

Linking epigenetic age acceleration to self-reported daily memory lapses: evidence from the National Study of Daily Experiences

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Abstract

DNA methylation algorithms, such as DunedinPACE, are increasingly used to study the mechanisms of aging and to identify associations with risk factors in adult development and aging. Growing evidence suggests that an increased pace of epigenetic aging is associated with cognitive impairment and dementia, but the correlation between epigenetic aging and subjective cognitive complaints (eg, forgetting a name or forgetting to take your medication), an early marker of dementia risk, remains unexplored. Using data from The National Study of Daily Experiences (NSDE) and Midlife in the United States (MIDUS; $N = 232$), we examined the relationship between epigenetic aging rate (ie, DunedinPACE) and self-reported daily memory lapses (ie, occurrence, irritation, interference) in midlife and older adults. We found no significant main effects of the rate of epigenetic aging on self-reported memory lapses; however, a significant chronological age interaction indicates that among the comparatively younger adults in the sample (age 40–49), faster than average rates of aging (ie, higher DunedinPACE) were associated with more prospective memory lapses approximately a decade later as well as greater reports of prospective memory lapse irritation and interference. Additionally, for respondents in their forties, a higher DunedinPACE was associated with both greater prospective memory lapse irritation and interference. These results suggest that early midlife may be a sensitive period during which the rate of epigenetic aging is more influential on cognitive health outcomes.

Keywords: DNA methylation, Ecological momentary assessment, Memory failure, Epigenetic clock

Introduction

Subtle cognitive changes are important early markers of later mild cognitive impairment (MCI) and the onset of Alzheimer's Disease and related dementias (AD/ADRD). These changes in cognition can precede disease onset by decades, providing support for the view that, for many, dementia is a midlife disease.^{1,2} Subjective memory complaints (ie, memory lapses) allow researchers to detect these subtle cognitive changes.^{3,4} Memory lapses, such as a forgotten appointment or trouble recalling someone's name, seem relatively minor, yet they are related to later, significant cognitive decline.^{5,6} Also, the extent to which they report these lapses as irritating or interfering with daily life could represent greater deviation from their baseline functioning. Identifying the early time points at which memory

lapses are observed and examining individuals' interpretations of these lapses will help us discover the underlying mechanisms responsible for normative cognitive aging and pathological cognitive decline.

Given the links between subjective memory complaints and later cognitive decline, researchers are examining factors underlying, and perhaps even preceding, subtle cognitive changes that may be responsible for these complaints. Indeed, subjective reports of memory lapses, irritation, and inference in daily life may represent subtle indicators associated with early cognitive vulnerability.⁷ Though subjective memory has exhibited small-to-moderate associations with performance-based memory function,⁸ subjective memory complaints have been shown to be associated with early biomarkers of AD (eg, amyloid- β) in cases where performance-

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Memory lapses can also be predictive of other experiences at the individual and daily level¹⁵ and clarify the emotional (irritation) and practical/operational (interference) consequences of those lapses. Considering that prospective memory is especially

Epigenetic age measurement tools provide innovative insights into aging processes, and the potential to advance understanding of interindividual differences in cognitive aging. The current study employs the Dunedin Pace of Aging Calculated from the Epigenome (DunedinPACE) to examine individual differences in prospective and retrospective memory lapses in everyday life.

DunedinPACE, cognitive aging, and memory lapses

DunedinPACE distinguishes faster and slower aging rates by considering an overall decline in system integrity across many tissue types and is named for the cohort from which it was developed, the Dunedin Study.⁹ Notably, it is distinguished from prior generation epigenetic clocks by using methylation probes with high reliability from *longitudinal* cohort data. Specifically, age-related biomarker changes were tracked in residents in Dunedin, New Zealand, born from 1972 to 1973 at four time-points between 26 and 45 years of age to distinguish unique methylation patterns related to age-related decline.⁹ A DunedinPACE value >1 indicates a faster rate of aging, while a value <1 indicates a decelerated rate. For example, an individual with a DunedinPACE score of 1.2 is aging 20% faster than the reference population (mean = 1.0), while a score of 0.8 indicates that the rate of aging is 20% slower when compared to an average rate. Elliott and colleagues¹¹ demonstrated that, by age 45, a faster pace of aging was linked to various cognitive difficulties (IQ decline, memory, processing speed) in the Dunedin cohort.

Recent evidence has documented a link between epigenetic aging and cognitive performance,^{9,10,32} yet critical gaps remain on its potential role in understanding individual differences in *subjective* memory lapses and their appraisals with predictive utility for informing cognitive aging and AD/ADRD risk.

Chronological age is widely used to explain associations between age and memory failures. However, there continues to be variation in the types and numbers of memory lapses in individuals of the same age cohorts. Thus, epigenetic age markers may be better able to explain individual differences in the subclinical presentations of cognitive aging where chronological ages are equal.

