HHS Public Access

Author manuscript

Psychoneuroendocrinology. Author manuscript; available in PMC 2024 February 01.

Published in final edited form as:

Psychoneuroendocrinology. 2023 February ; 148: 105988. doi:10.1016/j.psyneuen.2022.105988.

Positive Social Factors Prospectively Predict Younger Epigenetic Age: Findings from the Health and Retirement Study

Abby R. Hillmann, B.S.[1,*], **Roma Dhingra**[2], **Rebecca G. Reed, Ph.D.**[1]

[1]Department of Psychology, Dietrich School of Arts and Sciences, University of Pittsburgh, Pittsburgh, PA, USA.

[2]Department of Biology, Georgetown College, Georgetown University, Washington, DC, USA

Abstract

Objectives: Positive social factors may slow biological aging, but this has yet to be rigorously tested. This study investigated whether baseline levels or changes over time in social support and contact frequency prospectively predicted epigenetic age.

Method: Health and Retirement Study participants (N=1,912, 46.3% male, aged 42–87 at baseline) reported longitudinal social support and contact frequency data up to 3 times between 2006 to 2016 and provided blood in 2016. Baseline levels (intercepts) and changes over time (slopes) in social support from and contact frequency with spouses, children, friends, and other family were outputted from multilevel models and used to predict epigenetic age, estimated from Horvath, Hannum, GrimAge, PhenoAge, and Dunedin Pace of Aging.

Results: In models adjusted for demographic and health characteristics, higher baseline levels of support from and contact frequency with friends were prospectively associated with a slower Pace of Aging (support: p=.002; contact: p=0.009) and a lower GrimAge (contact: p=.001). In addition, higher contact frequency with children at baseline was prospectively associated with a lower GrimAge (p<.001), and higher contact frequency with family at baseline and an increase in family contact over time was associated with a lower Hannum age (baseline: p=.005; slope: p=.015).

Conclusions: Perceived support from and contact with close others, particularly friends, may have implications for healthy biological aging. Notably, the effect sizes for friends were comparable to the effect of body mass index on epigenetic age. Positive social factors were generally associated with second- and third-generation clocks, which may be more sensitive to psychosocial factors than first-generation clocks.

[*]Correspondence: Abby Hillmann, 210 S. Bouquet St., University of Pittsburgh, Pittsburgh PA 15260. arh151@pitt.edu.

Conflicts of Interest

None declared.

Keywords

epigenetic aging; social support; contact frequency; DunedinPoAm38; DNA methylation

1. Introduction

There is considerable evidence linking social relationships to immune function, chronic illness, and mortality risk (Holt-Lunstad et al., 2010; Pressman & Cohen, 2005). Positive aspects of social relationships may be especially beneficial for health. In particular, social support, which refers to resources a relationship provides, and contact frequency, an objective measure of the quantity of interactions an individual has, are associated with slower development and progression of morbidity as well as lower risk of mortality (Brummett et al., 2005; Holt-Lunstad et al., 2010; Shor & Roelfs, 2015; Uchino, 2009). One potential pathway between positive social factors and morbidity and mortality is via biological aging, a measure of the cumulative physiological decline that occurs with age.

Primary hallmarks of biological aging include telomere attrition, mitochondrial dysfunction, cellular senescence, and epigenetic alterations; further downstream are integrative hallmarks such as cellular communication, which encompasses increases in inflammation (López-Otín et al., 2013). Cross-sectionally, both low social support across relationship domains and low support specifically from spouses and friends have been associated with hallmarks of biological aging, including shorter telomere length (Barger & Cribbet, 2016; Carroll et al., 2013; but see Lincoln et al., 2019 for contradictory effects) and higher levels of inflammation (Nilsson et al., 2020; Uchino et al., 2018). Less work has examined links between contact frequency and aging biomarkers; more commonly, a composite measure of social isolation is used that combines low contact frequency with other factors such as the total number of social network ties and frequency of participation in activities or clubs (Ford et al., 2006; Helminen et al., 1997). Meta-analytic evidence (N=64,071 across 16 studies) suggests social isolation composite measures are cross-sectionally linked to higher levels of inflammation (Smith et al., 2020). In addition, a composite measure of social isolation prospectively associates with an “older” phenotypic age, a measure of biological age that translates nine blood chemistry biomarkers into an estimated age based on an individual’s risk of death (Crowe et al., 2021). Including contact frequency in composite measures of social isolation is a limitation of research in this area because it limits ability to understand what proportion of the variation in health outcomes is explained specifically by contact frequency, as opposed to other social factors (e.g., participation in group activities or number of social network ties). One study to date reports a concurrent association between lower contact frequency with friends and family and higher odds of inflammation (OR=1.54, CI= 0.70–3.73; Heffner et al., 2011). However, it is unknown how contact frequency relates to other aspects of biological aging.

The current study focuses on epigenetic age, a marker of biological aging, which quantifies DNA methylation at CpG sites throughout the genome and reflects physiological dysregulation that may precede other common hallmarks of biological aging (López-Otín et al., 2013). Using machine learning techniques, researchers have developed epigenetic

clocks based on unique patterns of DNA methylation that predict different outcomes. First-generation clocks, including Horvath (Horvath, 2013) and Hannum (Hannum et al., 2013), were trained to predict chronological age. Second-generation clocks, including PhenoAge (Levine et al., 2018) and GrimAge (Lu et al., 2019), were trained to predict healthspan and time-to-death. Most recently, third-generation clocks called Pace of Aging measures were developed and trained to predict between-person differences in the rate of organ system deterioration over a fixed time period (Belsky et al., 2020).

To date, no studies have assessed social support and contact frequency as predictors of epigenetic age. Many prior studies assessing social relationships and aging biomarkers are cross-sectional and have failed to implicate social factors as prospectively predicting health outcomes. Moreover, cross-sectional studies fail to capture *changes over time* in relationships that may be adaptive. For example, increases over time in social support and contact frequency, particularly with close others, may show beneficial health effects because they may reduce the physiological effects of stress and promote positive affect (Carstensen et al., 1999). Furthermore, the effects of social support and contact frequency on aging biomarkers may also differ depending on *who* is providing the support or contact (i.e., the relationship type). For instance, friend support and contact may be especially relevant for aging biomarkers (McHugh Power et al., 2019; Nilsson et al., 2020) because relationships with friends are usually voluntary compared to relationships with family members (e.g., children and extended family), which can be obligatory and have negative consequences (Sharifian et al., 2019; Shor & Roelfs, 2015). In addition, being married and receiving spousal support are associated with healthier aging biomarkers (Barger & Cribbet, 2016; Mainous III et al., 2011). Altogether, these findings are not conclusive as to which relationship type may be most important, particularly because few studies simultaneously examine multiple relationship types together; however, friends and spouses may have stronger effects on aging biomarkers.

