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Linear Mixed Model Analysis of Polygenic Hazard Score on Verbal Memory Decline in Alzheimer's Disease

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This multicentered research project was approved by institutional review boards (IRB) at each site and obtained authorized written informed consent from participants (http://adni.loni.usc.edu/). There was an IRB exemption for current secondary data analysis.

The authors have no conflicts of interest to report.

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Abstract

***Background*:** Alzheimer's disease (AD) is a chronic, progressive, degenerative disease characterized by cognitive dysfunction, including verbal memory loss. Studies were lacking in examining the longitudinal effect of polygenic hazard score on the Rey Auditory Verbal Learning Test-Delayed Total (AVDELTOT) score (a common measure of verbal memory). A key step in analyzing longitudinal changes in cognitive measures using a linear mixed model (LMM) is choosing a suitable covariance structure.

***Objectives*:** The study aims to determine the association between the polygenic hazard score and the AVDELTOT score accounting for repeated measures (the covariance structure).

***Methods*:** The AVDELTOT scores were collected at baseline, 12, 24, 36, and 48 months from 283 participants with AD, 347 with cognitive normal, and 846 with mild cognitive impairment in the Alzheimer's Disease Neuroimaging Initiative. The Bayesian information criterion statistic was used to select the best covariance structure from 10 covariance structures in longitudinal analysis of AVDELTOT scores. The multivariable, LMM was used to investigate the effect of polygenic hazard score status (low *vs*. medium *vs.* high) on changes in AVDELTOT scores while adjusted for age, gender, education, *APOE-ε4* genotype, and baseline Mini-Mental State Examination (MMSE) score.

***Results*:** One-way analysis of variance revealed significant differences in AVDELTOT scores, MMSE, and polygenic hazard score among AD diagnoses at baseline. Bayesian information criterion favored the compound symmetry covariance structure in the LMM analysis. Using the multivariate LMM, the *APOE-ε4* allele and high polygenic hazard score value was significantly associated with AVDELTOT declines. Significant polygenic hazard score status by follow-up visit interactions was discovered.

***Conclusion*:** Our findings provide the first evidence of the effect of polygenic hazard score status and *APOE-ε4* allele on declines in verbal memory in people with AD.

Keywords: Alzheimer's disease, *APOE-ε4*, covariance structure, linear mixed model, polygenic hazard score, verbal memory

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disease with memory problems centered on episodic memory (Lane et al., 2018). It is known that physiological changes occur in the brain many years before AD is diagnosed (Jack et al., 2013). Yet, the direct role of changes such as amyloid deposits and tau deposition has recently had conflicting reports as they were described as being present in cognitively unimpaired older adults (Sullivan et al., 2021). Knowing this makes it critical to understand the progression of the disease from a population health perspective. Understanding factors that can further elucidate AD progression characteristics will be needed for clinical care. Typically, diagnostic criteria of AD include assessment of general cognitive decline, observance of changes in personality, cognitive tests that elicit the loss of long- and short-term memories, loss of language memory and fluency, and onset of atypical behaviors (Jack et al., 2013; Weller & Budson, 2018). Once diagnosed, one way to consider progression is through measurement of verbal memory and verbal fluency, but longitudinal studies are needed on verbal memory and fluency tests (Mura et al., 2022)

AD has a substantial genetic component with heritability of 58% to 79% (Gatz et al., 2006); while 95% of all people with AD are defined as late-onset AD (defined as AD with an onset age $\geq$ 65 years; Bettens et al., 2010). Genome-wide association studies (GWAS) have identified more than 30 known risk loci for AD (Jansen et al., 2019; Kunkle et al., 2019), and recently, genome-wide data in a genetic epidemiology framework were used to develop a polygenic hazard score (PHS) to quantify the age-associated risk for developing AD (Desikan et al., 2017). The PHS has been used to predict overall risk of AD, age at onset, clinical phenotypes, and in the design of AD clinical trials (Desikan et al., 2017; Kauppi et al., 2018; Tan et al., 2017).

