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Lifestyle and the Aging Brain: Interactive Effects of Modifiable Lifestyle Behaviors and Cognitive Ability in Men From Midlife to Old Age

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Abstract

We examined the influence of lifestyle on brain aging after nearly 30 years, and tested the hypothesis that young adult general cognitive ability (GCA) would moderate these effects. In the community-dwelling Vietnam Era Twin Study of Aging (VETSA), 431 largely non-Hispanic

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white men completed a test of GCA at mean age 20. We created a modifiable lifestyle behavior composite from data collected at mean age 40. During VETSA, MRI-based measures at mean age 68 included predicted brain age difference (PBAD), Alzheimer's disease (AD) brain signature, and abnormal white matter scores. There were significant main effects of young adult GCA and lifestyle on PBAD and the AD signature (*ps*≤.012), and a GCA-by-lifestyle interaction on both (*ps*≤.006). Regardless of GCA level, having more favorable lifestyle behaviors predicted less advanced brain age and less AD-like brain aging. Unfavorable lifestyles predicted advanced brain aging in those with lower age 20 GCA, but did not affect brain aging in those with higher age 20 GCA. Targeting early lifestyle modification may promote dementia risk reduction, especially among lower reserve individuals.

Keywords

General cognitive ability; Modifiable lifestyle behavior; brain aging; Alzheimer's disease brain signature; mild cognitive impairment; white matter abnormalities; cognitive reserve

1. Introduction

The 2020 Lancet commission reported on 12 modifiable risk factors associated with dementia prevention, intervention, and care, and concluded that modification of these risks could reduce dementia incidence by as much as 40% (Livingston et al., 2020). Many of these risk factors overlap those analyzed in the 2019 World Health Organization (WHO) guidelines for risk reduction of cognitive decline and dementia (World Health Organization, 2019). The Lancet commission report also emphasized a life course approach, highlighting periods during the life course when different risk factors may have greater impact. Few studies, however, examine early lifestyle risks in relation to later life outcomes. Here we focus on one group of modifiable risks—lifestyle behaviors (e.g., tobacco smoking, physical activity, social engagement, alcohol consumption and diet)—prior to age 45.

There is growing evidence that more favorable lifestyle factors may promote resistance to premature brain aging. Among adults ages 55–85, for example, a favorable lifestyle composite was associated with having a healthier brain (Bittner et al., 2019). Adults who neither drank nor smoked showed less brain aging than expected compared with those with one or both of these behaviors (Ning et al., 2020). Cross-sectional associations of brain age with smoking and alcohol consumption have been observed in middle-aged adults (Cole, 2020; Cole et al., 2019; Hatton et al., 2018). The evidence for diet is mixed. Diet is included as a lifestyle risk by the WHO (World Health Organization, 2019) but not by the Lancet commission (Livingston et al., 2020). The Lancet authors conclude, however, that "For some risk factors, the pattern of risk and the individual's other health, both physical and mental, might be especially important. Currently, the evidence suggests a Mediterranean or Scandinavian diet might have value in preventing cognitive decline in people with intact cognition, particularly as one component of a healthy lifestyle. (p. 429)." Research consistently supports a dose-dependent response such that having multiple risky lifestyle behaviors worsens outcomes (Peters et al., 2019). Advanced brain aging may be one mechanism by which problematic lifestyle behaviors contribute to heightened dementia risk

(Franke et al., 2010; Gaser et al., 2013; Stern et al., 2020). In addition, young adult cognitive ability may moderate the effects of lifestyle behaviors on aging-related brain changes or Alzheimer's disease (AD)-related pathology (Karama et al., 2014; McGurn et al., 2008; Stern et al., 2020).

In recent years, new approaches to quantifying healthy brain aging have emerged. Machine learning algorithms have been applied to MRI brain morphometry data to create indices of predicted brain age that compare individuals' brain age with their chronological age or brains of their peers (Cole et al., 2019; Franke et al., 2010; Liem et al., 2017). Evidence supports the position that predicted brain age measures are sensitive early indicators of possible decline or dysfunction. For instance, predicted brain age of people with AD appears older than their chronological age by about 10 years (Franke et al., 2010) and brain age is more advanced in adults with mild cognitive impairment (MCI) who progressed to AD than those who did not (Gaser et al., 2013). Among adults who progressed to AD across three years, longitudinal increases in predicted brain age were greater in *APOE-ε*4 carriers than non-carriers (Lowe et al., 2016). Adults with higher levels of cognitive decline from childhood had more advanced brain age in midlife (Elliott et al., 2019) and worse objective cognitive impairment was associated with more advanced predicted brain age (Liem et al., 2017).

Other specialized composite scores of MRI-based brain morphometry (i.e., brain signatures) have been developed that focus on AD-related atrophy as manifestations of brain aging (Dickerson and Sperling, 2009; McEvoy et al., 2011; Pettigrew et al., 2016; Williams et al., in press). AD-brain signatures have demonstrated associations with AD symptom severity and AD-related biomarkers, and are predictive of progression to AD (Bakkour et al., 2013; Dickerson and Sperling, 2009; McEvoy et al., 2009; McEvoy et al., 2011). An MRI-based AD-brain signature previously developed by members of our team in an independent sample identified seven cortical regions of interest (ROIs) plus hippocampal volume and ROI-specific weights that reflect the differential rates of atrophy across regions observed in AD; this AD signature measure differentiated between cognitively normal older adults and adults with mild AD and predicted progression from cognitively unimpaired to MCI and MCI to AD (McEvoy et al., 2009; McEvoy et al., 2011; Williams et al., in press). White matter abnormalities also increase with age and are associated with lifestyle factors related to cardiovascular risk (Bangen et al., 2018; de Lange et al., 2020; Fennema-Notestine et al., 2016).

