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Fatness, fitness and the aging brain: A cross sectional study of the associations between a physiological estimate of brain age and physical fitness, activity, sleep, and body composition

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Abstract

Introduction: Changes in brain structure and function occur with aging. However, there is substantial heterogeneity both in terms of when these changes begin, and the rate at which they progress. Understanding the mechanisms and/or behaviors underlying this heterogeneity may allow us to act to target and slow negative changes associated with aging.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynirp.2022.100146.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Methods: Using T1 weighted MRI images, we applied a novel algorithm to determine the physiological age of the brain (brain-predicted age) and the predicted age difference between this physiologically based estimate and chronological age (BrainPAD) to 551 sedentary adults aged 65 to 84 with self-reported cognitive complaint measured at baseline as part of a larger study. We also assessed maximal aerobic capacity with a graded exercise test, physical activity and sleep with accelerometers, and body composition with dual energy x-ray absorptiometry. Associations were explored both linearly and logistically using categorical groupings.

Results: Visceral Adipose Tissue (VAT), Total Sleep Time (TST) and maximal aerobic capacity all showed significant associations with BrainPAD. Greater VAT was associated with higher (i.e,. older than chronological) BrainPAD ($r = 0.149$ $p = 0.001$)Greater TST was associated with higher BrainPAD ($r = 0.087$ $p = 0.042$) and greater aerobic capacity was associated with lower BrainPAD ($r = -0.088$ $p = 0.040$). With linear regression, both VAT and TST remained significant ($p = 0.036$ and 0.008 respectively). Each kg of VAT predicted a 0.741 year increase in BrainPAD, and each hour of increased TST predicted a 0.735 year increase in BrainPAD. Maximal aerobic capacity did not retain statistical significance in fully adjusted linear models.

Discussion: Accumulation of visceral adipose tissue and greater total sleep time, but not aerobic capacity, total daily physical activity, or sleep quantity and/or quality are associated with brains that are physiologically older than would be expected based upon chronological age alone (BrainPAD).

Keywords

BrainAge; Visceral adipose tissue; Sleep quantity; Maximal cardiovascular fitness; Successful aging; Body composition

1. Introduction

Advancing age is associated with declines in both grey and white matter volume (Harada et al., 2013), increases in white matter hyperintensities (Scharf et al., 2019), and reduced cortical thickness (Salat et al., 2004). Functionally, aging leads to reduced ability to retrieve newly learned information (Bier et al., 2017; Cargin et al., 2007) decreased executive function and processing speed (Salthouse, 2010), and increased likelihood of developing cognitive impairment (Overton et al., 2019) and neurodegenerative disease (Erickson et al., 2018; Lopez and Kuller, 2019). However, there is substantial heterogeneity in these changes across individuals both in terms of age of onset, and the rate of progression (Harada et al., 2013). Understanding the mechanisms and/or behaviors underlying this heterogeneity may lead to interventions that target the negative brain changes associated with aging. This is particularly useful if there are lifestyle factors which could be modified by public health interventions designed to promote successful (brain) aging.

Differences in individual physical fitness and exercise habits have been hypothesized to explain some of the observed differences in brain structure and function. Large cohort studies have found strong correlations between physical fitness and activity levels and both brain volume and risk of developing cognitive dysfunction (Tan et al., 2017; Zhu et al., 2015). Further, recent systematic reviews of cross-sectional studies using magnetic

resonance imaging (MRI) have found that higher levels of fitness and regular moderate-to-vigorous intensity activity are sometimes associated with higher volume of grey matter in the hippocampus and prefrontal cortex (Erickson et al., 2014). However, this is not universally true depending upon clinical status (Burns et al., 2008; Raz et al., 2005). More generally, studies relating physical fitness to brain structural integrity have yielded variable findings and sometimes small effect sizes (Sexton et al., 2016; Bugg and Head, 2011; Burns et al., 2008). Further, inferring causality in cross-sectional studies is uncertain because age related changes in grey matter is highly heterogeneous (Fjell and Walhovd, 2010) and observed changes in older adults can be affected by brain development in youth (Tamnes et al., 2013).

Similarly, body composition has been hypothesized to have meaningful associations with brain volume and cognitive function independent of its impact on cardiovascular function. For example, Kharabian Masouleh et al. (2016) found that higher BMI was associated with lower grey matter volume in multiple brain regions even after controlling for confounding variables associated with fitness. Further, two recent systematic reviews of cross-sectional studies of obesity and brain structure suggest that obesity, particularly central obesity, is often correlated structurally with reduction in grey matter volume and reduced cortical thickness (S. X. Sui and Pasco, 2020) and functionally with impaired cognition (Tanaka et al., 2020). There is also substantial evidence linking central obesity with cardiovascular disease (Britton et al., 2013; Mahabadi et al., 2009), cancer (Britton et al., 2013; Kang et al., 2010) and all-cause mortality (Kuk et al., 2006; S. W. Lee et al., 2018). As such, although there are suggestions that observed associations between brain structure and obesity reflect a shared etiology, the potential that centrally located visceral fat is a modifiable target for intervention across multiple disease states, including those affecting the brain, seems worthy of further investigation. Additionally, Kullmann et al. (2020a) may have identified a mechanism for these observed changes, noting that insulin sensitivity in the brain is strongly associated with volume of visceral fat. Importantly, this is one of the few studies reporting correlations from dual x-ray absorptiometry (DXA) derived visceral fat, rather than comparatively crude measures of obesity such as BMI, or proxy measures of visceral adiposity such as waist circumference.

