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Probing Connections Between Social Connectedness, Mortality Risk, and Brain Age: A Preregistered Study

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Many lifestyle and psychosocial factors are associated with a longer lifespan; central among these is social connectedness, or the feeling of belongingness, identification, and bond as part of meaningful human relationships. Decades of research have established that social connectedness is related not only to better mental health (e.g., less loneliness and depression) but also to improved physical health (e.g., decreased inflammatory markers, reduced cortisol activity). Recent methodological advances allow for the investigation of a novel marker of biological health by deriving a predicted "age of the brain" from a structural neuroimaging scan. Discrepancies between a person's algorithm-predicted brain-age and chronological age (i.e., the brain-age gap) have been found to predict mortality and psychopathology risk with accuracy rivaling other known measures of aging. This preregistered investigation uses the Midlife in the United States (MIDUS) study to examine connections between the quality of social connections, the brain-age gap, and markers of mortality risk to understand the longevity-promoting associations of social connectedness from a novel biological vantage point. While social connectedness was associated with markers of mortality risk (number of chronic conditions and ability to perform activities of daily living), our models did not find significant links between social connectedness and the brain-age gap, or the brain-age gap and mortality risk. Supplemental and sensitivity analyses suggest alternate approaches to investigating these associations and overcoming limitations. While plentiful evidence underscores that being socially connected is good for the mind, future research should continue to consider whether it impacts neural markers of aging and longevity.

Keywords: relationships, social connections, brain age

Supplemental materials: https://doi.org/10.1037/pspi0000465.supp

One of the oldest human pursuits is the search for longevity; for centuries, alchemists, healers, philosophers, medics, scientists, and more have worked to lengthen our lifespan and stave off mortality. Extensive research documents the many factors that powerfully predict a decreased mortality risk. These span the more researched and physiological factors, such as diet and exercise (Chrysohoou & Stefanadis, 2013; Fontana & Partridge, 2015; Gremeaux et al., 2012), to the less-understood interpersonal factors. *Social connectedness* is one such factor that captures the sense of belongingness, identification, and bond we as humans feel with each other. Social connectedness is an essential ingredient to meaningful human relationships and staving off the potential detrimental consequences of loneliness, including a shorter lifespan (Bel et al., 2009; Haslam et al., 2015).

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All data used in our analyses were sourced from the Midlife in the United States (MIDUS) Series. A description of the data set and findings from MIDUS studies is available at https://www.midus.wisc.edu/. Publicly available data are available for download from the Inter-University Consortium for Political and Social Research website (https://www.icpsr.umich.edu/web/ICPSR/series/203). Further, our team computed the brain age variable using the protocol developed and shared by Kaufmann and colleagues (https://github.com/tobias-kaufmann/brainage). To facilitate further explorations of brain age in the MIDUS sample, we share the brain age variable on our project GitHub. All the code used for this project is publicly available and accessible from our project GitHub at https://anonymous.4open.science/r/SocConnectionBrainAgeGap-B5E2/.

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Social Connectedness and Mortality Risk

Social connection not only makes us and others feel good, but may also extend our lives (Holt-Lunstad, 2017; House et al., 1988; Rico-Uribe et al., 2018). Multiple epidemiological and longitudinal studies have underscored that both the quality and quantity of social connection are strongly associated with decreased mortality risk (Berkman & Syme, 1979; Seeman et al., 1987; Tatangelo et al., 2017; Yang et al., 2016). Seminal work by Berkman and Syme (1979) established that men and women who lacked social contacts were more than twice as likely to die earlier compared to their socially connected counterparts. Importantly, these results held after accounting for the influence of a variety of health determinants such as physical health, socioeconomic status, health practices (e.g., smoking, alcohol consumption), and use of preventative care services (Berkman & Syme, 1979). Follow-up investigations established that the mortality risk for the less-socially connected only increased with age (Seeman et al., 1987).

Since these early findings, well-replicated work across countries and cultures has established a life expectancy advantage for more socially connected people while controlling for other longevity-boosting explanations (e.g., physical activity) (Giles et al., 2005; Glass et al., 1999). A meta-analysis surveying 148 studies and 308,849 participants found a 50% increased likelihood of survival across time for participants with stronger social connections (Holt-Lunstad et al., 2010). When considering multidimensional assessments of social connections, the effect size estimate was even stronger, corresponding to a 91% increased likelihood of survival. This aggregate effect size of social relationships on longevity is much larger in magnitude than other well-known predictors of decreased mortality including alcohol abstinence, increased physical activity, and leaner body mass index (BMI; Holt-Lunstad et al., 2010; House et al., 1988). Findings from the 85-year Harvard Study on Adult Development found that the single most important factor influencing well-being throughout the lifespan was the quality of interpersonal relationships (Waldinger & Schulz, 2023).

Further emphasizing the health-promoting benefit of social connection is a sizable literature establishing that coupled individuals have longer, and healthier, lives compared to single counterparts (Robles et al., 2014; Tatangelo et al., 2017). A recent meta-analysis examining 33 studies of longitudinal cohorts with samples both large and multinational found consistently poorer health among widowed, unmarried, and single individuals regardless of age (Tatangelo et al., 2017). The surveyed studies included sample sizes ranging from 765 participants to 29.8 million health records, and populations from countries across North America, South America, Europe, Asia, and Africa. It is clear from these studies of diverse and well-characterized cohorts that social connectedness has powerful implications for prolonging our lives. This strong association begs the question, *how* exactly might social connectedness contribute to increased risk for mortality?

Biomarkers of Health and Relations to Social Connectedness

Biomarkers of health provide a pathway through which social connectedness may be associated with one's lifespan. A decreased risk of mortality relies on satisfactory physical health and the body's ability to fight off illness (Danner et al., 2001; Murphy & Topel, 2006). Thus, various biomarkers of health directly relate to mortality risk through modulation of central physiological, genetic, and neuroendocrine systems such as blood pressure, immune system functioning, cortisol stress response, and others (Cruces et al., 2014; Gaffey et al., 2016; Piferi & Lawler, 2006). Both social connectedness and, conversely, a *lack of* meaningful social connection (i.e., *loneliness*) are associated with these same assays of physical health. Increased social connectedness may promote a longer and healthier life through the modulation of biological pathways including cortisol production, immune system gene expression, and the cardiovascular system (Steptoe et al., 2009).

Studies have linked social connectedness to several biomarkers of physical health including lower heart rate, higher heart rate variability, lower blood pressure, lower markers of inflammation, shorter telomere lengths, enhanced oxytocin levels, and reduced cortisol reactivity (Carroll et al., 2013; Colonnello et al., 2017; Kemp et al., 2017; Steptoe et al., 2009). For example, an examination of over 14,000 people across three nationally representative, longitudinal, population-based samples found a dose–response relationship between social connectedness and improved physiological functioning across the lifespan (i.e., from adolescence to young adulthood and late adulthood) for multiple biomarkers including systolic blood pressure and inflammation (Yang et al., 2016). The lack of social connectedness was as much of a risk factor to inflammation (measured by a well-known biomarker, C-reactive protein [CRP]) as was physical inactivity, underscoring the health-altering effects of social connectedness (Yang et al., 2016). These studies converge to highlight the link between social connectedness and physiological, genetic, and neurochemical measures of physical health.

