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Gene dose of apolipoprotein E and age-related hearing loss

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Abstract

Next to outer hair cell dysfunction, age-related hearing loss may be explained by apolipoprotein E (APOE) genotype. In the Leiden 85-plus Study, a population-based study, the participants were 85 years old. We measured hearing loss by pure-tone audiometry in 435 participants in relation to APOE. Results demonstrated that those with the APOE-ε4/ε4 genotype had the highest levels of hearing loss (n = 6; 56.1 dB), those with the APOE-ε3/ε4 or ε2/ε4 genotype (n = 89) had intermediate levels of hearing loss (51.0 dB), and those without the APOE-ε4 allele (n = 340) had the lowest levels of hearing loss (48.9 dB), p for trend = 0.02. Eighty percent of participants had hearing loss of 35 dB and more, that is, hearing impairment. The APOE-ε4 allele was associated with a 2.0-fold increased risk of hearing impairment (confidence interval [CI 95%], 1.0–4.0), compared with those without the APOE-ε4 allele. The risk for hearing impairment in subjects with the APOE-ε4 allele remained similar after adjustment for cardiovascular disease, stroke, and cognitive impairment. Our results suggest that the APOE-ε4 allele contributes to age-related hearing loss.

Keywords: APOE genotype; Age-related hearing loss; Oldest old; Population study

1. Introduction

The prevalence and severity of hearing loss increases with age (Gates and Mills, 2005). Age-related hearing loss affects up to 80% of people aged 80 years and more. It is a disabling condition associated with problems in daily life, social isolation, depression, and a lower quality of life (Gates and Mills, 2005). Because of the impact of age-related hearing loss on all aspects of everyday life and possibilities for prevention, it is essential to understand more about the pathophysiological basis of this disorder.

Population-based studies, neuropathological studies, and animal studies suggest that generalized atherosclerosis contributes to age-related hearing loss (Gates and Mills, 2005; Cruickshanks et al., 1998; Helzner et al., 2011; Gratton et al., 1996; Spicer and Schulte, 2002). Neurophysiological studies show that there is a reduction of amplitudes of action potentials recorded in animal models, indicating diminished neural activity in the auditory nerve (Spiess et al., 2002; Schulte and Schmiedt, 1992). The basis of this diminished activity can possibly be attributed to primary degeneration of spiral ganglion cells, that is, the group of nerve cells that send a representation of sound from the cochlea to the brain (Spiess et al., 2002; Schulte and Schmiedt, 1992).

The apolipoprotein E (APOE) genotype is unique. Studies show that APOE contributes to maintenance and repair of neuronal cell membranes; moreover, it is the strongest genetic risk factor, contributing to age-related disorders such as Alzheimer's disease (Corder et al., 1993), general-

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ized atherosclerosis (Paternoster et al., 2010), and macular degeneration (McKay et al., 2011). We hypothesized that the APOE genotype contributes to age-related hearing loss; we are unaware of other studies assessing the contribution of APOE genotype to age-related hearing loss. We determined whether APOE contributes to age-related hearing loss in an unselected population-based cohort of elderly individuals aged 85 years.

2. Methods

2.1. The Leiden 85-plus Study

The Leiden 85-plus Study is a population-based study of inhabitants of the city of Leiden. Between 1 September 1997 and 1 September 1999, 599 participants aged 85 years were enrolled (response 87%) (Gussekloo et al., 2003). The Medical Ethical Committee of the Leiden University Medical Center approved the study, and all participants gave informed consent.

2.2. Hearing

Within the first year of the baseline measurement, all participants of the Leiden 85-plus Study were invited to participate in the additional hearing study. During a home visit by a physician or a trained assistant, audiological tests were performed and questionnaires on hearing loss were administered (Gussekloo et al., 2003). Excessive cerumen, if present, was removed from the participant's ears before audiometric measurements. Hearing loss was measured using pure-tone audiometry because pure-tone audiometry is the golden standard to determine hearing threshold (Gates and Mills, 2005; Cruickshanks et al., 1998; Helzner et al., 2011). We therefore used a portable Diagnostic Audiometer (AD 28 Interacoustics, Assens, Denmark). Air conduction thresholds were obtained separately for the left and right ear at frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz. When necessary, masking was added to the opposite ear. Special attention was paid to reducing possible effects of background noise. Hearing loss was estimated as the average hearing loss in dB at 1000, 2000, and 4000 Hz for the best ear (Fletcher index). Hearing impairment was defined as a hearing loss more than 35 dB for the best ear, in line with the Dutch health authorities' definition.