Finally, sleep quantity and quality appear to have associations with elements of brain structure, particularly cortical brain volume (Sexton et al., 2014, Baril et al., 2021) and the microarchitecture of white matter including the observed number of white-matter hyperintensities indicative of reduced microstructural integrity and stability (Khalsa et al., 2017, Baril et al., 2021). It appears that there may be an optimal amount of sleep for neurorestoration, with cognitive decline associated with both shorter (Mohlenhoff et al., 2018) and longer (Mohlenhoff et al., 2018; Faubel et al., 2009) sleep durations. Diseases that manifest during sleep periods may also play a role in neurodegeneration with obstructive sleep apnea (OSA) having been associated with increased prevalence of blood markers associated with developing Alzheimer’s Disease (Andrade et al., 2018), and the use of Continuous Positive Airway Pressure (CPAP) appearing to improve cognitive outcomes in individuals with OSA (Andrade et al., 2018; Mullins et al., 2020). One recent study using a BrainAge algorithm has also linked brains that are older than chronological age would suggest with poor sleep quality (Ramduny et al., 2022). However, the strength of the

associations between sleep quantity and quality and brain health is variable, ranging from substantial and wide-spread across multiple regions of the brain (Lo et al., 2014; Thurston et al., 2020), to statistically non-significant (Kocevska et al., 2019) or localized to relatively small tracts within the brain (Khalsa et al., 2017).

To provide a more comprehensive analysis of age-related changes to brain structure, new tools that leverage the capacity of machine learning algorithms have emerged. Commonly considered a way to determine the *physiological* age of the brain (hereafter called brain-predicted age), these tools utilize regional brain measures from MRI acquired from large samples who range widely in age to calculate a biological brain age. The difference between this biological age and an individual's chronological age is called the Brain Predicted Age Difference (BrainPAD). In essence, a negative BrainPAD is indicative of a brain younger than chronological age would assume. Conversely a positive BrainPAD is indicative of an older than "expected" brain. In the last decade, these tools have been able to predict age in both healthy adolescents (Franke et al., 2012) and older adult populations (Cole et al., 2018; de Lange et al., 2020) with a high degree of accuracy. Further, outputs from these algorithms show high test/retest reliability (Cole et al., 2017) and correctly identify higher baseline brain age cross-sectionally and accelerated brain aging longitudinally in clinical populations manifesting symptoms of cognitive decline including development of Alzheimers Disease (Franke et al., 2010), multiple sclerosis (Cole et al., 2019; Cole et al., 2020), stroke (Richard et al., 2020), dementia (Biondo et al., 2022) and traumatic brain injury (Cole et al., 2015). In addition to providing potentially meaningful clinical data, as a single easily understood numeric score, BrainPAD may offer a meaningful public health tool that can be understood by the general public and can be used to promote brain healthy activities and behaviors.

While this tool shows potential as a biomarker for brain health, there is some evidence that suggests that positive BrainPAD (i.e., older than expected brain age) may be the result of early life changes in brain structure instead of behavioral patterns of middle and older adulthood (Vidal-Pineiro et al., 2021) which would limit its effectiveness as a tool for understanding the effect of modifiable behaviors on brain health. However, there is also evidence that suggests that modifiable lifestyle factors may have an impact on BrainPAD. Specifically, a large-scale epidemiological study drawn from the UK Biobank sample has identified modifiable lifestyle factors, including physical fitness and body composition, that contribute meaningfully to BrainPAD in adults ages 50 and older (Smith et al., 2019), and self-reported physical activity has been reported to be associated with younger than expected brain-predicted age across multiple studies (Steffner et al., 2016; Bittner et al., 2021). Given these data, and the equivocal findings to date regarding the role(s) of physical fitness and activity levels, body composition, and sleep on brain health within the older adult population, further exploring cross-sectional associations is important to better understand the potential clinical and research applications of this new tool. These analyses contribute to the understanding of brain-predicted age and BrainPAD by using high accuracy/precision objective measures of aerobic capacity, body composition, physical activity, and sleep to offer robust analyses that minimize sources of error than might come from estimation algorithms, proxy measures, or self-report within a relatively large population of presumptively healthy adults located in the United States. We hypothesized that superior cardiorespiratory fitness (as measured by estimated maximal aerobic capacity)

and higher levels of daily physical activity would be associated with a younger brain relative to chronological age (i.e., a smaller or negative BrainPAD). Additionally, we hypothesized that higher levels of adiposity, particularly higher levels of VAT, would be associated with older brains relative to chronological age (i.e. a larger or more positive BrainPAD) and that better sleep, as measured by number of minutes of sleep and overall sleep efficiency, would be associated with smaller/more negative BrainPAD.

2. Methods

2.1. Participants

Data were drawn from baseline measurements of a multicenter 2×2 factorial randomized interventional clinical trial set in two urban areas and approved by Institutional Review Boards at both the University of California, San Diego, and Washington University in St. Louis. This group has been described elsewhere (Wetherell et al., 2020). In brief, a total of 607 sedentary adults aged 65 to 84 with self-reported cognitive complaints, but without cognitive impairment indicative of developing dementia as defined by a score of <11 on Short Blessed Test (Katzman et al., 1983) were recruited. Individuals with diagnosed cognitive impairment or neurodegenerative disease were excluded. Additional exclusion criteria included conditions that would prohibit safe participation in the exercise intervention, current participation in cognitive training programs, currently engaging in >60 min/week of moderate or vigorous exercise, use of glucocorticoid or diabetes medications, and alcohol or substance abuse within 6 months. All participants signed informed consent.

