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Original Article

Accelerated biological aging and midlife frailty among U.S. military veterans

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Abstract

Injuries characterizing recent military service, such as traumatic brain injury and posttraumatic stress disorder, are linked to accelerated biological aging. If recent veterans have accelerated aging, they might also show early onset of aging-related phenotypes, such as frailty. In this study, we examined the prevalence of frailty and associations with biological aging using data from 1,654 post-9/11 veterans, who were followed for an average of 12.6 years. Biological aging was assessed using DunedinPACE, and frailty was assessed using 11 years of Jen Frailty Index scores from electronic health records. We found a high proportion of frailty—25.5% of post-9/11 veterans met frailty criteria during the study. This is roughly double the prevalence among community-dwelling older adults, despite the cohort's average age of 50.2 years at study end. Veterans with faster aging had higher initial frailty scores (β, 0.21; 95% CI, 0.15–0.27), higher peak frailty scores (β, 0.24; 95% CI, 0.18–0.30), and larger increases in frailty scores over time (β, 0.15; 95% CI, 0.09–0.21, all *ps* < .001). Faster aging was associated with a 62% (95% CI, 44%–82%) greater rate of incident frailty over the follow-up, while accounting for demographics, baseline health, and smoking. These results suggest post-9/11 veterans are at risk of early onset frailty, and this increased risk could be explained by accelerated rates of biological aging. Future research should replicate these results in nationally representative samples of post-9/11 veterans and explore whether screening for frailty should be implemented at younger ages for veterans.

Keywords: Biological aging, Frailty, Veterans, Military service, Post-9/11

Introduction

U.S. military personnel who served during the Gulf War or post-9/11 period will represent over 80% of living veterans within the next two decades.[1] Even now, these cohorts comprise the largest plurality of the 18 million living veterans,[1] and this proportion will grow over time. The injuries that characterized these periods of military service[2]—including traumatic brain injury, posttraumatic stress disorder, and exposure to environmental toxins—have been linked to poor health and accelerated rates of biological aging.[3–12] Accelerated aging is hypothesized to represent a "common cause" of multiple chronic diseases and premature mortality,[13–17] with cumulative effects on health that compound over time. Given risk for accelerated biological aging among Gulf War and post-9/11 veterans,[10] it is important

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to characterize whether these cohorts also show increased risk for aging-related phenotypes, particularly at younger ages than might be traditionally expected.

Frailty is a health-relevant phenotype associated with advanced chronological age.[13] Defined as a syndrome comprising lower levels of physical reserve and functioning,[18] frailty is typically assessed in older age, with a prevalence of 10%–15% of community-dwelling older adults.[19,20] If veterans who served during the post-9/11 period are biologically aging at an accelerated rate, it is possible that frailty will occur earlier in this population, particularly for veterans with faster aging. This would align with recent research showing post-9/11 veterans with accelerated biological aging are at greater risk of developing chronic disease and premature mortality[21] and evidence that non-veterans with faster aging have greater risk of frailty.[22] Frailty is associated with poorer prognosis after surgery,[23] multimorbidity,[24] and mortality,[25] including during midlife,[14] highlighting the importance of this aging-related phenotype.

In the current study, we examined the prevalence of frailty in a cohort of veterans ($n = 1{,}654$) who served in the post-9/11 period.[26] Veterans were largely in adulthood or midlife and averaged 50.2 years old at study end, at which point 91.1% were younger than 65. We also examined whether faster biological aging was associated with claims-based frailty scores assessed using Veteran Affairs' (VA) electronic health records (EHR). To do so, we used DunedinPACE,[27] a third-generation epigenetic measure of aging trained on longitudinal change in multiple biomarkers to index the rate of individuals' biological aging.[28,29] We also tested whether results varied based on whether veterans served during the Gulf War and provided results for two second-generation clocks (PC-GrimAge, PC-PhenoAge[30]).

