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151

Anne Viljanen

Genetic and Environmental Effects on Hearing Acuity and the Association between Hearing Acuity, Mobility and Falls in Older Women

JYVÄSKYLÄN YLIOPISTO

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ABSTRACT

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The purpose of this study was to examine the contribution of genetic and environmental effects to individual differences in hearing acuity and to explore whether hearing acuity is associated with mobility, postural balance, and falls.

This study is part of the Finnish Twin Study on Aging, which comprises 103 monozygotic and 114 dizygotic community-dwelling female twin pairs aged 63-76 years. Hearing acuity was assessed using standardized audiometric methods and a structured questionnaire. Maximal walking speed was measured over 10 meters, walking endurance as the distance covered in 6 minutes and difficulties in walking 2 kilometers according to self-report. Postural balance was indicated as a movement of center of pressure in semi-tandem stance assessed using a force platform. Information on falls was gathered for 12 months of follow-up with a fall calendar.

Quantitative genetic modeling showed that genetic effects accounted for over 60% of the total variance in hearing acuity of the better hearing ear at the low, mid and high frequencies, and in speech recognition. The remaining variance was due to environmental effects. Although overall heritability was rather constant across the frequency spectrum, at the low and high frequencies frequency-specific genetic and environmental effects together accounted for the majority of the total variance. Environmental effects were more prominent in the worse hearing ear. Self-reported hearing difficulties were accounted for solely by environmental factors.

Hearing impairments were associated with slower maximal walking speed, lower walking endurance and self-reported major difficulties in walking 2 kilometers. Poor hearing also predicted higher risk for new major walking difficulties during three-year follow-up and higher risk for falls, which was partially explained by the poorer hearing participants' poorer postural balance.

The results of this study suggest that some people may be genetically predisposed to hearing impairment in old age, hence this finding underlines the need for further genetic studies. Strategies to prevent hearing loss may have wide-ranging influences not only on older people´s ability to communicate, but also more widely on functional ability.

Keywords: aging, twin, heritability, hearing, mobility, postural balance, fall

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To my family
Arne, Leevi and Kaapo

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Jyväskylä, July 2010
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LIST OF ORIGINAL PUBLICATIONS

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

I Viljanen, A., Era, P., Kaprio, J., Pyykkö, I., Koskenvuo, M., Rantanen, T. 2007. Genetic and environmental influences on hearing in older women. Journal of Gerontology: Medical Sciences 62A, M447-452.

II Viljanen, A., Kaprio, J., Pyykkö, I., Sorri, M., Kauppinen, M., Koskenvuo, M., Rantanen, T. 2007. Genetic and environmental influences on hearing at different frequencies separately for the better and worse hearing ear in older women. International Journal of Audiology 46, 772-779.

III Viljanen, A., Kaprio, J., Pyykkö, I., Sorri, M., Koskenvuo, M., Rantanen, T. 2009. Hearing acuity as a predictor of walking difficulties in older women. Journal of the American Geriatrics Society 57, 2282-2286.

IV Viljanen, A., Kaprio, J., Pyykkö, I., Sorri, M., Pajala, S., Kauppinen, M., Koskenvuo, M., Rantanen, T. 2009. Hearing as a predictor of falls and postural balance in older female twins. Journal of Gerontology: Medical Sciences 64A, M312-317.

In addition, some previously unpublished results will be presented.

ABBREVIATIONS

A	Additive genetic effect
ARHI	Age-related hearing impairment
BEHL	Better ear hearing threshold level
BESRL	Better ear speech recognition threshold level
C	Shared environmental effects
CI	Confidence interval
COP	Center of pressure
D	Dominant genetic effect
DNA	Deoxyribonucleic acid
DZ	Dizygotic
E	Non-shared environmental effect
FITSA	Finnish Twin Study on Aging
HDL	High density lipoprotein
IGF1	Gene: Insulin-like growth factor 1
IRR	Incidence rate ratio
LDL	Low density lipoprotein
LL	Log likelihood
MMSE	Mini-Mental State Examination
MZ	Monozygotic
OR	Odds ratio
PTA	Pure-tone average
RR	Relative risk
SD	Standard deviation
XZ	Uncertain zygosity

CONTENTS

1 INTRODUCTION

Hearing impairments are one of the most common chronic conditions among older people. About every third 65-year-old and two-thirds of people aged 75 have at least mild hearing impairment (Davis 1989, Uimonen et al. 1999). Hearing impairments are in most cases medically non-curable, and a hearing-aid, or in the most severe cases a cochlear implant, is the treatment of choice. The number of hearing impaired people, as well as potential hearing-aid users, will increase dramatically in near future with increasing life-expectancy. Hearing impairments will present an economic challenge for the healthcare services (Sorri et al. 2001) and on the individual level may contribute, for example, to social isolation, depression, loss of self-esteem, physical disability and poorer overall quality of life (Strawbridge et al. 2000, Wallhagen et al. 2001, Arlinger 2003).

Age-related hearing impairment (ARHI) is most often the underlying cause of hearing deterioration in old age. ARHI is most typically progressive, symmetric, sensorineural and emphasized at high frequencies. Although hearing acuity declines with aging, age of onset, the progression and severity of the impairment show great variation. The etiological mechanisms leading to ARHI are not yet well understood, although various genetic and noxious environmental factors have been suggested as contributors to the process (Fransen et al. 2003, Gates & Mills 2005).

Quantitative genetic analyses using twin design is an effective method for assessing the relative contribution of genetic and environmental effects on inter-individual differences in multifactorial phenotypes, such as hearing (Neale & Cardon 1992, Plomin et al. 2001). However, studies on the relative contributions of genetic and environmental effects to hearing acuity in old age are scarce, and only two previous twin studies exist. According to Christensen et al. (2001) genetic effects accounted for 40% of variation in self-reported reduced hearing among twins aged 75 and older. Furthermore, according to Karlsson et al. (1997), the primary, correlation-based heritability of hearing acuity at the high-tone frequencies (3-8 kHz) was 47% in a study of 78 male twin pairs aged 65 years and older. Heritability describes the proportion of the overall variance that is attributed to genetic factors. It should be noted that heritability is always a population- and time-specific estimate, and it refers to the genetic contribution to individual differences at the population level, not to the phenotype of an individual (Plomin et al. 2001).

In the Framingham Heart Study, heritability, estimated on the basis of familial correlations, of the pure-tone averages of the better hearing ear was at low frequencies 26%, at mid frequencies 27% and at high frequencies 32%. The corresponding values for the worse hearing ear were 26%, 28% and 35% (Gates et al. 1999). According to the results of the genome-wide linkage analysis, based on the same sample with an age range of 32-89 years, the heritability for low frequencies was estimated to be 31% and for mid frequencies 38% (DeStefano et al. 2003).

Like hearing impairments, mobility problems are also common among older people and generally the result of multiple, diverse, and interacting causes. In some studies, poor hearing has been associated with perceived difficulties in mobility and physical functioning relevant to managing everyday life (Strawbridge et al. 2000, Wallhagen et al. 2001, Ayis et al. 2006), but non-significant findings have also been presented (Laforge et al. 1992, Lin et al. 2004). Previous studies have mainly based on self-reports of hearing and physical functioning, and no previous studies have been published on the association between audiometrically measured hearing acuity and objectively measured walking ability.

Postural balance, which is an important prerequisite for mobility, has also been associated with hearing. However, studies on the association between hearing acuity and postural balance as well as between hearing acuity and falls are limited and their results contradictory (Gerson et al. 1989, Era et al. 1996, Enrietto et al. 1999, Baloh et al. 2003, Purchase-Helzner et al. 2004, Evci et al. 2006).

The precise nature of the possible association between hearing and mobility is unclear. While the most obvious effect of hearing impairment is diminished ability to communicate, it is possible that people with poor hearing may restrict their participation in various social activities because of communication problems, and this hearing-induced inactivity may accelerate the disablement process. It has also been argued that auditory cues are important for spatial orientation, enabling for example, environmental hazards to be noticed and avoided (Dargent-Molina et al. 1996). Deprivation of environmental acoustic information due to impaired hearing may emerge as uncertainty and poorer functioning in mobility tasks, as well as increased risk for falls.

The structure and function of the inner ear also suggest that hearing and postural balance may share etiological factors in common. The hearing and vestibular organs are anatomically closely localized, share fluid-filled bony compartments and blood circulation, are both served by the 8^{th} cranial nerve and have similar mechanosensory receptor hair cells, which detect sound, head movements, and orientation in space. Loss of these receptor cells can occur in the cochlea (Schuknecht & Gacek 1993) and vestibular organ (Rosenhall 1973) through a degenerative aging process but also through a variety of insults, including exposure to noise and ototoxic drugs (Weinstein 2000, Cheng et al. 2005, Selimoglu 2007).

Only a few studies on the extent of genetic and environmental effects on walking speed, postural balance and falls exist. According to earlier results, approximately a third of the variance in maximal walking speed (Pajala et al. 2005, Tiainen 2006, Tiainen et al. 2007, Tiainen et al. 2008) as well as in postural balance (Pajala et al. 2004, El Haber et al. 2006) was accounted for by genetic factors. The rest of the variance in both traits was accounted for by shared and non-shared environmental effects. Furthermore, familial factors, consisting of genetic and shared environmental effects, explained altogether a third of the variability in susceptibility to falls (Pajala et al. 2006). No previous studies have been carried out to clarify whether hearing acuity and walking speed, and furthermore hearing acuity, postural balance and falls, share genetic or environmental influences in common for these traits.

The disablement process model presented by Nagi (1976) and later modified by Verbrugge and Jette (1994) forms the basis for the construction of the Finnish Twin Study on Aging (FITSA) (Rantanen et al. 2003) as well as for this thesis. According to that approach pathological changes in the hearing organ leads to hearing impairment, which can be detected for example by audiometry. Hearing impairments may cause direct functional limitations in communication and lead eventually to difficulties in performing activities of daily life, so called disability. People may for example restrict their social activity because of communication problems. Hearing impairments may lead to disability also through balance or walking difficulties. Falls may occur either because of decreased physical functioning or because of various environmental risk factors.

The purpose of this study was to examine the relative contribution of genetic and environmental effects in hearing acuity and to examine whether hearing acuity is associated with walking ability, postural balance and falls in older women. In addition, the present study examined whether hearing acuity and walking speed and furthermore hearing acuity, postural balance and falls share genetic or environmental effects in common.

2 REVIEW OF THE LITERATURE

2.1 Hearing in older people

The ability to receive and to interpret sound vibrations, to hear, is one of our senses. The sense of hearing is above all connected with communication, but acoustic information also enables us to orientate in the space surrounding us as well as notice and react to different environmental occurrences. Hearing is a multiphased phenomenon, which includes the detection, discrimination, recognition and comprehension of acoustic signals (Sorri & Huttunen 2008).

The process of hearing starts when outer ear collects air-conducted sound vibrations and channels them into the middle ear via the ear drum (tympanic membrane). Sound vibrations are converted into mechanical vibrations of the ossicular chain in the middle ear and transmitted into the fluid-filled cochlea in the inner ear. In the cochlea, on the surface of the basilar membrane, lies the organ of Corti where one row of inner and three rows of outer hair cells, as well as different supporting cells, are located. The inner hair cell detects a specific frequency of sound relative to its position along the basilar membrane. Hair cells at the apex of the cochlea detect low-frequency sounds and cells at the base of the cochlea high-frequency sounds. The inner hair cells are mechanosensory receptor cells which transform biomechanical energy into nerve impulses. The inner hair cells provide the major sensory transduction and the outer hair cells serve to increase sensitivity and frequency selectivity. According to present knowledge mammalian cochlea hair cells do not regenerate once they have been destroyed. The afferent nerve fibers leave the organ of Corti in an organized way. Fibers carrying low-frequency information are in the middle and high-frequency fibers are on the outside of the nerve bundle. After the auditory nerve leaves the cochlea, its next junction is the cochlear nucleus and furthermore, via different pathways the auditory cortex, which is also frequency-specifically, tonotopically, organized (Yost 2000).

Young, healthy person can hear sound frequencies from 20 to 20000 hertz (Hz). Because of the extreme variation in sound intensities that the ear can detect and discriminate, sound intensities are usually described in decibels (dB). The decibelscale is logarithmic and relative. One dB change in sound intensity is approximately the smallest change in sound intensity that a young person can distinguish. In clinical practice 0 dB is usually the reference value representing the most silent sound that a young, healthy person can hear at different frequencies (Yost 2000).

Air-conducted pure-tone thresholds are often regarded as the "golden standard" in the evaluation of hearing acuity. The purpose of pure-tone audiometry is to detect the softest sound (dB) at each frequency (Hz) that the testee can hear. Usually frequencies from 125 to 8000 Hz are measured in a soundproof booth and the results presented as an audiogram. Sound can be conducted to the inner ear via air but also via the cranial bones by using a bone conduction receiver instead of headphones. The difference between air- and bone-conducted hearing thresholds can reveal whether the hearing impairment is conductive, sensorineural or combined in nature (Yost 2000, Arlinger et al. 2008a).

Pure-tone thresholds do not necessarily reflect the person´s ability to hear in real-life situations. Older people often complain that although they hear well enough in a quiet environment, they have difficulties hearing conversation in a noisy environment, where several people are talking simultaneously. Different techniques have been developed for capture this phenomena. Speech audiometry emphasizes speech discrimination and recognition, in addition to sound detection, thus reflecting the functioning of the communication better than is achieved by using pure-tone thresholds alone. Various modifications of the test, using disturbed, distorted or interrupted speech, are also used in examinations (Era et al. 1986). Furthermore, when the disabling effects of hearing impairments are in focus, self-evaluation of a person´s hearing and ability to cope with hearing in daily life are particularly valuable. Several structured hearing questionnaires exist and are used in epidemiological studies (Bentler & Kramer 2000, Arlinger et al. 2008a).

Audiometry is a more objective measurement of hearing than a self-report; however, it requires good reactive co-operation by the testee and is dependent on the testee´s conscious response. In diagnostics, the results of audiometry are often complemented with different objective electro-acoustic measurements, for example tympanometry, auditory brainstem response, electrocochleography and otoacoustic emissions. Otoacoustic emissions are the sounds made by the motion of outer hair cells in the cochlea in response to auditory stimulation. Otoacoustic emissions can be recorded by a microphone fitted into the ear channel, and the results indicate the function of the outer hair cells. Electroacoustic measurements are particularly important in diagnoses of people who cannot respond voluntarily to sound, for example newborn babies (Kemp 2002, Arlinger et al. 2008b).

2.1.1 Age-related changes in hearing

Studies show a clear increase in the prevalence of hearing impairment with age (Wallhagen et al. 1997, Mäki-Torkko et al. 2001). Hearing impairments are in fact one of the commonest chronic conditions among older people (World Health Organization 2003). One-third of 65-year-olds and two-thirds of people aged 75 years have at least mild hearing impairment (Davis 1989, Uimonen et al. 1999). According to longitudinal studies pure-tone hearing thresholds decline by approximately 1 dB, and speech reception thresholds by approximately 2 dB per year among people aged 60 years and over. The rate of change is faster at higher compared to lower frequencies (Davis et al. 1990, Enrietto et al. 1999, Lee et al. 2005). According to Lee et al. (2005) the average change in pure-tone hearing thresholds was 0.7 dB per year at 0.25 kHz increasing gradually to 1.2 dB per year at 8 kHz. Should be noted that differences in study populations with respect to age, definitions of the degree of hearing impairment, and the measurements used to detect hearing impairments vary widely between studies, making comparisons between studies challenging.

Presby[a]cusis, is most often the underlying cause of hearing deterioration in old age. The term "presbyacusis" literally means hearing loss due solely to biological ageing, but there seems to be a consensus that age-related hearing loss is a result of accumulated effects of different lifetime exposures, medical disorders and their treatment, as well as hereditary susceptibility. The broader definition which includes all lifetime exposures seems to be justified, because it is practically impossible to isolate pure age effects from other lifetime environmental effects on hearing acuity in old age (Gates & Mills 2005). The term "age-related hearing impairment" has been preferred in this study for the same reason.

ARHI is most typically progressive, symmetric, sensorineural and emphasized at high frequencies. ARHI usually starts at the high frequencies and progresses to the lower frequencies as people get older. High-frequency sounds stimulate the hair cells at the basal end of the cochlea close to the round window and low-frequency sounds at the apical end of the cochlea. The hair cells at the basal end of the cochlea will be damaged before those at the apical end, and thus process of hearing loss is seen as a progression from the higher towards lower frequencies (Yost 2000, Gates & Mills 2005). In addition, degenerative central changes in the auditory cortex and nerve fibers have been associated with ARHI (Chisolm et al. 2003). Besides of reduced hearing sensitivity ARHI is characterized, for example, by reduced speech understanding, particularly in noisy environments, slowed central processing of acoustic information and impaired localisation of sound sources. Although hearing acuity declines with aging, age of onset, progression and severity of ARHI show great variation. The variation is at its largest at the high frequencies and increases with age (Yost 2000, Gates & Mills 2005).