2.2. Neuroimaging acquisition

3T MRI scanners were used to acquire high-resolution (1′ × 1′ × 1′mm) T1-weighted sagittal, magnetization-prepared rapid gradient echo (MP-RAGE; repetition time (TR) = 2300 ms; inversion time (TI) = 900 ms, echo time (TE) = 2.95 ms, flip angle = 9°; Acquisition time = 5 min) with real-time motion correction (PROMO). A study neurologist reviewed all images for excessive movement and/or incidental findings. Additionally, all scans were processed using FreeSurfer (version 6.0) to assess cortical thickness and provide a quantitative measure of image quality in the form of the Euler number (Fischl and Dale, 2000).

2.3. Development of cole brain-predicted age algorithm

Although several models to estimate brain-predicted age exist, we utilized a model developed by Dr. James Cole. This model was created from T1-weighted whole brain structural images from 3377 presumptively healthy individuals drawn from seven publicly available datasets (https://github.com/james-cole/brainageR/blob/master/README.md). SPM 12 was used to normalize and segment the images into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF). Vectors of each of these tissue types were created and masked to remove non-brain voxels. Correlational matrices between vectors were explored and reduced using Principle Components Analysis (PCA). Principle components accounting for the top 80% of the explained variance were retained. Ultimately, 435 unique variables were identified which contribute to the brain-predicted age estimation. The algorithm was developed using Guassian Processes Regression, and was implemented using the kernlab

package in R (Karatzoglou et al., 2004). During model development, the model was tested on 857 individuals drawn from the same larger set of pooled data. Pearson's correlation between predicted and chronological age was r = 0.973 with a mean absolute error of 3.9 years. This model was thought to be the most appropriate for this study based on the comparatively large number of individuals over the age of 65 within the training dataset. Model fit data comparing chronological age with brain predicted age in this population specifically is included in the supplementary materials.

2.4. Brain-predicted age processing of T1 weighted MRI images

SPM12 was utilized to segment and normalize the T1-weighted MRI scans. The Rnifti package in R was then applied to create vectors with mutually exclusive GM, WM, and CSF tissue compartments. The Kernlab package in R was then applied to quantify the 435 established variables and provide a brain-predicted age score. Visual quality control was conducted using FSL (Jenkinson et al., 2012). BrainPAD scores were calculated by subtracting chronological age from the derived 'brain' age. Positive scores reflect a brain that is older than would be predicted by chronological age alone. BrainPAD has been associated with increased mortality risk (Cole et al., 2018), increased likelihood of cognitive impairment (Liem et al., 2017), and poorer physical function on tests of muscular strength and pulmonary function (Cole et al., 2018).

2.5. Assessment of brain-predicted age values and images for inclusion

Images rated by a board certified neuroradiologist as poor quality or had notes indicating that their scans were uninterpretable were excluded. Additionally, individuals with a FreeSurfer derived Euler number larger than physiologically likely for their age were excluded (Fischl and Dale, 2000). The brain images for remaining scans were visually inspected by a trained research associate to exclude motion artifact (indicated by excessive blurriness) or abnormal mass. Because longitudinal data were available for many individuals, baseline values for brain-predicted age were compared against follow up scans (at 6- and 18-months post baseline) and those that differed by >25% were excluded on the presumption that changes of that magnitude were unlikely to be observed in such a short time frame, even with intervention.

2.6. Physical measures (GXT, DXA, accelerometery)

2.6.1. Graded Exercise Testing (GXT)—A GXT to volitional maximal exertion was conducted on either a treadmill (Quinton QStress, Cardiac Science, Chelmsford, Mass) or cycle ergometer (LODE Excalibur Sport, Netherlands). Participants were monitored at rest and throughout exercise with a 12 lead ECG by the study physician. Participants were familiarized with the safety elements of the exercise device, and coached to find a comfortable walking speed between 2.0 and 4.0 miles per hour (treadmill) or practiced at a workload of 0.33 W/kg (cycle), at which they warmed up for 3–5 min. Participants were then returned to a seated position and heart rate was monitored until it was less than 75 beats per minute, or had returned to baseline, whichever was higher. Assuming normal heart rate and blood pressure responses, participants began a progressive exercise protocol in which they walked at their chosen speed or cycled at 0.33 W/kg for the first 2-min stage and

increased by 2.5% elevation (treadmill) or 0.33 W/kg (cycle) each 2-min stage thereafter and continued until the participant was unable/unwilling to continue, or the study physician ended the test based on physiological changes. Heart rate, rate of perceived exertion, and blood pressure were recorded during the final 30 s of each stage.

Maximal exercise capacity was calculated in metabolic equivalents of task (METs) using formulas published by the American College of Sports Medicine based upon speed and grade ("ACSM's Guidelines for Exercise Testing and Prescription - American College of Sports Medicine - Google Books," n.d.) Based upon an expected linear relationship between oxygen uptake and workload, partial stages were scored in 30 s increments (i.e. if participants completed 30 s of a new stage, their score was $METs_{lastcompletedstage} + 0.25* METs_{difference}$)

2.7. Body composition using dual X-ray absorptiometry (DXA)

Body composition was assessed by DXA using a GE Lunar Prodigy densitometer at one site and an iDXA (GE/Lunar, Madison, WI) at the other. Both scanners utilized EnCore software (versions 14.1 and 16.1 respectively) for estimation of body composition. While we acknowledge the likelihood of small differences in soft tissue between these two machines, a full cross-calibration study was not feasible; instead, we compared data from 9 volunteers measured on both machines within a 2-week timeframe and found good agreement across sites (R = 0.982 to 0.997 depending upon metric).

