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Sonum Tharwani March 30, 2018

Physical Activity May be a Modifiable Risk Factor for Cognitive Decline in African Americans and Caucasians at High Risk for Developing Alzheimer's Disease

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An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Sciences with Honors

Department of Neuroscience and Behavioral Biology

2018

Abstract

Physical Activity may be a Modifiable Risk Factor for Cognitive Decline in African Americans and Caucasians at High Risk for Developing Alzheimer's Disease

By Sonum Tharwani

Significance: More than 5 million people in the U.S. are currently living with Alzheimer's Disease (AD) and that will triple by 2050. Individuals with a parental history of AD are more likely to become afflicted with AD than those without. African Americans (AAs) are 64 percent more likely to develop AD than Caucasians (CCs), which increases the public health burden of AD in the US as the non-Caucasian population becomes the majority. In an effort to prevent AD, we must identify high risk individuals and implement economically feasible and modifiable treatment regimens. Physical activity levels (PA) during midlife (ages 40-65) may have the potential to reduce the risk of developing AD.

Objective: To investigate the potential relationship between PA, cognition, and AD brain biomarkers (Aβ and tau) in middle-aged individuals at high risk for AD, due to age, race, and a parental history of AD.

Design: Observational study.

Participants: Study included 61 cognitively normal subjects (M=59.6 +/- 6.9 years), comprised of 27 African Americans (M= 60.3 +/- 8.1 years) and 34 Caucasians (M=59.06 +/- 6.0 years), with a parental history of AD.

Measures: CHAMPS Activities Questionnaire for Older Adults to measure PA, comprehensive cognitive testing battery, and AD brain biomarkers in cerebrospinal fluid (Aβ and tau).

Results: Cognitive test performance differed between AAs and CCs, such that CCs outperformed AAs on 9 out of 10 assessments. Increased PA frequency were related to better scores on tests of executive function and working memory in AAs. Higher PA caloric expenditure associated with better executive function in CCs.

Conclusion: Physical activity is a safe, affordable, and modifiable risk factor. Current research shows that even late life PA can result in favorable health outcomes. It is possible that the increased prevalence of AD in AAs can be reduced through an active lifestyle. Further research should delineate the modality, intensity, and duration of PA needed to maximize benefits on cognition and reduce AD risk in AAs and CCs. Alternate mechanisms by which PA may directly benefit brain health, such as inflammation and improved cerebral blood flow, should also be considered.

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Acknowledgements

This work would not be possible without the financial support of the Scholarly Inquiry Research Grant provided by Emory University.

I am especially indebted to Dr. Whitney Wharton for being supportive of my career goals and for working actively to provide me with the resources to pursue those goals. Additionally, I would like to thank her for her encouragement and endless support. The knowledge and wisdom she has imparted upon me has been invaluable and of great help throughout my project.

I would like to thank the laboratory's clinical research coordinators, Danielle D. Verble and Hannah Pak, for providing me with extensive personal and professional guidance as well as assisting with subject recruitment and data collection.

I would like to thank Dr. Hu for his demonstration of statistical testing.

I would like to thank my committee members, Dr. Leah Roesch and Dr. Myra Woodworth-Hobbs, for providing their time, patience, and intellectual contribution to my development as a scientist and the completion of this thesis.

Lastly, I am grateful to Alexandra Nutaitis, Alexandra Brown, Ryan Shin, Kayla Hamilton, and all of the other people with whom I have had the pleasure to work with during this project and in the laboratory during the last three years.

