

Epigenetic Age Acceleration and Hearing Function in US Older Adults

Jessica S. West,^{1,2,3} Qinyi Chen,⁴ Sherri L. Smith,^{1,2,5} Jianxin Bao,¹ Fei Zou,^{6,7} Yi-Ju Li,^{8,9} and Rong Jiang^{1,10}

Objectives: Hearing loss is a prevalent condition in older adults. Epigenetic age acceleration has emerged as a potential biomarker for age-related diseases; however, there is limited evidence of the link between epigenetic age acceleration and hearing loss in older adults or how it varies by sex. This study is to investigate (1) the association between epigenetic age acceleration and hearing function and (2) sex differences in this association.

Design: Data from the Health and Retirement Study, a large, nationally representative sample of adults aged 50 yrs and older, were analyzed. The study included 1755 adults from the 2016 sample with epigenetic data. Epigenetic age acceleration included five epigenetic clocks: Horvath's age acceleration (HorvathAA), Hannum's age acceleration (HannumAA), phenotypic age acceleration (PhenoAA), GrimAge acceleration (GrimAA), and methylation-based pace of aging estimate (DunedinPoAm). Multivariable regression models assessed the association between epigenetic age acceleration and mean hearing test score (linear) and hearing loss (logistic).

Results: The mean chronological age of 68.4 (SD = 9.4) was higher than the mean epigenetic age ranging from 53.9 (SD = 8.9) for HannumAge to 67.1 (SD = 8.6) for GrimAge. Overall, 58.4% of participants had hearing loss, with a mean hearing test score of 4.6 (1.4). Phenotypic age acceleration, GrimAA, and methylation-based pace of aging estimate were significantly associated with lower hearing test scores (β [95% confidence interval {CI}] = -0.081 [-0.15 to -0.01]; -0.150 [-0.22 to -0.08]; -0.089 [-0.16 to -0.02], respectively). These associations remained significant in females, while only GrimAA was still significant in males. GrimAA was associated with higher odds of hearing loss (odds ratio [95% CI] = 1.23 [1.05 to 1.44]), and remained significant in females (1.47 [1.18 to 1.83]), but not in males.

Conclusions: This study highlights the potential of epigenetic age acceleration as a biomarker for hearing loss in older adults and underscores the importance of sex differences in aging research. Findings suggest further research is needed to explore epigenetic mechanisms as potential targets for interventions to mitigate hearing loss in older adults, particularly among females.

Key words: Epigenetic age acceleration, Epigenetic clocks, Health and Retirement Study, Hearing loss.

Abbreviations: AA = age acceleration; CI = confidence interval; DunedinPoAm = methylation-based pace of aging estimate; GrimAA = GrimAge acceleration; HannumAA = Hannum's age acceleration; HL = hearing loss; HorvathAA = Horvath's age acceleration; HRS = Health and Retirement Study; OR = odds ratio; PhenoAA = phenotypic age acceleration.

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INTRODUCTION

Hearing loss is a common health problem in US adults (Whitson et al. 2018), making it a significant public health concern as the US population of older adults increases (Administration on Aging 2024). Hearing loss occurs when any component of the auditory (hearing) system functions improperly, resulting in the partial or complete inability to perceive sounds in one or both ears (West et al. 2021). The prevalence of hearing loss increases with age: 8.5% of adults aged 55 to 64 yrs, 25% of those aged 65 to 74 yrs, and 50% of those aged 75 yrs and older (Goman & Lin 2016; Cunningham & Tucci 2017). The prevalence increases among the oldest old to 81.4% for those aged 80 yrs or older (Lin et al. 2011; Sharma et al. 2020) and 93.8% for those aged 90 yrs or older (Sharma et al. 2020).

Hearing loss is a complex condition with both environmental and genetic factors likely playing a role in its development (Viljanen et al. 2007; Wolber et al. 2012). Twin studies estimate that genetic factors could account for 40 to 70% of the onset of hearing loss among individuals with similar lifestyles (Momi et al. 2015). This variability may arise because, although age is widely recognized as the strongest risk factor for a variety of chronic diseases, including hearing loss, people vary dramatically in their speed of aging (Wang & Puel 2020; Ong et al. 2022). Thus, individuals with the same chronological age may vary in declines of their functional abilities (Ryan 2021), leading to the development of the term "biological age" to explain the difference between decline in functional capacity that is separate from chronological age (Levine et al. 2018).

The variability in human aging complicates the identification of potential predictive markers for the development of hearing loss that could guide prevention or intervention strategies to slow physiological dysfunction (Wang et al. 2023). Research increasingly shows that age-related chronic diseases share underlying biological mechanisms (Ferrucci et al. 2018). One such mechanism is DNA methylation, a process that involves DNA modifications that do not alter the primary nucleotide sequence and that contribute to age-related physiological

¹Department of Head and Neck Surgery & Communication Sciences, Duke University School of Medicine, Durham, North Carolina, USA; ²Center for Study of Aging and Human Development, Duke University School of Medicine, Durham, North Carolina, USA; ³Duke University Population Research Institute, Duke University, Durham, North Carolina, USA; ⁴Division of Social Sciences, Duke Kunshan University, Kunshan, China; ⁵Department of Population Health Sciences, Duke University, Durham, North Carolina, USA; ⁶Department of Biostatistics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; ⁷Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; ⁸Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina, USA; ⁹Duke Molecular Physiology Institute, Duke University School of Medicine, Durham, North Carolina, USA; and ¹⁰Duke Cancer Institute, Durham, North Carolina, USA.

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deterioration (Hannum et al. 2013; Horvath 2013; Oblak et al. 2021; An et al. 2025; Moubadder et al. 2025). Epigenetic ages have been developed to assess the speed of aging by measuring these epigenetic changes as they unfold predictably over time and providing an estimate of biological age (Ryan 2021; An et al. 2025).