Aging studies with premorbid measures of general cognitive ability (GCA) assessed in childhood or early adulthood are rare. However, these studies are important because they help to address the issue of reverse causation and the contribution of early risk factors. For instance, age 11 childhood GCA was a risk factor for vascular dementia, but not AD, in a 1921 Scottish birth cohort (McGurn et al., 2008). Higher age 11 GCA was associated with thicker cortex at age 73 in a 1936 Scottish birth cohort (Karama et al., 2014). Worse cognitive and brain health at age 3 predicted more advanced brain age in adults at age 45 (Elliott et al., 2019). Early cognitive ability, then, may promote resistance to accelerated brain aging and AD-related brain atrophy. Thus, examining whether GCA moderates associations of lifestyle behaviors with brain aging or AD-related brain pathology

indicators may further our understanding of contributors to brain resistance and resilience, and inform more targeted allocation of screening and intervention resources. Interactions between early GCA and lifestyle in relation to brain aging are understudied and seldom examined across the life course.

In the present study we investigated whether young adult GCA moderated associations between modifiable lifestyle behaviors assessed in early midlife and three indicators of brain aging assessed in old age. In men from the Vietnam Era Twin Study of Aging (VETSA), we examined main effects of GCA assessed when participants were approximately age 20 and a modifiable lifestyle behavior index assessed at mean age 40 on predicted brain age difference scores (PBAD), AD-brain signatures, and abnormal white matter assessed at mean age 68, as well as the GCA-by-lifestyle interaction. We hypothesized that having more unfavorable lifestyle behaviors or lower GCA would be associated with having an older than predicted brain compared with chronological age and smaller cortical thickness/hippocampal volume in AD-specific brain regions. We also hypothesized that the association between lifestyle and indicators of brain aging would be greatest among those with lower GCA; that is, having lower GCA in conjunction with less favorable lifestyles at midlife would predict more advanced brain aging in old age. Finally, we examined associations between brain aging measures and MCI at mean age 68 in order to assess associations between brain aging and cognitive impairment.

2. MATERIAL AND METHODS

2.1. Participants

Participants were community-dwelling, non-patient men participating in VETSA (2001-current) (Kremen et al., 2019b). VETSA comprises a sample of male-male twins from the nationally representative Vietnam Era Twin Registry (VETR) (Henderson et al., 1990). VETSA participants were randomly recruited from 3322 twin pairs from the Harvard Drug Study of VETR twins conducted in 1992 (Tsuang et al., 2001). Participants were not selected on the basis of any diagnostic or substance use behaviors. VETSA participants are similar to American men in their age range with respect to health and lifestyle characteristics (Centers for Disease Control and Prevention, 2007). Although all participants served in the military at some time during the Vietnam Era (1965–1975), the majority (~80%) reported no combat exposure.

Participants were on average 19.5 years old (SD=1.3; range=17–26; 1965–1975) at the young adult cognitive assessment, 40.03 years at the early midlife assessment (SD=2.7; range=34–44; 1990), and 67.5 years (SD=2.6; range=66–73; 2016–2019) at the time of the MRI in VETSA 3 (2015–2021). At the age 40 assessment, participants were in good health with only 15.9% reporting hypertension, 1.4% diabetes, 3.9% any cardiovascular disease. Average body mass index was 25.61 (SD=3.19). We refer to these assessments by the mean age at each time point: 20, 40, and 68. All participants provided written informed consent and the protocols were approved by institutional human subjects review boards at each institution.

2.2. Procedures

2.2.1. Young Adult Cognitive Ability—Participants completed the Armed Forces Qualification Test (AFQT) at induction into the military (between 1965 and 1975). The AFQT is a standardized, validated 100-item multiple-choice paper-and-pencil test of general cognitive ability (Uhlaner, 1952). The AFQT includes 4 components: vocabulary, arithmetic, spatial processing (e.g., determining what folded or unfolded boxes would look like if unfolded or folded, respectively) and knowledge and reasoning about tools (e.g., seeing a gadget/object and having to choose which of several others goes with it based on how they connect or work together). The first two components tap crystallized abilities and the latter two tap fluid abilities. This test is highly correlated with other tests of GCA such as Wechsler Adult Intelligence Scale (r = 0.84); average intelligence of VETSA participants was estimated at 105 (Lyons et al., 2009).

2.2.2. Early Midlife Modifiable Lifestyle Behaviors—Participants completed a mailed health survey at age 40 that queried about smoking, alcohol consumption, social engagement, physical activity and diet (see survey items and scoring in Supplemental Table 1) (Henderson et al., 1990), as well as health and demographic measures. Each modifiable lifestyle indicator was operationalized based on standard criteria and coded as favorable (1) or unfavorable (0) (Licher et al., 2019; Lourida et al., 2019).

Cigarette smoking status was defined as current smoker (unfavorable) versus never/former (favorable). Unfavorable alcohol consumption was defined as consuming more than 2 drinks of beer, wine, or hard liquor per day across the past 14 days. Social engagement was operationalized by first summing engagement across 6 measures: marriage (currently married=favorable), involvement in religious activities more than twice a month (yes=favorable), involvement in clubs/organizations (yes=favorable), number of close friends (≥3=favorable), number of close relatives (≥3=favorable), and number of close people connected with at least once a month (≥3=favorable) (Licher et al., 2019). Scores of 0–2 were categorized as unfavorable and 3–6 as favorable social engagement. Favorable physical activity reflected regular engagement in moderate-to-vigorous activity based on items from the College Alumni Physical Activity Questionnaire, a measure frequently used in epidemiological studies (Ainsworth et al., 1993; Paffenbarger et al., 1978). Favorable diet was coded if a participant met dietary recommendations for 3 of 5 food groups per week: fish, fruits and vegetables, dairy, red meat, and/or processed meat. Table 1 displays the proportion of favorable classifications for each indicator. Frequencies of the five modifiable lifestyle behaviors at age 40 ranged from a low of 53% who met criteria for a favorable diet to 87% who met criteria for favorable alcohol consumption. Correlations between the individual lifestyle measures and the brain age-related phenotypes are shown in Supplemental Table 2. The five modifiable lifestyle behavior indicators were summed to create a lifestyle composite (0–5), with higher scores reflecting more favorable lifestyle behaviors.