It is clinically significant to understand the links between verbal memory and learning with the progression of AD since impaired verbal memory is linked to progressive aphasia (Foxe et al., 2021). AD studies frequently use the Rey Auditory Verbal Learning Test (RAVLT) to assess immediate or delayed recall and recognition memory (van den Berg et al., 2020). Though AD's risks, progression, and phenotypes have been a research focus, no study has focused on the PHS score on RAVLT measures. The RAVLT is commonly used to assess verbal memory and has been extensively validated for use in cognitively normal and impaired people (Poreh et al., 2012). It is known that age, education, and gender may influence RAVLT performance (Magalhães & Hamdan, 2010), which has been used to distinguish AD, mild cognitive impairment (MCI), and cognitively normal (CN; Ding et al., 2019; Messinis et al., 2016).

In addition to the lack of understanding of PHS on AVDELTOT scores, studies have not reported analysis of longitudinal changes of continuous outcomes of AD with a suitable covariance structure using a linear mixed model (LMM; George & Aban, 2015; Littell et al., 2000). LMMs, including both fixed and random effects, have been proposed to analyze the longitudinal effect of *APOE-ε4* allele on AD-related phenotypes (e.g., Fokoh et al., 2021; Mormino et al., 2014; Paranjpe et al., 2019; Sutphen et al., 2015). For example, one study reported significant interactions between Aβ and *APOE-ε4* status in predicting change in logical memory scores in healthy individuals using LMM (Mormino et al., 2014). Subsequently, a pilot study on patients with heart failure suggested no significant association of *APOE-ε4* allele with delayed (recall) memory (Pressler et al., 2017). Through repeated measures of longitudinal study over time are correlated, LMMs can be used to account for repeated measures in longitudinal studies (Wang, 2016; West et al., 2014). This study fills the current gap in the scientific

knowledge related to the association between repeated measures for AD by comparing 10 covariance structures in longitudinal analysis of the AVDELTOT score in AD using LMM and examining the effect of PHS status on longitudinal declines in AVDELTOT scores.

Methods

Sample

Data used in this study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership and began in 2004. Currently, the ADNI has undergone four phases: ADNI1, ADNI GO, ADNI2, and ADNI3. The ADNI project is ongoing and employs a multicenter, longitudinal design aiming to understand relationships among clinical and cognitive assessments, imaging, genetic information, and biochemical biomarkers currently used for the early diagnosis of AD. The primary goal of ADNI has been to test whether the collected information can be combined to measure and understand the progression of MCI and early AD. The ADNI study provides services in the United States and Canada. There was an institutional review board exemption for the current study due to secondary data analysis.

Measures

Social Demographics

This analysis included three demographic measures: gender, age, and race/ethnicity. Gender was self-reported as either male or female. Age was classified into three groups: ≤ 65 years, 66–75 years, and 76+ years. Years of education were classified into ≤ 12 years, 13–16 years, and 17+ years. Only non-Hispanic White individuals were used for the present analysis.

Cognitive Phenotypes

The Folstein Mini-Mental State Examination (MMSE) is a brief questionnaire that measures global cognitive impairment by evaluating five cognitive domains: orientation, registration, attention and calculation, recall, and language (Folstein et al., 1983). The MMSE has well-established psychometrics, with scores on the Folstein MMSE ranging from 0–30, with 30 being no cognitive impairment.

The RAVLT—a commonly used test of verbal episodic memory—includes a list of 15 unrelated words presented orally to the subject (Schmidt, 1996). The test has five consecutive learning trials: repetitions to learn the unstructured verbal material, followed by a 30-min delayed period for free recall, and a subsequent recognition trial that includes 30 words (15 from the learning trials), and 15 unrelated words. A learning score is calculated using the difference between the last and the first immediate recall trials. In the present study, we used the 30-min auditory verbal delayed recall total (AVDELTOT) score, which ranges from 0 to 15.

APOE Genotypes

The data of *APOE-ε4* genotypes were extracted from the ADNI database. *APOE-ε4* carriers were defined as individuals with at least one ε4 allele (ε4/ ε4, ε4/ ε3, or ε4/ ε2 as *APOE-ε4*-1+), while non-carriers were defined as individuals with no ε4 allele (*APOE-ε4*-0; Table 1).

Polygenic Hazard Score (PHS)

The PHS data were downloaded from the ADNI website (desikanlab.html; Desikan et al., 2017). The PHS data were based on AD-associated single nucleotide polymorphisms (SNPs)

from previous GWAS data, such as the International Genomics of Alzheimer's Project and the Alzheimer's Disease Genetics Consortium. Everyone has a PHS to reflect an individual's risk for developing AD based on age and genotype. The PHS has been replicated in Phase 2 of the Alzheimer's Disease Genetics Consortium, the National Institute on Aging Alzheimer's Disease Centers, and ADNI. In the present study, the PHS was categorized as low, medium, and high according to the tertile distribution of PHS in all participants.