2.3. APOE genotype

Two common nucleotide polymorphisms constitute the ε2/ε3/ε4 alleles. For genotyping, two TaqMan assays were used (Applied Biosystems, Foster City, CA, USA).

2.4. Possible confounders

Generalized atherosclerosis and cognitive impairment were considered possible confounders because these are age-related disorders associated with APOE genotype. Measurements of generalized atherosclerosis had special emphasis within the Leiden 85-plus Study (Gussekloo et al., 2003). The burden of generalized atherosclerosis was rated by the presence of cardiovascular pathology at baseline, as assessed by history taking from treating physicians and electrocardiography (ECG). Cardiovascular pathologies included 1) myocardial infarction (clinical diagnosis or on ECG), 2) angina pectoris or myocardial ischemia on ECG, 3) claudicatio intermittens, and 4) arterial surgery. For all participants, ECGs were recorded on a Siemens Siccard 440 (Erlangen, Germany) and transmitted electronically to the ECG Core Laboratory in Glasgow for automated Minnesota coding. Myocardial infarction was assessed by Minnesota codes 1-1, 1-2, and 1-3, and myocardial ischemia was assessed by Minnesota codes 4-1, 4-2, 4-3, 5-1, 5-2, and 5-3. This approximation for the burden of generalized atherosclerosis follows the classification from the Second Manifestation of ARTerial Disease Study, an established proxy for generalized atherosclerosis, which showed that the number of cardiovascular pathologies is related to the severity of atherosclerosis measured as intima-media thickness and arterial stiffness (Simons et al., 1999). Cognitive impairment was defined as a Mini-Mental State Examination score lower than 24 points (Tombaugh and McIntyre, 1992). The presence of stroke in medical history was assessed by interviewing treating physicians of all participants. Stroke was considered a possible confounder because it could be argued that stroke can involve hearing loss owing to damage within the central auditory pathways, whereas we intended to determine hearing loss associated with age-related hearing loss, that is, peripheral auditory pathways; moreover, incidence and outcome of stroke could be associated with APOE genotype (Martínez-González and Sudlow, 2006; Biffi et al., 2010).

2.5. Statistical analysis

We examined the association between APOE genotype and risk of hearing impairment, using standard logistic regression models. The various APOE alleles were categorized into two categories, that is, presence or absence of the APOE-ε4 allele. Risks for hearing impairment were estimated with odds ratios using those without the APOE-ε4 allele as reference. In an additional analysis, we adjusted for possible confounders, including generalized atherosclerosis, stroke, and cognitive impairment. Furthermore, we determined the strength of association using linear mixed models, that is, we determined the p for trend for APOE genotype (those without the APOE-ε4 allele vs. those with one APOE-ε4 allele vs. homozygote APOE-ε4/ε4 participants) against hearing loss as measured at baseline. These models use all available data and appropriately handle missing data. Owing to their flexibility, mixed models are the preferred choice for the analysis of such data. The models we used also included APOE genotypes and hearing loss at 250, 500, 1000, 2000, 4000, and 8000 Hz. The estimate for the various APOE genotypes reflects the impact of the different APOE$^-$ alleles (those without the APOE-ε4 allele vs. those

