as the (unchanged) percentage of the non-measurable CAR at 1.0 kHz. This was done because an air-bone gap in the stimulated ear will elevate the CAR threshold proportionately. After correcting for the air-bone gap, the median CAR thresholds in the OM+VT+ and the OM+VT- sub-cohort were both 95 dB SPL at 1.0 kHz. In the OM- group, the median CAR threshold after air-bone gap correction was 90

dB SPL. Histograms of the CAR thresholds at the frequencies 0.5, 2.0, and 4.0 kHz were largely comparable to those at 1.0 kHz (data not shown).

Table 1. Basic characteristics of study population

	OM+VT+	OM+VT-	OM-
Number of subjects	51	132	174
Male	47 %	48 %	43 %
Median OM score* (P_{25}, P_{75})	100 (75,112)	61 (51,74)	9 (0,14)
Number of VT insertions			
0	-	264	-
1	58	-	-
≥ 2	44	-	-
Age at first VT insertion			
0 - 2 yr.	2	-	-
2 - 4 yr.	80	-	-
> 4 yr.	20	-	-
Tympanosclerosis	64 %	9 %	1 %
Atrophy	22 %	6 %	-
Attic retraction	21 %	9 %	-
Pars tensa retraction	16 %	3 %	-
Perforation	6 %	1 %	-
Mean air-bone gap (0.5,1.0, 2.0 kHz)^	3.6	2.4	2.2

Abbreviations: OM, otitis media; VT, ventilation tubes; +, positive history; - negative history.
*Sum of proportion of OM with effusion and of acute OM episodes up to 8 years of age (range 0-200). ^ The averaged thresholds of 0.5, 1.0 and 2.0 kHz of each ear were used.

The distribution of the measurable CAR thresholds for the three OM groups appears as a Gaussian distribution, with a mean between 90 to 95 dB SPL. This suggests that the data of Figure 1a and 1b can be subdivided in another way across the two OM+ subgroups: namely, data on the ears with a measurable CAR and on those with a non-measurable CAR. The differences between these two new groups of ears were analyzed in more detail. The effect of the middle-ear status of the probe ear on the acoustic reflex response was investigated. Middle-ear status was specified in audiometric characteristics (air-bone gap) and tympanic membrane appearance. Ears with a measurable CAR had an air-bone gap of 2.5 dB HL at 1.0 kHz in the probe ear; for ears with a non-measurable CAR this was 4.7 dB HL. A further analysis showed that an air-bone gap >5 dB in the probe ear increased the risk of a non-measurable CAR at 1.0 kHz by about one-and-a-half. Equally, air-bone gaps in the probe ear at 0.5, 2.0, and 4.0 kHz affected the CAR thresholds at the corresponding frequencies and were associated with an increased prevalence of non-measurable CAR.

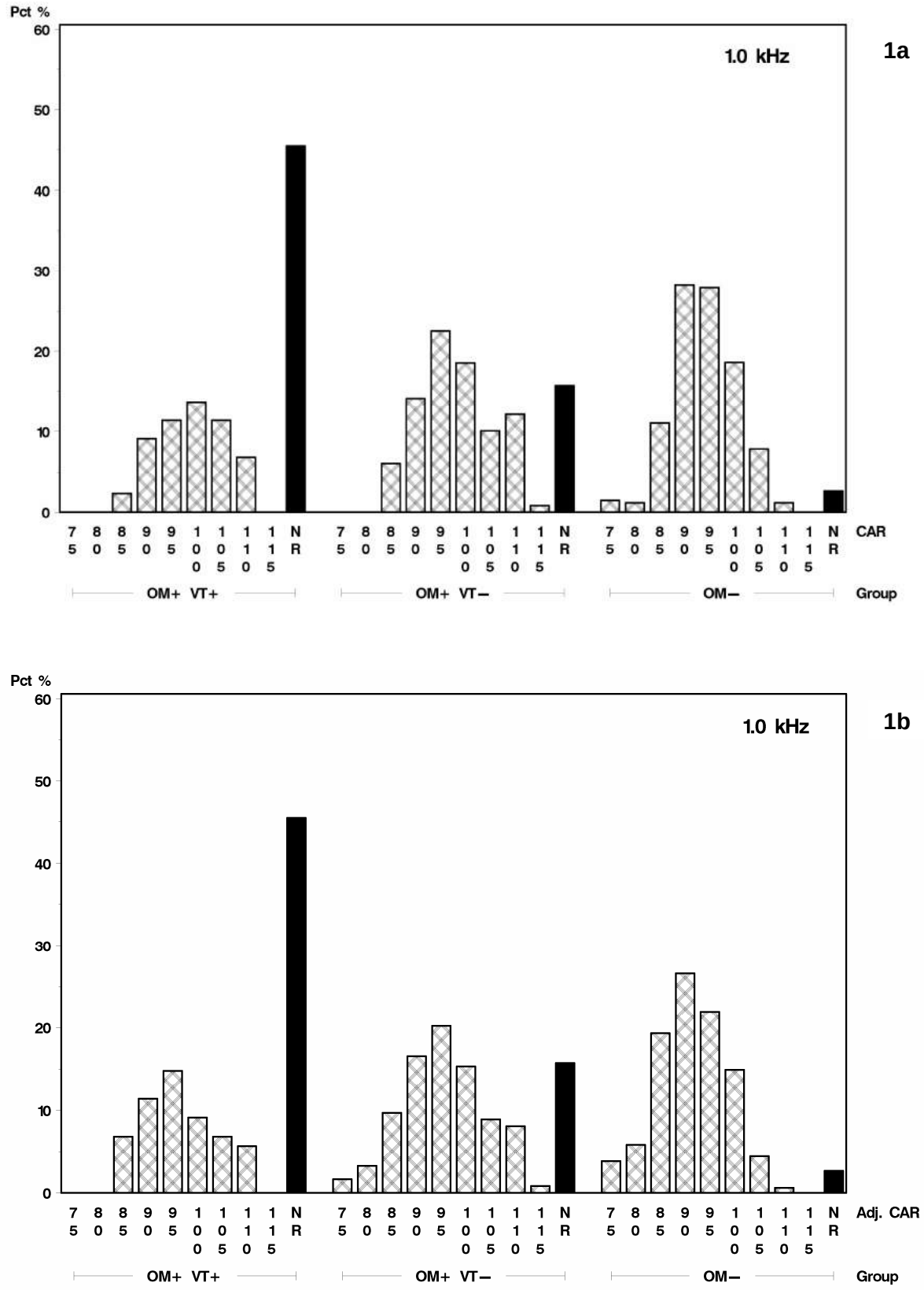


Figure 1. Distribution of contralateral acoustic reflex thresholds in decibel sound pressure level at 1.0 kHz before (1a) and after (1b) subtraction of air-bone gap in stimulus ear. Abbreviations: OM, otitis media; VT, ventilation tubes; +, positive history; - negative history; CAR, contralateral acoustic reflex.

Further, Table 2 shows the relation between the presence of tympanic membrane abnormalities and the CAR in the probe ear. All tympanic membrane abnormalities were more frequently present in ears with a non-measurable CAR. Ears with a non-measurable CAR had tympanosclerosis about three times more often than ears with a measurable CAR. The same trend was seen for ears with atrophy and a retraction of the pars flaccida. Retraction pocket of the pars tensa was seen infrequently, but three out of the four ears with this feature had a non-measurable CAR. The effect of the presence of tympanic membrane abnormalities on CAR at 0.5, 2.0, and 4.0 kHz was grossly similar to the pattern determined at 1.0 kHz.

Table 2. Presence of tympanic membrane abnormalities in relation to the contralateral acoustic reflex

Tympanic Membrane Abnormality	**Measurable CAR**	**Non-Measurable CAR**
Tympanosclerosis	16%	47%
Atrophy	5%	18%
Atelectasis	2%	13%
Retraction pars flaccida	7%	21%

Abbreviations: CAR, contralateral acoustic reflex.

Our results suggested that not only middle-ear status but also treatment of otitis media by ventilation tube insertion affects the acoustic reflex response. Therefore, we investigated whether a history of ventilation tube treatment had any independent predictive value for CAR response, going beyond the indicators of tympanic membrane appearance and air-bone gap in the probe ear. To do so, we compared two multivariate regression models. The first one (non-CAR= $\alpha \cdot VT$) contains the history of ventilation tubes as the only explanatory variable. The second model (non-CAR= $\alpha \cdot VT + \beta \cdot TMA + \gamma \cdot ABG$) contains the three variables of interest, viz. history of ventilation tubes (VT), specific tympanic membrane abnormality in the probe ear (TMA), and air-bone gap in the probe ear (ABG). These analyses showed that after entering all pertinent factors of middle-ear status, a history of ventilation tubes was an additional significant predictor of a non-measurable reflex. The effect of ventilation tube treatment on non-measurable CAR was even more evident when either tympanosclerosis or atrophy was included (likelihood ratio test of comparison of model I and model II, $p=0.02$). Introducing of atelectasis in the model also increased the explained variance

significantly (p=0.01). Then, including retraction of the pars flaccida increased the effect, but only marginally (p=0.06). This analysis demonstrates that there is a strong assiciation between a history of ventilation tube treatment and a non-measurable CAR. Furthermore, it shows that this association is partly, though importantly, mediated by the presence of an air-bone gap and tympanic membrane abnormalities in the probe ear.

DISCUSSION

Previous research on adolescents with a history of OME showed poorer CAR than in adolescents with no OME history (viz. elevated CAR thresholds[2-4]). In contrast, the present study shows that in large numbers of adolescents with an OME history, CAR can be evoked at stimulus levels well within the normal range (after correction for a possible air-bone gap in the stimulus ear); see Figure 1a and 1b. However, among those subjects who were treated by ventilation tube insertion (OM+VT+), the CAR was non-measurable in nearly half of them. To further investigate which factors can contribute to CAR response, two new groups of subjects with an OME history were formed. One subgroup consisted of subjects with (normal) measurable CAR thresholds, while the subjects in the second subgroup had non-measurable CAR thresholds. Ears with a measurable CAR at 1.0 kHz had a somewhat smaller mean air-bone gap in the probe ear (mean 2.5 dB) than those with a non-measurable CAR (mean 4.7 dB). This difference in air-bone gap is small but statistically significant, and it suggests that the middle-ear status of the probe ear might play a role. Additional analysis showed that tympanosclerosis, atrophy, atelectasis, pars tensa and/or pars flaccida retraction in the probe ear were all associated with an increased prevalence of non-measurable CAR. It is known that tympanic membrane abnormalities are a frequent result of treatment by ventilation tube insertion.[10-16] Thus, it is reasonable to expect worse CAR data in treated ears than in untreated ears. Moreover, persistent tympanic membrane abnormalities are associated with conductive hearing loss.[17] In a multivariate regression analysis, we demonstrated that the effect of a history of ventilation tube insertion on CAR response is partly independent, though it is enhanced by the intercorrelated status of the middle ear, viz. the presence of tympanic membrane abnormalities and an air-bone gap.

Stephenson[3], in a retrospective study, reported elevated acoustic reflex thresholds in subjects with a history of otitis media in childhood. However, the investigators did not divide their subjects into those having been treated versus non-treated by ventilation tube insertion. Our data show that such a division is of

importance to understand acoustic reflex characteristics. Welsch and Dawes[4] replicated and extended Stephenson's work using old data from a large, prospective, general-population based study (n=631). That analysis was based on audiometric data obtained from 11-year-old subjects as well as otoscopic and acoustic reflex data obtained from them at age 15. Unfortunately, because the investigators provided little information on the measurements of the acoustic reflex, it is not clear whether the acoustic reflex could be evoked in all their subjects. Welsch and Dawes reported that the association between elevated acoustic reflex thresholds and history of childhood otitis media resulted from the presence of tympanic membrane abnormalities. It was suggested that even after adjustment for audiometric thresholds, the acoustic reflex characteristic remained associated with tympanic membrane status. Surprisingly, by comparing their OM1 (least affected) and OM3 (most affected) groups, audiometric thresholds differed by as much as a mean of 5 dB HL, while the difference in mean acoustic reflex thresholds was only 2 dB. This suggests that their elevated acoustic reflex thresholds were explained only by the difference in audiometric thresholds.

We hypothesize that a non-measurable CAR could possibly be explained as a problem of reflex detection. As described by Hüttenbrink[18,19], minor middle-ear abnormalities might significantly influence the quasi-static behavior of the middle-ear ossicular system. As has been suggested in the literature, abnormal hyperoxic conditions in the middle ear as a result of a perforated tympanic membrane might harm the delicate middle-ear system.[20,21] Combining these observations, it is hypothesized that although the CAR was elicited in all subjects, middle-ear abnormalities have caused impaired transmission of the quasi-static stapes movement to the tympanic membrane. Thus, even though the stapedius muscle itself contracts, the presence of minor middle-ear damage might prevent registration of changes in admittance.

Another explanation for deviations in acoustic reflex thresholds could be an impairment of the central or peripheral neuronal pathways of the acoustic reflex arc. Stephenson[3] reasoned that central factors probably do not play a role. Our results provide robust evidence in support of that hypothesis. If central auditory deprivation would lead to poorer CARs, the group with the longest periods of poor hearing, i.e. the OM+VT- group, would be expected to have been affected most. However, our study showed that the OM+VT+ group was more frequently affected. This suggests that central auditory deprivation is not a likely cause.

The results of this study allow us to draw the following conclusions:

1. A non-measurable contralateral acoustic reflex history is associated with a history of otitis media in normal-hearing subjects.
2. The prevalence of a non-measurable contralateral acoustic reflex is higher in ears that had been treated with ventilation tubes in childhood. This association is further explained by the presence of tympanic membrane abnormalities.

REFERENCES

1. Borg E, Counter SA. The middle-ear muscles. *Sci Am* 1989;261:74-80.
2. Ryding M, Konradsson K, Kalm O, Prellner K. Auditory consequences of recurrent acute purulent otitis media. *Ann Otol Rhinol Laryngol* 2002;111:261-266.
3. Stephenson H, Higson JM, Haggard MP, Dutson M, Rogers M, Schilder AG. The acoustic reflex in adults with histories of otitis media in childhood. *Ear Hear* 1997;18:62-72.
4. Welch D, Dawes PJ. The effects of childhood otitis media on the acoustic reflex threshold at age 15. *Int J Audiol*2006:353-359.
5. Zielhuis GA, Rach GH, van den Broek P. Screening for otitis media with effusion in preschool children. *Lancet* 1989;1:311-314.
6. Schilder AGM, Zielhuis GA, Haggard MP, van den Broek P. Long-term effects of otitis media with effusion: otomicroscopic findings. *Am J Otol* 1995;16:365-372.
7. de Beer BA, Snik A, Schilder AG, Graamans K, Zielhuis GA. The effect of otitis media in childhood on the development of middle ear admittance on reaching adulthood. *Arch Otolaryngol Head Neck Surg* 2005;2005:777-781.
8. de Beer BA, Schilder AG, Ingels K, Snik AF, Zielhuis GA, Graamans K. Hearing loss in young adults who had ventilation tube insertion in childhood. *Ann Otol Rhinol Laryngol* 2004;113:438-444.
9. ISO 389. Acoustics. Reference zero for the calibration of audiometric equipment. Geneva, Switserland: International Organization of Standardization 1991.
10. de Beer BA, Schilder AG, Zielhuis GA, Graamans K. Natural course of tympanic membrane pathology related to otitis media and ventilation tubes between ages 8 and 18 years. *Otol Neurotol* 2005;26:1016-1021.
11. Valtonen H, Tuomilehto H, Qvarnberg Y, Nuutinen J. A 14-year prospective follow-up study of children treated early in life with tympanostomy tubes: Part 1: Clinical outcomes. *Arch Otolaryngol Head Neck Surg* 2005;131:293-298.
12. Ryding M, White P, Kalm O. Eustachian tube function and tympanic membrane findings after chronic secretory otitis media. *Int J Pediatr Otorhinolaryngol* 2004;68:197-204.
13. Daly KA, Hunter LL, Lindgren BR, Margolis R, Giebink GS. Chronic otitis media with effusion sequelae in children treated with tubes. *Arch Otolaryngol Head Neck Surg* 2003;129:517-522.
14. Maw AR, Bawden R. Tympanic membrane atrophy, scarring, atelectasis and attic retraction in persistent, untreated otitis media with effusion and following ventilation tube insertion. *Int J Pediatr Otorhinolaryngol* 1994;30:189-204.
15. Stangerup SE, Tos M, Arnesen R, Larsen P. A cohort study of point prevalence of eardrum pathology in children and teenagers from age 5 to age 16. *Eur Arch Otorhinolaryngol* 1994;251:399-403.
16. Sederberg-Olsen JF, Sederberg-Olsen AE, Jensen AM. Late results of treatment with ventilation tubes for secretory otitis media in ENT practice. *Acta Otolaryngol* 1989;108:448-455.
17. Schilder AGM, Zielhuis GA, Straatman H, van den Broek P. Long-term effects of otitis media with effusion: auditory findings. In: Schilder AGM. Long-term Effects of Otitis Media with Effusion in Children. Nijmegen, The Netherlandss: SSN Publishers; 1993: 47-65.