Methods

Participants and study design

Veterans were enrolled from 2005 to 2016 in the Veterans Integrated Service Networks 6 (VISN 6) Mental Illness Research, Education, and Clinical Center (MIRECC) Post-Deployment Mental Health Study,[26] a multi-site study of veterans who served in the post-9/11 period. The Durham, Richmond, W.G. Bill Hefner VA and Central Virginia VA Health Care Systems' Institutional Review Boards approved the study protocol, and all participants provided informed consent. Prospective assessment of frailty included the period from 2014 to the end of 2024. Veterans in the Post Deployment Mental Health (PDMH) were included in this study if they had DNA methylation (DNAm) and EHR-derived frailty scores, resulting in a sample of 1,654 veterans (Figure S1, see online supplementary material for a color version of this figure). The sample (1,279 men, 375 women) included 841 non-Hispanic Black veterans and 813 non-Hispanic White veterans. Full cohort demographic characteristics are included in Table S1, and missingness among study variables is reported in Table S2.

Measures

Biological aging

Whole blood was collected at the baseline PDMH assessment and analyzed using the Infinium HumanMethylation450 or MethylationEPIC v1.0 Beadchip (Illumina Inc., San Diego, CA) to derive DNAm data.[11,21] Internal replicates were checked for consistency using single nucleotide polymorphisms on each array. Quality control was performed using the minfi[31] and ChAMP[32] R packages. Probe quality control and data normalization were performed within each batch using the R package wateRmelon.[33] Raw beta values were normalized using the dasen approach, and batch and chip adjustments were completed using ComBat in the R package sva.[34] DunedinPACE, PC-GrimAge, and PC-PhenoAge scores were generated using published algorithms.[27,30,35] PC-GrimAge and PC-PhenoAge were also residualized on chronological age.[30]

Technical DNAm covariates

A dummy variable was created to denote whether DNAm data were generated using 450k or EPIC chips. Estimated white blood cell counts [T lymphocytes (CD4+ and CD8+), B cells (CD19+), monocytes (CD14+), NK cells (CD56+) and neutrophils] were derived using FlowSorted.Blood.450k and FlowSorted.Blood.EPIC packages.[36]

Frailty

Frailty was assessed using the JEN Frailty Index[25,37] (JFI), a risk score generated using EHR claims-based data over a 1-year lookback. JFI scores include 13 domains: minor ambulatory limitations, severe ambulatory limitations, chronic mental illness, chronic developmental disability, dementia, sensory disorders, self-care impairment, syncope, cancer, chronic medical disease, pneumonia, renal disorders, and other systemic disorders. Annual JFI scores were generated by Geriatrics & Extended Care Data & Analysis Center (GECDAC) using VA and VA-paid community care data from 2014 (the first year such data were made available) to 12/31/2024, resulting in 11 years of JFI scores. Veterans had an average of 9.6 frailty scores over the 11 years of assessment, with 74.2% having 10 or 11 scores. Scores ranged from 0 to 12 in this sample. In line with prior work,[25,37] scores of 6 or greater indicated frailty.

Baseline health

Baseline health was assessed using Charlson Comorbidity Index scores generated from chronic disease diagnoses in the VA EHR,[38,39] as described previously.[21]

Smoking

Lifetime exposure to tobacco[40] was assessed using a validated DNAm measure.[41]

Demographics

Participants reported their age, sex, race, ethnicity, and years of education. Sex, race, and ethnicity self-reports were confirmed using genetic data.

Data analysis

We first examined the prevalence of frailty in the PDMH cohort. We then specified models that tested associations between DunedinPACE aging scores and frailty scores. These included initial frailty scores, peak frailty scores (maximum JFI score), and change in frailty scores over time. Initial frailty and change in frailty were calculated using latent variable scores

derived from a latent growth curve model. Exported intercept and slope factor scores represented initial frailty and change in frailty, respectively. We next specified models assessing frailty status, specifically whether DunedinPACE was associated with reaching frailty (eg, JFI scores ≥ 6) for any JFI assessment or new onset among veterans who did not have frailty at their initial JFI assessment. We also report receiver operating curve (ROC) analysis results predicting frailty status. General linear models predicting JFI scores and frailty status accounted for missing data using full information maximum likelihood estimation. Survival models predicting frailty onset used Cox-proportional hazard models and excluded individuals with frailty at the initial assessment (*n*, 40) or missing baseline covariate data (*n*, 47). All models adjusted for baseline health, demographics (age, gender, race and ethnicity, and education), technical DNAm covariates (chip type, white blood cell count proportions), year of enrollment to account for differences in time to initial frailty assessment, and smoking. Models assessing change in frailty also controlled for initial frailty. Estimates were scaled to 1 *SD* of DunedinPACE aging scores, and models were run in MPLUS[42].41