Techniques to estimate epigenetic ages have evolved through three generations, each enhancing the accuracy, generalizability, and biological relevance of DNA methylation-based age prediction, and are widely used in aging and disease research (Margiotti et al. 2023). The first generation of epigenetic panels, HorvathAge (Horvath 2013) and HannumAge (Hannum et al. 2013), were developed using a machine learning algorithm trained to predict chronological age. Second-generation epigenetic panels, PhenoAge (Levine et al. 2018) and GrimAge (Lu et al. 2019), incorporated additional health and mortality-related markers. While the first- and second-generation epigenetic panels assess biological age in years, the latest generation assesses the Pace-of-Aging (DunedinPoAm) (Belsky et al. 2020), which measures the rate of aging using longitudinal change in 18 biomarkers capturing biological aging over time. Epigenetic age acceleration (AA) for first- and second-generation panels can be estimated either as the difference between an individual's epigenetic and chronological ages (Ryan 2021), or as the residual from a regression model predicting epigenetic age from chronological age (Hannum et al. 2013; Chen et al. 2016; Ryan 2021). Epigenetic AA represents the relative difference between chronological and epigenetic age, where positive values indicate faster biological aging and negative values indicate slower biological aging.

Epigenetic AA has been shown to be predictive of mortality and many age-associated diseases. Epigenetic panels can accurately predict all-cause mortality (even after controlling for mortality-associated risk factors) (Chen et al. 2016), cancer, cardiovascular disease, frailty, and cognitive decline (Marioni et al. 2015; Breitling et al. 2016; Zheng et al. 2016; Jiang et al. 2022). Epigenetic research in the hearing sciences has been limited, but there is emerging evidence of the relevance of epigenetic mechanisms for hearing loss (Walters & Cox 2019; Leso et al. 2020; Kuo et al. 2021; Nwanaji-Enwerem et al. 2025; Wang et al. 2025). Using the Baltimore Longitudinal Study of Aging, Kuo et al. (2021) found that two epigenetic AAs, Lu's GrimAge acceleration (GrimAA) (Lu et al. 2019) and Belsky's methylation-based pace of aging estimate (DunedinPoAm) (Belsky et al. 2020), had a positive and statistically significant association with audiometrically defined hearing. In contrast, Hannum's age acceleration (HannumAA) (Hannum et al. 2013), Horvath's age acceleration (HorvathAA) (Horvath 2013), and Levine's aggregate measure of phenotypic age acceleration (PhenoAA) (Levine et al. 2018) were not associated with hearing. While informative, Kuo et al. (2021) study is limited by a small sample ($n = 236$) of participants from a cohort who tend to be healthier than the general population and because the hearing and DNA methylation data were not collected in the same wave.

In the context of hearing loss, gender/sex differences exist that may contribute to differences in epigenetic AA. Men have a higher prevalence of hearing loss compared with women in the US (West & Lynch 2021), which may reflect cultural and social norms around gender leading to differential exposure to risk factors for hearing loss (Campos-Serna et al. 2013;

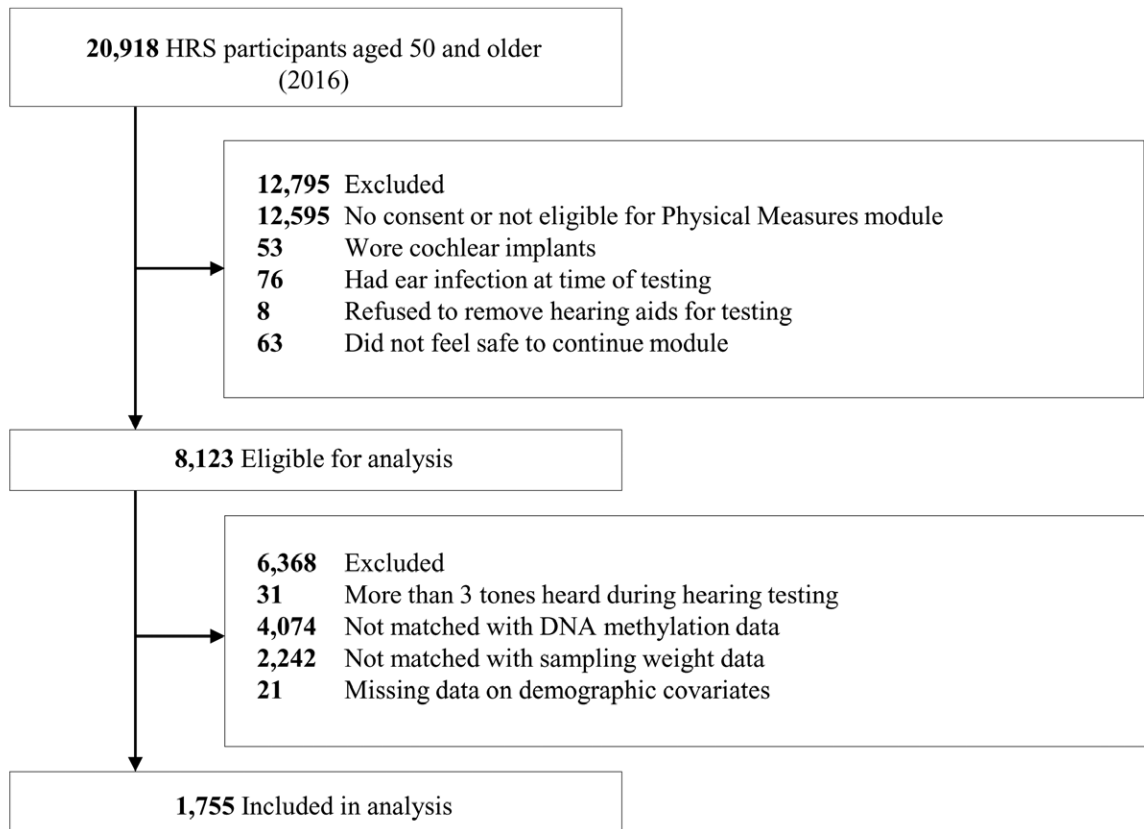
Reavis et al. 2023), as men are more likely than women to be employed in jobs at high risk for noise exposure (Lie et al. 2016; Themann & Masterson 2019). Alternatively, this pattern may be due to biological factors: there is evidence of slight sex differences in ear electrophysiology which may make the male ear more sensitive to aging (Nolan 2020), while estrogen and its signaling pathways may be protective against hearing loss in females (Shuster et al. 2019; Reavis et al. 2023). Male sex is also a risk factor for increased epigenetic aging (Oblak et al. 2021)—higher male epigenetic aging is evidenced by age 50, but average rates of epigenetic age change do not differ by sex after age 50 (Li et al. 2020). It is possible that menopause increases epigenetic age such that while men experience a faster pace of aging before age 50, female aging increases in pace after menopause (Levine et al. 2018).

