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BRIEF REPORT

An Older Subjective Age Is Related to Accelerated Epigenetic Aging

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The present study examined the prospective association between subjective age and epigenetic clock in 2,253 adults (Mean age = 67.40, *SD* = 8.17) from the Health and Retirement Study. Subjective age and demographic factors were assessed in 2008/2010 and epigenetic clock was assessed in 2016 using the DNA methylation (DNAm) PhenoAge. Regression analysis revealed that an older subjective age was associated with accelerated epigenetic aging; mediation analysis revealed that self-rated health and CRP accounted for this association. The findings indicate that individuals who feel older than their chronological age are biologically older, in part because of their perceived health and inflammatory profiles.

Keywords: subjective age, epigenetic clock, inflammation, self-rated health, DNA methylation

Epigenetic clocks are estimates of biological age derived from DNA -methylation (DNAm) patterns. Epigenetic clocks are valuable markers of biological aging that explain some of the individual differences in the rate of aging and in susceptibility to age-related disease and senescence (Horvath & Raj, 2018; Levine et al., 2015). Indeed, accelerated epigenetic age, which refers to an epigenetic age that is higher than chronological age, is related to lower physical and mental fitness (Marioni et al., 2015), cognitive decline and dementia (Levine et al., 2015), and ultimately higher risk of mortality (Chen et al., 2016; Fransquet et al., 2019). Although chronological age is related to epigenetic clocks (Marioni et al., 2019), there are individual differences in the dynamics of epigenetic aging, with individuals experiencing either accelerated or slowed epigenetic aging (Horvath & Raj, 2018). These findings suggest that beyond chronological age, other factors may contribute to the rate of epigenetic aging. In particular, subjective age, how old or young individuals feel relative to their chronological age, is thought to capture a part of the heterogeneity in the rate of aging (Kotter-Grühn et al., 2016). The present study aims to extend existing knowledge by examining the relation between subjective age and epigenetic aging.

Subjective age is conceptualized as a marker of aging and has been associated with a range of age-related outcomes. An older subjective age, for example, is associated with IADL limitations (Rippon & Steptoe, 2018), greater depressive symptoms (Alonso Debreczni & Bailey, 2020), and declines in cognition (Stephan et al., 2016) over time. Furthermore, feeling older than one's chronological age is related to an increased risk of cardiovascular diseases (Stephan et al., 2020), dementia (Stephan, Sutin, Luchetti, et al., 2018), and mortality (Rippon & Steptoe, 2015; Stephan, Sutin & Terracciano, 2018).

The link between subjective age and health-related outcomes, including mortality, suggests that it may be related to epigenetic markers of aging. Indeed, accelerated epigenetic aging may be an intermediate mechanism that explains why feeling older than one's age is associated with worse health outcomes. There is already indirect evidence for an association between subjective age and epigenetic clock. Indeed, subjective age is related to a range of health, behavioral, emotional, and biological factors that have been related to epigenetic aging in past research. Specifically, an older subjective age is related to poor self-rated health (Spuling et al., 2013) which is associated with accelerated epigenetic aging (Belsky et al., 2020). An older subjective age is also associated with greater physical inactivity (Wienert et al., 2016) and poor sleep quality (Stephan et al., 2017) that are linked with accelerated epigenetic aging (Quach et al., 2017). Furthermore, feeling older than one's chronological age is associated with higher depressive symptoms (Rippon & Steptoe, 2018) and anxiety (Stephan et al., 2017), and there is evidence that depression (Han et al., 2018) and stress (Wolf et al., 2019) are related to accelerated biological aging. In addition, an older subjective age is related to lower cognitive performance (Stephan et al., 2016), which is associated with accelerated epigenetic age (Marioni et al., 2015). An older subjective age is also associated with higher body mass index (BMI; Stephan et al., 2019) that has been related to higher epigenetic age (Horvath et al., 2014). At the biological level, feeling older is related to higher systemic inflammation, illustrated by higher level of c-reactive protein (CRP; Stephan et al., 2015a), which is associated with epigenetic age acceleration (Irvin et al., 2018). This evidence thus suggests that the age individuals feel may be related to their biological age.

