scientific reports

Check for updates

OPEN

The biphasic impact of apolipoprotein E ε4 allele on age-related hearing loss

Jae Sang Han[1], Sung goo Yoo[2,3], Sun jung Lee[2,3], Hyun Jin Lee[4], In Young Choi[2,3,5]✉ & Kyoung Ho Park[1,5]✉

Both the ε4 variant of the *apolipoprotein E* (*APOE*) gene and hearing loss are well-known risk factors for Alzheimer's disease. However, previous studies have produced inconsistent findings regarding the association between *APOE* genotypes and hearing levels, necessitating further investigation. The aim of this study was to investigate the relationship between *APOE* genotypes and hearing levels. This retrospective study analyzed clinical data from a clinical data warehouse of seven affiliated Catholic Medical Center hospitals. The study included 1,162 participants with records of *APOE* genotypes, audiometric tests, and cognitive function tests. In Generalized linear mixed model analysis, ε4 carriers exhibited lower pure tone audiometry thresholds with an estimate of -0.353 (SE = 0.126, p = 0.005). However, the interaction term for age and *APOE* ε4 had a coefficient of 0.577 (SE = 0.214 p = 0.006), suggesting that the *APOE* ε4 gene may accelerate hearing deterioration with age. Subgroup analysis based on an age cut-off of 75 revealed that ε4 carriers had better hearing at younger ages, but showed no significant difference at older ages. These results indicate that the ε4 allele may have a biphasic effect on hearing levels depending on age.

Keywords Apolipoprotein E, Hearing loss, Aging

In the aging population, hearing loss is a major concern[1]. The importance of hearing loss has been increasing as it is considered to be a critical modifiable risk factor for dementia[2]. The Lancet Commission stated that hearing loss is the leading factor responsible for dementia in middle age[3]. Therefore, identifying risk factors of hearing loss is important for the early detection and rehabilitation of hearing loss.

The *apolipoprotein E* (*APOE*) ε4 allele is the most important genetic risk factor for Alzheimer's disease[3,4]. *APOE* exhibits an important role in peripheral cholesterol metabolism and cholesterol transport in the central nervous system. Three *APOE* isoforms (ε2, ε3 and ε4) have been identified in human, and the e4 allele is associated with Alzheimer disease[5].

Given that both hearing loss and the *APOE* ε4 allele are common risk factors for Alzheimer's disease, their potential association has been investigated. In an animal study using *APOE* knockout mice, stenosis of the spiral modiolar artery caused by atherosclerosis induced hair cell loss and high frequency hearing loss[6]. However, several previous cohort studies have reported contradictory results. Some studies suggested that the *APOE* ε4 allele had a negative effect on hearing levels[7,8], other studies reported no association[9–12], and one study even showed a protective effect of the *APOE* ε4 allele on hearing[13].

In this retrospective multicenter cohort study, we aimed to investigate the relationship between *APOE* genotypes and sensorineural hearing loss.

[1]Department of Otolaryngology-Head and Neck Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-Daero, Seocho-gu, Seoul 06591, Republic of Korea. [2]Department of Medical Informatics, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea. [3]Department of Biomedicine and Health Sciences, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea. [4]Department of Otolaryngology-Head and Neck Surgery, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea. [5]These authors contributed equally: In Young Choi and Kyoung Ho Park. ✉email: iychoi@catholic.ac.kr; khpent@catholic.ac.kr

Methods

Clinical data warehouse

Clinical data was extracted from a clinical data warehouse (CDW) that includes data from seven affiliated Catholic Medical Center (CMC) hospitals (Seoul St. Mary's Hospital, Yeouido St. Mary's Hospital, Uijeongbu St. Mary's Hospital, Bucheon St. Mary's Hospital, Eunpyeong St. Mary's Hospital, St. Vincent's Hospital and Incheon St. Mary's Hospital). The CMC CDW includes a fully anonymized database of approximately 15 million electronic medical records; researchers can extract data based on required inclusion and exclusion criteria[14].

This study was approved by the Ethics Committee of Seoul St. Mary's Hospital (No. KC21WISI0924) and followed the tenets of the Declaration of Helsinki. Since this study is a retrospective cohort study using anonymized clinical data in CDW, the requirement for informed consent was waived by Ethics Committee of Seoul St. Mary's Hospital.

Study population

We enrolled 2,458 subjects aged 20–100 years with *APOE* genotype information from seven affiliated hospitals. The follow-up period was from January 2006 to December 2021. Patients without audiometric and cognitive function testing were removed. Only participants with records of *APOE* genotypes, audiometric, and cognitive function testing were included. Additionally, cases indicating conductive or mixed-type hearing loss, where the average air-conduction threshold and bone-conduction threshold in pure-tone audiometry (PTA) were ≥ 10 dB HL, were excluded. Thus, the final dataset included 1,162 patients.

Clinical outcomes

APOE genotyping

DNA was extracted from blood samples using the QIAmp Blood DNA Maxi Kit protocol (Qiagen, Valencia, CA). TaqMan SNP genotyping assays (Applied Biosystems, Foster City, CA) were used to determine the genotypes for two *APOE* SNPs, rs429358 (ε4) and rs7412 (ε2). The participants were classified into two groups based on *APOE* ε4 variations: ε4 negative group (ε2/ε2 or ε2/ε3 or ε3/ε3) and ε4 positive group (ε2/ε4 or ε3/ε4 or ε4/ε4). The ε4 (-) group served as the comparison group for all analyses.

Hearing tests

Audiometric tests were conducted in a soundproof booth using the GSI 61TM audiometer (Grason-Stadler, Inc., St. Eden Prairie, MN), calibrated to meet American National Standards Institute standards (S3.6-1996). The PTA thresholds were reported in decibels of hearing level, and the PTA averages were calculated using the hearing thresholds at 0.5, 1, 2, and 4 kHz. In cases of asymmetric hearing thresholds, the better-hearing ear threshold was used for analysis. Hearing loss was defined in accordance with the World Health Organization's definition of impairment as a four-frequency average of PTA exceeding 25 dB HL[15]. The speech discrimination score (SDS) test was performed using the standardized Korean version of phonetically balanced monosyllabic words and reported as a percentage[16].

