Physical activity, body mass index, and brain atrophy in Alzheimer’s disease


Abstract

The purpose of this study was to use a novel imaging biomarker to assess associations between physical activity (PA), body mass index (BMI), and brain structure in normal aging, mild cognitive impairment, and Alzheimer’s dementia. We studied 963 participants (mean age: 74.1 ± 4.4 years) from the multisite Cardiovascular Health Study including healthy controls (n = 724), Alzheimer’s dementia patients (n = 104), and people with mild cognitive impairment (n = 135). Volumetric brain images were processed using tensor-based morphometry to analyze regional brain volumes. We regressed the local brain tissue volume on reported PA and computed BMI, and performed conjunction analyses using both variables. Covariates included age, sex, and study site. PA was independently associated with greater whole brain and regional brain volumes and reduced ventricular dilation. People with higher BMI had lower whole brain and regional brain volumes. A PA-BMI conjunction analysis showed brain preservation with PA and volume loss with increased BMI in overlapping brain regions. In one of the largest voxel-based cross-sectional studies to date, PA and lower BMI may be beneficial to the brain across the spectrum of aging and neurodegeneration.

1. Introduction

Alzheimer’s disease (AD) is the most common cause of dementia and the number of persons predicted to have the disease in the United States alone will increase to 13.5 million from 2.2 million by the year 2050 (Sperling et al., 2011). Currently, about 34 million people worldwide have the disease, and lifestyle factors that are modifiable in principle, such as physical inactivity and obesity, are associated with a heightened risk for AD. If these associations were related to the risk of expressing clinical dementia, then increasing physical activity and decreasing the prevalence of obesity may reduce the number of AD cases by an estimated 50% (Barnes and Yaffe, 2011). These estimates are the foundation for developing prevention strategies, which are becoming particularly important given the relatively poor efficacy of current drug treatments for AD.

Lack of physical activity (PA) may be the most important modifiable risk factor for AD in the United States and the third most important worldwide (after low education and smoking) (Barnes et al., 2011).
Midlife obesity also contributes to a substantial proportion of cases worldwide and in the United States (Barnes and Yaffe, 2011). Thus, the risk of AD might be reduced by systematically increasing PA (Chang et al., 2010; Lautenschlager et al., 2008; Rolland et al., 2008; van Gelder et al., 2004) and reducing obesity. We have previously shown that self-reported PA in healthy elderly people is associated with larger regional brain volumes and reduced risk for future conversion to AD or its prodrome, mild cognitive impairment (MCI) (Ernickson et al., 2010; Petersen et al., 1999). Higher body mass index (BMI) in midlife is associated with structural brain changes, cognitive decline, and an increased risk of AD in late life (Crnok et al., 2010). This suggests that differences in brain structure are a useful intermediary in understanding the association between risk modifiers such as PA and BMI, and the clinical manifestations of neurodegeneration, in this case AD and MCI.

Here, we set out to assess the associations between self-reported PA, computed BMI, and regional brain volumes in a large cohort including people with MCI and AD. We were especially interested in understanding whether potential effects of these variables were more easily detected in some parts of the brain relative to others, or if it was simply a pervasive association across the entire brain. To answer this, we used tensor-based morphometry (TBM), which creates detailed 3D maps pinpointing brain regions with the strongest statistical associations with PA and/or BMI, throughout the brain. To find out if it was simply a pervasive association across the entire brain, and not an intermediary in understanding the association between risk modifiers such as PA and BMI, and the clinical manifestations of neurodegeneration, in this case AD and MCI.

2. Methods

2.1. Participants

The Cardiovascular Health Study (CHS) is a multisite, population-based longitudinal study of coronary heart disease and stroke in individuals aged 65 years and older (Fried et al., 1991). CHS recruitment was based on the Medicare eligibility lists in: Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. In a first wave, 5201 participants were recruited from 1989 to 1990. In a second assessment, 687 African-Americans were recruited from 1992 to 1993 leading to a cohort of 5888 participants. The institutional review board at each site approved the study methods, and all participants gave written informed consent.

