Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Impact of Calcium Signaling Pathway Genes on age-related deterioration in hearing: A longitudinal study

Xiao-Long Li
The College of Public Health of Qingdao University
Yong-Qiang Sun
Qilu Hospital (Qingdao), Shandong University
Hui Liang
Qingdao Municipal Center for Disease Control and Prevention
Jing-kai Zhang
Weifang Center for Disease Control and Prevention
Tan Tan
Huangdao District Center For Disease Control and Prevention
Zi-Cheng Jin
Qingdao Municipal Center for Disease Control and Prevention
Hai-Nan Cao
Qingdao Municipal Hospital
Hua Zhang
Qingdao Municipal Center for Disease Control and Prevention
Tong Zhou
Qingdao Municipal Center for Disease Control and Prevention
Hai-Ping Duan
duan_hp@126.com

The College of Public Health of Qingdao University

Research Article

Keywords: Weighted allele score, Age-related hearing loss, Calcium Signaling Pathway Genes

Posted Date: July 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9811655/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Age-related hearing impairment has attracted increasing attention recently. It is caused by genetic and environmental factors. A number of ARHI-related genes have been found. This study aimed to detect the potential association between Calcium Signaling Pathway Genes and age-related deterioration in hearing by means of weighted allele score.

Methods

This study utilized a longitudinal design, conducting a survey on 471 elderly participants from two communities in Qingdao, China, in 2018, and a follow-up survey was conducted again in 2024. We selected 56 single nucleotide polymorphisms (SNPs) from nine calcium signaling pathway-related genes (*NR3C1*, *PRKCA*, *CCKAR*, *CACNA1C*, *TRPM1*, *RAC1*, *BCL11B*, *ATG12*, *DCP1B*) to construct a polygenic risk score (PRS). Multilevel linear regression models were employed to analyze the association between the PRS and both baseline hearing level (PTA baseline) and its rate of decline (PTA change).

Results

Research has shown that the PRS for the calcium signaling pathway is significantly associated with PTA baseline (β = -0.063, P = 0.008) and PTA change (β = -0.074, P < 0.001). Sensitivity analyses matching yielded similar results. After stratifying by age, the association between PRS and PTA change was more pronounced in individuals aged ≥ 70 years (Pinteraction = 0.011).

Conclusions

This longitudinal study presents the first evidence that genetic variations in genes related to the calcium signaling pathway are associated with the progression of age-related deterioration in hearing.

1. Introduction

Age-related hearing impairment (ARHI) is a form of sensorineural hearing loss characterized by symmetrical bilateral and progressive declines in auditory function as individuals age[1]. With increasing life expectancy and a growing proportion of elderly individuals, the prevalence of ARHI is rising[2]. In China, over half of the middle-aged and elderly population experiences some degree of hearing impairment[3]. A study conducted in northern China revealed that all participants aged 80 and above exhibited hearing impairment[4]. This condition not only adversely affects personal communication and

quality of life, often leading to depression and social isolation[5], but is also strongly associated with cognitive decline, which is critical for the elderly to maintain independence[6].

The association between calcium (Ca^{2+}) and age-related hearing loss has garnered considerable attention in recent years. Emerging research indicates that calcium dysregulation is a critical factor contributing to cochlear degeneration[7]. Maintaining calcium homeostasis is essential for preserving the integrity of cochlear structures, such as hair cells, which are vital for auditory signal transduction[8, 9]. Disruptions in calcium signaling can lead to oxidative stress, mitochondrial dysfunction, and apoptosis, all of which are implicated in the progression of ARHI[10–12]. Furthermore, calcium plays a significant role in the inflammatory processes that contribute to ARHI[13]. Dysregulation of calcium can exacerbate inflammatory responses in the cochlea, resulting in increased oxidative stress and cellular damage[10, 13].