Based on the histopathologic findings on the inner ear by Schuknecht (1955, 1964) presbyacusis has traditionally been classified theoretically into four main types: sensory, neural, strial, and cochlear conductive presbyacusis. Histologically sensory presbyacusis is seen as hair cell loss at the basal end of the cochlea, and for high frequencies steeply descending audiometric curve indicates this type of hearing loss. Neural presbyacusis is characterized by loss of cochlear neurons and a progressive loss of speech discrimination in the presence of rather stable pure tone thresholds. Strial presbyacusis is characterized by atrophy of the stria vascularis and a flat pure tone threshold audiometric pattern. Stria vascularis provides the basic metabolic control of the cochlea and it plays a part in maintenance of the electrical polarization of the endolymph in the scala media (Yost 2000). Cochlear conductive presbyacusis is highly hypothetical. It is characterized by a gradually descending audiometric curve without a pathologic correlate. Later Schuknecht and Gacek (1993) added two more categories into classification: mixed and indeterminate. Many individual cases do not separate into any specific type of presbyacusis but are rather a mixture of different types. Furthermore, the study by Schuknecht and Gacek (1993) revealed that approximately every fourth case of presbyacusis was indeterminate, because the cochlear changes were inadequate to explain hearing impairment.

In addition to sensorineural age-related changes in hearing, changes may occur in the outer and middle ear, causing the conductive type of hearing loss. Although age-related changes are common in the outer and middle ear, in most cases such changes play only a minimal role in the transmission of sounds (Weinstein 2000, Chisolm et al. 2003).

2.1.2 Factors underlying hearing acuity

Although hearing impairments become more prevalent with age, old people with intact hearing also exist. Furthermore, among rural African tribal people a level of hearing deterioration corresponding to that seen among western populations has not been found in some studies, suggesting the contribution of factors other than age per se, such as ethnicity, nutrition and noise exposure (Rosen et al. 1962, Jarvis & Van Heerden 1967).

Gender and ethnicity

The prevalence of hearing impairments is somewhat higher among men than women, particularly at the high frequencies (Wilson et al. 1999, Helzner et al. 2005a, Hietanen et al. 2005, Agrawal et al. 2008). The deterioration of hearing also commences earlier among men than women (Davis 1995). In women, hearing decline seems to coincide with the menopause (Hederstierna et al. 2010). It has been suggested that gender difference in hearing acuity may be due to the hearingprotective effects of estrogen hormone (Hultcrantz et al. 2006, Hederstierna et al. 2007). However, in some studies the gender difference has been obscured after accounting for noise exposure (Helzner et al. 2005a).

White populations, both men and women, have poorer hearing than black populations (Lee et al. 2004, Agrawal et al. 2008), but there is no definite explanation for the mechanisms underlying racial differences in hearing function. It has been suggested that black people are less susceptible to noise (Jerger et al.

1986, Henselman et al. 1995, Ishii & Talbott 1998) and that melanin plays a protective role in hearing (Barrenas & Lindgren 1991). Also higher bone mineral density among black compared to white people may serve as a protective factor (Seeman 1997, Looker et al. 2009).

Genetic factors

Previous studies have indicated that hearing acuity in old age is a trait influenced by interplay between genetic and environmental factors (Karlsson et al. 1997, Gates et al. 1999, Christensen et al. 2001, DeStefano et al. 2003). In a Danish study of 866 pairs of male and female twin-pairs, additive genetic effects accounted for 40% of the age- and gender-adjusted variation in self-reported reduced hearing for the age-group 70 years and older. The remaining variance was due to non-familial environmental effects (Christensen et al. 2001). In a Swedish study of 78 male twin pairs in an age-group of 65 years and above, the primary, correlation-based heritability of hearing in the high-tone frequencies (3-8 kHz) was 47% (Karlsson et al. 1997). In the Framingham Heart Study heritability, estimated on the basis of familial correlations, of the pure-tone averages of the better hearing ear was 26% at low, 27% at mid and 32% at high frequencies. The corresponding values for the worse hearing ear were 26%, 28% and 35% (Gates et al. 1999). According to the results of the genome-wide linkage analysis, based on the same sample with an age range of 32-89 years, the heritability for low frequencies was estimated to be 31% and for mid frequencies 38% (DeStefano et al. 2003). Heritability estimates describe the relative contribution of genetic effects to the total phenotypic variance (Rijsdijk & Sham 2002).

Studies to reveal the genetic factors contributing to ARHI have been conducted very recently, mostly in the 21st century. Genomewide linkage analysis to ARHI has found suggestive evidence for altogether seven susceptibility regions in chromosomes 3 (Garringer et al. 2006), 10, 11, 14 and 18 (DeStefano et al. 2003). Some of these regions are known to overlap with genes responsible for congenital deafness and Usher syndrome, which is the most common disease causing deafblindness (Hope et al. 1997, Saihan et al. 2009). However, Huyghe et al. (2008) were unable to confirm these regions. Instead, they identified a significant locus on chromosome 8 for an ARHI trait, which correlated with the shape of the audiogram. This finding was confirmed in another study by the same research group and furthermore GRHL2 (Gene: Grainyhead-like 2) was identified as an ARHI susceptibility gene (Van Laer et al. 2008). The same group very recently conducted the first whole genome association study for ARHI and in that study they identified the gene GRM7 (Gene: Glutamate receptor, metabotropic 7) to contribute to the risk of developing ARHI (Friedman et al. 2009). In previous association studies with candidate susceptibility genes for example KCNQ4 (Gene: Potassium voltage-gated channel, kqt-like subfamily, member 4) (Van Eyken et al. 2006), NAT2 (Gene: N-acetyltransferase 2 (arylamine N-acetyltransferase)) (Unal et al. 2005, Van Eyken et al. 2007a), and GSTM1 (Gene: Glutathione S-transferase mu 1) (Van Eyken et al. 2007a) have been suggested to be associated with ARHI.

Animal studies, mainly mouse models, have also been conducted to find candidate genes for late-onset progressive hearing impairment. In mice ten different age-related hearing loss loci have been identified so far (Vrijens et al. 2008). Interestingly, mouse studies have indicated that some of the age-related hearing loss genes revealed so far affect both age-related and noise-induced hearing loss, making individuals with a particular age-related hearing loss genotype also more susceptible to noise damage (Erway et al. 1996, Davis et al. 1999, Davis et al. 2001, Morita et al. 2007). It has been noted that noise exposure may lead to cochlear damage in genetically susceptible ears even at levels which are not damaging to normally susceptible ears (Davis et al. 1999).

Environmental factors

The best known environmental factor affecting hearing loss is exposure to noise, during either work or leisure time. Exposure to a burst of sound above 130 dB, for example an explosion, may cause a sudden dramatic deterioration in hearing due to direct mechanical damage of the organ of Corti. As opposed to a sudden acoustic trauma, exposure to continuous or intermittent loud noise for a long period of time may impair hearing because of the metabolic decompensation of the organ of Corti. The overall noise-induced biological damage to the cochlea is dependent on the level of the noise (dB) and the duration of the exposure. Similar cochlear damage may result after exposure to a higher level of noise for a short period of time or after exposure to a lower level of noise over a longer period of time. Noise is commonly considered to be harmful starting from 85 dB if the exposure lasts 8 hours per day. A pure-tone audiogram of noise-induced hearing loss typically shows a notch at frequencies around 3 to 6 kHz. However it should be noted that, as with aging and/or other effects contribute to hearing loss in higher frequencies, this notch may be obscured and entirely disappear (ACOEM Noise and Hearing Conservation Committee 2003, Henderson et al. 2006, Rabinowitz et al. 2006, Arlinger et al. 2008c, Arlinger et al. 2008d, Konings et al. 2009).

Another important occupational exposure, beside noise, is exposure to different chemicals. For example toluene and styrene, which are commonly used industrial solvents, can result in hearing loss. In animal and human studies, solvents have been shown to have a toxic effect on both the cochlea and central nervous system. Solvent-induced hearing loss occurs most typically in the mid- or high-frequency regions. In addition, a synergistic effect of noise and solvents on hearing acuity has been noted (Fuente & McPherson 2006, Hodgkinson & Prasher 2006, Johnson 2007).

Some lifestyle factors, such as tobacco smoking (Nomura et al. 2005, Fransen et al. 2008, Agrawal et al. 2009) and alcohol abuse (Rosenhall et al. 1993, Popelka et al. 2000) have been associated with impaired hearing, although contradictory results also exist (Brant et al. 1996, Itoh et al. 2001, Nomura et al. 2005). Moderate intake of alcohol has shown to have either no effect (Brant et al. 1996) or have even a positive effect on hearing (Popelka et al. 2000, Itoh et al. 2001, Helzner et al. 2005a, Fransen et al. 2008, Gopinath et al. 2010). The mechanism of ototoxicity of smoking or alcohol is not clear. It has been suggested that elevated blood levels of nicotine and carbon monoxide may decrease oxygen supply in the inner ear leading to cochlear damage (Ludvig et al. 2005, Van Eyken et al. 2007b). Moderate intake of alcohol has shown both a cardioprotective and hearingprotective effect. In some studies moderate alcohol consumption has been associated particularly with hearing in low-frequency regions. Atherosclerotic processes might be more important in low- compared to high-frequency hearing loss, because disruption of the stria vascularis affects in particular the apical region of the cochlea (Gates et al. 1993, Gopinath et al. 2010). It is also possible that moderate, compared to excessive, intake of alcohol coincides with other positive lifestyle factors, like better diet quality and physical activity, all of which are cardioprotective in nature and may thus also positively affect hearing (Poortinga 2007).

Low socio-economic status is considered to be a risk factor for contributing to the development of different chronic conditions, including hearing impairment (Rosenhall et al. 1999). However, the precise nature of the association between socio-economic status and hearing remains unclear. Hearing is more often harmfully affected by different direct noxious exposures in the workplace, and by negative life-style factors, in persons with lower compared to higher socio-economic status. Furthermore access to health care facilities between socio-economic strata may contribute to health disparities (Adler & Newman 2002, Poortinga 2007).

Medical factors

In addition to ARHI and different environmental exposures, hearing loss may be caused by auditory traumas (Fitzgerald 1996) or different diseases and their medication. Otosclerosis (Menger & Tange 2003, Moumoulidis et al. 2007) and Meniere´s disease (Jen 2008, Sajjadi & Paparella 2008) are both ear diseases, which usually manifest at the middle age. In otosclerosis the ossicular chain, especially the stapedial footplate, calcifies leading to conductive type of hearing loss. Meniere´s disease is characterized by episodes of vertigo, sensorineural hearing loss, tinnitus and/or aural pressure. The exact etiology of both otosclerosis and Meniere´s disease remain unclear. The prevalence of the clinical otosclerosis is approximately 1% (Markou & Goudakos 2009) and Meniere´s disease 0.5% (Havia et al. 2005), although estimates of prevalence vary widely between different studies.

Different systemic diseases and conditions, such as elevated blood pressure (McCormick et al. 1982, Pyykkö et al. 1987, Brant et al. 1996, Rosenhall & Sundh 2006), diabetes mellitus (Kakarlapudi et al. 2003, Bainbridge et al. 2008) and rheumatoid arthritis (Ozturk et al. 2004, Takatsu et al. 2005) have also been associated with impaired hearing in some studies. Results on the association between hearing acuity and bone mineral density has been inconsistent (Clark et al. 1995, Guneri et al. 1996, Chole & McKenna 2001, Clayton et al. 2004, Monsell 2004, Purchase-Helzner et al. 2004, Helzner et al. 2005b).

Some medications may be ototoxic in nature. Aminoglycoside antibiotics and chemotherapeutic agent, cisplatin, are two major classes of ototoxic drugs currently in use. Both of those drugs may lead to a high-frequency sensorineural hearing loss (Rybak & Whitworth 2005, Rybak 2007, Selimoglu 2007, Guthrie 2008). Older people are particularly vulnerable to toxic effects of drugs, because of physiological as well as disease-related alterations in organ function due to aging. In addition, comorbidity and consequent polypharmacy are common among older people, complicating drug therapy (Weinstein 2000, Cusack 2004, Klotz 2009).

Identifying the relative contributions of the different risk factors are challenging, because different exposures and medical conditions may have their own, an additive, or even a synergistic adverse effect on hearing (Hodgkinson & Prasher 2006, Van Eyken et al. 2007b). Furthermore, associations between different risk factors and hearing acuity have been shown in many cases to be age-, gender- and race-dependent (Helzner et al. 2005a). It is also noticeable, that the data on hearing acuity in carefully controlled studies show considerable case-to-case variation, indicating that individual susceptibility to environmental risk factors plays a significant role in the hearing loss process. For example, it is well known that people exposed to the same noise do not suffer the same degree of hearing loss (Taylor et al. 1965). It is possible, that genetic factors either underlie the rate of change in hearing loss or determine how vulnerable the inner ear is to risk factors for hearing loss such as noise exposure, thereby making some people more prone or resistant to hearing loss (Erway et al. 1996, Davis et al. 1999, Davis et al. 2001). Environmental exposure may lead to cochlear damage in genetically susceptible persons even at levels which are not damaging to normally susceptible ears (Davis et al. 1999). To conclude; Gates and Mills (2005) suggest that noise exposure, smoking, medication, hypertension and family history are the five most obvious risk factors for age-related hearing impairment.

Today no cure for ARHI exists and thus a hearing aid is the treatment of choice. According to current knowledge mammalian cochlear hair cells do not spontaneously regenerate once they have been lost. However hair cell regeneration of mammalian vestibular sensory epithelia has been shown to occur (Forge et al. 1993, Warchol et al. 1993, Montcouquiol & Corwin 2001), as has cochlear hair cell regeneration in birds and other non-mammalian vertebrates (Cotanche 1987, Cruz et al. 1987, Corwin & Cotanche 1988, Ryals & Rubel 1988, Lippe et al. 1991, Yost 2000). These findings have led to consideration of the idea that regeneration of cochlear hair cells may be the ultimate remedy for hearing loss. Recently promising, although still tentative, advances have been made in stem cell biology, gene therapy, cell cycle regulation and pharmacotherapeutics to define and validate regenerative medical interventions for mammalian hair cell loss (Cotanche 2008, Brigande & Heller 2009).

2.1.3 Hearing acuity in association with mobility, balance and falls

Hearing impairments may contribute to multiple negative outcomes like social isolation, depression, loss of self-esteem, and poorer overall quality of life

(Strawbridge et al. 2000, Wallhagen et al. 2001, Arlinger 2003). Several studies have also indicated a positive association between self-assessed hearing impairment and difficulties in activities of daily living and/or instrumental activities of daily living as well as physical functioning tasks (Dargent-Molina et al. 1996, Keller et al. 1999, Lee et al. 1999, Reuben et al. 1999, Pope & Sowers 2000, Strawbridge et al. 2000, Wallhagen et al. 2001, Spiers et al. 2005). Activities of daily living include basic daily self-care tasks such as eating, bathing, toileting, dressing and getting around indoors (Katz et al. 1963). Instrumental activities of daily living include more demanding tasks such as housekeeping, preparing food, shopping, using public transportation and handling finances (Lawton & Brody 1969). The association between hearing acuity and physical functioning has also been addressed in studies using a whispered voice test (Keller et al. 1999) or pure tone audiometry (Reuben et al. 1999). In a longitudinal study Ayis et al. (2006) demonstrated an association between self-reported baseline hearing problems and decline in mobility over a one-year follow-up. Participants with hearing problems had almost three times higher odds (Odds ratio; OR 2.8 [95% confidence interval; CI 1.1-7.3]) on mobility decline compared to those with no hearing problems. The association was observed after controlling for socio-demographic factors and health conditions. Mobility decline was defined in that study as inability to walk 400 yards (366 m), or climb up or down stairs, or get on a bus anymore. Although an association between hearing and physical functioning has been observed in many studies, non significant results on the association have also been reported (Laforge et al. 1992, Lin et al. 2004). Previous studies have mainly based on self-reports on hearing and physical functioning and no previous studies on the association between audiometrically measured hearing acuity and objectively measured walking ability exist.