2.2. The CHS Memory Study

In 1991 and 1992, 3608 of the CHS enrollees participated in the CHS Memory Study (CHS-MS) and underwent a low-resolution magnetic resonance imaging (MRI) scan of the brain. In 1998 and 1999, a follow up high-resolution MRI scan and neurobehavioral evaluations were completed for all available, living participants (n = 2101) (Kuller et al., 2003). Because of the late inclusion of the high-resolution spoiled-gradient echo (SPGR) sequence into the scanning protocol, not all participants had high-resolution anatomical imaging. Thus, the present study includes only the data from the 963 CHS-CS participants who had an SPGR scan and whose MRI data met quality control standards. Prior CHS quality control measures included visual review of scans by a neuroradiologist, to ensure that no large space occupying lesions existed that could potentially hinder analysis (Bryan et al., 1997; Raji et al., 2009). We also performed our own visual assessment to ensure against any cropping of brain tissue from the scan field of view or corruption of MR images in the TBM processing stream.

Participant demographics are shown in Table 1. A separate column identifies sites that were independently correlated with study variables, based on analysis of variance (ANOVA). Hagerstown and Pittsburgh were the sites most frequently correlated with the variables characterized in this study based on the ANOVA weighting the correlation of these sites against the 2 other study locations (p < 0.05). Of the 963 participants included, APOE4 genotype was available in 894 and 221 (24.7%) were APOE4 positive. Full methods for obtaining the APOE4 genotypes in our study are described elsewhere (Kuller et al., 1998).

Neurobehavioral evaluations were assessed to determine the presence of any disorder that could affect cognition. Participants were classified as having normal cognition, MCI, or AD (Lopez et al., 2003b). The diagnosis of dementia was based on deficits in performance in 2 or more cognitive domains that were sufficiently severe to affect activities of daily living and their history of normal intellectual function before the onset of cognitive abnormalities; a memory deficit was not required for the diagnosis of dementia (Lopez et al., 2012). The Adjudication Committee consisted of experts in dementia who had access to the historical CHS cognitive test scores, primarily the Modified Mini Mental Status Examination (3MSE) (and subscales), Benton Visual Retention Test, and the DSST, as well as the CES-D scores. The committee also reviewed data from vision and hearing tests, history of alcohol intake, activities of daily living questionnaire, IQ-CODE, Dementia Questionnaire, vital status, date of death where relevant, history of hospitalizations, medications to treat dementia, findings from MRI scans, results of neuropsychological assessments, and hospital records (Lopez et al., 2003a).

### Table 1

Characteristics of CHS Memory Study participants with MRI in 1998 and 1999 by CHS site

<table>
<thead>
<tr>
<th>Study site</th>
<th>Number of MRI scans analyzed</th>
<th>Age</th>
<th>Sex, male, % (n)</th>
<th>Race, white, % (n)</th>
<th>Time taken to walk 15 feet</th>
<th>BMIa</th>
<th>Number of infarcts</th>
<th>Sulcal grade (0–9, worst)</th>
<th>Ventricular grade (0–9, worst)</th>
<th>White matter grade (0–9, worst)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winston-Salem</td>
<td>18</td>
<td>23.9 (3.4)</td>
<td>61 (11)</td>
<td>100 (18)</td>
<td>4.8 (0.9)</td>
<td>0.39 (0.7)</td>
<td>4.11 (1.3)</td>
<td>3.72 (0.83)</td>
<td>3.19 (1.9)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Sacramento</td>
<td>315</td>
<td>26.4 (4.3)</td>
<td>41 (130)</td>
<td>92 (289)</td>
<td>6.3 (3.1)</td>
<td>0.59 (1.0)</td>
<td>3.9 (1.4)</td>
<td>3.86 (1.4)</td>
<td>2.88 (1.7)</td>
<td>34 (107)</td>
</tr>
<tr>
<td>Hagerstown</td>
<td>192</td>
<td>27.0 (4.5)</td>
<td>44 (84)</td>
<td>99 (190)</td>
<td>7.4 (4.6)</td>
<td>0.53 (0.99)</td>
<td>3.89 (1.7)</td>
<td>3.48 (1.2)</td>
<td>2.34 (1.5)</td>
<td>30 (58)</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>438</td>
<td>26.6 (4.2)</td>
<td>40 (176)</td>
<td>80 (348)</td>
<td>5.6 (4.6)</td>
<td>0.48 (0.89)</td>
<td>4.2 (1.6)</td>
<td>3.71 (1.4)</td>
<td>2.45 (1.6)</td>
<td>30 (130)</td>
</tr>
<tr>
<td>Total sample</td>
<td>963</td>
<td>26.6 (4.3)</td>
<td>42 (401)</td>
<td>88 (845)</td>
<td>5.7 (3.2)</td>
<td>0.52 (0.96)</td>
<td>4.2 (1.6)</td>
<td>3.72 (1.4)</td>
<td>2.58 (1.6)</td>
<td>31 (300)</td>
</tr>
</tbody>
</table>