Our previous research has focused on the relationship between genetic factors and hearing impairment, indicating that genetic risk may contribute to impairment in auditory function. Variations in *NR3C1*[14] polymorphisms may influence the binding of glucocorticoids and glucocorticoid receptors, potentially leading to impaired immune responses and diminished anti-inflammatory effects, which may affect age-related hearing impairment. Variations in *BCL11B*[15] gene polymorphisms may disrupt the ionic homeostasis of the endolymph, leading to the depolarization of hair cells and ultimately resulting in hearing loss. Moreover, a study has shown that variations in *ATG1*[16] gene polymorphisms also be associated with Hearing Loss. These genes are all associated with the calcium signaling pathway, suggesting that calcium signaling pathway genes may be associated with ARHI. However, the majority of these studies employ a cross-sectional design, limiting our capacity to ascertain whether genetic factors accelerate age-related auditory deterioration. These limitations obstruct efforts to quantify the extent to which genetic factors influence the progression of age-related hearing decline over time[17].

This study utilized Longitudinal Ageing Survey in Chengyang (LASCy), an ongoing prospective cohort study targeting the population aged 50 years or over in Qingdao, China. By leveraging repeated audiometric measurements, we aimed to employ Polygenic risk score (PRS) to investigate the association between genetic variations in calcium signaling pathway-related genes and baseline differences, as well as the rate of hearing threshold decline. This approach provides insights into the role of these genetic variations in the progression of age-related hearing deterioration.

2. Materials and methods

2.1. Study subjects

LASCy comprised a comprehensive array of participant-related information, encompassing demographics, health conditions, lifestyle, economic status, biological data, genetic data, and physical and psychological health questions. Briefly, the baseline survey was conducted in August 2018. Participants were recruited by permanent residents of Qingdao (residents for a minimum of five years) in

two communities in Chengyang District, Qingdao City, China. A total of 1,062 participants completed the baseline assessment, which included sequential measurements of fasting blood samples, blood pressure, pure tone hearing thresholds, bone mineral density, along with a standardized self-reported questionnaire. Subsequently, all participants received annual health examinations, that is, a Basic Public Health Service Programme examination, and were followed up with a questionnaire in 2024. All surveys were administered in a face-to-face manner by investigators who had undergone rigorous training. Approval for this study was granted by the Medical Ethics Committee of the Qingdao Municipal Centre for Disease Control and Prevention (ID: 202401). The participants signed a written informed consent form.

For the current analysis, we used data from LASCy collected between 2018 and 2024. Participants were excluded in the following cases: (1) those who had not gene data (n = 257); (2) those who had<2 ARHI data (n = 28) ; and (3) those for whom not participate follow-up survey in 2024 (n = 306). Consequently, the final study sample comprised 471 participants. The detailed flowchart of the sample exclusion process was displayed in Fig. 1.

2.2. audiometric test

Initially, we cleaned the external auditory canal, followed by an examination of the eardrum, and concluded with a hearing test. Participants were instructed to enter a quiet room (≤ 40 dB (A)) for a brief rest. The air conduction hearing test was administered by a certified audiometrician using a Pure Tone Audiometer (Orbiter 922, Madsen) and a headset (TDH39). Starting with the self-reported better hearing ear, we measured the pure tone air conduction thresholds at frequencies of 0.5, 1.0, 2.0, and 4.0 kHz for both ears, with readings precise to 1 dB HL. Following the World Health Organization recommendations (1997), the pure tone average (PTA) for the better hearing ear threshold at 0.5, 1.0, 2.0, and 4.0 kHz was designated as the dependent variable[18].

2.3. Genotyping and quality controls

A GWAS study on ARHI in middle-aged and elderly individuals based on 131 pairs of dizygotic twins submitted a list of significant genes (P < 0.05) to the Gene Set Enrichment Analysis (GSEA) website (https://www.gseamsigdb.org/gsea/msigdb/index.jsp) to explore the relevant pathways enriched by these significant genes [19]. Through this GWAS analysis, pathway enrichment analysis found that the the calcium signaling pathway is closely associated with ARHI. Therefore, polymorphisms in genes related to the Calcium signaling pathway may influence the onset or progression of ARHI [20–23]. Using a candidate gene selection method, combined with previously reported candidate gene association studies, nine genes (*NR3C1, PRKCA, CCKAR, CACNA1C, TRPM1, RAC1, BCL11B, ATG12, DCP1B*) involved in the calcium signaling pathway were screened out [14–16,24–27].