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Significance

Alzheimer's disease (AD) is an irreversible, progressive brain disorder that has emerged as one of the biggest threats to public health and personal well-being among older adults (Xu & Qiu, 2018). Accounting for 60-80% of all dementia cases, AD is one of the most alarming age-related diseases due to the loss of personal identity and an increased dependence on caregivers (CGs) (alz.org, 2017; Hinton and Levkoff, 1999). More than 5 million people in the U.S. are currently living with AD and by mid-century this prevalence is expected to triple (alz.org, 2017). In 2017, the costs of caring for those with AD summated to 259 billion with nearly one in every five Medicare dollars spent on the disease (alz.org, 2017). Also, in comparison to CGs of those without dementia, twice as many CGs of those with dementia report that their health has deteriorated due to care responsibilities (alz.org, 2017). Clearly, AD is a source of substantial financial and emotional strain for both patients and their loved ones. Disease-modifying treatments have been unsuccessful, prompting investigation of lifestyle factors (e.g. diet, exercise, smoking, cognitive stimulation) and their potential influence on cognitive health and disease prevention (Flicker, 2010).

Introduction

Extensive research demonstrates that physical activity (PA) has neuroprotective effects on cognitive decline (Cass, 2017). Aerobic PA may have particular cognitive benefits and a salutary physiological influence on brain health (Ahlskog et al., 2011). Encouraging data from animal models has directed human studies to investigate the potential effects of PA on neural systems involved in learning and memory. For instance, PA up-regulates the release of neurotrophins, particularly brain-derived neurotrophic factor (BDNF) and vascular endothelial

growth factor (VEGF) (Piepmeier and Etnier, 2015; Cotman and Berchtold, 2007). Increased BDNF in plasma among older adults was associated with hippocampal volume and spatial memory (Erickson et al., 2010). VEGF levels correlate with improved cognition, yet individuals who have AD are known to express decreased levels of this growth factor (Tang et al., 2013). Lastly, research has shown that increased aerobic activity reduces gray matter loss in aging humans, regionally specific to areas that support executive function and memory function. (i.e. prefrontal cortex and hippocampus) (Colcombe et al., 2003; Erickson et al., 2011).

Epidemiological studies have also addressed the impact of PA on AD. Results revealed that high levels of PA during midlife is associated with reduced risk of AD later in life, while an inactive lifestyle increases the risk of developing AD by 250% (Laurin et al., 2001; Friedland et al., 2001). Midlife (40-65 years of age) proves to be a critical time for lifestyle intervention, since several vascular and inflammatory risk factors impact the brain and body during this time (Whitmer et al., 2005; Hughes and Ganguli, 2009). Also, AD specific brain pathology (i.e. Aβ plaques and neurofibrillary tangles of tau protein) has shown to manifest approximately 15 years before AD symptom onset (Braak et al., 2011; Bateman et al., 2012).

Since PA has shown potential for reducing AD risk, researchers have sought to determine the extent to which PA may modulate the deposition of Aβ plaque load and neurofibrillary tangle count in the brain (Serrano-Pozo et al., 2011). Evolving evidence continues to associate PA with reduced Aβ and tau burden, as indicated by increased levels of Aβ and decreased levels of tau in cerebrospinal fluid (CSF) (Brown et al., 2013; Stillman et al, 2017; Liang et al., 2010; Law et al., 2018). In a cross-sectional study of middle-aged participants at high risk for AD, a physically active lifestyle attenuated age-related Aβ deposition (Okonkwo et al., 2014).

As a modifiable risk factor, PA routines can be incorporated into one's daily routine without detrimental side effects associated with medications. According to the 2008 U.S. Physical Activity Guidelines (PAG), at least 150 minutes of moderate to vigorous PA per week is required for health benefits in adults (U.S. Department of Health and Human Services, 2008). Although the older population faces many barriers to exercise—such as poor balance, illness, fatigue, fear of injury—strategies have been developed to overcome these issues and optimize the benefits of PA in this population (Nied and Franklin, 2002). However, nearly one-third of the global adult population does not meet the PAG, and adults aged 65 and older exhibit even lower levels of PA (Hallal et al., 2012). Individuals at higher risk for AD show more sedentary behavior than those not at risk, thereby decreasing their adherence to healthy levels of PA further (Loprinzi, 2015).