Poor hearing is rarely mentioned as a risk factor for falls, but some studies have indicated a positive association between hearing and postural balance, and furthermore, between hearing and falls. According to Baloh et al. (2003) the deterioration in pure-tone hearing threshold level at 1 kHz was significantly correlated (r=-0.35) with the change in Tinetti gait and balance scores (Tinetti et al. 1986) among older people during 8-10 years of follow-up. Gerson et al. (1989) found an increased risk for self-reported imbalance with people who reported impaired hearing and Evci et al. (2006) demonstrated that the incidence of home accidents, most often falls, was 30% higher in people with than without hearing problems. Occupational health studies have shown that greater noise exposure at work correlates with impaired postural balance (Oosterveld et al. 1982, Era & Heikkinen 1985, Juntunen et al. 1987, Kilburn et al. 1992, Golz et al. 2001). Subjects with more severe noise-induced hearing loss showed more sway in a balancetest than those with less severe or no hearing loss (Juntunen et al. 1987). However, in some studies only a minor or no association has been found between hearing acuity and postural balance (Era et al. 1996, Enrietto et al. 1999, Hofer et al. 2003) or falls (Purchase-Helzner et al. 2004).

Among older people multiple sensory deficits is common, and may further increase the risk for falls compared to people with only one sensory deficit

(Crews & Campbell 2004, Kulmala et al. 2009). According to the study by Kulmala et al. (2009) visual acuity alone was not statistically significantly related to falls in a one-year follow-up. On the contrary subjects with both vision and hearing impairment had over fourfold (Incidence rate ratio [IRR] 4.2 [95% CI 1.5-11.3]) and those with both vision, hearing and balance impairment had even further increased risk (IRR 29.4 [95% CI 5.8-148.3]) for falls, compared to those with good vision.

2.2 Mobility, balance and falls in older people

Mobility, defined as the ability to move independently from one point to another, is a fundamental element of several basic, as well as instrumental activities of daily living. Mobility disability occurs when person's ability to move does not meet the demands of the environment (Patla & Schumway-Cook 1999). In this study the term mobility is used to describe a person´s ability to walk, thus ignoring mobility using, for example, a wheelchair or motorized vehicle.

Difficulties in mobility may lead to loss of independence and social isolation, hence decreasing quality of life (Sudarsky 2001, Bootsma-van der Wiel et al. 2002, Netuveli et al. 2006). Furthermore, walking difficulties may lead to institutionalization (Montero-Odasso et al. 2005, Verghese et al. 2006, von Bonsdorff et al. 2006) and higher risk for mortality (Lyyra et al. 2005, Verghese et al. 2006). Perhaps the most obvious corollary of walking difficulties is falling (Tinetti et al. 1995a, Hausdorff et al. 1997, Montero-Odasso et al. 2005, Snijders et al. 2007).

2.2.1 Walking ability

Walking ability can be assessed using various, either self-report or performance-based methods, which capture different levels of the disablement process model. Self-reported mobility indicates, in particular, disability while performance-based tests indicate functional limitations in the model (Nagi 1976, Verbrugge & Jette 1994). Questionnaires or interviews about walking ability usually concerns difficulties in performing daily tasks, for example walking a specified distance indoors or outdoors. Furthermore, questions about task modification are important to capture preclinical mobility limitation (Fried et al. 2001a, Mänty et al. 2007, Mänty et al. 2010). Questionnaires are especially valuable in large population-based studies and in situations where the study participant is not able to perform the functional test.

Walking speed is a commonly used indicator of mobility and a strong predictor of future mobility disability (Guralnik et al. 2000). Walking speed can be measured over different distances, either at customary or maximal speed. Short, distance-based walking tests, such as the 10-meter walking test, assess peak walking velocity, which mainly reflects lower extremity neuro-muscular function. Longer, time-based walking tests, such as the 6-minute walking test, assess endurance and cardio-respiratory fitness rather than walking speed per se. In laboratory-settings more sophisticated computerized kinetic gait analysis can be utilized to describe more precisely different dimensions of the walking cycle; these include step length, stride length, step width and the duration of the stance, swing and double-support phases (Alexander 1996, Solway et al. 2001, Pearson et al. 2004, Graham et al. 2008).

In the Finnish population-based Health 2000 –study, under a tenth of the participants aged 55-64 years, but already a half of the participants aged 75-84 years reported difficulties walking 500 meters (Koskinen et al. 2004). According to the Medicare Current Beneficiary Community Survey, 53% of the participants aged 65 or over had no mobility limitation, 31% had mild, and 16% moderate or severe limitation. Mobility limitations were classified according to self reports on walking difficulties and need of help to walk (Shumway-Cook et al. 2005).

With aging, walking speed declines and gait may become more shuffling and cautious. Among women in their twenties, mean maximal walking speed is 2.5 m/s decreasing to 1.7 m/s among women in their seventies. In men walking speed is 0.4 m/s higher than in women in old age (Bohannon et al. 1996, Bohannon 1997). In gait analysis shorter step length, wider step width and a relatively increased proportion of time spent in the double-support phase have been observed (Alexander 1996, Jankovic et al. 2001, Menz et al. 2003, Snijders et al. 2007).

Walking is a multifactorial motor skill, which relies on smooth cooperation between the musculo-skeletal, senso-neural and cardio-respiratory organ systems in relation to the demands of the environment (Dickinson et al. 2000). Walking is traditionally seen as an automatic motor task, but in recent decades attention has been drawn also to the cognitive and affective dimensions of walking (Snijders et al. 2007). Nowadays gait disorders are not seen as an inevitable feature of old age per se, but rather a result of the increased prevalence and severity of multiple diseases and impairments with increasing age (Bootsma-van der Wiel et al. 2002, Snijders et al. 2007). Walking difficulties have been associated for example with arthritis, diabetes, angina pectoris, Parkinson´s disease, and stroke. Furthermore declines in strength and postural balance as well as sensory deficits, cognitive impairments and depressive mood have shown to precede walking difficulties (Alexander 1996, Fried & Guralnik 1997, Sudarsky 2001, Bootsma-van der Wiel et al. 2002, Tiedemann et al. 2005, Callisaya et al. 2009). Multiple chronic diseases or deficits may have an additive and possibly even a synergistic impact on mobility (Guralnik et al. 2001). For example, Rantanen et al. (1999) established a much higher risk for severe walking impairments among older women who had both strength and postural balance impairments, compared to those with only one of those impairments.

2.2.2 Postural balance

Mobility relies on postural balance. Human stability has been defined as the inherent ability of a person to maintain, achieve or restore a specific state of balance and not to fall. Postural control describes the act of maintaining, achieving or restoring a state of balance during any posture or activity (Pollock et al. 2000). In this study the term postural balance is used as a synonym for human stability.

According to the systems approach, postural control is seen as complex motor skill derived from the interaction of multiple body systems and environmental factors (Woollacott & Shumway-Cook 1990). Because of this complex nature of postural control, several different methods have been developed to assess it. In clinical settings the assessment of postural balance is usually based on various performance-based tests, such as the Berg Balance Scale (Berg et al. 1989) or Tinetti Performance-Oriented Mobility Assessment (Tinetti 1986). The development of technological solutions has enabled postural balance also to be measured quantitatively. For example, force platform–based measurements provide detailed information about body sway velocity and direction in different more or less demanding standing positions. Among high-functioning community-dwelling older people, functional balancetests may lose their power because of the ceiling effect. On the other hand, among the oldest people more demanding test positions, for example the tandem stance, may suffer from the floor effect (Era et al. 2006).

U-shaped association between age and postural balance has been proposed (Hytönen et al. 1993, Sihvonen 2004). Sihvonen (2004) conducted force platform balancetests to 593 people aged 8 to 93 years. According to her results, the youngest and the oldest participants showed the highest sway velocities and velocity moments compared to the participants in the midrange of the age spectrum. The standing balance decline in adulthood has been shown to be most evident from around 60 years and more pronounced among men than women (Era et al. 2006, Sihvonen 2004).

The maintenance of postural balance is a process where the correct output of the musculo-skeletal system relies on the interaction of the vestibular, somatosensory, and visual inputs, and the adaptation of these inputs to the demands of the task and environment (Pollock et al. 2000, Shumway-Cook & Woollacott 2000, Peterka 2002, Woollacott & Shumway-Cook 2002, Horak 2006). The age-related deterioration in postural balance may be due to different physiological mechanisms (Marchetti & Whitney 2005), such as the reduction of the receptor cells in the vestibular organ (Rosenhall 1973, Engström et al. 1974), impaired peripheral sensation (Kristinsdottir et al. 1997), increased reaction time (Lord et al. 1992, Lord et al. 1994, Lord & Dayhew 2001) and changes in the visual functions (Lee & Scudds 2003), including visual acuity (Lord et al. 1991), contrast sensitivity (Lord et al. 1991, Lord & Menz 2000, Szabo et al. 2008) and depth perception (Nevitt et al. 1989, Lord & Dayhew 2001). Furthermore, muscle strength, and particularly the velocity to produce force, so called explosive power, decline in old age affecting to the ability to maintain a stable posture (Bassey et al. 1992, Skelton et al. 1994, Skelton et al. 2002, Petrella et al. 2005). Explosive power has shown to be crucial, especially maintaining a well-balanced posture in mobility tasks or when a response to sudden, severe perturbation is needed (Foldvari et al. 2000, Skelton et al. 2002, Sayers et al. 2005).

Adaptive central nervous system processes are needed in postural control to integrate sensory inputs and initiate appropriate motor response. Furthermore, cognitive and particularly attentional allocation deficits, assessed often as performance in dual-task situations, have been indicated as important contributors to instability (Camicioli et al. 1997, Lundin-Olsson et al. 1997, Woollacott & Shumway-Cook 2002, Horak 2006).

The abovementioned physiological impairments may be aging-related or due to many different chronic conditions, such as diabetes (Resnick et al. 2002, Suominen et al. 2008), Parkinson's disease (Horak et al. 1996, Wood et al. 2002, Maurer et al. 2003), stroke (Campbell et al. 1989, de Oliveira et al. 2008), and age-related macular degeneration (Szabo et al. 2008). Among older people the co-existence of multiple impairments is a common problem, increasing further the challenge to postural control (Lord et al. 1994, Tinetti et al. 1995b). It has been argued, that despite the cause or causes, when one component of the sensory, motor or central processing system is deficient, there is a greater reliance on the remaining components (Peterka 2002, Sturnieks et al. 2008). It is also worth noting that, depending on the type of impairment and demands of the environment, people use different strategies to compensate for their impairments. Thus, impairments alone do not necessarily lead to functional deficits (Horak 2006).

2.2.3 Falls

The most obvious adverse event of walking difficulties and postural balance problems is falling. Falls have been studied extensively, but there is a lot of variation between studies in how falls have been defined, measured or analyzed (Hauer et al. 2006). In this study a fall is defined as "unintentionally coming to rest on the ground, floor, or other lower level for reasons other than sudden onset of acute illness or overwhelming external force" as has been suggested by the Kellogg International Work Group on Prevention of Falls by the Elderly (1987).

Information about falls is typically collected using either retrospective or prospective methods. Retrospective reporting includes telephone or face-to-face interviews, or postal questionnaires, with varying recall periods. Prospective reporting is usually based on postcard, calendar or diary surveillance. Prospective methods are usually preferred, because recall can be problematic in retrospective studies (Peel 2000, Hauer et al. 2006, Mackenzie et al. 2006). According to the recommendation of the Prevention of Falls Network Europe (ProFaNe) "falls should be recorded using prospective daily recording and a notification system with a minimum of monthly reporting. Telephone or face-to-face interview should be used to rectify missing data and to ascertain further details of falls and injuries" (Lamb et al. 2005).

Falls may be harmless "pratfalls" but they may also have serious consequences. Approximately every third community-dwelling adult aged 65 years and older falls at least once a year and half of those occurrences are recurrent in nature. Every fifth fall needs medical attention and 5-10% of falls cause fractures or other severe injury. The incidence of falls and fall-related injuries are even more common among persons aged 80 years and over, or living in long-term institutional care (Tinetti et al. 1988, Nevitt et al. 1991, Luukinen et al. 1995, Tinetti et al. 1995a, Rubenstein & Josephson 2002, Salva et al. 2004). In Finland, in the year 2007, falls caused the death of 867 persons aged 65 years and older. This accounted for 2% of all deaths and 65% of accidental deaths among persons in that age-group (National Institute of Health and Welfare 2009).

There is an abundance of studies and many review articles about falls and their causes, consequences and prevention (see, for example: Rubenstein et al. 1994, van Weel et al. 1995, Leipzig et al. 1999, AGS guideline 2001, Rubenstein & Josephson 2002, Frank & Patla 2003, Moreland et al. 2004, National Institute for Clinical Excellence (NICE) 2004, Kannus et al. 2005a, McClure et al. 2005, Piirtola & Era 2006, Ganz et al. 2007, Hijmans et al. 2007, Karlsson et al. 2008, Sherrington et al. 2008, Härlein et al. 2009, Vaapio et al. 2009). According to a review on the risk factors for falls identified in 16 studies, muscle weakness was the most important single risk factor. In ten out of eleven studies muscle weakness was associated with higher fall risk. Persons with muscle weakness had over four times higher fall-risk (mean relative risk; RR or OR 4.4 [range 1.5-10.3]) compared to those without muscle weakness. In order of importance, other significant risk factors for falls were: history of falls, gait deficits, balance deficits, use of assistive device, visual deficit, arthritis, impaired functioning in activities of daily living, depression, cognitive impairment and age over 80 years (AGS guideline 2001, Perell et al. 2001, National Institute for Clinical Excellence (NICE) 2004). In addition, according to meta-analyses of 29 studies, psychotropic, type 1A antiarrhythmic, diuretic and digoxin medication use were associated with one or more falls and, furthermore, subjects reporting three or more medications of any type were at increased risk of recurrent falls (Leipzig et al. 1999). In the National Institute for Clinical Excellence (NICE) guideline (2004) fear of falling, low body mass, diabetes, urinary incontinence and environmental hazards were also identified as important single risk factors for falls.

Although it is important to identify single risk factors for falls, it is perhaps even more important to appreciate the interaction and probable synergism between multiple risk factors. Several studies have demonstrated that risk of falling increases as the number of risk factors increases. In a study by Tinetti et al. (1988) the percentage of elderly fallers increased from 8% for those with no fall risk factors to 78% for those with four or more risk factors. The risk factors included sedative use, cognitive impairment, lower-extremity disability, palmomental reflex, foot problems, and balance-and-gait abnormalities. According to Robbins et al. (1989) hip weakness, poor balance and taking over 4 prescribed medications were most strongly related to falling. The predicted one-year risk for falling was 12% for persons with none of those three risk factors, but 100% for persons with all three risk factors. Findings were similar both among non-institutionalized and institutionalized persons.

Falls may have multiple negative impacts on an older person's well-being. Falls and fall-related injuries have been associated with reduced functioning, restricted activity, morbidity, institutionalization and even mortality (Gill et al. 2004, Stel et al. 2004, Kannus et al. 2005b). Falling once increases the risk of a subsequent fall (AGS quideline 2001, Ganz et al. 2007). In addition to physical injuries, falls may have negative psychological and social consequences. Falls may inflict fear of falling and loss of the self-confidence needed to walk safely, which may decrease participation in various activities and thereby accelerate the disablement process (Howland et al. 1998, Bruce et al. 2002, Delbaere et al. 2004). Since falls and fall-related injuries cause, in the worst case, a great deal of suffering for the faller and her/his close individuals, and are also an economic burden to aging societies, it is essential to find an effective way to prevent new incidents.

2.2.4 Genetic effects on mobility, balance and falls

Only a few twin studies about walking ability, postural balance and falls exist. According to earlier results of the FITSA study, 15-35% of the variance in maximal walking speed was accounted for by additive genetic effects, 27-44% by shared and 38-41% by non-shared environmental effects (Pajala et al. 2005, Tiainen 2006, Tiainen et al. 2007, Tiainen et al. 2008). In a bivariate model, 16% of walking speed and 20% of walking endurance were accounted for by genetic influences common for both traits (Ortega-Alonso et al. 2006). According to Carmelli et al. (2000) in older male twins genetic effects accounted for 42% of the variance in customary walking speed and the rest of the variance was accounted for by non-shared environmental effects.

In previous twin studies approximately a third of the individual differences in postural balance was accounted for by additive genetic effects (Pajala et al. 2004, El Haber et al. 2006, Wagner et al. 2009). The rest of the variance was accounted for by shared and non-shared (Pajala et al. 2004), or solely by non-shared environmental influences (El Haber et al. 2006, Wagner et al. 2009). Furthermore, familial factors accounted for over a third of the variability in the susceptibility to fall. However, according to study by Pajala et al. (2006) no definite conclusion was reached as to whether these familial factors were genetic or non-genetic in nature. The proportion of genetic variance seems to be higher for recurrent than occasional fall.