The deleterious impact of stress may be at the heart of the link between social connectedness and physical health biomarkers. The experience of loneliness, or not having social connections, is unpleasant and stressful (Yang et al., 2014), predicting higher rates of mood disorders and suicide (Erzen & Çikrikci, 2018; Stravynski & Boyer, 2001). It is clear that chronic activation of the body's stress response can lead to downstream consequences across multiple physiological systems (McEwen, 1998; McEwen & Stellar, 1993; Seeman et al., 2002). The stress of loneliness and a lack of social support increases risk for disease and mortality through chronic activation of immune, neuroendocrine, and metabolic systems (Cacioppo & Hawkley, 2003; Kemp et al., 2017; Penwell & Larkin, 2010). The concept of *allostatic load* operationalizes the "wear-and-tear" across the body's components of the stress response, including the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system, cardiovascular system, metabolic pathways, and other physiological systems (Seeman et al., 1997). Multiple studies have connected a lack of meaningful social relationships to increased wear-and-tear in the body's physiological systems, finding that more lonely people have higher allostatic load and that positive social experiences are associated with lower allostatic load (Beckie, 2012; Juster et al., 2010; Quadt et al., 2020; Seeman et al., 2002). This stress-induced wear-and-tear across multiple physiological pathways exerts a toll on the body and the brain, predicting later mortality risk, physical decline, and cognitive decline (Seeman et al., 1997).

Critically, increased allostatic load and stress have been strongly linked with changes in neurobiological structure and function (de Kloet et al., 2005; Lupien et al., 2018). Increased stress impacts the brain both primarily, as the brain is the central coordinator

of the stress response (McEwen, 2017), and secondarily via the consequences of chronic activation of the stress response system. The physical structure and function of neurons in areas such as the hippocampus, amygdala, and prefrontal cortex adapt in response to acute and chronic challenges in the environment via a variety of neurobiological mechanisms such as changes in glucocorticoid receptor responsivity, regulation of excitatory amino acids (e.g., glutamate), and resistance to insulin and other metabolic hormones (McEwen, 2017). The resulting consequences are adaptations that can be viewed via neuroimaging such as altered structure in the hippocampus, amygdala, and prefrontal cortex (Lupien et al., 2018). While this link between stress and changes in brain structure is clear (Booth et al., 2015; McEwen, 2017), the role of social connectedness in buffering against the biological embedding of stress in the brain, and subsequent cascades to decreased mortality risk, is unknown.

Research has found that social connections may protect against some of the many downstream and deleterious physical consequences of stress (Cassel, 1976; Cobb, 1976; Cohen & Wills, 1985; Uchino, 2006), suggesting that the presence of quality social connections could have a stress-buffering role on brain-based biomarkers of health, too. For instance, women with metastatic breast cancer reporting high quality social support had lower cortisol levels than women who reported low quality social support (Turner-Cobb et al., 2000). In another study, pregnant women who reported low social support had higher cortisol levels in response to psychological distress than their counterparts with high social support (Giesbrecht et al., 2013).

This stress-buffering effect of social connectedness has also been observed through experimental manipulation. For example, Cohen et al. (2015) exposed participants to a virus and measured perceived social support and interpersonal stress in the 2 weeks following virus exposure. Individuals experiencing more interpersonal stress and low social support had the highest likelihood of infection. Put another way, high levels of social support buffered against any association between stress and infection (Cohen et al., 2015). Taken together, evidence suggests that a lack of social connections may leave individuals more vulnerable to stressors in their lives while supportive connections buffer against some of the deleterious biological and physiological consequences of the stress response. The role that social connections may play in changes to brain structure and subsequent mortality risk has been unexplored and presents an additional vantage point for understanding the longevity-promoting side effects of interpersonal relationships.

The Brain as a Common Pathway

While there appears to be a link between social connectedness, physical health, and decreased mortality risk, there are critical gaps in our understanding of how social connectedness relates to healthy aging in the brain. The importance of filling this gap cannot be understated, given that the brain both coordinates, and is impacted by, the stress response (e.g., through modulation of the hypothalamic–pituitary–adrenal axis and regulating cortisol circulation).The brain's modulation of neurochemical and electrical signals drives cognitions, emotions, and behaviors and is directly related to mental health symptoms (e.g., depression, dementia, psychosis, mania) as well as other central nervous system disorders (e.g., Parkinson's disease, multiple sclerosis).

An exploration of the association between social connections, aging in the brain, and longevity unlocks an important, and unexplored, vantage point into understanding how our social behavior can promote brain health and subsequently prolong our lives. While the brain's essential role in regulating hormones and governing the stress system, as well as vulnerability to the impacts of stress, make it a prime target for exploring the associations between social connectedness, physical health, and mortality risk, methodological limitations have hampered such an investigation. Until recently, there did not exist a way to measure aging in the brain from a neuroimaging scan.

An emerging conceptualization of aging called *brain age* provides an exciting opportunity to increase our understanding of the associations between social connectedness, physical health, and mortality risk. In the past few years, machine learning algorithms to calculate the "age of the brain" have been developed and publicly shared (see Cole et al., 2018; Kaufmann et al., 2019); this critical advancement overcomes methodological obstacles that have thus far prevented research from exploring these questions. These algorithms are trained on large data sets to predict individuals' brain ages based on multiple aspects of neuroimaging scans (e.g., over 1,000 features of the brain comprised of thickness, area, and volume measurements from the cerebral cortex, cerebellum, and subcortex). The resulting parameters can be used in other, independent data sets to estimate a new participant's brain age (Cole et al., 2018).

The study of brain age is in its infancy; nonetheless, nascent literature suggests that brain age is a potent predictor of mental health and lifespan. These studies have focused on the brain-age gap, or an index of the discrepancies between an individual's brain age and their chronological age. For instance, Cole et al. (2018) found that each additional year discrepancy between brain age and chronological age predicted a 6.1% relative increase in the risk of death for individuals between 72 and 80 years of age. The brain-age gap not only significantly predicted mortality risk but also outperformed epigenetic measures of aging (i.e., DNA-methylation) in predicting mortality risk in this same sample.

The brain-age gap has been related to other maladaptive outcomes in addition to mortality risk. Recent work found that the discrepancy between chronological age and brain age predicted several brain-based disorders including dementia, schizophrenia, and multiple sclerosis (Kaufmann et al., 2019). Brain-age gaps were not only more prevalent among many of these common disorders but also predicted level of impairment (Kaufmann et al., 2019). Larger brain-age gaps were associated with lower levels of psychological, social, and occupational functioning among individuals with schizophrenia, higher degree of disability among individuals with multiple sclerosis, and lower cognitive functioning among individuals with mild cognitive impairment or dementia (Kaufmann et al., 2019). This novel and predictive measure is an intriguing biomarker that may clarify the associations between social connectedness and healthy aging in the brain. The derivation of brain-age estimates relies on a multitude of neuroimaging parameters that have been found to be impacted by chronic stress, such as cortical thickness (Averill et al., 2017; Monninger et al., 2020), and therefore implicate the brain-age gap as a critical exploration underpinning the stress-buffering role of interpersonal relations on biological health and decreased mortality risk.

Understanding how social connectedness is associated to the brain-age gap and mortality risk may emphasize that social connectedness affects even more processes than previously known, a timely investigation following the COVID-19 pandemic and resulting social

isolation. While much is known about the associations between social connection and indices of well-being (e.g., happiness), extension of this work to a novel biomarker, the brain-age gap (i.e., the discrepancy between algorithm-predicted age and chronological age) overcomes limitations of other work by not relying on self-report or monoinformant measures of well-being (i.e., the brain-age gap can be thought of as a more "objective" measure). This work is an initial step toward understanding these associations with more specificity, as future work could elaborate on social connectedness and biological aging to explore these effects in other areas of the body, investigating whether these benefits trigger a coordinated set of biological processes that occur throughout the body or are localized to the brain.