Results

We first examined the frailty characteristics and prevalence in the cohort. Average JFI scores increased from 2.44 in 2014 (2.7% frailty) to 3.62 in 2024 (14.1% frailty; frailty proportions by year are in Table S2). Over follow-up, 25.5% of post-9/11 veterans met criteria for frailty during at least one assessment, including 24.6% of veterans younger than 65—compared to 34.5% of the 148 veterans older than 65.

Biological aging and frailty scores

We next examined associations between DunedinPACE aging scores and frailty scores. Veterans with faster DunedinPACE had higher initial frailty scores (β, 0.21; 95% CI, 0.15–0.27, $p < .001$; Figure 1) and higher peak frailty scores (β, 0.24; 95% CI, 0.18–0.30; $p < .001$). Over the next decade, veterans with faster DunedinPACE also had larger increases in their frailty scores (β, 0.15; 95% CI, 0.09–0.21; $p < .001$).

Biological aging and frailty status

We then examined associations between DunedinPACE aging scores and frailty status. Veterans with faster DunedinPACE were 85% more likely to meet criteria for frailty over the study (*OR*, 1.85; 95% CI, 1.59–2.17; $p < .001$). Among veterans who did not meet criteria for frailty at baseline, faster DunedinPACE were associated with a 61% increased rate of new onset frailty during follow-up (*HR*, 1.61; 95% CI, 1.42–1.83, $p < .001$; Figure 2).

When examining frailty status using ROC analyses, DunedinPACE independently showed a fair ability to predict frailty (AUC = 0.66, 95% CI, 0.63–0.69). This predictive strength was equal to using a combination of demographics and baseline health status (AUC = 0.66, 95% CI, 0.63–0.69) and larger than using baseline health status alone (AUC = 0.57, 95% CI, 0.53–0.60). AUC increased to acceptable levels when DunedinPACE and other DNAm-derived measures (cell counts, smoking methylation scores) were added to demographics and baseline health status (AUC = 0.71, 95% CI, 0.68–0.73).

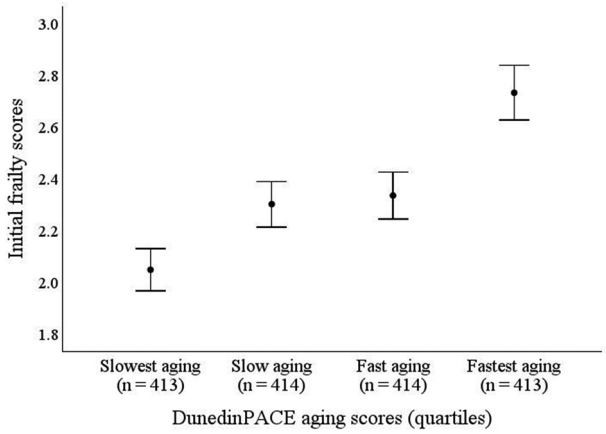
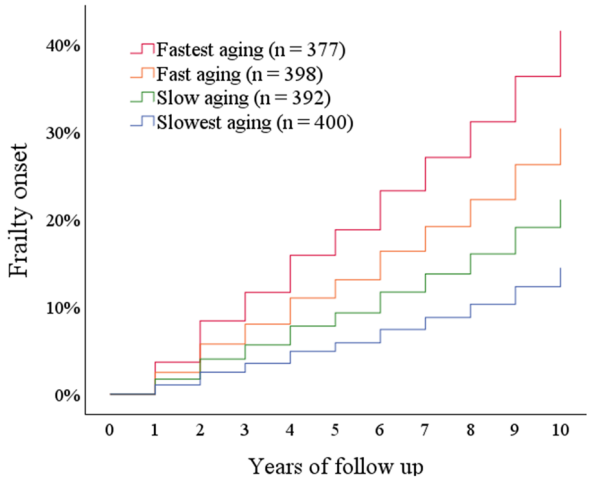