No candidate genes have been suggested so far for walking ability or postural balance. According to the genome-wide linkage analysis by Tiainen et al. (2008) the strongest suggestive evidence of a linkage to maximal walking speed was observed on chromosome 13. Furthermore, Cappola et al. (2001) reported a weak association between low serum IGF1 (Gene: Insulin-like growth factor 1) levels and slow walking speed among older women.

2.3 Quantitative genetic method

Although many of the greatest successes in the field of molecular genetics have concerned monogenic diseases, there is growing interest in identifying genes predisposing to multifactorial, or so called complex diseases, such as presbyacusis. Multifactorial diseases, or phenotypes, are influenced by several genes and multiple environmental factors. Genetic epidemiology seeks to investigate the role of both genes and environment in complex diseases. Environment means in this context everything except genes. The primary goal of genetic epidemiology is to resolve the genetic constitution of a disease or a phenotype. More precisely, it is to establish whether the trait has a genetic component and what the relative size of that component is in relation to environmental components, and furthermore, to identify the gene or genes responsible for the genetic component. Once genes have been identified, their impact can be quantified and their role in different environments clarified.

The core idea of quantitative genetics is to resolve what causes greater similarity of close relatives compared to people who are not related. Quantitative genetics is based on the findings of Gregor Mendel (1822-1884), who demonstrated the transmission of hereditary elements from generation to generation in pea plants (Mendel 1866). Sir Francis Galton (1822-1911), known as the father of behavioral genetics, raised the question about the role of nature vs. nurture for growth in his studies among twins. Galton was also one of the first to describe the age-related pattern in hearing loss. He conducted experiments with different animal species and humans using a whistle, later named after him, and found out that different species have different upper-limits of hearing, and that, in particular, the ability to hear high-tone sounds decreases with aging (Galton 1874, 1883, 1885). Furthermore in 1918 the geneticist and statistician Sir Ronald Fisher (1890-1962) published an article on the correlation between relatives on the supposition of a Mendelian inheritance, forming the theoretical basis for subsequent analyses of quantitative genetics (Fisher 1918).

Quantitative genetics utilizes samples of relatives who are at least partially genetically or environmentally related, such as twin, family or adoption–samples, or a mixture of these. The twin study method is most widely used in quantitative genetics as it has several advantages over family or adoption studies. In family studies differentiation between genetic and common environmental effects is challenging and extended family pedigrees with different types of relatives are needed for the analyses. Collecting such large pedigrees is particularly laborious and in studies of some phenotypes age- or cohort-differences between generations may present an analytical challenge. Adoption studies have been criticized for non-generalizability of the results. Adoption data may be biased by parental conditions or selective placement. Obviously the limited availability of adoptees also restricts the usage of this method (Plomin et al. 2001).

The first classical twin studies were published in 1924 by Herman Siemens and Curtis Merriman in two independent reports (Rende et al. 1990). Classical twin studies are based on the comparison of similarities between identical, monozygotic (MZ) and non-identical, dizygotic (DZ) twins. MZ twins arise from one fertilized egg and consequently share all of their genes. DZ twins arise from two eggs fertilized by two different sperm, thus sharing on average 50% of their segregating genes. Consequently, the greater similarity between MZ twin pairs compared to DZ twin pairs is evidence for genetic influence on the trait, and discordance between MZ twins is caused by individual environmental effects only (Neale & Cardon 1992, Plomin et al. 2001).

The specific aim of quantitative genetics is to estimate the relative contribution of genetic and environmental effects to variance in diseases or phenotypes. Phenotypic variation can be composed into additive genetic effects (A), non-additive, dominant, genetic effects (D), shared environmental effects (C) and non-shared environmental effects (E). Additive genetic effects represent the sum of the effects of individual alleles at all loci influencing the trait. Dominant genetic effects represent interactions between alleles at the same locus. An allele is an alternative form of a given gene and locus refers to the site of a gene on a chromosome. Shared environmental effects are common for both twins, for example childhood environment, and non-shared environmental effects are unique to each twin, for example accidents. Shared environmental effects contribute to similarities and non-shared environmental effects to differences within family members. Estimates do not refer to any particular gene or specified environmental factor. Furthermore, estimates are always time- and population-specific, revealing nothing about single individuals (Plomin et al. 2001, Rijsdijk & Sham 2002).

Twin method is based on several assumptions which need to be taken into account when conducting a study. MZ and DZ twins should share their environment to the same extent. No major gene-environment interaction should exist. Pairing of mates in the population should occur at random. And, twins should be representative of the target population. If violations in assumptions occur, this may lead to incorrect estimates of genetic and environmental effects (Kyvik 2000, Rijsdijk & Sham 2002).

3 AIMS OF THE STUDY

The purpose of this study among older women was, first, to examine to what extent genetic and environmental effects account for individual differences in hearing acuity, and second, to study whether hearing acuity is associated with walking ability, postural balance, and falls.

The specific aims of the study were:

1. To study genetic and environmental influences on the hearing threshold level at different frequencies, the speech recognition threshold level and self-rated hearing. (I, II)
2. To study whether the hearing acuity at speech frequencies and the speech recognition threshold of the better ear share genetic and environmental effects in common. (I)
3. To study whether hearing acuity at the low, mid and high frequencies are accounted for by genetic and environmental effects either common or specific to each frequency level; separate analyses for the better and worse hearing ear. (II)
4. To study whether hearing acuity is cross-sectionally associated with walking ability and whether poor hearing predicts walking difficulties. (III)
5. To study whether hearing acuity and walking speed share genetic and environmental effects in common.
6. To study whether hearing acuity is cross-sectionally associated with postural balance and whether poor hearing predicts falls. (IV)
7. To study whether hearing acuity, postural balance and falls share genetic and environmental effects in common. (IV)

The associations examined in this study are presented in Figure 1.

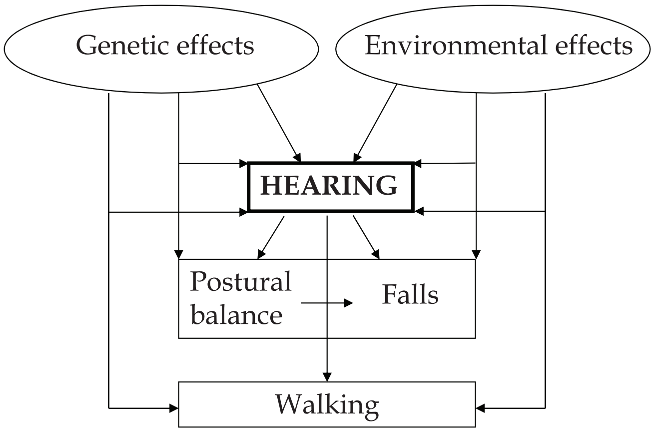

FIGURE 1 The associations examined in this study.

4 PARTICIPANTS AND METHODS

4.1 Recruitment of participants

This study is part of the Finnish Twin Study on Aging (FITSA), a broader project on the contribution of genetic and environmental factors to the disablement process in older women. The participants were recruited from the nationwide Finnish Twin Cohort, which is located at the Department of Public Health at the University of Helsinki. The Finnish Twin Cohort comprises all same-gender twin pairs born before 1958 with both co-twins alive in 1975 consisting of 13 888 adult twin pairs of known zygosity based on a validated questionnaire about the twin sisters' similarity in appearance in childhood. Twins were determined as MZ, DZ or XZ (uncertain zygosity) according to their answers. There were 1260 respondent female twin pairs born in 1924-1937 in the Finnish Twin Cohort (Kaprio et al. 1978, Sarna et al. 1978, Kaprio & Koskenvuo 2002). Of those 63 to 76 year old women, an invitation to take part in the FITSA study was sent in August 2000 to every MZ twin pair (n=178) and approximately to every third DZ twin pair (n=212) aiming to get as equivalent number of MZ and DZ twin pairs as possible. Furthermore, an invitation was sent to 24 twin pairs with previously uncertain zygosity. Zygosity was ascertained for every FITSA participant using deoxyribonucleic acid (DNA) extracted from a venous blood sample by a battery of highly polymorphic gene markers. After the DNA determination, four XZ twin pairs were classified as MZ and nine as DZ twin pairs. Furthermore, two DZ twin pairs proved to be MZ and one MZ twin pair proved to be DZ. After the DNA determination, the final sample consisted of 103 MZ and 114 DZ twin pairs. To be recruited for the study, both individuals of the twin pair had to agree and to be able to travel to the University of Jyväskylä to participate in the laboratory measurements. The main reasons for non-participation were refusal, poor health status or death of one or both twin sisters after vital status had been updated for all cohort members (Figure 2).

Follow-up measurements were conducted after three years. Altogether 419 women participated in the follow-up study, of whom 313 participated in the laboratory measurements and filled in a questionnaire, while 106 women responded solely to the postal questionnaire. The questionnaires were checked, and where they were incomplete the missing answers were filled in during face to face interviews at the laboratory or over the telephone. Altogether, 24 telephoneinterviews were conducted. During the follow-up, 7 participants died and 8 participants dropped out for health reasons (Figure 2).

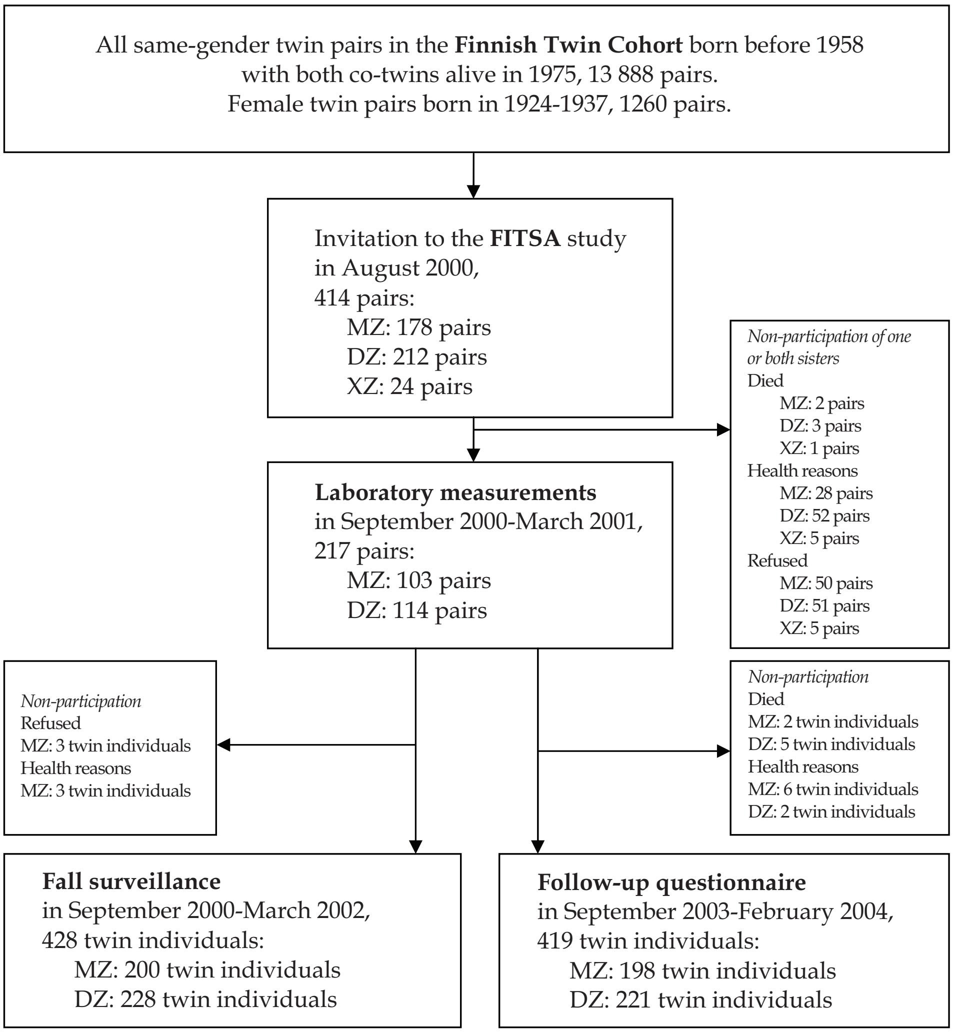

FIGURE 2 Recruitment and follow-up of the participants.

The most common self-reported ear disease of the participants was otosclerosis. Because otosclerosis is a highly inheritable disorder (Menger & Tange 2003) and might confuse the results of the genetic analyses, five persons (1 MZ and 4 DZ twins) who reported having the disease were excluded from the analysis.

The FITSA study protocol was approved by the Ethics Committee of the Central Finland Health Care District. Before the laboratory examinations, the participants were informed about the study and gave their written informed consent. This study was carried out according to good clinical and scientific practices.

4.2 Measurements

During winter 2000 to 2001, and again during winter 2003 to 2004, the participants came to the Sports and Health Laboratory at the University of Jyväskylä from all over Finland and took part in a five-hour laboratory test-battery. The examinations included a physician's examination, and multiple clinical tests on health and functional capacity. Both twin sisters came to the laboratory at the same time and received their individual test schedules on their arrival at 08:00, 09:00 or 10.00 a.m. (Figure 3). Usually three pairs were tested on the same day.

08:00 ARRIVAL AT THE LABORATORY	
TWIN 1	TWIN 2
08:30 Blood tests	08:30 **Hearing examination**
09:00 Clinical examination	09:00 Blood tests
09:30 Visual examination	09:30 Clinical examination
10:00 Muscle strength measurements	10:00 Bone and muscle area measurements
10:30 Bone and muscle area measurements	10:30 Muscle strength measurements
11:00 LUNCH	
11:30 **Hearing examination**	11:30 Balance measurements
12:00 Balance measurements	12:00 Visual examination
12:30 Functional assessment and respiratory function	12:30 Walking tests: 10 m and 6 min
13:00 Walking tests: 10 m and 6 min	13:00 Functional assessment and respiratory function
13:30 END OF EXAMINATION	

FIGURE 3 Test schedule for twin 1 and twin 2 who arrived at the laboratory at 08:00 (modified from Tiainen 2006).

4.2.1 Hearing

Audiometry

One experienced audiology assistant performed all the audiometric measurements in a soundproof booth using a clinical audiometer Madsen OB 822 equipped with cassette player NAD 6140 and headset TDH 39 (Madsen Electronics, Taastrup, Denmark). Before the measurements, the equipment was calibrated according to ISO 389 standard (International Organization for Standardization 1975). The better hearing ear was measured first, if the subject reported asymmetrical hearing. If no difference between the ears was reported, the right ear was tested first.

Air-conducted pure-tone hearing

Air-conduction pure-tone hearing thresholds were measured at the frequencies of 0.125, 0.25, 0.5, 1, 2, 4 and 8 kHz for each ear separately according to ISO 8253-1 standard (International Organization for Standardization 1989). Briefly, the assessment started at a frequency of 1 kHz and an intensity of 40 dB. Thresholds were then assessed at the frequencies of 2, 4 and 8 kHz. After the high frequencies, the threshold at 1 kHz was checked and if the difference between the threshold values was more than 10 dB, all the threshold values were reassessed. Hearing thresholds were then measured at the frequencies of 0.5, 0.25 and 0.125 kHz. The threshold value indicates the smallest sound intensity of the bracketing series heard. If the overall difference between the ears was more than 30-40 dB at different frequencies, a narrow band masking signal was used during the measurements of the poorer ear.

In the analysis, the better ear hearing threshold level (BEHL) was used and defined as a pure-tone average (PTA) of the thresholds at 0.5-4 kHz. The cut-off value between normal hearing and hearing impairment was set at 21 dB. A person was defined as having at least a mild hearing impairment if the $BEHL_{0.5\text{-}4\ kHz}$ was ≥ 21 dB (I, III, IV). The PTA of the thresholds at 0.125-0.5 kHz indicated hearing acuity at the low, 1-2 kHz at the mid and 4-8 kHz at the high frequencies (II). Classifications of BEHL and hearing impairments are based on values proposed by European Union working group and are in common use in the field of audiology (Stephens 2001). If at any frequency no response was obtained due to the severity of the hearing loss, a value of 130 dB was used in the calculations as recommended by the British Society of Audiology (1988).

To describe the audiogram configurations the mid-frequency-based classification by Sorri et al. (2000) with a minor modification was used. In the classification the PTA of the mid frequencies is used as a reference and compared with the means of the low and high frequencies. In the flat class the differences between the PTAs of the mid and low as well as mid and high frequencies are less than 15 dB. In this study, the flat class was further divided into normal flat hearing and impaired flat hearing. Individuals whose hearing threshold at any frequency was ≥ 21 dB were defined as having impaired flat hearing. According to the mid-frequency-based classification, the other four configurations are ascending, descending, U-shaped and A-shaped (II).