2.2.3. Age 68 Data Collection—Data collection at age 68 (2015–2019) included a detailed medical history interview, socio-demographic data, in-depth cognitive testing, and structural MRI for those who passed a standard MRI safety screening (N=481). More details

on VETSA ascertainment and procedures are published elsewhere (Kremen et al., 2013; Kremen et al., 2019b; Kremen et al., 2006).

2.2.3.1. MRI acquisition and processing.: T1-, T2, and proton-density weighted images providing high anatomical detail were acquired on 2 GE 3T Discovery 750× scanners (GE Healthcare, Waukesha, WI, USA) with an 8-channel phased array head coil (scanner 1 N=336, scanner 2 N=145) at the University of California, San Diego. Subcortical segmentation and surface-based cortical parcellation were performed using FreeSurfer version 5.3 (Fischl, 2012). Detailed protocols for the MRI acquisition, processing, and creation of MRI based measures at age 68 are provided in the Supplement.

2.2.3.2. Predicted brain age difference score, AD-brain signature, and Abnormal White Matter measures.: We used the Brain-Age Regression Analysis and Computation Utility software BARACUS v0.9.4 (Hatton et al., 2018; Liem et al., 2017) to create a predicted brain age difference score (PBAD). BARACUS uses linear support vector regression models to predict brain age in adults derived from each individual's FreeSurfer statistics. The difference score is calculated by subtracting predicted brain age (referred to as "stacked-anatomy" brain age in BARACUS) from chronological age (i.e., chronological age – predicted brain age). A negative PBAD is indicative of brain age that is estimated to be older than one's chronological age. One participant was excluded due to brain cancer and two due to brain damage of unknown origin. Because regression approaches to estimating brain-age are prone to a common statistical bias by which brain age of older participants is underestimated, brain age of younger participants is overestimated, and predictions are most accurate for participants closer in age to the training set (de Lange and Cole, 2020). Mean age for the Liem et al. 2017 training set was 58.68, SD 15.17 (range 19–82). The VETSA participants' narrow age range (mean 67.5 years; SD=2.6; range=66–73) being relatively close to the mean age of the training set helps reduce the effects of the statistically induced age bias. In addition, we adjusted models for chronological age as a covariate, a method shown to be effective for correcting for age bias in brain-age related research (de Lange and Cole, 2020).

The AD-brain signature is a weighted average of thickness in 7 cortical regions based on the Desikan-Killiany atlas (Desikan et al., 2006; Fischl et al., 2004) plus hippocampal volume, with separate weights for left and right hemisphere regions (McEvoy et al., 2009; McEvoy et al., 2011). We regressed out age and scanner for each ROI, as well as estimated intracranial volume for the measure of hippocampal volume. Standardized residuals of ROIs were then weighted accordingly and summed together to form the AD-brain signature scores. Higher values of the AD-brain signature reflect greater thickness and/or hippocampal volume in these regions, indicating brains that are less AD-like; negative AD signature values indicate more AD-like brains.

A multi-channel segmentation approach was used to measure abnormal white matter (i.e., white matter hyperintensities) (Fennema-Notestine et al., 2016). For analyses, we use the ratio of abnormal white matter to total white matter volume (AWM ratio). AWM quantification and the frequency atlas were previously reported (Fennema-Notestine et al., 2016).

2.2.3.4. Mild Cognitive Impairment (MCI).: The Jak-Bondi approach was used to diagnose amnestic or nonamnestic MCI (Jak et al., 2015; Kremen et al., 2014) based on 18 cognitive tests assessing memory, executive function, attention, language, visuospatial ability, and processing speed. Criteria for impairment within a cognitive domain required performance on 2 or more tests within that domain that were each more than 1.5 SDs below age- and education-adjusted normative means. Test scores were adjusted for young adult GCA before determining if they were below the impairment threshold in order to differentiate decline from lifelong poor performance. At age 68, 411 (86.16%) were classified as cognitively unimpaired, 25 (5.24%) as nonamnestic MCI, and 41 (8.60%) as amnestic MCI; overall, 66 (13.84%) had MCI.

2.3. Covariates

At age 40 participants reported whether a doctor ever diagnosed them (yes/no) with angina pectoris, congestive heart failure, coronary heart disease, damaged heart valves, heart attack/myocardial infarction, phlebitis/thrombophlebitis, stroke, asthma, chronic obstructive pulmonary disease, emphysema, alcoholic hepatitis, or cirrhosis of the liver. Responses were grouped into a cardiovascular index (3.9% with any cardiovascular), respiratory index (5.4% with any respiratory), or a liver disease index (<.5% with any liver disease). Due to the low frequency of health problems, the final cardiovascular, respiratory, and liver disease problem indices were each categorized as presence of any relevant disorder versus none (1=yes; 0=no).

Separate items assessed doctor diagnosed hypertension, diabetes and depression (1=yes; 0=no). Age 40 obesity was coded as BMI ≥30 versus <30 based on self-reported height and weight. Self-reported stroke at age 68 was also included as a covariate. *APOE* genotype was classified as having any ε4 alleles (ε4+) versus none (ε4-). Some data were missing for *APOE* (N=63) because not all participants provided blood or were genotyped. Ethnicity was defined as non-Hispanic white versus other. Participants were excluded if they reported a doctor had diagnosed them with seizure disorder, multiple sclerosis, HIV, or schizophrenia (N=6), leaving a final N of 431.