The current study aimed to investigate (1) the association between epigenetic AA and hearing function and (2) sex differences in this association using a large, nationally representative sample of adults aged 50 yrs and older from the Health and Retirement Study (HRS). Identifying the potential biological mechanisms or predictive aging markers that would explain the development of hearing loss in older adults could help lead to advancements in interventions to mitigate, delay, or prevent the onset of hearing loss in older adults.

MATERIALS AND METHODS

Data Source

Data come from the HRS, a longitudinal, nationally representative survey of US adults over the age of 50 yrs (Juster & Suzman 1995). The HRS is sponsored by the National Institute on Aging (grant number U01AG009740) and has been documented extensively elsewhere (Juster & Suzman 1995; Sonnega et al. 2014; RAND 2021). Objective hearing measures were collected in the Physical Measures module of Wave 13 (2016), so the current study is restricted to this wave. Our analysis begins with 20,918 participants who were alive/not missing and aged 50 yrs of age and older in 2016. We restricted the sample to participants who signed the Physical Measures module consent form ($n = 8325$) and were eligible to participate in this module ($n = 8323$). Participants were ineligible for the hearing screening if they wore cochlear implants ($n = 53$), had an ear infection at the time of testing ($n = 76$), refused to remove their hearing aids for the test ($n = 8$), or did not feel safe continuing the module ($n = 63$). Participants were excluded if they reported more than 3 tones per ear ($n = 31$). This dataset of 8092 participants was merged with the 2016 HRS Venous Blood Study, which is an epigenetic clock database containing 13 epigenetic clocks developed from DNA methylation data ($n = 4018$). The 2 merged datasets resulted in a sample of 1840 participants with both hearing and epigenetic clock data. The database containing sampling weight variables for epigenetic clocks was merged in (resulting $n = 1776$). After listwise exclusion of missing data among the covariates ($n = 21$), the final sample used for the current study is comprised of 1755 participants (Fig. 1). Given the low proportion (<5%) of missing sampling weights and covariates, we excluded these participants from the final analysis, as the small amount of missing data was unlikely to bias the results. The study was approved by the local institutional review board.



Note: HRS, Health and Retirement Study.

Fig. 1. Study cohort inclusion criteria, HRS, 2016. HRS indicates Health and Retirement Study.

DNA Methylation and Epigenetic AA

DNA methylation assays were performed using the Infinium Methylation EPIC BeadChip on the 2016 Venous Blood Study participants ($n = 4104$) (Crimmins et al. 2020). Samples were randomized across testing plates by key demographic characteristics including age, HRS cohort, sex, education, and race/ethnicity. Data preprocessing and quality control were performed using the *minfi* package in R. Probes with a detection $p > 0.01$ were removed. Samples with more than 5% missing data or mismatched sex were excluded, resulting in a final sample of 4018 participants. Before the epigenetic clock estimation, missing beta methylation values were imputed to the mean value of the given probe for all samples.

All epigenetic ages were computed using DNA methylation data based on each biological age algorithm. HorvathAA (Horvath 2013), HannumAA (Hannum et al. 2013), PhenoAA (Levine et al. 2018), GrimAA (Lu et al. 2019), and DunedinPoAm (Belsky et al. 2020) were evaluated in the current study. All measures of epigenetic AA, except for DunedinPoAm, were estimated as residuals from regressing each epigenetic age on the individual's chronological age. A 1-unit increase reflects a biologically 1-yr older than chronological age, whereas a 1-unit decrease indicates a 1-yr deceleration in biological aging. Each unit of DunedinPoAm represents the rate of biological aging, with 1 unit indicating 1 yr of biological aging per year of chronological aging.

Hearing Function

Hearing function was measured using the HearCheck Screener (Siemens Audiologische Technik GmbH 2007), a handheld hearing screening device that produces a fixed series of 6 pure tones per ear: 3 decreasing intensity levels (55, 35, and 20 dB HL) at 1000 Hz followed by 3 decreasing intensity levels (75, 55, and 35 dB HL) at 3000 Hz. The screening test was administered to each ear separately, and participants raised a finger to indicate when they heard a tone. For each ear, a score was created by summing the number of tones heard in the 1000 Hz test (range 0 to 3) and 3000 Hz test (range 0 to 3) for a total number of tones heard per ear (range 0 to 6). Higher scores indicate better hearing. We calculated two measures of hearing function following previous research (Ray et al. 2018; Stephan et al. 2022): (1) overall hearing test score mean (continuous) as the average of scores for both ears (similar to Kuo et al. (2021) for comparison of findings), and (2) hearing loss, defined as hearing fewer than six tones in the better hearing ear (no hearing loss [reference] or has some degree of pure-tone hearing loss).

Covariates

Covariates included chronological age, sex, race/ethnicity, cardiovascular risk score, and smoking history. Race and ethnicity were assessed using two self-reported measures: (1) do you consider yourself Hispanic or Latino (no/yes), and (2) what race do you consider yourself to be: White, Black or

TABLE 1. Characteristics of the overall sample and by sex, 2016 Health and Retirement Study (n = 1755)*

| Characteristics | Overall | Male | Female | p Value† |
|--|---------------|--------------|---------------|----------|
| | (n = 1755) | (n = 748) | (n = 1007) | |
| Age (yrs, mean, SD) | 68.4 (9.4) | 67.7 (8.8) | 68.9 (9.7) | 0.074 |
| Hearing Test scores (mean, SD) | 4.6 (1.4) | 4.4 (1.4) | 4.7 (1.3) | 0.001 |
| Hearing loss | | | | 0.051 |
| Yes | 1101 (58.4) | 508 (61.9) | 593 (55.5) | |
| No | 654 (41.6) | 240 (38.2) | 414 (44.5) | |
| Epigenetic age (yrs, mean, SD): | | | | |
| HorvathAge | 65.04 (9.41) | 64.96 (8.85) | 65.10 (9.87) | 0.839 |
| HannumAge | 53.89 (8.91) | 54.39 (8.56) | 53.48 (9.19) | 0.178 |
| PhenoAge | 56.53 (10.05) | 56.86 (9.44) | 56.25 (10.54) | 0.433 |
| GrimAge | 67.09 (8.56) | 68.41 (8.29) | 65.96 (8.63) | <0.001 |
| Epigenetic age acceleration (mean, SD) | | | | |
| HorvathAA | 0.07 (6.32) | 0.47 (5.90) | −0.27 (6.64) | 0.091 |
| HannumAA | 0.18 (5.15) | 1.19 (4.97) | −0.68 (5.14) | <0.001 |
| PhenoAA | −0.01 (7.04) | 0.84 (6.78) | −0.72 (7.19) | 0.002 |
| GrimAA | −0.27 (4.81) | 1.56 (4.79) | −1.82 (4.27) | <0.001 |
| DunedinPoAm | 1.07 (0.09) | 1.08 (0.09) | 1.06 (0.09) | <0.001 |
| Race and ethnicity (n, %) | | | | 0.766 |
| Non-Hispanic White | 1167 (77.8) | 507 (79.0) | 660 (76.8) | |
| Non-Hispanic Black | 287 (10.3) | 105 (9.8) | 182 (10.8) | |
| Non-Hispanic other | 49 (3.1) | 21 (3.1) | 28 (3.2) | |
| Hispanic | 252 (8.7) | 115 (8.1) | 137 (9.2) | |
| Tobacco use (n, %) | | | | <0.001 |
| Never smoker | 770 (44.4) | 254 (36.4) | 516 (50.2) | |
| Ever smoker | 985 (55.6) | 494 (63.6) | 491 (48.8) | |
| Cardiovascular Risk Score (mean, SD)‡ | 1.2 (1.0) | 1.3 (1.0) | 1.1 (1.0) | 0.024 |