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Data were drawn from the Health and Retirement Study (HRS), a nationally representative longitudinal study of Americans older than 50 years. The HRS is sponsored by the National Institute on Aging (NIA-U01AG009740) and conducted by the University of Michigan. HRS data are publicly available at http://hrsonline.isr.umich.edu/.

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Using a large longitudinal sample of older adults, the purpose of the present study is to examine the prospective association between subjective age and epigenetic clock. It was hypothesized that an older subjective age would be related to accelerated epigenetic aging. Additional analyses tested whether health-related (self-rated health), behavioral (physical activity, sleep), affective (depressive symptoms, anxiety), cognitive (cognitive performance), and biological (CRP, BMI) factors mediated this association.

Method

Participants

Data were drawn from the Health and Retirement Study (HRS), a nationally representative longitudinal study of Americans older than 50 years. The HRS is sponsored by the National Institute on Aging (NIA-U01AG009740) and conducted by the University of Michigan. HRS public files used in this study were de-identified, publicly available and as a result were exempt from local IRB approval. Epigenetic clocks were obtained from a non-random subsample of people who participated in the 2016 Venous Blood Study. The sample includes all participants from the 2016 Healthy Cognitive Aging Project (HCAP) who provided blood samples, plus younger participants designated for future HCAP assessments, and a subsample of non-HCAP participants. Informed consent was obtained from all participants. Epigenetic clocks were obtained from a total of 4,018 individuals. Of these participants, complete data on subjective age and demographic factors were obtained in 2008/2010 from 2,285 participants. The final analytical sample was 2,253 participants aged from 50 to 94 years at baseline (Mean age = 67.40, SD = 8.17), after removing for outliers on subjective age. Individuals with complete data were younger (d = 0.34), had a younger subjective age (d = 0.14), more years of education (d = 0.11), and were more likely to be white, than those without complete data. No differences were found for sex. HRS data are publicly available at http://hrsonline.isr.umich.edu/.

Measures

Subjective Age

Participants were asked to report the age they felt in years using the following item "Many people feel older or younger than they actually are. What age do you feel?." Chronological age was subtracted from felt age and then divided by chronological age, resulting in a proportional discrepancy score. Positive values indicated an older subjective age and negative values indicated a younger subjective age (e.g., a subjective age = −.20 indicated feeling 20% younger than chronological age). Outliers with a score three standard deviations above or below the mean proportional discrepancy were excluded from the analysis (N = 32).

Epigenetic Clocks

The present study used data on the epigenetic clocks generated by the HRS (Crimmins et al., 2020) and made available to the public (https://hrs.isr.umich.edu). Briefly, HRS used DNA methylation assays with the Infinium Methylation EPIC BeadChip at the University of Minnesota. Methylation probes with suboptimal performance (using a detection p value threshold of 0.01) were removed from the final dataset (around 3.4%, n = 29,431 out of 866,091). Analysis for detection p value failed samples was done after removal of detection p value failed probes. A 5% cut-off (minfi) was applied to remove 58 samples, as well as sex mismatched samples and any controls (cell lines, blinded duplicates). High quality methylation data are available for 97.9% samples (n = 4,018; see, Crimmins et al., 2020).

The DNAm PhenoAge clock developed by Levine et al. (2018) was used in the present study. This DNAm clock was developed using as a criterion a composite of nine markers of tissue and immune function (albumin, creatinine, serum glucose, CRP, lymphocyte percent, mean (red) cell volume, red cell distribution width, alkaline phosphatase, white blood cell count) and age. This multisystem measure of phenotypic age was predicted by DNAm PhenoAge based on 513 CpGs in whole blood from the same sample. Based upon recent research (Stevenson et al., 2019), DNAm PhenoAge was regressed on chronological age, and residuals were used to define DNAm PhenoAge acceleration. A positive residual indicated age acceleration whereas a negative residual indicated age deceleration.