Cognitive function

Cognitive function was evaluated using the Mini-Mental State Examination (MMSE), a brief screening tool developed to assess the overall cognitive function of elderly individuals. The MMSE comprises orientation, attention, memory, language, and visual-spatial skill tests. Scores range from 0 to 30, with lower scores indicating poorer cognitive function. Cognitive impairment was defined as a MMSE score lower than 24. The MMSE test results conducted on the closest date were extracted and employed, in accordance with the baseline audiometric test.

Other covariates

In the reviewed prior research, several potential confounding variables that are connected with hearing loss and cognitive impairment have been discovered. Data on the sex of the patient, the patient's age when the audiometry test was performed, and lipid tests were collected. The study used ICD-10 diagnostic codes to filter hearing loss due to diabetes (E11) and hypertension (I10). Standard procedures were used to determine total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), and triglycerides (TG) levels. For the summary statistics, laboratory findings obtained 50 days before and 50 days after the date of the hearing test were used.

Statistical analysis

Means, standard deviations, and percentages were used to characterize demographic and clinical variables. The student's t-test was used to analyze the continuous variables in the summary statistics. The Chi-square test was used to analyze the categorical variables. Participants' *APOE* allele frequency distributions (ε4 +) were compared to those of the established general population (ε4 –).

In this study, we aimed to investigate the effect of the *APOE* ε4 genotype on PTA thresholds. The dataset included various demographic and clinical variables such as MMSE, low-density lipoprotein (LDL), triglycerides (TG), high-density lipoprotein (HDL), total cholesterol (TC), presence of diabetes and hypertension. The primary outcome variable was PTA measure in dB HL, and the primary predictor of interest was the presence of the *APOE* ε4 allele. To comprehensively assess the characteristics of the data, we conducted univariate analyses considering the presence of the E4 allele, MMSE scores, four lipid tests (HDL-C, LDL-C, TC, TG), as well as the presence of diabetes and hypertension. However, due to the correlations among the covariates, we aimed to

control the model by including only a minimal set of covariates in the multivariate analysis. Therefore, only the presence of hypertension and diabetes were included in the multivariate analysis.

We fitted a Generalized Linear Mixed Model (GLMM) using a Gamma distribution with a log link to investigate the relationship between PTA and several predictors, including age, *APOE* ε4 allele status, sex, diabetes, and hypertension status. The model also accounted for random effects at both the individual level and the frequencies of PTA. To address potential overfitting issues in the non-parametric regression analysis, we performed a tenfold cross-validation. As shown in the equation below, we included age, sex, and the presence of diabetes and hypertension as covariates to estimate hearing thresholds. Additionally, the presence of the *APOE* ε4 genotype and the interaction term between genotype and age were included as fixed effects to estimate hearing loss. The GLMM allowed us to model the correlation within clusters and to include random intercepts for each subject ($\boldsymbol{u_i}$) and each frequency of PTA ($\boldsymbol{u_j}$), reflecting repeated measures for each patient. In this model μij represents the expected PTA score for individual $\boldsymbol{i}$ at frequency $\boldsymbol{j}$. To analyse PTA across all frequencies simultaneously, we transformed the independent hearing thresholds at each frequency into a stacked data format. The effects at each frequency were then compared by examining the size of the random effects. To standardize the levels of the variables, numerical variables were transformed using min–max normalization. The p-values for coefficients less than 0.05 indicated statistically significant relationships.

$$log\left(\mu ij\right) = a_0 + \beta_1 age + \beta_2 APOE\varepsilon 4 + \beta_3\left(age \times APOE\varepsilon 4\right) + \beta_4 sex + \beta_5 diabetes + \beta_6 hypertension + u_i + u_j + \varepsilon_{ij}$$

Based on the results of our GLMM analysis, we discovered that the *APOE* ε4 genotype plays a moderating role in age-related hearing loss. As shown in Fig. 1A, there is a noticeable reversal in the average estimated hearing threshold at a specific age. Consequently, to closely observe the critical age at which the average hearing levels between groups with and with the *APOE* ε4 genotype is reversed, we conducted ROC (Receiver Operating Characteristic) analysis and Kaplan–Meier analysis. The area under the ROC curve (AUC) is a graph that compares the true positive rate (sensitivity) against the false positive rate (1 – specificity). The positive likelihood ratio, also known as LR + (sensitivity/1 – specificity), expresses the degree to which positive outcomes are significantly more common among individuals who have hearing impairment compared with those who do not[17] A higher LR + number has an excellent diagnostic informative value; hence, the optimal cut-off was determined based on the highest LR + . We utilized Kaplan–Meier plots to visually observe changes in the proportion of individuals with hearing loss across different age groups and *APOE* genotype groups. Hearing loss was classified as a PTA threshold of 25 dB HL or higher, as previously described.

Results

Demographic statistics according to APOE ε4 status

Table 1 shows descriptive statistics by *APOE* ε4 status. Among the 1,162 individuals, 280 were ε4 allele carriers and the remaining 882 did not have the ε4 allele. There was no significant variation in the average age of the population (75.7 years) based on genotype. The incidence rate of cognitive impairment (MMSE < 24) was higher in the ε4 (+) group, while the incidence rate of hearing loss based on PTA (> 25 dB HL) was higher in the ε4 (−) group.