African Americans (AAs) are 64% more likely to develop AD than non-Hispanic whites, or Caucasians (CCs), and individuals with a parental history of AD are ten times more likely to become afflicted with the disease (Steenland et al., 2015; alz.org, 2018). Notably, AAs are also more likely than CCs to have multiple members with dementia in the same family (Green et al., 2002). It is possible that a large component of the increased prevalence of AD in AAs may be a result of modifiable risk factors including PA. While researchers have reported the impact of PA on cognitive function, there is limited data investigating similar associations in racial and ethnic minority populations in the U.S. (Barnes and Bennett, 2014). To assess the influence of PA as a modifiable risk factor for cognitive decline in a high-risk cohort, we investigated the relationship between PA, AD brain biomarkers (Aβ plaques, tau), and cognition in cognitively normal, middle-aged AAs and CCs with a parental history of AD.

Methods

Study Sample: Sixty-one subjects (M=59.6 +/- 6.9 years), comprised of 27 African Americans (M= 60.3 +/- 8.1 years) and 34 Caucasians (M=59.06 +/- 6.0 years), took part in this pilot study. Participants were recruited from Emory's Alzheimer's Disease Research Center (ADRC) database, physician referrals from Emory Cognitive Neurology Clinics, community events, and conferences. Individuals enrolled meet the inclusion criteria for two NIH-funded clinical trials—ASCEND (Association between Cardiovascular Risk and Preclinical Alzheimer's Disease Pathology) or HEART (Health Evaluation in African Americans using RAS Therapy) (PI: Wharton). Cognitive normalcy was based on 1) the absence of subjective memory complaint, 2) no treatment for MCI or AD, and 3) absence of any significant neurologic disease or psychiatric condition that may impair cognition (i.e. Parkinson's disease, multi-infarct dementia, Lewy body dementia, frontotemporal dementia, Huntington's disease). Parental AD diagnosis was verified using a validated Dementia Questionnaire and medical records when available. The physical activity substudy was funded by Emory University's Scholarly Inquiry Research Grant (SIRE) (PI: Tharwani), thereby allowing for the CHAMPS Activities questionnaire to be emailed to all ASCEND and HEART participants via a secure, IRB approved web link. Respondents were compensated with a $10 Amazon electronic gift card for completing the CHAMPS questionnaire.

Inclusion Criteria
Age over 45 years
Cognitively Normal
Parent with Alzheimer's Disease
*African American (Only for HEART)

Physical Activity Assessment: Physical activity was assessed via the self-report CHAMPS Activities Questionnaire for Older Adults (Stewart et al., 2001). Examples of activities in the CHAMPS Questionnaire include: dancing, golfing, tennis, skating, working around the house, gardening, jogging, walking to do errands, leisure walking, swimming, yoga, riding a bicycle, and practicing sports. The questionnaire consists of 41 questions and takes approximately 10-15 minutes to complete. Subjects enrolled in ASCEND and HEART were sent an individual web link to the survey through RedCap, a password protected secure online database. This questionnaire is reliable, valid, and sensitive for changes in PA over time in older adults (Stewart et al., 2001). The measures obtained from the CHAMPS questionnaire are recorded for one week of PA and include: total caloric expenditure, total caloric expenditure of moderate-intensity activities, frequency of all physical activities, and frequency of moderate-intensity activities. Caloric expenditure took into consideration participant weight, total duration of PA participation per week, and adjusted MET values for activities in an older population. Further details regarding calculations can be found from the instructions provided in Stewart et al. (2001).

AD Brain Biomarkers (Tau and Aβ): Twenty-two mL CSF samples were collected at three time points (Baseline, Year 1, and Year 2) for ASCEND participants and two time points (Baseline, 8 month) for HEART participants. The CSF measures from Baseline study visits were included in this study. CSF Aβ, total tau (T-tau), and phosphorylated tau (P-tau) concentrations are determined using sandwich ELISA. CSF Aβ and T-tau was assayed by Dr. Henrik Zetterberg, an expert in CSF AD biomarkers in Sweden, using XMap technology.