Examining chronological age as a potential moderator of associations with memory lapses is important because the implications of accelerated biological aging for memory lapses may differ across midlife and older adulthood. Midlife is a developmental period characterized by substantial occupational, family, and social demands—potential sources of stress that may accelerate aging and increase the likelihood of memory lapses and their level of disruption to daily life.³³ For example, forgetting an appointment or failing to complete an intended task may be particularly disruptive for adults in midlife balancing multiple competing responsibilities. Moreover, emerging evidence suggests that accelerated biological aging in midlife is associated with earlier declines in cognitive and physiological functioning, suggesting that accelerated aging in midlife may be particularly consequential for long-term health outcomes.³⁴ In contrast, comparatively older adults often report fewer stressors, but they may be experiencing subtle cognitive changes that require compensatory strategies, or they may have reduced awareness of cognitive difficulties.⁶ Memory lapses in later life, then, may reflect changes rooted in midlife as opposed to the current pace of biological aging. The growing studies that show how changes in midlife may play an important role in determining outcomes later in life supports our tests of chronological age differences in the associations

between epigenetic aging and daily memory lapses in adults in midlife and older adulthood.

The current study

We examine the association between blood-based epigenetic biomarkers and daily memory lapses across adulthood and will provide evidence that biological aging processes are linked to subtle everyday cognitive experiences that emerge years before the cognitive declines typically assessed in aging research, extending risk detection into early midlife. Using a national sample of adults ranging from early midlife to older adulthood, the goal of the current research is to explore the associations of epigenetic aging, as measured by epigenetic clocks, with the frequency and impact of daily memory lapses and whether these associations differ by chronological age. Examining these associations across a broad adult age range makes it possible to evaluate whether links between biological aging and subtle cognitive experiences emerge earlier in adulthood, informing windows for early intervention. Importantly, this study differentiates between prospective and retrospective memory lapses, as these forms of everyday cognitive complaints may have distinct age-related and functional implications.^{4,6,16} Building on evidence that accelerated biological aging is linked to poorer cognitive performance,^{9,10,30-32} we hypothesized that individuals with faster biological aging would report more frequent daily memory lapses and greater negative appraisals of these lapses (ie, more irritation and interference with daily routine), and that these associations vary by chronological age, such that the associations are stronger among middle aged adults compared to older adults, given emerging evidence that accelerated aging may signal earlier vulnerability in midlife.^{11,34} Accordingly, our primary hypothesis focused on DunedinPACE because its emphasis on ongoing aging processes makes it well suited for examining subtle, everyday cognitive experiences that may precede measurable cognitive impairment, whereas analyses of GrimAge2 and PhenoAge intended to assess the generalizability of findings across complementary epigenetic clocks. We examined these predictions using a national sample of adults ranging from early midlife to older adulthood.

Methods

Participants and procedures

The present study combines data from multiple projects of the Midlife in the United States (MIDUS),^{35,36} a national study of health and well-being across the adult lifespan. Blood samples for epigenetic aging analyses were collected as part of the biomarker project during the second wave of MIDUS (MIDUS 2; 2004-2009), in which participants completed an overnight clinic visit and provided biological specimens. DNA methylation data were available for 1310 participants from the MIDUS 2 and Refresher biomarker projects, of whom 511 were from the MIDUS 2 biomarker project. The National Study of Daily Experiences (NSDE, a subproject of MIDUS)³⁵ introduced measures of daily memory lapses and their appraisals in its third wave (NSDE 3; 2017-2019). The sample used for this study consisted of a subset of 232 MIDUS participants (age range: 43-

91 years; mean age: 60.74 years; 63% female) from the MIDUS 2 biomarker project, which assessed biological aging, who also completed NSDE 3 approximately 10 years later, when daily memory lapses were measured. The prospective analyses were limited to MIDUS 2 participants because comparable follow-up data were not yet available for the Refresher biomarker cohort at the time of the present study. The protocol was approved by Penn State University's Institutional Review Board (PRAMS00042558), Clemson University's Institutional Review Board (2023-0053), and Northern Arizona University's Institutional Review Board (2020855). All data were de-identified prior to analyses. Written informed consent was obtained from all participants prior to data collection.

During the MIDUS 2 biomarker visit, participants provided whole blood samples as part of a DNA methylation-based epigenetic aging assessment. Whole blood was collected using BD Vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) with ethylenediaminetetraacetic acid anticoagulant, from which DNA was later extracted and tested for suitable yield and integrity. Samples were subjected to genome-wide methylation profiling using the Illumina Methylation EPIC microarray (Illumina, Inc., San Diego, CA, USA). DNAm profiling was conducted in 2019, and in 2022 these data were used to compute epigenetic clocks using the established algorithms, including DunedinPACE (see more information on data collection and the derivation of epigenetic clocks in MIDUS on the website: <https://midus.colectica.org/>). Because NSDE 3 data (~2017-2019) were collected a decade after MIDUS biomarker data (~2004-2009), analyzing datasets from these two longitudinal waves and subprojects provides an opportunity to examine the prospective associations between epigenetic aging and daily memory lapses approximately a decade later. Because multiple validated epigenetic clocks were available in MIDUS, several measures were evaluated; however, we designated DunedinPACE as the primary focus of this paper as it most closely aligned with our hypotheses of subtle cognitive functioning and biological aging.