The purpose of the current study was to identify whether initial levels and changes over time in perceived support and contact frequency from different relationship types (i.e., spouses, children, friends, and family) are associated with epigenetic age estimated from five clocks: Horvath, Hannum, PhenoAge, GrimAge, and Pace of Aging. With no prior evidence for associations between social relationships and DNA methylation measures, multiple epigenetic clocks were included in this analysis to examine which ones are associated with social factors. This study used publicly available data from the Health and Retirement Study (HRS), which includes information on the perceived support from and contact frequency with one's close relationships over 8 years (cohort 1: 2006–2014, cohort 2: 2008–2016) and epigenetic data at one time point (2016). The longitudinal social data allowed us to investigate whether initial levels of social support and contact frequency in midlife predicted epigenetic age up to 10 years later, and how trajectories of these social factors over time may also influence epigenetic age. We hypothesized that more perceived support from and contact frequency with social network members at the initial visit and increases over time would be associated with a younger epigenetic age and a slower Pace of Aging. In particular, we examined different relationship types including spouses, children, friends, and other family, and explored whether support and contact from friends and spouses showed the strongest effects.

2. Methods

2.1 Participants and Procedures

Participants were from the Health and Retirement Study (HRS), a nationally representative study of adults over the age of 50 and their spouses. Social support and contact frequency data were analyzed from the leave behind questionnaires, which were collected every 4 years, up to 3 times per person, from 2006–2016. Epigenetic data were assessed once in the Venous Blood Study in 2016. Covariates were assessed at the time of blood draw and pulled from the RAND cooperation longitudinal data set. Of the 4,018 HRS participants with epigenetic data, 2,025 participants had some prospective social support and contact frequency data across all relationship types (spouse, children, friend, family), but 1,966 had no more than one missing item on social support and contact frequency at each wave of data collection between 2006–2016; of those, 1,912 had data on all main covariates and formed the final sample for analyses (766 participants began in 2006, 656 in 2008, 331 in 2010, and 159 in 2014; 831 participants had 3 waves of data; 464 had 2 waves; and 617 had 1 wave). Participants (N=1,912) were on average 63.57 years old at their initial wave (referred to as “baseline” throughout), 71.51 years old at the time of blood draw (SD= 8.92, range: 50 to 96), 46.3% male, and the majority were White (82.4%), with the remainder as Black (11.1%) and other (6.5%). Participants included in this study significantly differed on age, sex, and race from those with epigenetic data but excluded from this analysis; our sample was older (71.51 vs. 67.61 years, t(3993)= −13.20, p<.001), included a higher percentage of men and White participants (men: 46.3% vs. 37.1%, X^2= 34.35, p<.001; White: 82.4% vs 68.6%, X^2= 101.28, p <.001) and a lower percentage of Black and other race participants (Black: 11.1% vs. 22.1%, X^2= 86.81, p<.001; other: 6.5% vs. 9.3%, X^2= 10.0, p=.002).

2.2 Measures

2.2.1 Perceived Social Support.—Perceived social support from spouses, children, friends, and other family (assessed separately) was measured using three items, including “How much do they really understand the way you feel about things?”; “How much can you rely on them if you have a serious problem?”; and “How much can you open up to them if you need to talk about your worries?”. Responses ranged from “1=a lot” to “4=not at all”. Items were reverse coded so that higher scores correspond to greater perceived support. Social support from each relationship type was examined separately. The scale was reliable between people across waves (subsample with 2–3 waves: $R_{kFspouse}$= .90–.93; $R_{kFchildren}$= .89–.92; $R_{kFfriends}$= .88–.94; $R_{kFfamily}$= .91–.94) and had lower but adequate reliability within people over time (subsample with 2–3 waves: $R_{cspouse}$= .59–.64; $R_{cchildren}$=.62–.63; $R_{cfriends}$= .72; $R_{cfamily}$= .75–.76) (Cranford et al., 2006). Within-person reliabilities are typically lower than between-person reliabilities (e.g., Cranford et al., 2006), and low within-person reliabilities will follow from high intraclass correlations (ICC_{spouse} = .67; $ICC_{children}$=.62).

2.2.2 Contact Frequency.—The contact frequency with children, friends, and other family (assessed separately) was measured using three items, including how often do you do each of the following: meet in person, speak on the phone, or write/email. Responses included: “1=three or more times a week”; “2= once or twice a week”; “3=once or twice

a month"; "4=every few months"; "5=once or twice a year"; "6=less than once a year or never". Items were reverse coded so that higher scores correspond with more contact. Contact frequency with each relationship type was examined separately.

2.2.3 Epigenetic Age.—Epigenetic age was quantified by measuring methylation at CpG sites. DNA methylation data are based on assays conducted using the Infinium Methylation EPIC BeadChip at the University of Minnesota. Analysis of duplicate samples showed a correlation of >0.97 for all CpG sites. Prior to estimating the epigenetic clocks, missing methylation values were imputed with the mean beta methylation value of the given probe across all samples (Crimmins et al., 2020). Epigenetic age was estimated from the first- and second-generation epigenetic clocks Horvath 1, Hannum, PhenoAge, and GrimAge, and the Pace of Aging measure, DunedinPoAm38.

2.2.4 Covariates.—Covariates were selected a priori that could influence epigenetic age and included sex, race, chronological age, body mass index (BMI), smoking status, time elapsed in years between the baseline visit and blood draw (calculated as date of blood draw – date of baseline visit), and a comorbidity index, calculated as the sum of the following physician-diagnosed diseases: hypertension, diabetes, cancer, chronic lung disease, heart disease, stroke, arthritis, and emotional/psychiatric problems. All covariates were measured at the same time as epigenetic age (2016), with the exception of the comorbidity index, which was assessed at baseline to adjust for initial health status. Last, in post-hoc sensitivity analyses, we included education as an additional covariate. Education was categorized by highest degree (0= college or higher; some college=1, High school/GED= 2; less than high school=3, with college or higher as the reference) and collected at the earliest available time point.