Neuropsychological Testing: Cognitive testing was evaluated using a one hour comprehensive testing battery known to reliably and validly assess cognition in clinical trials enrolling middle-aged individuals with a parental history of AD. The cognitive testing is administered on paper and conducted by trained research personnel in the Wharton laboratory. The thirteen neuropsychological tests include: Montreal Cognitive Assessment (MOCA), Benson Figure Copy and Recall, Buschke, Multilingual Naming Test (MINT), Mental Rotation Test (MRT), Trail Making Test A and B, and Digit-Span Forward and Backwards. These tests represent specific cognitive domains reportedly affected in early AD including: global cognition (MOCA), visuomotor skills (Benson Figure), verbal memory (Buschke), language and verbal fluency (MINT), visuospatial ability (Mental Rotation Test), working memory (Digit Span) and executive function (Trail-Making Test A and B) (Nasreddine et al., 2005; Possin et al., 2011; Buschke, 1973; Spreen and Strauss, 1998; Vandenberg and Kuse, 1978; Dodrill, 1978; Stroop et al., 1935).

Data Analysis: The primary study objective was to evaluate the potential relationship between cognitive function and PA in individuals at high risk for developing AD. Questionnaire responses, cognitive test results, and Aβ and tau levels were stored in REDCap. Researchers utilized IBM SPSS Statistics Version 25 to analyze the data. All tests were two-tailed and used a significance of 0.05. To test for group differences between AAs and CCs in demographics, PA, and cognitive performance, we conducted Independent-Sample-T-tests for equality of means with equal variance assumed. Correlations between cognitive performance and PA were assessed using Pearson's r partial correlations controlling for age, education, and sex. Pearson's r correlations between AD brain biomarkers (Aβ and tau) and PA were controlled for age and sex.

Results

Table 1 shows demographic data for 27 AA and 34 CC subjects. Our high-risk sample of individuals with a parental history of AD is middle aged (M= 59.58 +/- 6.90), mostly female (68.9%), and highly educated (85.2% received graduate or postgraduate education). AAs and CCs did not differ on age, education, smoking, and fatigue. More AA females than CC females were included in the study and AAs reported significant less income compared to CCs.

Table 2 shows the results of the vascular measures by race. While AAs and CCs did not differ on blood pressure or nocturnal dipping patterns, AAs have a significantly higher BMI than CCs.

Table 3 describes the results of an independent samples t-test reporting racial differences on cognitive testing, Scores confirmed that participants were cognitively normal. Caucasians outperformed AAs on 9 out of the 10 assessments. Tests included domains of global cognition, verbal memory, language, and executive function ($p<.05$) and modestly outperform AAs on a test of working memory ($p=.073$).

Table 4 shows Pearson's r partial correlations between PA and cognition by race controlling for age, education, and sex. The PA domains measured include: caloric expenditure of all PA per week, caloric expenditure of moderate intensity PA per week, frequency of all PA per week, and frequency of moderate intensity PA per week. In AAs, better scores in domains of executive function ($p=.036$) and working memory ($p=.046$) correlated with more frequent moderate-intensity PA. Trends were found with better executive function and higher PA caloric expenditure, moderate intensity PA caloric expenditure and increased PA frequency ($p=.055$, $p=.097$, $p=.057$). CCs showed correlations between better executive function and increased PA

caloric expenditure (p=.042). In addition, trends were found with better executive function and both moderate intensity PA caloric expenditure and PA frequency (p=.056, p=.082).

Table 5 reports means of self-report PA from the CHAMPS Activities Questionnaire for Older Adults, by race. Higher frequency and caloric expenditure values indicate higher activity level. Stewart et al. (2001) utilized the CHAMPS questionnaire in adults (M= 72.9 +/- 4.8) to define PA caloric expenditure and frequency levels for 3 cohorts: sedentary, somewhat active, and already active. The already active cohort reports a mean of 3386 ± 219 and 2328 ± 181 calories for PA caloric expenditure and moderate intensity PA caloric expenditure, respectively. The PA frequency and moderate intensity PA frequency means were 17.33 ± .9 and 8.81 ± .5 times per week, respectively. Although the sample in Stewart et al. (2001) is slightly older, we can use it as a reference to indicate high or low levels of activity. In our study, AAs exceed these means for all PA measures and CCs were marginally below for 3 of the 4 measures. Overall, self-reported PA measures indicate higher than average PA participation in both races.