Statistical Methods

Baseline Descriptive Statistics

The categorical variables were presented in their raw values along with the proportions for categorical variables, and continuous variables were introduced in the form of mean ± standard deviation (SD). A chi-square test was used to examine the associations of categorical variables with AD diagnostics. At the same time, a one-way analysis of variance was performed to determine the differences in continuous variables among AD diagnostics.

LMM

The LMM, including fixed and random effects for a continuous outcome variable in a longitudinal study, can be expressed as equation (1).

$$Y_{ijk} = \mu + \alpha_i + b_{ij} + \gamma_k + (\alpha\gamma)_{ik} + \varepsilon_{ijk} \quad (1)$$

Where

Y_{iik} is the value of the outcome for individual $_j$ at follow-up time $_k$ with treatment (or covariate) $_i$

μ is the intercept of the model

α_i is the effect for treatment (or covariate) $_i$

b_{ij} is a random effect for subject $_j$ with treatment (or covariate) $_i$

$\gamma_k$is the effect of time (follow-up visit) $_k$

$(\alpha\gamma)_{ik}$ is the effect for treatment (or covariate) x time interaction

ε_{ijk} is the random error associated with outcome at time $_k$ on the $_j^{th}$ individual for treatment (or covariate) $_i$

The Bayesian information criterion (BIC) statistic (Simonoff, 2003) was used to select the best covariance structure from 10 commonly used covariance structures: Ante-dependence (ANTE), Autoregressive (AR), Heterogeneous Autoregressive (ARH), First-order, Autoregressive moving average (ARMA), Compound Symmetry (CS), Heterogeneous Compound Symmetry (CSH), Huynh-Feldt (HF), banded Toeplitz structure (TOEP), Unstructured (UN), and Variance Components (VC). The model with smaller BIC fits the data better.

The multivariable repeated measures LMMs, including PHS status as fixed effect and subject as random effect, were used to examine the longitudinal changes in AVDELTOT score as a continuous trait adjusting for age, sex, race, education, *APOE-ε4,* and MMSE. The interaction between PHS status and follow-up visits was tested. The repeated measures longitudinal analyses were performed using PROC MIXED in SAS (version 9.4). All statistical analysis was performed using SAS 9.4.

Results

Baseline Descriptive Statistics

After merging data, the total sample size of the baseline data was 1,476, including 283 with AD, 347 with CN, and 846 with MCI (Table 1). All persons were non-Hispanic White with AVDELTOT scores, *APOE-□4*, and PHS values. The AD group had lower mean values in the MMSE indicative of cognitive impairment, while the CN and MCI group had MMSE scores that could be interpreted as cognitively unimpaired. The AD group showed lower mean scores for the AVDELTOT but higher PHS scores than those in CN and MCI groups.

Covariance Structure Selection in LMM

In the LMMs, the BIC statistics favored the CS structure (Table 2). The BIC value for CS was 25,076.3, which was lower than any other covariance structure. By the CS structure, we mean that the correlation between two repeated measures was constant irrespective of the lag or length of time between them. We chose CS as the favorite model for further analysis.

LMM Analysis of AVDELTOT Scores

Using a CS model, the multivariable LMM analysis results are presented in Table 3. All the variables were associated with AVDELTOT scores ($p < .05$). The *APOE-ε4* was significantly associated with AVDELTOT declines ($t = -3.80$, $p = .0001$), while low and medium PHS status compared with high PHS were positively associated with AVDELTOT scores ($t = 2.26$, $p = .0240$ and $t = 3.14$, $p = .0017$, respectively). Furthermore, AD and MCI were negatively associated with AVDELTOT scores compared with CN ($t = -13.55$, $p < .0001$ and $t = -8.90$, $p < .0001$, respectively).

The AVDELTOT scores significantly declined at 12 months, 36 months, and 48 months compared with baseline (p = .0065, < .0001, and .0033, respectively). Significant interactions were found between PHS-Low and 12 months (p = .0200), PHS-Low and PHS-Medium and 36 months (p = .0048 and .0104, respectively), PHS-Low and PHS-Medium and 48 months (p = .0217 and.0436, respectively). A graphical display of two-way interactions between PHS statis and visits is further shown in Figure 1.