Measures

Epigenetic clocks

Three epigenetic clocks assessed have robust predictive potential for morbidity and mortality, and AD/ADRD risk, and their sensitivity to social determinants of health: DunedinPACE,¹⁰ PhenoAge,²⁶ and GrimAge2.²⁵ While our focus on pace of aging in the present study led to examining DunedinPACE, we provide additional analyses with PhenoAge and GrimAge2 for transparency and to evaluate the generalizability and robustness of findings across different epigenetic clocks available in MIDUS (see [Supplemental Material](#)). Relative to first-generation epigenetic age measures, second-generation clocks (PhenoAge and GrimAge2) show higher predictive validity for disease and mortality. For analysis, the PhenoAge and GrimAge2 clocks were regressed on chronological age to compute residual values that index how much older or younger a person is biologically relative to their chronological age.

DunedinPACE is a DNA methylation-based algorithm that was developed by training a predictive model on longitudinal

changes in 19 biomarkers reflecting health status (body mass index, waist-hip ratio, glycosylated hemoglobin, leptin, blood pressure, cardiorespiratory fitness, forced vital capacity ratio, forced expiratory volume, total cholesterol, triglycerides, high density lipoprotein, lipoprotein(a), apolipoprotein B100/A1 ratio, estimated glomerular filtration rate, blood urea nitrogen, high sensitivity CRP, white blood cell count, mean periodontal attachment loss and number of dental-carries-affected tooth surfaces).⁹ DNAm data were then regressed on this longitudinal measure to derive an index of the rate of biological aging.³⁷ In the present study, DunedinPACE values were computed by applying this previously validated algorithm to DNA methylation data collected from MIDUS participants. Given its high test-retest reliability, DunedinPACE is a pertinent measurement for intervention trials and natural experiment studies investigating how behavioral or environmental modification changes the rate of aging.¹⁰ A value greater than one indicates accelerated aging, meaning that an individual's biological age is advancing faster than the average rate.

Daily memory lapses

Over the course of eight consecutive daily telephone interviews, participants reported whether they experienced each of several prospective and retrospective memory lapse types that had occurred in the previous 24 hours. The daily memory lapses checklist (DMLC)⁴ contains five items that pertain to prospective memory lapses (memory for future behaviors and activities) and four items that pertain to retrospective memory lapses (memory for previously learned information). Items on the prospective subscale included forgetting to complete an errand or chore, to take a medication, to finish something you started, an appointment, or the reason for entering a room. Items on the retrospective subscale included items such as forgetting someone's name and forgetting a word during a conversation, forgetting where you put something, or forgetting important information. For each subscale, the reports of lapses were summed to create a composite number reflecting the number of distinct memory lapse types endorsed each day (prospective range: 0-5; retrospective range: 0-4). Thus, repeated occurrences of the same lapse type within a day contributed a single endorsement for that type. Daily reliability was 0.75 for prospective lapses and 0.87 for retrospective lapses.

Appraisals of memory lapses

When participants reported at least one memory lapse, they were asked to rate its negative impact in two domains: irritation ("How much did forgetting these things bother you?") and interference ("How much did forgetting these things interfere with your routine today?"). Participants responded to both measures for both prospective and retrospective items using a scale ranging from 1 (not at all) to 10 (very much), leading to four outcome measures: prospective irritation ($M_{\text{reliability}} = 0.78$), prospective interference ($M_{\text{reliability}} = 0.70$), retrospective irritation ($M_{\text{reliability}} = 0.77$), and retrospective interference ($M_{\text{reliability}} = 0.72$). Higher values indicated more negative impact from memory lapses.

Covariates

Chronological age (measured in years, hereafter age) was included as a covariate and tested as a moderator. Unless otherwise specified, all covariates included were from Wave 2. All models adjusted for sex (male vs female), race/ethnicity (non-Hispanic white vs all other groups), education (1-12, highest grade completed; continuous), and self-rated health (1-5, poor to excellent; continuous). Race and ethnicity categories were combined because the number of participants identifying as Hispanic ethnicity was relatively small ($n=33$, 1.88%), which limited statistical stability for separate subgroup analyses. Behavioral health covariates included: average alcohol use in the past month (none; <1-4 days/week; ≥ 5 days/week), smoking status (never/former/current), and regular exercise or physical activity (yes/no). Models also included Wave 3 daily stress exposures based on the Daily Inventory of Stressful Events (range: 0-4),³⁸ specified at the within-person day-level to adjust for day-to-day context in models of daily memory lapses.

Statistical analysis

We first calculated descriptive statistics and summary scores at both person and day levels. Next, we used multilevel modeling to account for the nested structure of the data (days at level 1 nested within persons at level 2). Multilevel Poisson regression models were conducted to determine the associations between epigenetic clocks and the frequency of each type of daily memory lapse (ie, prospective and retrospective). To assess whether the associations between epigenetic clocks and daily memory lapses varied by chronological age, we added interaction terms between epigenetic clocks and age. A Monte Carlo simulation based on the primary DunedinPACE $\times$ age interaction model indicated that the analytic sample provided 91% power to detect this interaction. Simple slope analyses were subsequently performed to illustrate significant interaction effects.