*Unless indicated otherwise, values are presented as the unweighted number (weighted %) or weighted means (weighted SD) of participants.

†p Value column indicates differences between males and females (χ^2 tests for differences in proportions, t tests for differences in means).

‡The composite cardiovascular risk score comprises self-reported doctor's diagnoses of high blood pressure, diabetes, heart disease, and stroke.

DunedinPoAm, methylation-based pace of aging estimate; GrimAA, GrimAge acceleration; HannumAA, Hannum's age acceleration; HorvathAA, Horvath's age acceleration; PhenoAA, phenotypic age acceleration.

African American, American Indian, Alaska Native, Asian, Native Hawaiian, Pacific Islander, or something else? Due to small sample sizes, the HRS combines American Indian, Alaska Native, Asian, Native Hawaiian, or Pacific Islander participants into an “other” category to protect participant confidentiality. We classified participants as non-Hispanic White [reference] participants, non-Hispanic Black/African American participants, non-Hispanic other race participants, or Hispanic participants. To account for potential confounding by cardiovascular diseases, a composite cardiovascular risk score was created by assigning one point for each self-reported doctor-diagnosed condition—high blood pressure, diabetes, heart disease, or stroke—and then summing the total score (range 0 to 4). Self-reported smoking history was dichotomized as never smoker or ever smoker (current or past smoker).

Statistical Analysis

The overall distributions of study variables were assessed for the entire sample and by sex. Chi-square tests examined differences in proportions, and t tests examined differences in means. Logistic regression models were performed to examine the association between epigenetic AA (independent variable) and hearing loss (dependent variable), adjusting for chronological age, sex, and race/ethnicity (Model 1), composite cardiovascular risk score (Model 2), and smoking history (Model 3). The odds of hearing loss as a function of epigenetic AA were estimated. Linear regression models were conducted to assess the epigenetic AA and overall hearing test score mean, similar to the approach by Kuo et al.

(2021). The linear regression models were adjusted for covariates in a similar approach to the logistic regression analysis.

We also conducted sex-stratified analyses by running Models 1 to 3 separately for males and females to assess whether the observed associations differ by sex. All standardized estimates were reported with 95% confidence interval (CI). The analysis was conducted using the *survey* package in R 4.3.2 to account for sampling weights.

RESULTS

Table 1 presents the distributions of the study variables for the entire sample and by sex (unweighted number [weighted percent] or weighted mean [weighted SD]). The sample is predominantly comprised of non-Hispanic White (77.8%) and female (54.2%) participants with a smoking history (55.6%), and most participants had hearing loss (58.4%). The mean chronological age (SD) was 68.4 (9.4) yrs, higher than the mean epigenetic ages: HorvathAge (65.04 [9.41]), HannumAge (53.89 [8.91]), PhenoAge (56.53 [10.05]), and GrimAge (67.09 [8.56]). This pattern is consistent with previous research (Kuo et al. 2021). The mean pace of aging estimated by DNA methylation (DunedinPoAm) was 1.07 (0.09).

Females had better hearing test scores (4.7 [1.3]) compared with males (4.4 [1.4]; $p = .001$). Females had a younger GrimAge (65.96 [8.63]) than males (68.41 [8.29]; $p < 0.001$). Compared with males, females exhibited lower epigenetic AA across multiple measures including HannumAA (mean [SD]: −0.68 [5.14] versus 1.19 [4.97]; $p < 0.001$), GrimAA (−1.82 [4.27] versus

1.56 [4.79]; $p < 0.001$), and PhenoAA (-0.72 [7.19] versus 0.84 [6.78]; $p = 0.002$). In contrast, DunedinPoAm was slightly lower in females (1.06 [0.09]) compared with in males (1.08 [0.09]; $p < 0.001$). Males were more likely to have a positive smoking history (63.6%) compared with females (48.8%; $p < 0.001$) and had higher composite cardiovascular risk scores (1.3 [1.0]) than females (1.1 [1.0]; $p = 0.024$).

To compare with Kuo et al.'s study (2021), linear regression models were performed to test the association between epigenetic AA measures and overall hearing test mean scores from the HearCheck Screener (Table 2 and Fig. 2A). We reported the association as the change in hearing test score per 1 SD increase in epigenetic AA. Across all three models, PhenoAA, GrimAA, and DunedinPoAm were each negatively associated with hearing test scores, indicating that these measures of epigenetic AA are associated with poorer hearing. In the fully adjusted models (Table 2, Model 3, and Fig. 2A), PhenoAA was associated with -0.081 (95% CI = -0.15 to -0.01 ; $p = 0.018$) lower mean hearing scores, GrimAA with -0.150 (95% CI = -0.22 to -0.08 ; $p < 0.001$) lower scores, and DunedinPoAm with -0.089 (95% CI = -0.16 to -0.02 ; $p = 0.009$) lower scores.