Key: BMI, body mass index; CHS, Cardiovascular Health Study; MRI, magnetic resonance imaging; SD, standard deviation.

* Mean (SD).

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**References:**

2.3. Assessment of physical activity and body mass index

PA was assessed at baseline and updated 10 years later, within 1 year on average, of the high-resolution MRI scan. PA was assessed by the modified Minnesota Leisure-Time Activities Questionnaire (Elosua et al., 1994; Folsom et al., 1986), which evaluates the duration and frequency of PA. We selected “blocks walked over 1 week” as a main measure of PA, as it is the simplest form of physical activity so most individuals in our study would be likely to do it. In addition, we previously reported that the average number of blocks walked in 1 week is associated with variation in gray matter volume (Erickson et al., 2010) with 12 city blocks equal to approximately 1 mile. On average, people with MCI and AD had lower levels of physical activity than those with normal cognition ($t = 3.6, p < 0.001$). All participants had weight (pounds or kilograms) and height (inches or centimeters) measures taken during the physical exam, both at baseline and 9 years later, in the same year that the high-resolution MRI data were acquired; BMI was computed as: weight (kg) $\times$ (height [m]$^2$), using a constant to account for the unit conversion. For these analyses, we used PA measurements from year 10 of the study and BMI measurements from year 9 of the study.

2.4. Structural MRI

MRI using the SPGR sequence was completed at each of the 4 sites using 1.5 Tesla scanners, as detailed elsewhere (Bryan et al., 1994). The scanning protocol used in 1998 and 1999 included a sagittal T1-weighted localized sequence, an axial T1-weighted spin-density, and T2-weighted images. The axial images were 5 mm thick without interslice gaps. White matter hyperintensities, an imaging marker of small vessel ischemic disease, were visually determined using a standardized semiquantitative white matter grade (WMG) that is fully described in prior work (Raji et al., 2012).

For the specific TBM methods used to process the brain images, please refer to Supplementary Data.

2.5. Voxelwise linear regressions

At each point in the brain, a linear regression model (Calabrese et al., 2011; Chu et al., 2009a, 2009b) was fitted to model relationships between regional brain volumes and our factors of interest. Predictors included the site of data acquisition (represented by 3 "dummy variables": $B_1$, $B_2$, and $B_3$), the age of the participant ($B_4$), sex ($B_5$), race ($B_6$), years of education ($B_7$), diagnosis ($B_8$), BMI—year 9 ($B_9$), and physical activity—year 10 ($B_{10}$). This led to the following regression model:

$$\text{Volume (Jacobian)} = B_0 + (B_1, B_2, B_3) \cdot \text{Site} + B_4 \cdot \text{Age} + B_5 \cdot \text{Sex} + B_6 \cdot \text{Race} + B_7 \cdot \text{Education} + B_8 \cdot \text{Diagnosis} + B_9 \cdot \text{BMI} + B_{10} \cdot \text{Physical activity} + \text{residual error}$$