Mediators

All mediators were assessed at baseline. Self-rated health was measured with the single item, "Would you say your health is excellent, very good, good, fair, or poor?." Answers were given on a scale from 1 (*excellent*) to 5 (*poor*). Physical inactivity was computed as the mean of two items asking for the frequency of vigorous and moderate activities, using a scale from 1 "more than once a week" to 4 "hardly ever or never." Four questions were used to assess sleep quality: "How often do you have trouble falling asleep?," "How often do you have trouble with waking up during the night?," "How often do you have trouble with waking up too early and not being able to fall asleep again?," and "How often do you feel really rested when you wake up in the morning?" (reverse scored). A scale from 1 "never or rarely" to 3 "most of the time" was used. Answers to the four items were averaged, with higher score indicating lower sleep quality. Depressive symptoms were measured using the eight-item version of the Center for Epidemiologic Studies Depression scale (Wallace et al., 2000). Participants reported whether they had experienced eight specific symptoms for much of the past week. The sum of the symptoms was taken, with higher scores indicating more depressive symptoms. A five-item version of the Beck Anxiety Inventory scale was used to assess anxiety (Smith et al., 2013). Participants were asked to report how often they experienced five symptoms during the past week on a scale from 1 (*never*) to 4 (*most of the time*). The average of the five items was computed, with higher score indicating higher anxiety. Cognition was measured using the modified Telephone Interview for Cognitive Status (TICSm; Crimmins et al., 2011). The TICSm assessed episodic memory with immediate and delayed recall of 10 words, working memory with serial seven subtraction, and mental processing speed with backward counting. Performance on the three tasks was summed to give a composite TICSm score ranging from 0 to 27. BMI was derived as kg/m^2 using staff-assessed weight and height. CRP was obtained from blood samples assayed at the University of Vermont using a standard ELIZA assay. To obtain a blood sample, the participant's finger was cleansed with an alcohol swab, pricked

with a sterile lancet, and the blood droplets were placed on specially treated filter paper (see, Crimmins et al., 2013).

Covariates

Age, sex, education (in years), and race were included as covariates in each analysis.

Data Analysis

The association between subjective age and DNAm PhenoAge acceleration at follow-up was tested using regression analyses. DNAm PhenoAge acceleration was regressed on subjective age, controlling for age, sex, education, and race. The mediational role of self-rated health, physical inactivity, sleep, depressive symptoms, anxiety, cognition, BMI, and CRP was tested using the PROCESS macro, using 5,000 bootstrapped samples and 95% CI (Hayes, 2018). The mediators were included simultaneously. In addition, logistic regression analysis was conducted to identify whether subjective age was related to the likelihood of accelerated epigenetic aging. In this analysis, positive residuals (indicating accelerated epigenetic aging) were coded as 1 and negative residuals (indicating slower epigenetic aging) were coded as 0.

Two sensitivity analyses were conducted. First, an alternative measure of DNAm PhenoAge acceleration was computed by subtracting chronological age from DNAm PhenoAge and divided by chronological age. Second, we tested whether the association replicated using a first-generation epigenetic clock, the Horvath DNAm Age (see, Crimmins et al., 2020; Horvath, 2013).

Results

Descriptive statistics and correlations between all study variables are in Table 1. Regression analysis revealed that subjective age was positively related to DNAm PhenoAge acceleration without controlling for demographic covariates ($\beta = .06$, $p < .05$), and this relationship persisted when demographic factors were included ($\beta = .05$, $p < .05$; Table 2). This result suggests that an older subjective age is associated with accelerated epigenetic aging. The association between subjective age and DNAm PhenoAge acceleration was stronger than chronological age and race, and almost comparable to education and sex. Logistic regression revealed that subjective age predicted the likelihood of accelerated epigenetic aging (*OR*: 1.10, 95% CI: 1.01–1.20, $p < .05$). This result suggests that one standard deviation of an older subjective age was related to a 10% higher probability of accelerated biological aging. The mediation analysis indicates that self-rated health and CRP accounted for the association between subjective aging and epigenetic aging. Self-rated health and CRP explained 48% and 12% of the link between subjective age and DNAm PhenoAge acceleration, respectively (Table 2).

Sensitivity analyses showed that the association between subjective age and DNAm PhenoAge acceleration remained the same when a proportional discrepancy score for epigenetic aging was used ($\beta = .05$, $p < .05$). In addition, the association between an older subjective age and accelerated epigenetic aging was replicated using Horvath PhenoAge ($\beta = .04$, $p < .05$).