Table 6 shows that there are no significant correlations between PA and AD brain biomarkers, specifically Aβ-42, T-tau, and P-tau, in AAs and CCs.

Discussion

This study investigated the influence of physical activity on cognition in individuals at high risk for AD. To our knowledge, results are novel given the unique cohort of healthy, racially diverse, middle-aged individuals with a parental history of AD. Our results show significant racial differences between AAs and CCs on cognitive measures of global cognition, verbal memory, language, and executive function, all of which are affected in early AD (Silverberg et al., 2011). These cognitive disparities cannot be explained by age, education, smoking status, or fatigue. Vascular risk factors were comparable between AAs and CCs, in contrast to previous epidemiological findings of a higher burden in AAs (Egan et al., 2010).

Results show positive correlations between PA and cognition with significant relationships between PA and executive function in both racial groups. Increased PA frequency was related to better scores on tests of executive function in AAs. Higher PA caloric expenditure was associated with better executive function in CCs. However, AAs demonstrated an additional benefit of PA on working memory, such that more frequent moderate intensity PA per week were related to cognitive benefits. Our findings align with previous studies demonstrating PA as a modifiable risk factor that positively influences cognitive performance in both rodents and humans (Voss et al., 2011). It is important to note that the relationship between PA and cognition was observed with PA frequency in AAs and PA caloric expenditure in CCs. In this study, PA caloric expenditure is calculated using both the duration and intensity of PA (i.e. METS). Intense exercise induces oxidative stress, and AAs are known to have higher levels of oxidative stress than CCs; therefore, it is critical to understand the appropriate exercise levels needed to prevent an exaggerated oxidative stress response in AAs (Hozawa et al., 2007; Feairheller et al., 2011).

Future studies should investigate whether frequent PA throughout the week produces more benefits in one population, such as AAs, and whether intensity of PA bouts benefits another.

Although PA correlated with executive function in both AAs and CCs, AAs demonstrated an additional benefit of PA on working memory. This may suggest the presence of a gene-environment interaction. The e4 allele of the APOE gene has been identified as a significant risk factor for AD, yet e4 alone is neither necessary nor sufficient for the development of dementia (Deeny et al., 2008). Considering this allele is consistently found to be higher in the AA population than CCs, it is possible that PA has increased benefits on cognition in e4+ individuals than non-e4 carriers (Logue et al., 2011; Rovio et al., 2005). In addition, Deeny et al. (2008) report a decreased reaction time on a working memory test with increased level of PA only in e4+ carriers, therefore highlighting the potential for PA to have specific cognitive effects. In addition to APOE, a common single nucleotide polymorphism (SNP) has been identified in the BDNF gene that is associated with increased susceptibility to cognitive deficits (Egan et al., 2003; Nascimento et al., 2015). In adult mice, the genotypes of the BDNF polymorphism moderate the beneficial neuroplasticity effects induced by physical exercise (Ieraci et al., 2016). Taken together, these studies stress the importance of considering genetic factors, such as racial differences in allele frequencies, when investigating the differential influence of PA on cognition.

AAs and CCs reported similar PA frequencies and PA caloric expenditure per week. In fact, AAs report a slightly higher caloric expenditure per week than CCs, albeit not significant. These findings are interesting and unexpected when compared to the national PA participation. In year 2015, only 16.9% of the middle-aged U.S. population (ages 55-64) met the 2008 Federal Physical Activity recommendations of 500-1,000 MET minutes per week, or 150 minutes of

moderate-intensity activity per week (National Center for Health Statistics, 2017; Nelson et al., 2007). In our sample, conversions from caloric expenditure to MET minutes revealed approximately 74% of our overall sample and 81.5% and 66.7% of AAs and CCs, respectively, meeting or exceeding federal PA guidelines. It is possible, as research participants with a parental history of AD, these individuals view exercise as a way to prevent the onset of future disease (Kirchhoff et al., 2008).