We used these voxelwise (at each point in the brain) multiple regressions to compute regression coefficients and assess whether the covariates of interest predicted volumetric differences anywhere in the brain. Statistical or “$p$-value” maps were generated to visualize the pattern of voxelwise significance. To control for false positives, we enforced a standard false discovery rate (FDR) correction for multiple statistical comparisons across voxels in the whole brain and inside each brain lobe, using the conventionally accepted false-positive rate of 5% ($q = 0.05$) (Benjamini and Hochberg, 1995; Chu et al., 2009b). Regions associated with PA and BMI were visualized using unstandardized beta maps to indicate the direction of change (expansion or contraction).

To perform the PA-BMI, PA-Dx, and BMI-Dx conjunction analyses, we used a script to combine the “$p$-value” maps from the 2 covariates of interest (taking the maximum or least significant $p$-value from the 2 maps being conjoined) and then enforced FDR correction to determine the overall significance of the map, in the same way as mentioned previously.

For exploratory analyses restricted to either cognitively normal or cognitively impaired subjects, we used the original regression model but with a limited population. For exploratory analyses involving statistical interactions, we used the entire subject population but added a term to the original regression model, involving the multiplication of 2 covariates of interest. Each covariate was “mean centered” before multiplication, when modeling the statistical interaction.

3. Results

3.1. Influences on brain structure

We found that higher physical activity levels were associated with significantly higher whole brain (FDR $q = 0.05$, critical uncorrected $p = 0.0008$) and parietal lobe volume, with reduced ventricular dilation. As found before (Ho et al., 2010a; Raji et al., 2010a), subjects with higher BMI had significantly lower whole brain ($N = 963$, FDR $q = 0.05$, critical uncorrected $p = 0.0398$) and regional volumes in frontal, temporal, parietal, and occipital lobes with the strongest associations in the frontal and occipital lobes. More specifically, higher BMI was related to volumetric brain tissue reductions in the orbitofrontal cortex and anterior cingulate gyrus. The PA-BMI conjunction analysis showed that physical activity and higher BMI had overlapping associations with volume of the orbitofrontal cortex, posterior cingulate gyrus, and posterior hippocampus.

AD and/or MCI was significantly correlated with lower brain volume across the whole brain, with pervasive associations revealing frontal lobe atrophy and ventricular dilation. We were unable to find significance with the PA-Dx conjunction; however, significant $p$-values in the BMI-Dx conjunction analysis show where BMI and diagnosis are both associated with lower regional volumes across the whole brain, particularly in the frontal lobe region.

Fig. 1A and B present 2 orthogonal slices that show the independent correlation of BMI (upper panels) and of PA (middle panels), as well as the significant correlation resulting from the conjunction analysis (lower panels), at different locations in the brain. Fig. 2 duplicates the orthogonal slice in Fig. 1B and was sufficient to compare the significant correlation of BMI (upper panels) with the separate correlation of AD and/or MCI (middle panels) and to display the conjunctural analysis results of BMI and diagnosis (lower panel). As mentioned, the $p$-value map resulting from the PA-Dx analysis revealed no statistical significance in common brain regions and is consequently not shown as a figure.