Seeing as the brain is the organ of behavior, understanding the association between the quality of social connections, the brain-age gap, and mortality risk brings us closer to an understanding of mechanism. Once establishing an initial association between social connectedness, the brain-age gap, and mortality risk, future work could localize alterations that could give us insight into processes that are driving the longevity-promoting associations of social connectedness. Recent research establishing the ages of multiple organ systems (cardiovascular, pulmonary, musculoskeletal, immune, renal, hepatic, metabolic, and brain) in a sample of over 1,000 observations found that ages of these organs systems were heterogenous and unique, and that aging in one organ system influenced aging in another (Tian et al., 2023). Authors then associated organ ages with specific and modifiable risk and resilience factors that could inform interventions targeted at specific body systems. Pinpointing individuals at risk for accelerated brain age (e.g., potentially individuals who are less socially connected) could identify ways to intervene before disease onset and slow down the aging of this specific organ.

With respect to the brain-age gap serving as a novel biological mechanism at the whole-organ level, there are emerging concerns about the reproducibility, reliability, and magnitude of potential effects in neuroimaging research (Marek et al., 2022). Evidence suggests that, compared to other commonly used methods of neuroimaging (Elliott et al., 2020; Poldrack et al., 2015) brain-age is a more reliable estimation of biology (Bacas et al., 2023) due in part to the algorithms' reliance on a high number of features. Applying this novel tool to what we already know about social connectedness, biomarkers, and longevity contributes a potentially more reliable and reproducible understanding of neurobiology's role. An investigation using this timely innovation may fill in key knowledge gaps as we continue to explore how social connectedness boosts our health and lifespans.

The Present Study

It is clear from prior work that social connectedness is associated with physiological markers of healthy aging and predicts decreased mortality risk. Recent methodological advances allowing researchers to calculate "the age" of the brain relative to chronological age provide an opportunity to explore the pathway linking social connectedness and a longer lifespan. This study explores the potentially protective role that social connections may have in decreasing the rate of biological aging of the brain and risk of mortality.

We test associations between social connectedness and the brain-age gap in a well-known cohort that has been critical for our understanding of successful aging—the Midlife in the United States (MIDUS) study. This data set is an ongoing, almost 30-year-long investigation with rich measures of psychological factors, lifestyle variables, mortality, and neuroimaging data. The well-phenotyped individuals that are part of the MIDUS study data set have been a key platform for many ground-breaking discoveries related to aging, including linking social connection and support to biomarkers of health (Creaven et al., 2020; Donoho et al., 2013).

Here, we test several hypotheses exploring associations between social connectedness, brain age, and mortality risk in the MIDUS data set. First, we aimed to expand findings linking the quality of social connectedness with a longer lifespan by examining the association between positive relations with others and mortality risk; we hypothesized that more positive relations with others would predict a decrease in markers of mortality risk. Second, we investigated the connection between the quality of social connections and the brain-age gap, predicting that more positive relations with others would be associated with a younger brain age relative to chronological age. Last, we planned to test an indirect effects model, considering whether the gap between chronological age and brain age statistically accounted for part of the association between positive relations with others and mortality risk. This investigation explores whether a younger brain age relative to chronological age can be added to the list of benefits associated with quality interpersonal relationships.

Method

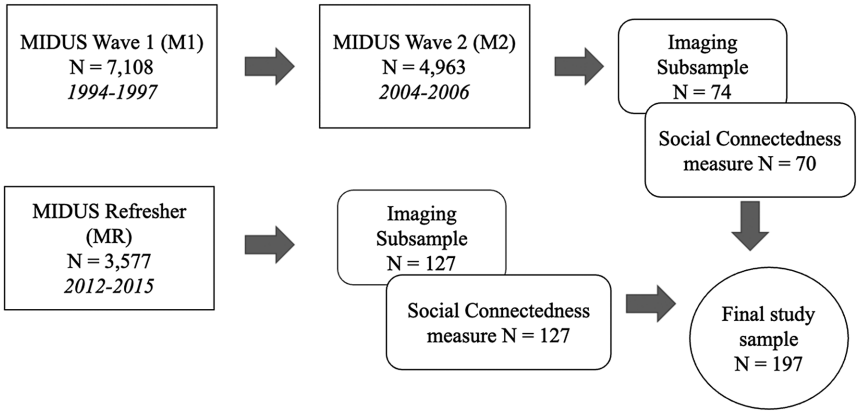
Data for these analyses are drawn from a subset of the MIDUS Longitudinal Study of Health and Well-being, a 30-year investigation of over 10,000 adults (ages 35–85) across multiple waves. Detailed information on MIDUS study design, sampling, recruitment, retention, and other study details for MIDUS have been described elsewhere (https://www.midus.wisc.edu/). Data and documentation for MIDUS are freely available through the Inter-University Consortium for Political and Social Research website (https://www.icpsr.umich.edu/web/ICPSR/series/203). Self-report and demographic data were downloaded from the MIDUS Colectica website (https://midus.colectica.org). Neuroimaging data were accessed through a data sharing agreement via the MIDUS website. All cleaning and coding scripts are available at our study GitHub along with instructions on how to access the publicly available data from MIDUS.

MIDUS Study Sample (Core and Refresher Cohorts)

This study combines MIDUS participants from the Core wave of study recruitment (Core/M1 $n = 7{,}108$) and a second data recruitment effort to "refresh" the sample due to attrition (MIDUS Refresher [MR] $n = 3{,}577$). Our sample consists of participants who have complete data (i.e., magnetic resonance imaging [MRI] scans, social connectedness measure, and other variables) for a final sample of 197 participants. See below for a more detailed description on study recruitment and a visualization of sample flow (Figure 1); for further details, please visit the MIDUS website.

Participants from the Core sample were recruited between 1994 and 1997 through (a) random-digit-dialing, (b) being a sibling of someone recruited through random-digit dialing, or (c) a national twin registry. Participants from the Core Wave 1 (M1) were recruited for a second wave of data collection (Core Wave 2/M2, $n = 4{,}963$) between 2004 and 2006. Of this Wave 2 subsample a further

Figure 1
Visualization of MIDUS Study Flow and Recruitment



Note. MIDUS = Midlife in the United States.

subgroup of individuals who were able to travel to the laboratory at the University of Wisconsin–Madison completed neuroimaging scans (n = 74). From this imaging subsample, 70 participants completed the social connectedness measure. Participants from the Refresher sample were recruited between 2012 and 2015 (n = 3,577), of which a subsample completed neuroimaging scans at a follow-up visit that took place between 2012 to 2016 (n = 127). From this second imaging subsample, all participants completed the social connectedness measure for an overall neuroimaging subsample of 197. All participants were right-handed and were screened to ensure MRI compatibility.

Ethics Information

The MIDUS project is reviewed and approved by regional institutional review boards. Consent was provided by all participants.

Design

Main Measures

The Quality of Social Connections

We operationalized the quality of social connection in the MIDUS data set using the Positive Relations with Others subscale of the well-validated Psychological Well-Being Scale (Ryff, 1989; Ryff & Keyes, 1995). The Positive Relations with Others subscale is comprised of seven questions assessing social connectedness (e.g., "Maintaining close relationships has been difficult and frustrating for me," "People would describe me as a giving person, willing to share my time with others" [reverse coded])." Participants responded on a scale from 1 to 7 (1 = strongly agree, 7 = strongly disagree); higher values on this measure indicate more positive relations with others. Previous investigations of the Positive Relations with Others subscale in the MIDUS data set have found the variable to be useful in examining indicators of health; for example, Positive Relations with Others was one of two Psychological Well-Being subscales to be associated with decreases in the inflammatory marker interleukin−6 (Friedman & Ryff, 2012).