Participants were coached to remove all potential artifact (metal, hard plastic, etc.) and were positioned in line with best practice recommendations (Thurlow et al., 2018). In the event participants were unable to completely fit on the table, a "hemi scan" was acquired scanning only the left arm and/or leg as needed. The software automatically replicated the values from the scanned limb for the limb that was "missing."

2.8. Accelerometry for physical activity and sleep

Physical activity and sleep were measured objectively using the ActiGraph GT9X+ Link (ActiGraph Inc., Pensacola, FL, USA), a tri-axial accelerometer that has previously been used among adults, children, and adolescents in the National Health and Nutrition Examination Survey (Troiano et al., 2008) and has consistently been shown to be both valid and reliable (John and Freedson, 2012; Robusto and Trost, 2012; Warren et al., 2010). Participants were asked to wear the device continuously on their non-dominant wrist, except while bathing or swimming, for ten consecutive days. The wear location and time period are in-line with the best practices and result in high levels of acceptability and compliance among participants (Freedson et al., 2012; Matthews et al., 2012; Troiano et al., 2014; Tudor-Locke et al., 2015). Upon return, data were immediately downloaded and screened by hour for completeness and irregularities/malfunction (John and Freedson, 2012; Troiano et al., 2008, 2014), and algorithms designed to detect periods of non-wear were applied (Choi et al., 2011, 2012). Raw data were processed into "counts" (ActiGraph's proprietary metric) per minute in the x, y and z axis independently and the vector magnitude of all three axis collectively. This metric incorporates intensity, frequency, and duration of acceleration and

has been recommended for assessing the total volume of physical activity in a 24-h period (Bassett et al., 2015) and can also be utilized to distinguish between sleep and wakefulness.

Bedtime was derived from contemporaneously maintained sleep journals in which participants recorded the time that they went to bed (i. e. tried to fall asleep) and the time that they first awoke. These times windows were assessed for sleep vs. awake on a minute-by-minute basis using an algorithm validated for use in adults (Cole et al., 1992). If no journal was provided, sleep onset and wake times were manually determined by a specially trained researcher using previously validated methods developed by Full et al. (2018). Additional derived values include sleep latency, wake after sleep onset in terms of number and length, and sleep efficiency. Individuals were also classified as normal or abnormal sleepers based on NIA recommendations for older adults of seven to nine total hours of sleep time per night.

2.9. Genotyping analysis

The Apolipoprotein E (APOE): gene encodes a protein involved in the metabolism of fats. The presence of a specific allele (APOE4) is implicated in the development of Alzheimer's disease (Uddin et al., 2019; Zhang and Hong, 2015) and cardiovascular disease (Mahley, 2016). APOE genotyping was run on samples in duplicate on a 12K Flex QuantStudios (ThermoFisher, Waltham MA) PCR instrument following standardized procedures for normalizing, priming, plating, and analyzing.

2.10. Statistical analysis

All statistical analyses were conducted using SPSS version 27 with two-tailed p values. Descriptive statistics (proportions, means ± standard deviations) were used to characterize demographic variables and t-tests were used to compare differences by sex and location. We then evaluated correlations between the variables of interest and chronological age, brain-predicted age, and BrainPAD. All analyses utilizing BrainPAD included chronological age as a covariate, resulting in partial Pearson's correlations. Modifiable variables that showed statistically significant correlation with BrainPAD were further explored with univariate linear modelling. Due to observed significant difference by sex and location across multiple variables, and the strong association between chronological age and brain-predicted age, sex, location, and chronological age were included as potential covariates in all linear and comparative models. Education, baseline outcomes on tests of cognitive function and APOE status were also explored as potential covariates. Participants were excluded from any analysis for which they had missing values.

Additionally, we used ANCOVA techniques to examine whether BrainPAD differed by group according to established cut points linked to health in other physiologic systems. When considering body composition, the sample was divided using sex specific cut points for VAT mass derived for an older population based upon association with increased cardiometabolic risk (Meredith-Jones et al., 2021). For maximal aerobic capacity (i.e. maximal METs), we split the sample into study specific quartiles and also applied sex and age specific $VO2_{max}$ cutpoints derived from US population level data gathered by the Cooper Clinic across multiple decades ("ACSM's Guidelines for Exercise Testing and

Prescription - American College of Sports Medicine - Google Books," n.d.; Kaminsky et al., 2015). Finally, categorical grouping for total sleep time were created using National Institute of Aging (NIA) recommendations of 7–9 h of sleep for older adults (US Department of HHS, n.d.).

2.11. Data availability

The data used in these analysis, and longitudinal data from this participant group are held by investigators at Washington University in St. Louis and can be made available following a formal request that includes a project outline, and a data sharing agreement between institutions. Additionally, at least one investigator from either Washington University in St. Louis or the University of California, San Diego will need to be included on the authorship team.

3. Results

Sample Analysis:

After excluding individuals whose MRI scans were suboptimal (Rosen et al., 2018), and those missing comparator values for aerobic capacity, accelerometry, and body composition, a total of 551 participants were included in most analysis. 18 additional participants were excluded from some analyses for partial missing data (n = 10 for maximal aerobic capacity and 8 for VAT). A PRISMA diagram detailing reasons behind participant exclusion is presented in the supplementary materials and sample descriptive data for the explored metrics separated by location are detailed in Table 1.