Generalized linear mixed model

The GLMM results provided insights into the relationship between various covariates and PTA thresholds. The model included fixed effects for age, sex, hypertension, diabetes, and the interaction between age and the presence of the APOE ε4 allele. Random effects were included to account for repeated measures within individuals and across frequencies. As shown in Table 2, age was identified as a significant factor influencing hearing ability, with an estimate of 1.784 (SE = 0.096, $p < 0.001$). This means that each additional year of age is associated with an increase of 1.741 in the PTA threshold, indicating a decline in hearing ability as individuals grow older. Additionally, sex differences were observed, with males having higher PTA thresholds than females. The estimate for males was 0.136 (SE = 0.026, $p < 0.001$), suggesting that males generally experience worse hearing than females.

Results for individuals with the *APOE* ε4 allele indicated an estimate of − 0.363 (SE = 0.126, $p = 0.005$), suggesting that individuals carrying this allele tend to have lower PTA thresholds. However, as seen in Fig. 1A, the estimated PTA values by age intersect at a certain point depending on the presence of the allele. This suggests that the *APOE* ε4 allele acts as a moderating variable in age-related hearing loss. The interaction term for age and *APOE* ε4 has a coefficient of 0.557 (SE = 0.214, $p = 0.006$), suggesting that the *APOE* ε4 gene may accelerate the decline in hearing ability with age. On the other hand, as observed in Fig. 1B, there was no moderating effect of sex on the relationship between age and PTA thresholds.

Kaplan–Meier plot

In the Kaplan–Meier plot (Fig. 2), the probability of hearing loss-free survival between the ε4 (+) group and the ε4 (−) group was different depending on age at the time of the test. The probability of hearing loss–free survival was higher in the ε4 (+) group at a younger age, while the ε4 (−) group had a higher probability of hearing loss–free survival at an older age.

ROC analysis for determining cut-off value

ROC analysis was used to derive the optimal age cut-off value for subgroup analysis. The appropriate hearing impairment age threshold was determined using data from the prediction model. The AUC was 0.77, with a 95% confidence range of 0.74–0.79. The optimal cut-off value of 75.5 was determined based on predictive sensitivity of 73.1% and a specificity of 69.3% (Fig. 3).

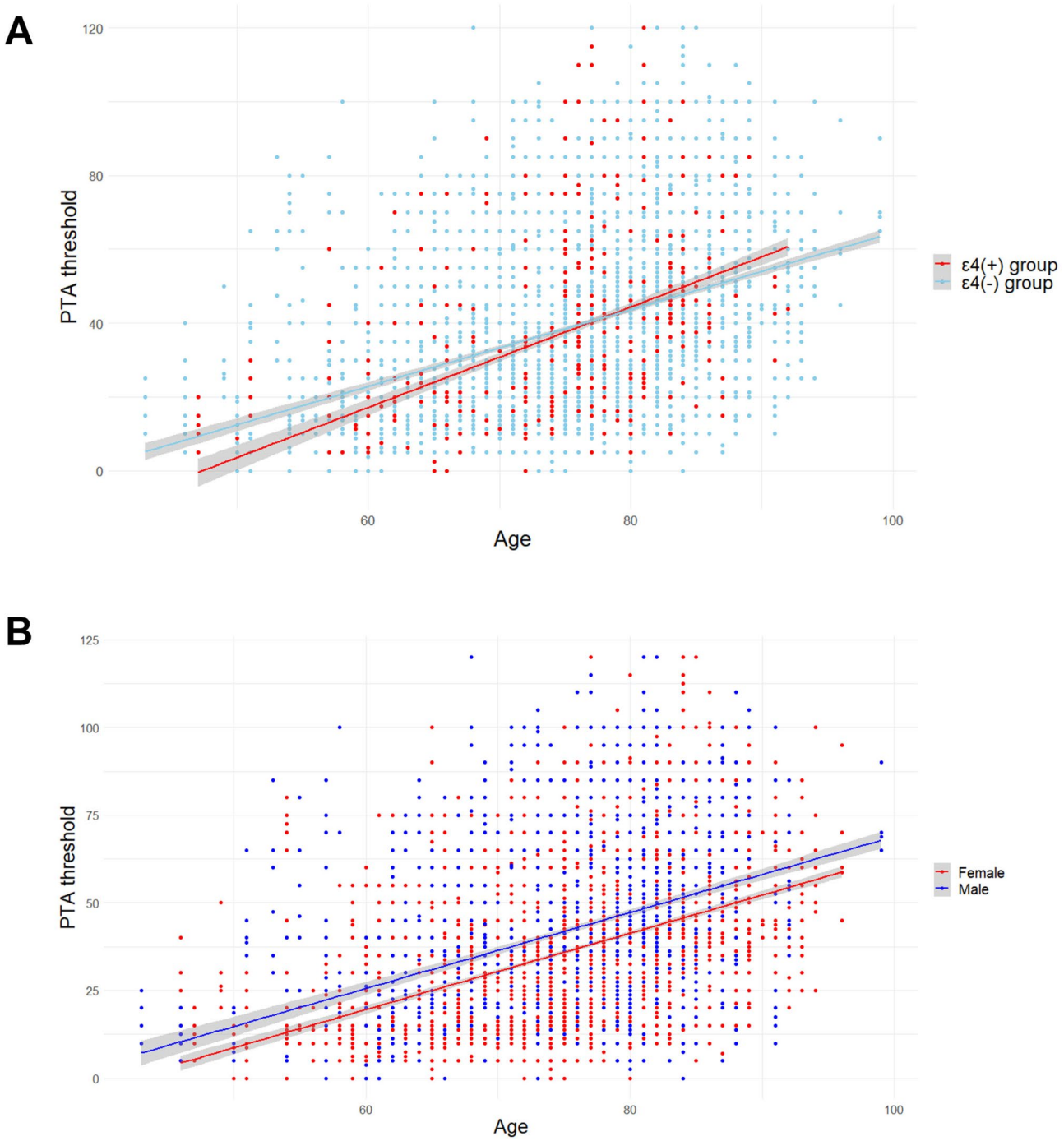

Fig. 1. Relationship between age and pure tone audiometry (PTA) thresholds by apolipoprotein E genotypes and sexes. A, The ε4 (+) group shows lower PTA thresholds at younger ages compared to the ε4 (−) group, but the thresholds increase rapidly with age. B, Women generally exhibit lower PTA thresholds, and the rate of hearing deterioration with age does not differ between sexes.

