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Research Report

Association of Epigenetic Age Acceleration With Incident Mild Cognitive Impairment and Dementia Among Older Women

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Abstract

Background: Epigenetic age acceleration (AgeAccel), which indicates faster biological aging relative to chronological age, has been associated with lower cognitive function. However, the association of AgeAccel with mild cognitive impairment (MCI) or dementia is not well-understood. We examined associations of 4 AgeAccel measures with incident MCI and dementia.

Methods: This prospective analysis included 578 older women from the Women's Health Initiative Memory Study selected for a case–cohort study of coronary heart disease (CHD). Women were free of CHD and cognitive impairment at baseline. Associations of AgeAccel measures (intrinsic AgeAccel [IEAA], extrinsic AgeAccel [EEAA], AgeAccelPheno, and AgeAccelGrim) with risks for incident adjudicated diagnoses of MCI and dementia overall and stratified by incident CHD status were evaluated.

Results: IEAA was not significantly associated with MCI (HR, 1.23; 95% CI, 0.99–1.53), dementia (HR, 1.10; 95% CI, 0.88–1.38), or cognitive impairment (HR, 1.18; 95% CI, 0.99–1.40). In stratified analysis by incident CHD status, there was a 39% (HR, 1.39; 95% CI, 1.07–1.81) significantly higher risk of MCI for every 5-year increase in IEAA among women who developed CHD during follow-up. Other AgeAccel measures were not significantly associated with MCI or dementia.

Conclusions: IEAA was not significantly associated with cognitive impairment overall but was associated with impairment among women who developed CHD. Larger studies designed to examine associations of AgeAccel with cognitive impairment are needed, including exploration of whether associations are stronger in the setting of underlying vascular pathologies.

Epigenetic clocks are DNA methylation (DNAm)-based biomarkers estimating the underlying biological age (ie, DNAm age) of a cell or tissue (1). DNAm age represents underlying innate aging processes (eg, intracellular changes that lead to a loss of cellular identity and cell composition changes) that are linked to declines in tissue function that occur with aging (1). A higher DNAm age relative to chronological age, or "epigenetic age acceleration (AgeAccel)," indicates faster biological aging of a cell or tissue than expected based on chronological age alone (1). AgeAccel has been associated with higher risks of many age-related phenotypes, including cardiovascular disease, cancer, and all-cause mortality (1). However, the association of AgeAccel with cognitive outcomes is less well-understood.

Some studies have linked blood-based AgeAccel to lower cognitive function (2–5). A meta-analysis among 4 535 White and African American adults observed that AgeAccel was associated with lower verbal fluency (3). A prospective study among 304 White and African American adults found an association of AgeAccel with cognitive decline among men on tests evaluating visual memory/visuoconstructive ability and attention/processing speed (2). To our knowledge, only one prior study examined AgeAccel in relation to dementia, and no study has examined adjudicated mild cognitive impairment (MCI) (6,7). Few studies have the data to evaluate the prospective relationship between AgeAccel, MCI, and dementia.

In this prospective analysis, we examined whether 4 measures of blood-based AgeAccel were associated with higher risks of MCI and dementia among older women.

Method

Study Design

The Women's Health Initiative Memory Study (WHIMS), an ancillary study to the WHI Hormone Therapy (HT) trials, investigated the effects of hormone therapy on cognitive outcomes among 7 427 women 65–80 years without cognitive impairment at randomization in 1995–1998 (8). Annual follow-up for cognitive outcomes continued through 2007. In 2008, WHIMS transitioned to annual telephone-administered cognitive assessments in the WHIMS Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO) study (N = 2 900), which is currently ongoing (9).