There was a significant difference by sex for height ($p < 0.001$), weight ($p < 0.001$), percentage of body fat ($p < 0.001$), VAT ($p < 0.001$), and $VO2_{max}$ ($p < 0.001$) with men having higher values in all areas, indicating they were taller, heavier, and had relatively greater cardiovascular fitness. There was also a significant difference by sex for total physical activity and total sleep time (TST) with women being more active ($p < 0.001$) and sleeping longer ($p < 0.001$) when compared to men. Finally, men showed a significantly older BrainAge ($p = 0.007$) compared to women. This may be partially explained by the difference in chronological age ($p = 0.081$), although the difference was not substantial enough to reach statistical significance. There was also a significant difference by location for gender distribution ($p = 0.022$), chronological age ($p = 0.004$), brain-predicted age ($p = <0.001$), BrainPAD ($p = 0.001$), total physical activity ($p = 0.014$) and maximal aerobic capacity ($p = <0.001$) with participants from San Diego more likely to be female and older both in terms of chronological and brain-predicted age. Additionally, participants from San Diego had a lower average level of maximal aerobic capacity, but greater total physical activity. Some of the differences in brain-predicted age across location (mean = 4.0 years) can be explained by differences in chronological age (mean = 1.2 years). Given these observed differences, sex and location were included as covariates in all analyses. Additionally, given the commonly observed trend towards negative BrainPAD in chronologically older individuals, partial Pearson's correlations were generated using chronological age as an additional covariate.

Correlations between the metrics of interest and chronological age, brain-predicted age, and BrainPAD are shown in Table 2.

As expected, older chronological age was associated with higher brain-predicted age (r = 0.555, p=<0.001) but lower BrainPAD (r = − 0.116, p = 0.006). Additionally, we observed a negative correlation between chronological age and both BMI (r = − 0.138 p = 0.001) and body fat percentage (r = − 0.128 p = 0.003) and associations between older chronological age and lower maximal aerobic capacity (r = − 0.285 p < 0.001) and physical activity (r = − 0.177 p < 0.001) and greater TST (r = 0.114 p = 0.008). When linear-age bias correction was applied to control for chronological age (Smith et al., 2019) VAT, maximal aerobic capacity, and TST showed significant association with BrainPAD, with greater VAT associated with higher BrainPAD (r = 0.149 p=<0.001), greater MET capacity associated with lower BrainPAD (r = − 0.088 p = 0.040), and more total sleep associated with higher Brain-PAD (r = 0.087 p = 0.042).

The results of linear regression models that include all of the correlated predictors are shown in Table 3.

When explored independently, VAT, maximal aerobic capacity, and TST were significant after controlling for chronological age, sex, and location (p = 0.003, 0.018, and 0.007 and β = 0.969, − 0.382 and 0.752 respectively). Tables showing these linear regressions are included in the supplemental materials as Tables S1, S2 and S3. Adding additional covariates of education and APOE status did not substantially affect model fit or regression terms of key metrics. When all significant terms, as well as chronological age, sex, and location, were included in the model, both VAT and TST remained significant (p = 0.036 and 0.008 respectively) with each kg of VAT predicting a 0.741 year increase in BrainPAD (indicative of older brains compared to chronological age) and each hour of increased sleep predicting a 0.735 year increase in BrainPAD. Each MET increase in maximal aerobic capacity predicted a 0.242 year decline in BrainPAD but was no longer significant in fully adjusted models (p = 0.170).

Similar to the findings from linear regression, when controlling for chronological age, sex, location, total sleep time, and cardiorespiratory fitness, ANCOVA based exploration of differences by cardiovascular risk categories predicted by VAT indicated significant difference in BrainPAD. (p = 0.038; Mean Difference = 1.16 years; $\eta 2$ = 0.008). Group differences by VAT predicted risk category are shown graphically in Fig. 1.

At 6.4 h/night, the mean total sleep time for this population was under NIA recommendations for older adults, and only one individual had >9 h of sleep/night. When dichotomizing based upon meeting vs. not meeting the recommended 7 h of nightly sleep this sample had unequal group size with 394 (74%) not meeting recommendations and only 136 (26%) meeting or exceeding recommendations. When these groups were compared, while controlling for chronological age, sex, location, cardiovascular fitness, and VAT, we found significant differences in BrainPAD with those sleeping less than the recommended amount having lower BrainPAD than those achieving recommended nightly sleep duration

(p = 0.030, Mean Difference = − 1.287 years; η2 = 0.009). Group differences are visually presented in Fig. 2.

When US population level quintiles were used to explore categorical relationship between BrainPAD and maximal aerobic capacity (Kaminsky et al., 2015), the groups' numbers were strongly unbalanced to the least fit (only 7% of the population were in the most fit category, and the sample mean of 7.1 METS falls in the second from the worst category). After controlling for chronological age, sex, location, TST and VAT, this categorical grouping did not show significant group differences (p = 0.086; η2 = 0.016) with only the second-from-the-fittest category having potentially meaningful (although non-significant) difference from the other categories. When the sample was split into nearly equally sized quartiles groups using measured MET values from within the sample population there was significant difference between groups (p = 0.042). Bonferroni adjusted post hoc analysis indicates only significant difference between the second-from-the-fittest compared to the most fit category (p = 0.033 CI: − 0.107 to − 4.111), although there did appear to be a trend towards more negative BrainPAD with increasing fitness. Fig. 3 below presents these data graphically.