Additionally, because cell types can influence DNA methylation (Crimmins et al., 2021), in sensitivity analyses we further adjusted for the percentages of several different cell types as measured by flow cytometry (described in Crimmins et al., 2021), including: CD4+ total (CD3+ CD19− CD8− CD4+), CD8+ total (CD3+ CD19− CD8+ CD4−), CD8 TemRA (CD3+ CD19− CD8+ CD4− CD45RA+ CCR7− CD28−), CD8 naïve (CD3+ CD19− CD8+ CD4− CD45RA+ CCR7+ CD28+), B cells (CD3− CD19+), Natural Killer cells (CD3− CD19− CD20− CD14− CD16+ CD56+), and monocytes (CD3− CD19− CD20− CD14+). Fewer participants had flow cytometry data so the sample size for the sensitivity analyses that further controlled for cell types was N= 1,745.

3. Data Analysis

To obtain baseline levels and slopes over time of perceived social support and contact frequency, multilevel models with repeated measures (level 1) of perceived social support and contact frequency within people (level 2) were used. Multilevel models account for missing data without the need for data imputation. Data were analyzed using the lme (linear mixed effects) function from the nlme library (3.1.152) in R (version 4.0.4). Models were estimated using maximum likelihood estimation and included a random intercept and slope to account for individual differences in baseline levels and changes over time in social factors. Intercepts and slopes of social support and contact frequency from each

relationship type (spouse, children, friend, and family) were outputted from the multilevel models and tested individually as predictors of epigenetic age estimates to determine if baseline levels or changes over time in social factors were related to epigenetic age. All analyses were conducted using the following epigenetic clocks: Horvath, Hannum, PhenoAge, GrimAge, and Pace of Aging. All models controlled for the covariates listed in section 2.2.4: sex, race, chronological age, BMI, and smoking status (all at the time of the blood draw), the time between the baseline visit and blood draw, and a comorbidity index assessed at baseline. Education was further controlled for in additional post-hoc sensitivity analyses. Main effects models tested relationship types individually and were corrected for multiple comparisons using the Benjamini Hochberg correction method (Q=.05; Benjamini & Hochberg, 1995); corrections accounted for the number of relationship types tested and were assessed separately for slopes and intercept values. Only main effects that withstood correction for multiple comparisons are discussed. Unstandardized (b) and standardized (*ß*) estimates are reported for main effects models.

The resulting statistically significant associations were further probed in a series of planned sensitivity analyses. First, relationship types were tested together in a social support model (i.e., social support from spouse, children, friends, and family) and tested together in a contact frequency model (i.e., contact frequency with children, friends, and family). Then, models were further adjusted for cell types. Finally, within each relationship type that had a significant main effect association, social support and contact frequency were pitted against each other in the same model; and then further adjusted for cell types.

4. Results

Characteristics of the full sample are depicted in Table 1 and bivariate correlations among study variables are in Supplemental Table 1. Across the relationship domains, social support from spouses, children, friends, and other family were positively correlated (r = .10–.43); in addition, contact frequency with children, friends, and other family were also positively correlated (r = .37–.48). Overall, correlations between social support and contact frequency were small to moderate (r =.04–.50), indicating they are distinct social constructs. The epigenetic clocks were interrelated, with the smallest correlations between the Pace of Aging measure and all other clocks (r = .09–.38) and the strongest correlations between Horvath and Hannum (r = .77) and GrimAge and Hannum (r =.75).

4.1 Multilevel Models: Baseline levels and change in social support and contact frequency over time

Baseline levels (intercepts) and changes over time (slopes) in social support and contact frequency were outputted from multilevel models to be used in regression analyses. Results from the multilevel models (see Supplemental Tables 2 and 3) indicated that all baseline levels (intercepts) of social support and contact frequency were significantly different from zero (p<.0001). In terms of changes over time, there were no changes in perceived social support from spouses (b=.005, SE=.009, t= .52, p=.61), friends (b=−.018, SE=.013, t= −1.38, p=.17), or other family (b=.003, SE=.015, t= .22, p=.82), but there was a significant increase in perceived support from children (b=.043, SE=.011, t= 3.86, p<.001). There

were no significant changes over time in contact with children (b=−.090, SE=.052, t= 1.72, p=.086)[1], friends (b=−.016, SE=.056, t=−.28, p=.78), or other family (b=.012, SE=.058, t=.21, p=.84). Therefore, the associations between changes in social factors over time (slopes) and epigenetic clocks should be interpreted in the context that although some slopes varied significantly between people, most were on average stable. Despite this, understanding whether the stability of relationships in older adulthood influences epigenetic aging is still important, as lifespan developmental theories highlight the need to examine both change and constancy/stability in longitudinal research (e.g., Nesselroade & Baltes, 1979).

4.2 Effects of Social Support on Epigenetic Age

Regression models tested the effects of baseline levels and changes over time in social support from spouses, children, friends, and other family on each epigenetic age estimate. Support providers were first tested individually and corrected for multiple comparisons (results in Table 2; standardized effects for significant main effects and covariates are reported in Supplemental Table 4); then, in sensitivity analyses, all support providers were tested together in the same model (results in Supplemental Table 5), and finally, were further corrected for cell proportions (Supplemental Table 5).

4.2.1. Spouse.—There were no main effects of spousal support on epigenetic age (Table 2). However, in sensitivity analyses, an association between an increase in spousal support over time and faster Pace of Aging emerged after including all support providers in the same model (b=20.39, SE=9.76, t=2.088, p=.037), and it remained after further adjusting for cell types (b=24.87, SE=10.085, t=2.47, p=.014) (Supplemental Table 5).

4.2.2 Children.—There were no statistically significant main effects of children support on epigenetic age.

4.2.3 Friends.—More perceived support from friends at baseline was associated with a lower GrimAge (b=−.41, SE=.21, t= −1.99, p=.047) and a slower Pace of Aging (b=−.014, SE=.004, t= −3.16, p=.002), but the association with GrimAge did not withstand correction for multiple comparisons (Table 2). In sensitivity analyses, the Pace of Aging association remained significant when including all support providers in the same model (b=−.012, SE=.005, t= −2.40, p=.016), but was no longer statistically significant after adjusting for cell proportions (b=−.010, SE=.005, t= −1.95, p=.051) (Supplemental Table 5).

4.2.4. Other Family.—There were no statistically significant main effects of other family support on epigenetic age.

4.3 Effects of Contact Frequency on Epigenetic Age

Regression models tested the main effects of baseline levels and changes over time in contact frequency with children, friends, and other family on each epigenetic age estimate.