Subgroup analysis

In the subgroup analysis, the ε4 (+) group demonstrated significantly better hearing levels in both mean PTA and SDS among individuals younger than 75 years old ($P < 0.01$, T-test). In the older subgroup (≥ 75 years), the mean age of the ε4 (+) group was significantly lower than the ε4 (−) group and audiologic tests indicated no significant difference between the two groups (Table 3).

		Total (n = 1162)	ε4 (+) group (n = 280)	ε4 (−) group (n = 882)	*P*
Sex	Male	456 (39.2%)	111 (39.6%)	345 (39.1%)	0.931
	Female	706 (60.8%)	169 (60.4%)	537 (60.9%)	
Age	Mean (SE)	75.7 ± 9.3	75.1 ± 7.6	75.9 ± 8.6	0.134
APOE Genotypes	ε2/ε2	5 (0.6%)			
	ε2/ε3	100 (8.6%)			
	ε3/ε3	777 (66.8%)			
	ε2/ε4	12 (4.3%)			
	ε3/ε4	240 (20.6%)			
	ε4/ε4	28 (2.4%)			
MMSE	Mean (SE)	22.76 ± 6.7	22.4 ± 6.0	22.9 ± 6.5	0.228
	Normal (MMSE ≥ 24)	671 (42.3%)	144 (51.4%)	527 (59.8%)	0.017*
	Abnormal (MMSE < 24)	491 (57.7%)	136 (48.6%)	355 (40.2%)	
PTA[a] (dB HL)	Mean (SE)	34.22 ± 17.7	33.0 ± 17.7	34.6 ± 17.8	0.190
	Normal (PTA ≤ 25)	433 (37.3%)	122 (43.6%)	311 (35.3%)	0.015*
	Hearing Loss (PTA > 25)	729 (62.7%)	158 (56.4%)	571 (64.7%)	
SDS	Mean (SE) (n = 622)	78.98 ± 23.87	82.0 ± 21.1	78.0 ± 24.2	0.054
Diabetes	Normal	826 (71.1%)	203 (72.5%)	623 (70.6%)	0.600
	Abnormal	336 (28.9%)	77 (27.5%)	259 (29.4%)	
Hypertension	Normal	555 (47.8%)	135 (48.2%)	420 (47.6%)	0.916
	Abnormal	607 (52.2%)	145 (51.8%)	462 (52.4%)	
Lipid tests	LDL Cholesterol (mmol/L) (n = 497)	98.97 ± 38.12	101.3 ± 31.7	98.2 ± 34.6	0.390
	HDL Cholesterol (mmol/L) (n = 596)	51.7 ± 16.2	51.4 ± 16.2	51.8 ± 14.4	0.782
	Total Cholesterol (mmol/L) (n = 618)	175.8 ± 45.02	178.5 ± 39.7	174.9 ± 40.4	0.337
	Triglyceride (mmol/L) (n = 606)	120.8 ± 74.93	120.8 ± 65.3	120.8 ± 87.2	0.999

Table 1. Descriptive statistics by *Apolipoprotein E* ε4 status. [a]Average of 500, 1000, 2000, 4000 Hz frequency thresholds. *APOE*, *apolipoprotein E*; MMSE, Mini-Mental State Examination; PTA, pure tone audiometry; SDS, speech discrimination score; LDL, low density lipoprotein; HDL, high density lipoprotein.

Discussion

In the context of the ongoing discussion regarding the potential correlation between *APOE* genotype and hearing loss, which has yielded conflicting outcomes to date, our study has produced the following conclusions. Firstly, ε4 allele carriers show that hearing deteriorates more rapidly with increasing age compared to non-carriers, with no differences regarding sex. Secondly, among ε4 carriers, hearing is better before the age of 75, but this difference diminishes after the age of 75 due to the rapid deterioration of hearing with age.

To the best of our knowledge, seven studies have been published investigating the correlation between *APOE* genotype and hearing loss, with conflicting results reported (Table 4). Our findings provide insight into the discrepancies among previous studies, which may be attributed to variations in the age range of the cohorts examined. A potential explanation for the inconsistent results of prior investigations could be the age of the cohorts studied. Specifically, five of the previous studies evaluated hearing loss using PTA in cohorts with an average age ranging from 64 to 72 years and failed to identify a significant correlation between the ε4 genotype and hearing loss or reported a positive relationship with good hearing[9–13]. In contrast, Kurniawan et al. identified a significant association between the ε4 genotype and hearing loss in the oldest cohort examined, with a mean age of 85 years[8]. Our investigation found that the ε4 variant had a protective effect before the age of 75.5, but a detrimental effect thereafter. This likely explains the negative impact of the ε4 allele variant observed in the older age group. Kim et al. reported a higher risk of hearing loss in male ε4 carriers in a relatively young cohort; however, this study relied on self-reporting rather than audiometry, which may be subject to age and sex-related biases[7]. Given that subjective hearing impairment can be influenced by age and sex, as previously noted[18], we suggest that our results, which show no significant differences in analysis by sex, are more reliable.