This prospective analysis included WHIMS women who were selected for a WHI ancillary study to identify genomic determinants of coronary heart disease (CHD). The ancillary study was a nested case–cohort of 2 098 women from the larger WHI without baseline CHD (10). Cases were defined as the first incident adjudicated myocardial infarction, angina, coronary revascularization, or CHD death through March 1, 2019. DNAm analyses were performed using baseline blood samples (ie, when women were randomized into WHIMS) at HudsonAlpha Institute of Biotechnology (Huntsville, AL) with the Illumina Infinium HumanMethylation450 BeadChip (Illumina, Inc., San Diego, CA), which measures DNAm at 485 577 CpG sites (11). The DNAm data protocol is described elsewhere (11). A total of 578 women free of CHD and cognitive impairment at WHIMS baseline were included in the final analytic sample (Supplementary Figure 1). This study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Epigenetic Age Acceleration

DNAm age was determined for 4 different epigenetic clocks using the Horvath age calculator (https://dnamage.genetics.ucla.edu/). AgeAccel was the residual from a linear regression model regressing DNAm age on chronological age; a positive value indicates faster epigenetic aging (ie, an individual is biologically older than their years) and a negative value indicates slower epigenetic aging (ie, an individual is biologically younger than their years). We analyzed 4 AgeAccel measures, which were weakly to moderately correlated with each other (range of correlation coefficients, 0.09–0.47).

Intrinsic epigenetic age acceleration
Intrinsic epigenetic age acceleration (IEAA) was developed using the Horvath clock (12), which uses 353 CpGs to define DNAm age. The Horvath clock can estimate the DNAm age of any cell or tissue and has shown similar brain and blood cell DNAm ages (12). IEAA was defined as the residual from regressing DNAm age on chronological age and estimated measures of white blood cell counts (naïve cytotoxic T cells, late differentiated cytotoxic T cells, and plasma B cells) to control for confounding from blood cell composition changes that occur with aging (13). IEAA measures cell-intrinsic methylation changes, representing a fundamental cell aging process that is widely conserved across cell types (1).

Extrinsic epigenetic age acceleration
Extrinsic epigenetic age acceleration (EEAA) is based on Hannum's DNAm age, calculated using 71 CpGs. EEAA is a weighted average of DNAm age and estimated white blood cell counts that change with age (13,14). EEAA was computed as the residual variation of a univariate model regressing the weighted DNAm age estimate on chronological age. EEAA tracks intrinsic epigenetic changes and age-related changes in white blood cell-type composition.

AgeAccelPheno
AgeAccelPheno was the residual of a linear regression model regressing PhenoAge on chronological age. PhenoAge was estimated using an algorithm based on 513 CpGs highly predictive of a composite measure of various physiological indicators (eg, albumin, glucose) and chronological age. AgeAccelPheno has outperformed both IEAA and EEAA in predicting age-related phenotypes across multiple tissues, including brain and blood (15).

AgeAccelGrim
AgeAccelGrim was the residual of a linear regression model regressing GrimAge on chronological age (16). GrimAge was developed in 2 stages (16). First, DNAm-based surrogates of pack-years of smoking and 12 plasma proteins (eg, cystatin C, adrenomedullin), including several that were associated with cognitive function and other age-related phenotypes, were identified. In the second stage, time-to-mortality was regressed on the DNAm-based surrogates identified in the first step. In total, 1 030 CpG sites that jointly predicted mortality risk were identified to estimate GrimAge.

Outcomes

MCI and dementia were ascertained and adjudicated annually through December 31, 2019. The WHIMS protocol for detecting

MCI and dementia is described elsewhere (8). Briefly, participants completed the Modified Mini-Mental State Examination, with those scoring below specific cut points (<80 for those with ≤8 years of education and <88 for those with ≥9 years of education) completing a modified Consortium to Establish a Registry for Alzheimer's Disease battery of neuropsychological tests and standardized tests. A physician with expertise in dementia diagnosis classified women as having no dementia, MCI, or probable dementia. MCI diagnosis was based on Petersen's criteria, and dementia diagnosis was based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria. All data were sent to the WHIMS Clinical Coordinating Center for review and central adjudication of final diagnosis by an adjudication panel consisting of a neurologist, geriatric psychiatrist, and geropsychologist. WHIMS-ECHO used a common, validated protocol of telephone-based cognitive assessments and informant interviews (8), and a similar protocol to that of WHIMS for ascertainment and central adjudication of final diagnosis.