3.2. Exploratory analyses

In an exploratory analysis restricted to the 724 cognitively normal participants, we found that BMI and PA remained strong predictors of brain structure. The inverse relationship with BMI resulted in a critical $p = 0.0379$ across the whole brain. PA did not reach significance across the whole brain, but the volume of the parietal lobe was significantly associated with PA (critical $p = 0.0021$). Again, all the same covariates were used in the “controls only” model. This analysis confirmed that the association between PA and brain volume was significant in normal controls. In the same fashion, we analyzed data from the 239 cognitively impaired participants, and BMI maintained a significant association with brain volume.
Fig. 1. (A) indicates brain location #1. (Top panel) Whole brain 3D maps show areas where regional brain volumes correlated significantly with BMI after controlling for site, age, sex, race, educational level, and diagnosis, plus PA (N = 963; FDR q = 0.05, critical uncorrected p = 0.0398). (Middle panel) Maps show brain regions significantly associated with PA (blocks walked) after correcting for the same effects, plus BMI (N = 963; FDR q = 0.05, critical uncorrected p = 0.0008). Beta maps were significant after standard correction for multiple comparisons and represent the estimated degree of tissue excess or deficit at each voxel, as a percentage, for each unit gain in BMI and/or physical activity. (Lower panel) 3D maps show regions of significant brain volume differences from both higher BMI and physical activity using a conjunction analysis displayed over a study-specific template. P maps are corrected for multiple comparisons on the basis of FDR (FDR q-level = 0.05, critical uncorrected p = 0.0006). The same slices are shown in each panel, and images are displayed in radiological convention (left side of the brain shown on the right). (B) indicates brain location #2. (Top panel) Whole brain 3D maps show areas where regional brain volumes correlated significantly with BMI after controlling for site, age, sex, race, educational level, and diagnosis, plus PA (N = 963; FDR q = 0.05, critical uncorrected p = 0.0398). (Middle panel) Maps show brain regions significantly associated with PA (blocks walked) after correcting for the same effects, plus BMI (N = 963; FDR q = 0.05, critical uncorrected p = 0.0008). Beta maps were significant after standard correction for multiple comparisons and represent the estimated degree of tissue excess or deficit at each voxel, as a percentage, for each unit gain in BMI and/or physical activity. (Lower panel) 3D maps show regions of significant brain volume differences from both higher BMI and PA using a conjunction analysis displayed over a study-specific template. P maps are corrected for multiple comparisons on the basis of FDR (FDR q-level = 0.05, critical uncorrected p = 0.0006). The same slices are shown in each panel, and images are displayed in radiological convention (left side of the brain shown on the right). Abbreviations: BMI, body mass index; FDR, false discovery rate; PA, physical activity.
volume (critical \( p = 0.0250 \)), but PA was no longer significant in any area. An analysis was also run to test for statistical interactions between PA and diagnosis (CTL = 0; MCI and/or dementia = 1). This was added to the model to test whether the association between PA and brain volume was influenced by diagnosis. There was no statistically significant interaction between PA and Dx \(( p > 0.05)\); there was also no change in the significance of PA and BMI when this term was included (BMI: critical \( p = 0.0396 \); PA: critical \( p = 0.0003 \)). This suggests that the association between PA and brain volume did not depend on whether or not a participant was cognitively impaired or that we were underpowered to detect such a dependency.

In addition to confirming that cognitive impairment did not significantly moderate the association between PA and brain volume, the confounding influence of mobility on PA and its relationship with brain structure was explored via a statistical interaction between PA and mobility. It is important to understand any effect of mobility, as a less mobile person may be less able to be physically active. When included in the regression model, mobility, as defined as the time to walk 15 feet, was not statistically significant. Also, the significance of PA and BMI were maintained after including this variable in the model. Therefore, the relationship of PA with brain structure was not influenced by mobility restrictions.

Another statistical analysis was run to model the relationship of small vessel ischemic disease as measured by WMG (Longstreth, et al., 1996; Raji et al., 2012) with brain volume. In Longstreth et al. (1996) examples of single slices from complete scans used by board certified neuroradiologists to grade white matter are presented. Grading ranges from 1 to 8 and consists of descriptions of the periventricular rim, levels of subcortical disease, and identification of periventricular lesions and confluence. Studies with no white matter findings were graded 0, and those with findings more remarkable than the highest grade (grade 8) were scored 9. Here, we included a statistical interaction term between PA and WMG. Our analysis using this measure showed a significant correlation in the occipital lobe (critical \( p = 0.0004 \)), which suggests a dependency of the PA-brain structure relationship on WMG.

Finally, an interaction between PA and APOE4 was modeled to determine whether the association of PA with brain volume was moderated by genotype, but this term was not statistically significant \(( p < 0.05)\). Therefore, the potential effect of PA on brain structure did not vary as a function of APOE4 status.