Our findings suggest a biphasic effect where individuals with *APOE* ε4 allele variants initially exhibit better hearing at a younger age, followed by a rapid deterioration in hearing with advancing age. Additionally, our results indicate a reversal of the earlier hearing protective effect of the *APOE* ε4 allele around the age of 75.5. Considering that the incidences of Alzheimer's disease regarding *APOE* genotypes significantly differ from about 70 years of age, it is thought that the onset of hearing loss appears at a later age of about 5 years than Alzheimer's

Baseline model (Marginal R^2 = 0.17, Conditional R^2 = 0.72)			
Fixed Effect (Predictors)	**Estimates**	**Std. Error**	**P**
Age	1.802	0.181	< 0.001***
ε4 (+)	-0.389	0.212	0.003**
ε4 (+) * Age	0.649	0.368	0.003**
Random Effect	**Variance**	**Std. Deviation**	
Subjects	0.169	0.131	
Frequency	0.111	0.098	
Model evaluation	Log-likelihood	RMSE	
	3656.5	0.146	
Fully Adjusted model (Marginal R^2 = 0.19, Conditional R^2 = 0.73)			
Fixed Effect (Predictors)	**Estimates**	**Std. Error**	**P**
Age	1.784	0.096	< 0.001***
Sex (Male)	0.136	0.026	< 0.001***
Hypertension (yes)	0.024	0.027	0.356
Diabetes (yes)	0.092	0.028	0.001**
ε4 (+)	-0.353	0.126	0.005**
ε4 (+) * Age	0.577	0.214	0.006**
Random Effect	**Variance**	**Std. Deviation**	
Subjects	0.160	0.401	
Frequency	0.109	0.331	
Model evaluation	**Log-likelihood**	**RMSE**	
	3838.4	0.144	

Table 2. The Result of Generalized Linear mixed regression analysis. RMSE, root mean squared error.

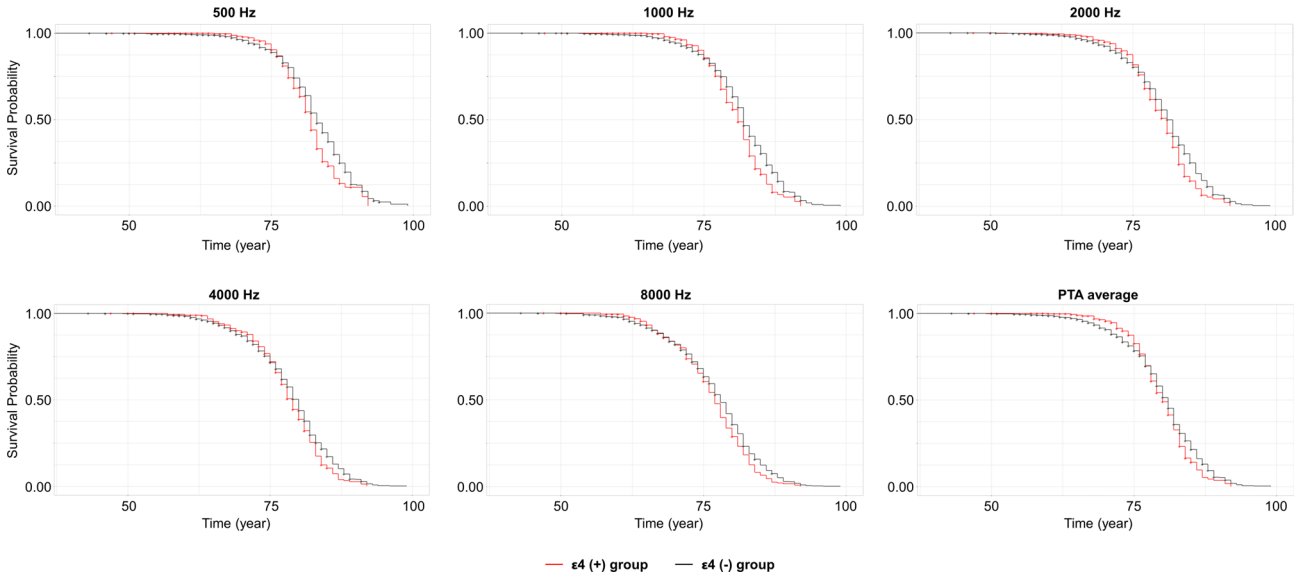

Fig. 2. Kaplan–Meier plot for hearing loss-free survival. Before the age of 75, the ε4 (+) group had a higher probability of hearing loss-free survival compared with the ε4 (−) group. The ε4 (−) group exhibited a higher likelihood of hearing loss-free survival after the age of 75. PTA, pure-tone audiometry.

disease[19,20]. The reason why the ε4 allele increases Alzheimer's disease prevalence is thought to be because of amyloid-β accumulation and tau-mediated neurodegeneration[21]. As with *APOE* genotypes, there exists a debate concerning the link between amyloid-β and tau protein and their correlation with hearing loss[22–25]. A study has reported an association between higher amyloid-β and tau burden and age-related hearing loss[22]. Furthermore, in an animal study using transgenic mice expressing amyloid-β, hair cell loss in the cochlear basal turn due to amyloid-β has been observed, and tau protein has been demonstrated to synergistically enhance amyloid-β-induced hearing loss[23]. Nonetheless, the underlying mechanism by which the ε4 allele impacts hearing loss remains inadequately investigated. A previous investigation using *APOE* knock-out mice suggested that hyperlipidemia and atherosclerosis may damage the cochlea *APOE* plays an important role in lipoprotein metabolism

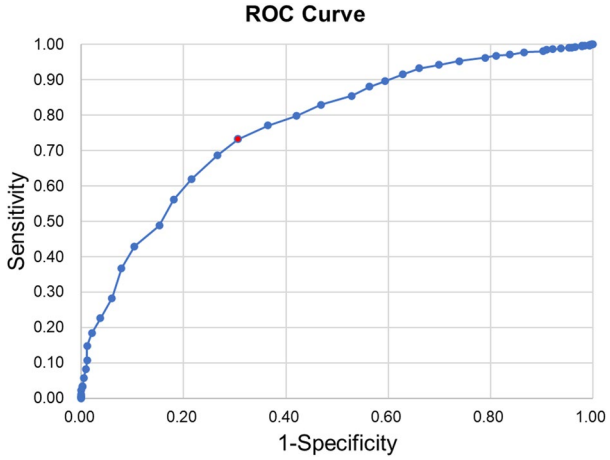

Fig. 3. Receiver operating characteristic (ROC) curve to investigate the optimal age cut-off value. The optimal cut-off value was 75.5-year-old based on predictive sensitivity of 73.1% and a specificity of 69.3%. AUC, area under the ROC curve.