Speech discrimination
The speech discrimination test was carried out using the phonetically balanced Finnish word lists (Palva 1952). All the words in the lists are bisyllabic and were presented through earphones from a cassette player. The first volume presented was calculated as the mean of the air-conduction pure-tone hearing thresholds at 0.5, 1 and 2 kHz plus 10 dB rounded off to the nearest five. The words were given in 5-word groups at each level. The volume was decreased in 5 dB steps until the level was reached at which all responses were incorrect or the respondent announced that she could not hear the words. The speech recognition threshold level was calculated by subtracting the number of correctly recognised words from the starting volume rounded off to the nearest five. The better ear speech recognition threshold level (BESRL) was defined as the better ear according to the $BEHL_{0.5\text{-}4\ kHz}$, meaning that the results of the BESRL and $BEHL_{0.5\text{-}4\ kHz}$ are obtained from the same ear.

Self-reported hearing
As a part of the hearing examination, participants were interviewed about their hearing ability in different circumstances, ownership of different hearing devices, ear diseases, acoustic traumas and noise exposure. Self-reported hearing was assessed according to the question "How is your hearing ability?" Response options were: good (no problems), slightly reduced or substantially reduced. For the analysis, self-reported hearing difficulties were dichotomized into no problems and problems, which included slightly or substantially reduced hearing.

4.2.2 Walking

Maximal walking speed
Maximal walking speed over 10 meters was measured in the laboratory corridor using photocells for timing (Aniansson et al. 1980). Three meters were allowed for acceleration. Participants were instructed to "walk as fast as possible, without compromising your safety". The measurer walked beside the participant offering no encouragement during the test. The use of a walking-aid was allowed if needed. The test was done twice, and the faster performance documented as the result. Maximal walking speed (m/s) was calculated by dividing the 10 meter distance with the time taken to walk it.

Walking endurance
Walking endurance was assessed using a validated 6-minute walking test (American Thoracic Society 2002). The participants walked back and forth a 50-meter indoor straight track for 6 minutes, and the distance (m) covered during that time was recorded. The measurer walked beside the participant offering no encouragement during the test. The use of a walking-aid was allowed if needed.

Walking difficulties
Self-rated walking difficulties were assessed using a structured questionnaire according to the question: "Do you have difficulties in walking two kilometers

on end without resting?” Response options were: no difficulties, minor difficulties, major difficulties, and unable. Those who reported major difficulties or being unable to walk 2 km were categorized as having major self-reported difficulties in walking 2 km.

4.2.3 Postural balance

Postural sway was measured with the subject standing in stocking feet in a semi-tandem position on the force platform. In the semi-tandem stance one foot was placed one-half of a foot length ahead of the other, with feet touching. Participants were advised to stand as still as possible, keep their arms down by their sides and with their gaze fixed at a marked point at eye level at the distance of 2 m.

The Good Balance System (Metitur Ltd, Jyväskylä, Finland) was used for the assessments. Sway was recorded for 20 s. From the movement of the center of pressure (COP), three outcome variables were calculated: mean medio-lateral and antero-posterior sway velocity (mm/s) and the velocity moment (mm^2/s). To compensate for the possible effect of higher locations of the center of mass among taller participants, the absolute sway variables were adjusted for the participant´s height [(sway variable/subject’s height in cm) X 180] (Era et al. 1996).

Semi-tandem stance was measured as part of the larger postural balance -battery which also included measurements in side-by-side stance with eyes open and closed and tandem stance with eyes open. Postural balance in semi-tandem stance was selected for this study, because most of the participants were able to do the test, and it discriminates balance performance better than the side-by-side stance.

4.2.4 Fall surveillance

After the first laboratory measurements information on falls was gathered for a follow-up period of 12 months. Participants marked daily on a calendar whether they fell or not. At the end of each month, participants mailed their calendar page to the research center. If the participant forgot to mail the calendar page, she was reminded by telephone. If a fall was reported, the participant was interviewed over the phone about the occurrence, circumstances, causes, and consequences of the fall. In this study participants were categorized according to whether they had at least one fall or at least two falls or at least one injurious fall. Injuries included fractures, bruises, lacerations, and pain.

Three persons refused and three persons were unable for health reasons to participate in the fall surveillance (Figure 2). During the fall follow-up 3 persons died and 12 persons did not return all of their calendar pages. The data of these 15 persons were included in the analysis up to the month their participation ceased.

4.2.5 Health, medication and health-related habits

The presence of self-reported chronic diseases, prescribed medications and smoking habits were confirmed by a physician during the clinical examination. Cognitive function was screened with the Mini-Mental State Examination (MMSE) (Folstein et al. 1975). Body mass index was calculated by dividing measured body weight by height squared (kg/m^2). Low- and high-density lipoproteins (LDL, HDL) as well as total blood cholesterol levels were determined from a venous blood sample. Supine systolic and diastolic blood pressure was measured using an automatic sphygmomanometer. Information about education, hearing aid ownership, noise exposure, frequent middle ear infections (>3 episodes), hearing disorders and accidents, e.g. explosions, tympanic membrane perforations or severe head injuries, was gathered using a structured questionnaire. Habitual level of physical activity was assessed based on self-report. To be categorized as sedentary a person reported no other regular activity but light walking two or fewer times a week. People rated as moderately active walked or did other light exercise at least three times a week, but no exercise more intensive than that. Those reporting moderate or vigorous exercise at least three times a week were categorized as physically active (Grimby 1986).

4.3 Statistical analyses

The variables were examined for normality and distribution. The BEHL and BESRL were transformed by the square root of the inverse: $f(x)= 1/\sqrt{BEHL}$, $f(x)=1/\sqrt{BESRL}$ and the PTAs of the low, mid and high frequencies by the formula f(x)=1/low**0.1, f(x)=1/mid**0.1 and f(x)=1/high**0.1. In the further analyses these transformed values multiplied by 10 were used to avoid difficulties arising from small variable values. For the sway variables natural logarithmic transformation were used. After the transformation, the absolute values of Skewness and Kurtosis were acceptable. The level of statistical significance was set at $p<.05$.

Data were analysed with the PRELIS version 2.51 module of LISREL (PRELIS 2.51 module of LISREL for Windows 2005), SPSS version 14.0.2 (SPSS for Windows 2006) and Stata version 9.0 (Stata for Windows 2005) statistical program packages. Quantitative genetic modeling was done with the Mx program using full information maximum likelihood with raw data input. Genetic modeling by Mx is based on structural equation models which are premised on the matrix algebra calculations (Neale et al. 2003).

4.3.1 Individual-based analyses

Mean differences in maximal walking speed and endurance as well as the proportion of people with self-reported difficulties in walking two kilometers between persons with and without hearing impairment were compared with

Wald tests adjusted for within-pair dependency resulting from the sampling of twin pairs (III). Similarly, an adjusted Wald test was used to compare whether COP movements and the proportion of fallers differed between the hearing acuity quartiles (IV) and whether participants with and without hearing impairment differed according to background characteristic variables (III). The adjusted Wald test is equivalent to t-tests and chi-square tests for unrelated individuals.

Logistic regression models were used to analyse whether impaired hearing was associated with major walking difficulties at baseline and whether hearing impairment at baseline predicted onset of major walking difficulties at follow-up three years later (III). Incidence rate ratios (IRR) for falls in the one-year fall follow-up were computed from a negative binomial regression model (IV). Negative binomial regression modeling takes into account that fall events are non-independent incidents and that the occurrence of a single fall makes a subsequent fall more likely. IRRs are interpreted as the relative risk estimates. The age and interdependency of twin sisters were taken into account in all the regression models.

4.3.2 Twinpair-based analyses

The equalities of the means of the continuous variables and distributions of the categorical variables between the MZ and DZ twins were calculated and tested using an adjusted Wald test. The equality of the variances between the zygosity groups was tested using the variance ratio test. The within-pair dependence of twin individuals was taken into account in the analyses.

Tetrachoric correlations for binary variables were calculated separately for both zygosity groups (I). These correlations provide indicative estimates of the importance of genetic and environmental influences on the trait.

Concordance analyses

Twin similarity for presence of hearing impairment is summarised separately for both MZ and DZ pairs by estimates of probandwise concordance and its 95% confidence intervals (I). The probandwise concordance rate is the probability that the co-twin of the affected twin will also be affected. Probandwise concordance is calculated with the formula 2 × concordant pairs / (2 × concordant pairs + discordant pairs) (Smith 1974, Rijsdijk & Sham 2002). MZ twin pairs discordant for hearing acuity were also identified to compare the fall risk of the better hearing sister to her co-twin with poorer hearing acuity (IV). This genetically controlled case-control analysis provides information about whether the studied traits correlate with each other regardless of genetic factors.

Genetic modeling

Univariate analyses

Genetic and environmental influences contributing to BEHL and BESRL (I) as well as to the low, mid and high frequencies (II) were estimated first with univariate models. In the basic univariate twin model correlation for the additive and dominant genetic effects is defined as 1 between MZ twins and 0.5 and 0.25, respectively, between DZ twins. By definition, the correlation for shared environmental effects is 1 between both MZ and DZ twins, if the twins are reared together in the same home. Likewise, non-shared environmental effects are uncorrelated between MZ and DZ twins, being a source of variance which will result in differences among family members (Figure 4). The aim of genetic modeling is to find a model which provides a theoretically meaningful interpretation, fits the data well and has as few explanatory parameters as possible. The fit of the hierarchical submodels (AE, DE, CE, E) against the full model (ADE or ACE) were assessed with the -2 log likelihood (LL) difference tests. Non-additive genetic effects and shared environmental effects cannot be estimated simultaneously when the data consists only of pairs of twins raised together (Rijsdijk & Sham 2002). In all the models age was included as a covariate.

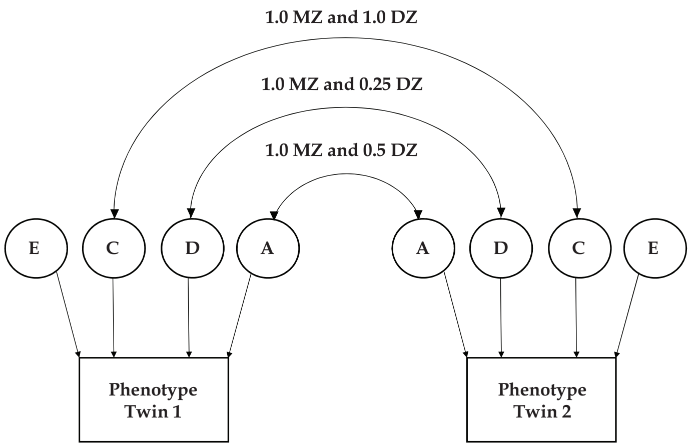

FIGURE 4 Path diagram for the univariate twin model with additive (A) and dominant (D) genetic effects, and shared (C) and non-shared (E) environmental effects. Correlations between monozygotic (MZ) and dizygotic (DZ) twins are presented in the figure.

Multivariate analyses

A bivariate Cholesky decomposition model was used to estimate whether BEHL and BESRL (I), BEHL and walking speed, and BEHL and postural balance (IV) are influenced by same genetic and environmental effects. The full Cholesky decomposition model contains A, E and either C or D effects which are common for both of the observed traits. Furthermore, the model allows for A, E and either C or D effects which load only onto one of the observed traits (Figure 5).

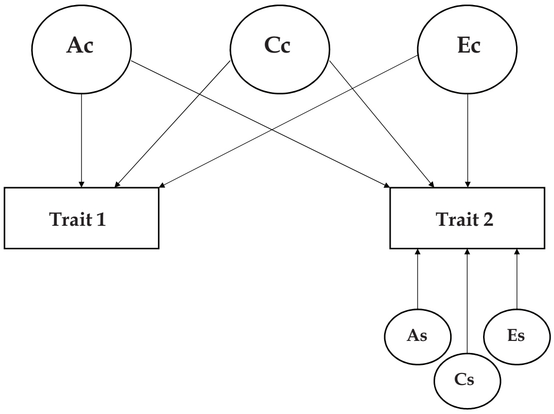

FIGURE 5 The full Cholesky decomposition ACE model including additive genetic effects (A) and shared (C) and non-shared (E) environmental effects. Lowercase c refers to influences common to both traits, and s influences specific to trait 2.

A trivariate independent pathway model was used to describe whether the genetic and environmental influences were common or specific to hearing acuity at the different frequency levels (II). The full independent pathway model consists of genetic and environmental effects which are common to all traits and which are trait-specific (Figure 6).

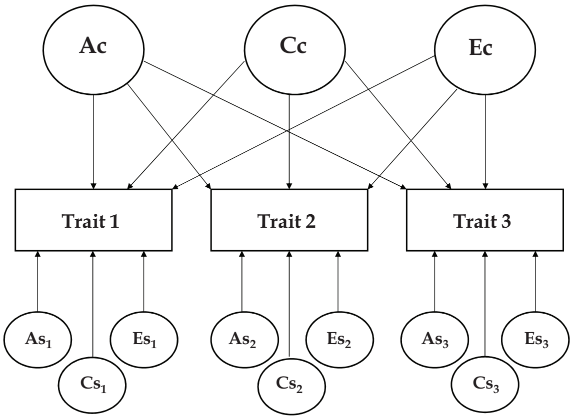

FIGURE 6 The full independent pathway ACE model including additive genetic effects (A) and shared (C) and non-shared (E) environmental effects. Lowercase c refers to influences common to all traits, and s influences specific to each trait.

To obtain the more parsimonious model, the full ACE or ADE multivariate model was modified by dropping out the weakest non-significant parameters one by one, until the model with the best fit was obtained. The fit of the reduced nested model was assessed by subtracting the -2LL and degrees of freedom of the obtained model from the -2LL and degrees of freedom of the full ACE or ADE model (Neale et al. 2003). Age was included as a covariate in the models.

5 RESULTS

5.1 Characteristics according to hearing acuity (III)

Altogether 179 (41%) participants had impaired audiometrically measured hearing ($BEHL_{0.5\text{-}4\ kHz} \geq 21$ dB). Nine participants with hearing impairment ($BEHL_{0.5\text{-}4\ kHz} \geq 21$ dB) had a hearing aid. The participants with hearing impairment were statistically significantly older, shorter, had less education in years and more chronic diseases than the participants without hearing impairment. Exposure to noise and frequent middle ear infections were reported more often by participants with than without hearing impairment. There were no differences between participants with and without hearing impairment in terms of body weight, body mass index, systolic or diastolic blood pressure, the cholesterol levels, number of prescription medicines, or MMSE score. The proportion of participants with exposure to impulse noise, ear diseases other than middle ear infections, auditory accidents, cardiovascular diseases, rheumatoid arthritis, osteoporosis or diabetes did not differ according to hearing acuity. There were also no differences in physical activity or smoking status between women with and without hearing impairment (Table 1).

TABLE 1 Characteristics according to hearing acuity.

Descriptive variable	$BEHL_{0.5\text{-}4\ kHz}$ < 21 dB n=255, (59%)		$BEHL_{0.5\text{-}4\ kHz}$ ≥ 21 dB n=179, (41%)		
	Mean	(SD)	Mean	(SD)	p
Age	68.0	(3.2)	69.5	(3.5)	<.001
Weight (kg)	70.2	(12.6)	69.9	(11.0)	.814
Height (cm)	159.5	(6.1)	157.3	(6.0)	.001
Body mass index (kg/m^2)	27.7	(5.0)	28.3	(4.4)	.242
Blood pressure, systolic (mm/Hg)	149.2	(22.3)	150.3	(21.2)	.636
Blood pressure, diastolic (mm/Hg)	86.0	(10.4)	85.7	(10.3)	.752
Total cholesterol (mmol/l)	5.5	(0.9)	5.5	(0.9)	.894
Low-density lipoprotein, LDL (mmol/l)	3.5	(0.9)	3.6	(0.9)	.270
High-density lipoprotein, HDL (mmol/l)	1.6	(0.4)	1.5	(0.4)	.324
Number of chronic diseases	1.9	(1.4)	2.2	(1.5)	.049
Number of medicines	2.0	(2.0)	2.1	(2.0)	.819
Mini-Mental State Examination score (max. 30)	27.1	(2.3)	26.8	(2.4)	.210
Education in years	9.0	(3.3)	8.2	(2.7)	.014
	n	(%)	n	(%)	p
Hearing aid ownership	0	(0)	9	(5)	.005
Otitis media (over 3 times)	18	(10)	24	(19)	.035
Ear disease other than otitis media	6	(3)	4	(2)	.938
Acoustic trauma	3	(1)	3	(2)	.669
Noise exposure (work or leisure)	45	(19)	48	(29)	.028
Impulse noise exposure (work or leisure)	13	(5)	15	(9)	.210
Diabetes mellitus	10	(4)	15	(8)	.109
Cardiovascular disease	138	(54)	99	(55)	.825
Arthritis	10	(4)	8	(4)	.785
Osteoporosis	6	(2)	5	(3)	.810
Smoking	10	(4)	11	(6)	.357
Physical activity					
Sedentary	67	(26)	56	(31)	.447
Moderately active	136	(54)	84	(47)	
Active	52	(20)	39	(22)	

BEHL, Better ear hearing threshold level
SD, Standard deviation

5.2 Genetic and environmental effects on hearing acuity (I-II)

MZ and DZ twins did not differ according to background characteristics, listed in Table 1, with the exceptions of age and HDL cholesterol. The mean age of the MZ (68.3 year) and DZ twins (68.9 year) did not differ but the variance of age was significantly larger for the MZ than DZ twins (14.1 vs. 9.5, p=.004). The mean HDL cholesterol (1.6 mmol/l vs. 1.5 mmol/l, p=.009) and its variance (0.2 vs. 0.1, p=.001) was higher in the MZ than in DZ twins.