4. Discussion

The imaging method in our study, TBM, is used as a biomarker of atrophy and is reasonably novel compared with traditional morphometry methods such as tracing structures on scans. It has been used before but the biological results can be considered evidence of the method’s value in its sensitivity to biological factors that affect regional brain volumes. In other words, the results can be seen as biomarkers of biological processes. The influence of measurable lifestyle factors such as PA and BMI is revealed via direct association with this biomarker and may present itself via effects on the brain that influence structure and also risk of disease, such as AD. Conjunction analyses revealed areas associated with both PA and BMI as well as BMI and dementia. By showing areas that shrink with BMI and are at risk for neurodegeneration in AD, our results support evidence that increased BMI is a potent risk factor which is associated with increased atrophy in areas at risk for AD. We were unable to detect a significant conjunction between areas affected by PA and AD. This would be consistent with the lack of PA significance in the AD-only analysis and may be because of
low statistical power and/or less physical activity in subjects with AD.

Taken together with prior work, this study has several key implications. First, PA, as measured by the amount a person walks, is related to brain structure in later life, as is BMI. Greater amounts of walking are associated with larger relative brain volumes, especially in the parietal lobe. This finding was strong enough to survive after controlling for BMI, a standard measure of obesity, which we were unable to achieve in earlier human studies using PA and BMI (Ho et al., 2010a). Given the frequently pervasive association of BMI with brain volume as shown in such human studies (Ho et al., 2010a, 2010b), this is novel and may be because of greater statistical power for detecting this relationship with a larger sample size. The association between BMI and brain structure is also strong even when accounting for PA; however, this is more in line with expectations because of the strong correlation of BMI. These results suggest that the potential benefit of PA on brain volume might be because of more than simply a lower BMI; likewise, the negative correlation of BMI with brain volume is likely because of more than just a lack of PA.

These data build on our prior work in a subset of this sample (N = 299) showing that PA (i.e., blocks walked) at baseline was related to greater brain volumes measured 9 years later in a human cohort (Erickson et al., 2010), independent of BMI. Collectively, this work is consistent with the hypothesis that increasing PA later in life could improve brain health. This assertion is supported by 1 randomized controlled trial showing that hippocampal volume can respond positively to exercise training over the course of a year in a randomized trial of cognitively normal individuals (Erickson et al., 2011). We have also shown that hippocampal volume may be higher in people with lower BMI in a prior study of persons with AD (Ho et al., 2011).

Our study further reveals that associations between PA, BMI, and brain structure may be present across a range of cognitive status. This is consistent with our prior work with BMI in human imaging studies (Ho et al., 2010a, 2011). PA did not vary as a function of diagnostic classification, which is important as prior work on PA and brain structure has focused on cognitively normal individuals; (however, see Honea et al., 2009; Vidoni et al., 2012). If our observation is confirmed, it may be reasonable to test PA as an adjuvant therapy for AD as shown in prior human investigation (Li et al., 2012).

Multiple Randomized Controlled Trials (RCTs) show the positive benefits of PA on both brain structure and function in human studies (Colcombe et al., 2003, 2006; Pereira et al., 2007). Although our study cannot establish causal link between PA and brain structure, other work suggests that there is such a link between aerobic PA and improved preserved regional brain volumes in cognitively normal (Burdette et al., 2010; Hotting et al., 2012; Ruchwerg et al., 2011) and AD populations (Burns et al., 2008). The overall relationship between PA and brain structure has also been reported in numerous epidemiologic and observational studies. According to one review, 20 of 24 longitudinal human epidemiologic studies found that PA was associated with a reduced risk for cognitive decline and dementia (Rolland et al., 2008). More recently, a study of over 4761 elderly human subjects found that midlife PA was associated with reduced prevalence of dementia and cognitive decline 26 years later (Chang et al., 2010). Also, a meta-analysis of 29 RCTs examining the influence of PA on cognitive function showed that aerobic PA confers improvements in human attention and processing speed, executive function, and memory (Smith et al., 2010).