2.4. Statistical analysis

We conducted linear mixed models in SAS 9.4 using maximum likelihood methods. Interactions of GCA and lifestyle were tested by fitting a linear model with main effects of young adult GCA, the lifestyle index, and the interaction term. Models adjusted for chronological age in part to correct for the effects of regression bias in the PBAD measures (de Lange and Cole, 2020). Other covariates included ethnicity/race, age 40 cardiovascular problems, hypertension, obesity, diabetes, respiratory problems, liver disease, depression, *APOE* genotype, height, and stroke. Outcome variables at age 68 were PBAD, AD-brain signature, and the AWM ratio. As the VETSA contained twin pairs and analyses were at the level of the individual, models accounted for the non-independence of observations by including family as a random effect. Results are reported based on two-tailed Wald tests.

3. RESULTS

3.1. Descriptive statistics and preliminary analyses.

The sample was 90% non-Hispanic white; average education was 13.98 (SD=2.07) years. As seen in Table 1, 21% of the sample met criteria for favorable ratings on all 5 behaviors (mean lifestyle=3.66, SD=1.01). Young adult GCA predicted age 40 lifestyle (r = 0.22, p<0.0001); higher GCA was associated with more favorable lifestyle behaviors (Supplemental Table 3). The strongest individual associations with GCA were with diet (r = 0.13) and tobacco smoking (r = 0.23) (Supplemental Table 2). Correlations among the three age 68 brain phenotypes ranged from r = 0.54 (p< 0.0001) between PBAD and the AD brain signature to r = −0.23 (p<0.0001) between the AD signature and AWM ratio. Being an *APOE*-ε4 carrier was not associated with any measure. Correlations among all measures are shown in Supplemental Table 3.

3.2. Multivariable analyses.

As hypothesized, there were significant main effects of young adult GCA [F (1,115) = 9.85, p = 0.002] and the age 40 lifestyle composite [F (1,115) = 6.40, p=0.012] on PBAD. Young adult GCA [F (1,78) = 8.77, p = 0.004] and age 40 lifestyle composite [F (1,78) = 11.28, p = 0.001] were also significantly associated with the AD-brain signature (Table 2). Participants with lower young adult GCA or fewer early midlife favorable lifestyle behaviors had a predicted brain age that was older than expected given their chronological age, and their brains were more similar to those of individuals with AD. AWM ratio was not associated with GCA [F (1,103) = 1.32, p = 0.25] or lifestyle [F (1,103) = 3.60, p = 0.06], or the interaction (Table 3).

The GCA-by-lifestyle interaction was significant for PBAD [F (1,115) = 8.31, p = 0.005] and the AD-brain signature [F (1,78) = 7.84, p = 0.006], but not for the AWM ratio [F (1,103) = 0.97, p = 0.33]. The GCA-by-lifestyle interaction for PBAD is depicted in Figure 1. For ease of illustration, we created 2 lifestyle groups splitting the lifestyle composite at the mean: unfavorable = 0–3 favorable behaviors; 4–5 behaviors favorable behaviors =favorable lifestyle. For those with both lower young adult GCA and unfavorable lifestyles at mean age 40, predicted brain age was older than chronological age, suggesting advanced brain aging. The difference between these lifestyle groups was greater for those with lower GCA. The AD-brain signature relationship followed a similar pattern (Figure 2). Unfavorable lifestyles were not associated with advanced brain aging or more AD-like brain signatures in those with higher GCA. In the figures it appears there are some high GCA participants with unfavorable lifestyles whose predicted brain age difference scores were better than high GCA participants with favorable lifestyles. The confidence intervals are wide and overlap, however. As seen in Figure S1, very few participants had both high GCA (e.g., more than 1.5 SD above the mean) and unfavorable lifestyles.

We examined post-hoc whether brain aging was global or more specific to AD-related brain regions by re-running the mixed models adjusting the AD-brain signature model for PBAD. All of the associations were attenuated [GCA: F (1,92) = 1.96, p = 0.165 ; lifestyle: F (1,92)

= 3.22, $p = 0.076$, and GCA-by-lifestyle interaction: F (1,92) = 1.74, $p = 0.190$] which suggests that the effects of GCA and lifestyle on the brain were more global.

Finally, in order to determine whether brain aging was associated with cognitive impairment, we examined the relationship between the brain outcomes and MCI status at age 68. The overall association between PBAD and MCI was significant (F (2,106) = 3.17; $p = 0.05$). Non-amnestic MCI was associated with having an older than predicted brain age compared with the group with amnestic MCI (t (106) = −2.21, $p = 0.03$, 95%CI −1.129; −0.061) or the group with no cognitive impairment (t (106) = −2.46; $p = 0.02$; 95%CI −0.981; −0.105). There was no difference between the group with amnestic MCI and the group with no impairment (t (106) = 0.30, $p = 0.768$, 95%CI −0.298, 0.402). Overall associations with MCI were not significant for the AD-brain signature measure (F (2,71) = 0.13, $p = 0.877$) or for the AWM ratio (F (2,95) = 1.33, $p = 0.269$).

4. DISCUSSION

Young adult GCA, early midlife modifiable lifestyle behaviors and their interaction predicted global brain aging and AD-brain signature decades later in older adulthood. Participants were cognitively intact and in good health at the baseline cognitive and lifestyle assessments. Both higher levels of young adult GCA and having an early midlife favorable lifestyle—one involving not smoking, low alcohol consumption, healthy diet, physical activity, and social engagement—were protective with respect to later brain outcomes. The poorest brain outcomes occurred among those with both lower cognitive ability and more unfavorable lifestyle behaviors. In contrast, higher GCA was protective even in combination with unfavorable lifestyle behaviors.