Parameter		Age < 75				Age ≥ 75			
		Total (n = 442)	ε4 (+) (n = 113)	ε4 (−) (n = 329)	*P*	Total (n = 720)	ε4 (+) (n = 167)	ε4 (−) (n = 553)	*P*
Age (years)	67.13 ± 6.4	67.6 ± 5.4	67.0 ± 6.2	0.326	81.03 ± 4.7	80.2 ± 3.9	81.3 ± 4.4	0.002**	
Sex	Male	154 (34.8%)	37 (32.7%)	117 (35.6%)	0.669	302 (41.9%)	74 (43.3%)	228 (41.2%)	0.640
	Female	288 (65.2%)	76 (67.3%)	212 (64.4%)		418 (58.1%)	93 (55.7%)	325 (58.8%)	
	MMSE	25.4 ± 4.6	25.2 ± 4.5	25.5 ± 4.8	0.615	21.12 ± 7.2	20.4 ± 6.1	21.3 ± 6.8	0.119
	PTA[a] (dB HL)	24.4 ± 14.7	21.1 ± 11.1	25.6 ± 14.5	0.001***	29.17 ± 17.63	41.1 ± 16.8	40.0 ± 17.4	0.471
	SDS (%)	90.1 ± 12.5	94.9 ± 9.0	88.7 ± 13.8	< 0.001***	73.23 ± 26.9	75.5 ± 22.4	72.5 ± 26.4	0.305
Diabetes	Normal	339 (75.7%)	90 (77.6%)	249 (75.0%)	0.665	487 (68.2%)	113 (68.9%)	374 (68.0%)	0.903
	Abnormal	109 (24.3%)	26 (22.4%)	83 (25.0%)		227 (31.8%)	51 (31.1%)	176 (32.0%)	
Hyper tension	Normal	257 (57.4%)	67 (57.8%)	190 (57.2%)	> .999	298 (4107%)	68 (41.5%)	230 (41.8%)	> .999
	Abnormal	191 (42.6%)	49 (42.2%)	142 (42.8%)		416 (58.3%)	96 (58.5%)	320 (58.2%)	
Lipid tests	LDL Cholesterol (mmol/L)	93.8 ± 33.5	95.4 ± 31.1	93.4 ± 34.2	0.678	105.8 ± 33.3	108.2 ± 31.3	105.1 ± 34.1	0.547
	HDL Cholesterol (mmol/L)	50.8 ± 14.9	50.2 ± 17.3	51.0 ± 14.2	0.725	53.0 ± 14.63	52.9 ± 14.5	53.0 ± 14.7	0.977
	Total Cholesterol (mmol/L)	169.0 ± 39.5	168.1 ± 37.7	169.3 ± 40.1	0.678	185.5 ± 39.2	192.2 ± 38.4	183.3 ± 39.4	0.115
	Triglyceride (mmol/L)	118.6 ± 80.6	119.7 ± 61.1	118.4 ± 85.8	0.875	123.8 ± 84.9	122.2 ± 71.1	124.4 ± 89.4	0.845

Table 3. Summary statistics for the group of patients < 75- and ≥ 75-year-old. [a]Average of 500, 1000, 2000, 4000 Hz frequency thresholds. MMSE, Mini-Mental State Examination; PTA, pure tone audiometry; SDS, speech discrimination score; LDL, low density lipoprotein; HDL, high density lipoprotein.

and can increase LDL-cholesterol levels in ε4 allele carriers[26]. Several studies have reported a potential negative impact of elevated LDL-cholesterol levels on hearing loss[27]. However, the effect of *APOE* on hearing cannot be fully explained by its role in lipid metabolism alone. First, lipid profile results did not significantly differ in the present study. Second, the biphasic effect observed in our study cannot be explained by lipid metabolism alone, which changes monotonically. Thirdly, there are differing findings on the correlation between blood lipid levels and hearing loss, with some studies reporting weak or no correlation[28].

Most of the studies on *APOE* genotypes have been focused on the negative effects of the *APOE* ε4 allele; however, recent investigations provided some indicators for positive effects. Several studies have shown that innate immune biomarkers are reduced in ε4 carriers, implying that ε4 allele carriers may be more protected from inflammatory burden through lower innate immune sensing and faster clearance following the resolution of an acute inflammatory spike[29–32]. In the study of Garcia et al.[31], C-reactive protein (CRP) levels were 30% lower in ε4 carriers compared with homozygous ε3/ε3 individuals, and ε4 carriers exhibited a lower eosinophil to lymphocyte ratio and lower total leukocytes, suggesting that ε4 allele may play a beneficial role in the immune response, despite the fact that ε4 carriers have higher blood lipid levels. These Janus-like characteristics of the ε4 allele provide clues for understanding the results of our study. We hypothesized that the positive effect of ε4 allele on the immune response may be a reason for the hearing protective effect at a younger age, while the negative effects of blood lipids accelerate the hearing loss at an older age. Nevertheless, this remains a hypothesis since