We conducted multiple sensitivity analyses. First, while we used age at Wave 3 in the analyses to be concurrent with the timing of the daily memory lapse assessments, we also adjusted for elapsed years between Waves 2 and 3 to determine whether the findings were influenced by variability in the timing between the biological aging assessment and the daily memory lapse assessment across participants. Second, we included an additional interaction term between DunedinPACE and quadratic age (age²) to check for non-linear associations with age. We then estimated multilevel logistic regression models in which each type of memory lapse was re-coded as a binary outcome (ie, 0 = no memory lapse; 1 = at least one memory lapse) to test whether the findings were sensitive to the low-frequency/zero-inflated distribution of memory lapse variables. As a final sensitivity analysis, we additionally adjusted for baseline Brief Test of Adult Cognition by Telephone (BTACT) composite scores as an indicator of objective cognitive performance to examine whether associations between DunedinPACE and daily memory lapses were independent of general cognitive functioning.

For appraisals of memory lapses (1-10 scale of irritation and interference ratings for prospective and retrospective lapses),

we fit linear multilevel mixed-effects models with restricted maximum likelihood (REML) estimation. These models included both main effects and DunedinPACE $\times$ age interaction terms. Person-level continuous variables were grand-mean centered, and the day-level variable was person-mean centered. All analyses were performed using Stata 19 (Stata Corporation, College Station, TX, USA).

Results

Table 1 summarizes the descriptive characteristics of key variables. The average age of respondents was 60.74 years ($SD=9.63$), and 63% of respondents ($n=146$) were female. More than two-thirds ($n=163$; 71%) were non-Hispanic whites. Over half of the participants ($n=130$; 56%) were nonsmokers (ie, never smokers), and 29% ($n=67$) were former smokers. About one third ($n=82$, 35.34%) reported no alcohol consumption in the past month. Respondents recorded an average of 0.28 and 0.48 prospective and retrospective types of memory lapses per day, respectively. Of those reporting prospective memory lapses, the perceived consequences were reported as 1.41 and 1.57 for irritation and interference, respectively. For retrospective memory lapse appraisals, respondents recorded severity as 1.57 for irritation and 1.20 for interference. Zero-order correlations between the continuous study variables are shown in Table S1.

Table 2 presents the multilevel Poisson model results for the associations between epigenetic clocks and each type of memory lapse. There were no statistically significant main effects of epigenetic clocks on the daily number of prospective or retrospective memory lapse types in adjusted models (Table 2, Model 2). However, a significant DunedinPACE $\times$ age interaction emerged for both prospective lapses (IRR = 0.81, 95% CI [0.71, 0.92], $p < .01$) and retrospective lapses (IRR = 0.86, 95% CI [0.77, 0.97], $p < .05$; Table 2, Model 3). Interpreted in the original DunedinPACE unit, each additional year of the mean age, the per-unit DunedinPACE effect on the expected daily number of prospective memory lapse types endorsed is multiplied by 0.81, and the expected daily number of retrospective memory lapse types endorsed is multiplied by 0.86. This result implies that for each additional year of age, the association between faster biological aging and prospective memory lapse types is reduced by $\sim 19\%$ and $\sim 14\%$ for retrospective memory lapses.

In all analyses, we used age from Wave 3 to align with the timing of the daily memory lapse assessment. Given that the timing between Wave 2 and Wave 3 data collections varied across participants, we performed sensitivity analyses that added elapsed years (age at Wave 3—age at Wave 2) as an additional covariate. Elapsed-years was not significant and did not change the results (see Table S2); thus, we report models that only included Wave 3 age.

Figure 1 demonstrates the fitted interaction results for prospective memory lapse types endorsed (Panel A). The Johnson-Neyman plots illustrate the specific ages for which DunedinPACE is significantly associated with the number of prospective memory lapse types per day (Panel B).^{39,40} To probe the DunedinPACE $\times$ age interaction, we estimated simple slopes for four age groups: 45, 55, 65, and 75, corresponding to

Table 1 Descriptive statistics of main study variables ($N = 232$).

Variables	n (%) / mean (SD)	Range
PhenoAge residuals	-4.20 (5.87)	-23.81 to 15.98
GrimAge2 residuals	-3.17 (4.84)	-14.26 to 10.55
DunedinPACE	0.99 (0.13)	0.53 to 1.37
Age (in years)	60.74 (9.63)	43 to 91
40-49	35 (15.09)	
50-59	71 (30.60)	
60-69	80 (34.48)	
70-79	39 (16.81)	
80-91	7 (3.02)	
Female	146 (62.93)	
Non-Hispanic White	163 (70.56)	
Education	7.48 (2.62)	1 to 12
Self-rated health	3.69 (0.92)	1 to 5
Smoking		
None	130 (56.03)	
Former	67 (28.88)	
Current	35 (15.09)	
Alcohol use		
None	82 (35.34)	
<1 to 4 drinks per week	118 (50.86)	
≥5 drinks per week	32 (13.79)	
Engaging in regular exercise (yes)	182 (78.45)	
Daily measures		
Prospective memory (PM) lapses	0.28 (0.62)	0 to 5
Retrospective memory (RM) lapses	0.48 (0.80)	0 to 4
PM Irritation	1.41 (1.33)	1 to 10
PM Interference	1.15 (0.80)	1 to 10
RM Irritation	1.57 (1.56)	1 to 10
RM Interference	1.20 (0.90)	1 to 10
Number of daily stressors	0.49 (0.73)	0 to 4