Young adult cognitive ability was modestly associated with lifestyle behaviors two decades later. It may be that GCA is related to the choices a person makes or options a person has about lifestyle. Individuals with higher cognitive ability may be more likely to follow health guidelines or have higher socioeconomic status that provides greater access to healthcare and resources, including relationships with significant others (Franz et al., 2015; Scarmeas and Stern, 2003). Compared to single individuals, married people, for instance, tend to smoke and drink less, engage in healthier eating, and have shared income (Kelly et al., 2017; Mortimer et al., 2012). Favorable lifestyle behaviors also appear to contribute to brain health during aging through multiple pathways that may reduce cardiovascular dysfunction and neurotoxic effects (Cardenas et al., 2020; Matloff et al., 2020; Mende, 2019). Which, if any, of these effects are causal is uncertain. Early adult cognitive ability may directly or indirectly help slow the development of disease pathology through its influence on behavior. Neither GCA nor lifestyle appeared to be protective for abnormal white matter. It may have been too early in the life course to see associations with lifestyle behaviors or it may be that other factors mediate this relationship. To our knowledge, no other studies have examined the interaction of lifestyle and young adult GCA on brain morphometry across such a long period of time from early midlife.

In studies of older adults, measures of advanced brain aging have been associated with or have predicted progression to AD and MCI (Gaser et al., 2013; Lowe et al., 2016). In

one study, brain age of people with AD appeared older than their chronological age by about 10 years (Franke et al., 2010). One might reason that unfavorable lifestyle would tend to be more related to aging in AD-related brain areas, which then increases risk for MCI. However, the fact that associations between lifestyle and the AD brain signature were reduced after controlling for PBAD suggests that the effects are more global rather than AD-specific in this sample. PBAD was associated with MCI but the effect was specific to non-amnestic—rather than amnestic—MCI. The absence of an association between the AD-brain signature and MCI is also consistent with this finding. One study showed, however, that nearly one-third of patients with AD pathology at autopsy were non-amnestic during their early cognitive decline (Bertoux et al., 2020). Given the relatively young age of this sample, it is thus plausible that some of the non-amnestic MCI cases may progress to AD.

The concepts of reserve, resistance, and maintenance of cognitive and brain health have been of major interest in aging and dementia research, although, definitions of these constructs are still debated (Bartres-Faz et al., 2020; Stern et al., 2021). According to Stern et al. (Stern et al., 2021), “The concept of cognitive reserve (CR) explains differential individual susceptibility to age- or disease-related brain changes…. It proposes that IQ, as well as a set of life exposures such as education, occupation, and late life leisure activities promote more resilient or flexible cognitive processing that is better preserved in the face of brain changes.”(Stern et al., 2021) Measures of early cognitive ability have been used extensively as indicators (so-called proxies) of cognitive reserve (McQuail et al., 2020; Stern et al., 2003; Tucker and Stern, 2011). That being the case, it is reasonable to also consider our measure of young adult GCA as an index of cognitive reserve. An advantage of focusing on young adult cognitive ability is that this measure is the least confounded by aging or pathology in our data but also likely reflects cognitive reserve/resources available early in life that may promote later resistance or resilience to aging and/or pathology. Similarly, Montine et al. [2019] refer to pre-existing reserve capacity and stress the importance of measuring reserve capacity prior to the development of brain injury (Montine et al., 2019). There is also some evidence that cognitive reserve is associated with better brain reserve even at relatively young ages (Elliott et al., 2019; Hackman et al., 2010; Karama et al., 2014; Stern et al., 2020). That association could not be tested in this sample since participants did not have MRIs in their early 20s.

The young adult GCA measure is also important because, as an index that is less confounded by aging effects, it circumvents the problem of possible reverse causation. As such, these results also shed light on the nature of resistance in the brain (Arenaza-Urquijo and Vemuri, 2020; Stern et al., 2020). There is evidence that overall cognitive ability tends to peak in the 20s-to-early 30s, so these participants may have been close to peak cognitive ability at the time of the age 20 assessment (Kremen et al., 2019a). In addition, the lifestyle composite data were collected earlier in the life course compared with most studies of long-term effects of lifestyle on the brain (Livingston et al., 2020; Orgeta et al., 2019). The results indicate that despite potential disadvantages of low cognitive ability, favorable lifestyle may have slowed or conferred resistance to advanced brain aging. This is represented in the figures by the relatively flat slope for the favorable lifestyle group. Higher GCA, in turn, also conferred resilience against the deleterious effects of unfavorable lifestyle behaviors (Arenaza-Urquijo and Vemuri, 2020; Neth et al., 2019; Stern et al., 2020). This is represented in the figures

by the steeper slope for the unfavorable lifestyle group with respect to brain outcomes. Less advanced brain aging may also suggest brain maintenance (Nyberg et al., 2012), but confirmation of brain maintenance requires longitudinal brain data.

Our study provides additional support for the life course model proposed by the Lancet commission, in particular, for the potential benefits of early interventions (Livingston et al., 2020). A brain health risk reduction agenda could be effective in reducing risk for dementia (Orgeta et al., 2019; World Health Organization, 2019). Both the U.K. National Institute of Health and Care Excellence, and the U.S. National Institutes of Health list smoking and social integration as among the top modifiable risk factors for dementia. From a life course perspective, the present study suggests that the long-term influence of lifestyle habits occurs across longer periods than typically examined. The 2020 Lancet Commission reported that 40% of dementia incidence can be attributed to 12 modifiable risk factors (Livingston et al., 2020). Although this remains to be fully supported by clinical trials, in one randomized controlled intervention involving social interaction brain volume did increase across 40 weeks (Mortimer et al., 2012). Smoking, alcohol consumption, diet, physical activity, and social integration in the first half of the life cycle may be potential modifiable targets for early intervention for brain health, which may in turn reduce the risk of dementia.