Statistical Analysis

Associations of AgeAccel measures with MCI and dementia were determined using Cox proportional hazards regression models. AgeAccel measures were analyzed as continuous variables, with separate models for each AgeAccel measure. MCI and dementia were examined separately and together. MCI and dementia outcomes were not mutually exclusive; for example, there were women with MCI who also developed dementia. Similar to previous WHIMS studies, follow-up time was defined from the date of WHIMS randomization (study baseline), when DNA data were collected, to the date of the cognitive assessment that triggered the first diagnosis of MCI or dementia, or the date of the final cognitive assessment, whichever came first (17). Models were adjusted for the following potential confounders collected at the baseline visit, which were selected based on prior studies of AgeAccel and cognitive function (2–4): chronological age, hormone therapy trial arm, race/ethnicity, education, body mass index, smoking, alcohol consumption, hypertension, diabetes, and low density lipoprotein (LDL) cholesterol. Models were also adjusted for CHD, given the case–cohort design of the study from which AgeAccel measures were derived. Models were not adjusted for baseline cognitive function (Modified Mini-Mental State score) or depressive symptoms, as these factors did not appreciably change the findings. We lacked data on APOE e4 status for all women to control for this factor. We calculated power for the minimum effect size detectable with ≥80% power for a 1-year increase in AgeAccel, assuming $\alpha = 0.004$ (due to examination of 4 epigenetic clocks across 3 outcomes) and a 5% standard deviation (*SD*). There was power to detect an HR of 1.11 in MCI (*N* = 540) and dementia (*N* = 543) analyses. There was power to detect an HR of 1.08 in combined cognitive impairment analyses (*N* = 578).

Models were stratified by incident CHD status, given that vascular pathologies are associated both with AgeAccel and cognitive impairment (1,18,19). We hypothesized that associations of AgeAccel with cognitive outcomes would therefore be stronger in women with underlying vascular pathologies. Interactions were tested by including product terms of AgeAccel measures with incident CHD status in the models. Models among women without incident CHD did not control for diabetes, due to limited numbers of women with diabetes. The timing of CHD diagnosis with respect to MCI or dementia diagnosis was not considered, as the objective of the stratified analysis was to determine whether findings vary by underlying vascular pathologies. The proportional hazards

assumption was assessed using Kolmogorov-type supremum tests using cumulative sums of martingale residuals. We also conducted sensitivity analyses including stroke as part of the definition of CHD in our analyses, given that stroke is associated with higher risk of dementia (19).

Statistical analyses were conducted using SAS, Version 9.4. Multiple imputation was used to impute missing covariates via the fully conditional specification method in the PROC MI procedure in SAS. The following covariates had missing data (all <2.5%): education, smoking, body mass index, hypertension, diabetes, alcohol consumption, and LDL. All variables in the multivariable model were used for imputation. Models were fit for each of 10 imputed data sets, and results were pooled across models.

Results

Mean age was 70.2 (*SD* 3.9) years, 299 developed CHD during follow-up, and 279 did not develop CHD (Table 1). During a mean follow-up of 11.2 (*SD* 5.5, range 0.9–22.3) years, 55 (9.5%) of 578 women developed MCI, 59 (10.2%) developed dementia, and 94 (16.3%) developed cognitive impairment (ie, MCI or dementia).

IEAA was not significantly associated with MCI (HR, 1.23; 95% CI, 0.99–1.53), dementia (HR, 1.10; 95% CI, 0.88–1.38), or cognitive impairment (HR, 1.18; 95% CI, 0.99–1.40) (Table 2). Associations of other AgeAccel measures with MCI, dementia, or cognitive impairment were not significant.

Among women who developed CHD during follow-up, every 5-year increase in IEAA was significantly associated with 39% (HR, 1.39; 95% CI, 1.07–1.81) higher risk of MCI (Table 3). IEAA was not significantly associated with higher risk of dementia (HR, 1.19; 95% CI, 0.91–1.56) but was associated with a 24% (HR, 1.24; 95% CI, 1.01–1.52) significantly higher risk of cognitive impairment among women who developed CHD. Other AgeAccel measures were not significantly associated with these outcomes in women who developed CHD. There were no significant associations with cognitive outcomes among women who did not develop CHD. There were no significant interactions between AgeAccel measures and CHD in the models (Table 3). In sensitivity analyses including stroke as part of the definition of CHD, findings were similar (data not shown).