We selected 56 SNPs from the 9 genes associated with the calcium signaling pathwaybased on findings from previous genome-wide association studies (GWAS) [19]. We searched on NCBI-SNP (https://www.ncbi.nlm.nih.gov/snp/), East Asian Samples of 1000 Genomes Project

(https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/). The selected SNPs were required to have a minor allele frequency (MAF) greater than 0.05, genotyping rate > 0.99, sample missingness < 0.02, heterozygosity $P > 1x10^{-6}$, imputation 'info score' > 0.8, and a maximum linkage disequilibrium correlation (r^2) below 0.2 in the Han Chinese population from Beijing, China (CHB). Blood samples were collected in pre-prepared tubes containing EDTA anticoagulant, and white blood cells were isolated within 2 hours of collection. DNA was extracted from venous blood samples using a DNA extraction kit from BioTeke Corporation, and the optical density (OD) was measured with a NanoDrop 2000 spectrophotometer. After performing 1.25% agarose gel electrophoresis, the qualified DNA was transferred to a 96-well plate and stored at -20°C for future use. Utilizing the sequence information of the SNPs, we employed Assay Design 3.1 to create primers for PCR and single-base extension.We obtained SpectroCHIP following PCR amplification, alkaline phosphatase treatment of the product, single-base elongation reaction, resin purification, and chip spot sampling. The SpectroCHIP was analyzed using a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometer to acquire genotyping data. We referenced the East Asian samples from the 1000 Genomes Project, designating the high-frequency allele as the major allele and the low-frequency allele as the minor allele.

2.4. Covariates

The following variables, procured from the baseline questionnaires, were included as covariates: age (<70 or ≥ 70) [28], sex (female or male), education (No, Primary, junior high school, senior high school, college and above), hypertension (No, Yes), diabetes (No, Yes), alcohol intake (No, Yes), and smoking (No, Yes).

2.5. Statistical analysis

Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]), while categorical variables are expressed as number (%). We assessed the Hardy–Weinberg equilibrium (HWE) for each SNP.

The weighted allele score was employed to estimate the magnitude of genetic effects. This score is calculated by multiplying the number of SNP mutant alleles in a gene by their corresponding weights, followed by summing these products[29]. The weights were derived from the current dataset utilizing a tenfold cross-validation method[30]. Specifically, we randomly divided the data into ten samples. Given that the total number of subjects was 471, we selected the first nine samples to contain 47 subjects each, while the tenth sample included 48 subjects. Subsequently, the SNP data from the first nine samples served as independent variables, with hearing levels as the dependent variable for logistic regression analysis. The regression coefficients obtained were utilized as the weights for the tenth sample, and the weight calculation for the remaining samples followed the same procedure.

The formula is as follows:

$$\text{Allele score}=(W1\times SNP1 + W2\times SNP2+\cdots+Wi\times SNPi)/(W1 + W2+\cdots+Wi)$$

i: the number of SNPs involved in constructing the allele score. SNP_i: the number of minor alleles in a SNP. W_i: the weight of each SNP.

A multilevel linear regression analysis was conducted to investigate the associations between the PRS and both the PTA baseline and PTA change. An interaction analysis between the PRS and PTA change was performed. Employing two models: Model 1, which did not adjust for covariates, and Model 2, which adjusted for age, gender, education, hypertension, diabetes, smoking, and drinking. Multiple imputation was performed for all variables, and the pre-imputation data were utilized for our sensitivity analysis(n = 435).

All statistical analyses were conducted using Stata 18.0. The P values < 0.05 were regarded as statistically significant.

3. Results

3.1. Basic characteristics of participants

A total of 471 elderly participants were included in this study. Their baseline demographic are summarized in Table 1. The mean age of the participants was 67.32 ± 5.249 years, with the majority aged between 60 and 69 years. A slightly higher proportion of the participants were female. The PTA baseline was 44.56 ± 12.33 dB, indicating mild to moderate hearing loss on average. During the follow-up period, PTA change was 11.68 ± 7.95 dB, demonstrating a significant longitudinal deterioration in hearing acuity across the cohort.