It is worth noting that APOE status not have a statistically significant impact on either linear or categorical outcomes for aerobic capacity, TST, or VAT. Further, when ANCOVA analysis was completed on APOE on/off categories there was no significant difference in BrainPAD between those that had the APOE4 allelle and those that did not after controlling for chronological age, sex, location, aerobic capacity, TST, and VAT. (p = 0.062 95% CI: 0.056 to − 2.181)

4. Discussion

This research was designed to determine if the novel metric of BrainPAD varied based upon maximal aerobic capacity, body composition, physical activity and/or sleep in a sample of healthy but sedentary older adults. The data presented here contribute to our understanding of the associations between excess visceral adiposity and amount of sleep, and their possible contributions to accelerated (brain) aging. Given the recent evidence presented by Vidal-Pineiro et al. (2021) suggesting that positive BrainPAD is likely the result of early life influences on brain structure, with only minimal contributions from behaviors during middle and older adulthood, it is important to avoid mistaking correlation for causation when discussing the importance of these data. In particular, the observed links between visceral adiposity and BrainPAD could be the result of early life influence(s) that contribute to the development of both phenomena. However, given that VAT has been implicated in elevated risk for disease development across multiple non-brain systems (Britton et al., 2013; Kang et al., 2010; Kullmann et al., 2020b; Lee et al., 2018; Mahabadi et al., 2009), and links between excess adiposity and deteriorating brain health in terms of both structure and function have been observed previously (Sui and Pasco, 2020; Tanaka et al., 2020), it does seem worthwhile to explore the potential links between visceral fatness and brain age. Multiple mechanisms to explain the detrimental impact of VAT across systems have been proposed. In the cardiovascular and metabolic systems, VAT has been linked to increased cytokine activation and oxidative stress (Pou et al., 2007), a higher likelihood of developing insulin resistance (Kabir et al., 2005) and increased levels of chronic inflammation and

consequent reduced immunity (Shoelson et al., 2006). Although the brain is often considered an immune-privileged organ, system wide inflammation has been associated with increased oxidative damage in the brain as well (Miller et al., 2018; Pugazhenthi et al., 2017).

It is also worth noting that to-date much of the data regarding visceral adiposity has been based on proxy measures like waist circumference, with high quality assessment of VAT through DXA-based imaging only reaching widespread availability in the last decade. Further, the duration during which an individual carries excess visceral fat may have a meaningful impact on health status, including brain aging. Thus, further research to stratify risk by VAT mass and/or volume and duration of excess adiposity offer opportunity to better understand the directionality and clinical relevance of this relationship. Additionally, longitudinal analyses that explore the time course relationship between changes in visceral fat and the rate of brain aging may inform interventions targeting VAT to improve brain health.

These data also indicate associations between sleep quantity and BrainPAD. The results of these analyses, specifically finding that less than currently recommended amount of sleep is associated with younger than chronologically predicted brains, stands in contrast with much of the current literature that indicate that both too little and too much sleep is associated with older age (Kocevska et al., 2019, 2021) and also with diminished structural brain health (Andrade et al., 2018; Khalsa et al., 2017), reduced performance on standardized cognitive tests (Faubel et al., 2009; Mohlenhoff et al., 2018), higher incidence of Alzheimer's Disease (Lucey et al., 2021) and a higher likelihood of developing cardiovascular disease (Cappuccio et al., 2008). Further, when exploring sleep's associations with BrainAge in particular, the research of Ramduny et al. (2022) found that better self-reported sleep *quality* was associated with negative BrainPAD, whereas our data indicated no difference in BrainPAD based on objectively measured quality, but significant difference based on total quantity of sleep, a metric which was not reported by Ramduny et al. (2022). While further study is needed, these data indicate that the current recommendation of 7–9 h of sleep per night may be too much for optimal brain health. Alternatively, it may be that metrics other than total sleep time, like slow wave or REM sleep, are responsible for the observed differences.

Finally, while overall levels of daily physical activity have meaningful correlations with both chronological age and brain-predicted age, they do not appear to contribute to BrainPAD. This is consistent with existing research indicating that physical activity, particularly moderate to vigorous activity (MVPA), declines with age (Shin et al., 2018; Westerterp, 2018), and that reduced physical activity is associated with reduced brain volume and increased structural and functional disruption (Erickson et al., 2014; Sexton et al., 2016). Given that the potential participants in this study were specifically excluded if they engaged in over 60 min/week of MVPA, it is perhaps unsurprising that we do not see substantial contribution to BrainPAD based on activity. Further, because our accelerometer measurement devices were wrist worn, quantifying activity into accurate intensity levels is not feasible, forcing associations to be made using a counts per minute metric across all (non-sleep) wear time. This method risks treating high levels of light activity and low levels of MVPA combined with high volume of sedentary behavior as identical for activity classification purposes.

Finally, while aerobic capacity is well correlated with both chronological and brain-predicted age, it appears to have minimal impact on BrainPAD when considered in the linear regression analysis, and there does not appear to be differences across traditionally defined categorical groups based upon fitness level. Further, although significant difference between groups is observed when the sample is divided into roughly evenly sized groups, observed differences do not seem to be linear. There does appear, however, to be a trend towards younger than predicted brains in the most fit individuals. This is somewhat consistent with evidence linking cardiovascular fitness with other disease states in which there is a threshold of fitness that is protective (although further improvement provides minimal additional benefit) (X. Sui et al., 2007, Grundy et al., 2012; C. do Lee et al., 1999). Further analyses, particularly longitudinal observations of rates of change in both aerobic capacity and brain-predicted age, are needed.