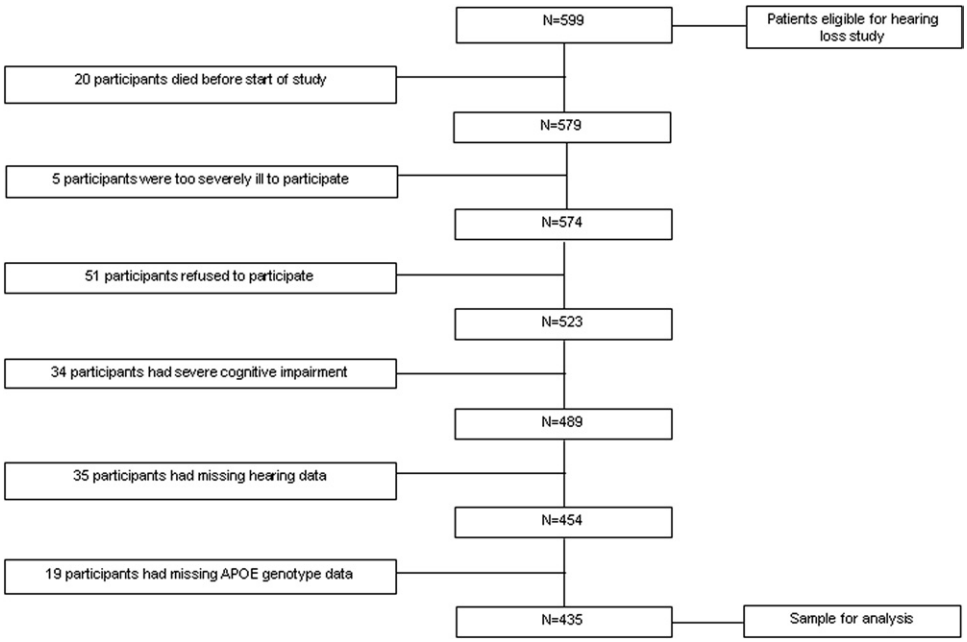

Fig. 1. Flowchart of participants.

with one APOE-ε4 allele vs. homozygote APOE-ε4/ε4 participants) on hearing loss.

3. Results

3.1. Participants

Data on hearing in 454 participants in the hearing study from the Leiden 85-plus Study have been described elsewhere (Gussekloo et al., 2003). Complete hearing data and APOE genotype were available for 435 participants (Fig. 1). The baseline characteristics of the total cohort, that is, all participants from the Leiden 85-plus Study, and the 435 participants with complete data on hearing loss and APOE genotype are given in Table 1. There were no significant differences in sociodemographic and clinical characteristics between the 435 participants from the current study and the

Table 1
Baseline and clinical characteristics of the participants of the hearing loss study within the Leiden 85-plus Study

Characteristic		Hearing loss measurements	
	Total cohort (n = 599)	Absent (n = 164)	Present (n = 435)
Age (years)	85	85	85
Female	397 (66.3%)	107 (65.2%)	290 (66.7%)
Low level of education	386 (64.4%)	111 (67.7%)	275 (63.2%)
Cardiovascular disease	378 (63.1%)	101 (61.6%)	279 (64.1%)
Stroke	62 (10.4%)	24 (14.6%)	38 (8.7%)
Cognition (median MMSE score)	27		
Hearing loss			
Overall hearing loss (dB, mean, sd)[a]	—	—	49.4 (14.7)
Hearing impairment[b]	—	—	358 (82.3%)
APOE genotype[c]	(n = 546)	(n = 113)	(n = 435)
ε2ε2	4 (0.7%)	3 (2.7%)	1 (0.2%)
ε2ε3	90 (16.5%)	23 (20.3%)	69 (15.9%)
ε2ε4	13 (2.4%)	2 (1.8%)	11 (2.5%)
ε3ε3	324 (59.3%)	55 (48.7%)	270 (62.1%)
ε3ε4	100 (18.3%)	23 (20.3%)	78 (17.9%)
ε4ε4	15 (2.7%)	7 (6.2%)	6 (1.4%)
Total ε4-carrier (either ε2ε4, ε3ε4, ε4ε4)	128 (23.4%)	32 (28.3%)	95 (21.8%)

[a] Hearing loss was estimated as the average hearing loss in dB at 1000, 2000, and 4000 Hz with the best ear.
[b] Hearing impairment is defined as a hearing loss of more than 35 dB, measured with the best ear, at 1000, 2000, and 4000 Hz.
[c] APOE genotype was determined in the total cohort of participants (n = 546), in participants without hearing loss measurement (n = 113), and in participants included in the current study (n = 435); number of subjects and percentages are calculated for the here aforementioned numbers.

164 of the 599 participants from the Leiden 85-plus Study not participating in the hearing study (chi-square, all $p > 0.05$).

3.2. APOE and hearing

Figure 2 shows that those with the APOE-ε4/ε4 genotype had the highest levels of hearing loss (n = 6; overall mean hearing loss, 56.1 dB), those with the APOE-ε3/ε4 or ε2/ε4 genotype (n = 89) had intermediate levels of hearing loss (51.0 dB), and those without the APOE-ε4 allele (n = 340) had the lowest levels of hearing loss (48.9 dB), p for trend = 0.02. Presence of cardiovascular disease was associated with a 2.4-fold increased risk of hearing impairment compared with those without cardiovascular disease (Table 2). No significant association was found between cognitive impairment and hearing impairment. The presence of APOE-ε4 allele was associated with a 2.0-fold increased risk of hearing impairment, compared with those without the APOE-ε4 allele (Table 2). The odds ratio remained similar after adjustment for cardiovascular disease, stroke, and cognitive impairment was made.