Figure 1. Initial frailty scores derived from latent growth curve modeling and grouped by quartiles of the normalized DunedinPACE aging scores (slowest aging ≤ −0.66 *SD* below the mean, −0.65 *SD* ≤ slow aging ≤ −0.02 *SD*, −0.02 *SD* ≤ fast aging ≤ 0.68 *SD*, and 0.69 *SD* ≤ fastest aging. Error bars represent 95% confidence intervals. Statistical tests in the main text used continuous DunedinPACE scores unless otherwise noted (ie, aging quartiles were created for visualization only).



No. at risk

Full sample	1567	1497	1422	1360	1291	1224	1141	1042	925	848	811
Fastest aging	377	351	326	305	284	262	242	218	196	157	145
Fast aging	398	382	363	345	326	309	281	258	229	175	168
Slow aging	392	382	366	353	340	327	311	288	255	204	191
Slowest aging	400	382	367	357	341	326	307	278	245	183	178

Figure 2. Survival curves illustrating onset (1—survival) of frailty among veterans who did not meet criteria for frailty in their first assessment (ie, incident frailty) grouped by quartiles of DunedinPACE aging scores. Compared to the slowest aging group (reference), veterans were more likely to become frail if they were in the slow aging group (*OR*, 1.61; 95% CI, 1.12–2.32; $p = .011$), fast aging group (*OR*, 2.32; 95% CI, 1.62–3.33; $p < .001$), or fastest aging group (*OR*, 3.44; 95% CI 2.34–5.06; $p < .001$). Proportions of frailty during any period of this study for these groups ranged from 12.1% for the slowest aging group, to 21.3% for the slow aging group, 28.5% for the fast aging group, and 40.0% for the fastest aging group. Statistical tests in the main text used continuous DunedinPACE scores unless otherwise noted (ie, aging quartiles were created for visualization only).

Gulf War status

A subset of post-9/11 veterans (*n*, 497; 30%) served during the Persian Gulf War. We tested whether these veterans showed similar patterns of frailty and aging to veterans who did not serve in the Gulf War period. As might be expected, Gulf War

veterans were older at study end ($M = 59.6$ years old; $SD = 6.0$) compared to non-Gulf War veterans ($M = 46.2$ years old; $SD = 8.9$). Gulf War veterans were more likely to meet criteria for frailty during the study (32.8% compared to 22.3%), though this difference was fully accounted for by differences in chronological age. Epigenetic age was associated with initial frailty, peak frailty, change in frailty, frailty status, and frailty onset to a similar degree among veterans who did and did not serve during the Gulf War period. In short, post-9/11 veterans who served during the Gulf War had a greater prevalence of frailty due to an older average age, but associations with DunedinPACE were consistent across the post-9/11 cohort, regardless of Gulf War status.

Sensitivity analyses

We conducted three sensitivity analyses. First, we linked DunedinPACE aging scores to the intercept and slope of frailty in latent growth curve models and showed that all results replicated in an integrated structural equation model (Supplemental Analysis 1).

Second, we moderated our primary associations by sex, race and ethnicity, and age. None of the associations for frailty outcomes (initial frailty, peak frailty, change in frailty, frailty status, and frailty onset) were moderated by these characteristics, with one exception. Age moderated the association between DunedinPACE and change in frailty scores over time (β, 0.06; 95% CI, 0.01–0.11; $p = .023$), such that DunedinPACE was more strongly associated with change in frailty among older veterans.