Total number of daily assessments = 1757. Epigenetic aging variables and health behavioral variables (smoking, alcohol use, and regular exercise) were obtained from the MIDUS Biomarker Project 2 assessment. Demographic variables and self-reported health were obtained from MIDUS 2. Daily memory lapse and daily stressor variables were obtained from NSDE 3. Race and ethnicity were combined because the number of participants identifying as Hispanic ethnicity was relatively small in the analytic sample. Regular exercise was coded dichotomously (0 = no, 1 = yes).

Abbreviations: MIDUS, Midlife in the United States; NSDE, National Study of Daily Experiences.

Table 2 Multilevel Poisson regression models of DunedinPACE.

	Prospective memory lapse						Retrospective memory lapse					
	Model 1: Unadjusted		Model 2: Adjusted		Model 3: Age moderation		Model 1: Unadjusted		Model 2: Adjusted		Model 3: Age moderation	
	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI	IRR	95% CI
DPACE	2.26	0.55-9.32	1.65	0.33-8.16	8.38*	1.29-54.39	0.61	0.17-2.17	0.59	0.15-2.35	2.04	0.39-10.64
Age			0.99	0.98-1.02	1.00	0.99-1.02			1.01*	1.00-1.03	1.02*	1.01-1.04
DPACE × Age					0.81**	0.71-0.92					0.86*	0.77-0.97

Adjusted models include biological sex, race/ethnicity, education, self-rated health, alcohol use, smoking, exercise, and daily stressors.

** $p < .01$. * $p < .05$.

Abbreviations: DPACE, DunedinPACE; IRR, incidence rate ratio.

participants in their 40s, 50s, 60s, and 70+. These analyses revealed that higher DunedinPACE was associated with more frequent reporting of prospective lapse types among participants in their 40s ($B = 1.30$, $SE = 0.60$, $p = .029$). For retrospective lapses, higher DunedinPACE was associated with fewer lapses 10 years later among adults 70 years of age or older ($B = -1.73$, $SE = 0.86$, $p = .044$) (see Figure 2B). Full simple slope estimates for all age strata are provided in Table S3. To examine potential non-linear effects of age, we tested a quadratic age × DunedinPACE interaction term. The results indicated no significant quadratic effect (see Table S4). For sensitivity analysis, we conducted multilevel logistic regression models by coding the outcomes as a binary variable indicating whether participants endorsed at least one memory lapse type any given day (ie, none versus at least once). The results were consistent with the primary analyses, suggesting that the findings were robust across different modeling approaches (see Table S5).

Table 3 presents the results for the association of DunedinPACE and its interaction with age and appraisals of endorsed prospective memory lapse types. The unadjusted model (Model 1) indicated that higher DunedinPACE was significantly associated with more irritation from prospective memory interference ($b = 0.50$, $SE = 0.23$, $p = .031$). However, this effect diminished after adjusting for the covariates.

Further, significant interaction effects emerged between DunedinPACE and age for both prospective irritation ($b = -0.10$, $SE = 0.04$, $p = .017$) and prospective interference ($b = -0.005$, $SE = 0.02$, $p = .024$), indicating that the association between DunedinPACE and prospective memory appraisals was stronger among younger respondents. Figure 1 presents the fitted interaction results for prospective memory lapse irritation (C) and interference (E). The Johnson-Neyman plots illustrate the specific ages for which DunedinPACE is significantly associated with prospective memory lapse irritation (D) and interference (F). Associations of memory lapse occurrence or appraisals were not significant with the second-generation clocks PhenoAge and GrimAge (Tables S7 and S8).

The simple slope analyses using the DunedinPACE findings revealed that the association was significant only among respondents in their 40s. Specifically, higher DunedinPACE was significantly associated with higher prospective irritation ($B = 1.77$, $SE = 0.84$, $p = .036$) and prospective interference ($B = 1.05$, $SE = 0.47$, $p = .024$) for respondents in their 40s. More detailed results can be found in Table S5. Nonsignificant results for PhenoAge and GrimAge from the Poisson regression models