Table 1
demographic characteristics for study participants.

Variable Category	n (%) or Mean ± SD
Age	67.32 ± 5.249
<70 ≥ 70	344(73%)
	127(27%)
Sex	193(41%)
male	
female	278(59%)
Smoke	109(23.13%)
yes	
no	362(76.87%)
alcohol	163(34.68%)
yesno	308(65.32%)
education	48(10.2%)
no	260(55.3%)
primary	134(28.5%)
junior high school	27(5.7%)
senior high school	1(0.2%)
college and above	230(48.9%)
Hypertension	240(51.1%)
yes	82(17.4%)
no	388(82.6%)
Diabetes	44.56 ± 12.33
yes	11.68 ± 7.95
no	
PTA baseline(dB)	
PTA change(dB)	

3.2. The association of PRS with PTA baseline and the PTA change

The linear regression results for the PRS with PTA baseline and the PTA change are detailed in Table 2. Firstly, regarding baseline hearing, a significant negative association with the PRS was observed. This relationship remained consistent in both the crude model (β = -0.064, P = 0.007) and after adjusting for age, sex, education, hypertension, diabetes, smoking, and alcohol consumption (β = -0.063, P = 0.008). Moreover, for the longitudinal rate of hearing decline, the PRS was significantly correlated with PTA change in both Model 1 (β = -0.075, P < 0.001) and Model 2 (β = -0.074, P < 0.001). This result remained robust in the sensitivity analysis (Table S2).

Table 2
Multiple Linear Regression of PRS with PTA baseline and PTA change.

PTA baseline	***β***	**Model 1**	***P***	***β***	**Model 2**	***P***
		95%CI			***95%CI***	
	-0.064	**(-0.110, -0.017)**	**0.007***	**-0.063**	**(-0.104, -0.016)**	**0.008***
PTA change	**-0.075**	**(-0.105, -0.046)**	**<0.001***	**-0.074**	**(-0.106, -0.046)**	**<0.001***

Note: *P<0.05, Model 1 did not adjust for covariates, Model 2 was adjusted for age, gender, education, hypertension, diabetes, smoking, and drinking.

3.3. Interaction and subgroup analysis

To investigate whether environmental factors modify the association between the PRS and PTA change, we conducted multiplicative interaction analysis and subgroup analysis (Fig. 2). The results indicate that age is a significant moderating factor between PRS and PTA change (Pinteraction = 0.011). Among individuals aged 70 years and older, the negative association between PRS and hearing loss progression was substantially stronger (β = −0.130, P < 0.001). In those younger than 70 years, while a significant negative association was also present (β = −0.048, P = 0.005), the effect size was notably smaller compared to the older cohort.

In contrast, no significant interactions were observed between PRS and sex, history of diabetes, or history of cardiovascular disease. Notably, the interaction with diabetes approached the threshold of significance in the adjusted model (P = 0.052), although it did not reach statistical significance.

4. Discussion

This longitudinal study systematically investigates the associations between PRS related to calcium signaling pathway genes and both the baseline hearing level and its rate of progression in age-related deterioration in hearing. Our findings demonstrate that a higher PRS is significantly associated with

better baseline hearing function and, more importantly, with a slower rate of hearing threshold decline over time. This suggests that genetic variations within the calcium signaling pathway may play a protective role against the progression of age-related deterioration in hearing.

Ca^{2+} serve as ubiquitous intracellular messengers, essential for various cochlear functions, including mechanoelectrical transduction in hair cells[31], synaptic transmission at the inner hair cell–afferent neuron interface[32], and the maintenance of cellular integrity. Dysregulation of calcium signaling is a well-established mediator of oxidative stress, mitochondrial dysfunction, and apoptotic pathways, all of which are implicated in the aging cochlea. Our findings align with this mechanistic background, suggesting that inherited genetic variations that promote more stable calcium homeostasis may confer resilience against these age-related degenerative processes, thereby preserving auditory function.