18. Huttenbrink KB. The mechanics of the middle-ear at static air pressures: the role of the ossicular joints, the function of the middle-ear muscles and the behaviour of stapedial prostheses. *Acta Otolaryngol Suppl* 1988;451:1-35.
19. Huttenbrink KB. Die Bewegung de Gehörknöchelchen durch die Mittelohrmuskel-Kontraktion. *Laryngorhinootologie* 1989;68:614-621.
20. Karlidag T, Ilhan N, Kaygusuz I, Keles E, Yalcin S. Comparison of free radicals and antioxidant enzymes in chronic otitis media with and without tympanosclerosis. *Laryngoscope* 2004;114:85-89.
21. Cagdas KK. The role of experimental myringosclerosis in interpretation of tympanograms and its possible clinical implications. *Med Hypotheses* 2005;64:1132-1134.

6

Hearing deficits in young adults who had a history of otitis media in childhood: use of personal stereos had no effect on hearing

B.A. de Beer
K. Graamans
A.F.M. Snik
K. Ingels
G.A. Zielhuis

Pediatrics 2003; 111: e304-308

ABSTRACT

Objective: To test the hypothesis proposed in a recent French study that a history of recurrent otitis media in childhood increases susceptibility to hearing loss from frequent exposure to a personal stereo during development to early adulthood.

Methods: A subcohort of 358 young adults selected from a historic cohort study, all aged 18 years and with a well-documented otitis media history (secretory and acute), provided data on the sound level and length of exposure to personal stereos. Four contrasting groups were formed: those with the highest or lowest personal stereo exposure combined with a positive or negative history of otitis media (n=238). The main outcome measure was hearing thresholds from pure-tone audiometry (0.5-8 kHz).

Results: Young adults with a history of recurrent otitis media in childhood did not show greater susceptibility to hearing loss from personal stereo use than their peers without a history of otitis media. However, a history of recurrent otitis media was associated with significant mean air conduction hearing loss of 4 dB and a mean bone conduction hearing loss of 2 dB compared to the subjects without a history of otitis media.

Conclusion: Recurrent otitis media in childhood may have an irreversible effect on the middle ear and the cochlea and may lead to hearing deficits in later life. No interaction with personal stereo exposure is seen.

INTRODUCTION

Otitis media is one of the most common childhood diseases. Although it is responsible for a great deal of medical consultations, the clinical relevance of the disease has been repeatedly questioned. Controversy in management exists because of the large rate of spontaneous recovery, the low rate of complications, and the poor effectiveness of medication (antibiotics) and surgery (ventilation tubes, adenoidectomy).[1-4] Treatment with ventilation tubes has even shown adverse effects on hearing in the long term. However, this was demonstrated in small numbers.[5]

Job and colleagues[6,7] have published the results of an explorative study on conscripts for the French army, aged 18 to 24 years. They found that the combination of a history of recurrent otitis media and exposure to personal stereos (PS) for more than 1 hour a day resulted in a mean hearing loss of 11 dB HL at 0.5 to 8.0 kHz as measured by pure-tone audiometry. In contrast, hearing loss was not found to be associated with a history of otitis media without frequent personal stereo exposure, or to frequent personal stereo exposure without a history of otitis media. Therefore, Job et al. hypothesized that persons with and without a history of otitis media in childhood have different susceptibility to hearing damage from personal stereo exposure. Their study was criticized because of its explorative nature and the retrospective assessment of otitis media.[8,9] A prospective follow-up study on children with a documented history of otitis media was recommended to test the hypothesis.

The otherwise healthy birth cohort of the Nijmegen Otitis Media Study[10] provides a unique opportunity to perform this test, because data on otitis media have been meticulously documented. The aim of this study was to evaluate whether a history of recurrent otitis media in childhood increases susceptibility to hearing loss from frequent exposure to a personal stereo during development to early adulthood.

POPULATION AND METHODS

Subjects of study

A cohort (n=1439) born in 1982-1983 formed the basis for this investigation.[10,11] The vast majority of this birth cohort (n=1328) had been screened for otitis media with effusion by means of tympanometry from 24 to 48 months of age at 3 monthly intervals. At the first of these screenings, a thorough history of (treatment for) middle ear diseases had been taken from birth onwards. At the age of 8 years, 946 children from this cohort had been re-evaluated: extensive audiometrical assessment had been performed, and a detailed history had been taken focusing

on (treatment for) middle ear diseases from 48 months of age onwards. At the time of this study the participants were 18 years old. We were able to trace 677 out of 946 who were re-evaluated at 8 years. Participants were ranked according to the presence or absence of a history of otitis media by composing a cumulative score based on the documented number of episodes of either otitis media with effusion (OME) or acute otitis media (AOM) from birth to 8 years of age. In this cumulative otitis media (OM) score, OME was defined as the proportion of flat (type B) tympanograms or the presence of ventilation tubes out of all documented tympanometric measurements, while AOM was defined as the proportion of events of otalgia with fever and/or otorrhoea out of all documented reports. The OM score ranged from 0 to 200. The subjects in the highest and lowest tertiles of this OM score (n=528) were selected to form two groups with either a positive (OM+) or a negative (OM-) otitis media history. A total of 358 out of these 528 persons agreed to participate in this study. Five subjects were excluded from the analyses because of missing data, the presence of neurofibromatosis, bilateral OME, or congenital deafness. In 5 persons with a large unilateral tympanic membrane perforation, or unilateral eradication of a cholesteatoma, only the healthy ear was included in the analyses. A further subdivision was made of these 358 subjects based on the use of a personal stereo (vide infra).
Approval for the study was obtained from the Ethics Committee of the University Medical Center Nijmegen.

Exposure to music from personal stereos

A personal stereo exposure score was assessed for all the participants in the study. This PS exposure score was based on a combination of the cumulative length of exposure to a PS from the age of 8 years until the present and the sound level of the music typical for that individual. Information on the cumulative hours of exposure in each year the subject had used a PS was obtained using a standardized questionnaire with detailed questions. Information on the sound level was obtained during a PS listening test; participants were asked to bring their favorite disc with pop music and their PS, if available. The investigators provided standard headphones (Philips SBC HS500; Philips, Eindhoven, the Netherlands) or earphones (Sony D-C21; Sony, Tokyo, Japan). The subjects were asked to listen to their favorite piece of pop music and to set the volume to the level they usually listened to. We then measured the A-weighted equivalent sound pressure level (SPL) of a 2-minute track with an integrating sound level meter (Brüell & Kjaer type 2260; Brüel&Kjaer, Naerum, Denmark) electrically coupled to the output of the PS. To obtain the actual SPL in the external ear canal, the

head/earphones were calibrated on artificial ears (Brüell & Kjaer type 4152 and type 4153; Brüel&Kjaer).

The PS exposure score was calculated as the product of the cumulative length of exposure and the calibrated SPL, expressed in SPL per 24 hours and standardized to a SPL of 85 A-weighted decibels (the occupational noise exposure limit in the European Community), according to the model developed by Passchier-Vermeer.[12] Thus, for each individual the PS exposure score estimated the total sound energy accumulated over the years of exposure since the age of 8. All of the participants were ranked according to this score. Only the participants in the highest and lowest tertiles were selected for statistical analyses, to compose a group with a high PS score (PS+) and a group with a low score (PS-).

To investigate separate and combined correlation between otitis media in childhood (OM+ and OM-), PS exposure (PS+ and PS-) and hearing levels at 18 years, four contrasting groups were formed: OM-/PS-, OM-/PS+, OM+/PS- and OM+/PS+ (total n=238).

Outcome measurements

All the participants underwent standardized otomicroscopy of the external ear canal and the tympanic membrane.

Pure-tone audiometry was performed in an audiometric testing booth using an Interacoustic Clinical Audiometer AC40 (Interacoustics, Assens, Denmark) and TDH 39P headphones (Telephonics, Huntington, New York) that were calibrated according to ISO 389 standards.[13] Air conduction thresholds were measured in both ears at the frequencies 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, and 8.0 kHz. Bone conduction thresholds were measured in one ear at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, and 8.0 kHz . If the air conduction thresholds exceeded +10 dB HL, bone conduction thresholds were measured in both ears with standard masking techniques. Hearing loss was expressed in dB HL. The subjects were asked to refrain from exposure to loud music during the 24 hours before these audiological examinations. A Tymp87 Middle Ear Analyzer (Danplex, Copenhagen, Denmark) was used for tympanometry.

The participants also completed a questionnaire to obtain information on their otological status (including signs of auditory problems), participation in pop music activities (e.g. visits to discotheques, rock concerts or house parties and employment as a disc jockey or stage technician) and on exposure to noise at work or during recreational activities. Occupational noise exposure was defined as having worked in noise for longer than six months without any appropriate ear protection. Exposure to recreational noise included playing a musical instrument,

being actively involved in indoor ball sports, riding a motorcycle, shooting or hunting, and operating model cars or planes. All questions pertained to the past 10 years, ie, the period since the previous follow-up evaluation.
Self-reported middle ear disease was verified with data from the medical records with the consent of the participants.

Statistical analysis

Principal analyses focused on differences in the distribution of average hearing level in individuals at the frequencies 0.25 to 8 kHz. Differences between groups were tested by Student's *t*-test and analysis of variance at each frequency. Gender and exposure to sources of noise other than a PS (occupational noise, recreational noise and noise from participation in pop music activities) were evaluated as potential confounders.
All analyses were performed with SAS statistical software (version 6.12;SAS,Cary, North Carolina, USA).

Table 1. Distribution of gender, OM history, PS use and exposure to noise other than a PS in the four contrasting groups

	OM-/PS-	OM-/PS+	OM+/PS-	OM+/PS+
Number	55	62	64	57
Male	45%	40%	44%	49%
Work in noise[¶]	4%	11%	9%	25%
OM score[† *]	9 (0 – 22)	9 (0 – 21)	64 (42 – 113)	73 (47 – 130)
- OME[‡]	4 (0 – 21)	0 (0 – 13)	46 (20 – 79)	45 (14 – 83)
- AOM[§]	0 (0 – 18)	9 (0 – 18)	27 (0 – 55)	30 (0 – 70)
PS score[‖ *]	0 (0 – 0)	5 (2 – 43)	0 (0 – 1)	9 (2 – 87)
Pop music activities[†† *]	184 (21 – 446)	276 (18 – 488)	219 (26 – 467)	297 (90 – 656)

[*] Median (5[th] percentile and 95[th] pecentile) [†] Proportion of cumulative number of OM episodes during childhood (0 to 8 years of age) out of all documented measurements (range 0-200); [‡]Proportion of cumulative number of OM with effusion episodes (range 0-100); [§] Proportion of cumulative number of acute OM episodes (range 0-100); [‖] Value of the total sound energy due to PS exposure expressed in equivalent years of continuous exposure to 85 A-weighed decibels; [¶] Proportion of subjects with occupational noise exposure for longer than 6 months without any appropriate ear protection; [††] Cumulative frequency of exposure to pop music activities other than PS. Abbreviations: OM, otitis media; PS, personal stereo exposure; +, positive history; -, negative history.

RESULTS

Each of the four contrasting groups (OM-/PS-, OM-/PS+, OM+/PS-, OM+/PS+) contained 55 to 64 subjects aged 18 years (Table 1). The distributions of OM scores did not differ significantly between the two OM- groups (median 9) or between the two OM+ groups (median 63 and 72, $p>0.05$). The distributions of the PS scores did not differ between the PS+ and PS- groups. In the OM+/PS+ group, more subjects had been exposed to occupational noise without any appropriate ear protection than the other groups ($p<0.01$).

The two PS+ groups had been exposed to more pop music activities than the two PS- groups ($p<0.01$). Discotheque visits contributed most to the cumulative exposure to pop music activities. Exposure to recreational noise was rare and equally distributed over the four groups (data not shown).

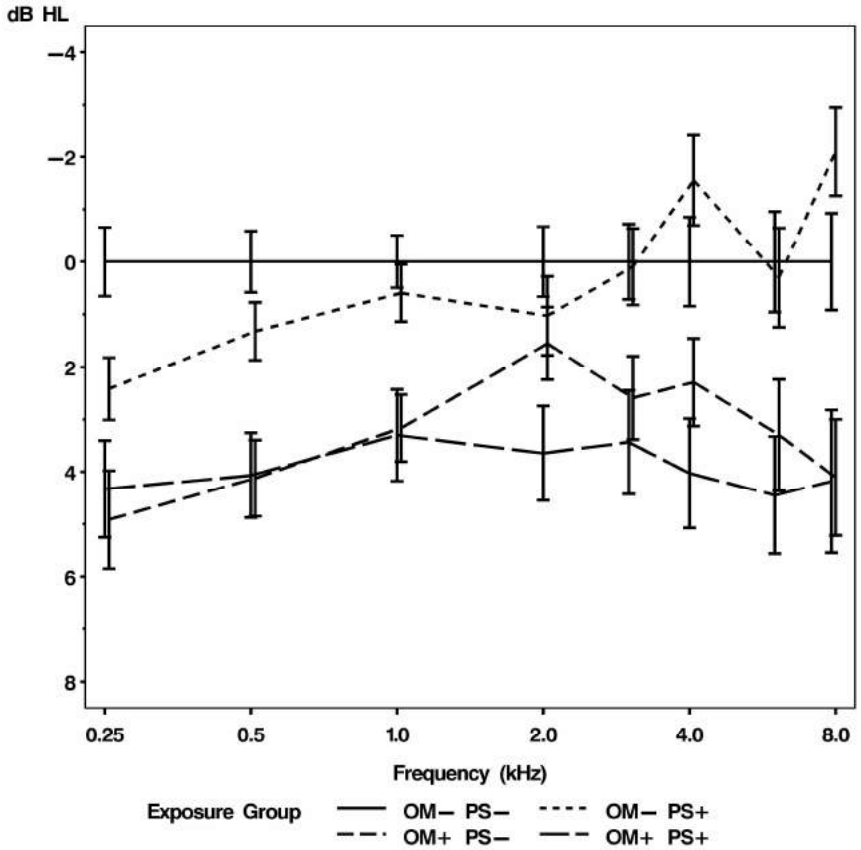
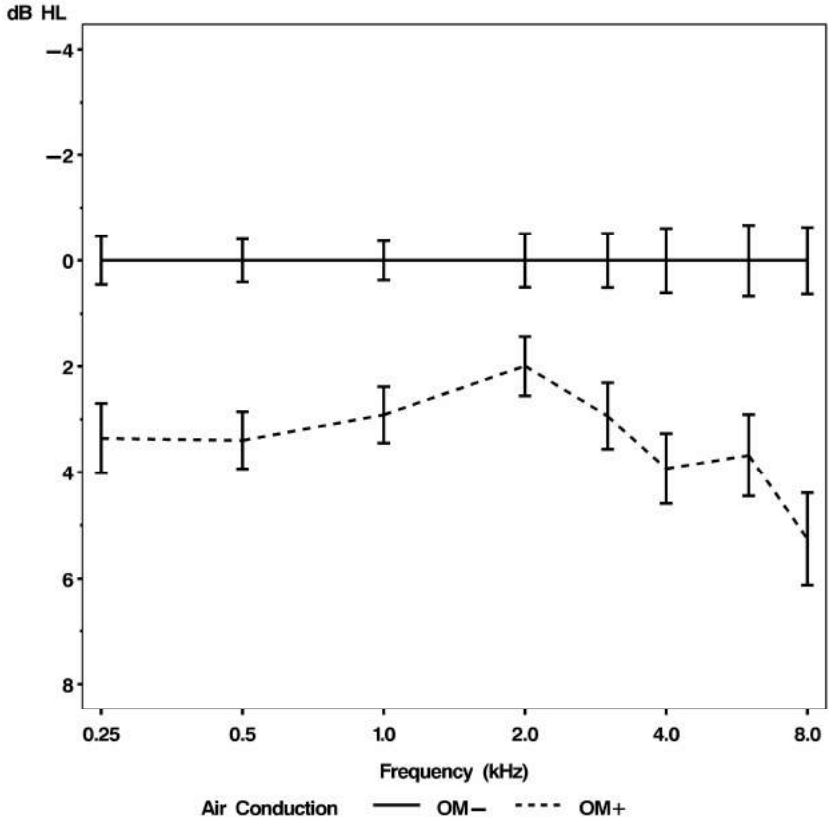


Figure 1. Mean air conduction thresholds in subjects with and without a history of otitis media and with and without PS use. All thresholds relative to the hearing level of the OM-PS- reference group. Abbreviations: OM, otitis media; VT, ventilation tubes; PS, personal stereo use; +, positive history; - negative history.