Overall, these findings are moderately consistent with the current literature in which excess adiposity in consistently linked with structural and cognitive decline (S. X. Sui and Pasco, 2020; Tanaka et al., 2020). However, the results linking less than the currently recommended amount of total sleep with younger brains is contrary to much of the existing literature (Andrade et al., 2018; Khalsa et al., 2017; Lucey et al., 2021). Meanwhile, links between brain structure and aerobic capacity and regular physical activity have been less consistently observed, and observed changes are more likely to be localized to specific regions like the hippocampus or prefronal cortex. (Firth et al., 2018; Herold et al., 2019; Petrik and Encinas, 2019).

This study had several strengths centered on the high-quality measurements of a large older adult population. In particular, the use of whole-brain MRI imaging for brain-predicted age calculation, maximal exercise tests to assess aerobic capacity, DXA to assess body composition, and objective tools to measure physical activity and sleep mean that there were fewer sources of error than might come from estimation algorithms, proxy measures, or self-report. However, there were also limitations. Chief among these was the cross-sectional nature of the study, making it impossible to indicate the directionality of observed relationships and the possibility of a shared etiology or mechanism accounting for the observed associations. Further, our population of older adults expressing cognitive complaints, but without observable impairment, may also not be truly representative of the larger presumptively healthy older adult population. Additionally, the fact that we only captured night-time sleep behavior and did not gather data on daytime napping may have contributed to an underestimation of total sleep time leading to incomplete/incorrect analysis of the relationship between sleep and BrainPAD. Further, the degree to which the observed associations are explained by the examined metrics is small. Finally, the sample was drawn from a self-reportedly sedentary population of older adults, and as such may not be applicable to younger and/or more active populations.

5. Conclusion

In this population of presumptively healthy older adults residing in the United States, the age of the brain, as described by the difference in the *biological* age of the brain vs. the chronological age of the individual, is negatively associated (i.e., older than expected)

with accumulation of visceral adipose tissue and increased total sleep time, but not aerobic capacity, total daily physical activity or sleep quality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

Abbreviations:

BrainPAD	Brain Predicted Age Difference

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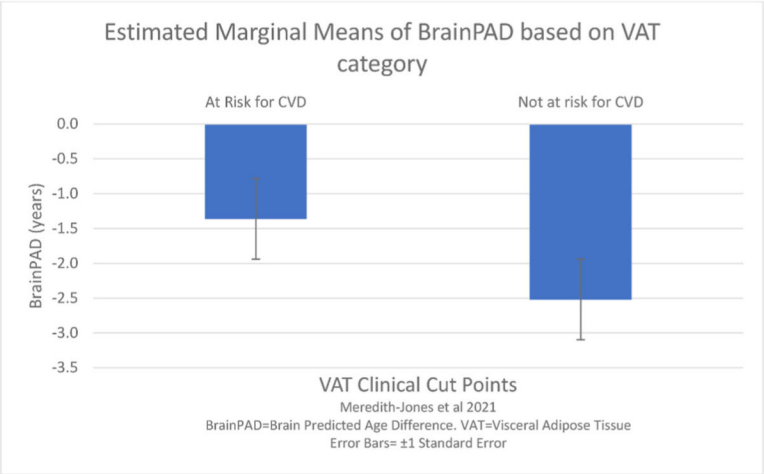

Fig. 1.
Group Differences in BrainPAD based on VAT risk category.

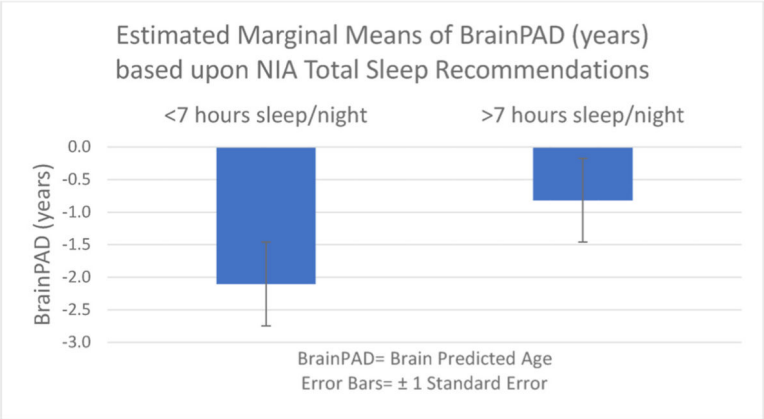

Fig. 2.

Group Differences in BrainPAD based on Meeting vs. Not Meeting NIA Total Sleep Time Recommendations.

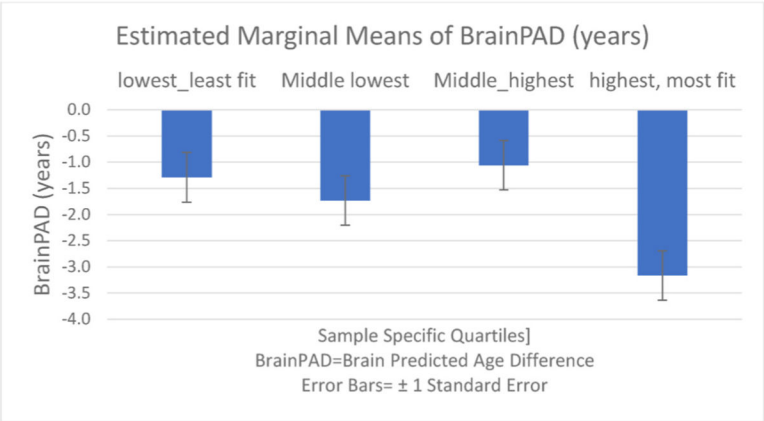

Fig. 3.