Discussion

In this preliminary analysis among older women, associations of AgeAccel measures with cognitive outcomes did not reach statistical significance. In stratified analysis, we found that every 5-year increase in IEAA was significantly associated with 39% higher risk of MCI among women who developed CHD. This finding suggests that the epigenetic aging process as assessed by IEAA may precede and accelerate neuropathological brain aging among older women with underlying vascular pathologies. Findings should be interpreted with caution, however, due to the relatively small number of MCI and dementia cases and limited power.

Associations of AgeAccel measures with cognitive function have been mixed. A small study found a significant association of higher EEAA but not IEAA with cognitive decline in men (2). A recent study in male twins found that IEAA, but not EEAA, AgeAccelGrim, or AgeAccelPheno, was associated with a decline in executive function and memory function, independent of smoking, body mass index, hypertension, and alcohol (5). A prior study among 488 White older adults showed no associations of IEAA, EEAA, AgeAccelGrim, or

Table 1. Baseline Characteristics of Study Sample, Women's Health Initiative Memory Study

	Overall	Developed CHD	Did Not Develop CHD	*p* Value
Age, years, mean (*SD*)	70.2 (3.9)	70.3 (3.7)	70.0 (4.0)	.27
Race/ethnicity, no. (%)				
White	518 (89.6)	267 (89.3)	251 (90.0)	.84
African American	43 (7.4)	22 (7.4)	21 (7.5)	
Hispanic	17 (2.9)	10 (3.3)	7 (2.5)	
Educational level*, no. (%)				
Less than high school	43 (7.5)	25 (8.4)	18 (6.5)	.14
High school	129 (22.4)	62 (20.8)	67 (24.2)	
Some college	233 (40.5)	132 (44.3)	101 (36.5)	
College graduate	170 (29.6)	79 (26.5)	91 (32.9)	
Smoking status†, no. (%)				
Never smoker	314 (55.2)	155 (52.5)	159 (58.0)	.41
Past smoker	218 (38.3)	119 (40.3)	99 (36.1)	
Current smoker	37 (6.5)	21 (7.1)	16 (5.8)	
Alcohol consumption‡, no. (%)				
Nondrinker	82 (14.3)	34 (11.5)	48 (17.3)	.002
Past drinker	96 (16.7)	64 (21.6)	32 (11.6)	
Current drinker	396 (69.0)	199 (67.0)	197 (71.1)	
Body mass index, kg/m², mean (*SD*)	28.6 (5.5)	28.9 (5.4)	28.2 (5.7)	.11
Diabetes§, no. (%)	43 (7.5)	35 (11.7)	8 (2.9)	<.001
Hypertension‖, no. (%)	323 (56.0)	200 (66.9)	123 (44.2)	<.001
LDL cholesterol, mmol/L, mean (*SD*)	154.9 (38.3)	157.1 (38.0)	152.5 (38.6)	.16
IEAA, mean (*SD*)	–0.04 (5.27)	0.01 (5.47)	–0.10 (5.05)	.80
EEAA, mean (*SD*)	0.15 (6.73)	0.52 (6.87)	–0.24 (6.56)	.18
AgeAccelGrim, mean (*SD*)	–0.28 (3.58)	–0.03 (3.55)	–0.54 (3.60)	.09
AgeAccelPheno, mean (*SD*)	–0.12 (7.01)	0.20 (7.37)	–0.47 (6.59)	.25

Notes: AgeAccelGrim = epigenetic age acceleration according to GrimAge clock; AgeAccelPheno = epigenetic age acceleration according to PhenoAge clock; CHD = coronary heart disease; EEAA = extrinsic epigenetic age acceleration; IEAA = intrinsic epigenetic age acceleration; LDL = low density lipoprotein; *SD* = standard deviation. *N* for overall sample = 578; *N* for developed CHD = 299; *N* for did not develop CHD = 279.

  *Out of 575 women (298 with CHD; 277 without CHD).

  †Out of 569 women (295 with CHD; 274 without CHD).

  ‡Out of 574 women (297 with CHD; 277 without CHD).

  §Out of 575 women (299 with CHD; 276 without CHD).

  ‖Out of 577 women (299 with CHD; 278 without CHD).