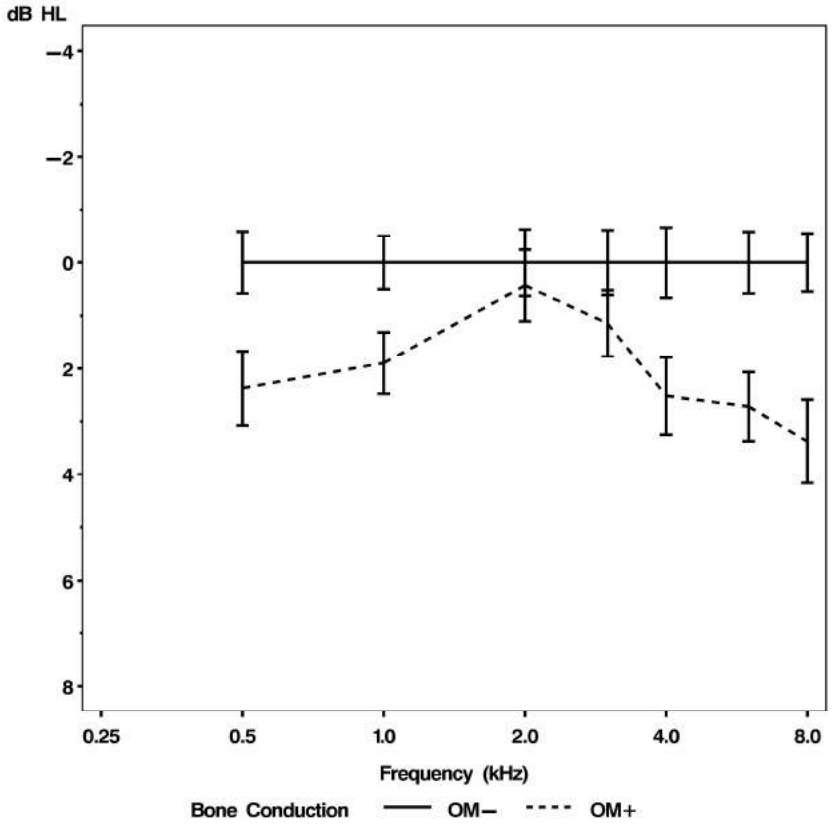
Air conduction thresholds from pure-tone audiometry are plotted in Figure 1 for the three groups with exposure to OM and/or PS, relative to the hearing thresholds in the OM-PS- reference group. When we compared PS+ to PS- for each stratum of the OM score, the audiograms appeared to be fairly similar. No significant difference in hearing threshold could be demonstrated at any of the frequencies, except for 0.25 kHz in the OM- groups ($p>0.10$). In contrast, there was a significant difference in hearing thresholds between the OM+ and OM- groups that was independent of the PS score. Subjects in the OM+ groups showed consistently higher air conduction thresholds (about 4 dB HL) than the corresponding OM- groups at all the frequencies from 0.25 to 8 kHz (Figure 1).
The differences were significant when the two strata for PS were merged ($p<0.01$).
We also evaluated potential confounders, such as exposure to other sources of noise. Exposure to occupational noise, recreational noise and noise resulting from pop music activities did not have any significant effect on hearing.
To further explore the lack of correlation between PS use and hearing acuity, analyses were performed on the participants whose PS exposure score was in the upper 15% (PS++) of the PS+ group. Again, no significant differences in hearing thresholds were found between the PS++ group and the PS- group ($p>0.10$).
In the subsequent analyses, the PS+ groups and the PS- groups were merged to increase power. Figure 2a shows the air conduction thresholds, while figure 2b shows the bone conduction thresholds for the OM+ and the OM- groups. Figure 2a shows that air conduction thresholds in the OM+ group were about 4 dB HL poorer than those in the OM- group. Figure 2b shows that part (about 2 dB) of the difference in air conduction thresholds between the OM- and OM+ groups was a result of differences in bone conduction thresholds, as the latter were significantly affected at all frequencies except for 2.0 kHz.

Discussion

The aim of this study was to investigate whether repeated otitis media episodes in early childhood or infancy led to increased sensitivity to hearing loss due to frequent personal stereo use in later childhood and adolescence. We did not find any evidence of a differential effect of personal stereo exposure in subjects with and without a history of otitis media in childhood. As the quality of our data can be considered superior to that in the study by Job et al.[6,7], we assume that the interaction effect found by Job is a chance finding.



2a



2b

Figure 2. Mean air conduction (2a) and bone conduction thresholds (2b) in subjects with a history of otitis media (n=121) relative to the hearing level of the OM- reference group (n=117). Abbreviations: OM, otitis media; +, positive history; - negative history.

Regardless of the otitis media history, we did not find any significant correlation between frequent personal stereo exposure and hearing acuity. This is in accordance with the observations of Job et al, who showed a small but nonsignificant effect. The same has been demonstrated in several other cross-sectional and longitudinal investigations.[14-17]

The most striking result in the present study was that the hearing thresholds in the subjects with a documented history of recurrent otitis media episodes in childhood were significantly poorer than those in the participants without a history of otitis media. Data on occurrence of otitis media (secretory and acute) had been objectively documented for each individual over the period from birth to 8 years. In addition, the data on the sound level and duration of exposure to pop music from a personal stereo were accurately documented. Furthermore, we controlled for all additional deleterious effects on hearing that occurred in the period between childhood and early adulthood. Hearing loss could not be explained by differences in personal stereo exposure, occupational noise exposure or noise exposure from recreational activities or from pop music activities other than personal stereos. Therefore we consider that we have strong arguments on which to base our conclusion that the association between recurrent otitis media episodes in childhood and poorer hearing in later life is unequivocal. This conclusion is supported by other publications in which it was suggested that otitis media in childhood (or its treatment) led to hearing deficits in the long-term.[18-21] However, the follow-up periods in the latter studies were shorter and the population sizes were smaller.

We observed that the subgroups of young adults with and without a documented history of otitis media had different air conduction thresholds (mean difference of 4 dB) and different bone conduction thresholds (mean difference of 2 dB). It seems that otitis media has caused irreversible damage to the middle ear as well as the cochlea. The pathophysiological mechanisms responsible for these effects remain to be investigated.

This 4 dB difference in mean hearing level between young adults with or without a history of otitis media should not be disregarded, although it might seem irrelevant in clinical practice. This value concerns the mean difference in hearing acuity, which might have a substantial impact on a population level.[22] The relevance of our finding is further supported by Brooks[23], who estimated that elderly with mixed hearing loss (ie, a combination of sensorineural and conductive deficits) caused by middle ear disease in childhood would be in need for a hearing aid 10 years earlier (ie, from 75 years to 65 years).

Important points for consideration in current clinical and public health practice are these:

1. Exposure to pop music from personal stereos at the levels established in this population had not led to any measurable hearing deficits.
2. In this population, a history of otitis media in childhood had not increased susceptibility to hearing loss of exposure to pop music from personal stereos during development to early adulthood, which contradicts the hypothesis proposed by Job et al.[6,7]
3. Contrary to the prevailing belief, recurrent otitis media in childhood should be taken seriously because it might lead to hearing deficits in young adulthood.

REFERENCES

1. Takata GS, Chan LS, Shekelle P, Morton SC, Mason W, Marcy SM. Evidence assessment of management of acute otitis media: I. The role of antibiotics in treatment of uncomplicated acute otitis media. *Pediatrics* 2001;108:239-247.
2. Rovers MM, Straatman H, Ingels K, Van der Wilt GJ, Van den Broek P, Zielhuis GA. The effect of short-term ventilation tubes versus watchful waiting on hearing in young children with persistent otitis media with effusion: a randomized trial. *Ear Hear* 2001;22:191-199.
3. Shapiro AM, Bluestone CD. Otitis media reassessed. Up-to-date answers to some basic questions. *Postgrad Med* 1995;97:73-82.
4. Schilder AG, Zielhuis GA, Haggard MP, Van den Broek P. Long-term effects of otitis media with effusion: otomicroscopic findings. *Am J Otol* 1995;16:365-372.
5. Margolis RH, Saly GL, Hunter LL. High-frequency hearing loss and wideband middle ear impedance in children with otitis media histories. *Ear Hear* 2000;21:206-211.
6. Job A, Raynal M, Rondet P. Hearing loss and use of personal stereos in young adults with antecedents of otitis media [letter]. *Lancet* 1999;353:35.
7. Job A, Raynal M, Tricoire A, Signoret J, Rondet P. Hearing status of French youth aged from 18 to 24 years in 1997: a cross-sectional epidemiological study in the selection centres of the army in Vincennes and Lyon. *Rev Epidemiol Sante Publique* 2000;48:227-237.
8. Cates C. Personal stereos and hearing loss. *Lancet* 1999;353:756.
9. Smith P, Davis A. Social noise and hearing loss. *Lancet* 1999;353:1185.
10. Zielhuis GA, Rach GH, Van den Broek P. Screening for otitis media with effusion in preschool children. *Lancet* 1989;1:311-314.
11. Schilder AG, Zielhuis GA, Van den Broek P. The otological profile of a cohort of Dutch 7.5-8-year-olds. *Clin Otolaryngol* 1993;18:48-54.
12. Passchier-Vermeer W, Vos H, Steenbekkers JHM. Pop music through headphones and hearing loss. Leiden, the Netherlands: Netherlands Organization for Applied Scientific Research; 1998 Report No.: 98.036.
13. ISO 389. Acoustics. Standard reference zero for the calibration of pure-tone audiometers. Geneva, Switzerland: International Organization for Standardization; 1998.
14. Mostafapour SP, Lahargoue K, Gates GA. Noise-induced hearing loss in young adults: the role of personal listening devices and other sources of leisure noise. *Laryngoscope* 1998;108:1832-1839.
15. Turunen-Rise I, Flottorp G, Tvete O. Personal cassette players ('Walkman'). Do they cause noise-induced hearing loss? *Scand Audiol* 1991;20:239-244.
16. Rice CG, Rossi G, Olina M. Damage risk from personal cassette players. *Br J Audiol* 1987; 21:279-288.
17. Medical Research Council Institute of Hearing Research. Damage to hearing arising from leisure noise. *Br J Audiol* 1986;20:157-164.

18. Sorri M, Rantakallio P. Secretory otitis media and hearing loss. *Acta Otolaryngol* 1988; 457(suppl):94-99.
19. Lopponen H, Sorri M, Pekkala R, Penna J. Secretory otitis media and high-frequency hearing loss. *Acta Otolaryngol* 1992;493(suppl):99-107.
20. Sorri M, Maki-Torkko E, Alho OP. Otitis media and long-term follow-up of hearing. *Acta Otolaryngol* 1995;115:193-195.
21. Hunter LL, Margolis RH, Rykken JR, Le CT, Daly KA, Giebink GS. High frequency hearing loss associated with otitis media. *Ear Hear* 1996;17:1-11.
22. Rose G, Day S. The population mean predicts the number of deviant individuals. *BMJ* 1990; 301:1031-1034.
23. Brooks DN. Possible long-term consequences of middle ear effusion. *Ann Otol Rhinol Laryngol* 1980;89(suppl):246-248.

7

Hearing of otologically healthy young adults at age 18

B.A. de Beer
K. Graamans
G.A. Zielhuis
A.F.M. Snik

Submitted

ABSTRACT

Objective: To test the validity of the ISO 389, the reference zero for normal hearing subjects.

Study design: Prospective historical cohort study.

Methods: Follow-up study of birth cohort from age 2 to 18 years with meticulous otological examination including history-taking, otoscopy and audiometry. Both air conduction thresholds (0.25 kHz to 8.0 kHz and 8.0 kHz to 16.0 kHz) and bone conduction thresholds (0.5 kHz to 4.0 kHz) were measured. Subjects of this cohort were defined as otologically healthy when they had not experienced substantial otitis media in childhood. Noise exposure was also taken into account and was assessed with a questionnaire.

Results: In both the low and the high frequencies of the speech frequency range of air conduction, the measured thresholds are significantly different from the ISO 389 reference zero. In the mid-frequencies, the ISO reference does fit. The thresholds measured in our cohort were comparable to the data presented in the literature; moreover, most values were close to the reference zero. A striking misfit with the ISO 389 reference was found at 2.0 and 3.0 kHz for bone conduction audiometry. Just 0.5 kHz and 4.0 kHz were equal to the reference zero. Noise exposure was limited in this cohort and has not led to any measurable hearing deficit.

Conclusions: This study cohort seems to be the best representative sample so far of otologically healthy subjects due to the longitudinal follow-up of their otological status. The mean hearing thresholds are different from the ISO 389 reference. This study demonstrates once again the need to revise the ISO 389 for air conduction audiometry and to critically evaluate the bone conduction thresholds at 2.0 and 3.0 kHz.

INTRODUCTION

During the 1960s, the International Organization of Standardization (ISO) formulated a reference zero for the calibration of audiometric equipment[1]. The ISO norms for air conduction audiometry were based on several studies of otologically healthy subjects from different countries. However, there was significant spread in the data (as discussed in Lutman and Davis[2] and Buren[3]). In the nineties, several studies were published showing that mean air conduction thresholds in young adults did not conform to the calibration guidelines, especially at 0.25 and 0.5 kHz, and at 6.0 and 8.0 kHz.[2-6] However, these studies also showed significant variability. Several causes have been suggested for the spread between studies: subject selection (did the included subjects constitute a representative sample?); small sample sizes; exclusion criteria (how was 'otologically healthy' defined?); as well as the precise audiometric procedures used in each case. Any study group that is assembled to make a proper evaluation of hearing thresholds is supposed to form a representative sample from which a subgroup with otologically healthy ears can be drawn. Otologically healthy ears might be defined as ears with a history of no signs or symptoms of middle ear disease and no exposure to excessive noise. Working along these lines, Lutman and Davis[2] and Smith and colleagues[4] used extensive questionnaires to select otologically healthy subjects from representative groups of young adults. Although retrospective questionnaires might be helpful, the outcomes are not always reliable with respect to ear problems during childhood. For instance, Buren et al.[3] excluded all patients with any sign of present or past ear disease; they were excluded only on the grounds of otoscopic findings. However, their study group of adolescents was comprised of subjects from a senior high school; thus, it was not necessarily a representative sample. Rahko-Laitila et al.[5] did study a large representative subgroup. Since childhood, these subjects were followed up longitudinally with regard to their middle ear status. Their selection of otologically healthy subjects was based upon otoscopic and tympanometric findings. However, they did not take any history of noise exposure into account.