Table 2 and Figure 2A also present results from the sex-stratified linear regression analyses. Among females, four measures of epigenetic AA were associated with lower mean hearing test scores. Similar to the nonstratified Model 3, PhenoAA ($\beta = -0.093$, 95% CI = -0.17 to -0.01 ; $p = 0.025$), GrimAA ($\beta = -0.173$, 95% CI = -0.27 to -0.08 ; $p < 0.001$), and DunedinPoAm ($\beta = -0.107$, 95% CI = -0.19 to -0.03 ; $p = 0.012$) were all significantly associated with lower mean hearing scores (Model 3) for females. In addition, HannumAA was associated with -0.101 (95% CI = -0.18 to -0.02 ; $p = 0.017$) lower scores. Among males, GrimAA was significantly associated with ($\beta = -0.167$, 95% CI = -0.28 to -0.06 ; $p = 0.004$) lower mean hearing scores in Model 1 and remained significant with the addition of the composite cardiovascular risk score (β

= -0.145 , 95% CI = -0.25 to -0.04 ; $p = 0.010$) in Model 2 and smoking history ($\beta = -0.131$, 95% CI = -0.25 to -0.01 ; $p = 0.036$) in Model 3. The other epigenetic AA measures were not associated with hearing test scores in the fully adjusted model.

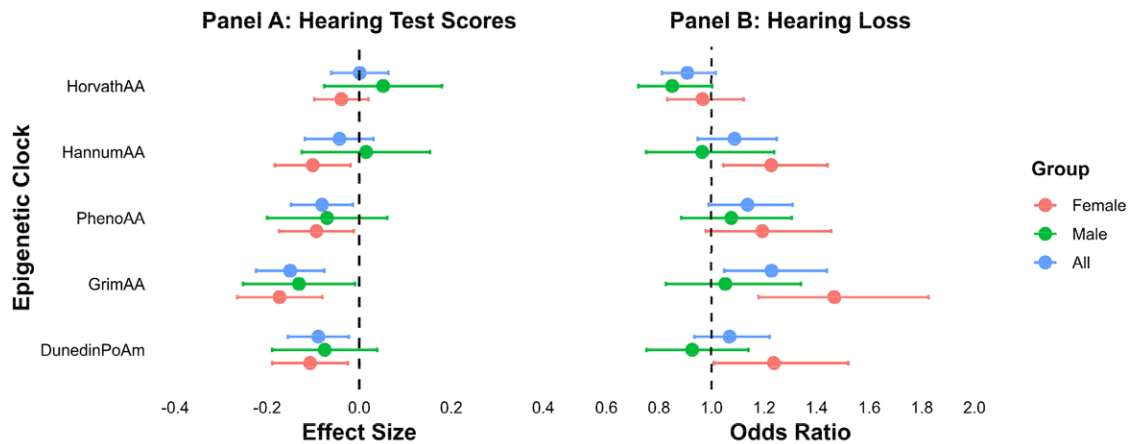
Logistic regression models investigated the association between epigenetic AA and the binary hearing loss measure (odds ratio [OR] [95% CI]) (Table 3 and Fig. 2B). Note that the binary hearing loss measure was defined as failing at least one of the tones on the HearCheck Screener. In Model 1, GrimAA was significantly associated with 1.28 times higher odds of hearing loss (OR = 1.28, 95% CI = 1.10 to 1.48; $p = 0.002$). This association remained significant after adjusting for the composite cardiovascular risk score in Model 2 (OR = 1.25, 95% CI = 1.08 to 1.45; $p = 0.003$) and smoking history in Model 3 (OR = 1.23, 95% CI = 1.05 to 1.44; $p = 0.012$). PhenoAA was significantly associated with 1.16 (95% CI = 1.01 to 1.33; $p = 0.034$) higher odds of hearing loss in Model 1, but became nonsignificant after controlling for the composite cardiovascular risk score in Model 2 (OR = 1.14, 95% CI = 0.99 to 1.31; $p = 0.062$) and remained nonsignificant after including smoking history in Model 3 (OR = 1.14, 95% CI = 0.99 to 1.31; $p = 0.067$).

In the sex-stratified analysis, PhenoAA was no longer significantly associated with hearing loss either in males or females (Table 3, Models 1 to 3, and Fig. 2B), while GrimAA remained significantly associated with hearing loss only among females (Table 3, Models 1 to 3, and Fig. 2B), with a direction and magnitude consistent with the full sample. In males, HorvathAA was associated with a lower odds of hearing loss (OR = 0.85, 95% CI = 0.72 to 1.00; $p = 0.046$) in Model 1, but did not remain significant after controlling for the composite cardiovascular risk score or smoking history. In females, in addition to GrimAA, two epigenetic AA measures were associated with an increased odds of hearing loss. HannumAA was significantly associated with 1.23 times higher odds of hearing loss (95% CI = 1.04 to 1.46; $p = 0.016$) (Model 1), which persisted after the addition of the composite cardiovascular risk score (OR = 1.23, 95% CI = 1.05 to

TABLE 2. Linear regression estimates of association between epigenetic age acceleration measures and hearing function, 2016 Health and Retirement Study (n = 1755)