RCTs have explored the effects of exercise in people with dementia. One RCT investigated the effectiveness of exercise programs at 5 nursing homes containing 134 ambulatory patients with mild to severe AD, and concluded that a simple exercise program leads to a slower decline in the ability to perform activities of daily living (ADLs) (Rolland et al., 2007). Another RCT investigated the effects of intense and long-term exercise in 210 home-dwelling patients with AD, showing beneficial effects on physical functioning and mobility (Pitkala et al., 2010). Comprehensive reviews of such RCTs have produced mixed results. One review of 16 studies found that physical activity was beneficial in all stages of dementia, and that multicomponent interventions involving endurance, strength, and balance can improve physical functioning and basic activities of daily living in elderly human subjects with dementia (Blankevoort et al., 2010). A second review of 13 human RCT’s confirmed this, citing evidence that physical activity interventions improve physical function in older people with dementia (Potter et al., 2011). However, a review of 2 human RCTs and 1 meta-analysis concluded that there was insufficient evidence that physical activity programs are effective in managing or improving cognition in people with dementia (Forbes et al., 2008). This review was later updated to include 16 trials and conclude there is promising evidence that exercise programs can have a significant impact in improving ability to perform ADLs and possibly in improving cognition in people with dementia (Forbes et al., 2013).

Studies associating BMI and brain structure show mixed results. We have mentioned several studies where our group as well as others have shown that higher BMI or midlife obesity is linked with cognitive decline in humans including brain volume deficits and increased risk of dementia (Barnes and Yaffe, 2011; Ho et al., 2010a; Raji et al., 2010a). However, these same studies cite support that suggests lower BMI and rapid weight loss in later life is associated with dementia. This has been appropriately labeled the “obesity paradox.” Prior longitudinal studies have suggested the possibility of a U-shaped association whereby there was a significant curvilinear association between BMI and cognitive function scores at baseline, concluding that BMI in the elderly individuals is not predictive of cognitive decline in a normal community human population (Sturman et al., 2008). BMI is typically analyzed as a categorical variable comprised of underweight, normal, overweight, and obese labels. The U-shape association suggests that volume loss is seen with both underweight and obese categories. To test this hypothesis with our data, we performed an ANOVA with a polynomial contrast using these categories to test for a U-shaped association against total gray matter volume as a proportion of total intracranial volume derived from voxel based analyses previously conducted. Covariates included age, gender, race, AD, MCI, site and white matter grade, and was done in all 963 CHS subjects. Our results showed that the estimated means from the ANOVA is not U-shaped but linear. Thus, our BMI analysis clearly shows an inverse relationship between BMI and brain volume whereby brain volume steadily decreases as BMI increases in the elderly individuals.

PA may influence brain structure and reduce AD risk through multiple physiologic mechanisms. They may be broadly grouped into 3 categories: (1) counteraction of AD pathology, such as amyloid effects; (2) influencing the levels of neurotrophic factors and neurotransmitters, that may optimize neuronal function; and (3) reducing vascular risk factors that can independently compromise brain structure. With respect to the first category, people aged 55–88 years have lower levels of amyloid plaque as imaged with Pittsburgh Compound B if they had at least 7.5 metabolic equivalent hours of PA per week (Liang et al., 2010). Further, exercise reduces hippocampal tau, in a transgenic mouse model of AD when compared with sedentary mice (Belarbi et al., 2009). PA can promote gene expression in the dentate gyrus of the hippocampus and can increase the expression of brain-derived neurotrophic factor in animal and human studies (Intlekofer and Cotman, 2012; Li et al., 2012). PA also reduces some vascular risk factors such as obesity
and type 2 diabetes mellitus, that are independent risk factors for AD, in a recent review (Ahlskog et al., 2011). Our exploratory analysis is consistent with the third mechanism, that is, that PA may reduce small vessel disease as indicated by the presence of white matter hyperintensities. PA may preserve brain structure by countering downstream effects of vascular risk factors such as hypertension that promote white matter injury with subsequent brain atrophy in human studies (Raji et al., 2012; Wiseman et al., 2004).