There are several limitations to this study. Participants were all men and mostly non-Hispanic white. Thus, results may not generalize across genders or different racial/ethnic origins. Lifestyle indicators were self-reported, although that is typical for such measures (Licher et al., 2019; Lourida et al., 2019). We also cannot definitively rule out whether brain morphometry was already different at the time the lifestyle behaviors were assessed since there were no neuroimaging data from that time. Because patterns of atrophy for global brain aging might be different from the patterns associated with AD (Habes et al., 2016) further follow-up will be needed to determine the extent to which PBAD may be a longitudinal risk factor for MCI, AD, or other dementias.

CONCLUSIONS

Given the large number of people likely to develop dementia in the next decades, early identification of modifiable risk factors may be a cost-effective key to identifying and reducing the incidence and burden of AD and other dementias. Our results highlight the potential value of focusing preventive efforts earlier in development and not just in later life. Given the evidence suggesting that favorable lifestyle confers resistance to advanced brain aging, particularly among those with lower cognitive ability, efforts at prevention could be prioritized and targeted. With the increasing numbers of individuals with MCI and AD combined with a lack of effective treatments, early risk reduction and prevention can be major components in efforts to facilitate maintenance of brain integrity, thereby mitigating individual and societal health, economic, and social burden.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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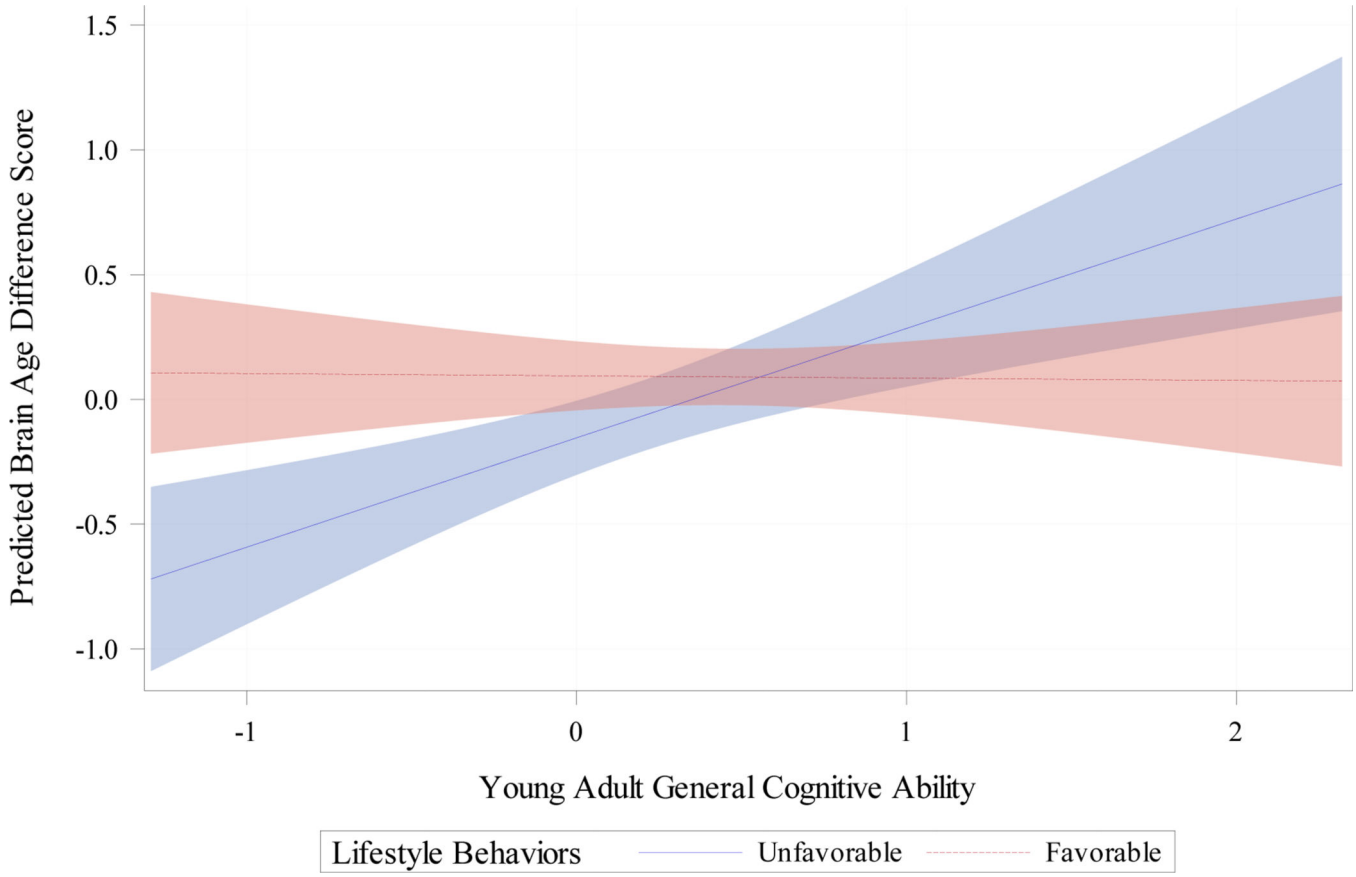

Figure 1.

Interaction between Young Adult General Cognitive Ability (GCA) and Lifestyle Behaviors on Predicted Brain Age Difference Scores in Old Age. Figure depicts the association of the interaction between standardized young adult GCA (mean=0, sd=1) and age 40 favorable (4 or 5 favorable lifestyle behaviors) versus unfavorable lifestyle (0,1,2,3 lifestyle behaviors) on predicted brain age difference (PBAD) score at age 68. Higher PBAD scores reflect a younger than predicted brain age compared with chronological age. PBAD scores are standardized (mean=0, sd=1).