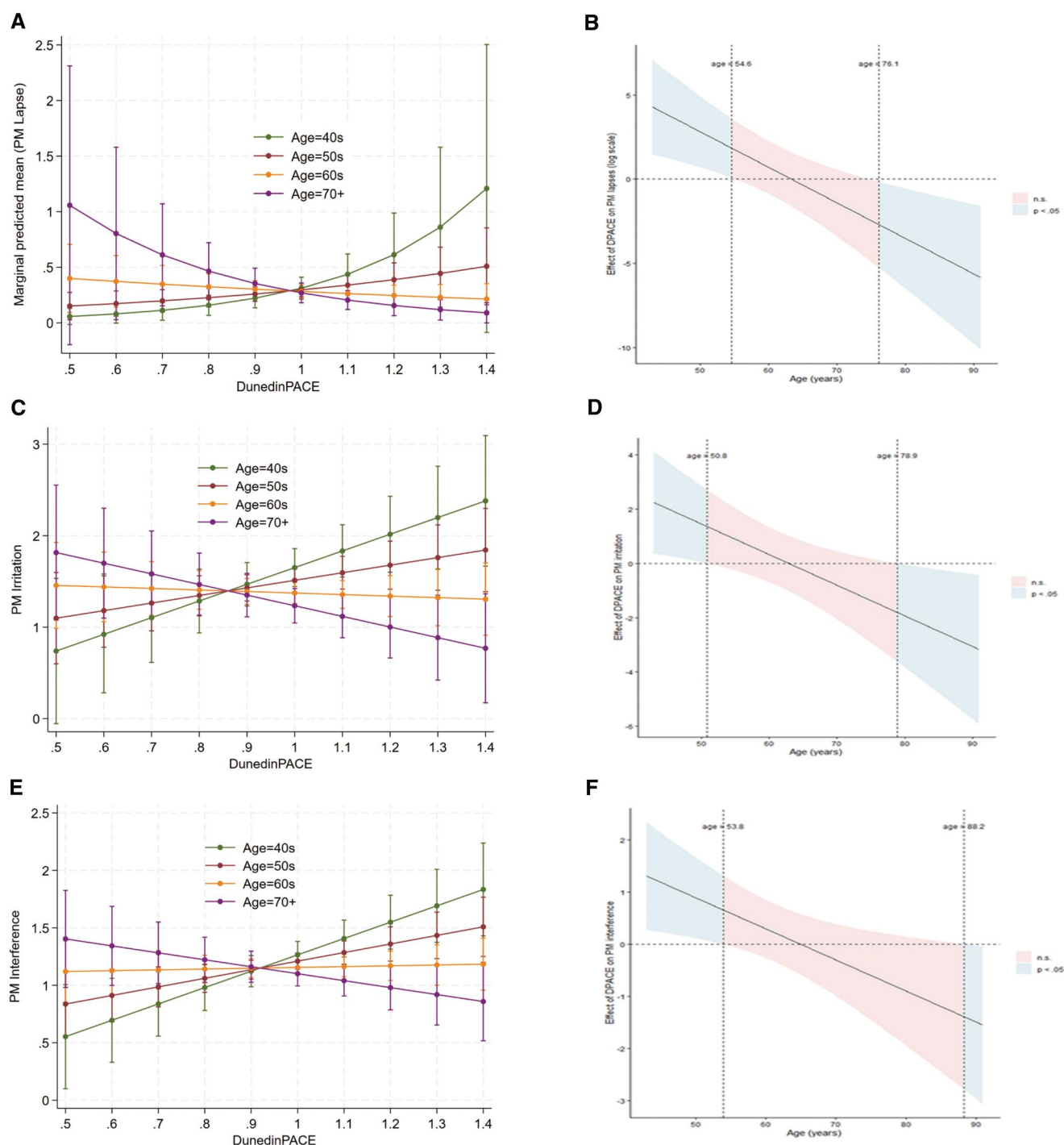


Figure 1 Association of DunedinPACE and prospective memory lapses. (A, C, E) Interaction effects of DunedinPACE and age on prospective memory lapse frequency, irritation, and interference, respectively. (B, D, F) Moderating role of age (years) in the association between DunedinPACE and prospective memory lapse frequency, irritation, and interference, respectively, estimated via Johnson-Neyman test ($\alpha = 0.05$). Shaded areas mark significant (blue) and non-significant (pink) age ranges for the simple effect of DunedinPACE.

Abbreviations: n.s., not significant; PM, prospective memory lapse.

are presented in Table S7, and the results from appraisals of irritation and interference related to prospective memory lapses are presented in Table S8. In addition, to evaluate potential selection bias, we compared included and excluded participants from the NSDE 3 on demographic and health characteristics (see

Table S9). Included participants were slightly younger and less likely to identify as non-Hispanic White than excluded participants. No significant differences were observed in education, self-rated health, or objective cognitive functioning (BTACT). As a final sensitivity analysis, we additionally adjusted for baseline