The Psychological Well-Being Scale was administered twice to participants in the Core waves of data collection (Core Wave 1 Project 1 [M1P1] and Core Wave 2 Project 1 [M2P1]) and once to the Refresher sample (Refresher Project 1 [MRP1]). For this investigation, we considered reports of Positive Relations with Others from M2 for the Core sample. Psychometric properties for this constructed variable are reported for each wave of data collection in MIDUS documentation (e.g., M1P1, M2P1, and MRP1). Past work has found item-level correlation within the Positive Relations with Others variable for each wave: M1P1 (three-item version) α = .58; M2P1 (seven-item version) α = .78, and MRP1 (seven-item version) α = .789. Further details on this variable can be found at https://midus.wisc.edu.

Neuroimaging

MRI data were collected on a GE SIGNA 3.0 Tesla high-speed MRI scanner (MR750 GE Healthcare, Waukesha, WI) with an 8-channel head coil. T1-weighted anatomical images were collected with the following parameters: repetition time = 8.2 ms, echo time = 3.2 ms, flip angle = 12°, field of view = 256 mm, 256 × 256 matrix, 160 axial slices, inversion time = 450 ms, with 1-mm isotropic voxels. acquisition matrix = 256 × 256, field of view = 240 mm, 124 × 1.1 mm axial slices (Grupe et al., 2018; Urban-Wojcik et al., 2022). Structural images were processed using FreeSurfer imaging analysis suite (v 7.1.0; https://surfer.nmr.mgh.harvard.edu/), which includes motion correction, averaging of multiple volumetric T1-weighted images, removal of nonbrain tissue, automated Talairach transformation, segmentation of cortical and subcortical structure, and other corrections (Urban-Wojcik et al., 2022).

The Brain-Age Gap

Our main variable of interest is the brain-age gap, which is calculated by subtracting chronological age from the algorithm-predicted age of the brain (i.e., brain-age gap = algorithm-predicted age—chronological age). Algorithm-predicted age of the brain (i.e., "brain age") was calculated from raw T1-weighted MRI scans using

the open-access algorithm pioneered by Kaufmann et al. (2019), referred to as "XGBoost."

Various algorithms have been written to calculate brain age, including XGBoost, brainageR, and DeepBrainNet; recent work from our group examining the reliability of brain age algorithm found excellent reliability ($r > 0.9$) for each algorithm in new samples (Bacas et al., 2023). Based on this empirical work, we determined that the XGBoost algorithm by Kaufmann et al. (2019) was the superior choice for predicting psychopathological correlates of brain age and is also the algorithm that considers the highest number of features and is resistant to high motion within scans (Bacas et al., 2023; Hanson et al., 2023). This algorithm is described by Kaufmann et al. (2019) in detail and relevant code is available (https://github.com/tobias-kaufmann/brainage). Current literature suggests that algorithms that consider more features of a neuroimaging scan may be more reliable (Jirsaraie et al., 2023). The XGBoost algorithm uses gradient tree boosting to consider 1,118 features of the brain comprised of thickness, area, and volume measurements from a multimodal parcellation of the cerebral cortex, cerebellum, and subcortex. These features are extracted using Freesurfer software, which is accessible via https://Brainlife.io (https://surfer.nmr.mgh.harvard.edu/fswiki/ReleaseNotes), a free, publicly funded, cloud-computing platform for developing reproducible neuroimaging processing pipelines and sharing data (Avesani et al., 2019).

The XGBoost algorithm was trained on a massive sample (N = 39,827, female = 18,990 or roughly 48%) consisting of healthy controls ages 3–89 years old from 42 different data sets. All training data passed automatic quality control procedures. Kaufmann and colleagues employed fivefold cross-validation and trained separate models for male and female brain age to account for potential variation between the subsamples. The main variable of interest for these analyses is the subsequently calculated brain-age gap, or the discrepancy between chronological age and algorithm-predicted brain age. Chronological age is not used as a feature to train brain age; rather, it is incorporated into the computation of the brain-age gap (i.e., algorithm-predicted brain age minus chronological age).

We deployed this XGBoost algorithm by first completing standard processing approaches in Freesurfer 7.1 (https://surfer.nmr.mgh.harvard.edu). The technical details of this software suite are described in prior publications (Dale et al., 1999; Fischl et al., 1999, 2002, 2004). Briefly, this processing includes motion correction and intensity normalization of T1-weighted images, removal of nonbrain tissue (Ségonne et al., 2004) automated Talairach transformation, segmentation of white matter and gray matter volumetric structures, and derivation of cortical thickness. The XGBoost algorithm takes processed T1-weighted images as input and then calculates the algorithm-predicted age for each scan using gradient tree boosting. We additionally computed brain-age using four alternative algorithms. These data are available on the study GitHub, and further details are present in the Supplemental Material.

Mortality Risk

Mortality risk was operationalized through (a) the number of chronic conditions reported; and (b) ability to perform usual physical, social, and other role-related activities. M2 and MR participants self-reported the number of chronic conditions experienced in the past 12 months by responding "Yes" or "No" to a checklist of 30 items (e.g., asthma, thyroid disease, ulcers, migraines, sleep problems). The total number of chronic conditions is a summed score of the items to which participants responded "Yes" (i.e., ranges from 0 to 30).

Participants also reported on the extent to which their health interfered with their ability to complete three basic activities of daily living (ADLs; e.g., bathing/dressing oneself, walking one block, climbing one flight of stairs) and seven instrumental activities of daily living (IADLs; e.g., climbing several flights of stairs, lifting/carrying groceries) on 4-point scales (1 = *a lot*, 2 = *some*, 3 = *a little*, 4 = *not at all*). Items were then reverse coded so that higher scores reflect greater difficulty in performing ADLs and IADLs. The total scores for ADLs and IADLs were summed to form a single composite ADLs score.

We also conducted exploratory analyses with participant mortality records collected by the MIDUS team at the University of Wisconsin–Madison. These records include month and year of death and *International Classification of Diseases* codes for underlying cause of death and were updated through the Spring 2021 for the MIDUS Core cohort and July 2022 for the MIDUS Refresher cohort. We considered these analyses exploratory due to concerns over power (i.e., 11 participants out of 197 in the imaging subsample had died).

Covariates

Our main analyses contained the following variables as covariates: chronological age, biological sex, race, and recruitment group. For analyses with the brain-age gap variable, we added a variable operationalizing time between assessment and MRI scan. We also considered sensitivity analyses with other known correlates of longevity (Vaillant & Mukamal, 2001), including associations between income, psychopathology, childhood social class, and BMI and our main outcomes of interest.

Sample Origin

A dichotomous variable representing which wave the participant was recruited from (M2 vs. MR) was used as a covariate in analyses, following other investigations of similar constructs in the MIDUS sample (e.g., Urban-Wojcik et al., 2022).

Chronological Age

Participant age at scan was operationalized with the MIDUS variable "Respondent age at P5 visit."

Assessment Lag Time

The amount of time between M2/MR assessment and the neuroimaging scan was operationalized for each participant by the discrepancy in age between the two assessments (i.e., age at M2/MR assessment subtracted from age at MRI visit).