The cited studies all show that the mean hearing thresholds were poorer than the ISO reference zero, especially at the low and high frequencies in the speech frequency range; the poorest results were recorded at 6.0 kHz. Variability in the published data might indeed be ascribed to subject selection and the definition of otological health. Thus, there is still a need for normative baseline data. The aim of the present study is to test the validity of the reference zero formulated by ISO for air- and bone conduction thresholds at conventional as well as high frequencies. This aim was pursued by measuring hearing thresholds in a relatively

large representative sample of young adults with a prospectively recorded blank otological history.

POPULATION AND METHODS

The adolescents enrolled in this study participated in OME studies that were conducted in the 1980s and 1990s.[7,8] All of the subjects were born between September 1, 1982 and August 31, 1984 in Nijmegen, a middle-sized provincial town in the Netherlands. The ear-related morbidity of the subjects was recorded from birth onwards. They were examined otologically and audiometrically from age 2 to 4 years (every three months) and again when 8 years old. Their status prior to these examinations was assessed by means of extensive questionnaires on the occurrence and treatment of ear diseases and hearing disorders. On the basis of data on their previous status, an Otitis Media (OM) score was calculated (range 0 to 200). In the calculations, otalgia with fever or an occurrence of otorrhea was classified as acute otitis media, while a flat (type B) tympanogram was classified as otitis media with effusion. The calculation of this OM score has been described in a previous report.[9] More than half of the subjects selected for inclusion in the present analysis had an OM score of zero, while 90% had a score below 11. The maximum score in this subgroup was 21. In other words, the study group comprised 175 otologically healthy subjects, viz. 75 male and 100 female adolescents. They were re-evaluated at the age of 18 years.

Otomicroscopy, tympanometry and pure-tone audiometry were performed in every young adult enrolled in the study. Otomicroscopy was performed by the first author. Abnormalities in the appearance of the tympanic membrane did not constitute a reason for exclusion. Audiometric measurements were carried out according to the terms of ISO 8253[10] at the Audiological Center of the Raboud University Nijmegen Medical Centre. All subjects were examined in one of two identical double-walled soundproof booths that met all the requirements of the ISO norm. The persons who performed the audiometric measurements were qualified audiometricians.

Pure-tone audiometry was performed with the Interacoustic Clinical Audiometer AC40 (Interacoustics, Assens, Denmark) combined with the TDH 39P headphones (Telephonics, Huntington, New York) for air conduction measurements, the B71 transducer for bone conduction examinations, and the Koss HV/1a headphone (Koss Corp., Milwaukee, Wisconsin) for extended high-frequency testing. Just before starting the study, the audiometers were calibrated according to ISO 389 standards.[11-14] Air conduction thresholds were determined in both ears for the

frequencies 0.25 kHz to 8.0 kHz, including 3.0 and 6.0 kHz. Bone conduction thresholds were determined in one ear at 0.5 kHz, 1.0, 2.0, 3.0 and 4.0 kHz. Thresholds at 6.0 and 8.0 kHz were not included, because at these frequencies the sounds radiated by the B71 transducer might be audible via airborne stimulation.[15] If at any frequency the air conduction threshold exceeded the bone conduction threshold by 10 dB hearing level (HL), bone conduction thresholds were measured in both ears with standard masking techniques. All thresholds that were determined were recorded. This means that the records may include a negative air-bone gap; i.e., a bone conduction threshold that is worse than the air conduction threshold. Finally, air conduction thresholds in the high-frequency range (8.0, 12.0 and 16.0 kHz) were examined and expressed in decibel sound pressure levels (SPL). The 8.0 kHz stimulus was measured twice: first with the TDH 39P headphones in the conventional frequency range, and then in the extended frequency range with the Koss HV/1a headphones. Throughout the entire study, the right ear was examined first in all subjects.

Impedance measures of the middle ear were obtained with a Tymp87 Middle Ear Analyzer (Danplex, Copenhagen, Denmark) using a 226 Hz probe tone. The pump speed was 200 daPa/s, and the pressure was swept from +200 to -400 daPa. Acoustic reflex measurements were performed at the subject's peak middle ear pressure, usually at atmospheric pressure. The threshold of the contralateral acoustic reflex was measured starting at 1.0 kHz with an 80 dB SPL loud tone. If the reflex was not present, the presentation level was increased in steps of 5 dB up to 110 dB SPL. If the reflex was present at 80 dB SPL stimulation, the stimulus level was decreased.

Levels of noise exposure were determined by means of an extended questionnaire and an experiment with volume settings. These data covered the duration of exposure to loud sounds. The participants were questioned about any exposure to (loud) occupational noise and various sources of music exposure: listening to a personal stereo device; going to discotheques, rock concerts, or 'house parties'; and working as a disc jockey or stage technician. Furthermore, they were asked about the volume settings they selected when listening to their personal stereo devices. These settings were measured in a trial run by attaching a volume detector to the devices. It should be noted that noise exposure did not serve as an exclusion criterion in the present study; instead, it was taken as a variable.

All computations were performed using SAS statistical software (version 6.12; SAS, Cary, North Carolina) The standard error was calculated where appropriate. In addition to the calculated means, medians, and standard deviations (SD), we

also took the minimum and maximum values of both air conduction and bone conduction thresholds into account. All data presented here pertain to the right or left ear or to the average of both ears within an individual.

RESULTS

Health status of the subjects

Only two subjects had experienced two documented episodes with a bilaterally flat tympanogram before they were 8 years old. The rest had either not experienced (documented) OME or had had only one episode by that time. The parents of 35 subjects reported one (documented) event of otalgia with fever during the same period. All others reported no AOM episodes before the age of 8. No participant in this subpopulation had experienced OME or AOM between 8 and 18 years of age.

When assessed at 18 years of age, none of the subjects showed tympanic membrane abnormalities, except for four individuals. Slight myringosclerosis was found in five of their ears. The severity of the myringosclerosis was considered slight when the sclerotic plaque covered less than one quadrant of the tympanic membrane.

Tympanometry showed that over 98% (n= 344) of the ears had a normal type A tympanogram. Three individuals had a one-sided negative middle ear pressure (type C tympanogram). In one individual, the middle-ear pressure was negative on both sides. The mean static admittance of all ears was 0.82 cm^3, with 90% range values between 0.37 and 1.66 cm^3. The acoustic reflex measurements were carried out successfully in 174 right ears and 171 left ears. Any missing values were due to technical problems. The mean acoustic reflex threshold was 86 dB SPL, with a standard deviation of +/- 8 dB; the reflex was evoked with a 1.0 kHz tone. The reflex could not be measured when no reflex was detected at the highest stimulation level of 110 dB SPL. This happened in about 2% of the ears at 1.0 kHz.

The level of exposure to noise at venues with loud music and through personal stereo devices was determined in this study cohort. Over the past 5 years, i.e., when the subjects were between age 14 and 18, on average these youths listened to a personal stereo for 239 hours a year (SD 392 hours). Furthermore, the participants made an average of 50 visits (SD 26 times) a year to venues with loud music (i.e., going to discotheques and ‘house parties’ or working as a disc jockey). Only 10 subjects were exposed to occupational noise. They were required to wear appropriate ear protection, and all of them did.

Table 1a. Air conduction thresholds in otologically healthy subjects, right ear

			Air Conduction dB HL		
Frequency, kHz	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
0.25	5.2	6.0	-10	5	30
0.50	2.5	4.8	-5	0	20
1.0	0.7	4.5	-10	0	15
2.0	1.2	5.6	-10	0	25
3.0	-0.5	6.0	-10	0	20
4.0	0.1	6.3	-10	0	15
6.0	7.3	7.8	-10	5	30
8.0	1.7	7.9	-10	5	35
			Air Conduction dB SPL		
8.0	20	8	-2	18	48
12.0	20	10	7	17	77
16.0	48	19	16	46	96

Table 1b. Air conduction thresholds in otologically healthy subjects, left ear

			Air Conduction dB HL		
Frequency, kHz	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
0.25	6.9	6.4	-10	5	30
0.50	3.1	5.9	-10	5	30
1.0	0.3	5.0	-10	0	25
2.0	1.3	6.3	-10	0	20
3.0	0.5	6.2	-10	0	20
4.0	1.8	7.7	-10	0	20
6.0	9.6	8.6	-10	10	40
8.0	4.6	8.4	-10	5	30
			Air Conduction dB SPL		
8.0	22	8	3	23	48
12.0	13	9	-3	12	47
16.0	46	17	16	46	106

Abbreviations: dB HL, decibel hearing level; dB SPL, decibel sound pressure level

Audiometry

Table 1 shows the mean air conduction thresholds, standard deviations, median, minimum and maximum for the right and left ear separately. The data for both sexes have been combined, as there was no appreciable difference between the outcomes for males and females. Only in the air conduction thresholds at 3.0 and 4.0 kHz was there a statistically significant difference in favor of females ($p<0.01$).

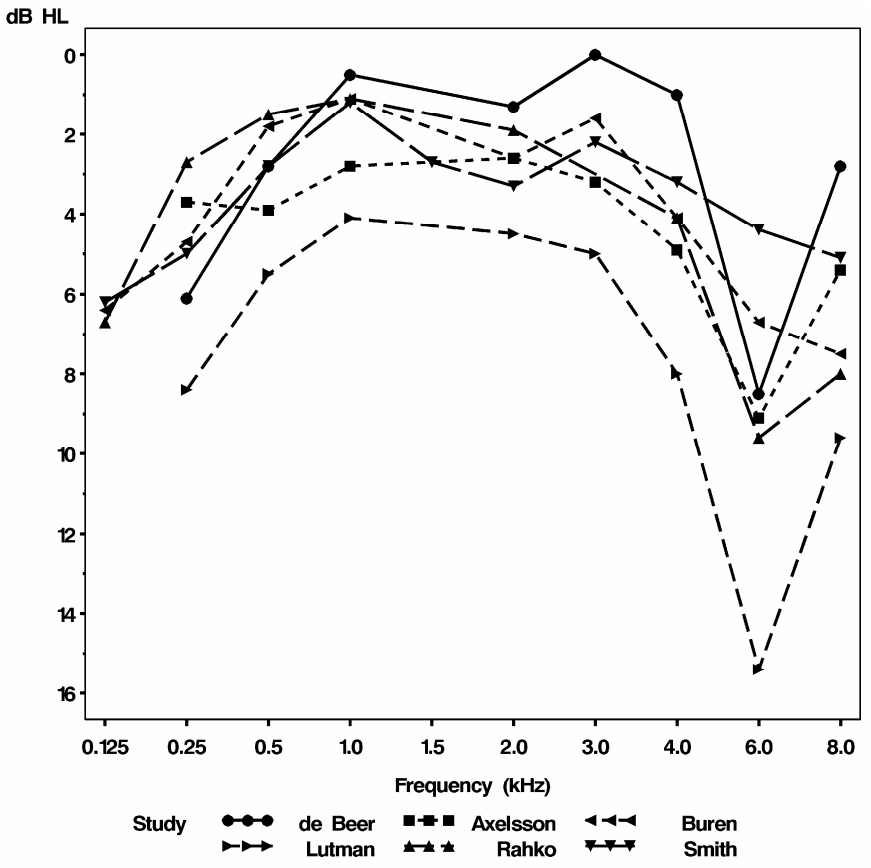


Figure 1. Mean values of air conduction thresholds in decibel hearing levels of both ears; comparison with literature data. Smith[4], n=93; otologically normal subjects aged 18 to 25. Axelsson[6], n=500; unscreened subjects aged 18. Rahko-Laitila[5], n=534; otologically normal subjects aged 14. Lutman[2], n=241; screened subjects aged 18 to 30. Buren[3], n=69; otologically normal subjects aged 17 to 22.

Figure 1 shows the mean value of air conduction hearing thresholds for both ears, not only as observed in the present study but also as reported in comparable sources in the literature. For the frequencies of 1.0 to 4.0 kHz, the mean values are close to zero, suggesting that ISO 389-1[11] works well. However, the mean hearing thresholds for 0.25 kHz, 6.0 and 8.0 kHz were inconsistent with the zero reference value of ISO 389.[11,12] Particularly at 6.0 kHz, the mean value is highly deviant. Statistical analysis showed that the mean value for air conduction thresholds of both ears was statistically different from the ISO zero value. This was observed at all frequencies except 3.0 kHz ($p<0.05$).

In order to compare our findings with the literature, the extended high-frequency thresholds were expressed in dB SPL using ISO 389-5.[14] Figure 2 shows the mean value of the hearing threshold in the high-frequency range for both ears. This figure shows that our data fall well within the range of the data in the literature. However, we see a significant spread between the studies.

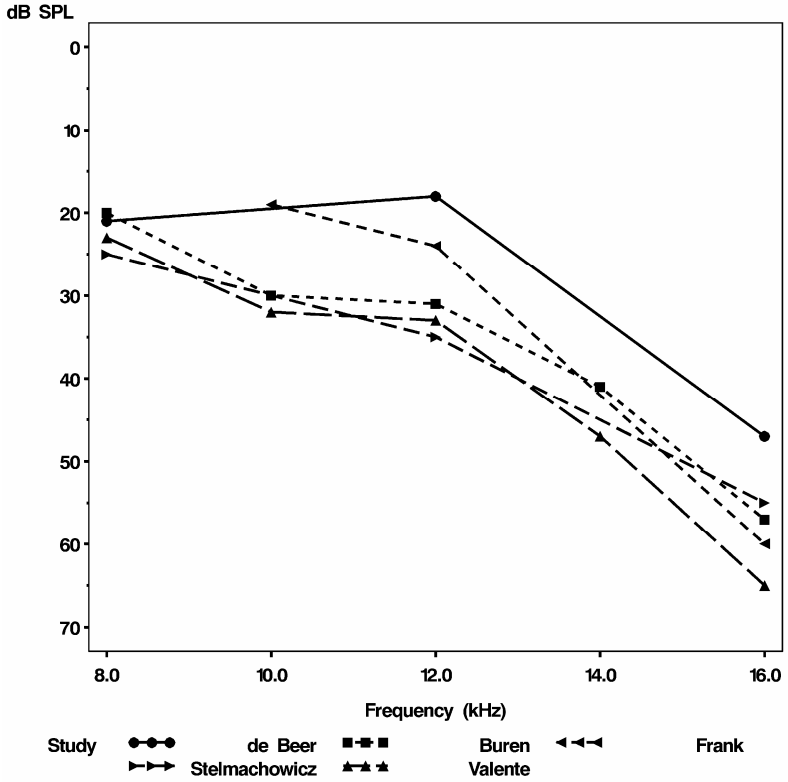


Figure 2. Mean values of extended high-frequency thresholds in decibel sound pressure levels of both ears; comparison with literature data. Buren[3], n=69; subjects aged 17 to 22. Stelmachowicz[17], n=10, subjects aged 10 to 19. Frank[18], n=100, subjects aged 18 to 28. Valente[16], n=24, subjects aged 21 to 25. All data pertain to otologically normal subjects.

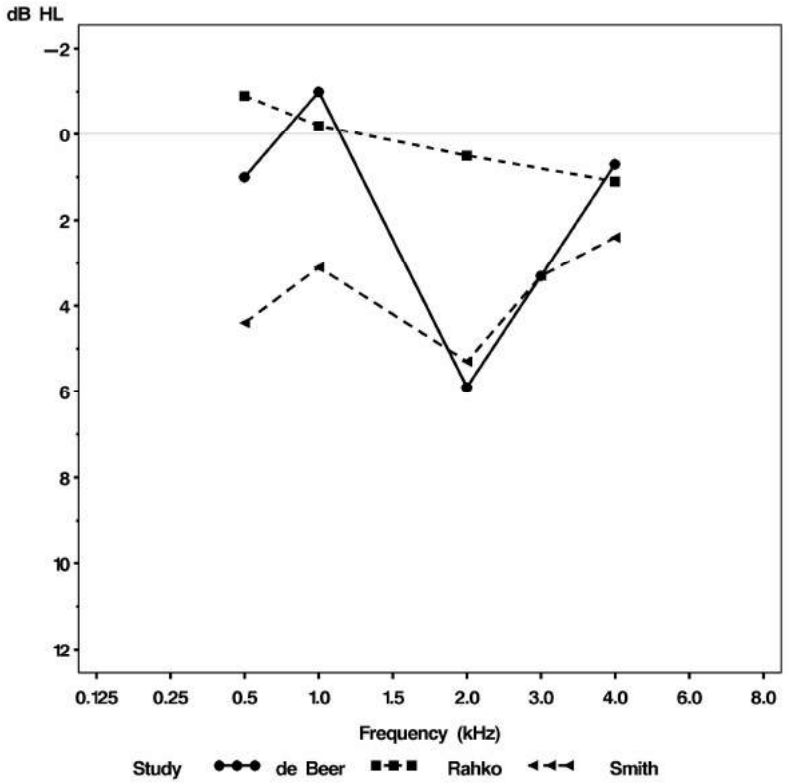


Figure 3. Mean values of bone conduction thresholds in decibel hearing level of both ears; comparison with literature data. Smith[4], n=93; subjects aged 18 to 25. Rahko-Laitila[5], n=534; subjects aged 14. All data pertain to otologically normal subjects.