A key finding from our interaction analysis is the significant multiplicative interaction between the PRS and age. As individuals age, the influence of genetic factors becomes increasingly pronounced. This observation is biologically plausible, as the cumulative burden of cellular stress and damage associated with advancing age may render the cochlea more dependent on robust regulatory mechanisms, such as those governed by calcium signaling, to maintain its functionality.

However, this study has several limitations. Firstly, the sample size was insufficient, and the study population was confined to a single city in China (Qingdao), which limits the generalizability of the findings. Furthermore, noise exposure was not directly measured; instead, this limitation makes it impossible to entirely rule out confounding effects from both occupational and non-occupational noise.

In conclusion, this study presents the first longitudinal evidence that the PRS derived from calcium signaling pathway genes is associated with the progression of age-related hearing deterioration. These findings offer valuable genetic insights and establish a foundation for further exploration of the underlying molecular mechanisms and potential personalized prevention strategies. Future research involving larger sample sizes is essential to validate these findings and to further elucidate the specific role of the calcium signaling pathway in auditory aging.

Abbreviations

ARHI
Age-related hearing impairment
PRS
Polygenic risk score
GWAS
Genome-wide association study
SNP
Single nucleotide polymorphism
GSEA

Gene Set Enrichment Analysis
MAF
Minor allele frequency
CHB
Han Chinese population from Beijing, China
LASCy
Longitudinal Ageing Survey in Chengyang
PTA
Pure tone average
HWE
Hardy–Weinberg equilibrium

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the Medical Ethics Committee of Qingdao Municipal Center for Disease Control and Prevention in Qingdao, China (ID: 202401). All subjects signed informed consent forms.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the Qingdao Science and Technology Demonstration Project Benefiting People (23-2-8-smjk-18-nsh) and the Qingdao Key Medical and Health Discipline Project (2025060).

Author Contribution

Conceptualization: X.L.L. , T.Q.S. , H.P.D. Data curation: H.L. , J.K.Z. , T.T. , Z.C.J. Formal analysis: X.L.L. , Y.Q.S. , H.N.C. Funding acquisition: H.P.D. Investigation: H.L. , T.Z. , H.Z. Methodology: X.L.L. , Y.Q.S. , H.P.D. Project administration: H.P.D. , H.Z. Resources: H.P.D. , T.Z. Software: X.L.L. , Y.Q.S. ,

H.N.C.Supervision: H.P.D. , H.Z.Validation: H.L. , J.K.Z. , T.T. Visualization: X.L.L. , Y.Q.S. , Z.C.J. Writing – original draft: X.L.L. , Y.Q.S. Writing – review & editing: All authors. All authors read and approved the final manuscript.

Acknowledgement

We appreciate the local Health Bureau, local Center for Disease Control and Prevention, other relevant governments and persons, investigators, and respondents for their support to this research.

Data Availability

https://pan.baidu.com/s/1LixPUdgTFrti4W5f0GnsAg (extract code is a4b5), 1LixPUdgTFrti4W5f0GnsAg.