Group Differences in BrainPAD based on Sample Specific Quartiles of Maximal Cardiovascular Fitness.

Table 1

Sample descriptive statistics.

		Total (n = 551)	SD (n = 275)	WUSTL (n = 276)	p for difference between locations
% Female	%	74	78	69	**0.022**
Chronological Age	Yr	71.5 (4.8)	72.1 (4.9)	70.9 (4.7)	**0.004**
Brain predicted age	Yr	69.6 (7.4)	71.6 (7.3)	67.6 (7)	**<0.001**
Predicted BrainAge Difference (BPAD)	Yr	− 1.9 (6.2)	− 0.5 (6.4)	− 3.4 (5.7)	**<0.001**
Education	Yr	16.2 (2.2)	16.2 (2)	16.1 (2.3)	.709
% APOE E4 genotype	%	30	26	34	**0.025**
Height	M	1.7 (0.1)	1.6 (0.1)	1.7 (0.1)	**<0.001**
Weight	Kg	77.6 (16.6)	75.1 (16.5)	80 (16.4)	**0.001**
BMI	kg/m2	28.1 (5.1)	27.8 (5.3)	28.4 (5)	0.173
Body Fat	%	39.8 (7.6)	40.1 (7.3)	39.5 (7.9)	0.376
Visceral Adipose Tissue	Kg	1.3 (0.9)	1.3 (0.9)	1.4 (1)	0.228
Resting Heart Rate	BPM	69 (10)	68 (10)	69 (10)	0.100
Estimated Maximal Capacity	METS	7.1 (1.8)	6.6 (1.5)	7.6 (1.9)	**<0.001**
Total Physical Activity	CPM	1941 (509)	1994 (532)	1888 (480)	**0.014**
Total Sleep Time	hours/night	6.4 (0.9)	6.4 (0.9)	6.4 (1.0)	0.941
Sleep Efficiency	%	84.3 (6.6)	84.3 (6.0)	84.3 (7.2)	0.976

All values presented as mean (SD) unless otherwise noted BMI=Body Mass Index; CPM=Counts per Minute.

Table 2

Correlations between chronological age, Brain Predicted Age Difference (BrainPAD) and key physiological metrics.

	Chronological Age	Brain Predicted Age	BrainPAD (adjusted for chronological age)
Chronological Age		**0.555 (<0.001)**	
BMI (kg/m^2)	**−0.138 (0.001)**	− 0.037 (0.392)	0.048 (0.257)
Body Fat Percentage (%)	**−0.128 (0.003)**	− 0.064 (0.136)	0.008 (0.850)
Visceral Adipose Tissue (kg)	0.012 (0.773)	**0.132 (0.002)**	**0.152 (<0.001)**
Resting Heart Rate (bpm)	0.014 (0.75)	0.011 (0.796)	0.004 (0.924)
Estimated Maximal Capacity (METS)	**−0.285 (<0.001)**	**−0.259 (<0.001)**	**−0.127 (0.003)**
Total Physical Activity (counts/min)	**−0.177 (<0.001)**	**−0.147 (<0.001)**	− 0.062 (0.150)
Total Sleep Time (hours)	**0.114 (0.008)**	**0.134 (0.002)**	**0.087 (0.042)**
Sleep Efficiency (%)	0.064 (0.137)	0.06 (0.165)	0.030 (0.483)
Education (years)	− 0.49 (0.258)	0.02 (0.65)	0.055 (0.199)
APOE E4 genotype (yes/no)	− 0.17 (0.7)	0.03 (0.488)	0.013 (0.760)

All values presented as Pearson's Correlation Coefficient (r) and p value of association BMI=Body Mass Index; VAT=Visceral Adipose Tissue; METS= Metabolic Equivalent of Task; bpm= beats per minute.

Table 3

Linear regression analysis of all correlated variables (VAT, Maximal Aerobic Capacity, Total Sleep Time) and BrainPAD.

Model Summary	**R**	**R^2**	**Adjusted R^2**	**SEE**	**P-value**
	0.330	0.109	0.099	5.8317	**0.008**
Predictors	**Unstandardized β**	**SE**	**Standardized β coefficient**	***t***	***p*-value**
Constant	11.805	4.762		2.479	**0.013**
Visceral Adipose Tissue (kg)[a]	0.741	0.352	0.111	2.106	**0.036**
Total Sleep Time (hours/night)[b]	0.735	0.276	0.113	2.66	**0.008**
Covariates					
Chronological Age (yrs)	− 0.208	0.058	− 0.162	− 3.604	**<0.001**
Sex[c]	1.399	0.781	0.100	1.791	0.074
Maximal Aerobic Capacity (METS)[d]	− 0.242	0.176	− 0.071	−1.374	0.17
Location[e]	− 2.978	0.536	− 0.243	− 5.56	**<0.001**

[a]Visceral Adipose Tissue derived from Dual X-Ray Absorptiometry.

[b]Total Sleep Time in gathered from accelerometry averaged across 4+ nights of collection.

[c]Female = 1, Male = 2.

[d]METS estimated based upon final speed/grade on treadmill during Graded Exercise Test.

[e]UCSD = 1, WUSTL = 2.