| Epigenetic Measurement | Model 1 | | | Model 2 | | | Model 3 | | |
|------------------------|----------|----------------|------------------|----------|----------------|------------------|----------|----------------|------------------|
| | Estimate | 95% CI | p Value | Estimate | 95% CI | p Value | Estimate | 95% CI | p Value |
| HorvathAA | -0.003 | -0.07 to 0.06 | 0.926 | -0.001 | -0.06 to 0.06 | 0.979 | 0.001 | -0.06 to 0.06 | 0.974 |
| HannumAA | -0.054 | -0.13 to 0.02 | 0.164 | -0.043 | -0.12 to 0.03 | 0.251 | -0.043 | -0.12 to 0.03 | 0.249 |
| PhenoAA | -0.094 | -0.16 to -0.03 | 0.006 | -0.081 | -0.15 to -0.01 | 0.018 | -0.081 | -0.15 to -0.01 | 0.018 |
| GrimAA | -0.166 | -0.23 to -0.10 | <0.001 | -0.150 | -0.22 to -0.08 | <0.001 | -0.150 | -0.22 to -0.08 | <0.001 |
| DunedinPoAm | -0.107 | -0.17 to -0.05 | 0.001 | -0.095 | -0.16 to -0.03 | 0.004 | -0.089 | -0.16 to -0.02 | 0.009 |
| Male | | | | | | | | | |
| HorvathAA | 0.054 | -0.07 to 0.18 | 0.389 | 0.052 | -0.08 to 0.18 | 0.415 | 0.052 | -0.08 to 0.18 | 0.420 |
| HannumAA | 0.011 | -0.13 to 0.15 | 0.871 | 0.017 | -0.12 to 0.16 | 0.807 | 0.015 | -0.13 to 0.15 | 0.834 |
| PhenoAA | -0.086 | -0.22 to 0.04 | 0.186 | -0.073 | -0.20 to 0.06 | 0.264 | -0.070 | -0.20 to 0.06 | 0.287 |
| GrimAA | -0.167 | -0.28 to -0.06 | 0.004 | -0.145 | -0.25 to -0.04 | 0.010 | -0.131 | -0.25 to -0.01 | 0.036 |
| DunedinPoAm | -0.110 | -0.22 to -0.00 | 0.042 | -0.089 | -0.19 to 0.02 | 0.095 | -0.075 | -0.19 to 0.04 | 0.191 |
| Female | | | | | | | | | |
| HorvathAA | -0.042 | -0.10 to 0.02 | 0.160 | -0.040 | -0.10 to 0.02 | 0.192 | -0.039 | -0.10 to 0.02 | 0.193 |
| HannumAA | -0.109 | -0.19 to -0.02 | 0.013 | -0.101 | -0.18 to -0.02 | 0.017 | -0.101 | -0.18 to -0.02 | 0.017 |
| PhenoAA | -0.101 | -0.18 to -0.03 | 0.009 | -0.093 | -0.17 to -0.01 | 0.027 | -0.093 | -0.17 to -0.01 | 0.025 |
| GrimAA | -0.167 | -0.25 to -0.09 | <0.001 | -0.158 | -0.24 to -0.07 | <0.001 | -0.173 | -0.27 to -0.08 | <0.001 |
| DunedinPoAm | -0.109 | -0.20 to -0.03 | 0.008 | -0.103 | -0.19 to -0.02 | 0.015 | -0.107 | -0.19 to -0.03 | 0.012 |

Linear regression models were used to calculate the association between epigenetic age acceleration and hearing test scores (continuous). Bold values indicate $p < 0.05$. Model 1: Adjusted for chronological age, sex, and race/ethnicity. Model 2: Adjusted for chronological age, sex, race/ethnicity, and composite cardiovascular risk score. Model 3: Adjusted for chronological age, sex, race/ethnicity, composite cardiovascular risk score, and smoking history. Sex stratification: Models 1–3 stratified by sex. CI, confidence interval; DunedinPoAm, methylation-based pace of aging estimate; GrimAA, GrimAge acceleration; HannumAA, Hannum's age acceleration; HorvathAA, Horvath's age acceleration; PhenoAA, phenotypic age acceleration.



Note: Results for Panel A are based on Table 2, Model 3. Results for Panel B are based on Table 3, Model 3.

Fig. 2. Effect sizes of epigenetic age acceleration measures on hearing test scores (A) and hearing loss (B). DunedinPoAm indicates methylation-based pace of aging estimate, HannumAA, Hannum's age acceleration; HorvathAA, Horvath's age acceleration; GrimAA, GrimAge acceleration; PhenoAA, phenotypic age acceleration.

TABLE 3. Logistic regression estimates of association between epigenetic age acceleration measures and hearing loss, 2016 Health and Retirement Study (n = 1755)

| Epigenetic Measurement | Model 1 | | | Model 2 | | | Model 3 | | |
|------------------------|---------|-----------|--------------|---------|-----------|--------------|---------|-----------|--------------|
| | OR | 95% CI | p Value | OR | 95% CI | p Value | OR | 95% CI | p Value |
| HorvathAA | 0.92 | 0.82–1.03 | 0.128 | 0.91 | 0.82–1.02 | 0.115 | 0.91 | 0.81–1.02 | 0.090 |
| HannumAA | 1.10 | 0.96–1.27 | 0.165 | 1.09 | 0.95–1.25 | 0.220 | 1.09 | 0.95–1.25 | 0.219 |
| PhenoAA | 1.16 | 1.01–1.33 | 0.034 | 1.14 | 0.99–1.31 | 0.062 | 1.14 | 0.99–1.31 | 0.067 |
| GrimAA | 1.28 | 1.10–1.48 | 0.002 | 1.25 | 1.08–1.45 | 0.003 | 1.23 | 1.05–1.44 | 0.012 |
| DunedinPoAm | 1.11 | 0.97–1.28 | 0.120 | 1.10 | 0.96–1.25 | 0.179 | 1.07 | 0.94–1.22 | 0.323 |
| Male | | | | | | | | | |
| HorvathAA | 0.85 | 0.72–1.00 | 0.046 | 0.85 | 0.72–1.00 | 0.055 | 0.85 | 0.72–1.00 | 0.056 |
| HannumAA | 0.96 | 0.76–1.23 | 0.758 | 0.96 | 0.75–1.22 | 0.719 | 0.97 | 0.75–1.24 | 0.783 |
| PhenoAA | 1.11 | 0.91–1.36 | 0.297 | 1.09 | 0.90–1.32 | 0.369 | 1.08 | 0.89–1.31 | 0.449 |
| GrimAA | 1.19 | 0.95–1.48 | 0.121 | 1.15 | 0.93–1.42 | 0.192 | 1.05 | 0.83–1.34 | 0.661 |
| DunedinPoAm | 1.03 | 0.85–1.24 | 0.768 | 0.99 | 0.83–1.19 | 0.934 | 0.93 | 0.75–1.14 | 0.474 |
| Female | | | | | | | | | |
| HorvathAA | 0.97 | 0.83–1.13 | 0.659 | 0.96 | 0.83–1.12 | 0.635 | 0.97 | 0.83–1.12 | 0.652 |
| HannumAA | 1.23 | 1.04–1.46 | 0.016 | 1.23 | 1.05–1.44 | 0.014 | 1.23 | 1.05–1.44 | 0.013 |
| PhenoAA | 1.20 | 0.99–1.45 | 0.066 | 1.20 | 0.98–1.46 | 0.076 | 1.20 | 0.98–1.46 | 0.077 |
| GrimAA | 1.38 | 1.12–1.70 | 0.003 | 1.38 | 1.12–1.71 | 0.003 | 1.47 | 1.18–1.83 | 0.001 |
| DunedinPoAm | 1.21 | 0.98–1.50 | 0.070 | 1.21 | 0.98–1.49 | 0.075 | 1.24 | 1.01–1.52 | 0.042 |

Logistic regression models were used to calculate the association between epigenetic age acceleration and hearing loss (binary variable). Bold values indicate $p < 0.05$. Model 1: Adjusted for chronological age, sex, and race/ethnicity. Model 2: Adjusted for chronological age, sex, race/ethnicity, and composite cardiovascular risk score. Model 3: Adjusted for chronological age, sex, and race/ethnicity, composite cardiovascular risk score, and smoking history. Sex stratification: Models 1–3 stratified by sex. CI, confidence interval; DunedinPoAm, methylation-based pace of aging estimate; GrimAA, GrimAge acceleration; HannumAA, Hannum's age acceleration; HorvathAA, Horvath's age acceleration; OR, odds ratio; PhenoAA, phenotypic age acceleration.