In our study, higher levels of PA in AAs, especially with a female majority, is of particular interest because current literature points to 66% of AA women failing to meet PA guidelines in 2014 (Joseph et al., 2015). The AA women population has the highest prevalence of physical inactivity than any other race and sex demographic group (Joseph et al., 2015). Increased prevalence of inactivity could be explained by the barriers to PA engagement identified specifically in AAs such as physical appearance concerns, lack of social support or a workout partner, and caregiving responsibilities, all of which have been reported to be less applicable to CCs. (Kirchhoff et al., 2008; King et al., 2000). This may suggest that AAs in this study overcame barriers to engage in a healthy PA routine. Although not included in the PA analysis of the CHAMPS Activities questionnaire as a scored question, a distractor question regarding church attendance is included (Stewart et al., 2001). Eighty-five percent of AAs, or 23 of the 27 participants, reported church attendance while only 60% of CCs, or 20 of the 34 participants, attended church (p=.043). Furthermore, AAs were found to spend more time at church per week than CCs. A growing body of research indicates that AAs tend to receive more support from their fellow church members than do older whites (Taylor et al., 2004). Hence, a faith-based intervention, as such, may serve as social support, linking one to a helping

community that shares information and provides resources for self-care practices such as a workout partner (Pickard et al., 2011; Sharma et al., 2005)

Lastly, we found that PA levels did not correlate with Aβ and tau protein levels in either racial group. Previous literature in humans has shown PA to decrease Aβ and tau deposition in the brain (Okonkwo et al., 2014). However, most of the studies have used enforced exercise regimens in which mice were required to run on a wheel. Therefore, certain translational limitations of rodent models (i.e. different temporal profiles of plaque deposition) may explain our conflicting results (Elder et al., 2010). An observational study by Liang et al (2010) found active individuals who met American Heart Association (AHA) exercise guidelines (i.e. 30 minutes of moderate exercise 5 days/week) to have significantly higher Aβ-42 levels, or a reduced Aβ burden, than individuals who did not meet guidelines. Although duration of reported PA levels can not be confirmed in our cohort due to limitations of self-report, post-hoc analyses show only 8 of our 61 participants to report activity levels under AHA guidelines. Hence, since our cohort reports high levels of PA, we were unable to compare a large enough sample size of individuals who were active versus inactive. Furthermore, the questionnaire utilized in the Liang et al (2010) study asked for only walking, running, and jogging activity. It is possible that the CHAMPS Activities questionnaire introduces activities that are less planned and more inconsistent (i.e. light work around the house). Hence, a PA measure that focuses on exercise rather than all PA may be needed to reproduce similar results.

Increased PA frequency in AAs and PA caloric expenditure in CCs correlated with better cognitive outcomes, however PA did not associate with Aβ or tau levels. It is possible that the mechanisms linking PA's benefits on cognition may be a different AD related brain change (vs Aβ and tau pathology), such as increased cerebral blood flow (CBF). Aging, one of the primary

risk factors of AD, has been associated with progressive decline in CBF (Ogoh et al., 2014). Exercise-induced improvements in cognitive function have been associated with improved CBF to the hippocampus (Pereira et al., 2007). This finding is particularly important considering the hippocampus is involved with memory processing and a loss of memory is one of the first symptoms reported by AD patients (Jahn et al., 2013). Overall, evidence suggests that aerobic exercise may reverse aging- and AD-related changes in CBF (Baker et al., 2011; Querido and Sheel, 2007). Therefore, improved brain blood flow may be a mechanism by which individuals reap benefits from an active lifestyle.