[1]We identified 49 people (2.4%) who lost a child at some point between their baseline assessment and 2016; however, it is not known whether a person lost their only child versus. a person lost a child but has other children. Additionally, because the loss of a child applies to a very small proportion of our full sample, we did not remove these individuals from analyses.

Contact with children, friends, and family were first tested individually and corrected for multiple comparisons (results in Table 3; standardized effects for significant main effects and covariates are reported in Supplemental Tables 6–8); then, in sensitivity analyses, all relationship types were tested together in the same model (results in Supplemental Table 9), and finally, were further corrected for cell proportions (Supplemental Table 9).

4.3.1 Children.—More contact with children at baseline was associated with a lower GrimAge (b=−.25, SE=.058, t= −4.32, p<.001) (Table 3). In sensitivity analyses, this result remained statistically significant when contact frequency with children, friends, and family were tested together in the same model (b=−.25, SE=.066, t= −3.70, p<.001) and when further controlling for cell subtypes (b=−.23, SE=.068, t= −3.42, p=.001) (Supplemental Table 9).

4.3.2 Friends.—More contact with friends at baseline was associated with a lower GrimAge (b=−.18, SE=.054, t= −3.36, p=.001) and a slower Pace of Aging (b=−.003, SE=.001, t= −2.61, p=.009) (Table 3). In sensitivity analyses, these results remained statistically significant when contact frequencies with all relationship types were tested in the same models (GrimAge: b=−.13, SE=.059, t= −2.15, p=.032, Pace of Aging: b=−.003, SE=.001, t= −2.10, p=.036) and when further controlling for cell types (GrimAge: b=−.15, SE=.061, t= −2.39, p=.017, Page of Aging: b=−.003, SE=.001, t= −1.97, p=.049) (Supplemental Table 9).

4.3.3. Other Family.—Last, more contact with family at baseline, and an increase in family contact over time, were associated with a lower Hannum age (baseline: b=−.51, SE=.18, t= −2.83, p=.005; slope: b=−10.60, SE=4.37, t= −2.44, p=.015) (Table 3). In sensitivity analyses, these results remained significant when contact frequencies with all relationship types were tested in the same model (baseline: b=−.44, SE=.19, t= −2.92, p=.022, slope: b=−9.71, SE=4.60, t= −2.11, p=.035) and when further controlling for cell-subtypes (baseline: b=−.47, SE=.20, t= −2.40, p=.016, slope: b=−11.041, SE=4.63, t= −2.38, p=.017) (Supplemental Table 9).

4.4 Testing Social Support and Contact Frequency Together Within Relationship Types

All previous models tested social support (section 4.2) and contact frequency (4.3) separately. In the final set of planned sensitivity analyses, we tested social support and contact frequency together in the same model for each relationship type (Supplemental Tables 10–12).

4.4.1. Children.—When support from and contact frequency with children were entered into the same model, the original association between more contact with children at baseline and a lower GrimAge remained significant (b=−.25, SE=.063, t= −3.96, p<.001) and withstood further adjustment for cell types (b=−.23, SE=.065, t= −3.55, p<.001) (Supplemental Table 10).

4.4.2 Friends.—When support from and contact frequency with friends were entered into the same model, two of the three main effects remained. There were still statistically

significant associations between more friend support at baseline and slower Pace of Aging (b=−.010, SE=.005, t= −2.27, p=.023), and between more contact frequency with friends at baseline and a lower GrimAge (b=−.16, SE=.058, t= −2.79, p=.005); however, the association between more contact frequency with friends at baseline and a slower Pace of Aging was no longer statistically significant (p=.12) (Supplemental Table 11). When further controlling for cell type distributions, friend support at baseline was no longer associated with Pace of Aging (p=.070), but more contact frequency with friends at baseline remained significantly associated with a lower GrimAge (b=−.18, SE=.062, t= −2.91, p=.004 (Supplemental Table 11).

4.4.3 Other Family.—

When support from and contact with other family were tested in the same model, the associations between more family contact at baseline and increases in family contact over time relating to lower Hannum age remained significant (baseline: b=−.57, SE=.20, t= −2.86, p=.004; slope: −12.83, SE=4.72, t= −2.72, p=.007), and withstood further adjustment for cell type (baseline: b=−.47, SE=.20, t= −2.39, p=.017; slope: −11.97, SE=4.74, t= −2.52, p=.012) (see Supplemental Table 12).

4.5 Post-Hoc Sensitivity Analyses with Education

In post-hoc sensitivity analyses, we further controlled for education in main effects models that tested baseline levels and changes over time in social support (Supplemental Table 13) and contact frequency (Supplemental Table 14) on each epigenetic age estimate. The association between more contact with friends at baseline and slower Page of Aging was similar (b=−.003, SE=.001, t= −2.16, p=.031), but no longer withstood correction for multiple comparisons. All other previous main effects results remained unchanged.

5. Discussion

The current study examined whether perceived social support from and contact frequency with four different relationship types (i.e., spouse, children, friends, and other family) prospectively related to epigenetic age up to 10 years later using longitudinal data from the Health and Retirement Study. Results indicated that when social support and contact frequency were examined separately, the *friends* relationship domain emerged as the most robust main effect predictor of epigenetic age across both social support and contact frequency. Specifically, higher levels of social support from friends and more contact frequency with friends were both prospectively associated with a slower Pace of Aging up to 10 years later; in addition, more contact frequency with friends was also associated with a lower GrimAge. These results were independent of chronological age, race, sex, BMI, smoking, time elapsed in years between the baseline visit and blood draw, and baseline comorbidities; were robust across sensitivity analyses that tested support and contact from all relationship types in the same model, and then controlled for cell types; and remained in post-hoc analyses that further controlled for education, but the association between contact with friends and slower Pace of Aging weakened. The standardized effect sizes of friend support and friend contact on Pace of Aging were small to moderate but were comparable to the effects of BMI and about half as large as the effect of baseline comorbidities.

The health-relevance of friends in particular is supported by previous work (McHugh Power et al., 2019; Nilsson et al., 2020; Sharifian et al., 2019) and may be due to the voluntary nature of the relationship. Voluntary interactions with friends might be more often positive than interactions with family members, which could also accompany negative interactions, such as conflict or nagging behaviors (Gallant et al., 2007). Furthermore, older adults report that their interactions with family members are more likely to involve providing care or assistance, whereas interactions with friends are more likely to involve participation in leisure activities and having casual conversations (Rook & Ituarte, 1999). We did not have data on the content of nor emotions surrounding the different types of social contact, but future work that incorporates an ecological momentary assessment design could be wellsuited to assess whether these characteristics and consequences of interactions with friends versus family explain the positive health benefits we observed.