Table 2a. Bone conduction thresholds in otologically healthy subjects, right ear

	Right Ear Bone Conduction dB HL				
Frequency, kHz	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
0.5	1.1	6.9	-10	0	25
1.0	-1.1	5.5	-10	0	15
2.0	5.7	6.9	-10	5	30
3.0	3.0	7.0	-10	5	25
4.0	0.1	7.4	-10	0	20

Table 2b. Bone conduction thresholds in otologically healthy subjects, left ear

	Left Ear Bone Conduction dB HL				
Frequency, kHz	**Mean**	**SD**	**Minimum**	**Median**	**Maximum**
0.5	0.9	6.8	-10	0	20
1.0	-0.9	5.6	-10	0	25
2.0	6.0	6.7	-10	5	30
3.0	3.6	6.4	-10	5	20
4.0	1.3	7.6	-10	0	20

Abbreviation: dB HL, decibel hearing level

Table 2 shows the bone conduction thresholds for either ear. The mean value for both ears is depicted in Figure 3, along with the data from the literature. Obviously, the mean thresholds at 2.0 kHz and 3.0 kHz do not fit the ISO 389-3 values.[13] At 2.0 kHz, a mere 20% of our subjects had a bone conduction threshold beneath 0 dB. The mean bone conduction thresholds at 1.0, 2.0 and 3.0 kHz diverge from the ISO zero value, and the difference is statistically significant ($p<0.01$).

DISCUSSION

The aim of the present study is to validate the ISO zero reference for air- and bone conduction hearing thresholds. Baseline hearing thresholds were obtained from a unique representative group of young adults with a blank otological history, as prospectively recorded. One hundred and seventy-five subjects were followed from childhood to adulthood. The follow-up included frequent history-taking, otomicroscopy, and impedance and audiometric measurements. By age 18, the typmpanic membrane in 99% of the ears of these subjects had a perfectly virgin appearance. Their tympanograms showed maximum deflection at ambient pressure and had a normal elicitable acoustic reflex. Obviously, we could not

definitively exclude exposure to noise. However, we had no reason to assume a history of excessively loud and/or lengthy exposure.

In short, these subjects have a practically otitis-free history, normal impedance and acoustic reflex measures, and no excessive noise exposure that had resulted in any measurable hearing deficit. Our evaluation of their status constitutes the maximum obtainable proof that they represent an otologically healthy population sample.

Audiometry

Table 1 and Figure 1 show that the air conduction thresholds measured in otologically healthy 18-year-olds meet with the ISO 389 reference values only for the mid-frequencies in the conventional frequency range. This does not hold true for the 0.25 kHz at one end of the spectrum and 6.0 and 8.0 kHz at the other end, however. Strikingly, 6.0 kHz does not appear to fit the reference value. This observation seems to corroborate the general picture presented in the literature (see Figure 1). That mismatch is undesirable, particularly since noise exposure might affect hearing in this frequency range. A dip at 6.0 kHz could easily be interpreted as a sign of noise-induced hearing loss.[6] However, the dip at 6.0 kHz did not occur in the data presented by Smith et al.[4] (see Figure 1). Nor did it occur in the data of Buren.[3] Buren found a 5 dB HL deviation at 6.0 kHz. But at 8.0 kHz an even larger discrepancy of almost 8.0 dB HL was recorded. The hearing thresholds at 6.0 kHz found by Smith[4] were the lowest of all. As discussed in their publication, this finding was unexpected. It was not in agreement with earlier findings by the same group (Lutman and Davis[2]). Lutman and Davis reported a significant dip at 6.0 kHz. According to Smith[4], the discrepancy between the results of their two studies was caused by differences in the equipment they used to make the measurements.

Figure 2 shows the mean hearing thresholds at the extended high frequencies, compared to data in the literature. A large spread is found between the data of the cited studies, all of which comprised measurements in young ‘normal’ hearing subjects. Valente et al.[16] found a similar spread when they compared eight studies of high-frequency hearing in adults. More studies will be needed to elucidate these differences.

Figure 3 and Table 2 present our mean bone conduction thresholds. Especially the 2.0 kHz and 3.0 kHz data seem out of the ordinary. However, they are close to the data of Smith.[4] The other mean values are close to zero, as are all the mean thresholds of Rahko-Laitila et al.[5] As indicated in the Population and Methods section, we allowed a negative air-bone gap as an outcome. In clinical practice, if

a bone conduction threshold is poorer than the air conduction threshold, the bone conduction threshold is taken as being equal to the air conduction threshold. Indeed, comparing the bone conduction thresholds at 2.0 and 3.0 kHz with the air conduction thresholds, a mean negative air-bone gap as large as 4.5 dB and 3.3 dB were found, respectively. If we had corrected the bone conduction thresholds in the event of a negative air-bone gap, a good correspondence with the zero reference values would have been found. Smith[4] and colleagues did not analyze their data in this respect. Nonetheless, an evaluation of their data reveals that the bone conduction thresholds were worse than the air conduction thresholds in the same frequency range as well. In the present study, the two audiometers were calibrated just before the start of the testing period. However, inappropriate calibration of the audiometric equipment cannot be ruled out as a possible contributor to a negative air-bone gap.

In this cohort, the exposure to noise is limited at age 18 years. By that age, the exposure had not led to any measurable hearing deficit in these subjects. A relation between noise exposure and hearing acuity could not be established in the reports by Buren[3], Axelsson[6], and Lutman and Davis[2] either. Again, our results show that there is insufficient evidence to assume that noise-induced hearing loss in adolescents is a general finding. Furthermore, the absence of a relation between hearing acuity and noise exposure underlines that the observed dip in hearing at 6.0 kHz is not caused by noise exposure but is more likely to result from a wrong reference zero.

In conclusion, earlier studies have already shown that the ISO zero reference for the air- as well as the bone conduction threshold, as measured with well calibrated audiometric equipment in soundproof booths that meet ISO regulations, does not represent normal hearing in otologically healthy subjects. According to our prospectively obtained data on otological history, based on longitudinal observations and measures, our group of subjects might be the best representative sample of otologically healthy subjects that has been studied so far. Their mean hearing thresholds are well within the range of those reported in the literature. Moreover, the hearing thresholds for air conduction that we found were the lowest of any reported in the literature so far. This study demonstrates once more the need to revise the ISO 389 for air conduction thresholds. Moreover, a critical evaluation of the ISO 389 bone conduction thresholds at 2.0 and 3.0 kHz is needed.

REFERENCES

1. ISO 389R. Acoustics. Reference zero for the calibration of audiometric equipment. Part 1: Reference equivalent threshold sound pressure levels for pure tones and supra-aural earphones. Geneva, Switzerland: International Organization of Standardization 1964.
2. Lutman ME, Davis AC. The distribution of hearing threshold levels in the general population aged 18-30 years. *Audiology* 1994;33:327-350.
3. Buren M, Solem BS, Laukli E. Threshold of hearing (0.125-20 kHz) in children and youngsters. *Br J Audiol* 1992;26:23-31.
4. Smith P, Davis A, Ferguson M, Lutman M. Hearing in Young Adults: Report to ISO/TC43/WG1. *Noise Health* 1999;1:1-10.
5. Rahko-Laitila P, Karma P, Laippala P et al. The pure-tone hearing thresholds of otologically healthy 14-year-old children. *Audiology* 2001;40:171-177.
6. Axelsson A, Rosenhall U, Zachau G. Hearing in 18-year-old Swedish males. *Scand Audiol* 1994;23:129-134.
7. Zielhuis GA, Rach GH, van den Broek P. Screening for otitis media with effusion in preschool children. *Lancet* 1989;1:311-314.
8. Schilder AGM, Zielhuis GA, Haggard MP, van den Broek P. Long-term effects of otitis media with effusion: otomicroscopic findings. *Am J Otol* 1995;16:365-372.
9. De Beer BA, Graamans K, Snik AF, Ingels K, Zielhuis GA. Hearing deficits in young adults who had a history of otitis media in childhood: use of personal stereos had no effect on hearing. *Pediatrics* 2003;111:e304-e308.
10. ISO 8253-1. Acoustics. Audiometric test methods. Part 1: Basic pure tone air and bone conduction threshold audiometry. Geneva, Switzerland: International Organization of Standardization 1989.
11. ISO 389-1. Acoustics. Reference zero for the calibration of audiometric equipment. Part 1: Reference equivalent threshold sound pressure levels for pure tones and supra-aural earphones. Geneva, Switzerland: International Organization of Standardization 1998.
12. ISO 389-2. Acoustics. Reference zero for the calibration of audiometric equipment. Part 2: Reference equivalent threshold sound pressure levels for pure tones and insert earphones. Geneva, Switzerland: International Organization of Standardization 1994.
13. ISO 389-3. Acoustics. Reference zero for the calibration of audiometric equipment. Part 3: Reference equivalent threshold force levels for pure tones and bone vibrators. Geneva, Switzerland: International Organization of Standardization 1994.
14. ISO/TR 389-5. Acoustics. Reference zero for the calibration of audiometric equipment. Part 5: Reference equivalent threshold sound pressure levels for pure tones in the frequency range 8 kHz to 16 kHz. Geneva, Switzerland: International Organization of Standardization 1998.
15. Lightfoot GR, Hughes JB. Bone conduction errors at high frequencies: implications for clinical and medico-legal practice. *J Laryngol Otol* 1993;107:305-308.
16. Valente M, Potts LG, Valente M, French-St GM, Goebel J. High-frequency thresholds: sound suite versus hospital room. *J Am Acad Audiol* 1992;3:287-294.
17. Stelmachowicz PG, Beauchaine KA, Kalberer A, Kelly WJ, Jesteadt W. High-frequency audiometry: test reliability and procedural considerations. *J Acoust Soc Am* 1989;85:879-887.
18. Frank T. High-frequency hearing thresholds in young adults using a commercially available audiometer. *Ear Hear* 1990;11:450-454.

8

General discussion
Summary
Samenvatting en conclusies

GENERAL DISCUSSION

This thesis describes the long-term consequences of otitis media and its treatment with ventilation tube insertion. The subjects participating in this study come from a large and unique historic cohort; born in 1982-1983, they were followed until 2001 for middle ear infections and related factors.[1] Job et al.[2] brought up the idea of studying the long-term consequences of otitis media. They reported hearing loss due to exposure to pop music in young adult males with a history of otitis media. As theirs was an explorative, retrospective study with many shortcomings and no explanation of the pathophysiologic mechanism, we took the initiative for a new, prospective study. A power calculation was performed to determine the number of subjects needed to test the hypothesis that subjects with and without a history of otitis media have a different susceptibility to hearing loss due to frequent personal stereo exposure. According to the calculation, we had to recruit 360 subjects. Therefore in 2001, we invited only part of our original historic cohort to participate in the study. Those who did get invited were selected from the original cohort on the basis of the presence or absence of otitis media in childhood. These subjects underwent otomicroscopy, extensive audiologic testing and history taking on ear and hearing related problems and noise exposure. With this database we were able to address the hypothesis of Job et al., but we could also assess the long-term effects of both untreated and treated otitis media in a Dutch population of unselected, otherwise healthy subjects. Moreover, the cohort incorporated subjects who were not affected by middle ear disease in childhood, the intrinsic reference group. The audiologic findings in these otologically healthy subjects offered an opportunity to investigate the validity of the audiometric zero reference, ISO-398.

The functional consequences in treated as well as untreated otitis media were expressed in hearing loss. Hearing at 8 and 18 years of age in both treated and untreated otitis media groups was significantly worse than hearing among the controls. In addition, there was a significant difference in hearing between the treated and the untreated group, with worse hearing in the treated group. At pure-tone audiometry we found an average hearing loss of 4 to 9 dB HL at 0.25 to 8 kHz in the group with a history of ventilation tube insertions. A remarkable finding is that there was a sensorineural component of this hearing loss in both the treated and the untreated group. At the age of 8 years, decreased sensorineural hearing in the treated group was already evident, whereas in the untreated group bone conduction thresholds were not yet significantly different from those of the controls. We could not confirm that ears with a history of otitis media (treated and untreated) were more susceptible to hearing loss due to frequent personal stereo

exposure, as has been found by Job et al. We presume that this difference in results is due to differences in study design and study population. In the study by Job et al., the otologic antecedents were assessed retrospectively just by history taking.

It became clear that there is a great difference in structural consequences of treated and untreated otitis media as well. We found that in 72% of the treated ears versus 17% of the untreated ears, the tympanic membrane showed some type of abnormality, tympanosclerosis being the most prevalent. Most tympanic membrane abnormalities seem to disappear in time, with the exception of tympanosclerosis. A measure of the compliance of the middle ear system is static admittance. Static admittance values in untreated ears were comparable to the values measured in the controls. The treated ears showed a markedly high percentage of extremely high values, indicative of decreased stiffness of the middle ear system. These high values coincided to some extent with the presence of atrophy in the tympanic membrane. We also addressed the presence of the acoustic reflex as a structural consequence of otitis media. Nearly half of the treated ears had a non-measurable acoustic reflex. In the untreated ears, this figure was only 15%.

Finally we discussed the point that hearing levels in our controls, i.e. otologically healthy individuals, did not correspond with the thresholds of ISO 389, the zero reference for pure-tone audiometry. On both ends of the speech frequency range of air conduction, i.e. 0.25, 6.0 and 8.0 kHz, a substantial discrepancy was demonstrated with the zero reference. The bone conduction thresholds of ISO 389 also differed from the thresholds in our otologically clean group, in particular at 2.0 and 3.0 kHz.

This study focused on the long-term effects of otitis media and its treatment with ventilation tubes. Previously, some important studies in this field had been carried out by Danish researchers headed by Tos, Stangerup and Sederberg-Olsen[3-5], the Otitis Media Research Center in Minneapolis in the USA[6] and by Maw and Bawden in the UK.[7,8] Our findings of (progressive) hearing loss and a high prevalence rate of tympanic membrane abnormalities in treated ears are in accordance with the results of these studies.

Hearing at (young) adult age appears to be negatively influenced by otitis media in childhood, meaning that even after such a long period without middle ear problems, a mild hearing loss can persist or even worsen in adulthood. Most strikingly we showed that young adults with a history of insertion of ventilation tubes had poorer hearing than those not treated surgically for otitis media. As the

likelihood of being treated with ventilation tubes is associated with the severity of disease, we adjusted the treatment effect estimates for disease activity by means of a score. Without randomization, such a correction cannot be perfect. Fifteen years after the initial diagnosis, Skinner et al.[9] showed a small, non-significant difference in hearing between the treated and untreated ears, to the detriment of the treated ears. Hunter et al.[10] studied hearing loss as expressed in air conduction thresholds in treated subjects. This hearing loss was more pronounced in the older than the younger age group, suggesting that hearing loss in treated subjects was progressive in nature. Our results support this hypothesis. So far, the results of our study on the functional effects of treatment of otitis media are in accordance with the literature.