4. Discussion

In the Leiden 85-plus Study, a population-based study in 85 year olds, the presence of the APOE-ε4 allele was associated with age-related hearing loss over all frequencies. We showed a dose–response relationship between hearing loss and increasing presence of the APOE-ε4 allele. Those with the APOE-ε4/ε4 genotype had the highest level of hearing loss; those with the APOE-ε3/ε4 or ε2/ε4 genotype had intermediate levels of hearing loss; and those without the APOE-ε4 allele had the lowest levels of hearing loss. These findings were independent of atherosclerosis and cognitive function.

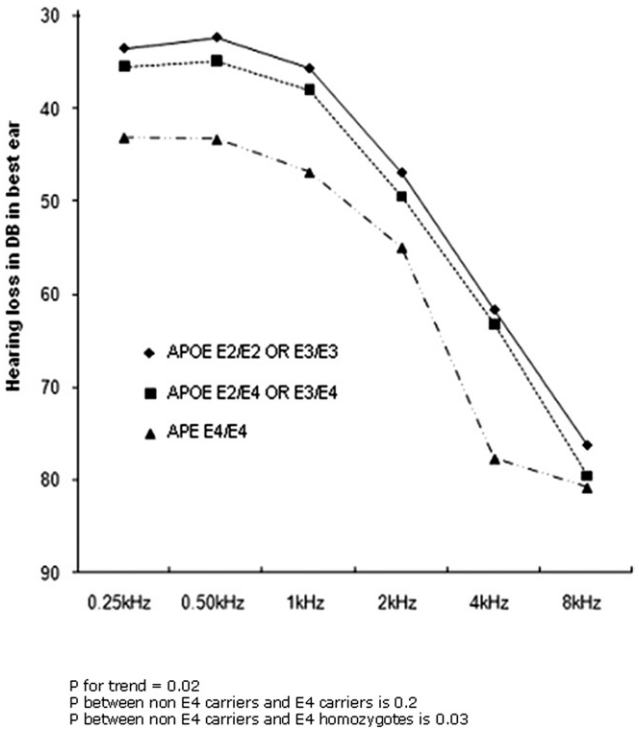

Fig. 2. Hearing loss, measured in the best ear, in relation to APOE genotype.

Table 2
Hearing impairment and cardiovascular disease, cognitive impairment, and presence of the APOE-ε4 allele

Variable	Hearing impairment		p
	Absent (n = 82)	Present (n = 353)	
Univariate model			
Cardiovascular disease			
Odds ratio (95% CI)	1[a]	2.4 (1.5–3.8)	<0.001
Cognitive impairment[b]			
Odds ratio (95% CI)	1[a]	1.5 (0.8–2.8)	0.2
APOE-ε4 allele			
Odds ratio (95% CI)	1[a]	2.0 (1.1–3.9)	0.03
Multivariate model[c]			
APOE-ε4 allele			
Odds ratio (95% CI)	1[a]	2.0 (1.0–4.0)	0.04

[a] Reference category.
[b] Presence of cognitive impairment is defined as a Mini-Mental State Examination score lower than 24 points.
[c] Risk of hearing impairment in subjects with the APOE-ε4 allele, after adjustments are made for cardiovascular disease, cognitive impairment, and stroke.

Our findings that the APOE genotype is associated with age-related hearing loss has, to our knowledge, not been described before and fit within the view that age-related hearing loss cannot only be attributed to outer hair cell dysfunction of the cochlea. Moreover, we argue that our findings are important because the contribution of, for instance, APOE (Fig. 1) to age-related hearing loss ranges between 6- and 10-dB hearing loss, thus explaining for 10–15% of age-related hearing loss in the high-frequency range (4000–8000 Hz) and 20–30% of age-related hearing loss occurring in the lower-frequency range (250–2000 Hz).