Third, to benchmark associations using other validated epigenetic measures of aging, we ran our primary models using two principles components-based (PC-based) epigenetic clocks, PC-GrimAge and PC-PhenoAge.[30] Broadly, PC-GrimAge showed similar magnitudes of associations as DunedinPACE, including significant associations with initial, peak, and new onset frailty. PC-PhenoAge also showed significant associations with frailty, though the magnitudes were smaller than those for PC-GrimAge and DunedinPACE. Notably, PC-GrimAge nor PC-PhenoAge were not associated with a change in frailty scores, and the predictive strength associated with frailty status was lower for both measures (both AUCs = 0.55, 95% CI 0.51–0.58) compared to DunedinPACE (AUC = 0.66). Full results are in Supplemental Analysis 2.

Discussion

In a cohort of 1,654 post-9/11 veterans predominantly in adulthood or midlife, we found over a quarter of the veterans screened positive for frailty during at least one year of assessment. This was despite more than 90% of the cohort being under 65 years of age, averaging 50 years old at study end. The proportion of frailty in this sample was roughly double the proportions observed among community-dwelling older adults (10%–16%)[19,20] and similar to the proportion of frailty in veterans over 65 years old (23.2%).[37] Beyond overall prevalence, we also found that post-9/11 veterans with faster biological aging had higher frailty scores and were more likely to become frail. Each *SD* increase in DunedinPACE was associated with an 85% increased risk of reaching frailty criteria and a 62% greater likelihood of developing new onset frailty over the decade of follow-up. Frailty was 3.3 times more common among the fastest aging veterans (40.0%) when compared to the slowest aging veterans (12.1%; Figure 2).

Notably, our model estimates accounted for baseline health status, smoking, and demographics, suggesting that aging scores capture more than simply health or multimorbidity. In fact, the increased risk for frailty associated with a 1 *SD* increase in DunedinPACE (61%) was roughly 3.5 times larger than the increased risk associated with a 1 *SD* change in baseline health status (17%). DunedinPACE aging scores showed fair ability to predict frailty status independently (AUC = 0.66), equal to the predictive strength of all demographic and baseline health status variables combined, and larger than baseline health status alone. When added to the demographic covariates, baseline health status, and other DNA-derived measures, DunedinPACE further increased the overall ability to predict frailty to acceptable levels (AUC = 0.71, ΔAUC = .05). These results suggest epigenetic measures of aging, particularly DunedinPACE, might be useful in predicting future risk for frailty, particularly when combined with other commonly collected demographic characteristics.

These findings provide additional validation that faster biological aging, particularly assessed by DunedinPACE, is associated with phenotypes that are expected to accompany more rapid aging and advanced chronological age. Of particular interest is that multiple epigenetic measures of aging, including two second-generation epigenetic clocks (PC-GrimAge and PC-PhenoAge) predicted both initial frailty and new onset frailty, though only DunedinPACE was associated with a change in frailty and showed fair levels of prediction. These results suggest DunedinPACE is capturing both initial frailty as well as prospective changes in frailty. DunedinPACE[27] was the first epigenetic measure of aging trained on longitudinal change in biomarkers over multiple decades,[28] which may help strengthen prospective associations. Evidence of predictive validity helps support the utility of epigenetic measures of aging as surrogate health outcomes in observational cohort studies and randomized control studies[28,29] when it is not feasible or desirable to wait years for clinical events (eg, disease or death). This utility could support the rapid testing and dissemination of geroprotective interventions, which is particularly relevant given recent evidence that epigenetic measures of aging are responsive to longevity and healthspan interventions.[43]

Our results have clinical implications, particularly for health systems—such as the Veterans Health Administration (VHA)—that provide care to veterans who served during the 21st century. Veterans from recent periods of military service (eg, post-9/11 and Gulf War eras) already represent the largest group of living veterans, and this proportion will grow over time.[1] Accelerated aging can increase risk for many costly diseases and premature mortality.[21] Veterans from these eras are largely in midlife and may experience age-related health concerns, such as frailty, earlier than typically expected. Future research should address whether screening tools used to assess risk among older adults should be implemented at younger ages for these cohorts, aiming to detect frail or pre-frail veterans younger than 65. Early identification of frailty is critical, as it is linked to important clinical endpoints relevant to the VHA and other health systems, including risk of suicide attempts,[44] long-term institutionalization,[25,34] and mortality.[25,45]