Table 2. Associations of Epigenetic Age Acceleration With Incident MCI and Dementia Among Older Women, Women's Health Initiative Memory Study (*N* = 578)

	No. of Cases of MCI or Dementia	Age- and Race/Ethnicity-Adjusted HR (95% CI)*	Multivariable-adjusted HR (95% CI)*,†
MCI	55		
IEAA		1.16 (0.94, 1.44)	1.23 (0.99, 1.53)
EEAA		1.07 (0.88, 1.29)	1.11 (0.91, 1.34)
AgeAccelGrim		0.78 (0.53, 1.14)	0.88 (0.57, 1.37)
AgeAccelPheno		1.13 (0.93, 1.36)	1.14 (0.94, 1.39)
Dementia	59		
IEAA		1.05 (0.85, 1.31)	1.10 (0.88, 1.38)
EEAA		0.93 (0.77, 1.13)	0.98 (0.80, 1.19)
AgeAccelGrim		1.00 (0.69, 1.44)	1.00 (0.67, 1.50)
AgeAccelPheno		1.03 (0.85, 1.25)	1.06 (0.87, 1.29)
Cognitive impairment	94		
IEAA		1.14 (0.97, 1.35)	1.18 (0.99, 1.40)
EEAA		1.02 (0.88, 1.18)	1.05 (0.91, 1.22)
AgeAccelGrim		0.93 (0.70, 1.25)	0.94 (0.68, 1.31)
AgeAccelPheno		1.08 (0.93, 1.26)	1.10 (0.94, 1.28)

Notes: AgeAccelGrim = epigenetic age acceleration according to GrimAge clock; AgeAccelPheno = epigenetic age acceleration according to PhenoAge clock; CHD = coronary heart disease; CI = confidence interval; EEAA = extrinsic epigenetic age acceleration; HR = hazard ratio; HT = hormone therapy; IEAA = intrinsic epigenetic age acceleration; LDL = low density lipoprotein; MCI = mild cognitive impairment.

  *HRs represent 5-year increases in epigenetic age acceleration associated with MCI and dementia.

  †Model adjusted for chronological age, HT trial arm, race/ethnicity, education, body mass index, smoking, alcohol consumption, CHD, diabetes, hypertension, and LDL cholesterol (*N* = 578).

Table 3. Associations of Epigenetic Age Acceleration With Incident MCI and Dementia by Incident CHD Status Among Older Women, Women's Health Initiative Memory Study*

	Developed CHD[†]		Did Not Develop CHD[‡]	
	Age- and Race/Ethnicity-Adjusted HR (95% CI)[§]	Multivariable-Adjusted HR (95% CI)[§]	Age- and Race/Ethnicity-Adjusted HR (95% CI)[§]	Multivariable-Adjusted HR (95% CI)[§]
MCI[l]				
IEAA	1.23 (0.96, 1.57)	1.39 (1.07, 1.81)	0.98 (0.67, 1.44)	1.00 (0.66, 1.53)
EEAA	1.14 (0.89, 1.46)	1.26 (0.95, 1.66)	0.95 (0.70, 1.30)	0.95 (0.69, 1.30)
AgeAccelGrim	0.70 (0.42, 1.18)	0.98 (0.54, 1.80)	0.85 (0.47, 1.55)	0.80 (0.40, 1.59)
AgeAccelPheno	1.15 (0.91, 1.44)	1.23 (0.95, 1.58)	1.06 (0.78, 1.45)	1.06 (0.77, 1.45)
Dementia[¶]				
IEAA	1.14 (0.88, 1.47)	1.19 (0.91, 1.56)	0.99 (0.68, 1.45)	1.02 (0.67, 1.54)
EEAA	1.00 (0.79, 1.28)	1.06 (0.80, 1.40)	0.88 (0.65, 1.19)	0.89 (0.65, 1.22)
AgeAccelGrim	0.85 (0.51, 1.42)	0.86 (0.50, 1.49)	1.18 (0.67, 2.07)	1.28 (0.69, 2.38)
AgeAccelPheno	1.04 (0.82, 1.32)	1.07 (0.82, 1.39)	1.06 (0.78, 1.43)	1.09 (0.80, 1.49)
Cognitive impairment[#]				
IEAA	1.18 (0.96, 1.43)	1.24 (1.01, 1.52)	1.06 (0.79, 1.42)	1.08 (0.78, 1.48)
EEAA	1.10 (0.90, 1.34)	1.17 (0.94, 1.45)	0.93 (0.73, 1.18)	0.94 (0.74, 1.19)
AgeAccelGrim	0.86 (0.58, 1.28)	0.93 (0.60, 1.45)	0.99 (0.64, 1.55)	0.96 (0.58, 1.59)
AgeAccelPheno	1.09 (0.91, 1.31)	1.11 (0.91, 1.35)	1.07 (0.84, 1.36)	1.11 (0.87, 1.41)