The median audiometric curves are shown in Figure 7 for the better and worse hearing ear separately for both zygosity groups. The median hearing threshold levels at the low $_{PTA\ 0.125\text{-}0.5\ kHz}$, mid $_{PTA\ 1\text{-}2\ kHz}$ and high $_{PTA\ 4\text{-}8\ kHz}$ frequencies were 13, 15 and 38 dB, respectively, for the better ear and 15, 20 and 45 dB for the worse ear.

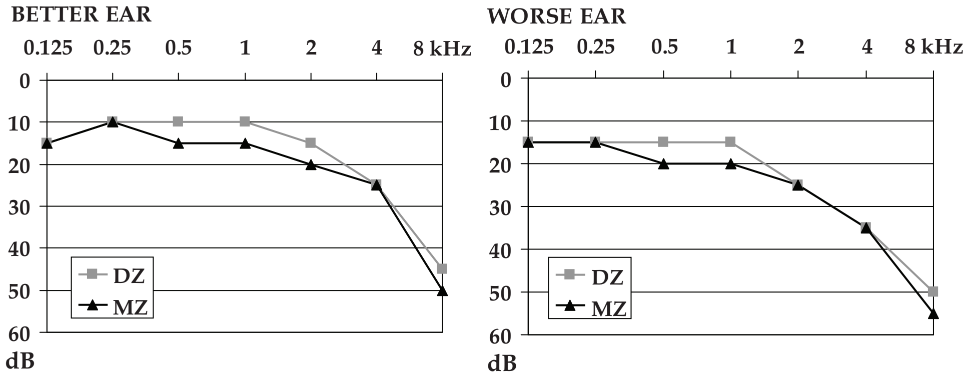

FIGURE 7 Median hearing thresholds (dB) at different frequencies (kHz), separately for both zygosity groups and both ears.

The variances of $BEHL_{0.5\text{-}4\ kHz}$ and BESRL and the means of $BEHL_{0.5\text{-}4\ kHz}$ between MZ and DZ twin individuals did not differ. The average BESRL was 4 dB better for DZ than MZ twins (p=.025). Furthermore no systematic differences were found between MZ and DZ twin individuals in the means for the better and worse hearing ear at the low $_{PTA\ 0.125\text{-}0.5\ kHz}$, mid $_{PTA\ 1\text{-}2\ kHz}$ and high $_{PTA\ 4\text{-}8\ kHz}$ frequencies, except in the means for the mid $_{PTA\ 1\text{-}2\ kHz}$ frequencies of the better ear, where the average hearing threshold was 6 dB better in DZ than MZ twins (p=.001) (Table 2). Statistically significant differences between MZ and DZ twin individuals were found in the variances of the low $_{PTA\ 0.125\text{-}0.5\ kHz}$ (p=.048) frequencies for the better ear and low $_{PTA\ 0.125\text{-}0.5\ kHz}$ (p=0.028) and mid $_{PTA\ 1\text{-}2\ kHz}$ (p=.048) frequencies for the worse ear.

The most frequent type of audiogram configuration was the descending type, which was found among approximately 67% of the participants. Approximately 21% of the participants had the impaired and 10% normal flat type of audiogram. There was no significant difference in the distribution of the audiogram configurations between MZ and DZ twins (Table 2).

TABLE 2 Auditory characteristics of twin individuals

	BETTER EAR			WORSE EAR		
	MZ twins n=205	DZ twins n=224		MZ twins n=205	DZ twins n=224	
	Mean (SD)	Mean (SD)	p	Mean (SD)	Mean (SD)	p
Low frequencies PTA 0.125-0.5 kHz, dB	17 (11)	14 (7)	.085†	23 (21)	19 (15)	.072†
Mid frequencies PTA 1-2 kHz, dB	21 (14)	15 (9)	.001†	28 (22)	23 (15)	.082†
High frequencies PTA 4-8 kHz, dB	39 (19)	37 (16)	.727†	46 (23)	44 (21)	.822†
BEHL PTA 0.5-4 kHz, dB	23 (14)	19 (9)	.097*			
BESRL, dB	20 (11)	16 (8)	.025*			
	n (%)	n (%)	p	n (%)	n (%)	p
Categorized BEHL$_{0.5\text{-}4\ kHz}$						
No impairment, <21 dB	106 (52)	147 (65)	.057			
Mild impairment, 21-39 dB	75 (36)	69 (31)				
Moderate impairment, 40-69 dB	22 (11)	8 (4)				
Severe impairment, 70-94 dB	1 (0.5)	- (-)				
Profound impairment, >94 dB	1 (0.5)	- (-)				
Audiogram configuration						
Flat, normal	22 (11)	34 (15)	.080	13 (6)	18 (8)	.402
Flat, impaired	46 (22)	31 (14)		58 (28)	44 (20)	
Descending	134 (65)	156 (70)		128 (63)	155 (69)	
Ascending	- (-)	1 (0.5)		1 (0.5)	3 (1)	
U-shape	3 (2)	- (-)		2 (1)	1 (0.5)	
A-shape	- (-)	2 (0.5)		3 (1.5)	3 (1.5)	

BEHL, Better ear hearing threshold level
BESRL, Better ear speech recognition threshold level
PTA, Pure-tone average
SD, Standard deviation
† Adjusted Wald test p -values are given to transformed values f(x)=(1/low**0.1)x10, f(x)=(1/mid**0.1)x10 and f(x)=(1/high**0.1)x10
* Adjusted Wald test p -values are given to transformed values (1/√BEHL)x10 and (1/√BESRL)x10

More DZ twins (50%) than MZ twins (38%) rated their hearing as good. Substantially reduced hearing was reported by 8% of MZ and 2% of DZ twins. Rest of the participants rated their hearing as slightly reduced. Difference in self-rated hearing between zygosity groups was statistically significant (p=.007).

Probandwise concordance and tetrachoric correlation for hearing impairment (BEHL$_{0.5\text{-}4\ kHz} \geq 21$ dB) was much higher for MZ than DZ twin pairs, suggesting a major genetic component. For self-rated hearing problems the probandwise concordances were almost the same for MZ and DZ twins, and DZ pairs showed higher tetrachoric correlations than MZ pairs (Table 3). This suggests that environmental influences alone underlie individual differences. No further genetic analyses were carried out for self-reported hearing.

TABLE 3 Familial aggregation of audiometrically measured and self-rated hearing problems

	Total number of twin pairs	Number of individuals with hearing problem	Concordant affected pairs n (% of all pairs)	Discordant pairs n (% of all pairs)	Probandwise concordance (95% CI)	Tetrachoric correlation (95% CI)
$BEHL_{0.5\text{-}4\ kHz} \geq 21$ dB						
MZ	102	99	40 (39)	19 (19)	0.81 (0.72-0.89)	0.84 (0.67-0.93)
DZ	112	77	17 (15)	43 (38)	0.44 (0.30-0.58)	0.26 (-0.05-0.53)
Self-rated problems in hearing						
MZ	102	127	41 (40)	45 (44)	0.65 (0.55-0.74)	0.12 (-0.19-0.42)
DZ	112	111	33 (30)	45 (40)	0.59 (0.49-0.70)	0.32 (0.04-0.56)

BEHL, Better ear hearing threshold level
CI, Confidence interval
Probandwise concordance=2 × concordant pairs / (2 × concordant pairs + discordant pairs)

The results of the univariate genetic models are shown in Table 4. For $BEHL_{0.5\text{-}4\ kHz}$ and BESRL, as well as for the better and worse ears low $_{PTA\ 0.125\text{-}0.5\ kHz}$, mid $_{PTA\ 1\text{-}2\ kHz}$ and high $_{PTA\ 4\text{-}8\ kHz}$ frequencies, the AE model showed the best fit with the data. Additive genetic effects accounted for 65 to 75% of the total variance in the better ear hearing acuity and 28 to 55% of the total variance in the worse ear hearing acuity. The remaining variance in all traits was due to non-shared environmental effects. The effect of age explained 2 to 12% of the variance in the better ear hearing acuity and 4 to 12% of the total variance in the worse ear hearing acuity.

TABLE 4 Standardized estimates of the most acceptable univariate genetic models at different frequencies separately for the better and worse ear.

	BETTER EAR		**WORSE EAR**	
	Standardized estimates, % (95% CI)		Standardized estimates, % (95% CI)	
	a^2	e^2	a^2	e^2
Low frequencies PTA 0.125-0.5 kHz, dB	65 (54-73)	35 (27-46)	28 (13-42)	72 (58-87)
Mid frequencies PTA 1-2 kHz, dB	75 (65-81)	25 (19-35)	48 (34-60)	52 (40-66)
High frequencies PTA 4-8 kHz, dB	67 (56-75)	33 (25-44)	55 (40-66)	45 (34-60)
BEHL PTA 0.5-4 kHz, dB	75 (67-81)	25 (19-33)		
BESRL	66 (55-74)	34 (26-45)		

a, additive genetic effects
e, non-shared environmental effects
BEHL, Better ear hearing threshold level
BESRL, Better ear speech recognition threshold level
CI, Confidence interval
PTA, Pure-tone average

Figure 8 summarizes the results of the bivariate genetic modeling for $BEHL_{0.5\text{-}4\ kHz}$ and BESRL. The AE model was selected on the basis of its best fit with the data and its theoretical acceptability. In the model, $BEHL_{0.5\text{-}4\ kHz}$ and BESRL shared an additive genetic component in common which explained 75% (95% CI 67-81%) of the variance in $BEHL_{0.5\text{-}4\ kHz}$ and 54% (95% CI 43-64%) of the variance in BESRL. An individual environmental factor in common to the two traits accounted for 25% (95% CI 19-33%) of the variance in $BEHL_{0.5\text{-}4\ kHz}$ and 17% (95% CI 10-27%) of the variance in BESRL. In addition, BESRL had its own additive genetic and individual environmental factors which explained the remaining variance.

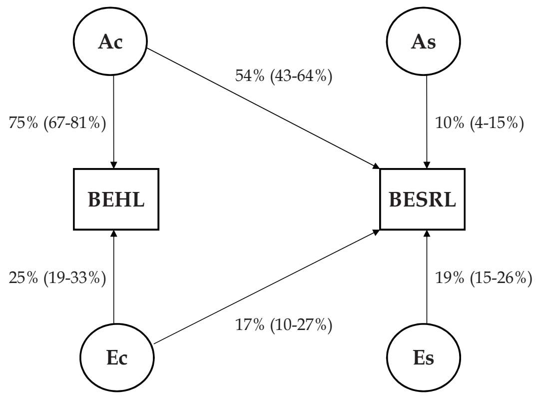

FIGURE 8 Reduced Cholesky decomposition model for better ear hearing threshold level ($BEHL_{0.5\text{-}4\ kHz}$) and better ear speech recognition threshold level (BESRL). Standardized proportions and 95% confidence intervals of additive genetic effects (A) and non-shared environmental effects (E) accounting for the variance. Lowercase *c* refers to influences common to both traits and *s* influences specific to BESRL.

The results of the more parsimonious independent pathway models for the low $_{PTA\ 0.125\text{-}0.5\ kHz}$, mid $_{PTA\ 1\text{-}2\ kHz}$ and high $_{PTA\ 4\text{-}8\ kHz}$ frequencies, separately for the better and worse ear are shown in Figure 9. In the better ear, additive genetic effects common to all frequency areas accounted for 24% (95% CI 15-35%), 74% (95% CI 65-81%) and 22 % (95% CI 12-32%) of the total variance at the low $_{PTA\ 0.125\text{-}0.5\ kHz}$, mid $_{PTA\ 1\text{-}2\ kHz}$ and high $_{PTA\ 4\text{-}8\ kHz}$ frequencies, respectively. In addition, frequency-specific additive genetic effects accounted for 40% (95% CI 28-50%) of the total variance at the low $_{PTA\ 0.125\text{-}0.5\ kHz}$ and 45% (95% CI 34-55%) at the high $_{PTA\ 4\text{-}8\ kHz}$ frequencies. In the worse ear, additive genetic effects in common accounted for 9% (95% CI 2-20%), 49% (95% CI 35-61%) and 21% (95% CI 9-35%) of the total variance at the low $_{PTA\ 0.125\text{-}0.5\ kHz}$, mid $_{PTA\ 1\text{-}2\ kHz}$ and high $_{PTA\ 4\text{-}8\ kHz}$ frequencies, respectively. In addition, frequency-specific additive genetic effects accounted for 35% (95% CI 22-47%) of the total variance at the high $_{PTA\ 4\text{-}8\ kHz}$ frequencies. The remainder of the variance in both ears was due to environmental effects.

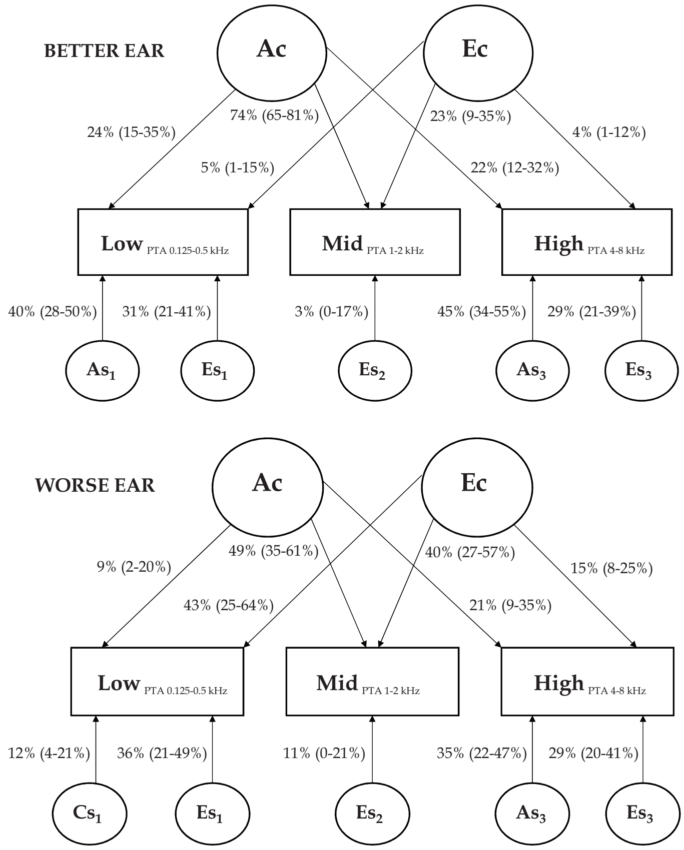

FIGURE 9 The most parsimonious models explaining the genetic and environmental effects on hearing acuity, described as a pure tone average (PTA), at low, mid and high frequencies for the better and worse hearing ear. Standardized proportions and 95% confidence intervals of additive genetic effects (A), shared environmental (C) and non-shared environmental effects (E) accounting for the variance. Lowercase *c* refers to influences common to all traits and *s* influences specific to each trait.

5.3 The association between hearing acuity and mobility (III)

At baseline, participants with hearing impairment ($BEHL_{0.5\text{-}4\ kHz} \geq 21$ dB) had slower maximal walking speed (1.7 m/s, standard deviation [SD] 0.3 vs. 1.8 m/s, SD 0.3, p=.007), lower walking endurance (520 m, SD 75 vs. 536m, SD 75, p=.080) and more self-reported major difficulties in walking two kilometers (13% vs. 6%, p=.023) than those without hearing impairment. In an age-adjusted logistic regression model, the women with hearing impairment had a two-fold risk (OR 2.09 [95% CI 1.01-4.33]) for major difficulties in walking two kilometers at baseline compared to those without hearing impairment. Further adjustments for height, number of chronic disease, cardiovascular disease, arthritis, diabetes, education in years, noise exposure at work or during leisure, cognitive impairment (MMSE score ≤ 24) or physical activity level, one at a time, did not materially change the result.