Besides conductive hearing loss, we observed a small sensorineural component in the hearing loss resulting from ventilation tube insertion. This phenomenon has not been previously reported in the literature. In our study the sensorineural hearing loss in treated subjects was 1 to 2.5 dB (0.5 to 4.0 kHz) worse than in the untreated subjects, a statistically significant difference. Such a distinct difference had not been detected ten years earlier. It is unclear whether the deterioration is progressive or that the increase in hearing threshold is due to greater sensitivity of an audiogram made at age 18 compared to one made at 8 years of age. At age 8, conductive hearing losses were greater, while sensorineural hearing losses were less pronounced. Intercurrent middle ear pathology at that age might be responsible for the former finding. It remains obscure why a sensorineural component is added to the conductive hearing loss in the course of time and what the pathophysiologic mechanism could be. The literature poses hypotheses about oxygen radicals or inflammation mediators with a prolonged effect on the cochlea.[11-13] Whatever the mechanism might be, a 1 to 2.5 dB difference in mean hearing level between treated and untreated subjects, although irrelevant at the individual level, might have a substantial impact at the level of the population and therefore should not be disregarded.[14] A mean effect in sensorineural hearing acuity of this size, if sustained or found to progress after the age of 18, might lead to a substantial earlier need for a presbyacusis related hearing aid.

Other studies found the same high incidence of tympanic membrane abnormalities related to a history of ventilation tubes that we found. In the present study the prevalence of treated ears with tympanosclerosis, atrophy, attic retraction and pars tensa retraction corresponds to the figures reported by others.[4,8,15-21] Tympanosclerosis seems to be directly related to ventilation tube insertion [17,22,23] In accordance with other studies, tympanosclerosis appears to be a persistent tympanic membrane abnormality [3,9,18,19,23], whereas other forms of

tympanic membrane abnormalities tend to resolve in time. Contrary to our observation, several reports found an increased prevalence of atrophy in treated ears during follow-up.[4-6,8,9] We classified atelectasis and retraction pockets of the pars tensa as separate tympanic membrane abnormalities. These entities could be interpreted as resulting from increased laxity of the tympanic membrane and consequently could be classified as atrophy. Just like Daly[24] we found that atrophy was highly correlated with the presence of a high static admittance. In the ears of the treated subjects there was a marked increase of static admittance value over time, which cannot be explained by age alone. Besides atrophy and possibly atelectasis and retraction pocket of pars tensa, there are other factors that might contribute to increased compliance in ears treated with ventilation tubes. For instance, otitis media is known for its propensity to result in atrophy of the lenticular process of the incus, leading to laxity of the incudostapedial joint. This could also contribute to an increased static admittance. It could be hypothesized that the process of atrophy of the incus runs a different course in treated and untreated ears.

This study has demonstrated that the acoustic reflex was not measurable in nearly half of the treated ears. This correlation could be explained only partly by an air-bone gap and tympanic membrane abnormalities at the probe ear. Apparently other factors, not yet known and measurable, induce permanent changes in the middle ear of a temporarily perforated (with ventilation tubes) tympanic membrane.

Secondary to our observation on late effects of treated and untreated otitis media, we also collected all ear and hearing related data on subjects that had not had such middle ear problems at all. With this control group we dispose of a well-documented otologically ‘clean’ and healthy population. We think this group could provide the basis for a revised and updated version of the audiometry zero reference, ISO 389 (1964). It was difficult to trace how ISO 389 was composed, since this reference norm was based on various studies conducted in the 1950s and 1960s, some of which had not been published. Our results on diverging air conduction thresholds at the low and higher frequencies did correspond with those from other studies of otologically healthy subjects.[25-29] The quality of the studies used for the composition of ISO 389 may be questioned. Moreover, it is conceivable that hearing acuity in men is subject to change.

Strengths and weaknesses

The original cohort was not only large but also unique to a study of the development of middle ear disease and its treatment over time. However, the

historic database is not equally informative over the whole age range from birth to adulthood. Tympanometry was performed frequently during the period of 2 to 4 years of age and once when the subjects were around 8 and 18 years old. Detailed questionnaires supplemented the disease information for the remainder of the age span and also provided data on topics such as risk factors, date of surgery and other medical interventions. Extensive audiometry was performed only at age 8 and 18.

It should be stressed that this was an observational study, just like the preceding studies based on this historic cohort. The first one (1984) documented and analyzed the prevalence of otitis media as well as its treatment. A major challenge in such a non-experimental study is to separate the effects of disease from the (adverse) effects of treatment. To that end a disease (load) score was developed: a measure for disease load up to the age of 4 years or till the age of the first ventilation tube treatment. This score was used in multivariate analyses to estimate the net effect of ventilation tubes.

The original cohort comprised 1328 children yet only 358 members of the cohort were selected for this study. In particular, those with either a high disease score (with or without treatment) or a low disease score (controls) who still lived in the vicinity of Nijmegen were invited for reexamination. This resulted in a high response. The final study population of 358 subjects was sufficiently large to meet the major research objectives and appeared to represent the domain of the study fairly well. The size of the control group is comparable to that in other studies on hearing in otologically healthy subjects.[25-28] The treated subjects form the smallest subgroup. It should be emphasized that the composition of the group did not change during follow-up, unlike most of the series in the literature. Moreover, the group was well defined and the subjects' medical history was meticulously documented.

Recommendations for clinical practice and future research

The results of this study provide new arguments for the discussion about the most appropriate management of otitis media and about the effect of ventilation tube insertion in particular. Ventilation tube insertion used to be considered the best management of otitis media with effusion after its introduction in the 1950s. Gradually criticism developed, starting in the 1980s. A relatively large number of studies focused on the effectiveness of ventilation tubes.[30] This led to awareness of the potentially adverse effects and a restrictive stance towards this type of therapy. Recent prospective and randomized controlled trials suggest that ventilation tube insertion has little if any beneficial effect on hearing and later

speech and language development.[31] However, there are also positive effects of ventilation tube insertion. Parental and clinical observations generally point at an important beneficial effect.[32,33] It should be stressed that in patient care even temporary relief of symptoms may be of value. The results of this study support the generally accepted recommendation for treatment of otitis media: observe a period of watchful waiting before embarking upon the insertion of ventilation tubes, which still is the best management for treating persisting middle ear effusion.[34] The recommended policy of an initial period of watchful waiting is based on the best available evidence.[30,34-37] Moreover, the results of this study emphasize the need for identification of subgroups who are at risk of developing the negative effects of otitis media.[38]

With respect to future research, we recommend making a strict differentiation between the conductive and the sensorineural component of hearing acuity. The vast majority of studies on otitis media related hearing loss report their results solely in terms of air conduction. We suggest mentioning the sensorineural component separately, thereby enabling a more precise evaluation of the possible side effects of treatment with ventilation tubes. We have shown that the sensorineural component of hearing loss related to ventilation tube insertion did actually increase in the period between 8 and 18 years of age. But just how this sensorineural hearing loss is brought about is unknown. Therefore, the pathogenetic mechanism of this ventilation tube-induced hearing loss should be elucidated. The composition and the biomechanical properties of the middle ear fluid may play a role, but so might the surgeon who inserts the ventilation tubes as well as the technical aspects of the intervention. We could speculate on whether the progressive nature of this alarming symptom remains persistent after 18 years of age and, if so, at what pace it progresses. Long-term studies would be needed to make further evaluations. To that end, the birth cohort of this study would provide a unique opportunity.

Finally, considering the results of this study, we suggest realizing an updated version of ISO 389, the audiometry zero reference.

REFERENCES

1. Schilder AGM. Long-term effects of otitis media with effusion in children. Nijmegen, the Netherlands: SSN Publishers Nijmegen; 1993.
2. Job A, Raynal M, Rondet P. Hearing loss and use of personal stereos in young adults with antecedents of otitis media. *Lancet* 1999;353:35.
3. Tos M, Stangerup SE, Larsen P. Dynamics of eardrum changes following secretory otitis. A prospective study. *Arch Otolaryngol Head Neck Surg* 1987;113:380-385.

4. Stangerup SE, Tos M, Arnesen R, Larsen P. A cohort study of point prevalence of eardrum pathology in children and teenagers from age 5 to age 16. *Eur Arch Otorhinolaryngol* 1994;251:399-403.
5. Sederberg-Olsen JF, Sederberg-Olsen AE, Jensen AM. Late sequelae related to treatment with ventilation tubes for secretory otitis media in ENT practice. In: Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances in Otitis Media. Proceedings of the 5th International Symposium.Hamilton, Ontario, Canada: BC Decker Inc, 1993:843-846.
6. Levine SC, Daly KA, Lindgren BR, Giebink GS. Tympanic membrane pathology in adolescents and young adults 12 to 16 years after tympanostomy tube insertion for chronic OME. In: Lim D, Bluestone CD, Casselbrant M, Klein J, Ogra P, eds. Recent Advances in Otitis Media. Proceedings of the 6th International Symposium.Hamilton: BC Decker Inc, 1996:376-379.
7. Maw AR, Bawden R. The long term outcome of secretory otitis media in children and the effects of surgical treatment: a ten year study. *Acta Otorhinolaryngol Belg* 1994;48:317-324.
8. Maw AR, Bawden R. Tympanic membrane atrophy, scarring, atelectasis and attic retraction in persistent, untreated otitis media with effusion and following ventilation tube insertion. *Int J Pediatr Otorhinolaryngol* 1994;30:189-204.
9. Skinner DW, Lesser TH, Richards SH. A 15 year follow-up of a controlled trial of the use of grommets in glue ear. *Clin Otolaryngol* 1988;13:341-346.
10. Hunter LL, Margolis RH, Rykken JR, Le CT, Daly KA, Giebink GS. High frequency hearing loss associated with otitis media. *Ear Hear* 1996;17:1-11.
11. Huang M, Dulon D, Schacht J. Outer hair cells as potential targets of inflammatory mediators. *Ann Otol Rhinol Laryngol Suppl* 1990;148:35-38.
12. Lim DJ, Kawauchi H, DeMaria TF. Role of middle ear endotoxin in inner ear inflammatory response and hydrops: long-term study. *Ann Otol Rhinol Laryngol Suppl* 1990;148:33-34.
13. Schachern PA, Paparella MM, Goycoolea MV, Duvall AJ, III, Choo YB. The permeability of the round window membrane during otitis media. *Arch Otolaryngol Head Neck Surg* 1987;113:625-629.
14. Rose G, Day S. The population mean predicts the number of deviant individuals. *BMJ* 1990;301:1031-1034.
15. Larsen P, Tos M, Stangerup SE. Progression of drum pathology following secretory otitis media. In: Lim D, Bluestone CD, Klein J, Nelson J.D., eds. Recent Advances in Otitis Media. Proceedings of the 4th International Symposium.Toronto: B.C. Decker Inc, 1987:34-38.
16. Sederberg-Olsen JF, Sederberg-Olsen AE, Jensen AM. Late results of treatment with ventilation tubes for secretory otitis media in ENT practice. *Acta Otolaryngol* 1989;108:448-455.
17. Schilder AGM, Zielhuis GA, Haggard MP, van den Broek P. Long-term effects of otitis media with effusion: otomicroscopic findings. *Am J Otol* 1995;16:365-372.
18. Daly KA, Hunter LL, Levine SC, Lindgren BR, Giebink GS. Relationships between otitis media sequelae and age. *Laryngoscope* 1998;108:1306-1310.
19. Rosenfeld RM, Isaacson G.C. Tympanotomy Tube Care and Consequences. In: Rosenfeld RM, Bluestone CD, eds. Evidence Based Otitis Media 2nd edition. 2nd ed. Hamiliton, Ontario: B.C. Decker Inc; 2003:460-481.
20. Ryding M, White P, Kalm O. Eustachian tube function and tympanic membrane findings after chronic secretory otitis media. *Int J Pediatr Otorhinolaryngol* 2004;68:197-204.
21. Riley DN, Herberger S, McBride G, Law K. Myringotomy and ventilation tube insertion: a ten-year follow-up. *J Laryngol Otol* 1997;111:257-261.
22. Tos M, Stangerup SE. Hearing loss in tympanosclerosis caused by grommets. *Arch Otolaryngol Head Neck Surg* 1989;115:931-935.
23. Maw AR. Development of tympanosclerosis in children with otitis media with effusion and ventilation tubes. *J Laryngol Otol* 1991;105:614-617.
24. Daly KA, Hunter LL, Lindgren BR, Margolis R, Giebink GS. Chronic otitis media with effusion sequelae in children treated with tubes. *Arch Otolaryngol Head Neck Surg* 2003;129:517-522.
25. Buren M, Solem BS, Laukli E. Threshold of hearing (0.125-20 kHz) in children and youngsters. *Br J Audiol* 1992;26:23-31.
26. Lutman ME, Davis AC. The distribution of hearing threshold levels in the general population aged 18-30 years. *Audiology* 1994;33:327-350.
27. Axelsson A, Rosenhall U, Zachau G. Hearing in 18-year-old Swedish males. *Scand Audiol* 1994;23:129-134.

28. Smith P, Davis A, Ferguson M, Lutman M. Hearing in Young Adults: Report to ISO/TC43/WG1. *Noise Health* 1999;1:1-10.
29. Rahko-Laitila P, Karma P, Laippala P et al. The pure-tone hearing thresholds of otologically healthy 14-year-old children. *Audiology* 2001;40:171-177.
30. Lous J, Fiellau-Nikolajsen M, Jeppesen AL. Secretory otitis media and language development: a six year follow-up study with case-control. *International Journal of Pediatric Otorhinolaryngology* 1988;15:185-203.
31. Roberts J, Hunter L, Gravel J et al. Otitis media, hearing loss, and language learning: controversies and current research. *J Dev Behav Pediatr* 2004;25:110-122.
32. Karkanevatos A, Lesser TH. Grommet insertion in children: a survey of parental perceptions. *J Laryngol Otol* 1998;112:732-741.
33. Rosenfeld RM, Bhaya MH, Bower CM et al. Impact of tympanostomy tubes on child quality of life. *Arch Otolaryngol Head Neck Surg* 2000;126:585-592.
34. Rosenfeld RM, Culpepper L, Doyle KJ et al. Clinical practice guideline: Otitis media with effusion. *Otolaryngol Head Neck Surg* 2004;130:S95-118.
35. Paradise JL, Feldman HM, Campbell TF et al. Tympanostomy tubes and developmental outcomes at 9 to 11 years of age. *N Engl J Med* 2007;356:248-261.
36. Rovers MM, Black N, Browning GG, Maw R, Zielhuis GA, Haggard MP. Grommets in otitis media with effusion: an individual patient data meta-analysis. *Arch Dis Child* 2005; 90:480-485.
37. Boomsma LJ, van Balen FA, Rovers MM, Wiersma T, Goudswaard AN. [The practice guideline 'Otitis media with effusion' (second revision) from the Dutch College of General Practitioners]. *Ned Tijdschr Geneeskd.* 2006;150:2028-2032.
38. Rovers MM, Schilder AG, Zielhuis GA, Rosenfeld RM. Otitis media. *Lancet* 2004;363:465-473.

SUMMARY

One of the most common pathologic conditions in children is otitis media with effusion. In this condition, fluid collects in the tympanic cavity, resulting in a temporary mild to moderate hearing loss (10 to max 50 dB). Treatment by inserting a ventilation tube is aimed at restoring hearing and preventing any potential developmental problems. However, opinions regarding risks and benefits of ventilation tube insertion vary greatly and therefore management of otitis media remain controversial. In the present study we investigate the long-term functional and structural consequences of both treated and untreated childhood otitis media. The material is drawn from the follow-up of the original Radboud University Nijmegen Ear Research cohort, an unselected, otherwise healthy population. The subjects of this study cohort were born in 1982-1983 and were followed until 2001 for otitis media and related factors. Two studies on this cohort preceded the present one: a preschool study (at age 2 to 4 years) and a school-age study (at about 8). In the preschool study, tympanometry was performed at three-month intervals. From the school age study, the results of tympanometry and pure-tone audiometry were available. For both studies, detailed questionnaires on ear disease and its treatment were filled in on each subject's current status and on the remainder of the age span. On that basis, an otitis media score was assessed retrospectively for each subject at age 18. The subjects in the highest and the lowest third of the otitis media score were invited to participate; eventually a subpopulation of 358 subjects was studied. Subjects in the highest third of the otitis media score were characterized as having a positive otitis media history (OM+). Some of them were treated by inserting a ventilation tube (OM+VT+), while the other part of the group remained untreated (OM+VT-). Subjects in the lowest third of the otitis media score were characterized as having a negative otitis media history (OM-); these subjects served as controls. The present study is focused on hearing and on the assessment of parameters of middle ear appearance and functioning.