The patients in our cohort who had AD were relatively early in their clinical course in human imaging studies (Raji et al., 2009). PA may benefit people who are early in their course of MCI and AD either by modifying the underlying neurodegenerative process or by affecting brain reserve in human studies (Stern et al., 1995, 1996). PA can reduce amyloid metabolism in APOE4 positive human individuals (Head et al., 2011) and the significant interaction between PA and WMG in the occipital lobe suggests that, at least in that region, the main effect of PA on brain structure is moderated by small vessel ischemic disease, as reflected by WMG.

The physiological mechanisms at work between BMI and brain structure have been widely explored and consist of several possibilities. Adiposity may contribute to a broader syndrome. The most commonly proposed mediators for the relationship between higher body tissue adiposity and brain structure include hypercortisolemia, reduced exercise, impaired respiratory function, inflammation, cardiovascular, hypertension, and/or hyperlipidemia, and type II diabetes mellitus (Raji et al., 2010a). The co-occurrence of at least 3 of the following cardiovascular factors including large waist circumference (or adiposity), increased triglycerides, elevated blood pressure, and fasting hyperglycemia has been referred to as “the metabolic syndrome” (Yaffe et al., 2007). Adiposity is also associated with insulin resistance and subsequent type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, degenerative joint disease, cancer disease, and lung disease (Poirier et al., 2006). Moreover, an elevated BMI is significantly correlated (p < 0.01) with a reduction in neuronal fiber bundle length, which is believed to contribute to brain atrophy. Finally, greater brain atrophy may occur in people with central leptin insufficiency, a marker of obesity. Leptin, a hormone produced by body fat tissue, acts on hypothalamic receptors in the brain to regulate appetite and energy expenditure, and on neurons in the arcuate nucleus to signal satiety following a meal in a recent ADNI human study (Rajagopalan et al., 2013). The exact mechanisms through which obesity leads to brain atrophy and cognitive decline are complex and may involve a number of factors such as diabetes, genetic vulnerability, brain metabolites, and cytokines. Much research has revealed the degree to which these factors are linked with obesity, but further analysis is required to understand the way these elements interact with each other in their effects on the brain.

Our study has limitations. First, given the observational nature of the design, it is impossible to establish causality between PA, BMI, or conjunctions, and brain structure. People with larger brains may be more likely to exercise or maintain low BMI; alternatively, once a person becomes ill, they may be less able to exercise or maintain their weight. To overcome this limitation in our sample, an RCT would be needed in a population of people with normal cognition and with MCI or AD. Second, although “blocks walked” is a useful measure of PA, it is subjective and not as reliable (or accurate) as objective measures of PA or cardiorespiratory fitness in several human studies (Erickson et al., 2012, 2013). Consequently, our study may underestimate the influence of PA on brain structure. It is also possible that self report of physical activity is biased by the cognitive impairment of those with memory disorders, although persons with AD and MCI in our study were generally early in their disease course and only 10% had been diagnosed at the time of this human study (Raji et al., 2010b).

One intriguing question our study raises is this: does a critical treatment window exist during the lifespan in which physical activity and reduced BMI will be most effective as preventive strategies for dementia? One future approach would be to study a proximal load of PA close to the collection of imaging biomarkers. Future directions may focus on other forms of PA such as resistance training, as recent human study suggests this specific type of exercise may also have brain benefits (Nagamatsu et al., 2012).

The strengths of our study include the fact that this is one of the largest voxel-based studies of human brain aging. The multisite community cohort structure allows for a wider generalization of our findings. In addition, the availability of the longitudinal lifestyle variables and the use of a sensitive morphometric analysis technique (i.e., TBM) are strengths of our project. Future intervention research is needed to determine whether PA and reduced BMI can improve brain health across the spectrum of normal aging and AD.

Disclosure statement

The authors have no potential financial or personal conflicts of interest including relationships with other people or organizations within 3 years of beginning the work submitted that could inappropriately influence this work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2014.05.036.

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