Table 1
Characteristics of the Sample and Bivariate Pearson Correlations Between the Variables of the Study

Variables	*M*/%	*SD*	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
1. Age	67.40	8.17	—												
2. Sex (% women)	59%	—	.07**	—											
3. Education	13.02	2.94	−.09***	.05*	—										
4. Race (% white)	86%	—	.10***	.06**	.17***	—									
5. Subjective age	−0.17	0.14	−.01	.05*	−.08***	.01	—								
6. DNAm PhenoAge	61.19	9.44	.00	.07**	−.07**	−.01	.06**	—							
7. Physical inactivity[a]	2.46	1.06	.06**	−.11***	−.20***	−.08***	.14***	.08***	—						
8. Sleep quality[a]	1.64	0.52	−.03	−.14***	−.13***	−.04	.15***	−.01	.16***	—					
9. Depressive symptoms[a]	1.12	1.74	−.06**	−.11***	−.18***	−.10***	.18***	.03	.24***	.42***	—				
10. Anxiety[a]	1.49	0.54	−.04	−.06**	−.20***	−.10***	.18***	.03	.14***	.28***	.45***	—			
11. Cognition[a]	16.17	3.79	−.22***	−.11***	.45***	.23***	−.06**	−.06**	−.17***	−.07**	−.15***	−.17***	—		
12. BMI[a]	29.78	5.86	−.14***	.02	−.08***	−.09***	.09***	−.07**	.18***	.04	.06*	.05*	−.02	—	
13. CRP[a]	3.80	8.18	−.05*	−.09***	−.15***	−.07**	.09***	.11***	.19***	.07**	.09***	.07**	−.07**	.34***	—
14. Self-rated health[a]	2.63	1.00	−.01	.00	−.28***	−.16***	.27***	.11***	.31***	.31***	.40***	.33***	−.24***	.20***	.18***

Note. $N = 2,253$.
[a] *N*'s differ because of missing data on the variables: $N_{\text{Physical Inactivity}} = 2,217$, $N_{\text{Sleep Quality}} = 2,238$, $N_{\text{Depressive Symptoms}} = 2,230$, $N_{\text{Anxiety}} = 2,227$, $N_{\text{Cognition}} = 2,238$, $N_{\text{BMI}} = 2,012$, $N_{\text{CRP}} = 1,997$, $N_{\text{Self-rated health}} = 2,251$.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 2
Summary of Regression Analysis and Bootstrap Analysis

Regression analysis[a]		Bootstrap analysis[b]				
Variables	DNAm PhenoAge β	Variables	*Effect of IV on MV* β	*Effect of MV on DV* β	*Direct effect of subjective age* β	*Indirect effect of subjective age*[c]
Age	−.01(−0.05;0.03)	Dependent variable (DV)				
Sex	.07**(0.03;0.11)	DNAm PhenoAge				
Education	−.07**(−0.11;−0.02)					
Race	−.01(−0.05;0.04)					
Subjective age	.05*(0.01;0.09)	Mediating variables (MV)			.01(−0.04;0.05)	
		Self-rated health	.25***(0.21;0.30)	.09**(0.03;0.14)		1.12(0.38;1.87)
		Physical inactivity	.11***(0.07;0.15)	.04(−0.01;0.09)		0.23(−0.04;0.54)
		Sleep quality	.15***(0.10;0.19)	−.03(−0.08;0.02)		−0.21(−0.59;0.16)
		Depressive symptoms	.17***(0.13;0.22)	−.02(−0.08;0.04)		−0.17(−0.71;0.31)
		Anxiety	.16***(0.12;0.21)	.03(−0.03;0.08)		0.21(−0.23;0.69)
		Cognition	−.03(−0.07;0.01)	.00(−0.05;0.06)		−0.008(−0.11;0.10)
		BMI	.09***(0.05;0.14)	.02(−0.03;0.07)		0.09(−0.13;0.36)
		CRP	.07**(0.03;0.12)	.08**(0.03;0.13)		0.28 (0.06;0.55)

Note. DV: dependent variable; IV: independent variable; MV: mediating variable.
[a] $N = 2,253$. [b] $N = 1839$. [c] Bootstrap estimates and 95% bias-corrected confidence interval for indirect effects of subjective age on DNAm PhenoAge through self-rated health, physical inactivity, sleep quality, depressive symptoms, anxiety, cognition, BMI, and CRP, controlling for demographic factors.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Discussion

The present study examined the association between subjective age and epigenetic clock. As expected, an older subjective age was prospectively related to accelerated epigenetic aging, controlling for demographic factors. Robustness checks indicated that the association replicated with alternative epigenetic clock markers. Furthermore, the association between subjective age and epigenetic clock was mediated by health-related and inflammatory factors. Therefore, this study extends existing knowledge by providing the novel evidence that subjective age is associated with biological age, as assessed through an epigenetic clock.