A bivariate Cholesky decomposition model was constructed to examine whether $BEHL_{0.5\text{-}4\ kHz}$ and walking speed have genetic or environmental effects in common. In the model hearing acuity and walking speed shared an additive genetic component which explained 6% (95% CI 2-13%) of the total variance in walking speed. The rest of the variance in walking speed was accounted for by trait-specific additive genetic effects (0.6% [95% CI 0.4-0.7%]), shared environmental effects (54% [95% CI 43-63%]) and non-shared environmental effects (39% [95% CI 31-48%]) (Figure 10).

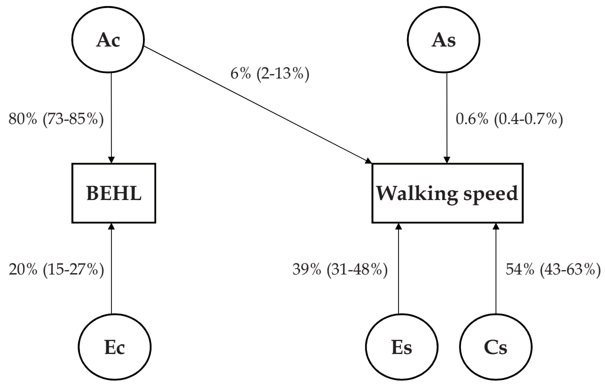

FIGURE 10 Reduced Cholesky decomposition model for better ear hearing threshold level ($BEHL_{0.5\text{-}4\ kHz}$) and maximal walking speed. Standardized proportions and 95% confidence intervals of additive genetic effects (A) and non-shared (E) and shared (C) environmental effects accounting for the variance. Lowercase *c* refers to influences common to both traits and *s* influences specific to walking speed.

During the 3-year follow-up, new major difficulties in walking two kilometers developed for 33 participants: 19 (13%) with and 14 (6%) without hearing impairment (p=.041). In an age-adjusted logistic regression model, women with hearing impairment had a two-fold risk for new major difficulties in walking two kilometers (OR 2.04 [95% CI 0.96-4.33]) compared to those without hearing impairment. Further adjustments for height, number of chronic disease, cardiovascular disease, arthritis, diabetes, education in years, noise exposure at work or during leisure, cognitive impairment (MMSE score ≤ 24) or physical activity level, one at a time, did not materially change the result.

5.4 The association between hearing acuity, balance and falls (IV)

The mean follow-up time for falls was 345 days (SD 39), comprising 4868 person-months. Altogether 199 participants reported 437 falls of which 44% were injurious. Approximately half (47%) of the participants fell at least once and 22% sustained ≥ 2 falls. Typically, falls occurred outdoors (79%) and during daytime between 11 a.m. and 5 p.m. (55%). During the winter from November to April the occurrence of falls was 38/month and in summer from May to October it was 35/month.

In the semi-tandem stance the mean COP velocity moment of all the participants was 48 mm²/s (SD 29), mediolateral velocity 15 mm/s (SD 4), and anteroposterior velocity 12 mm/s (SD 4).

For the analyses participants were categorized into quartiles according to $BEHL_{0.5\text{-}4\ kHz}$. In the first, the best, hearing quartile were people whose $BEHL_{0.5\text{-}4\ kHz}$ was better than 11.5 dB. The range for the second quartile was 11.5-17.5 dB, for the third quartile 18-27 dB and for the fourth, the poorest, quartile >27 dB. Fall rates for the best to the poorest hearing quartiles were 7.1, 6.7, 10.4 and 11.3 falls per 100 person-months. The proportion of people who had 2 or more falls was 30% in the poorest hearing quartile and 17% in the best hearing quartile (p=.042). The means of the COP velocity moment for the best to the poorest hearing quartiles were 40.7 mm²/s (SD 24.4), 46.3 mm²/s (SD 25.5), 50.6 mm²/s (SD 33.4) and 52.8 mm²/s (SD 32.0) (p-value for the trend =.003) (Table 5).

TABLE 5 Indices of COP movement variables and occurrence of falls according to different hearing acuity quartiles

	Hearing acuity ($BEHL_{0.5\text{-}4\ kHz}$) quartiles n=429				Between groups Wald test
	First (best) quartile (1)	Second quartile (2)	Third quartile (3)	Fourth (poorest) quartile (4)	1 - 4
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p*
COP movement in semi-tandem stance (n=420)					
mediolateral velocity (mm/s)	14.1 (3.3)[3,4]	15.1 (4.2)	15.7 (4.6)[1]	15.9 (4.3)[1]	.009
anteroposterior velocity (mm/s)	10.9 (4.2)[3,4]	11.4 (3.7)	12.2 (4.1)[1]	12.3 (3.8)[1]	.018
velocity moment (mm²/s)	40.7 (24.4)[3,4]	46.3 (25.5)	50.6 (33.4)[1]	52.8 (32.0)[1]	.003
Fall occurrence (n=423)	n (%)	n (%)	n (%)	n (%)	p
at least one fall	46 (43)	51 (49)	49 (45)	53 (53)	.583
at least two falls	18 (17)[4]	19 (18)	25 (23)	30 (30)[1]	.176
at least one injurious fall	27 (25)	30 (29)	27 (25)	37 (37)	.270

BEHL, Better ear hearing threshold level
COP, Center of pressure
SD, Standard deviation
* Adjusted Wald test p -values for COP variables are given for logarithmised values.
Hearing quartile limits from the first (best) to the fourth (poorest) were:
$BEHL_{0.5\text{-}4\ kHz}$ <11.5 dB, 11.5-17.5 dB, 18-27 dB and >27 dB.
Superscripts [1, 3, 4] indicate statistically significant differences (p -value < .05) between hearing acuity quartiles.

Age-adjusted IRR for falls, with the best hearing quartile as a reference, were 1.2 (95% CI 0.4-3.8) in the second, 4.1 (95% CI 1.1-15.6) in the third and 3.4 (95% CI 1.0-11.4) in the fourth (poorest) hearing quartiles. In a model adjusted for age, each unit increase in COP velocity moment, using logarithmised values, more than doubled the fall risk (IRR 2.2 [95% CI 1.1-4.5]). When both hearing and COP velocity moment were added into the model simultaneously, the increased risks for falls among those in the poorest hearing quartile decreased from 3.4 (95% CI 1.0-11.4) to 2.4 (95% CI 0.8-7.4) (Table 6).

TABLE 6 Incidence rate ratios (IRRs) and confidence intervals (95%CIs) for falls from negative binomial regression models adjusted for age.

	MODEL I (n=423) IRR (95% CI)	MODEL II (n=417) IRR (95% CI)	MODEL III (n=417) IRR (95% CI)
Second hearing quartile	1.2 (0.4-3.8)	-	0.7 (0.3-1.7)
Third hearing quartile	4.1 (1.1-15.6)	-	1.8 (0.6-5.8)
Fourth hearing quartile	3.4 (1.0-11.4)	-	2.4 (0.8-7.4)
COP velocity moment (mm^2/s)*	-	2.2 (1.1-4.5)	1.8 (0.9-3.4)

In MODEL I and MODEL III the first (best) hearing quartile is the reference group.
BEHL, Better ear hearing threshold level
COP, Center of pressure
* IRRs are calculated using logarithmised values.
Hearing quartile limits from the first (best) to the fourth (poorest) were:
$BEHL_{0.5\text{-}4\,kHz}$ <11.5 dB, 11.5-17.5 dB, 18-27 dB and >27 dB.

A bivariate Cholesky decomposition model was constructed to examine whether $BEHL_{0.5\text{-}4\,kHz}$ and COP velocity moment have genetic or environmental effects in common. No statistically significant effects in common were found. Further analysis were conducted among 18 MZ twin-pairs discordant for hearing acuity, with one sister having $BEHL_{0.5\text{-}4\,kHz} \geq 21$ dB and other sister < 21 dB. The age-adjusted IRR for falls among the sister with poorer hearing compared to the better hearing sister was 8.8 (95% CI 1.1-68.5), suggesting association independent of genetic factors between hearing acuity and falls.

6 DISCUSSION

Additive genetic effects accounted for over 60% of the total variance in hearing acuity at different frequencies as well as in speech recognition. Although overall heritability was rather constant across the frequency spectrum, it is noteworthy that at the low and high frequencies frequency-specific genetic and environmental effects together accounted for over 70% of the total variance. In the worse ear, the proportion of variance accounted for by genetic effects was smaller, particularly at the low frequencies. In contrast to the results of audiometry, self-reported hearing difficulties were predominantly accounted for by environmental factors.

Approximately half (41%) of older female participants in this study had impaired audiometrically measured hearing. Impaired hearing was associated cross-sectionally with poor mobility and poor postural balance, and impaired hearing also preceded mobility decline and falls.

6.1 Genetic and environmental effects on hearing acuity

The results of this study are in line with the findings by Wingfield et al. (2007) who conducted a twin study on the heritability of audiometrically measured hearing acuity at different frequencies. In their study, additive genetic effects accounted for 70% and 68% of the total phenotypic variation for mean hearing acuity at the middle (0.5-2 kHz) and high frequencies (4-8 kHz), respectively, for the better hearing ear. Corresponding percentages for the worse hearing ear were 41% and 54%. That study also supports the present finding that some of the genetic effects are common and some are specific to hearing acuity at different frequency-levels. The study sample consisted of 179 MZ and 150 DZ male twin pairs, aged 52 to 60 years, from the Vietnam Era Twin Registry.

The present results on heritability are also in line with the recent findings by McMahon et al. (2008) and Raynor et al. (2009) who both conducted a study of the familial aggregation of hearing loss among older people. According to

McMahon et al. (2008), women with a maternal family history of hearing loss had almost a three times higher odds (OR 3.0 [95% CI 1.6-5.6]) of moderate to severe hearing loss compared to women without a family history. Among men, paternal family effects were suggested (OR 2.0 [95% CI 1.0-3.9]). According to Raynor et al. (2009) age- and gender-adjusted heritability of hearing loss was 67%. Furthermore they revealed that siblings of individuals with hearing loss had almost five times higher odds of having hearing loss than siblings of participants without hearing loss. Corresponding gender stratified odds were 2.5 in men and 5.5 in women.

According to results of the present study and that by Wingfield et al. (2007) environmental effects were more prominent in the worse hearing ear and greater differences in heritability were found between the frequency levels in the worse than in the better ear. Noise is known to affect in particular the basal end of the cochlea, and in audiograms this is most typically seen at the high frequencies. Thus, noise-effects may be included among the specific environmental effects at high frequencies which, in this study, accounted for approximately one third of the total variance. Approximately 80% of the total variance at low frequencies in the worse ear was accounted for by environmental effects; half of that proportion was common to all frequency levels and half was specific to the low frequencies. No explanation for the difference in heritability between the low compared to other frequency levels in the worse ear was found.

According to present results, the better ear hearing threshold level and the better ear speech recognition threshold level were accounted for mainly by the same genetic and environmental effects, but there was also a specific genetic and a specific environmental effect affecting speech recognition. This may be explained by the different, more demanding cognitive and neural processing required for speech recognition than for detecting signals in pure-tone audiometry.

The heritability of hearing observed in this study was significantly higher than expected on the basis of a previous twin-study of self-rated hearing (Christensen et al. 2001). However, self-rated hearing and auditory tests differ from each other, and the results of these two measures may be complementary rather than being two measures of the same trait (Kempen et al. 1996, Jerger & Chmiel 1997, Hietanen et al. 2005). In FITSA data self-reported and audiometrically measured hearing correlated moderately. It can be assumed that auditory tests reflect auditory impairments while self-rated hearing gives information about the limitation on activity resulting from hearing impairments.

There were no major differences in the distributions of the audiogram configurations between the zygosity groups. The most frequent audiogram configurations in the present study were the descending and impaired flat types, which occurred among 67% and 21% of the participants, respectively. Degenerative changes of Corti´s organ are thought to lie behind the descending type and atrophy of the stria vascularis behind the flat type of audiogram configuration (Schuknecht & Gacek 1993). This assumption, although attractive, is difficult to evince in an aging population, as in presbyacusis the deterioration of hearing commences from the basal turn and progresses toward apex of the cochlea. The audiogram configuration that manifests at the onset of presbyacusis is of the high tone descending type, flattening as the disorder progresses (Yost 2000). Thus, the impaired flat audiogram does not necessarily reveal etiology but the severity and progression of outer hair cell loss. It may be that due to level of the degeneration of FITSA participants' ears, with respect to the outer hair cells of Corti´s organ, the variation in the audiogram configurations was small, rendering further analysis futile.

6.2 The association between hearing acuity, mobility, balance and falls

According to results of this study hearing acuity is associated with walking ability, postural balance and falls. There are several possible explanations for the association between hearing and mobility, although the precise nature of the association remains unclear.

First of all, it is possible that hearing correlates with mobility through mediating factors. This study showed that older women with poor hearing acuity had higher risk for falls than those with good hearing acuity and that higher fall-risk was partially explained by their poorer postural control. People with poorer hearing acuity showed greater COP displacement and velocity than people with good hearing acuity. Greater COP movement indicates poorer postural balance and correlates with increased risk for falls (Maki et al. 1994, Stel et al. 2003, Pajala et al. 2008).

Another explanation may lie in the ability to divide the attention when performing multiple tasks and to orientate to the environment. Compared to younger people, older people have to allocate a greater proportion of their attention to maintaining their postural balance during common daily activities, like walking (Lundin-Olsson et al. 1997). Impaired hearing may place additional demands on attention-sharing, thus making mobility more challenging. It has been argued that auditory cues are important for spatial orientation as these enable, for example, the noticing and avoidance of environmental hazards (Dargent-Molina et al. 1996). Deprivation of environmental acoustic information due to impaired hearing may emerge as uncertainty and poorer functioning in mobility tasks, thus also increasing fall risk. Because the most obvious effect of hearing impairment is diminished ability to communicate, it is possible that hearing-impaired people may restrict their social participation, thereby accelerating the disablement process.

Second, hearing and mobility may share common background factors, either genetic or environmental. In this study a minor common genetic effect between hearing acuity and walking speed was observed. One gene, which may merit further study is IGF1. IGF1 is crucial for intrauterine development and for postnatal growth and metabolism. In the cochlea deficiency of IGF1 may result in fewer hair cells at birth and earlier onset of sensorineural hearing loss in adulthood. Deletions of the IGF1 gene have been shown to cause retardation of intrauterine growth, severe short stature, and sensorineural deafness both in humans and in IGF1 knockout mice (Woods et al. 1996, Bonapace et al. 2003, Varela-Nieto et al. 2004). In previous studies low serum IGF1 levels have also been associated with lower muscle strength and power (Cappola et al. 2001, Barbieri et al. 2003) and, furthermore, with slower walking speed among older women (Cappola et al. 2001). In the present study the hearing-impaired participants had poorer walking ability, and interestingly they were also shorter than the participants without hearing impairment, which is in line with earlier findings on the effects of IGF1. Unfortunately no data which would allow to examine whether IGF1 contributes to the association between hearing and walking ability is available.

Socio-economic status may be one of the environmental background factors shared by hearing and mobility. According to the present results, the hearing-impaired participants had less education and were more often exposed to noise, which may reflect lower socio-economic status. In previous studies low socio-economic status has been associated not only with hearing impairment (Rosenhall et al. 1999) but also with slower walking speed (Rautio et al. 2005) and multiple other negative health-related indicators (Adler & Newman 2002). The precise nature of the pathway between socio-economic status and health is unresolved, and many different theories have been presented. In lower socio-economic positions the strains of manual labour as well as direct exposures in the workplace negatively influence health. In addition, differences in smoking, alcohol consumption, diet, physical exercise and access to health care facilities between socio-economic strata may contribute to health disparities (Adler & Newman 2002).

It is also possible that age-related hearing loss is one of the markers of frailty. Frailty is often described as a general decrease in functional status, resulting from declines in multiple physiological systems. Frailty is characterized by unintentional weight loss, weakness, exhaustion, slowness and low activity (Fried et al. 2001b). Hearing acuity may be linked to the cycle of frailty, for example through oxidative stress. Oxidative stress may contribute to different diseases and also directly both to a decline in muscle function and hair cell damage in the cochlea in old age (Evans & Halliwell 1999, Henderson et al. 2006, Ershler 2007, Jiang et al. 2007, Le & Keithley 2007, Wu et al. 2009). It should be noted that most of the participants in the present study were well-functioning non-frail persons, hence this theory of a linkage between hearing and frailty should be considered highly hypothetical.

According to results of the current study hearing impairments not only correlated with current walking ability but also predicted new mobility limitations over a three-year follow-up. However, the number of people developing new self-reported major difficulties in walking two kilometers was small in this study, and thus the statistical power was not sufficient in the prospective analyses. The finding is in line with the results of Ayis et al. (2006), who showed that self-rated hearing problems were associated with a decline in self-perceived mobility in a one-year follow-up among older people.