The association between hearing loss and the APOE-ε4 may well be found in the numerous actions of APOE. First, APOE is unique among apolipoproteins, in its special relevance to nervous tissue. It mobilizes and redistributes lipids, playing an important role in the reinnervation process of both the peripheral and central nervous systems (Ignatius et al., 1986). Second, APOE-ε4 is of particular interest concerning age-related disorders because it strongly contributes to neurodegenerative disorders such as dementia (Corder et al., 1993) and macular degeneration (Paternoster et al., 2010; McKay et al., 2011), generalized atherosclerosis, and stroke (Martínez-González and Sudlow, 2006; Biffi et al., 2010). Finally, APOE has been shown to have antioxidant and anti-inflammatory effects (Van Vliet et al., 2009). Improvement of the reinnervation process, reduction of the atherosclerosis burden, and the prevention of

oxidative stress may all protect against hearing loss. These protective effects are generally weakest for APOE-ε4 and strongest for APOE-ε2. Therefore, APOE-ε4 allele carriers may be at an increased risk of hearing impairment.

4.1. Strengths and limitations

A unique feature of the current study is the population-based sample of the very old, enabling us to answer the question whether APOE contributes to hearing loss. People aged 85 years are an ideal population to study possible causes of age-related hearing loss. The largest increase in prevalence of hearing loss occurs in participants aged 80 years and more (Gates and Mills, 2005; Cruickshanks et al., 1998). We used the pure-tone audiometry in measuring hearing loss, which is the most accepted method to determine age-related hearing loss in the general population and population-based studies. We did not use speech audiometry because of the clinical features of age-related hearing loss, which consist of threshold shifts and the decline of speech understanding (Pichora-Fuller et al., 2006).

We found that our results were unaffected when adjusted for possible confounders (atherosclerosis, stroke, and cognitive impairment) associated with age-related disorders and APOE genotype, which suggests that these confounders did not significantly influence the effect of APOE on hearing impairment. A limitation is the small number of homozygote APOE-ε4/ε4 participants (n = 6) in our study, that is, which suggests that our study lacks power, when one limits the analysis to homozygote APOE-ε4/ε4 only. However, in our study we showed a significant gene–dose relationship between hearing loss and increasing presence of the APOE-ε4 allele, that is, those with the APOE-ε4/ε4 genotype had the highest level of hearing loss, those with the APOE-ε3/ε4 or ε2/ε4 genotype had intermediate levels of hearing loss, and those without the APOE-ε4 allele had the lowest levels of hearing loss. Moreover, despite the small numbers of homozygote APOE-ε4/ε4 participants, a significant effect of APOE-ε4/ε4 on hearing loss and hearing impairment was found when compared with participants without the APOE-ε4 allele, suggesting the strength of the effect of homozygote APOE-ε4 on age-related hearing loss. Another possible limitation could be possible differences in prevalence of APOE-ε4 genotype compared with younger populations. The overall presence of APOE-ε4 genotype, that is, APOE-ε4 carriers, in our study was 21.8%. Prevalence figures of APOE-ε4 carriers in one Dutch population study and two international studies were roughly similar compared with our study (Longitudinal Aging Study Amsterdam [Gerritsen et al., 2011], 25.4%, mean age 75 years, n = 911; Framingham Heart Study [Kardaun et al., 2000], 20.3%, mean age 76 years, n = 840; and Honolulu Asia Aging study [van Himbergen et al., in press], 18.3%, mean age = 77 years, n = 3459).

5. Conclusion

Our study shows an apparent dose–response relationship between APOE genotype, that is, presence of the APOE-ε4 allele and hearing loss over all frequencies at old age. These findings suggest that APOE contributes to age-related hearing loss; however, independent confirmation of our novel findings in larger cohorts is necessary.

Disclosure statement

The authors do not have any actual or potential conflicts of financial or personal interest.

The data contained in this manuscript have not been previously published, have not been submitted elsewhere, and will not be submitted elsewhere while under consideration at *Neurobiology of Aging*. All participants in our study provided informed consent approved by Medical Ethical Committee of the Leiden University Medical Center. All authors have reviewed the manuscript, approved of its contents, and validated the accuracy of the data.

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Author contributions

Kurniawan and van Exel had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: van Exel and Westendorp.

Acquisition of data: de Craen, Gussekloo, van Exel, Westendorp.

Analysis and interpretation of data: Kurniawan, de Craen, Gussekloo, van Exel, Westendorp.

Manuscript draft: Kurniawan, van Exel.

Critical revision of the manuscript for important intellectual content: Kurniawan, Westendorp, de Craen, de Laat, Gussekloo, van Exel.

Statistical analysis: Kurniawan, de Craen, van Exel.

Obtained funding: Westendorp, Gussekloo.

Administrative, technical, or material support: Westendorp, de Craen, Gussekloo, de Laat, van Exel.

Study supervision: Westendorp, Gussekloo, de Craen, van Exel.

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