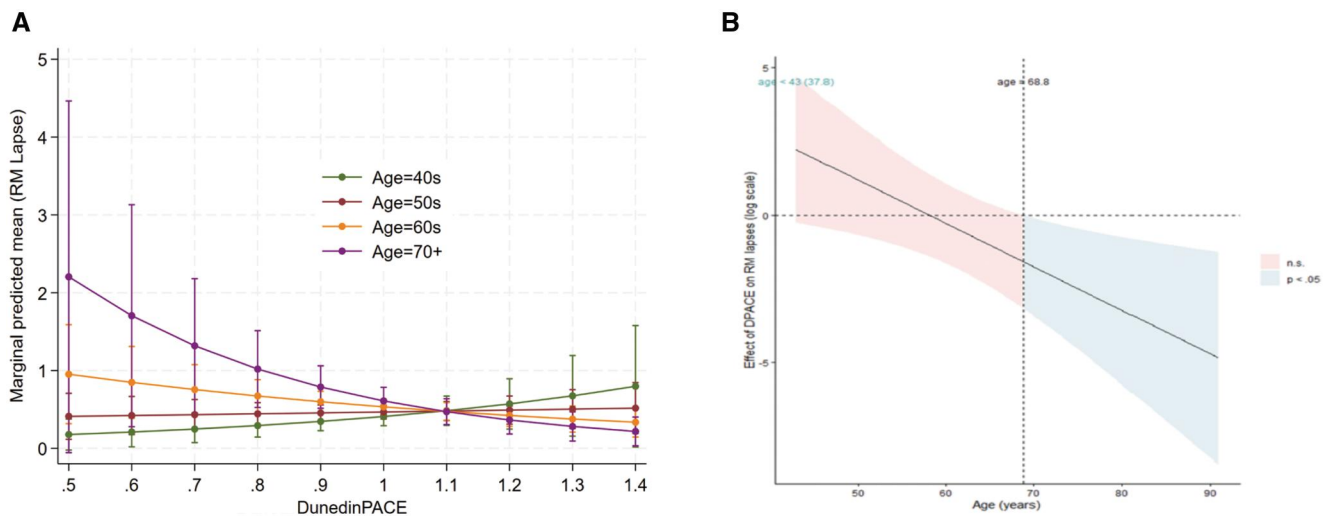


Figure 2 Association of DunedinPACE and retrospective memory lapse frequency. (A) Interaction effect of DunedinPACE and age on prospective memory lapse frequency. (B) Moderating role of age (years) in the association between DunedinPACE and retrospective memory lapse frequency. Abbreviations: n.s., not significant; RM, retrospective memory lapse.

BTACT cognitive performance. The overall pattern of findings was substantively similar to the results of primary analyses, suggesting that the association was independent of general cognitive performance (see Table S10).

Discussion

The current study examined the rate of epigenetic aging (ie, DunedinPACE) and how it was related to subjective memory lapses and their resulting irritation and interference. Results showed that this association varied by chronological age for both prospective and retrospective memory lapse occurrence. For prospective lapses, a faster pace of aging was associated with more frequent lapse occurrence only for younger midlife adults in their 40s and not for other age groups (50s, 60s, and 70s+). Additionally, a faster pace of aging was significantly associated with more prospective irritation and prospective interference among respondents when they were in their 40s. The unique association with DunedinPACE suggests that daily memory lapses are closely related to ongoing aging dynamics, consistent with the idea that these everyday cognitive indicators may capture subtle cognitive experiences relevant to early cognitive vulnerability.^{7,41} The interaction effects further suggest that associations between DunedinPACE and prospective memory lapses may emerge earlier in adulthood, particularly among adults in their 40s, when prospective memory lapses may reflect subtle variability in daily cognitive functioning. In contrast, epigenetic aging was significantly associated with retrospective memory lapses only for older adults aged 70+, where a faster rate of epigenetic aging was associated with fewer retrospective lapses for this age group. Epigenetic aging was not associated with appraisals of retrospective memory lapses regardless of age.

Our findings showed that an increase in the rate of epigenetic aging is associated with longitudinal changes in functional outcomes for younger midlife adults. Notably, a 10% increase in the rate of aging in an individual's 40s is indicative of reporting to forget nearly 1 additional memory lapse event per day a decade

later (see Table 2, Model 3, $b=0.81$ and $b=0.86$). Early midlife is marked by increased responsibilities related to family, time, and work demands, resulting in more opportunities for memory lapses. Moreover, these memory lapses may be more consequential and frustrating for younger midlife adults, as the impact on daily life can be more disruptive. This interpretation is consistent with lifespan studies emphasizing midlife as a critical period in which individuals balance demands, as well as growth and decline across domains.^{6,33} Additionally, the original DunedinPACE algorithm was trained with a sample of individuals, distinct from the MIDUS sample, who provided blood samples between 26 and 45 years of age; therefore, this particular measure of rate of aging may have added power when studying midlife populations.⁹

The null findings between epigenetic aging acceleration and prospective memory lapses in the older cohorts could be due to fewer daily opportunities or a lack of awareness that a memory lapse occurred. For example, comparative underreporting of prospective memory relative to retrospective memory in older respondents in this study may reflect underreporting, reduced awareness, or true differences in daily demands. For example, older adults may not realize they have forgotten to do something until they receive a reminder of the missed task later (eg, receiving a "bill past due" letter in the mail). The retrospective memory lapse items, in contrast, are more immediately obvious.⁶ Reduced awareness of cognitive difficulties and discrepancies in memory performance have been well documented in older adults in the context of cognitive decline.⁴² Indeed, while older age has been related to greater odds of reporting retrospective memory lapses, age was not related to the odds of reporting a prospective memory lapse.⁶

Age differences in association between epigenetic age acceleration and memory lapses

Other studies examining cognitive task performance have provided evidence of epigenetic aging predicting cognitive changes

Table 3 Multilevel mixed-effects models with DunedinPACE: Irritation and interference of prospective memory lapses.