Overall, when comparing the pattern of results from social support versus contact frequency on epigenetic age, there were more consistent associations with contact frequency. Specifically, when contact frequency was tested: alone within each relationship type; with social support within each relationship type; and with social support across all relationship types together, more contact with friends, family, and children significantly predicted lower epigenetic age, including after adjusting for cell types. The only contradictory finding, however, was that friend support and friend contact continued to predict Pace of Aging and GrimAge above and beyond each other, but the friend support association with Pace of Aging did not withstand cell type correction whereas the friend contact association with GrimAge did. In addition to friends, our results indicate more contact with children at baseline was associated with a lower GrimAge, and more contact with other family at baseline and increases over time in family contact were associated with a lower Hannum age. These findings add to the current social contact and health literature, which does not often focus on specific types of family contact but instead groups all family members together, such as by aggregating siblings, spouses, and children as “family”. For example, with this grouping approach, meta-analytic evidence suggests contact frequency with family does not have a significant effect on longevity (Shor & Roelfs, 2015). However, our findings suggest separating out the sources of family contact may be important to disentangle their health effects. Nevertheless, it remains unclear who may be driving the other family contact effect on epigenetic aging in our study; children and spouses were assessed separately, so the “other family” category could have included various immediate or extended family members, such as siblings, parents, or grandchildren. Each of these relationship types tend to be studied separately as they may relate to health – for example, more contact with grandchildren is associated with better self-rated health and fewer mobility limitations (Ku et al., 2013). However, it may also be informative to test various family relationship types simultaneously in multivariable models to highlight their relative effects on aging biomarkers.

There are several considerations regarding why contact frequency may have more consistent associations with epigenetic age than social support. Contact frequency could be more beneficial for healthy aging because it may more directly promote participation in health behaviors, such as physical activity (Loprinzi & Joyner, 2016; Shiovitz-Ezra & Litwin, 2012). We included BMI and smoking status as covariates in the current analyses to isolate

the effects of social factors above and beyond health indicators and behaviors, but they could also conceptually be on a pathway connecting contact frequency to epigenetic aging. In addition, a potential confounding consideration may be that it takes more effort and thus requires being "healthier" to contact social network members, particularly friends; however, this explanation is less likely because the measurement of contact frequency included contact by lower-effort methods, including phone and email. In addition, our analyses adjusted for the total number of comorbidities at baseline to control for variation in baseline physical health status. Last, we may have observed more consistent associations with contact frequency but not social support because contact frequency may have more direct effects on aging biomarkers whereas social support may operate more strongly as a stress buffer (Cohen, 2004). Therefore, we may not have observed the beneficial health effects of social support if the sample also had lower stress levels. However, this alternative stress-buffering model remains to be tested and is an area for future investigation with epigenetic aging.

There was one unexpected positive association between increases in spousal support over time and faster Pace of Aging. This effect was not explained by demographic or health covariates and remained in all sensitivity analyses. Furthermore, in post-hoc analyses we removed a subset of participants who became widowed between their initial visit and the blood draw (N=217), but their exclusion did not change the direction or significance of this unexpected result. This finding contradicts previous work demonstrating that higher spousal support predicts better biological aging in the form of longer telomere length (Barger & Cribbet, 2016). However, in our sample, this association was not present in the univariate analysis but only in the model where all relationship types were tested together and adjusted for cell types. Therefore, this effect can be interpreted as increases in spousal support *relative to* support from the other relationship types (family, children, friends). In this case, individuals may depend on spousal support because they have lower support from other relationship types, and previous work suggests lacking diversity in network ties is associated with poorer health (Ali et al., 2018). Moreover, an additional consideration is that spousal support had the lowest within-person reliability of the support measures, suggesting that this may not have captured total spousal support levels as accurately as the other relationship types, which may make these findings less credible.

Of the five clocks tested, social support and contact frequency were most consistently related to GrimAge and Pace of Aging, which are second- and third-generation clocks trained to predict health risk and organ system dysfunction; there were few associations with Hannum and no associations with Horvath, which are first-generation clocks trained to predict chronological age (Belsky et al., 2020; Lu et al., 2019). No studies to date have assessed the longitudinal relationship between social factors and epigenetic aging. Therefore, including a variety of clocks in this analysis contributes to our understanding of how different psychosocial factors may impact specific clocks. Our results align with initial work in this area demonstrating that environmental and psychological factors more often associate with second- and third-generation clocks but not first-generation clocks (Crimmins et al., 2021; Oblak et al., 2021; Schrempft et al., 2021). In addition, compared to first-generation clocks, second-generation, and third-generation clocks have on average slightly lower intraclass correlation coefficients (Higgins-Chen et al., 2022), which may suggest that these clocks are more malleable and sensitive to psychological factors. Last,

our results prospectively linking more support and contact with slower aging in terms of second- and third-generation clocks are important because these clocks are more predictive of age-related health outcomes as compared to first-generation clocks (Maddock et al., 2020).

The results should be considered in the context that, on average, social support and contact frequency for almost all relationship types did not change over the 10-year interval (2006–2016). Results from the multilevel models indicated that only perceived social support from children increased over time, which aligns with prior evidence that older adults receive more emotional and instrumental support from their children as they get older (Gurung et al., 2003). It is possible we did not observe other changes in social support because participants had high social support ratings across categories to begin with. In addition, we may not have observed changes in contact frequency because, according to the Socioemotional Selectivity Theory, close social relationships may actually be maintained into older adulthood (reflecting stability in levels over time), whereas peripheral social relationships are pruned; this pruning contributes to the well documented decline in social contacts across the lifespan (Carstensen et al., 1999). The Health and Retirement Study surveys only collected information on participants' perceived support from and contact frequency with social network members with whom participants reported they "felt close to". Therefore, we did not capture the removal of acquaintances or less-close members (e.g., neighbors, coworkers), which may be a missed opportunity because their pruning over time is thought to enhance psychological well-being and may also have beneficial implications for health (English & Carstensen, 2014; Huxhold et al., 2013).