Race

Participants self-reported their race by responding to the question "which of the following best describes your race?" and selecting one of the following options: White, Black and/or African American, Native American or Aleutian Islander, Asian or Pacific Islander, other, multiracial, or refuse to answer. For the purpose of our

analyses, we dichotomized responses into the category "person of color" (i.e., Black and/or African American, Native American or Aleutian Islander, Asian or Pacific Islander, other, or multiracial identity) versus "nonperson of color."

Biological Sex

Data on biological sex were collected via participant self-report and recorded as a binary indicator (0 = male, 1 = female). Neither a nonbinary indicator of biological sex nor a self-report measure on gender identity was available in this data set.

Income

A "total household income" variable was calculated by summing together (a) respondent's self-reported personal earning, pension, and social security income, (b) spouse's personal earning, pension, and social security income, and (c) other family member's personal earning, pension, and social security income.

Psychopathology

Researchers administered The World Health Organization Composite International Diagnostic Interview Short Form via the phone to participants and recorded whether participants met diagnostic criteria for depression, generalized anxiety disorder, and panic disorder (Kessler et al., 1998). We created a composite mental health diagnosis variable by summing together the binary indicators for each of these three diagnoses (e.g., a score of 3 would indicate that someone met criteria for all three diagnoses).

Body Mass Index

BMI is an indicator of risk for diseases that can occur with increased body fat (e.g., cardiovascular disease, diabetes; Rashid et al., 2003). Measures of height and weight were collected via self-report in M2 and M2, and BMI scores were computed (BMI = weight/height^2). For a subset of participants, height and weight measurements were obtained by clinical staff via a standardized protocol. Where available, and based on guidance from MIDUS documentation, the staff-obtained measure was used. When not available, the self-report measure of BMI was used.

Childhood Social Class

Participants in M1 and MR answered via self-report how they compared to other families in terms of finances growing up. Participants responded *a lot better off, somewhat better off, a little better off, same as average family, a little worse off, somewhat worse off, a lot worse off, or I do not know*. Participants also responded via self-report whether their family was on Welfare/Aid to Dependent Children growing up (0 = no, 1 = Yes). We z-scored each of these variables and summed them for a composite measure of childhood social class.

Sampling Plan

Data Inclusion/Exclusion

Participants who (a) completed the Positive Relations with Others measure of the Psychological Well-Being Scale and (b) a neuroimaging scan were included in our data analyses (N = 197). Structural neuroimaging scans were examined for quality by using the Computational Anatomy Toolbox 12 (CAT12) to generate a quantitative quality metric ("CAT12 score") (Gaser & Dahnke, 2016). This metric considers the following four measures of image quality: noise-to-contrast ratio, coefficient of joint variation, inhomogeneity-to-contrast ratio, and root-mean-squared voxel resolution. CAT12 normalizes and combines these measures using a kappa statistic-based framework, producing a score from 0 to 1 (higher values indicate better image quality). Additional information is available at https://www.neuro.uni-jena.de/cat/index.html#QA.

Power Analysis

While work connecting brain-age to different individual differences is still in its infancy, multiple past studies report medium effect sizes; for example, accelerated brain age has been associated with excessive worry (Cohen's d = 0.53), as well as symptoms of depression (Cohen's d = 0.61) (Karim et al., 2021). We computed power analyses for our partial indirect effects analysis using the R package "pwrss," which provides a framework for power analyses within a mediation framework. For the a path estimation—that is, an approximate effect size of the association between social connectedness and brain age, we used an estimation of $\beta = 0.29$. Due to the novelty of this exploration of social connectedness on brain age, there were no effect size estimates exactly; this estimate was derived from a recent publication on rumination on brain age, an approximate psychosocial process (Karim et al., 2021). For the b path, we used an estimation of $\beta = 0.545$ (Cole et al., 2018). Three various tests (Sobel, Aroian, and Goodman) at 80% power and a Type I error rate of 0.05 produced a sample size of 106, 108, and 104, respectively. With our sample size of 123, an a path estimate of $\beta = 0.29$, and b path estimate of $\beta = 0.545$, we were 85%–92% powered to detect an effect similar to what has been reported in the literature.

Analysis Plan

Descriptive statistics (means, medians, and standard deviations) and correlational analysis were conducted to describe the sample and report associations between brain data (calculated brain age and imaging scan quality), social connectedness, mortality risk (number of chronic health conditions and composite ADL score), variables related to mortality risk (income, psychopathology, childhood social status, and BMI), and other demographics (age, sex, race, and sample origin). Regression models considered associations between (a) the quality of social connections and mortality risk (c path), (b) the quality of social connections and the brain-age gap (a path), and (c) the brain-age gap and mortality risk (b path). All regression equations included chronological age, biological sex, race, and sample origin (i.e., M1/M2 or MR recruitment group). Regression equations for the a and b paths that include the brain-age gap also added a covariate modeling the amount of time between the self-report assessments and neuroimaging scan (i.e., assessment lag time).

Supplemental analyses considered the role of other contributors to main outcomes of interest. We conducted sensitivity analyses with other known correlates of longevity, considering the following additional covariates in adjusted main models: income, mental health diagnoses, childhood social class, and BMI (Vaillant & Mukamal, 2001). Specifically, we ran regression analyses with the additional independent variables (a) income, (b) mental health diagnosis, (c) childhood social class, and (d) BMI predicting both brain age (i.e., *a* path) and mortality risk (*c* path) in separate models (i.e., a different model for each additional covariate). We also ran exploratory analyses considering associations between social connectedness and mortality records.

Research Questions and Hypotheses

Research Question 1

Are there associations between social connectedness and mortality risk?

We hypothesized that positive relations with others would be associated with decreased mortality risk as measured by (a) the number of chronic conditions reported and (b) ability to perform ADLs. We tested the association between positive relations with others and mortality risk in two separate linear models (i.e., one for each mortality risk operationalization) that included covariates listed above. We report standardized and unstandardized beta coefficients for linear regression model as well as 95% confidence intervals for the coefficient estimates and p values, considering a two-sided $p < .05$ as statistically significant (see Table 1).

c Path

$$\begin{aligned}\text{ChronicConditions} = {} & \beta_1\text{PosRelationsOthers} + \beta_2\text{Age} \\ & + \beta_3\text{BiologicalSex} + \beta_4\text{Race} \\ & + \beta_5\text{SampleOrigin}, \end{aligned} \quad (1)$$

$$\begin{aligned}\text{ADLs} = {} & \beta_1\text{PosRelationsOthers} + \beta_2\text{Age} + \beta_3\text{BiologicalSex} \\ & + \beta_4\text{Race} + \beta_5\text{SampleOrigin}. \end{aligned} \quad (2)$$

Research Question 2

Are there associations between positive relations with others and the brain-age gap?

Linear regression was used to test the association between positive relations with others and the brain-age gap in a model that includes covariates listed above. We hypothesized that positive relations with others would predict the difference between chronological age and brain age (i.e., brain-age gap), such that higher positive relations with others would be associated with a narrower brain-age gap driven by a younger brain age relative to chronological age. We report standardized and unstandardized beta coefficients for the linear regression model as well as 95% confidence intervals for the coefficient estimates and p values, considering a two-sided $p < .05$ as statistically significant.

a Path

$$\begin{aligned}\text{BrainAgeGap} = {} & \beta_1\text{PosRelationsOthers} + \beta_2\text{Age} \\ & + \beta_3\text{BiologicalSex} + \beta_4\text{Race} \\ & + \beta_5\text{SampleOrigin} + \beta_6\text{LagTime}. \end{aligned} \quad (3)$$

Research Question 3

Are associations between positive relations with others and all-cause mortality statistically accounted for by the brain-age gap?