	Irritation						Interference					
	Model 1: Unadjusted		Model 2: Adjusted		Model 3: Age moderation		Model 1: Unadjusted		Model 2: Adjusted		Model 3: Age moderation	
	<i>b</i> (SE)	<i>p</i>	<i>b</i> (SE)	<i>p</i>	<i>b</i> (SE)	<i>p</i>	<i>b</i> (SE)	<i>p</i>	<i>b</i> (SE)	<i>p</i>	<i>b</i> (SE)	<i>p</i>
DSPACE	0.56 (0.43)	.196	0.12 (0.49)	.801	0.94 (0.59)	.112	0.50 (0.23)	.031*	0.19 (0.27)	.496	0.62 (0.33)	.060
Age			−0.01 (0.01)	.055	−0.01 (0.01)	.148			−0.001 (0.003)	.657	−0.001 (0.003)	.989
DSPACE × Age					−0.10 (0.04)	.017*					−0.005 (0.02)	.024*

Adjusted models include biological sex, race/ethnicity, education, self-rated health, alcohol use, smoking, exercise, and daily stressors.

**p* < .05.

Abbreviation: DSPACE, DunedinPACE.

in older populations across various measures of global cognition,^{43,44} executive functioning,⁴³ and memory.⁴⁵ DunedinPACE was developed using aging-relevant biomarkers across multiple organ systems from participants aged 26–45.⁹ In this way, it may be particularly sensitive in younger cohorts to pre-clinical instances of cognitive impairment, such as subjective memory complaints, relative to traditional age-prediction-based epigenetic clocks. Traditional, macro-scale performance-based cognitive measures, such as objective cognitive assessments administered to a participant, may be more sensitive to the cumulative effects of aging and non-linear neurological changes. On the other hand, subjective measures of cognitive health, such as daily memory lapses, may better capture aspects of ambulatory cognitive functioning, as cognitive functioning varies widely within individuals, across cognitive domains, and across days, aligning with prior work on within-person variability in cognitive aging.⁴⁶ Fluctuations in cognitive functioning are not discounted by averaging across multiple days, with daily measures providing a less aggregated representation of an individual's cognitive health and status.

Role of DunedinPACE for predicting memory lapses

Compared to prior-generation biological clocks, with high predictive validity for mortality risk, DunedinPACE was developed to interrogate multi-system physiological integrity and may have increased sensitivity when predicting specific phenotypic outcomes, such as cognitive changes.^{10,32} In fact, DunedinPACE has demonstrated a more consistent pattern of significant associations across a wide variety of objective cognitive measures as compared to the first- and second-generation clocks.⁹ The present study extends this prior work by establishing a link between DunedinPACE and subjective daily memory lapses and situates this work within extant literature on intensive repeated measurements that have established strong links between daily stress processes and overall cognitive performance.^{47,48} Self-rated constructs that are consistently linked to mortality are also significantly associated with increased DunedinPACE, which suggests a need for a combinatorial approach that incorporates both subjective and objective factors in health assessments.⁴⁵ Belsky and colleagues⁹ reported that participants who have negative health self-reports showed higher DunedinPACE, demonstrating the utility of self-reports for understanding systemic risk

for functional decline. Taken together, memory lapses and blood biomarker assessments signal a breakdown in system resilience, consistent with broader theories representing aging as a consequence of multisystem dysregulation.⁴⁹

While the current analyses were not designed to test mechanistic pathways, emerging evidence indicates that DNAm-based measures reflect many poor health outcomes.⁵⁰ Epigenetic clocks have repeatedly been associated with systemic inflammatory phenotypes and poor metabolic and vascular phenotypes, and in turn, with cognitive performance and trajectories, including preclinical brain aging and dementia risk. Mechanistically, inflammatory signaling, increased neuroinflammation,⁵¹ reduced brain vascular integrity, and impaired plasticity are implicated in poor brain health and reduced prospective memory functioning.⁵² In addition, epigenetic aging may alter gene expression patterns relevant to neuronal maintenance and stress responsivity,^{50,53,54} contributing to subtle disruptions in everyday cognitive performance. The stronger associations observed in early midlife may indicate that this is a period in which emerging biological dysregulation begins to manifest in subjective cognitive experiences but is not yet detectable via objective cognitive tests or more extensive neuropathology. Studies that integrate cognitive data with epigenetic and biological data are needed to directly evaluate and clarify the mechanisms linking accelerated biological aging to early cognitive vulnerability.

Limitations, future directions, and conclusions

There are many established measures of biological aging, with each incorporating unique quantification strategies and unique cell-, tissue-, and disease-related markers, which may limit comparability across studies. DNAm assays also present technical limitations, including measurement error⁵⁵ and variability arising from inherent differences in training models and probe selection (reviewed in Chervova et al.⁵⁶). Although DunedinPACE addresses these drawbacks by filtering probes and incorporating longitudinal data from a single birth cohort, these methodologies may introduce additional generalizability constraints and may not fully eliminate measurement-related limitations.

There was an approximately 10-year spacing of time between when the blood draws were collected to measure DunedinPACE and when memory lapses were measured in the NSDE. As

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