In Chapter 2, the long-term functional consequences for hearing are described for both treated and untreated otitis media. At 8 and 18 years of age, the treated subjects had worse hearing than the untreated subjects. The difference between treated and untreated subjects in conductive hearing loss remained stable over the period between 8 and 18 years of age. Treatment with ventilation tubes in childhood resulted in an average conductive hearing loss of 4 to 9 dB HL (0.25 to 8.0 kHz) at age 18. This hearing loss was more severe in subjects who had repeated tube insertions. Besides conductive hearing loss, we observed a

sensorineural component. Again, sensorineural hearing loss was more pronounced in treated subjects. Moreover, sensorineural hearing loss appeared to be progressive in the course of time from age 8 to 18 years. At 18 years, the sensorineural hearing loss in treated subjects was 1 to 2.5 dB HL (0.5 to 4.0 kHz) worse than the hearing in untreated subjects, a significant difference. At 8 years, there was not yet a significant difference in sensorineural hearing loss between the treated and the untreated subjects.
We confirmed that tympanic membrane abnormalities were frequently observed in treated subjects. The presence of tympanic membrane abnormalities was associated with poorer hearing. However, tympanic membrane abnormalities did not seem to be a prerequisite for (conductive) hearing loss in treated subjects.

Chapter 3 describes the course of tympanic membrane abnormalities over the period from 8 to 18 years in both treated and untreated subjects. Tympanic membrane abnormalities were a common finding in the short-term as well as the long-term follow-up. We observed a decline in the presence of tympanic membrane abnormalities. This decline suggests the existence of an intrinsic repair mechanism of the tympanic membrane. At 18 years, the prevalence of tympanic membrane abnormalities was 72% in treated subjects and 17% in untreated subjects, whereas at 8 years the prevalence figures were 92% in treated and 46% in untreated subjects. We confirmed that tympanosclerosis was directly related to ventilation tube treatment. In treated ears, tympanosclerosis was the most common finding. Moreover, it was the most persistent condition: about 70% of the ears with tympanosclerosis at 8 years still showed this condition at 18 years. Atrophy was more prevalent and more persistent in treated ears compared to untreated ears. Atelectasis of the middle ear, an uncommon observation in both treated and untreated subjects, rarely developed after the age of 8. Perforation of the tympanic membrane was a rare finding, although prevalence in treated subjects rose slightly: from 4% at 8 years to 7% at 18 years. In the whole study cohort, there was just one ear that had been treated for cholesteatoma.

Chapter 4 deals with stiffness of the middle ear system, as studied and expressed in static admittance values. We confirmed that these values generally increase with age. Our results show that static admittance at age 8 is a strong predictor of the value at 18, in light of the high correlation of individual values at 8 and 18 years. Both at 8 and 18 years of age, static admittance values were highest in the treated subjects. During follow-up, the difference in static admittance values between the treated and untreated subjects had increased. Moreover, we

observed an increase of extreme static admittance values in treated subjects, rising from 16% to 35% between age 8 and 18. A static admittance value was defined as extreme when it was higher than the 95th percentile static admittance value of the age-specific value for normal middle ears. In part, these extreme static admittance values coincided with the presence of atrophy of the tympanic membrane. By comparison of two multivariate regressionmodels, it was demonstrated that the effect of previous ventilation tube insertion on static admittance at age 18 years could not be explained by tympanic membrane abnormalities of whatever nature, except for atrophy. Only atrophy mediated the effect of ventilation tubes on the static admittance value. Furthermore, changes in tympanic membrane abnormalities did not appear to be related to changes in static admittance values over time.

Chapter 5 addresses the presence and threshold of the acoustic reflex in ears of treated and untreated subjects. The median threshold at 1.0 kHz was 105 dB SPL in the treated ears and 100 dB SPL in the untreated ears; this was 95 dB SPL in the control group. After correction for the air-bone gap at the stimulus ear, however, the threshold was 95 dB SPL in treated as well as untreated subjects. Remarkably, in 47% of the treated subjects, the acoustic reflex was not measurable. In the untreated subjects, 15% had a non-measurable acoustic reflex. Presence of tympanic membrane abnormalities as well as an air-bone gap in the probe ear (the ear in which the activating stimulus was measured) increased the rsik of a non-measurable acoustic reflex. In a multivariate regression analyses we demonstrated that the effect of a history of ventilation tube treatment on the acoustic reflex response is partly independent, though is enhanced by the intercorrelated status of the middle ear, viz. presence of tympanic membrane abnormalities and an air-bone gap.

Chapter 6 explores the hypothesis that a history of otitis media predisposes a young adult for increased susceptibility to hearing loss due to pop music exposure when listened to with personal stereo devices. We could not confirm this hypothesis. Exposure to pop music at levels established in this population had not led to any measurable hearing loss.

The availability of a control group of subjects without middle ear problems in their histories allowed us to document normal hearing levels in healthy young adults with a negative otologic history. In Chapter 7 their hearing thresholds were compared to the zero reference, as defined in ISO 389. It was demonstrated that

the measured hearing thresholds in the control group for both low and high frequencies in the speech frequency range did not correspond with the zero reference. The discrepancy at 0.25 kHz and 6.0 kHz was large: respectively 6.0 dB HL and 8.5 dB HL. At 8.0 kHz there was a statistically significant difference of 3.2 dB HL from the zero reference. For bone conduction thresholds, ISO 389 at 2.0 and 3.0 kHz showed differences in the thresholds of respectively 5.8 dB HL and 3.3 dB HL. We advocate revision of the ISO 389 reference thresholds for audiometry for both air conduction and bone conduction.

In Chapter 8, the overall conclusions of this thesis are discussed in light of present knowledge of the long-term consequences of otitis media and its treatment with ventilation tubes. The long-term follow-up of this historic cohort has produced a wealth of information. In addition to the known structural consequences of ventilation tube insertion, we showed some long-term functional sequelae, specifically conductive and sensorineural hearing loss. This delayed ventilation tube induced sensorineural hearing loss has not been mentioned before in the literature. How this sensorineural hearing loss evolves in the course of time, and whether it is sustained or progresses, is unknown. This hearing loss might lead to a substantial earlier need for a presbyacusis related hearing aid later in life. The aim of hearing improvement by insertion of ventilation tubes in children is quite the opposite of causing adverse effects on hearing later in life. The risks of adverse effects should be taken into consideration when ventilation tube insertion in children is envisaged. The difficulty of deciding to insert ventilation tubes as a treatment for otitis media lies in identifying children who are at risk for delayed and impaired speech and behavioral development when otitis media is left untreated. More research is needed to identify subgroups of children in whom the short-term benefits of improvement or the prevention of speech and language impairments or delays would outweigh the possible adverse effect on hearing later in life. For the time being, treatment by ventilation tube insertion remains indicated in clinical practice, until such time as these subgroups can be identified. Meanwhile, we have been alerted to the possible adverse long-term effects on hearing and should keep these in mind.

SAMENVATTING

Otitis media is één van de meest frequent vóórkomende aandoeningen op de kinderleeftijd. Vochtophoping in het middenoor gaat gepaard met een gering tot matig gehoorverlies (10 tot maximaal 50 dB). Het doel van behandeling met trommelvliesbuisjes is het vocht te verwijderen en daarmee het gehoor te herstellen en zo potentiële ontwikkelingsproblemen te voorkómen. Echter, het is nog onduidelijk welke de mogelijk negatieve gevolgen op de lange termijn zijn. Dit proefschrift beschrijft de functionele lange termijn gevolgen voor het gehoor en de structurele lange termijn gevolgen voor het middenoor (trommelvliesbeeld en functie middenoorstructuren) van zowel behandelde als niet-behandelde otitis media. Dit is een vervolgstudie van het KNOOP-onderzoek (1984-1987) (Katholieke Universiteit Nijmegen Oor Onderzoek Peuters) dat is uitgevoerd bij een gezond geboortecohort. De personen van dit cohort waren allen geboren in 1982-1983 en werden vervolgd tot en met 2001. Tijdens deze follow-up werd telkens gekeken naar een aantal aspecten van otitis media. Aan het onderhavige onderzoek gingen twee studies vooraf: een op peuterleeftijd (2-4 jaar) en een op lagere school leeftijd (ongeveer 8 jaar). Bij de peuter studie werd met een interval van telkens 3 maanden een tympanogram vervaardigd. Bij het onderzoek op lagere school leeftijd werd naast tympanometrie ook audiometrie gedaan. Bij beide studies werd aan de hand van een gedetailleerde vragenlijst informatie verzameld over ooraandoeningen en eventuele behandelingen op het moment zelf en de daaraan voorafgaande periode. Op de leeftijd van 18 jaar kon zodoende een zogenoemde otitis media score retrospectief worden vastgesteld. Voor dit onderzoek werden personen geselecteerd uit het hoogste en laagste derde deel van de otitis media score. Uiteindelijk bleken 358 personen voor dit onderzoek beschikbaar te zijn. Personen met de hoogste otitis media score waren personen met een gedocumenteerde voorgeschiedenis van otitis media. Een deel van hen was behandeld met trommelvliesbuisjes, terwijl het andere deel niet chirurgisch was behandeld. De mensen uit de laagste otitis media score hadden geen otitis media in de voorgeschiedenis en deze fungeerde als de controlegroep. Deze studie is toegespitst op gehoor en parameters van trommelvliesbeeld en middenoorfunctie van de onderzoekspopulatie.

In Hoofdstuk 2 worden de lange termijn gevolgen op het gehoor van zowel behandeling als geen behandeling van otitis media met trommelvliesbuisjes besproken. Zowel op 8 als op 18-jarige leeftijd hadden de personen die behandeling hadden ondergaan een slechter gehoor dan de personen die niet waren behandeld. Het verschil in gehoordrempels tussen de behandelde en niet-

behandelde personen bleef overigens gelijk in de periode van 8 tot 18 jaar. Op 18-jarige leeftijd bleek behandeling met trommelvliesbuisjes te hebben geresulteerd in gemiddelde drempels in het luchtgeleidingsaudiogram van 4 tot 9 dB HL (0.25 tot 8.0 kHz). Herhaling van behandeling met trommelvliesbuisjes leidde tot ernstiger gehoorverlies. Naast geleidingsverlies werd op 18-jarige leeftijd ook perceptief gehoorverlies geconstateerd. Ook het perceptieve gehoorverlies was voornamelijk aanwezig bij de behandelde personen. In het tijdsverloop van 8 tot 18 jaar blijkt dit perceptieve gehoorverlies bovendien progressief te zijn. Op 18-jarige leeftijd waren de gemiddelde perceptieve drempels 1 tot 2.5 dB HL (0.5 tot 4.0 kHz) slechter van de behandelde personen dan van de niet-behandelde personen. Dit verschil is statistisch significant. Op 8-jarige leeftijd was er nog niet een significant verschil in perceptieve gehoordrempels tussen behandelde en niet-behandelde personen aantoonbaar.
Ook deze studie laat zien dat trommelvliesafwijkingen vaker worden aangetroffen in de behandelde populatie dan in de niet-behandelde populatie. Behalve dat aanwezigheid van trommelvliesafwijkingen geassocieerd is met slechtere gehoor-drempels, zijn deze trommelvliesafwijkingen geen voorwaarde voor slechter gehoor in personen die behandeld zijn met trommelvliesbuisjes.

In hoofdstuk 3 word het vóórkomen en het natuurlijke beloop van trommelvlies-afwijkingen in de periode van 8 tot 18 jaar beschreven in de behandelde en de niet-behandelde populatie. Zowel in de studie op schoolleeftijd als in deze studie op jongvolwassen leeftijd werden er frequent trommelvliesafwijkingen geobserveerd. Dat er een duidelijke afname in vóórkomen van trommelvlies-afwijkingen geconstateerd werd, zou kunnen duiden op een intrinsiek herstel-mechanisme van het trommelvlies. Op 18-jarige leeftijd werden bij de behandelde populatie in 72% van de oren trommelvliesafwijkingen geobserveerd; in de niet-behandelde populatie was dit 17%. Op 8-jarige leeftijd waren deze getallen respectievelijk 92% en 46%. Aanwezigheid van tympanosclerose stond in direct verband met behandeling met trommelvliesbuisjes en was tevens de meest vóórkomende trommelvliesafwijking in de behandelde groep. Tympanosclerose heeft een blijvend karakter: in ca 70 % van de oren waarbij op 8-jarige leeftijd tympanosclerose aanwezig was, was dat op 18 jarige leeftijd nog steeds het geval. Atrofie van het trommelvlies was meer vóórkomend en vertoonde een meer blijvend karakter in de behandelde oren dan in de niet-behandelde oren. Atelectase van het middenoor was een zeldzame afwijking in zowel de behandelde als de niet-behandelde oren en ontstond slechts in een enkel geval na de leeftijd van 8 jaar. Slechts zelden was een trommelvliesperforatie te zien,

echter er was sprake van een lichte toename in de behandelde populatie: 4% op 8 jaar en 7% op 18 jaar. In de hele studie had slechts één persoon in een oor cholesteatoom ontwikkeld en was daarvoor behandeld.

Hoofdstuk 4 gaat in op een studie naar de stijfheid van het middenoorsysteem, uitgedrukt in compliantiewaarden. We vonden een bevestiging voor het verschijnsel dat compliantie van het middenoor toeneemt bij ouder worden. Uit onze resultaten bleek dat de middenoorcompliantie op 8 jaar een goede voorspeller was voor de waarde op 18 jaar, gezien de hoge correlatie tussen de individuele compliantiewaarden op 8 en 18 jarige leeftijd. De middenoor-compliantiewaarden van oren in de behandelde populatie waren op zowel de leeftijd van 8 als van 18 jaar de hoogste. Het verschil in compliantiewaarden tussen de oren in de behandelde populatie in vergelijking met de niet-behandelde populatie nam toe. In de periode van 8 naar 18 jaar steeg het aantal extreme hoge compliantiewaarden in de behandelde populatie van 16% naar 35%. Een compliantiewaarde werd gedefinieerd als extreem hoog wanneer het een waarde had dat hoger lag dan het 95ste percentiel van de verdeling van normale, leeftijdsgebonden middenoorcompliantiewaarden. Een deel van deze extreme compliantiewaarden werd vastgesteld in oren die ook atrofie van het trommelvlies vertoonden. In een vergelijking van twee multivariate regressiemodellen werd aangetoond dat het effect van trommelvliesbuisjes op de waarde van de middenoorcompliantie op 18-jarige leeftijd niet kon worden verklaard door aanwezigheid van trommelvliesafwijkingen, behoudens voor atrofie. Verandering van het trommelvliesbeeld door aan- of afwezigheid van trommelvliesafwijkingen bleek niet gerelateerd aan verandering in de middenoorcompliantiewaarde.

Hoofdstuk 5 behandelt de aanwezigheid en mate van de stapedius reflexdrempel in de behandelde en de niet-behandelde populatie. De mediane drempel van een opwekbare stapedius reflex bij 1.0 kHz was 105 dB SPL in de behandelde populatie en 100 dB SPL in de niet-behandelde populatie; dit was 95 dB SPL in de controlegroep. Nadat correctie voor het bestaan van een lucht- en been-geleidingsdrempelverschil (‘air-bone gap’) was toegepast, bleek de stapedius reflexdrempel voor de behandelde en de niet-behandelde populatie eveneens op 95 dB SPL te liggen. Wel was het opmerkelijk dat in de behandelde populatie 47% van de oren de stapedius reflex niet-opwekbaar was. In de niet-behandelde populatie was dit in 15% het geval. Er bleek een verband te bestaan tussen aanwezigheid van trommelvliesafwijkingen en/of een air-bone gap in het oor met de probe (oor waarin de reactie op de stimulus werd gemeten) en het niet-

opwekbaar zijn van de stapedius reflex. Door vergelijking van twee multivariabele regressiemodellen werd aangetoond dat het effect van behandeling met trommelvliesbuisjes op de opwekbaarheid van de stapedius reflex deels onafhankelijk is, maar wordt versterkt door de ermee samenhangende aanwezigheid van trommelvliesafwijkingen.