We planned to use linear regression models within an indirect effects analysis framework to test whether the brain-age gap statistically accounts for part of the association between positive relations with others and mortality risk. Our two models (i.e., one testing chronic conditions as the outcome representing mortality risk and one testing limitations to ADLs) included the same covariate set as the previous models. We hypothesized that participants' brain-age gap would account for part of the association between positive relations with others and mortality risk, such that brain-age gap values (i.e., discrepancy between predicted age of the brain and chorological age) would explain variance in the association between positive relations with others and mortality risk. We planned to achieve this through Monte Carlo simulation of the confidence intervals of the indirect effect (i.e., $a \times b$, where a is the coefficient representing *positive relations with others* predicting *brain-age gap* and b is the coefficient representing *brain-age gap* predicting *mortality risk*). This method has been established as advantageous over other methods of confidence interval construction for producing more precise estimates and is implemented through the R package "mediation" (Tingley et al., 2014).

b Path

$$\begin{aligned}\text{ChronicConditions} = {} & \beta_1\text{BrainAgeGap} + \beta_2\text{Age} \\ & + \beta_3\text{BiologicalSex} + \beta_4\text{Race} \\ & + \beta_5\text{SampleOrigin} + \beta_6\text{LagTime}, \end{aligned} \quad (4)$$

$$\begin{aligned}\text{ADLs} = {} & \beta_1\text{BrainAgeGap} + \beta_2\text{Age} + \beta_3\text{BiologicalSex} \\ & + \beta_4\text{Race} + \beta_5\text{SampleOrigin} + \beta_6\text{LagTime}. \end{aligned} \quad (5)$$

Data Imputation

Self-report measures were imputed using the full MIDUS sample to maximize the number of observations for the imaging analyses. Two hundred one individuals completed imaging across Core and MR samples. Of these observations, 197 had complete data. We used the full MIDUS sample and the "mice" package in R to impute missing variables (van Buuren & Groothuis-Oudshoorn, 2011). Research Question 1 reports results from full MIDUS ($N = 8{,}692$), while Research Questions 2 and 3 run analyses using the MIDUS imaging subsample, both raw ($N = 197$) and imputed ($N = 201$). Full details can be found in the Supplemental Material. For all analyses, analytic output and code, including standardized and unstandardized beta coefficients for regression models, as well as 95% confidence intervals for the coefficient estimates and p values, can be found in the Supplemental Material.

Table 1
Design Table: List of Research Questions and Corresponding Hypotheses

Question	Hypothesis	Sampling plan	Analysis plan	Interpretation given to different outcome
Research Question 1: What are the associations between the quality of positive relations with others and mortality risk?	H1-0. There will be no significant association between the quality of positive relations with others and mortality risk. H1-A. Higher quality positive relations with others will be associated with decreased mortality risk. H1-B. Higher quality positive relations with others will be associated with increased mortality risk.	$N = 197$	Linear regression, Equations 1 and 2	• Social connectedness does not statistically predict likelihood of experiencing chronic conditions/limitations to ADLs. • Social connectedness statistically predicts decreased likelihood of experiencing chronic conditions/limitations to ADLs. • Social connectedness statistically predicts increased likelihood of experiencing chronic conditions/limitations to ADLs.
Research Question 2: What are the associations between the quality of positive relations with others and the brain-age gap?	H1-0. There will be no significant association between the quality of positive relations with others and brain-age gap. H1-A. Higher quality positive relations with others will predict a positive brain-age gap. H1-B. Higher quality positive relations with others will predict a negative brain-age gap.	$N = 197$	Linear regression, Equation 3	• Social connectedness does not statistically predict discrepancy between one's brain age and one's chronological age. • Social connectedness does statistically predict a "younger" brain age compared to one's chronological age. • Social connectedness does statistically predict an "older" brain age compared to one's chronological age.
Research Question 3: How much variance in the association between the quality of positive relations with others and mortality risk is accounted for by the brain-age gap?	H1-0. The brain-age gap accounts for no variance in the association between the quality of positive relations with others and mortality risk H1-A. Brain age accounts for a significant portion of variance in the positive association between the quality of positive relations with others and mortality risk. H1-B. Brain age accounts for a significant portion of variance in the negative association between the quality of positive relations with others and mortality risk.	$N = 197$	Indirect effects analysis with linear regression, Equations 4 and 5	• The discrepancy between brain age and chronological age does not relate to social connectedness and likelihood of experiencing chronic conditions/limitations to ADLs. • The discrepancy between brain age and chronological age partially explains the association between more social connectedness and decreased likelihood of experiencing chronic conditions/limitations to ADLs. • The discrepancy between brain age and chronological age partially explains the association between more social connectedness and increased likelihood of experiencing chronic conditions/limitations to ADLs.

Note. H = hypothesis; ADLs = activities of daily living.

Results

Descriptive statistics are presented in Table 2 and correlations between key variables can be found in Table 3.

Research Question 1

Regression analyses found a significant association between positive relations with others and decreased mortality risk as measured by the number of chronic conditions reported in the full MIDUS sample ($N = 8{,}692$; $\beta = -0.04$, $t = -10.68$, $p < .01$). That is, as expected, increased social connectedness was correlated with a lower number of chronic health conditions. Similarly, linear models found that increased levels of social connectedness were associated with decreased difficulties completing ADLs in the full MIDUS sample ($\beta = -0.03$, $t = -18.23$, $p < .01$). Analyses with the imaging MIDUS subsample ($N = 201$) did not find significant effects for social connectedness on chronic health conditions ($\beta = -0.03$, $t = -1.21$, $p = .229$). However, social connectedness did significantly predict decreased difficulty to perform ADLs in this sample ($\beta = -0.03$, $t = -2.31$, $p = .021$). This pattern was true for both the imaging subsample with imputed data ($N = 201$) and nonimputed data ($N = 197$). Exploratory analyses considered the effect of social connectedness on mortality in the complete MIDUS sample, finding that increased social connectedness was associated with a 2.3% decrease in the odds of mortality (odds ratio = 0.98, $t = -5.21$, $p < .001$).

Research Question 2

We next examined the association between social connectedness and the brain-age gap in two subsamples of the MIDUS data set—the entire imaging sample ($N = 201$) with imputed behavioral data and the imaging sample relying on complete observations only ($N = 197$). We did not find support for our hypothesis that social connectedness would predict the brain-age gap in the imputed imaging sample ($\beta = -0.02$, $t = 0.08$, $p = .801$) or the raw imaging