References

1. Yamasoba T, et al. Current concepts in age-related hearing loss: epidemiology and mechanistic pathways. Hear Res. 2013;303:30–8. 10.1016/j.heares.2013.01.021.
2. Wells HRR, et al. GWAS Identifies 44 Independent Associated Genomic Loci for Self-Reported Adult Hearing Difficulty in UK Biobank. Am J Hum Genet. 2019;105:788–802. 10.1016/j.ajhg.2019.09.008.
3. Duan H, et al. Heritability of Age-Related Hearing Loss in Middle-Aged and Elderly Chinese: A Population-Based Twin Study. Ear Hear. 2019;40:253–9. 10.1097/AUD.0000000000000610.
4. Liu CQ, et al. Clinical observation on hearing conditions of centenarians in northern district of China. Acta Otolaryngol. 2015;135:451–8. 10.3109/00016489.2014.984876.
5. Heine C, Browning CJ. Communication and psychosocial consequences of sensory loss in older adults: overview and rehabilitation directions. Disabil Rehabil. 2002;24:763–73. 10.1080/09638280210129162.
6. Uchida Y, et al. Age-related hearing loss and cognitive decline - The potential mechanisms linking the two. Auris Nasus Larynx. 2019;46:1–9. 10.1016/j.anl.2018.08.010.
7. Arcangeli D, et al. Potentiometric Detection of Calcium Ions Using an Organic Electrochemical Transistor. ACS Omega. 2025;10:32202–15. 10.1021/acsomega.5c03720.
8. Liu Y et al. Key Signaling Pathways Regulate the Development and Survival of Auditory Hair Cells. Neural Plasticity. 2021, 1–12. 10.1155/2021/5522717 (2021).
9. Li Y, et al. Structural insights into calcium-dependent CIB2-TMC1 interaction in hair cell mechanotransduction. Commun Biology. 2025;8. 10.1038/s42003-025-07761-1.
10. Hu Y, Li J, Tian L, Zhang P, Zeng X. The Role of Calcium Signaling in Sensorineural Hearing Loss. Int J Med Sci. 2025;22:4063–76. 10.7150/ijms.119492.
11. Tan WJT, Song L. Role of mitochondrial dysfunction and oxidative stress in sensorineural hearing loss. Hear Res. 2023;434. 10.1016/j.heares.2023.108783.

12. Qi F, et al. Down-regulation of Cav1.3 in auditory pathway promotes age-related hearing loss by enhancing calcium-mediated oxidative stress in male mice. Aging. 2019;11(16):6490–502. 10.18632/aging.102203.
13. Lu M, et al. Upregulation of the Cav1.3 channel in inner hair cells by interleukin 6-dependent inflammaging contributes to age-related hearing loss. Aging Cell. 2024;23. 10.1111/acel.14305.
14. Song W, et al. Association between NR3C1 gene polymorphisms and age-related hearing impairment in Qingdao Chinese elderly. BMC Med Genomics. 2021;14:193. 10.1186/s12920-021-01044-4.
15. Ito T, et al. Association between BCL11B gene polymorphisms and age-related hearing loss in the elderly: A case-control study in Qingdao, China. PLoS ONE. 2024;19. 10.1371/journal.pone.0304770.
16. Zhu M, et al. Mutations in the gamma-actin gene (ACTG1) are associated with dominant progressive deafness (DFNA20/26). Am J Hum Genet. 2003;73:1082–91. 10.1086/379286.
17. Burgess S, Dudbridge F, Thompson SG. Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods. Stat Med. 2016;35:1880–906. 10.1002/sim.6835.
18. Momi SK, Wolber LE, Fabiane SM, MacGregor AJ, Williams FMK. Genetic and Environmental Factors in Age-Related Hearing Impairment. Twin Res Hum Genet. 2015;18:383–92. 10.1017/thg.2015.35.
19. Duan H et al. A Genome-Wide Association Study of Age-Related Hearing Impairment in Middle- and Old-Aged Chinese Twins. BioMed Research International. 2021, 10.1155/2021/3629624 (2021).
20. Chang C-L, Liou J. Homeostatic regulation of the PI(4,5)P 2 –Ca 2 + signaling system at ER–PM junctions. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids 1861, 862–73, 10.1016/j.bbalip.2016.02.015 (2016).
21. Nilius B, et al. Regulation of TRP channels: a voltage-lipid connection. Biochem Soc Trans. 2007;35(Pt 1):105–8. 10.1042/BST0350105.
22. Rodriguez L et al. Reduced phosphatidylinositol 4,5-bisphosphate synthesis impairs inner ear Ca2 + signaling and high-frequency hearing acquisition. Proceedings of the National Academy of Sciences 109, 14013–14018. 10.1073/pnas.1211869109 (2012).
23. Ivanova A, Atakpa-Adaji P, Phosphatidylinositol. 4,5-bisphosphate and calcium at ER-PM junctions — Complex interplay of simple messengers. Biochimica et Biophysica Acta (BBA) -. Mol Cell Res. 2023;1870. 10.1016/j.bbamcr.2023.119475.
24. Liao H-W, et al. Human DCP1 is crucial for mRNA decapping and possesses paralog-specific gene regulating functions. eLife. 2024;13. 10.7554/eLife.94811.
25. Clancy S, et al. Rac1 and Nectin3 are essential for PCP-directed axon guidance in the peripheral auditory system. bioRxiv 2024 Jun. 2024;7. 2024.06.05.597585.doi:10.1101/2024.06.05.597585.
26. Takumida M, Ishibashi T, Hamamoto T, Hirakawa K, Anniko M. Expression of transient receptor potential channel melastin (TRPM) 1–8 and TRPA1 (ankyrin) in mouse inner ear. Acta Otolaryngol. 2009;129:1050–60. 10.1080/00016480802570545.