An older subjective age was related to accelerated epigenetic aging through its association with worse self-rated health and higher CRP. This finding is consistent with existing research that found that individuals who feel older than their age have riskier health-related (Spuling et al., 2013) and inflammatory profiles (Stephan et al., 2015a) that manifest in accelerated biological aging (Belsky et al., 2020; Irvin et al., 2018; Stevenson et al., 2019). Of note, self-rated health was the strongest mediating variable of the association between subjective age and epigenetic aging and the strongest predictor of epigenetic clock. This finding is consistent with evidence for the role of self-rated health as a critical subjective marker of one's health status (Idler & Cartwright, 2018) that is consistently associated with a range of age-related outcomes including mortality (Lorem et al., 2020). In contrast, there was no evidence that physical inactivity, depressive symptoms, anxiety, BMI, and cognition mediated this association. There are other pathways, however, that are also likely to operate in this relationship. Subjective age is conceptualized as a marker of aging, which encapsulates a range of biological, functional, and early life factors (Stephan et al., 2015b; Thyagarajan et al., 2019) that may be associated with epigenetic aging. For example, an older subjective age reflects lower pulmonary and muscular functions, that are related to accelerated epigenetic aging (Stevenson et al., 2019). In addition, feeling older than one's chronological age in adulthood is indicative of lower childhood intelligence (Stephan, Sutin, Kornadt, et al., 2018), which has been found to relate to accelerated epigenetic aging (Stevenson et al., 2019). Future study should evaluate additional potential mediators to further advance knowledge on the interplay between biological and phenotypical markers of aging.

This study broadly adds to existing knowledge on the correlates of epigenetic clock. Past research has identified a range of demographic, biological, lifestyle, environmental, and early-life factors that are related to epigenetic aging (Fiorito et al., 2019; Stevenson et al., 2019; Zhao et al., 2019). The present study extends this research by showing that how old or young individuals feel is a psychological factor related to accelerated epigenetic aging. In addition, the size of this association was almost comparable to the size of the association between epigenetic clock and other recognized factors such as education. Furthermore, the identification of a relationship between subjective age and epigenetic aging could inform the mechanisms that link subjective age to a range of health-related outcomes among older adults, including dementia and mortality. In particular, there is consistent evidence for an association between an older subjective age and higher dementia

(Stephan, Sutin, Luchetti, et al., 2018) and mortality risk (Stephan, Sutin & Terracciano, 2018). Accelerated epigenetic aging has also been found to relate to risk of dementia (Levine et al., 2018) and death (Chen et al., 2016). Therefore, it is likely that feeling older than one's age is predictive of higher risk of dementia and mortality in part through its association with accelerated epigenetic aging.

The present study has several strengths including the test of the prospective association between subjective age and epigenetic aging in a large sample of older adults over 6–8 years, the test of several potential mediators, and the replication of the association using different epigenetic clocks and using different methods of estimation of epigenetic age acceleration. There are also several limitations. Causal interpretations were not possible because of the observational design of this study. Although subjective age was considered as a predictor of epigenetic clock, it is also likely that reciprocal relationships may exist. Indeed, accelerated epigenetic aging may predict an older subjective age over time. The findings are specific to a U.S. sample, and more research is needed to test whether the pattern of results generalizes to other cultures. The relationships between subjective age and the mediators were cross-sectional. Although subjective age may predict health-related, behavioral, affective, cognitive, and biological factors, it is also likely that these factors may be reflected in subjective age.

Despite these limitations, the present study provides novel evidence of a relationship between subjective age and epigenetic aging. The findings indicate individuals who feel older than their chronological age are also biologically older.

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