A second potential mechanism could also be reduced inflammation in the peripheral and central nervous system (Cotman and Berchtold, 2007). Several studies in the elderly (>60 years) have demonstrated PA-induced reduction of inflammatory markers, primarily C-reactive protein and interleukin-6 (Woods et al., 2012). In addition, physical inactivity has been associated with low-grade systemic inflammation in healthy subjects (Peterson and Pederson, 2005). Systemic inflammation exacerbates CNS inflammation and is associated with cognitive decline (Perry, 2004). Therefore, the anti-inflammatory effect of exercise may exert positive effects on cognition and subsequently reduce the risk for AD (Corey and Rogers, 2012).

Notably, racial differences have been found on baseline levels of inflammatory markers (CRP, IL-6 and tumor necrosis factor-a), with higher values in AAs (Paalani et al., 2011). Goldstein et al. (2001) found a significant interaction of interleukin-8 (IL-8), another inflammatory marker, and race on cognitive processing, such that as levels of IL-8 increased, AA demonstrated slower reaction times on visuomotor set shifting tasks. These findings propose inflammation as a potential mechanism for understanding how PA may affect cognition differently in AAs than CCs.

Notable strengths in our study includes a comprehensive battery of cognitive tests, a middle aged, racially diverse cohort, and a measure of PA that is racially sensitive and applicable to older populations (Reniscow et al., 2003; Stewart et al., 2001). It is important to note that AAs had a significantly higher BMI than CCs in our study; however, several of the risk factors associated with higher BMIs, such as diabetes and hypertension, are similar between racial groups. Further, Stewart et al. (2001) report no association between BMI and the exercise measures reported on the CHAMPS Activities Questionnaire. Thus, several confounding variables were eliminated to investigate the influence of PA on cognition. One limitation includes self reported exercise, though the validated CHAMPS Q was designed to address respondent's propensity to overstate exercise duration and frequency. This was achieved by including unscored questions concerning other rewarding activities such as doing volunteer work, attending church, and visiting friends or family.

In summary, results of this study stress the need for further research investigating the potential of PA as a safe, affordable and accessible lifestyle prescription for disease prevention in individuals at high risk for AD. Recent census data shows increasing racial and ethnic diversity within the elderly population of the United States (Bureau UC, 2000). Hence, further investigations of modifiable risk factors that target high-risk groups is essential. Results showed that increased levels of PA in AAs significantly benefit tests of working memory and executive function, thus future studies should continue to delineate the type, duration, and intensity of exercise needed to maximize the benefits of PA in this population. Finally, although animal research has outlined many of the possible mechanisms by which PA exerts its effects on brain function, we know very little about the mechanisms by which PA may reduce the risk for AD in

human populations. Future research on PA would benefit from including these measures to clarify the brain mechanisms with functional and diagnostic outcomes in people at risk for AD.

Table 1: Participant Demographics. (AAs= African Americans, CCs = Caucasians)

	AA (N=27)	CC (N=34)
Age	60.33 ±8.08	59.06 ± 5.97
Gender (% Female) *	85.2%	55.9%
College graduate or higher level of education	92.6%	79.5%
Income **		
Income $39,000 or less	18.5%	11.8%
Income $40,000-$79,000	51.8%	23.5%
Income $80,000 or more	29.6%	64.7%
Report having smoked	26.9%	32.4%
Report having smoked in the last month	3.7%	5.9%
Reported feeling tired or having little energy several days of the week or more	36.0%	32.3%

*$p < 0.05$
** $p < 0.001$

Table 2: Cardiovascular Data for All Participants. (AAs= African Americans, CCs = Caucasians)

	AA (N=27)	CC (N=34)
Body Mass Index (BMI)*	29.19 ± 4.85	25.56 ± 4.88
Systolic (mmHg)	127.04 ± 12.87	125.25 ±11.26
Diastolic (mmHg)	78.04 ± 7.36	76.63 ± 7.99
% Nocturnal Dipping	6.60 ± 5.87	9.00 ± 5.68
Diabetes	3.7%	0%