Table 2
Descriptive Statistics for Key Variables by Recruitment Sample

Characteristic	Core[a]	Refresher[a]	Overall[a]
Age (years)	57 (10)	47 (12)	51 (12)
Sex			
Female	50 (68%)	68 (54%)	118 (59%)
Male	24 (32%)	59 (46%)	83 (41%)
Latine/x			
Not Spanish/Hispanic	67 (100%)	125 (100%)	192 (100%)
Race			
White	45 (64%)	81 (64%)	126 (64%)
Black and/or African American	20 (29%)	38 (30%)	58 (29%)
Native American or Alaska Native Aleutian Islander/Eskimo	3 (4.3%)	2 (1.6%)	5 (2.5%)
Asian	1 (1.4%)	1 (0.8%)	2 (1.0%)
Native Hawaiian or Pacific Islander	0 (0%)	0 (0%)	0 (0%)
Other	1 (1.4%)	5 (3.9%)	6 (3.0%)
Education			
No school/some grade school	0 (0%)	0 (0%)	0 (0%)
Eighth grade/ junior high school	1 (1.4%)	0 (0%)	1 (0.5%)
Some high school	5 (7.1%)	8 (6.3%)	13 (6.6%)
General Education Development	2 (2.9%)	2 (1.6%)	4 (2.0%)
Graduated from high school	21 (30%)	19 (15%)	40 (20%)
1–2 years college, no degree yet	11 (16%)	20 (16%)	31 (16%)
3+ years college, no degree yet	4 (5.7%)	5 (3.9%)	9 (4.6%)
Grad 2-year/vocational school/associates degree	7 (10%)	17 (13%)	24 (12%)
Grad 4–5 year college/bachelor's degree	9 (13%)	31 (24%)	40 (20%)
Some graduate school	1 (1.4%)	3 (2.4%)	4 (2.0%)
Master's degree	9 (13%)	15 (12%)	24 (12%)
Professional degree (e.g., PhD, JD)	0 (0%)	7 (5.5%)	7 (3.6%)
Income			
Less than $10,000	4 (6.0%)	11 (8.9%)	15 (7.9%)
$10,000–$19,999	5 (7.5%)	5 (4.0%)	10 (5.2%)
$20,000–$29,999	11 (16%)	5 (4.0%)	16 (8.4%)
$30,000–$39,999	5 (7.5%)	10 (8.1%)	15 (7.9%)
$40,000–$49,999	7 (10%)	6 (4.8%)	13 (6.8%)
$50,000–$59,999	9 (13%)	10 (8.1%)	19 (9.9%)
$60,000–$69,999	5 (7.5%)	13 (10%)	18 (9.4%)
$70,000–$79,999	4 (6.0%)	9 (7.3%)	13 (6.8%)
$80,000–$89,999	4 (6.0%)	10 (8.1%)	14 (7.3%)
$90,000–$99,999	2 (3.0%)	6 (4.8%)	8 (4.2%)
$100,000–$149,999	8 (12%)	28 (23%)	36 (19%)
$150,000 or more	3 (4.5%)	11 (8.9%)	14 (7.3%)
Total	$N = 74$	$N = 127$	$N = 201$

[a] *M* (*SD*); *n* (%); *N* = *N*.

Table 3
Correlation Table of Key Study Variables

Characteristic	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Age	—														
2. Sex	.02	—													
3. Latine/x	.05	.04	—												
4. Race	.08	−.03	−.18*	—											
5. Income	−.14	−.22**	−.10	.25***	—										
6. Sample	−.41***	−.14	−.01	−.01	.19**	—									
7. Childhood finances	.16*	−.01	.01	.08	−.05	−.28***	—								
8. Childhood welfare	.12	−.03	−.09	.31***	.18*	−.05	−.36***	—							
9. BMI	.07	.11	−.02	−.19**	−.04	.01	−.01	−.13	—						
10. Panic Dx	.08	.12	.19**	.00	.10	−.05	.05	.02	.00	—					
11. Depression Dx	−.14	.04	−.05	.00	−.06	−.04	.03	−.10	.15*	.04	—				
12. Anxiety Dx	.10	.07	.23**	−.01	−.07	−.06	−.04	.07	−.01	.29***	.08	—			
13. Social connectedness	.12	.21**	−.08	.06	−.02	−.04	−.09	.05	.01	−.11	−.09	−.14	—		
14. Chronic conditions	.46***	.15*	.18*	−.01	−.21**	−.22**	.14	−.16*	.27***	.07	.12	.18*	.03	—	
15. ADLs	.22**	.03	.18*	−.33***	−.25***	−.12	.08	−.25***	.37***	.04	.23**	.13	−.17*	.44***	—

Note. Computed correlation used Pearson-method with pairwise-deletion. BMI = body mass index; Dx = diagnosis; ADLs = activities of daily living.
* $p < .05$. ** $p < .01$. *** $p < .001$.

sample (β = 0.01, t = 0.18, p = .859). Supplemental analyses exploring four other algorithms to calculate brain age and derive the brain-age gap were consistent with these results.

Research Question 3

Before testing whether the brain-age gap statistically accounts for part of the association between positive relations with others and mortality risk, we first ran *b* path analyses considering whether the brain-age gap predicted mortality risk. Contrary to predictions, the brain-age gap did not statistically predict mortality risk as operationalized by total chronic conditions in either the complete imaging sample (β = −0.01, t = −0.63, p = .526) or the raw imaging sample (β = −0.01, t = −0.35, p = .730). Similarly, the brain-age gap did not predict ability to perform ADLs in the imputed imaging sample (β = −0.00, t = −0.34, p = .733) or the raw imaging sample (β = −0.00, t = −0.15, p = .880). Results for all models were consistent with other algorithmic operationalizations of brain age and derivation of the brain-age gap (see Supplemental Material). We therefore did not test for statistical mediation due to not having a significant *a* or *b* path for our hypothesized models.

Supplemental Analyses

We report in the supplement additional analyses using four other algorithms to calculate brain age and derive the brain-age gap. These variables were used in exploratory analyses to query Research Questions 2 and 3. Results were consistent across all models (i.e., not significant). We also report (a) *c* path logistic regressions models with mortality data, (b) sensitivity analyses with known correlates of mortality (i.e., income, mental health diagnoses, childhood social class, and BMI) in *a* and *c* path models, and (c) exploratory analyses with models not including chronological age and data from participants with the highest-quality scans.

Discussion

This study sought to explore whether the brain-age gap, a novel marker for brain health, would be related to the known phenomenon that social connections are good for health. In the large MIDUS sample, our analyses replicate what decades of research has found: More social connectedness predicts decreased mortality risk through multiple operationalizations. That is, a higher number of self-reported positive relations with others was related to fewer chronic health conditions, reduced difficulty in completing ADLs, and in exploratory analyses, reduced odds of death. We did not find evidence that the brain age gap, or discrepancy between chronological age and algorithm-predicted brain age, was related to social connectedness or mortality risk. We consider how our results correspond to findings from other research and discuss limitations of our study below to encourage other researchers to explore this potentially fruitful area.

Our first finding that social connectedness is related to lower mortality risk echoes a vast body of literature suggesting that social relationships are beneficial for health and longevity (Rico-Uribe et al., 2018; Tatangelo et al., 2017; Yang et al., 2016). The pattern that social relationships are associated with mental and physical health has been replicated across a variety of disciplines, with social connections being related to less depression (Badri et al., 2021),

lower blood pressure (Steptoe et al., 2009), and lower likelihood of an early death (Holt-Lunstad et al., 2010).

We did not find statistically significant associations between social connectedness and the brain-age gap, or between the brain-age gap and mortality risk. Our investigation of the brain-age gap, a novel biomarker found to be predictive of mortality and cognitive decline (Anatürk et al., 2021; Cole et al., 2018), joins emerging work exploring the effects of social relationships on brain health. Research has only begun to explore links between social connectedness and the brain as a biomarker, with preliminary work on social *disconnectedness* finding support for this link (de Lange et al., 2021; Lay-Yee et al., 2023). Recent research has found that social isolation is related to accelerated brain aging (i.e., a larger brain-age gap) in a large ($N = 855$), longitudinal sample (Lay-Yee et al., 2023). Adults who experienced social isolation had a brain on average 1.73 years older than adults who were never isolated. This finding underscores the relevance of exploring social connections in relation to brain age; yet, discrepancies between study design and analytic approach may underlie differences. The investigators considered social isolation, or an "extreme lack of social ties"; in contrast, our work operationalized social connectedness as positive relations with others. Social connectedness and social isolation are not necessarily interchangeable, as social connectedness may have stress-buffering effects while social isolation may have stress-inducing accelerations on brain age.