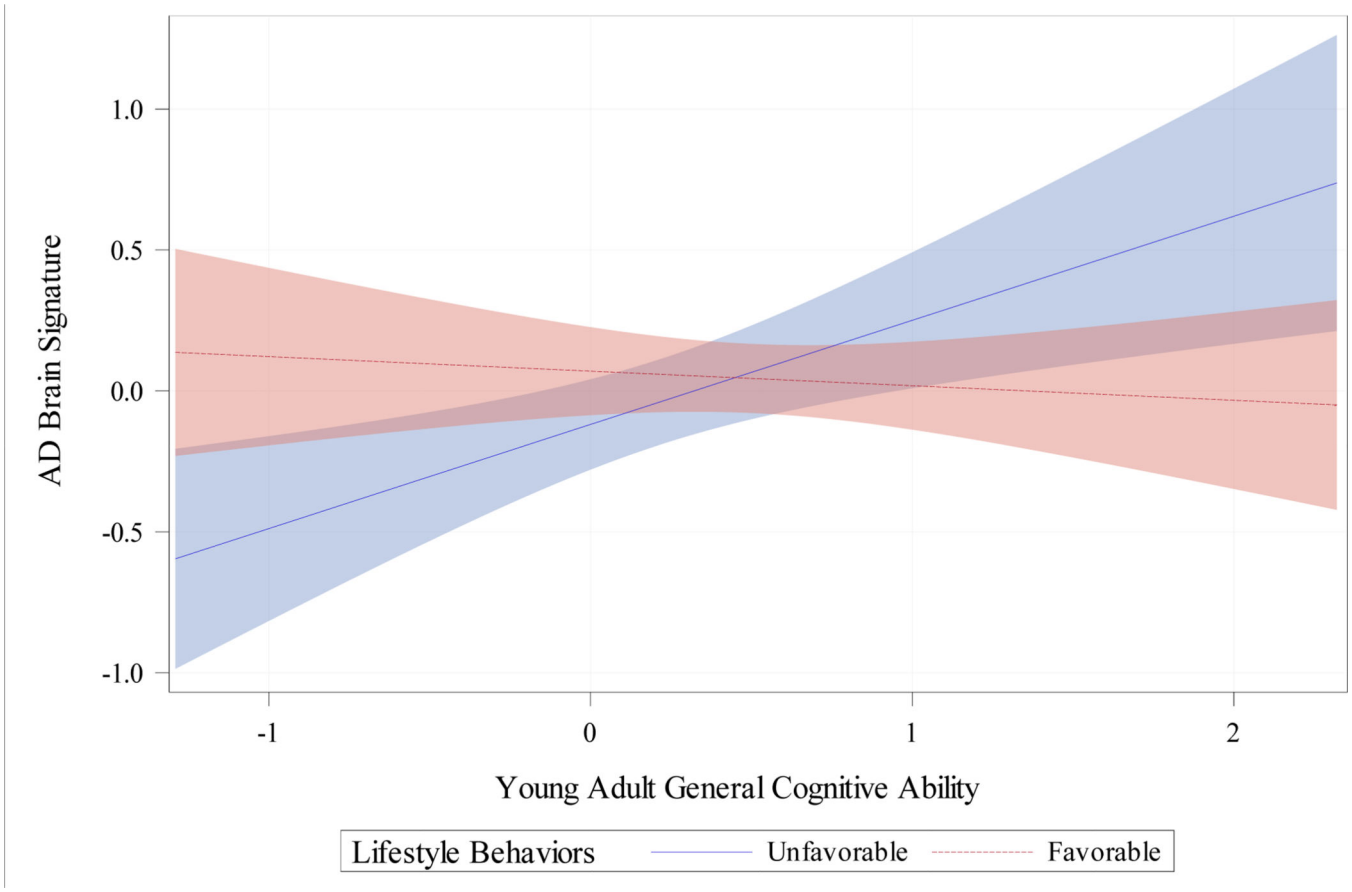

Figure 2.

Interaction between Young Adult General Cognitive Ability and Lifestyle Behaviors on Alzheimer's disease (AD) Brain Signature in Old Age. Figure depicts the association of the interaction between standardized young adult GCA (mean=0, sd=1) and age 40 favorable (4 or 5 favorable lifestyle behaviors) versus unfavorable lifestyle (0,1,2,3 lifestyle behaviors) on the AD-brain signature score at age 68. Higher AD-brain signature scores reflect a brain that is less similar to the brains of persons with AD. Brain signature scores are standardized (mean=0, sd=1).

Table 1.

Early Midlife Favorable Lifestyle Behaviors and Frequencies

Behavior	Definition of Favorable rating (0=unfavorable/1=favorable)	N (%) Favorable Lifestyle
Alcohol Consumption	Drinks < 2 drinks containing alcohol per day	398 (88.1%)
Diet	Consumes 3–5 Healthy food groups per day	235 (53.4%)
Exercise/Physical activity	Moderate to vigorous activity at least 3 days/week	372 (83.2%)
Social Engagement	Engages in 3–6 forms of social interaction regularly	345 (77.4%)
Tobacco Smoking	Never or former	328 (72.3%)
Lifestyle Composite	Sum of alcohol consumption, smoking, social engagement, diet & exercise; higher score=more favorable behaviors	0 = 1 (0.2%)
		1 = 10 (2.2%)
		2 = 49 (10.7%)
		3 = 119 (26.0%)
		4 = 182 (39.7%)
		5 = 97 (21.2%)

Note: Items are provided in the Supplemental Materials Table 1.

Table 2.

Linear Mixed Effects Models Predicting the Brain Age Difference Score (PBAD) and AD-Signature in Early Old Age.