Notes: AgeAccelGrim = epigenetic age acceleration according to GrimAge clock; AgeAccelPheno = epigenetic age acceleration according to PhenoAge clock; CHD = coronary heart disease; CI = confidence interval; EEAA = extrinsic epigenetic age acceleration; HR = hazard ratio; HT = hormone therapy; IEAA = intrinsic epigenetic age acceleration; LDL = low density lipoprotein; MCI = mild cognitive impairment.

*Models were adjusted for chronological age, HT trial arm, race/ethnicity, education, body mass index, smoking, alcohol consumption, hypertension, and LDL cholesterol. Models for CHD were additionally adjusted for diabetes.

[†]*N* for MCI analysis = 277, *N* for dementia analysis = 279, *N* for cognitive impairment analysis = 299; *n* = 32 incident MCI, *n* = 34 incident dementia, and *n* = 54 cognitive impairment.

[‡]*N* for MCI analysis = 262, *N* for dementia analysis = 264, *N* for cognitive impairment analysis = 279; *n* = 23 incident MCI, *n* = 25 incident dementia, and *n* = 40 incident cognitive impairment.

[§]HRs represent 5-year increases in epigenetic age acceleration associated with MCI and dementia.

[l]*p* Values for interaction with incident CHD status were: .15 (IEAA); .21 (EEAA); .79 (AgeAccelGrim); and .32 (AgeAccelPheno).

[¶]*p* Values for interaction with incident CHD status were: .44 (IEAA); .51 (EEAA); .32 (AgeAccelGrim); and .96 (AgeAccelPheno).

[#]*p* Values for interaction with incident CHD status were: .30 (IEAA); .24 (EEAA); .56 (AgeAccelGrim); and .69 (AgeAccelPheno).

AgeAccelPheno with dementia, independent of age, sex, smoking, APOE e4 status, and history of CHD (6). However, in contrast to our study, dementia was determined from medical records, which resulted in less sensitive detection; MCI was not examined; and interactions with CHD were not tested (6). We observed a significant association of IEAA with MCI among women who developed CHD but observed no associations for other clocks. Whereas the other clocks are based on either white blood cell counts, blood-based physiological indicators, or plasma proteins, IEAA is based on Horvath's clock, which was developed using more than 30 different cell types and tissues (including brain and blood) (12). This may partly explain IEAA's significant association with cognitive function in a prior study and its association with MCI in women who developed CHD in our study (5). Differential DNAm across the genome has been previously associated with dementia, supporting a role of epigenetic mechanisms in cognitive health (20). Vascular pathologies have been associated both with AgeAccel and cognitive impairment (1,18,19). However, the potential links between the underlying DNAm aging process to vascular pathologies and cognitive impairment need further investigation.

Strengths of this study include a well-characterized cohort, long follow-up, rigorous adjudication of MCI/dementia, and examination of 4 epigenetic clocks. The magnitudes of the associations of IEAA with MCI and cognitive impairment overall and especially among women with CHD were noteworthy, but many associations were not significant, likely due to limited numbers of MCI and dementia cases. It is possible that low cognitive function was associated with loss to follow-up, which may have led to undercounting of MCI and dementia cases. AgeAccel data came from a case–cohort study of CHD that was not specifically designed to determine associations of AgeAccel with cognitive outcomes. Finally, classification of dementia subtypes was not available.

These initial findings support a larger, well-powered study designed to examine associations of AgeAccel with cognitive outcomes and to determine whether associations are stronger in those with underlying vascular pathologies.

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

B.H.C. is an employee of FOXO Technologies.

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Conception or design of the work: A.H.S. and A.Z.L.; Acquisition and analysis of data: A.H.S., M.A.E., S.R.R., and S.H.; Preparation of manuscript: A.H.S.; Interpretation of data: All authors; Critical revision of the work for important intellectual content: All authors; Final approval of the version to be published: All authors.

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