Discussion

To the best of our knowledge, this is the first longitudinal analysis of the AVDELTOT scores in AD using repeated LMM measuring to examine the association between PHS status and AVDELTOT across time (longitudinal). In addition, we have considered the dependency of measures from the same subject (repeated measures/covariance structure). Researchers have elucidated that PHS scores help assess risk for AD, clinical phenotypes, and are predictive of general longitudinal decline (Desikan et al., 2017, Kauppi et al., 2018; Tan et al., 2017), but this present study adds valuable information about specific declines in verbal memory. We found significant differences in AVDELTOT scores among AD, MCI, and CN at baseline, which is interesting because it may be challenging to differentiate early AD from MCI clinically. Furthermore, the CS covariance structures outperformed the other models' LMM analysis of AVDELTOT scores. In addition, individuals with at least one *APOE-ε4* allele had significant AVDELTOT score declines compared with those without *APOE-ε4* allele, which is congruent with the known critical importance of the ε4 allele of *APOE* and AD progression (Sienski et al., 2021). Since we know that AD has a genetic component, the finding that higher PHS scores are not only associated with risk but also associated with a decline in AVDELTOT scores is

important. Discovering that those with medium PHS scores did not have as much decline in AVDELTOT scores affirms the complex and multifactorial risks for AD.

The LMM is commonly used to deal with correlated data in repeated measures of longitudinal studies (Wang, 2016; West et al., 2014). However, one crucial step in analysis of longitudinal changes in continuous outcomes using LMM is to choose a suitable covariance structure (George & Aban, 2015; Littell et al., 2000). A helpful tool for selecting a covariance structure is the use of information criteria (IC) such as AIC, the small sample corrected AIC (AICC), and BIC (George & Aban, 2015; Gomez et al., 2005; Littell et al., 2000). It has been suggested that the consistent IC (BIC) seemed to be more accurate than efficient (AIC, AICC) criteria (George & Aban, 2015; McNeish & Harring, 2020). For example, AIC, AICC, and BIC have been used to compare CS, AR, TOEP, and the UN covariance structures in analysis of longitudinal imaging data (George & Aban, 2015). In the present study, we compared 10 covariance structures in longitudinal analysis of the AVDELTOT score in AD using LMM. We found that CS had the lowest BIC value and was the best covariance structure. The CS structure assumed a correlation between two separate measurements, but the correlation was constant regardless of how far apart the measurements were. Then we examined the effect of PHS status on longitudinal declines in AVDELTOT scores using the CS covariance structure.

LMMs have been used to analyze longitudinal correlated data on the effect of *APOE-ε4* allele on AD-related phenotypes (e.g., Fokoh et al., 2021; Mormino et al., 2014; Paranjpe et al., 2019; Sutphen et al., 2015). One study reported significant interactions between Aβ and *APOE-ε4* allele status in predicting change in logical memory scores in healthy individuals using LMM

(Mormino et al., 2014). A pilot study on heart failure patients also suggested no significant association of *APOE-ε4* allele with delayed (recall) memory (Pressler et al., 2017). Moreover, the *APOE-ε4* allele was associated with decreased interhemispheric resting-state functional connectivity, which was attributed to carrier memory performance (Luo et al., 2016). One recent study found the effect of *APOE-ε4* genotype on the logical memory declines related to AD (Fokoh et al., 2021). The present study added that *APOE-ε4* allele was associated with longitudinal declines in verbal memory in AD. This finding is consistent with other recent studies that reported more rapid AD progression for those that pose the *APOE-ε4* (Chen et al., 2021).

The PHS has been used to predict individual risk of developing AD, AD age at onset, and clinical phenotypes, as well as help design AD clinical trials (Desikan et al., 2017; Kauppi et al., 2018; Tan et al., 2017). The present study further added that PHS scores are associated with the decline in AVDELTOT scores, and there are two-way interactions between PHS status and follow-up visits.

The findings from the present study are somewhat congruent with other research. In this study, we report significantly lower AVDELTOT scores of verbal memory in AD and MCI compared with CN individuals. The RAVLT score has been used to distinguish AD from MCI and dementia (Ding et al., 2019; Messinis et al., 2016). Likewise, the 30-min delayed recall score of the RAVLT has been used to predict Aβ status (Kandel et al., 2015). Moreover, one study examined sex differences in florbetapir positron emission tomography amyloid positivity (A^+) on verbal learning and memory performance and hippocampal volume in CN and early MCI

individuals (Caldwell et al., 2017). Another study investigated the relationship between the asymmetry magnitude in hippocampal subfields and verbal memory decline as assessed by RAVLT (Sarica et al., 2018).