The association between hearing acuity and postural balance was not explained by genetic or environmental influences in common for the traits in this study. When controlled for shared genetic and environmental effects in within twin pair comparisons, the poorer-hearing sister had a significantly higher risk for falls than her better-hearing twin sister, suggesting an association independent of genetic factors. Although the hearing and vestibular organs are anatomically and physiologically closely connected, they appear to have their own etiology in terms of genetic and environmental factors. However, the possibility that the hearing and vestibular organs share a common genetic and environmental background cannot completely be ruled out. The method, used in this study, of assessing postural balance while standing on a force platform does not provide data specifically about vestibular functions but rather describes the cooperation of all the subsystems involved in postural control. Further study with more specific quantitative vestibular function tests could deepen understanding of the factors underlying the association between hearing acuity and postural balance.

6.3 Methodological considerations

The FITSA study comprised a population-based sample of older well-functioning community-dwelling women. To be recruited for this study, both sisters of the twin pair had to participate and be able to travel to the research laboratory for the baseline measurements. Therefore, the present sample was composed of relatively healthy older people, and it is possible that some people with poor hearing dropped out, owing to health or communication problems. Furthermore, the requirement that both sisters of the twin-pair had to participate might have resulted in overestimation of twin similarity.

The sample was composed of non-clinical participants, allowing both good and poor hearing ability to contribute to the results. The audiometric measurements were performed in standardized conditions by one experienced audiology assistant. As the data were gathered for the FITSA study, only air-conducted pure-tone hearing threshold levels were assessed and no information about bone-conducted threshold levels is available. Bone-conducted hearing threshold levels would have strengthen analysis by revealing the type, sensorineural, conductive or mixed, of hearing loss. Also more precise information about different environmental exposures, like noise, ototoxic drugs and solvents, might have refined analysis.

The walking and postural sway measurements were done in standardized conditions and the results provide a reliable and valid description of the traits. Both baseline and follow-up data on self-reported walking difficulties were available for 97% of the participants. Moreover, falldata were gathered prospectively and systematically for a year, and the participation rate in the fall follow-up was very high (97%).

It should be noted that less than one-tenth of the FITSA participants had a more severe than mild hearing impairment ($BEHL_{0.5\text{-}4\ kHz} \geq 40$ dB) at baseline, and that possible changes in hearing acuity during the follow-up are not known. It is possible that, if the sample had consisted of participants with more severe hearing, walking and/or postural balance impairments, an even stronger association between hearing acuity and mobility would have emerged.

Twin studies are based on the assumptions of twinning mechanisms, random mating and an equal environment. The zygosity of the FITSA participants was confirmed using DNA by a battery of highly polymorphic gene markers, which is highly reliable method. Assortative mating of the twins´ parents with respect to the phenotype of interest will lead to overestimation of shared environmental effects, because the correlation between DZ twin pairs, relative to MZ twin pairs, increases (Neale & Cardon 1992, Rijsdijk & Sham 2002). No information about the FITSA participants´ parents or spouses is available, and thus one can only speculate on this issue.

A very basic assumption in twin studies is that environmentallycaused similarity in a trait of interest is approximately the same for both MZ and DZ twin pairs reared in the same family. If MZ twins are treated more similarly than DZ twins, this may lead to an overestimation of genetic factors. Similarity can be tested by comparing the means and variances of a trait between zygosity groups (Rijsdijk & Sham 2002). In this study some inconsistencies in the variances and means of the hearing threshold level at some frequencies were present. However, it can be assumed that such inconsistencies in the genetic modeling were not due to environmental differences. It can be assumed that the difference in hearing acuity between the zygosity groups was due to chance and might have disappeared had the sample been bigger.

In this study, genetic control of sensitivity to the environment, so called gene (G) - environment interaction, was not analysed, because precise data about environmental indices was lacking. If positive G × E interaction exists, it is estimated in E and if positive G × C interaction exists it is estimated in A. G × E interaction means for example, that genetically susceptible individuals will be free of disease (in this study hearing impairment) as long as the environment does not contain the pathogen (in this study, for example, noise exposure). Resistant individuals will be free of disease even in an environment where the pathogen exists (Neale & Cardon 1992, Rijsdijk & Sham 2002).

The representativeness of twin studies has often been criticized. It has, for example, been claimed that genuine differences in terms of pregnancy and birth prevail between twins and singletons. The validity of the results of this study is supported by the fact that the prevalence of audiometrically measured hearing problems in this twin-sample was similar to that in previous non-twin population-based studies (Davis 1989, Uimonen et al. 1999). There are differences in the intrauterine circumstances not only between twins and singletons, but also between MZ and DZ twins. All DZ twins have a placenta as well as chorion and amnion of their own. In contrast, 70-75% of MZ twins share the same placenta with monochorionic diamniotic membranes while 25-30% has completely separate placentas and membranes. Only 1-2% of MZ twins share a placenta and both chorion and amnion. If MZ twins share a placenta, it is possible that vascular connections will deteriorate the development of one twin. If this is the case, the intrauterine circumstances of MZ twins differ more than those of DZ twins, and this may lead to underestimation of genetic influences (Hall 2003, Silventoinen & Kaprio 2008). Unfortunately, no specific birthdata on the FITSA participants is available, and thus no firm conclusions can be drawn on this issue. However, interestingly, the MZ twins in this study had slightly poorer hearing than the DZ twins, a difference that might be associated with different intrauterine or birth circumstances.

It should also be noted that heritability is always a population- and gender-specific estimate (Plomin et al. 2001) and thus the results of this study cannot be directly generalized to other populations. Further studies among men and different age-groups, and with more severe hearing and mobility problems are needed.

6.4 Implications and future directions

According to this study age-related hearing loss, previously ascribed predominantly to environmental factors, appears to be largely accounted for by genetic factors. Results of this study suggest that subjects with a family history, say in a sibling, of age-related hearing loss may be genetically more predisposed to hearing loss in old age. The genetically more predisposed, more vulnerable subjects especially may benefit from protection from environmental exposures across their whole life-span. It would be important to create prevention strategies focusing on the early detection of persons at high risk for developing hearing impairment and the most effective ways to prevent hearing impairments.

This study also indicates that both common and trait-specific genes accounted for the variation in hearing at different frequency levels. Hearing loss seems to be a result of complex processes where different genes together with various kinds of environmental exposures are responsible for deterioration in hearing at different frequencies or more precisely in different tonotopic areas. It is not possible with the quantitative genetic method more precisely to identify the underlying genes, risk factors or mechanism. Further studies are needed to clarify the complex nature of the ARHI and to identify the chromosomal areas and furthermore, genes, which may have an effect on hearing acuity in old age.

In the future, it would be interesting to do a longitudinal quantitative genetic analysis on hearing acuity to find out whether the genetic influences are common or specific to different time-points. Longitudinal data would also enable analysis about the rate of change in hearing acuity. In future, it would also be interesting to study the possible interaction between genetic effects and different environmental exposures in relation to hearing acuity.

Hearing impairments are mainly considered to be communication disorders, but deficits in hearing may have more wide-ranging consequences than difficulties in conversation. According to results of this study, hearing impairments are associated with poor mobility, poor postural balance and falls, and thus have a direct effect on disability. Poor hearing may also reduce activity and participation, leading consequently to an inactive way of life and furthermore to disability and decreased quality of life. Primary and secondary prevention of hearing loss should be a priority when aiming to promote health and well-being in older people. Further studies are needed to clarify the precise mechanism between hearing and mobility, as well as between hearing and falls. Additional knowledge about possible association mechanisms and their modifiability are needed in planning effective interventions to prevent loss of mobility and falls.

7 MAIN FINDINGS AND CONCLUSIONS

The main findings and conclusions of the present study can be summarized as follows:

1. Genetic effects accounted for over 60 % of the variance in hearing acuity of the better hearing ear at the low, mid and high frequencies, as well as in speech recognition threshold level. The remaining variance was due to environmental effects. Self-reported hearing difficulties were accounted for solely by environmental factors.

2. The majority of the individual differences in hearing acuity at speech frequencies and the speech recognition threshold level of the better hearing ear were accounted for by the common genetic and environmental effects; however, a specific genetic and a specific environmental effect were also found that together accounted for approximately a third of the total variance in speech recognition.

3. Although overall heritability was rather constant across the frequency spectrum, at the low and high frequencies frequency-specific genetic and environmental effects together accounted for over 70% of the total variance in hearing acuity. Environmental effects were more prominent in the worse hearing ear.

4. Hearing impairments were associated with slower maximal walking speed, lower walking endurance and self-reported major difficulties in walking two kilometers. Hearing impairments also predicted a higher risk for new major walking difficulties during the three-year follow-up.

5. Hearing acuity and walking speed had a minor genetic effect in common.

6. Poor hearing acuity predicted a higher risk for falls. The higher fall risk was partially explained by the poorer postural balance of the poorer hearing participants.

7. Hearing acuity and postural balance did not have genetic or environmental effects in common.

In conclusion, the results of this study suggest, first, that some people may be genetically more predisposed to hearing impairment in old age than others. These results also indicate that different genes and different environmental exposures are responsible for hearing deterioration in different tonotopic areas. The next step would be to identify specific genes in hearing acuity which could lead to better understanding of the etiology of age-related hearing impairments and, consequently, to the better prevention and even cure of hearing impairments. However, for the present, modification of environmental risk factors, especially noise exposure, is the most feasible way of influencing hearing ability across the life span.

Second, the results of this study suggest that hearing impairments are associated with poor mobility, poor postural balance and falls, and thus have a direct effect on disability in older people. Primary and secondary prevention of hearing loss may have wide-ranging influences on older peoples' functional capacity. Furthermore, these results indicate that hearing impairments should be taken into account when planning interventions to prevent falls in older people.

YHTEENVETO

Kuulon tarkkuuden periytyvyys ja yhteys liikkumiskykyyn sekä kaatumisiin iäkkäillä naisilla

Kuulo-ongelmat ovat erittäin yleisiä iäkkäillä henkilöillä. Noin joka kolmas 65-vuotias ja kaksi kolmesta 75-vuotiaasta kärsii jonkinasteisesta kuulon heikkenemästä. Iäkkäiden henkilöiden kuulo-ongelmien taustalla on yleisimmin ns. ikäkuulo, jolla tarkoitetaan ikääntymiseen liittyvää, symmetristä, hitaasti kehittyvää kuulon heikkenemää. Ikäkuulolle on tyypillisintä kuulon heikkeneminen ensin korkeilla taajuuksilla, josta heikkeneminen etenee vähitellen puhealueen taajuuksille. Ikäkuuloon voi liittyä myös äänten voimakkuuksien, taajuuksien ja suuntien erotteluvaikeuksia, mikä vaikeuttaa kuulemista erityisesti hälyisessä ympäristössä. Ikäkuulon etiologiaa ei vielä tunneta tarkasti, mutta perimän ja erilaisten ympäristöllisten tekijöiden on havaittu olevan yhteydessä kuulon heikkenemiseen.

Kuulo-ongelmia pidetään usein pelkästään kommunikaatio-ongelmina, mutta heikentyneellä kuulolla voi olla myös laajemmalti vaikutusta iäkkäiden henkilöiden toimintakykyyn. Aiempaa tutkimustietoa kuulon yhteydestä liikkumiskykyyn ja kaatumisiin on niukasti eikä mahdollinen yhdistävä mekanismi ole selvillä. Kuulo ja tasapaino saattavat heiketä iäkkäillä henkilöillä suhteellisen samaa tahtia, koska sekä kuulo- että tasapainoelin sijaitsevat sisäkorvassa jakaen monia anatomisia ja fysiologisia komponentteja. Toisaalta yhteys saattaa selittyä ympäristön havainnoimisen kautta. Hyvä kuulo auttaa havainnoimaan ympäristöä ja välttämään mahdollisia kaatumisiin johtavia vaaratekijöitä antaen siten varmuutta liikkumiseen. On myös mahdollista, että kuulo-ongelmat johtavat yleiseen passivoitumiseen, mikäli heikkokuuloinen henkilö alkaa vältellä toisten ihmisten seuraa mahdollisten kommunikaatio-ongelmien vuoksi. Passiivinen elämäntapa saattaa puolestaan johtaa huonompaan fyysiseen toimintakykyyn mikä entisestään heikentää liikkumiskykyä ja lisää kaatumisten riskiä.

Tämän väitöskirjatutkimuksen tarkoituksena oli selvittää geneettisten ja ympäristöllisten tekijöiden suhteellista osuutta kuulon tarkkuuden kokonaisvaihtelusta. Lisäksi tutkittiin kuulon tarkkuuden yhteyttä liikkumiskykyyn, tasapainoon ja kaatumisiin. Tutkimus on osa laajempaa Finnish Twin Study on Aging (FITSA) –projektia, johon osallistui 103 identtistä ja 114 ei-identtistä 63-76 –vuotiasta naiskaksosparia. Kuulon tarkkuutta arvioitiin audiometriamittauksilla ja kyselylomakkeella. Kävelynopeus mitattiin 10 metrin matkalla maksimaalisella vauhdilla ja 6 minuutin aikana käveltynä matkana tavanomaisella vauhdilla. Lisäksi 2 kilometrin kävelyyn liittyvät vaikeudet kartoitettiin kyselylomakkeella. Kehon huojunta mitattiin voimalevyllä ja kaatumistiedot kerättiin postitse laboratoriomittauksia seuranneen 12 kuukauden ajalta.

Tulosten mukaan yli 60% paremman korvan kuulon tarkkuuden vaihtelusta matalilla, keski- ja korkeilla taajuuksilla selittyi geneettisillä tekijöillä, loppuvaihtelun selittyessä ympäristöllisillä tekijöillä. Vaikka periytyvyyden osuus oli melko vakio eri taajuusalueilla, on huomattavaa, että matalilla ja korkeilla taajuuksilla taajuusspesifit geneettiset ja ympäristölliset tekijät selittivät yhteensä yli 70% kokonaisvaihtelusta. Huonomman korvan kuulon tarkkuuden vaihtelusta selittyi suurempi osuus ympäristöllisillä tekijöillä. Geneettiset tekijät eivät selittäneet itse-arvioidun kuulon vaihtelua.

Yhteensä 41%:lla tutkituista henkilöistä oli heikentynyt audiometrisesti mitattu kuulo, kun kriteerinä käytettiin ≥21 dB keskiarvoa paremman korvan ilmajohtokynnyksistä 500-4000 Hz taajuuksilla. Heikentynyt kuulo oli yhteydessä hitaampaan mitattuun kävelynopeuteen sekä itse-arvioituihin kävelyvaikeuksiin 2 kilometrin matkalla. Heikko kuulo myös edelsi uusien kävelyvaikeuksien ilmaantumista kolmen vuoden seurannan aikana.

Vuoden seurannan aikana 47% tutkimukseen osallistuneista naisista kaatui vähintään kerran ja 22% osallistuneista kaatui useammin kuin kerran. Kaatumisen riski oli yli kolminkertainen huonoimmin kuulevilla henkilöillä verrattuna parhaiten kuuleviin henkilöihin. Osa kohonneesta kaatumisriskistä selittyi huonoimmin kuulevien henkilöiden heikommalla tasapainolla.

Yhteenvetona tämän tutkimuksen tuloksista voidaan todeta, että jotkut iäkkäät henkilöt saattavat olla geeniperimänsä vuoksi toisia alttiimpia kuulon heikkenemiselle. Tulokset viittaavat lisäksi siihen, että eri geenit ja ympäristölliset tekijät vaikuttavat kuulon tarkkuuteen eri taajuusalueilla. Tuloksia voidaan hyödyntää ikäkuuloon vaikuttavien geenien tutkimuksessa. Kuuloon vaikuttavien geenien parempi tunteminen edesauttaa ennaltaehkäisemään ja tulevaisuudessa mahdollisesti jopa parantamaan kuulovaurioita.

Toisaalta, tämän tutkimuksen tulosten mukaan heikentynyt kuulo saattaa olla yhteydessä iäkkäiden henkilöiden heikentyneeseen liikkumiskykyyn ja kaatumisiin. Kuulovaurioiden ennaltaehkäisyllä saattaakin olla positiivista vaikutusta paitsi iäkkäiden henkilöiden kommunikaatiokykyyn, myös laajemmalti heidän toimintakykyynsä ja itsenäiseen selviytymiseen. Pyrittäessä ehkäisemään kaatumistapaturmia tulee heikentynyt kuulo ottaa huomioon yhtenä kaatumisriskiä lisäävänä tekijänä. Lisää tutkimusta kuitenkin tarvitaan selvittämään kuuloa ja liikkumiskykyä, sekä kuuloa ja kaatumisia mahdollisesti yhdistäviä mekanismeja.

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