The current study had several strengths, including a large sample and longitudinal data spanning up to 10 years, which allowed us to test prospective as opposed to cross-sectional associations between social factors and epigenetic aging. This study also controlled for important demographic and health covariates, including baseline health status; examined two types of social factors, one subjective (social support) and one objective (contact frequency); and incorporated first- and second-generation epigenetic clocks, as well as Pace of Aging, one of the latest DNA methylation-based measures of biological aging. However, the results may only generalize to older adults in the United States, and the sample is predominantly White. Additionally, without significant changes in most social factors over time, we were unable to draw clear conclusions about the importance of changes in social support and contact frequency as they relate to epigenetic aging in older adults. Furthermore, by only assessing *close* relationships, this analysis does not capture the complexity of the full social network, including peripheral network members, nor does it capture how social support and contact frequency with these other network members may change across the adult lifespan. We also only tested the effects of positive social factors on epigenetic age, but future work may also consider the effects of explicitly negative aspects of social relationships (e.g., conflict). Lastly, with only one measurement of biological age, we could not test within-person associations between changes in social relationships and changes in epigenetic aging; in addition, although we included a baseline measure of comorbidity, we cannot rule out that the observed effects may be due to existing differences in baseline levels of epigenetic age.

5.1 Conclusions.

In conclusion, these findings suggest that greater perceived support and more contact frequency, particularly with friends, are prospectively associated with a lower GrimAge and slower Pace of Aging up to 10 years later. In addition, more contact frequency with children and other family are associated with a lower GrimAge and Hannum age. These results suggest that prevention and intervention efforts to improve social relationships, particularly with friends, and especially among older adults, who are more likely to report being socially isolated (Savikko et al., 2005), may help slow epigenetic aging and ultimately reduce risk of morbidity and mortality (Chen et al., 2016).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

The Health and Retirement Study (HRS) is sponsored by the National Institute on Aging (NIA U01AG009740) and is conducted by the University of Michigan. Support was provided by grants from the National Heart, Lung, and Blood Institute (T32HL007560) and the National Institute on Aging (AG056635). A.R.H acknowledges training received from the University of Michigan Genomics for Social Scientists Workshop (NIA R25 AG053227).

References

Ali T, Nilsson CJ, Weuve J, Rajan KB, & De Leon CFM (2018). Effects of social network diversity on mortality, cognition and physical function in the elderly: A longitudinal analysis of the Chicago Health and Aging Project (CHAP). J Epidemiol Community Health, 72(11), 990–996. [PubMed: 29970598]

Barger SD, & Cribbet MR (2016). Social support sources matter: Increased cellular aging among adults with unsupportive spouses. Biological Psychology, 115, 43–49. [PubMed: 26780266]

Belsky DW, Caspi A, Arseneault L, Baccarelli A, Corcoran DL, Gao X, Hannon E, Harrington HL, Rasmussen LJ, & Houts R (2020). Quantification of the pace of biological aging in humans through a blood test, the DunedinPoAm DNA methylation algorithm. Elife, 9, e54870. [PubMed: 32367804]

Benjamini Y, & Hochberg Y (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. Journal of the Royal Statistical Society: Series B (Methodological), 57(1), 289–300.

Carroll JE, Roux AVD, Fitzpatrick AL, & Seeman T (2013). Low social support is associated with shorter leukocyte telomere length in late life: Multi-Ethnic Study of Atherosclerosis (MESA). Psychosomatic Medicine, 75(2).

Carstensen LL, Isaacowitz DM, & Charles ST (1999). Taking time seriously: A theory of socioemotional selectivity. American Psychologist, 54(3), 165. [PubMed: 10199217]

Chen BH, Marioni RE, Colicino E, Peters MJ, Ward-Caviness CK, Tsai P-C, Roetker NS, Just AC, Demerath EW, & Guan W (2016). DNA methylation-based measures of biological age: Meta-analysis predicting time to death. Aging (Albany NY), 8(9), 1844. [PubMed: 27690265]

Cohen S (2004). Social relationships and health. American psychologist, 59(8), 676. [PubMed: 15554821]

Cranford JA, Shrout PE, Iida M, Rafaeli E, Yip T, & Bolger N (2006). A procedure for evaluating sensitivity to within-person change: Can mood measures in diary studies detect change reliably?. Personality and Social Psychology Bulletin, 32(7), 917–929. [PubMed: 16738025]

Crimmins E, Kim J, Fisher J, & Faul J (2020). HRS Epigenetic Clocks – Release 1.

Crimmins EM, Thyagarajan B, Levine ME, Weir DR, & Faul J (2021). Associations of age, sex, race/ethnicity, and education with 13 epigenetic clocks in a nationally representative US sample: The Health and Retirement Study. The Journals of Gerontology: Series A, 76(6), 1117–1123.

Crowe CL, Domingue BW, Graf GH, Keyes KM, Kwon D, & Belsky DW (2021). Associations of Loneliness and Social Isolation With Health Span and Life Span in the US Health and Retirement Study. The Journals of Gerontology: Series A, 76(11), 1997–2006.

English T, & Carstensen LL (2014). Selective narrowing of social networks across adulthood is associated with improved emotional experience in daily life. International Journal of Behavioral Development, 38(2), 195–202. [PubMed: 24910483]

Ford ES, Loucks EB, & Berkman LF (2006). Social Integration and Concentrations of C-Reactive Protein Among US Adults. Annals of Epidemiology, 16(2), 78–84. 10.1016/j.annepidem.2005.08.005 [PubMed: 16271297]

Gallant MP, Spitze GD, & Prohaska TR (2007). Help or hindrance? How family and friends influence chronic illness self-management among older adults. Research on Aging, 29(5), 375–409.