There are several strengths in this study. First, the ADNI is a longitudinal study that provides a large sample for analysis. Second, we conducted covariance structure selection in LMM analysis of AVDELTOT scores. Third, this is the first study to examine the association of PHS status with the longitudinal changes in AVDELTOT scores. Finally, we detected interactions between PHS status and follow-up visits.

Several limitations need to be acknowledged. First, the current study was time limited by the data set, which provided 4 years of follow-up. Second, the present study found longitudinal declines only in age 75 years and above group. Furthermore, this study does not account for current treatment of AD patients. In addition, the results of this study cannot be generalized to all the patient population since it was restricted to non-Hispanic White people.

There are many future implications from this work. Future study designs could include plans to investigate how *APOE-ε4* alleles and PHS affects early-onset AD patients and late-onset AD patients differently concerning the verbal memory test. As well, future studies could consider the incorporation of the PHS to better understand other specific aspects of disease progression.

Conclusion

This study provides new information about verbal learning and progression of AD and MCI. This study compared 10 covariance structures in the LMM analysis of longitudinal changes in AVDELTOT scores, found CS covariance structure is the best and identified differences in AVDELTOT scores among three diagnostic groups at baseline. Further, we described the significant decline in AVDELTOT scores at 4-year follow-ups. Using LMM analysis, our findings provide the first evidence of the longitudinal effect of *APOE-ε4* allele and PHS scores on the AVDELTOT scores related to AD and make it clear that verbal memory examination scores could be a good predictor for AD.

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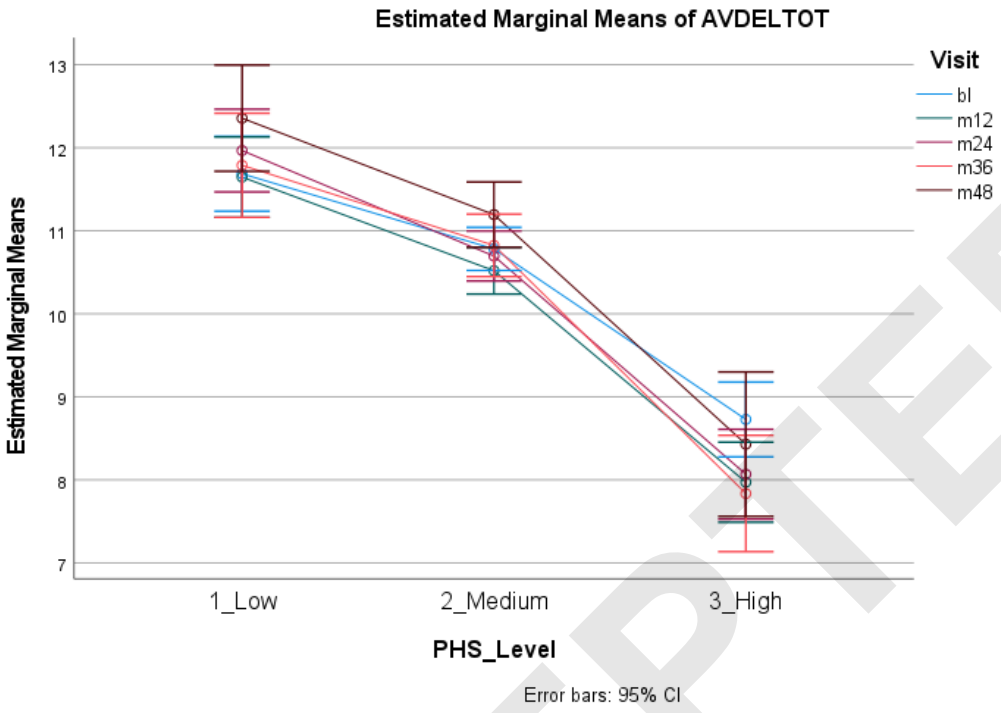
Figure Legend

FIGURE 1

PHS status by follow-up visit interaction for AVDELTOT score.

Figure 1



Note. PHS = Polygenic hazard score; AVDELTOT = Rey Auditory Verbal Learning Test-Delayed Total. The X axis is PHS status. The Y axis is the estimated marginal means of the AVDELTOT score. bl = baseline; m12, m24, m36 and m48 = 12, 24, 36 and 48 months, respectively.