Hoofdstuk 6 behandelt de hypothese dat een voorgeschiedenis met otitis media bij jongvolwassenen een verhoogde gevoeligheid geeft voor het ontstaan van lawaaischade door blootstelling aan popmuziek. Deze hypothese kon niet worden bevestigd. Popmuziek op het niveau waaraan onze onderzoekspopulatie blootgesteld was, leidde niet tot meetbare gehoorschade.

De aanwezigheid van een groep personen met de gedocumenteerde afwezigheid van middenoorproblemen (de controle groep), gaf de mogelijkheid om het gehoor van deze gezonde personen te beschrijven. In Hoofdstuk 7 worden de gehoordrempels van deze controle groep vergeleken met de referentie nullijn, de ISO 389. We toonden aan dat de door ons gemeten gehoordrempels in otologisch normalen in zowel de lage als hoge frequenties van het toondrempelaudiogram niet overeenkomen met de referentie nul-lijn. Het verschil in gehoordrempel op 0.25 kHz en 8.0 kHz was respectievelijk 6.0 dB HL en 8.5 dB HL. Bij 8.0 kHz was er een statistisch significant verschil van 3.2 dB HL met de referentie nul-lijn. De ISO 389 verschilde voor de beengeleidingsdrempels op 2.0 en 3.0 kHz met respectievelijk 5.8 dB HL en 3.3 dB HL. Ons inziens is revisie van de ISO 389 referentie voor zowel de lucht- als de beengeleiding gehoordrempels noodzakelijk.

In hoofdstuk 8 worden de conclusies van dit proefschrift besproken in het licht van de huidige kennis van de lange termijn gevolgen van otitis media en de behandeling ervan. De lange follow-up van dit geboortecohort heeft een weelde aan informatie opgeleverd. In navolging van het reeds bekende vóórkomen van structurele veranderingen van het middenoor na behandeling met trommelvliesbuisjes, liet deze studie ook zien dat er gevolgen zijn voor het gehoor door deze behandeling. Het ontstaan van een perceptief gehoorverlies door behandeling met trommelvliesbuisjes is niet eerder beschreven in de literatuur. Hoe dit perceptief gehoorverlies zich naderhand gedraagt, of het aanhoudt of verergert, is niet duidelijk. Dit gehoorverlies zou kunnen leiden tot de behoefte aan een hoortoestel op een jongere leeftijd dan verwacht kan worden op basis van ouderdomsslechthorendheid (presbyacusis). Het doel van het bereiken van gehoorverbetering door plaatsen van trommelvliesbuisjes bij kinderen staat lijnrecht

tegenover het bewerkstelligen van gehoorschade op de latere leeftijd. Het risico op gehoorschade op de lange termijn zou moeten meewegen in de besluitvorming tot het plaatsen van trommelvliesbuisjes bij kinderen met otitis media. De moeilijkheid bij de besluitvorming over de behandeling van otitis media is het vaststellen of kinderen gevaar lopen op het ontstaan of verergeren van ontwikkelingsstoornissen en/of achterstand bij afzien van behandeling. Verder onderzoek is nodig om subgroepen te identificeren bij wie de korte termijn winst van voorkómen van spraak-taalontwikkelingsachterstand opweegt tegen het mogelijk risico op het ontstaan van gehoorverlies op de latere leeftijd. Vooralsnog heeft behandeling met trommelvliesbuisjes voor otitis media zijn plaats in de klinische praktijk behouden. Men dient zich echter te realiseren dat deze behandeling niet geheel zonder risico's is op de lange termijn.

DANKWOORD

Een belangrijk onderdeel van dit proefschrift betreft mijn dankuiting aan alle mensen die direct en indirect betrokken waren bij de totstandkoming van dit wetenschapswerk. Om te beginnen mijn promotores:

Prof. dr. K. Graamans, als mijn hoofdpromotor en hoofdopleider ben ik u veel dank verschuldigd. Zodra duidelijk werd dat u hoofdpromotor ging worden, heeft u zich intensief met vorm en inhoud bemoeid en altijd weer werden de manuscripten snel en zorgvuldig van commentaar voorzien. Op de goede momenten wist u de druk en daarmee het werktempo op te voeren. Ik bewonder uw niet-aflatende streven naar heldere en duidelijke formuleringen.

Prof. dr. ir. G.A. Zielhuis, beste Gerhard, dank voor het vertrouwen in mij en jouw consciëntieuze begeleiding. Ik bewonder het in jou dat jij over vele zaken genoeg afweet om er rake opmerkingen over te maken. Met jouw helikoptervisie en ideeën over structuur weet jij de kwaliteit van zowel vorm als inhoud van het werk steevast te verhogen.

Prof. dr. ir. A.F.M. Snik, beste Ad, dank voor jouw enthousiasme en vertrouwen in een geslaagde afronding van de afzonderlijke artikelen en het boekwerk als een geheel. Jouw input was voor de audiologisch getinte artikelen van grote waarde.

Wim Lemmens, beste Wim, wat heb jij mij fantastisch geholpen met dit enorme databestand en de statistische bewerking ervan. Op het moment dat het databestand zijn huidige vorm begon aan te nemen, hebben wij veelvuldig contact gehad: rustigere perioden afgewisseld met zeer intensieve perioden. Zeker in deze laatste fase was jij er voor mij met jouw veelal ad hoc statistische oplossingen en om al mijn andere verhalen over kliniek en privé aan te horen.

De enthousiaste deelnemers en aanvankelijk hun ouders hebben gezorgd voor invulling van dit rijke gegevensbestand. Ik dank hen daarvoor. Ik dank ook de grondleggers van deze KNOOP studies: in het bijzonder prof. dr. P. van den Broek (emeritus hoogleraar KNO) en Gerhard Zielhuis. De eerste KNOOP studie die al 23 jaar geleden van start ging, is een succesvolle samenwerking tussen de afdelingen KNO en Epidemiologie & Biostatistiek van het UMC St Radboud gebleken. Dr. A.G.M. Schilder, dr. E.H. Grievink en dr. S.A.F. Peters promoveerden op de gegevens van vervolgstudies, 6 jaar na de eerste studie.

Uitwerking van het idee van een vervolgstudie van de inmiddels volwassen geworden KNOOP deelnemers werd ondersteund door een begeleidingscommissie, waaronder drs. W. Passchier-Vermeer van TNO preventie en gezondheid, prof. dr. C.W.R.J. Cremers, dr. K.J.A.O Ingels en dr. A.G.M. Schilder. Deze laatste twee personen hebben ook later in de studie een belangrijke bijdrage geleverd. Alle leden wil ik bedanken.

In de uitvoer van het project werd ik bijgestaan door Sonja van Oosterhout, die de gegevensverzameling mede coördineerde. Mijn dank daarvoor. De mailings werden extra succesvol doordat we ook een website met informatie hadden aangemaakt; met dank aan Ton Monasso. Op de studiedagen doorliepen de deelnemers een carrousel met onderzoek van de oren, audiologische metingen en het invullen van een elektronische vragenlijst (Hans Groenewoud bedankt voor het flitsende ontwerp). Dames van audiologie: Pieta Folman, Teja Repkes, Mieki Verbruggen, Mariska Brouwers, Esther Kleingeld, Yvonne de Graaf, Margot Frösch, Anke Kooijman, Evelien Verver, Iris Tijshen en Annemiek, allen dank ik jullie voor jullie enthousiasme om de jonge dames en heren deelnemers te audiometreren op jullie vrije vrijdagen en zaterdagen.

De finishing touch van de artikelen werd verzorgd door het sublieme redigeerwerk van Nancy van Weesep-Smith. Heel veel dank; fijn dat ik altijd weer op je kon rekenen. De verschijning van dit boekje zal nooit zo geslaagd zijn zonder de fantastische bijdrages van Diny Helsper-Peters, voor de lay-out van het binnenwerk en Bas Ben Zinep, voor het buitenwerk. Mirjam Albada Jelgersma, dank je voor jouw toegewijde vriendschap en je goede adviezen tijdens de afronding van dit boekje.

In de opstart fase van deze studie was ik gestationeerd op de afdeling Epidemiologie en Biostatistiek (EPIB) met kamergenoot Maroeska Rovers. Ik bewaar daar heel goede herinneringen aan. Zo werd ik ook altijd weer gastvrij ontvangen in ‘pension EPIB’ als ik kwam werken in een vrije studieweek en op mijn wetenschaps/ouderschapsverlofdagen.

Naast het verrichten van de studie en het schrijven van dit boekje, ben ik bovenal in opleiding tot KNO-arts. Alle KNO stafleden en opleiders van het UMC St Radboud, Rijnstate Ziekenhuis in Arnhem en het Canisius Wilhelmina Ziekenhuis in Nijmegen wil ik danken voor de leerzame opleidingsperiode. Mijn opleiding tot KNO-arts zit er bijna op en dus heb ik al heel wat collega-assistenten zien komen

en gaan. Alle assistenten ‘have been there’ en assistenten ‘to be’ bedankt voor de goede tijd die we samen hebben en hebben gehad. Verder wil ik ook alle andere mensen die werkzaam zijn binnen de verschillende afdelingen KNO van het UMC St Radboud en de beide perifere ziekenhuizen bedanken voor hun bijdrage aan een goede werksfeer. Ik kijk op een heel prettige opleidingstijd terug.

Vrienden en vriendinnen, jullie weten als geen ander dat om deze eindstreep te halen ik een heleboel heb moeten doen, beter gezegd ‘heb gedaan’, maar daardoor ook een heleboel heb moeten laten. Ik hoop de komende tijd nog veel van onze vriendschappen te mogen gaan genieten.

Paranimfen. Lieve Klaar, mijn oudere zus, ik geniet altijd zo van je verhalen over al je belevenissen. Op het gebied van time management zou ik zeker nog veel van je kunnen leren. Lieve Anne, met jou begon ik mijn wetenschappelijke carrière in Zuid-Afrika. Behalve een heel mooie reis en een bijzondere tijd, hebben we die periode niet onverdienstelijk afgesloten! Het geeft mij een vertrouwd gevoel dat jullie naast mij staan.
Lieve Pap en Mam, ‘een kind heb je voor je leven’ zeggen jullie wel eens; heerlijk dat ik altijd op jullie kan terugvallen.
Inge, zonder jouw lieve en warme opvang van onze dochter Nina, zou ik niet altijd zo vaak en zo lang van huis durven gaan. Ik ben je heel dankbaar.

Lieve Mark, zonder jouw nuchterheid en relativerende opmerkingen en adviezen zou ik deze fase in ons leven niet zo gemakkelijk zijn doorgerold. Met jouw liefde en steun zie ik elke nieuwe uitdaging met vertrouwen tegemoet.
Lieve Nina, mijn ‘covergirl’, jij bent de liefste en meest goedlachse peuter die je als moeder maar kunt wensen. Door jou en met jou staan we nu waar we staan. Ik verheug me erop om op de eerstvolgende zaterdagochtend op de markt te laten zien dat jij naast een toegewijde vader ook nog een moeder hebt, die veel van je houdt en heel trots op jou is.

CURRICULUM VITAE

Brechtje Aurelia de Beer werd op 20 februari 1974 geboren in Amsterdam. Na het doorlopen van de basisschool en de middelbare school behaalde zij in 1992 haar VWO-diploma aan het Sint Vitus College in Bussum. Aansluitend volgde zij aan het James Boswell instituut in Utrecht haar VWO certificaat Natuurkunde en werd zij beloond met de Roos prijs voor haar positieve inzet, enthousiasme en motivatie van de groep. In september 1992 ging zij voor 9 maanden naar Oxford en behaalde haar First Certificate for Englisch as Foreign Language (EFL) met de hoogste onderscheiding en het Proficiency Certificate for EFL. In 1993 begon zij aan haar studie Geneeskunde aan de Vrije Universiteit in Amsterdam. Voor afronding van het doctoraal examen werd een wetenschappelijke stage gelopen in Kaapstad, Zuid Afrika, die werd voltooid met een publicatie. Na het doorlopen van haar co-schappen behaalde zij haar artsexamen in juli 2000. Na een kortstondige aanstelling als AGNIO voor de chirurgische discipline in het Antoni van Leeuwenhoek Ziekenhuis in Amsterdam, startte zij in december 2000 het onderzoek dat heeft geleid tot deze dissertatie. Het betrof een vervolgonderzoek van een Nijmeegs geboortecohort op het voorkomen en de behandeling van middenoorontstekingen, bekend onder de naam KNOOP studies, en was een samenwerking tussen de afdeling Keel- Neus- Oorheelkunde (hoofd: prof. dr. K.Graamans) en de afdeling Epidemiologie en Biostatistiek (hoofd: prof. dr. ir. G.A. Zielhuis) van het Universitair Medisch Centrum Sint Radboud in Nijmegen. Subsidie voor het project werd gegeven door de instelling Zorgonderzoek Nederland Medische Wetenschappen (ZonMw, projectnummer 21000053). In juli 2002 begon zij aan haar opleiding tot KNO-arts met als hoofdopleider prof. dr. K. Graamans. In het ziekenhuis Rijnstate (Alysis groep) in Arnhem, opleider drs. E.J. van der Schans, en het Canisius Wilhelmina ziekenhuis in Nijmegen, opleider dr. J.A.M. Engel, werkte zij in het kader van opleidingsstages in regionale, algemene ziekenhuizen. Daarnaast organiseerde Brechtje mede het Vijfde Extraordinary Symposium on Recent Advances of Otitis Media, dat plaatsvond in Amsterdam in april 2005. In de najaarsvergadering van 2006 van de Nederlandse Vereniging voor Keel- Neus- en Oorheelkunde en Heelkunde van het Hoofd- Halsgebied behaalde zij de tweede plaats bij de uitreiking van de rotsbeendissectieprijs.

Brechtje leeft samen met haar partner Mark Hollander en hun dochter Nina (2006).

LIST OF PUBLICATIONS

De Beer B., Petrie A., Kalis N.N., Van der Merwe P.L. The diagnostic importance of murmers audible on the back in children with heart disease. *S Afr Med J* 1999; 89:cardiovascular suppl 2,C71-C74.

De Beer B.A., Graamans K., Snik A.F.M., Ingels K., Zielhuis G.A. Hearing deficit in young adults who had a history of otitis media in childhood: use of personal stereos had no effect on hearing. *Pediatrics* 2003; 111: e304-308

De Beer B.A., Schilder A.G.M., Ingels K., Snik A.F.M., Zielhuis G.A., Graamans K. Hearing loss in young adults who had ventilation tube insertion in childhood. *Annals of Otology Rhinology Laryngology* 2004; 113: 438-444

De Beer B.A., Schilder A.G.M., Zielhuis G.A., Graamans K. Natural course of tympanic membrane pathology related to otitis media and ventilation tubes between ages 8 and 18 years. *Otology & Neurotology* 2005; 26: 1016-1021

De Beer B.A., Snik A.F.M., Schilder A.G.M., Graamans K., Zielhuis G.A. The effect of otitis media in childhood on the development of middle ear admittance upon reaching adulthood. *Archives of Otolaryngology Head and Neck Surgery* 2005; 131: 777-781

De Beer B.A., Graamans K., Zielhuis G.A., Snik A.F.M. Non-measurable acoustic reflex in normal-hearing adults with a history of otitis media and ventilation tube insertion. *International Journal of Audiology 2007; accepted*

Publication of this thesis was financially supported by:
Atos Medical, Bayer, Beter Horen, Entercare B.V., HINK Groep B.V., Laser Vision, Stichting Atze Spoor Fonds, Stichting Michel Keijzerfonds, Tefa-Portanje, Veenhuis Medical Audio B.V. , A&A van Weenen.