1.44; $p = 0.014$) and smoking history (OR = 1.23, 95% CI = 1.05 to 1.44; $p = 0.013$). DunedinPoAm was not statistically associated with hearing loss in Model 1 or Model 2 but became significant in Model 3 (OR = 1.24, 95% CI = 1.01 to 1.52; $p = 0.042$).

To explore the differences across racial/ethnic groups, we conducted additional analyses. Supplementary Tables 1 and 2 in Supplemental Digital Content, <https://links.lww.com/EANDH/B844>, present the linear and logistic regression results using Model 3, respectively, stratified by sex and race/ethnicity. Due to small sample sizes of non-Hispanic Black/African American participants, non-Hispanic other race participants, and Hispanic participants, we collapse these participants into a “non-White” category and compare with non-Hispanic White participants. The patterns of results for White participants are consistent

with those presented in the main tables. In linear regression analyses, among males, GrimAA was associated with lower mean hearing test scores in Model 3 ($\beta = -0.156$, 95% CI = -0.30 to -0.01 ; $p = 0.037$). For females, PhenoAA ($\beta = -0.112$, 95% CI = -0.21 to -0.01 ; $p = 0.025$), GrimAA ($\beta = -0.179$, 95% CI = -0.29 to -0.07 ; $p = 0.002$), and DunedinPoAm ($\beta = -0.107$, 95% CI = -0.21 to -0.01 ; $p = 0.032$) were all significantly associated with lower mean hearing scores (Model 3). Among non-White participants, only HannumAA was significantly associated with lower mean hearing test scores in the non-sex-stratified analysis ($\beta = -0.142$, 95% CI = -0.28 to 0.00 ; $p = 0.048$). In logistic regression analyses, there were no statistically significant results for males, but HannumAA (OR = 1.24, 95% CI = 1.03 to 1.50; $p = 0.024$), GrimAA (OR

= 1.58, 95% CI = 1.23; 2.02; $p = 0.001$), and DunedinPoAM (OR = 1.26, 95% CI = 1.01 to 1.57; $p = 0.040$) were statistically significant for females. There were no statistically significant results among non-White participants.

DISCUSSION

We examined the association between epigenetic AA and objective hearing function measures among a large, nationally representative sample of adults aged 50 yrs and older. Our findings indicate that the association varies by (a) type of epigenetic AA measure and (b) by sex. First, GrimAA and DunedinPoAm were strongly associated with overall hearing test score in the full sample, which is consistent with Kuo et al.'s results (Kuo et al. 2021). We also found that PhenoAA was significantly associated with poorer hearing test score. This may be due to our larger sample size and more power to detect the effect of PhenoAA on hearing test score, compared with the smaller sample size in the previous study (Kuo et al. 2021).

When examining our binary measure of hearing loss, only GrimAA was significantly associated with higher odds of hearing loss across Models 1 to 3. PhenoAA was significant only in Model 1, while DunedinPoAm was not significant in any model. DunedinPoAm was trained on three waves of biomarker data from young adults at ages 26, 32, and 38 yrs (Belsky et al. 2020); thus, it may not capture age-related functional and phenotypic changes such as hearing loss, which increases in prevalence in mid-to-late life (Goman & Lin 2016). Furthermore, DunedinPoAm measures the rate of aging at a given point in time rather than cumulative biological damage, which may not directly reflect long-term cumulative burden contributing to auditory decline. In contrast, GrimAge and PhenoAge were derived to predict mortality, chronic disease risk, and age-related dysfunction, and thus may capture these aging processes more effectively. While PhenoAge was developed based on a set of clinical biomarkers including albumin, creatinine, glucose, C-reactive protein, and white blood cell count that can reflect inflammation and cardiovascular health (Levine et al. 2018), GrimAge was created to be more directly linked to cardiovascular risk factors due to its inclusion of smoking pack-years and DNAm-based surrogates of plasma proteins such as growth differentiation factor 15, and plasminogen activation inhibitor 1 (Lu et al. 2019), both of which are linked to cardiovascular risk (Toffler et al. 2016; Kato et al. 2023). This may explain why PhenoAA was no longer associated with hearing loss after adjustment for the composite cardiovascular risk score and smoking history in the current study. Our findings suggest that the association between hearing function and epigenetic AA is dependent on the ways they were constructed that may capture distinct aspects of aging (Oblak et al. 2021).

Second, results indicated sex differences in the influence of epigenetic AA on hearing. HannumAA, PhenoAA, GrimAA, and DunedinPoAm were significantly associated with worse hearing across Models 1 to 3 in females, and only GrimAA was significantly associated with hearing function in males. This is consistent with prior research showing that measures of epigenetic AA can differ by sex (McCrary et al. 2019; Crimmins et al. 2021; Carter et al. 2022). Our study is among the first to assess sex differences in the role of epigenetic AA for hearing function. The consistent association of GrimAA with worse hearing

in both sexes suggests that GrimAA may capture more general aging processes affecting hearing (Kuo et al. 2021). In contrast, measures like HannumAA, PhenoAA, and DunedinPoAm may be more sensitive to biological factors of hearing function influenced by sex. Future studies should explore mechanisms driving sex-specific differences in the associations between various types of epigenetic AA and hearing.

In supplementary analyses, we further stratified our sample by sex and race/ethnicity. Results from these analyses were consistent for White participants, but mostly statistically insignificant for non-White participants. This pattern of results is consistent with prior literature which finds that hearing loss prevalence and severity are greater and worse, respectively, among non-Hispanic White individuals compared with non-White individuals (Agrawal et al. 2008; Lin et al. 2012; West & Lynch 2021). However, small sample sizes among non-White participants may have limited statistical power to detect significant associations. Moreover, collapsing diverse racial/ethnic groups into a single “non-White” category may mask heterogeneity in associations that differ by specific group (e.g., Hispanic versus non-Hispanic Black participants). Future research with larger and more diverse sample sizes is needed to better understand the heterogeneity in sex and racial/ethnic differences in epigenetic AA and hearing loss.