Table 1
Descriptive Statistics at Baseline

Variable	CN	MCI	AD
Gender			
Male	185	493	160
Female	162	353	123
APOE- ε4 allele			
0	255	429	94
1+	92	417	189
PHS-Level			
Low	115	148	31
Medium	209	525	153
High	23	173	99
PHS			
Mean ±SD	0.03±0.67	0.43±0.78	0.80±0.85
Age (years)			
< 65	6	127	36
65-75	176	360	96
75+	166	359	151
Education (years)			
≤ 12	37	134	70
13-16	152	339	127
17+	158	373	86
MMSE			
Mean ±SD	29.10±1.10	27.80±1.79	23.21±2.03
AVDELTOT			
Mean ±SD	12.87±2.38	10.75±3.52	7.12±3.80

Note. CN = Cognitive normal; MCI = Mild cognitive impairment; AD = Alzheimer disease; PHS = Polygenic hazard score; MMSE = Mini mental state examination; AVDELTOT = Rey Auditory Verbal Learning Test-Delayed Total; SD = Standard deviation.

Table 2
Covariance Structure Selection in Linear Mixed Model Analysis

Structure	-2 Log Likelihood	BIC
ANTE(1)	25437.0	25502.6
AR(1)	25472.3	25486.9
ARH(1)	25469.2	25513.0
ARMA(1,1)	25059.8	25081.7
CS	25061.7	25076.3
CSH	25058.7	25102.5
HF	25046.5	25090.3
TOEP	25048.7	25085.2
UN	24994.6	25104.1
VC	26729.1	26736.4

Note. BIC = Bayesian information criterion statistic; ANTE = Ante-dependence; AR = Autoregressive; ARH = Heterogeneous Autoregressive; ARMA = First-order Autoregressive moving average; CS = Compound Symmetry; CSH = Heterogeneous Compound Symmetry, HF = Huynh-Feldt; TOEP = a banded Toeplitz structure; UN = Unstructured; VC = Variance Components

Table 3
Linear Mixed Model Analysis of Polygenic Hazard Score with AVDELTOT Score

Variable	β ± SE	*t* values	*p* values
Gender (ref=male)			
Female	-0.37±0.15	-2.48	.0133
*APOE- ε*4 (ref=0			
1+	-0.72±0.19	-3.80	.0001
PHS-level (ref=High)			
Low	0.75±0.33	2.26	.0240
Medium	0.77±0.25	3.14	.0017
Age (ref= <65)			
65-75	-0.07±0.07	-0.30	.7616
75+	0.68±0.07	-2.77	.0057
Education (ref= ≤ 12			
13-16	0.33±0.22	1.56	.1181
17+	0.53±0.22	2.41	.0160
Diagnosis (ref=CN)			
AD	-3.62±0.27	-13.55	<.0001
MCI	-1.64±0.18	-8.90	<.0001
MMSE	0.30±0.02	19.55	<.0001
Visit (ref=baseline)			
12 months	-0.52±0.19	-2.72	.0065
24 months	-0.34±0.21	-1.64	.1020
36 months	-1.04±0.25	-4.09	<.0001
48 months	-0.83±0.30	-2.94	.0033
Visit * *PHS-Level (ref=Baseline** PHS-High)			
12 months* PHS-Low	0.62±0.27	2.33	.0200
12 months* PHS-Medium	0.40±0.22	1.82	.0691
24 months* PHS-Low	0.48±0.28	1.69	.0905
24 months* PHS- Medium	0.15±0.24	0.64	.5247
36 months* PHS-Low	0.95±0.34	2.82	.0048
36 months* PHS- Medium	0.73±0.28	2.56	0.0104
48 months* PHS-Low	0.87±0.38	2.32	0.0217
48 months* PHS- Medium	0.66±0.33	2.02	0.0436

Note. AVDELTOT = Rey Auditory Verbal Learning Test-Delayed Total; PHS = Polygenic hazard score; CN = Cognitive normal; AD = Alzheimer Disease; MCI = Mild Cognitive Impairment; MMSE = Mini mental state examination; β = adjusted regression coefficient, SE = standard error.
p value is based on t test in multivariate linear mixed model adjusted for gender, age, education, diagnosis, visit, and MMSE.