Gurung RA, Taylor SE, & Seeman TE (2003). Accounting for changes in social support among married older adults: Insights from the MacArthur Studies of Successful Aging. Psychology and Aging, 18(3), 487. [PubMed: 14518810]

Heffner KL, Waring ME, Roberts MB, Eaton CB, & Gramling R (2011). Social isolation, C-reactive protein, and coronary heart disease mortality among community-dwelling adults. Social Science & Medicine, 72(9), 1482–1488. [PubMed: 21492978]

Helminen A, Rankinen T, Väisänen S, & Rauramaa R (1997). Social network in relation to plasma fibrinogen. Journal of Biosocial Science, 29(2), 129–139. [PubMed: 9881125]

Higgins-Chen AT, Thrush KL, Wang Y, Minteer CJ, Kuo PL, Wang M, … & Levine ME (2022). A computational solution for bolstering reliability of epigenetic clocks: Implications for clinical trials and longitudinal tracking. Nature aging, 2(7), 644–661. [PubMed: 36277076]

Holt-Lunstad J, Smith TB, & Layton JB (2010). Social relationships and mortality risk: A meta-analytic review. PLoS Medicine, 7(7), e1000316. [PubMed: 20668659]

Huxhold O, Fiori KL, & Windsor TD (2013). The dynamic interplay of social network characteristics, subjective well-being, and health: The costs and benefits of socio-emotional selectivity. Psychology and Aging, 28(1), 3. [PubMed: 23066804]

Ku L-JE, Stearns SC, Van Houtven CH, Lee S-YD, Dilworth-Anderson P, & Konrad TR (2013). Impact of caring for grandchildren on the health of grandparents in Taiwan. Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 68(6), 1009–1021. [PubMed: 24056691]

Levine ME, Lu AT, Quach A, Chen BH, Assimes TL, Bandinelli S, Hou L, Baccarelli AA, Stewart JD, & Li Y (2018). An epigenetic biomarker of aging for lifespan and healthspan. Aging (Albany NY), 10(4), 573. [PubMed: 29676998]

Lincoln KD, Lloyd DA, & Nguyen AW (2019). Social relationships and salivary telomere length among middle-aged and older african american and white adults. The Journals of Gerontology: Series B, 74(6), 1053–1061.

López-Otín C, Blasco MA, Partridge L, Serrano M, & Kroemer G (2013). The hallmarks of aging. Cell, 153(6), 1194–1217. [PubMed: 23746838]

Loprinzi PD, & Joyner C (2016). Source and size of emotional and financial-related social support network on physical activity behavior among older adults. Journal of Physical Activity and Health, 13(7), 776–779. [PubMed: 26900842]

Lu AT, Quach A, Wilson JG, Reiner AP, Aviv A, Raj K, Hou L, Baccarelli AA, Li Y, & Stewart JD (2019). DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging (Albany NY), 11(2), 303. [PubMed: 30669119]

Maddock J, Castillo-Fernandez J, Wong A, Cooper R, Richards M, Ong KK, Ploubidis GB, Goodman A, Kuh D, & Bell JT (2020). DNA methylation age and physical and cognitive aging. The Journals of Gerontology: Series A, 75(3), 504–511.

Mainous III AG, Everett CJ, Diaz VA, Baker R, Mangino M, Codd V, & Samani NJ (2011). Leukocyte telomere length and marital status among middle-aged adults. Age and Ageing, 40(1), 73–78. [PubMed: 20817935]

McHugh Power J, Carney S, Hannigan C, Brennan S, Wolfe H, Lynch M, Kee F, & Lawlor B (2019). Systemic inflammatory markers and sources of social support among older adults in the Memory Research Unit cohort. Journal of Health Psychology, 24(3), 397–406. [PubMed: 27815328]

Nesselroade JR, & Baltes PB (1979). Longitudinal research in the study of behavior and development. Academic Press.

Nilsson CJ, Nørgaard S, Foverskov E, Bruunsgaard H, Andersen PK, & Lund R (2020). Positive and negative aspects of social relations and low-grade inflammation in Copenhagen Aging and Midlife Biobank. European Journal of Ageing, 17(4), 531–546. [PubMed: 33381004]

Oblak L, van der Zaag J, Higgins-Chen AT, Levine ME, & Boks MP (2021). A systematic review of biological, social and environmental factors associated with epigenetic clock acceleration. Ageing Research Reviews, 101348. [PubMed: 33930583]

Pressman SD, & Cohen S (2005). Does positive affect influence health? Psychological Bulletin, 131(6), 925. [PubMed: 16351329]

Rook KS, & Ituarte PH (1999). Social control, social support, and companionship in older adults' family relationships and friendships. Personal Relationships, 6(2), 199–211.

Savikko N, Routasalo P, Tilvis RS, Strandberg TE, & Pitkälä KH (2005). Predictors and subjective causes of loneliness in an aged population. Archives of Gerontology and Geriatrics, 41(3), 223–233. [PubMed: 15908025]

Schrempft S, Belsky DW, Draganski B, Kliegel M, Vollenweider P, Marques-Vidal P, Preisig M, & Stringhini S (2021). Associations between life course socioeconomic conditions and the Pace of Aging. The Journals of Gerontology: Series A.

Sharifian N, Manly JJ, Brickman AM, & Zahodne LB (2019). Social network characteristics and cognitive functioning in ethnically diverse older adults: The role of network size and composition. Neuropsychology, 33(7), 956. [PubMed: 31192657]

Shiovitz-Ezra S, & Litwin H (2012). Social network type and health-related behaviors: Evidence from an American national survey. Social Science & Medicine, 75(5), 901–904. [PubMed: 22682660]

Shor E, & Roelfs DJ (2015). Social contact frequency and all-cause mortality: A meta-analysis and meta-regression. Social Science & Medicine, 128, 76–86. [PubMed: 25594955]

Smith KJ, Gavey S, Riddell NE, Kontari P, Victor CR, (2020). The association between loneliness, social isolation and inflammation: A systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews, 112, 519–541. 10.1016/j.neubiorev.2020.02.002 [PubMed: 32092313]

Uchino BN (2009). Understanding the links between social support and physical health: A life-span perspective with emphasis on the separability of perceived and received support. Perspectives on Psychological Science, 4(3), 236–255. [PubMed: 26158961]

Uchino BN, Trettevik R, Kent de Grey RG, Cronan S, Hogan J, & Baucom BR (2018). Social support, social integration, and inflammatory cytokines: A meta-analysis. Health Psychology, 37(5), 462. [PubMed: 29565600]

Highlights

- It is unknown whether positive social factors predict slower biological aging.
- We examined links between social support, contact frequency, and epigenetic age.
- More social support from friends predicted younger epigenetic age.
- More contact with children, friends, and family predicted younger epigenetic age.
- Social factors were more consistently linked to GrimAge and Pace of Aging clocks.

Table 1.