	Predicted Brain Age Difference Score (Higher score=younger/better)				Alzheimer's Disease Brain Signature (Higher score=younger/better)			
Effect	**Estimate (SE)**	**t Value**	**P > |t|**	**95%CI (lower, upper)**	**Estimate (SE)**	**t Value**	**P > |t|**	**95%CI (lower, upper)**
Intercept	−9.08 (2.16)	−4.20	<0.0001	−13.331, −4.823	−4.15 (2.14)	−1.94	0.054	−8.378, 0.069
Young adult GCA (age 20)	0.86 (0.27)	3.14	0.002	0.316, 1.398	0.82 (0.28)	2.96	0.004	0.269, 1.374
Modifiable lifestyle behaviors (Age 40)	0.13 (0.05)	2.53	0.013	0.029, 0.239	0.20 (0.06)	3.36	0.001	0.081, 0.315
GCA by lifestyle interaction	−0.20 (0.07)	−2.88	0.005	−0.338, −0.0626	−0.20 (0.07)	−2.80	0.006	−0.346, −0.058
Ethnicity(Ref=non-White)	0.32 (0.21)	1.51	0.134	−0.099, 0.734	0.47 (0.21)	2.21	0.030	0.0460, 0.891
Age at MRI	0.09 (0.02)	4.05	<0.0001	0.046, 0.135	−0.02 (0.02)	−0.76	0.450	−0.061, 0.027
Stroke (Ref=stroke)	0.21 (0.85)	0.83	0.401	−0.289, 0.704	0.60 (0.26)	2.29	0.024	0.080, 1.122
Early Midlife Covariates:								
Cardiovascular index (Ref=any CVD)	−0.10 (0.29)	−0.33	0.744	−0.678, 0.486	−0.02 (0.34)	−0.07	0.945	−0.691, 0.645
Obesity (Ref=BMI>=30)	−0.06 (0.22)	−0.30	0.766	−0.496, 0.366	−0.01 (0.22)	−0.05	0.957	−0.442, 0.418
Hypertension (Ref=hypertension)	0.21 (0.14)	1.52	0.130	−0.063, 0.484	0.21 (0.14)	1.48	0.144	−0.073, 0.489
Diabetes (Ref=diabetes)	0.18 (0.51)	0.36	0.717	−0.818, 1.186	0.71 (0.65)	1.09	0.278	−0.582, 1.997
Respiratory index (Ref=any respiratory disease)	−0.01 (0.21)	−0.06	0.949	−0.438, 0.411	−0.02 (0.33)	−0.39	0.697	−0.535, 0.360
Alcohol hepatitis/ Cirrhosis (Ref=hepatitis/ cirrhosis)	0.17 (0.85)	0.20	0.842	−1.509, 1.846	0.98 (0.78)	1.26	0.212	−0.570, 2.528
Depression (Ref=depression)	0.18 (0.51)	0.96	0.341	−0.195, 0.560	0.04 (0.19)	0.23	0.817	−0.340, 0.430
Height	0.02 (0.02)	1.30	0.195	−0.054, 0.312	0.03 (0.02)	0.23	0.817	−0.006, 0.050
APOE (Ref=e4+ carrier)	−0.04 (0.13)	−0.31	0.754	−0.291, 0.211	−0.03 (0.12)	−0.26	0.795	−0.282, 0.216

Abbreviations: GCA=General cognitive ability. *APOE*= Apolipoprotein E (e4+ indicates presence of any e4 allele). PBAD N=370; df=1,115; AD-brain signature N=323; df=1,78 (N lower due to missing covariates). Covariates are shown in the table, for health covariates presence =1/absence = 0. Models adjusted for the random effect of family.

Table 3.

Linear Mixed Effects Models Predicting the Abnormal White Matter Ratio in Early Old Age.

	Abnormal White Matter to Total White Matter Volume Ratio (high score=worse)			
Effect	**Estimate (SE)**	**t Value**	**P > |t|**	**95%CI (lower, upper)**
Intercept	−1.65 (2.12)	−0.78	0.437	−5.820, 2.522
Young adult GCA (age 20)	−0.34 (0.29)	−1.15	0.253	−0.920, 0.245
Modifiable lifestyle behaviors (Age 40)	−0.11 (0.06)	−1.90	0.061	−0.216, 0.005
GCA by lifestyle interaction	0.07 (0.07)	0.99	0.326	−0.074, 0.220
Ethnicity(Ref=non-White)	−0.07 (0.21)	−0.35	0.729	−0.497, 0.349
Age at MRI	0.06 (0.02)	2.86	0.005	0.019, 0.107
Stroke (Ref=stroke)	−0.69 (0.23)	−2.96	0.004	−1.153, −0.228
Early Midlife Covariates:				
Cardiovascular index (Ref=any CVD)	−0.16 (0.29)	−0.55	0.584	−0.725, 0.410
Obesity (Ref=BMI≥30)	−0.36 (0.22)	−1.60	0.112	−0.798, 0.084
Hypertension (Ref=hypertension)	0.15 (0.14)	1.08	0.283	−0.124, 0.421
Diabetes (Ref=diabetes)	0.46 (0.48)	0.95	0.345	−0.501, 1.421
Respiratory index (Ref=any respiratory disease)	0.12 (0.20)	0.59	0.555	−0.283, 0.525
Alcohol hepatitis/ Cirrhosis (Ref=hepatitis/cirrhosis)	−0.05 (0.81)	−0.06	0.951	−1.650, 1.551
Depression (Ref=depression)	−0.17 (0.20)	−0.85	0.400	−0.555, 0.223
Height	−0.02 (0.02)	−1.41	0.162	−0.055, 0.009
APOE (Ref=e4+ carrier)	0.10 (0.13)	0.75	0.453	−0.157, 0.349

Abbreviations: GCA=General cognitive ability; *APOE*= Apolipoprotein E (e4+ indicates presence of any e4 allele).

AWM ratio N=348; df=1,103. Covariates are shown in the table; for health covariates presence =1/absence = 0.

Model additionally adjusts for the random effect of family.