Altogether, our study contributes to the research area on aging and health by integrating epigenetic biomarkers with sensory health outcomes, specifically hearing loss. Building on previous research (Kuo et al. 2021), this study further explores the association between epigenetic AA and hearing function in US adults aged 50 yrs and over and highlights sex differences in hearing loss. The findings of this study have several important implications for aging populations. First, measures of epigenetic AA may serve as early indicators of hearing loss risk in US older adults. These findings may potentially help earlier detection and risk stratification in clinical and public health settings. It is important to note that the choice of the types of epigenetic AA may be crucial for early detection and prevention. In addition, understanding the adverse health risks related to hearing loss could help vulnerable populations, such as older adults, to adapt preventive strategies before significant hearing loss occurs.

Another implication of this research is that it reinforces the need to consider biological aging processes when studying sensory health differences. Our analyses indicate that hearing loss is correlated with epigenetic AA, and factors such as sex may influence the association between epigenetic aging and hearing function. These findings may guide future research to focus on the role of sex in epigenetic aging and hearing loss.

Finally, the observed associations between epigenetic AA and hearing outcomes suggest potential translational applications. Epigenetic clocks may serve as biomarkers for identifying individuals at increased risk of hearing loss. With further validation, these tools could be integrated into clinical screening protocols to support early detection and targeted interventions aimed at preserving auditory health in aging populations.

Although the observed regression coefficients were modest in size, they are consistent with effect sizes commonly reported in aging and epigenetic research. For example, studies examining epigenetic AA and hearing have reported similar magnitudes of association, such as GrimAA showing a coefficient of 0.20 in relation to hearing thresholds (Kuo et

al. 2021). In gerontology, small effect sizes (e.g., Pearson's $r \approx 0.10$ to 0.20) are typical and still considered meaningful, especially when replicated across studies and linked to progressive outcomes (Brydges 2019). Moreover, small-magnitude epigenetic associations may reflect subtle but biologically relevant changes that accumulate over time and contribute to age-related functional impairments (Breton et al. 2017). Even modest shifts in hearing thresholds may have significant implications for quality of life and public health when considered across aging populations. Our findings underscore the potential utility of epigenetic clocks as early indicators of sensory aging.

Results from the current study must be considered in light of limitations that could be addressed in future research. First, due to its cross-sectional design, we are unable to determine the temporal precedence of biological aging and subsequent hearing loss. As such, it is possible that reverse causality may be at play—where hearing loss contributes to accelerated biological aging. For example, hearing loss has been linked to increased social isolation, depression, and stress (Mick et al. 2014; West 2017; Lawrence et al. 2020; Shukla et al. 2020), all of which are known to influence biological aging processes. These psychosocial factors could potentially accelerate epigenetic aging, suggesting a bidirectional relationship that warrants further investigation. Future research using longitudinal data is needed to disentangle the directionality of the association. Second, DNA methylation in the HRS is measured via a blood sample, which may not be reflective of the DNA methylation process in inner ear cells or other tissues involved in hearing loss pathogenesis. Third, unmeasured variables may confound the association between epigenetic AA and hearing loss, including environmental or occupational noise exposure, ototoxic medication use, or hormone levels. In addition, socioeconomic status may influence both hearing and biological aging outcomes. For example, markers of socioeconomic status including education and income are associated with a higher prevalence of and greater risk for developing hearing loss (Cruikshanks et al. 2010, 2015; West & Lynch 2021). In addition, low socioeconomic status (measured as education, household income, wealth, and occupation) is associated with AA for GrimAge and DunedinPoAm (Moubadder et al. 2025). Future studies should incorporate comprehensive measures of socioeconomic status and detailed environmental and medical histories to better account for these potential confounders. While this study focuses on the epigenetic clocks that derive from specific cytosine-phosphate-guanin sites, future analyses of differential methylation at individual cytosine-phosphate-guanin—particularly those comprising the clocks—could enhance our understanding of the molecular mechanisms linking epigenetic aging to hearing loss.

Finally, our definition of hearing loss—hearing fewer than six tones in the better ear—was based on prior literature to maintain consistency across studies. However, we acknowledge that this threshold may underestimate clinically significant impairment and could influence both prevalence estimates and effect sizes. To address this limitation, we also analyzed continuous hearing test scores (0 to 6), which offer a more sensitive and informative measure of auditory function. The associations between epigenetic clocks and hearing scores remained significant and aligned with those observed

using the binary hearing loss definition, supporting the robustness of our findings.

CONCLUSIONS

This study indicates an association between epigenetic AA and hearing function in US older adults. It highlights epigenetic AA as a potential biomarker for hearing loss in older adults, and underscores the importance of considering sex differences in aging research. Future research is needed to explore epigenetic mechanisms as potential targets for interventions to mitigate hearing loss in older adults, particularly among females.

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The Health and Retirement Study (HRS) data are publicly available at <https://hrs.isr.umich.edu/>. For the current study, we analyzed the publicly available RAND HRS Longitudinal File 2020 (Latest release: May 2024 [V2]), the 2016 HRS Core (Latest release: Dec 2019 [Final V1.0]) data file, and the Cross-Wave Tracker File (Latest release: Nov 2024 [Early 2022 V2.0]). The 2016 Venous Blood Study dataset (Latest release: Sep 2024 [Final V2.0]) is available with a Sensitive Health Data Order Form. Because data are publicly available and deidentified, this study was exempted from additional review by Duke University Health System institutional review board (Pro00117475).

J.S.W. and R.J. performed study concept and design and interpretation of data. J.S.W., Q.C., and R.J. performed acquisition of data and drafting of manuscript. Q.C. and R.J. performed data analysis. J.S.W., Q.C., S.L.S., J.B., F.Z., Y.-J.L., and R.J. performed a critical review of the manuscript and final approval of version to be published.

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Address for correspondence: Rong Jiang, Duke University Medical Center, Box 3805, 40 Duke Medicine Circle, Durham, NC 27710, USA. E-mail: rong.jiang@duke.edu

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