Reference	Study design (Country)	Cohort number	Mean age (Range)	Hearing tests (side)	Hearing loss definition	ApoE ε4 genotype group	Results	Limitations
O'Grady et al. (2007)	Longitudinal cohort study (USA)	89	64 (34–95)	PTA, SA (not mentioned)	≥40 dB HL	allele frequencies	No association	Small cohort
C. Kurniawan et al. (2012)	Population-based study (Netherlands)	435	85	Portable PTA (better ear)	>35 dB HL (1000, 2000, 4000 Hz average)	ε4 (+)/(−)	ε4 genotype is related to hearing loss	Portable audiometer was used
Dawes et al. (2015)	Candidate gene association study (UK)	265	72 (59–88)	PTA (better ear)	NA	ε4 (+)/(−)	No association	
Mener et al. (2016)	Prospective observational study (USA)	1833	70–79	PTA (better ear)	NA	ε4 (+/+)/(+/-)/(−/−)	ε4 genotype is related to good hearing	ε4 (+/+) group had small number (n = 23) and was younger
Y.Morita et al. (2019)	Cross-sectional survey in prospective cohort study (Japan)	322	71 (60–89)	PTA (better ear)	>30 dB HL (average frequency between 0.25 and 8 kHz)	ε4 (+/+)/(+/−)/(−/−)	No association	
Sarant et al. (2020)	A cross-sectional study (Australia)	2006	66	PTA (better ear)	>25 dB HL (Average 500, 1000, 2000, and 4000 Hz)	ε4 (+/+)/(+/−)/(−/−)	No association	ε4 (+/+) group had small number (n = 35)
Kim et al. (2021)	A longitudinal cohort study (South Korea)	1092	61	ICD-10 code	NA	ε4 (+)/(−)	ε4 carrier & male : high risk of hearing loss (OR = 1.90)	No hearing tests
Present study	Retrospective multicentre study (South Korea)	1162	76	PTA (better ear)	>25 dB HL (Average 500, 1000, 2000, and 4000 Hz)	ε4 (+)/(−)	<75-year-old: ε4 genotype is related to better hearing ≥75-year-old: ε4 genotype is related to worse hearing	

Table 4. Summary of previous studies and current results. ApoE, Apolipoprotein E; PTA, pure tone audiometry; SA, speech audiometry; MMSE, mini mental state examination.

our study was not designed to reveal the pathophysiology of *APOE* genotypes and hearing levels. Therefore, further research in this area is necessary.

The present study demonstrates methodological strengths compared with previous research. The audiologic data analyzed in this study was obtained in a soundproof chamber using calibrated equipment, rendering it reliable. Additionally, the sample size was sufficiently large to produce trustworthy findings. Above all, our study has significant meaning in that it is the first report of a biphasic effect of the ε4 allele on hearing loss, with an age-related cut-off value determined through statistical analysis.

However, this study has several limitations. First, the cohort used in this study was limited to participants with Korean ethnicity and patients who visited hospitals. Therefore, the MMSE values of our study cohort exhibited lower results compared to the general population. Second, it was not feasible to analyze the effect of *APOE* ε4 dosage as the number of ε4 (+/+) individuals in the cohort was insufficient. Third, there is a limitation that the timing of the conducted assessments may not be uniform. Unlike the *APOE* genotype test, the MMSE test, audiometric assessment, and blood tests can vary based on the timing of the examination. Therefore, while it would be most ideal for all assessments to be conducted at the same time for analysis, it should be noted that this study acknowledges the presence of variations in the timing of assessments due to the retrospective nature of the research. Finally, due to limitations in the data available from medical records, we were unable to include various covariates. For instance, several risk factors for hearing loss, such as a history of noise exposure, smoking, familial history of hearing loss, race, and the use of ototoxic medications, as well as other audiological symptoms like tinnitus and hyperacusis, were not included in the analysis[33,34]. Additionally, genomic principal components, which could control for the polygenic risk of hearing loss and non-genetic confounders affecting the relationship between *APOE* and hearing loss, were not included as covariates.

The correlation between *APOE* genotype and hearing loss has yielded contradictory results in prior studies. Our study indicated that individuals with the ε4 allele experience a hearing protective effect at a younger age but undergo a more rapid deterioration in hearing as they age. This biphasic effect of the *APOE* genotype provides a clue to understanding the inconsistent findings of previous investigations. Further studies investigating the underlying mechanisms of this relationship are needed.

Data availability

The data that support the findings of this study are available on request from the corresponding author, K.H.P and I.Y.C. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Received: 2 April 2024; Accepted: 30 August 2024
Published online: 13 September 2024