Sample Descriptives for Analyses (N=1912)

	Mean	SD	Range
Sex (reference = males)	46.3%		
Age at blood draw (years)	71.51	8.92	50.0– 96.0
Age at baseline (years)	63.57	8.37	42.0– 87.0
Current Smoker (reference = no)	92.1%		0–1
Body Mass Index (kg/m^2)	28.6	5.79	14.6– 62.3
Time between baseline visit & blood draw (years)	7.96	2.3	2–10
Comorbidity Index	1.71	1.29	0–7
Race (reference = White)			
White	82.4%		
Black	11.1%		
Other	6.5%		
Education			
College or higher	25.2%		
Some college	5.9%		
High school or GED	53.5%		
Less than high school	15.4%		
Epigenetic Age			
Horvath Clock	67.35	9.62	29.9– 115
Hannum Clock	56.5	9.02	32–108
PhenoAge Clock	59.11	9.85	28.7– 101
GrimAge Clock	69.5	8.32	42.7– 97.0
Pace of Aging Clock	1.07	0.09	0.74– 1.39
Social Factors			
Friend Support Baseline	3.00	0.47	1.51– 3.81
Friend Support Slope	−0.0179	0.012	−0.09– 0.05
Children Support Baseline	3.22	0.485	1.46– 3.85
Children Support Slope	0.0430	0.0197	0.02–0.12
Family Support Baseline	2.85	0.552	1.34– 3.78
Family Support Slope	0.0033	0.02	−0.07– 0.1
Spouse Support Baseline	3.46	0.47	1.47– 3.92
Spouse Support Slope	0.0050	0.0	0.0– 0.01
Children Contact Baseline	12.1	1.84	5.00– 16.5
Children Contact Slope	−0.089	0.0013	−0.09– −0.08
Family Contact Baseline	10.1	1.86	4.82– 15.5
Family Contact Slope	0.0119	0.08	−0.19– 0.20
Friend Contact Baseline	11.2	2.13	4.89– 16.6
Friend Contact Slope	−0.0159	0.23	−1.02– 1.17

Note. Sex, race, smoking status, and body mass index are reported at the time of blood draw (2016), and comorbidities and education are reported at baseline. Means and standard deviations (SD) are displayed for continuous measures. Categorical variables (with reference levels) are displayed as percentages.

Table 2.

Baseline levels and change over time in social support (relationship types tested separately) predicting epigenetic age (N=1912)

	Horvath				Hannum				PhenoAge				GrimAge				
	ß	***b***	***SE***	***p***	***ß***	***b***	***SE***	***p***	***ß***	***b***	***SE***	***p***	***ß***	***b***	***SE***	***p***	***ß***
Spouse Baseline	0.02	0.51	0.36	0.159	−0.01	−0.15	0.29	0.607	−0.01	−0.18	0.37	0.630	0.00	0.05	0.21	0.822	−0.03
Spouse Slope	0.01	323.27	766.05	0.673	0.01	332.68	609.14	0.585	−0.01	−627.43	780.40	0.422	0.01	231.82	450.81	0.607	0.04
Children Baseline	0.06	1.17	3.39	0.730	0.02	0.35	2.69	0.897	−0.06	−1.27	3.45	0.712	−0.11	−1.86	1.99	0.350	−0.40
Children Slope	0.06	29.97	83.23	0.719	0.03	12.70	66.15	0.848	−0.07	−33.87	84.75	0.690	−0.09	−38.79	48.92	0.428	−0.39
Friend Baseline	−0.00	−0.00	0.35	0.991	0.00	0.07	0.28	0.791	0.00	0.08	0.36	0.814	**−0.02**	**−0.41**	**0.21**	**0.047**	**−0.07**
Friend Slope	0.01	9.20	13.74	0.503	0.02	12.46	10.92	0.254	0.02	20.51	13.98	0.143	−0.01	−10.75	8.07	0.183	−0.01
Family Baseline	−0.01	−0.13	0.46	0.775	−0.02	−0.25	0.36	0.491	0.00	0.02	0.47	0.964	−0.02	−0.23	0.27	0.392	**−0.08**
Family Slope	−0.01	−5.33	11.97	0.656	0.01	3.24	9.51	0.733	0.01	5.79	12.19	0.635	−0.01	−3.14	7.04	0.656	−0.03

Note. Standardized (ß) and unstandardized (b) estimates are displayed. Estimates are from adjusted models that include the following covariates: age, sex, race, BMI, smoking status, time between the baseline visit and the blood draw, and total number of comorbidities at baseline. Results that are $p < .05$ are in bold face.

*Results that withstood Benjamini Hochberg correction for multiple comparisons.

Table 3.

Baseline levels and change over time in social contact (relationship types tested separately) predicting epigenetic age (N=1912)

	Horvath				Hannum				PhenoAge				GrimAge				
	ß	***b***	***SE***	***p***	***ß***	***b***	***SE***	***p***	***ß***	***b***	***SE***	***p***	***ß***	***b***	***SE***	***p***	***ß***
Children Baseline	−0.02	−0.11	0.10	0.268	**−0.03**	**−0.16**	**0.08**	**0.042**	−0.03	−0.14	0.10	0.153	**−0.05**	**−0.25**	**0.06**	**<0.001** *	−0.04
Children Slope	−0.01	−59.08	136.25	0.665	−0.02	−115.43	108.23	0.286	−0.01	−96.31	138.73	0.488	−0.01	−66.66	79.73	0.403	0.02
Friend Baseline	−0.01	−0.06	0.09	0.534	−0.01	−0.06	0.07	0.403	0.00	0.01	0.09	0.883	**−0.05**	**−0.18**	**0.05**	**0.001** *	**−0.07**
Friend Slope	−0.04	−1.48	0.83	0.073	−0.01	−0.46	0.66	0.488	−0.00	−0.10	0.84	0.908	−0.02	−0.86	0.49	0.077	−0.03
Family Baseline	**−0.09**	**−0.45**	**0.23**	**0.049**	**−0.11**	**−0.51**	**0.18**	**0.005** *	0.00	0.01	0.23	0.954	−0.05	−0.20	−0.13	0.13	−0.11
Family Slope	**−0.10**	**−12.62**	**5.50**	**0.022**	**−0.09**	**−10.60**	**4.37**	**0.015** *	0.01	0.66	5.61	0.907	−0.04	−4.38	3.24	0.176	−0.11

Note. Standardized (*ß*) and unstandardized (b) estimates are displayed. Estimates are from adjusted models that include the following covariates: age, sex, race, BMI, smoking status, time between the baseline visit and the blood draw, and total number of comorbidities at baseline. Results that are $p < .05$ are in bold face.

* Results that withstood Benjamini Hochberg correction for multiple comparisons.