27. Ren J, et al. Association between Ca2 + Signaling Pathway-Related Gene Polymorphism and Age-Related Hearing Loss in Qingdao Chinese Elderly. Russian J Genet. 2022;58:1266–72. 10.1134/s1022795422100076.
28. Han S-Y, Seo HW, Lee SH, Chung JH. Revisiting Age-Related Normative Hearing Levels in Korea. J Korean Med Sci. 2025;40. 10.3346/jkms.2025.40.e3.
29. Palmer TM, et al. Using multiple genetic variants as instrumental variables for modifiable risk factors. Stat Methods Med Res. 2011;21:223–42. 10.1177/0962280210394459.
30. Burgess S, Thompson SG. Use of allele scores as instrumental variables for Mendelian randomization. Int J Epidemiol. 2013;42:1134–44. 10.1093/ije/dyt093.
31. Hong H, Trussell LO. Noise-Induced Hearing Loss Enhances Ca2+-Dependent Electrical Activity in Lateral Cochlear Efferents. J Neurosci. 2025;45. 10.1523/jneurosci.0850-25.2025.
32. Recio-Spinoso A. The impulse response of the organ of Corti at the apex of the intact cochlea. Sci Rep. 2025;15. 10.1038/s41598-025-21860-3.

Figures

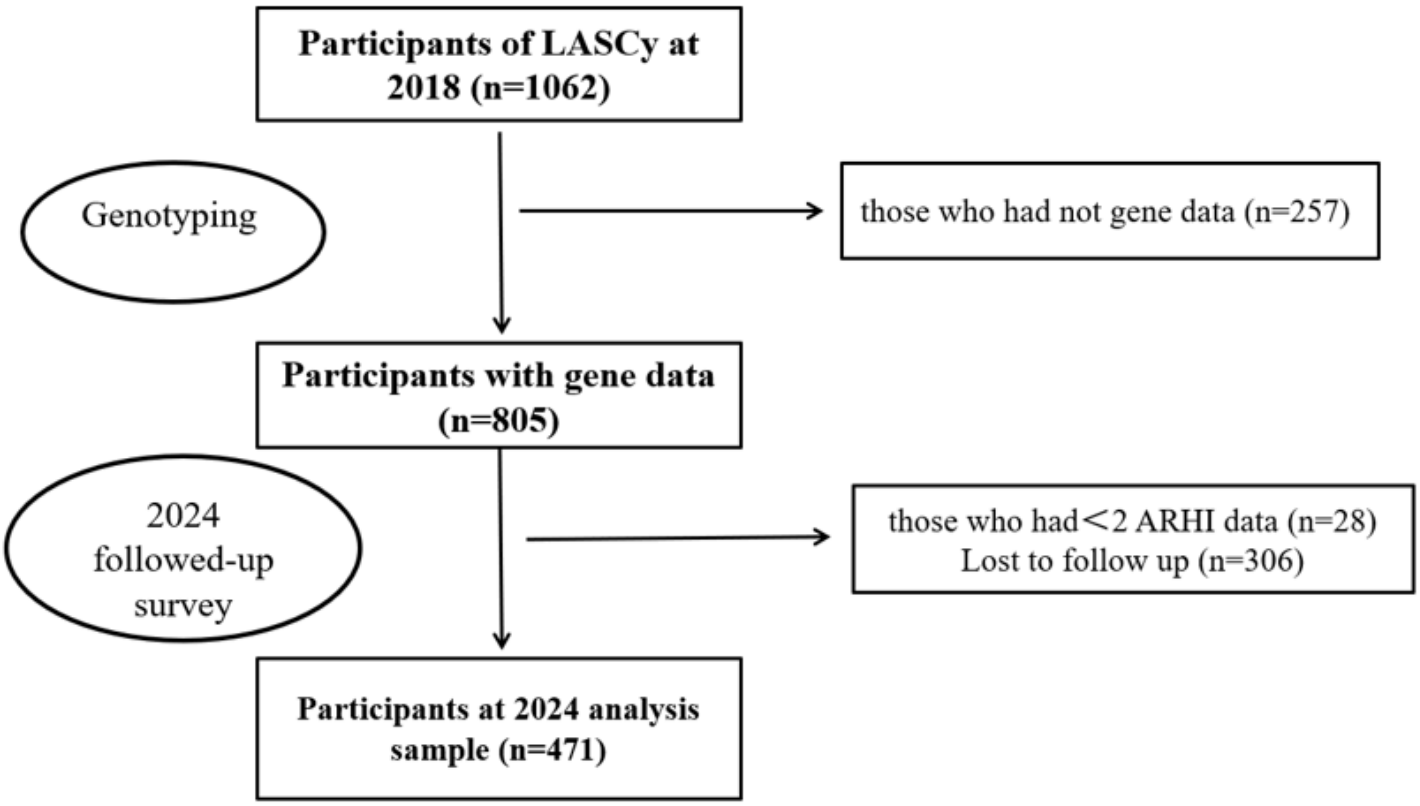

Figure 1. The flow diagram of study participants.

Figure 1

See image above for figure legend

Variable	β (95%CI)	P value	P for interaction
Age			0.011*
< 70	-0.048(-0.082,-0.015)	0.005	
≥ 70	-0.130(-0.194,-0.066)	<0.001	
Sex			0.491
Male	-0.053(-0.096,-0.010)	0.016	
Female	-0.084(-0.126,-0.042)	<0.001	
hypertension			0.37
Yes	-0.066(-0.114,-0.018)	0.007	
No	-0.090(-0.128,-0.052)	<0.001	
diabetes			0.052
Yes	0.002(-0.077,0.082)	0.955	
No	-0.089(-0.122,-0.056)	<0.001	
overall	-0.074(-0.106,-0.046)	<0.001	

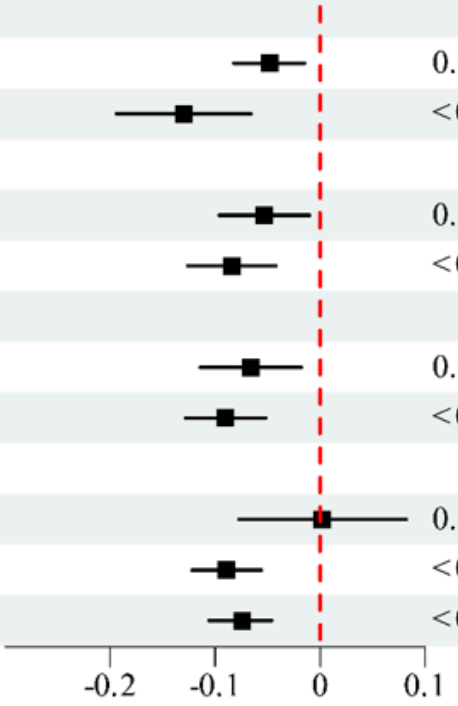

Figure 2. Subgroup analysis of linear regression results between PRS and PTA changes

Note: *P < 0.05, Model was adjusted for age, gender, education, hypertension, diabetes, smoking, and drinking.

Figure 2

See image above for figure legend

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementalmaterial.docx