References

1. Man, J. *et al.* Global, regional, and national burden of age-related hearing loss from 1990 to 2019. *Aging (Albany NY)* **13**, 25944–25959 (2021).
2. Johnson, J. C. S. *et al.* Hearing and dementia: From ears to brain. *Brain* **144**, 391–401 (2021).
3. Livingston, G. *et al.* Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet* **396**, 413–446 (2020).
4. Farrer, L. A. *et al.* Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *Jama* **278**, 1349–1356 (1997).
5. Chen, Y., Strickland, M. R., Soranno, A. & Holtzman, D. M. Apolipoprotein E: Structural insights and links to Alzheimer disease pathogenesis. *Neuron* **109**, 205–221 (2021).
6. Guo, Y., Zhang, C., Du, X., Nair, U. & Yoo, T. J. Morphological and functional alterations of the cochlea in apolipoprotein E gene deficient mice. *Hear. Res.* **208**, 54–67 (2005).
7. Kim, C. H., Son, K. J., Lee, J. H. & Kim, J. H. Sex differences in the association between the APOEε4 allele and hearing impairment: A longitudinal memory clinic study. *Arch. Gerontol. Geriatr.* **95**, 104418 (2021).
8. Kurniawan, C. *et al.* Gene dose of apolipoprotein E and age-related hearing loss. *Neurobiol. Aging* **33**(2230), e2237-2230.e2212 (2012).
9. Dawes, P. *et al.* No association between apolipoprotein E or N-acetyltransferase 2 gene polymorphisms and age-related hearing loss. *Laryngoscope* **125**, E33-38 (2015).
10. Morita, Y. *et al.* Age-related hearing loss is strongly associated with cognitive decline regardless of the APOE4 polymorphism. *Otol. Neurotol.* **40**, 1263–1267 (2019).
11. O'Grady, G. *et al.* Apolipoprotein E alleles and sensorineural hearing loss. *Int. J. Audiol.* **46**, 183–186 (2007).
12. Sarant, J. Z., Bowe, S. J., McEvoy, M. & Attia, J. The apolipoprotein allele and sensorineural hearing loss in older community-dwelling adults in Australia. *Ear. Hear.* **41**, 622–629 (2020).
13. Mener, D. J. *et al.* Apolipoprotein E allele and hearing thresholds in older adults. *Am. J. Alzheimers Dis. Other. Demen.* **31**, 34–39 (2016).
14. Park, S. J. *et al.* Machine learning prediction of dropping out of outpatients with alcohol use disorders. *PLoS ONE* **16**, e0255626 (2021).
15. Olusanya, B. O., Davis, A. C. & Hoffman, H. J. Hearing loss grades and the International classification of functioning, disability and health. *Bull. World Health Organ.* **97**, 725–728 (2019).
16. Byun, S. W. Frequencies of Korean phonemes and reliability of Korean phonetically balanced word lists. *Korean J. Otorhinolaryngol.-Head Neck Surg.* **44**, 485–489 (2001).
17. Yuan, G. *et al.* Defining optimal cutoff value of MGMT promoter methylation by ROC analysis for clinical setting in glioblastoma patients. *J. Neurooncol.* **133**, 193–201 (2017).
18. Kamil, R. J., Genther, D. J. & Lin, F. R. Factors associated with the accuracy of subjective assessments of hearing impairment. *Ear. Hear.* **36**, 164–167 (2015).
19. Reiman, E. M. *et al.* Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. *Nat. Commun.* **11**, 667 (2020).
20. Blacker, D. *et al.* ApoE-4 and age at onset of Alzheimer's disease: The NIMH genetics initiative. *Neurology* **48**, 139–147 (1997).
21. Yamazaki, Y., Zhao, N., Caulfield, T. R., Liu, C.-C. & Bu, G. Apolipoprotein E and Alzheimer disease: Pathobiology and targeting strategies. *Nat. Rev. Neurol.* **15**, 501–518 (2019).
22. Zheng, M. *et al.* Worsening hearing was associated with higher β-amyloid and tau burden in age-related hearing loss. *Sci. Rep.* **12**, 10493 (2022).
23. Omata, Y. *et al.* Expression of amyloid-β in mouse cochlear hair cells causes an early-onset auditory defect in high-frequency sound perception. *Aging (Albany NY)* **8**, 427–439 (2016).
24. Sarant, J. Z. *et al.* No influence of age-related hearing loss on brain amyloid-β. *J. Alzheimers Dis.* **85**, 359–367 (2022).
25. Irace, A. L., Rippon, B. Q., Brickman, A. M., Luchsinger, J. A. & Golub, J. S. The laterality of early age-related hearing loss and brain β-amyloid. *Otol. Neurotol.* **43**, e382–e390 (2022).
26. Khalil, Y. A., Rabès, J. P., Boileau, C. & Varret, M. APOE gene variants in primary dyslipidemia. *Atherosclerosis* **328**, 11–22 (2021).
27. Malgrange, B., Varela-Nieto, I., de Medina, P. & Paillasse, M. R. Targeting cholesterol homeostasis to fight hearing loss: A new perspective. *Front. Aging Neurosci.* **7**, 3 (2015).
28. Simpson, A. N., Matthews, L. J. & Dubno, J. R. Lipid and C-reactive protein levels as risk factors for hearing loss in older adults. *Otolaryngol. Head Neck Surg.* **148**, 664–670 (2013).
29. Lumsden, A. L., Mulugeta, A., Zhou, A. & Hyppönen, E. Apolipoprotein E (APOE) genotype-associated disease risks: A phenome-wide, registry-based, case-control study utilising the UK Biobank. *EBioMedicine* **59**, 102954 (2020).
30. Martiskainen, H. *et al.* Decreased plasma C-reactive protein levels in APOE ε4 allele carriers. *Ann. Clin. Transl. Neurol.* **5**, 1229–1240 (2018).
31. Garcia, A. R. *et al.* APOE4 is associated with elevated blood lipids and lower levels of innate immune biomarkers in a tropical Amerindian subsistence population. *eLife* **10**, e68231 (2021).
32. Trumble, B. C. *et al.* Apolipoprotein E4 is associated with improved cognitive function in Amazonian forager-horticulturalists with a high parasite burden. *Faseb. J.* **31**, 1508–1515 (2017).
33. Lin, F. R., Thorpe, R., Gordon-Salant, S. & Ferrucci, L. Hearing loss prevalence and risk factors among older adults in the United States. *J. Gerontol.: Ser. A* **66A**, 582–590 (2011).
34. Bernal-Robledano, A. *et al.* Cognitive screening and hearing assessment in patients with chronic tinnitus. *Clin. Exp. Otorhinolaryngol.* **17**, 15 (2024).

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grants funded by the Korea government (NRF-2019R1A5A2027588). The funding organization had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the decision to submit the article for publication; or in the preparation, review, or approval of the article.

Author contributions

Study concept and design: J.S.H., S.G.Y. Acquisition, analysis, or interpretation of data: J.S.H., S.G.Y., H.J.L., I.Y.C., K.H.P. Drafting of the manuscript: J.S.H., S.G.Y. Critical revision of the manuscript for important intellectual content: H.J.L., I.Y.C., K.H.P. Statistical analysis: S.G.Y., I.Y.C. Administrative, technical, or material support: S.J.L., I.Y.C., KHP Study supervision: I.Y.C., K.H.P.

Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to I.Y.C. or K.H.P.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.