Our findings point to an opportunity to intervene to slow aging and prevent the onset of chronic disease. The VHA has

a number of efficacious behavioral interventions, including the Gerofit,[46] Whole Health,[47] and MOVE[48] programs, which might also help slow aging. Similarly, glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have shown efficacy in reducing veterans' risk for a wide array of chronic diseases,[49] raising the possibility that GLP-1 medication might slow aging by reducing body mass or other changes in physiological function.[50] Providing behavioral or pharmacological interventions that might slow aging to veterans with accelerated midlife aging who are seeking care at the VA could help prevent the onset of disease, disability, and premature mortality. In addition, many U.S. veterans do not receive VA health care in any given year. Educating community providers on the characteristics and needs of post-9/11 veterans, including the potential for accelerated aging and early onset of frailty, would help support non-VA providers in delivering the highest quality care to veterans in community care settings.

The results of the current study should be interpreted within the context of several limitations. First, our EHR-derived measure of frailty can only capture data from VA sources that are included in medical records. Although these records include diagnoses for community care accessed through the VA, it is possible that these results will not generalize to veterans who have not received any care from VA sources or civilian populations. Similarly, JFI scores may not fully capture the entirety of the frailty phenotype and were provisioned using VA data beginning in 2014. Other self-report or functional measures of frailty would be important to test in future studies of post-9/11 veterans. Second, our results are observational and cannot determine whether accelerated aging causes increased incidence of frailty in this sample. Third, the PDMH largely includes post-9/11 veterans from VA hospitals in the mid-Atlantic region, who are likely to have high rates of healthcare utilization.[26] This cohort may not fully represent Gulf War or post-9/11 veterans' health or biological aging characteristics. Future studies should aim to examine midlife frailty in a representative sample of post-9/11 veterans.

Conclusions

In this study, we found that post-9/11 veterans had a high prevalence of frailty (25.5%) assessed using claims-based data, even though 90% of the sample was younger than 65 years old. In addition, we found that veterans with accelerated biological aging were at higher risk for frailty, including higher initial frailty and greater risk for incident frailty. These findings suggest post-9/11 veterans are at greater risk for frailty than might be expected given the age of this cohort, and that this risk might be explained, at least in part, by faster rates of biological aging in this population.

Supplementary material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of interest

Drs Terrie Moffitt and Avshalom Caspi are named as inventors on a license issued by Duke University for DunedinPACE. The algorithm to calculate DunedinPACE is publicly available: https://github.com/danbelsky/DunedinPACE. No other authors have conflicts of interest to report.

Data availability

Data from the Post Deployment Mental Health (PDMH) Study are part of a Veterans Affairs data repository and are available to researchers who request access through the VISN 6 MIRECC and follow the appropriate data access protocols. Medical record data from the Veteran Affairs Corporate Data Warehouse are available to researchers who request and are approved for access through the Office of Research and Development (ORD) Data Access Request Tracker (DART).

Author contributions

Concept and design: Kyle J. Bourassa, Kirsten H. Dillon, Avshalom Caspi, Terrie E. Moffitt, Harvey Jay Cohen, Nathan A. Kimbrel. Acquisition, analysis, and interpretation of data: Kyle J. Bourassa, Livia Anderson, Paul A. Dennis, Melanie E. Garrett, Allison E. Ashley-Koch. Drafting of manuscript: Bourassa. Critical revisions of the manuscript: Kirsten H. Dillon, Livia Anderson, Paul A. Dennis, Melanie E. Garrett, Harvey Jay Cohen, VA Mid Atlantic MIRECC Workgroup, Jennifer C. Naylor, Allison E. Ashley-Koch, Jean C. Beckham, Avshalom Caspi, Gregory A. Taylor, Katherine S. Hall, Terrie E. Moffitt, Nathan A. Kimbrel. Statistical analysis: Kyle J. Bourassa, Paul A. Dennis, Melanie E. Garrett. Obtained funding: Kyle J. Bourassa, Jennifer C. Naylor, Jean C. Beckham, Nathan A. Kimbrel. Administrative, technical, or material support: Livia Anderson, Melanie E. Garrett, Paul A. Dennis.

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