While we did not find support for links between positive social relations and brain age, distinguishing between the stress-buffering role of social connections and the stress-inducing role of social isolation is consistent with recent conceptual models discussing social safety versus threat as distinct mechanisms on health and longevity (Slavich, 2020; Slavich et al., 2023). A lack of social connections, or the experience of loneliness, may function as a risk factor, while social connections may be a resilience factor. Each of these experiences may exert different influences on physiological systems and brain aging. Social Safety Theory and evidence posits that social threats (e.g., social conflict, isolation, rejection) increase immune-related inflammation, which when chronically activated, has deleterious impacts on the brain (Slavich, 2020). A lack of social relationships may affect brain aging via activation of the chronic stress response and other mechanisms. However, having positive social connections may not have an analogous positive impact on brain health. More direct measures of social threat and social safety, as well as associations with inflammation and other potential mediators or moderators, could be fruitful avenues of exploration going forward.

Evidence suggests that there are certain moderators of the link between social connectedness and longevity that may be extended to aging in the brain, such that individuals who are less-socially connected and who have particular vulnerabilities are susceptible to having an older-than-expected brain age. For example, a large study found only that individuals who were socially isolated *and* genetically predisposed to loneliness had accelerated brain age, compared to individuals who reported being socially isolated but not lonely (de Lange et al., 2021). Along with risk variables such as propensity for loneliness, it will be important for future work to explore resilience variables, such as self-efficacy, that may buffer against a connection between social isolation and accelerated brain age.

Despite evidence suggesting that accelerated brain age is related to increased cognitive impairment and increased mortality risk (Cole et al., 2018), we did not find evidence that the brain-age gap was related to impaired functioning in our sample. This may be due to differences in operationalization of functioning; while self-reported chronic health conditions and ability to perform ADLs exist under the umbrella of aging and longevity, brain age may be more intimately connected to cognitive functioning. That is, accelerated brain age may be most connected to mild cognitive impairment, while various other health systems and abilities contribute to one's ability to carry out ADLs. Beyond the operationalizations of aging as chronic health conditions and ability to perform ADLs, we also considered the impact of social connectedness on mortality. We were not able to explore mortality as an outcome related to brain age due to the low rate of mortality in the imaging subsample (11 individuals, or 5% of the sample, had died). Future iterations of this work should consider exploring links between social connectedness, brain age, and mortality in larger samples.

Limitations

Several limitations likely contribute to the null results that may be overcome by future work. First, methodological decisions and sample limitations may underlie the lack of effects observed. While the entire MIDUS sample is a representative sample recruited through random-digit dialing, the imaging sample was restricted by participants' ability to travel to the scanning laboratory in Madison, WI. Notably, a majority of this imaging subsample identified as White (90%) and non-Hispanic (100%). According to the U.S. Census Bureau (2021) report, 59% of the U.S. population identifies as White/European ancestry alone (and not Hispanic or Latino/a), with the percentage world-wide being even smaller (U.S. Census Bureau, 2021). This underscores that any results from a predominantly White sample have informative, but reduced, generalizability. Further, race-based health inequities drive discrepancies in longevity and lifespan duration (De Ramos et al., 2022). Similar investigations in samples of racial and ethnic diversity are therefore a matter of equity and justice.

Given that the MIDUS imaging sample represents a small selection of the larger MIDUS sample, the power to detect any effect was substantially reduced. The true effect size may also be smaller than that which was used to perform power analyses, as not all brain age articles find effects (Kang et al., 2023). The MIDUS imaging subsample was also relatively young with the average age at neuroimaging scan being 51.5 years ($SD = 12.06$, range = 26–76 years). It may be the case that this sample is too young for the effects of social connectedness to have manifested in the brain in a statistically observable way. Further, to maximize the sample, several missing self-report datapoints were imputed and all neuroimaging observations were included. We controlled for scan quality, but this covariate does not speak to the ways in which poor scan quality may impact the derivation of the brain age variable.

The utilization of brain age is novel, and as such, there is debate over how to incorporate this metric and other variables into statistical models. The brain-age gap is calculated by subtracting chronological age from the algorithm-predicted brain age. Some scholars have not included chronological age as a separate covariate in statistical models; notably, the recent article finding that a lack of social connections in adulthood was associated with accelerated aging did not model chronological age as an independent variable (Lay-Yee et al., 2023). We did include age

as an independent variable, as ultimately, we are interested in the ability of the brain-age gap to predict aging-related phenotypes over and above chronological age. The impact of a brain-age gap is not constant across age—for example, a 60-year-old with a brain age that is 20 years older would be expected to have more health-related impairments than a 30-year-old with a brain age that is 20 years older, underscoring the importance of including chronological age as a covariate in models exploring the brain-age gap. This discrepancy in analytic approach contributes to the ongoing conversation about the most appropriate way to model these relations.

While brain age algorithms are useful and novel tools, algorithmic error in brain-age predictions is high (Bacas et al., 2023; Hanson et al., 2023). Basic work looking at reliability of brain age finds large prediction errors ranging from 4 to 5 years (Dörfel et al., 2023) and points to the need for a brain-age algorithm with lower out-of-sample prediction error. Work should be mindful when trying to consider individual differences on top of this. Lay-Yee et al. (2023) found a difference of 2 years accelerated age between a group of individuals who were never socially isolated and individual who were socially isolated as adults; however, within-group variability was quite large, especially when considering between-group effects (standard deviations of 7–8 years); this suggests high variability in these processes and their prediction. Additionally, brain age calculations rely on whole-brain inputs. Future studies should consider deviations in the brain from age-expected levels using other newly developed tools such as normative modeling via CentileBrain (Ge et al., 2024). Understanding the effects of social connectedness in a local part of the brain, instead of global impact, could contribute to mechanistic perspectives.

Future studies should continue to employ longitudinal modeling and consider multi-informant measures of these complex constructs. This research relied on neuroimaging and monoinformant self-reports on chronic health conditions, ADLs, and positive relations with others. Work has found that multidimensional assessment of social connectedness is particularly predictive of longevity (Holt-Lunstad, 2017). As an example, Lay-Yee et al. (2023) utilized multi-informant reports (two—three close others reporting on loneliness) at multiple datapoints throughout childhood and adulthood. Further, positive relationships with others represent one facet of many prosocial factors that may influence brain age and longevity (Hui et al., 2020). Work should consider composite variables of prosociality including charitability, compassion, and kindness (Hui et al., 2020; Lee et al., 2021) and gather multi-informant assessments of these variables.

Conclusions

This work underscores known associations between social connectedness and longevity and leaves open questions on the growing literature exploring brain age as a biomarker for aging. As expected, self-reported positive relationships with others were associated with several operationalizations of mortality risk, including chronic health conditions, ability to achieve ADLs, and mortality. We, however, did not find support for links between social connectedness and a discrepancy between algorithm-predicted brain age and chronological age (i.e., the brain-age gap), nor between the brain-age gap and mortality risk, in a sample of approximately 200 adults. Given the extensive research documenting the influence of social connectedness on longevity, future work should strive to conduct similar investigations in larger samples alongside improved brain-age algorithms and other metrics of "neural aging" (e.g., CentileBrain), incorporating the insights garnered through this registered report.

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