*$p < 0.05$

Table 3: Cognitive Data for All Participants. (AAs= African Americans, CCs = Caucasians)

	AA	CC
Global cognition*	25.91 ± 2.15*	27.0 ± 2.33*
Visuospatial Memory	11.59 ± 2.96	10.96 ± 2.88
Verbal Memory*	5.67 ± 3.32*	7.09 ± 2.82*
Language and Verbal Fluency*	29.25 ± 2.21*	30.48 ± 2.55*
Visuospatial Abilities	16.31 ± 4.78	17.57 ± 5.89
Working Memory (Forwards) †	9.95 ± 2.37 †	10.72 ± 2.38 †
Working Memory (Backwards)	6.22 ± 2.16	6.70 ± 2.90
Executive Function (Test A)	34.60 ± 10.76	29.61 ± 8.55
Executive Function (Test B)*	120.32 ± 102.45*	81.9 ± 42.56*
Executive Function (Test B Errors)	.77 ± 1.40	.67 ± 1.23

†<0.1
*$p < 0.05$

Table 4: Pearson's r correlations between cognition and physical activity. All correlations controlled for age, education, and sex. (AAs= African Americans, CCs = Caucasians)

AA=27 CC=34	Caloric Expenditure	Caloric Expenditure (Moderate Intensity)	Frequency	Frequency (Moderate Intensity)
Executive Function (Test A)				
AA	-.246	-.278	.063	.05
CC	***-.395**	† -.372	† -.341	-.174
Executive Function (Test B Errors)				
AA	† -.459	† -.403	† -.453	***-.497**
CC	.041	-.027	.309	-.013
Working Memory (Forward)				
AA	-.171	-.224	.27	***.477**
CC	.204	.27	-.047	.111

†<0.1
*$p < 0.05$

Table 5: Self-reported physical activity values from CHAMPS Activities Questionnaire for Older Adults. Caloric expenditure values represent the number of calories expended per week from physical activity. Frequency measures represent the total number of physical activity bouts per week. (AAs= African Americans, CCs = Caucasians)

	AA (N=27)	CC (N=34)
Caloric Expenditure	4534.99 ± 3623.50	3359. 52 ± 2431.03
Caloric Expenditure (Moderate Intensity)	3015.90 ± 2825.90	2145.92 ± 2104.96
Frequency	18.78 ± 10.25	20.40 ± 12.64
Frequency (Moderate Intensity)	8.96 ± 6.19	8.57 ± 7.32

Table 6: Pearson's r correlations between AD Brain Biomarkers and physical activity. Caloric expenditure values represent the number of calories expended per week from physical activity. Frequency measures represent the total number of physical activity bouts per week. All correlations controlled for age and sex. (AAs= African Americans, CCs = Caucasians)

AA=10 CC=27	Caloric Expenditure	Caloric Expenditure (Moderate Intensity)	Frequency	Frequency (Moderate Intensity)
Aβ-42				
AA	.229	.239	.303	.309
CC	-.075	.011	-.197	-.028
T-tau				
AA	.221	.209	.141	.214
CC	-.059	-.099	-.157	-.077
P-tau				
AA	.230	.218	.203	.292
CC	-.056	-.085	-.142	-.044

References

Ahlskog, J.E., Geda, Y.E., Graff-Radford, N.R., & Perterson, R.C. (2011). Physical exercise as a preventative or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc, 86,* 876-884.

alz.org (2017). 2017 Alzheimer's Disease Facts and Figures. Retrieved from: https://www.alz.org/ri/documents/facts2017_report(1).pdf

alz.org (2018). African-Americans and Alzheimer's. Retrieved from: https://www.alz.org/africanamerican/

Baker, L.D., Frank, L.L., Foster-Schubert, K., Green, P.S., Wilkinson, C.W., McTiernan, A.,…Craft, S. (2011). Aerobic Exercise improves cognition for older adults with glucose intolerance, A risk factor for Alzheimer's Disease. *J Alzheimers Dis, 22,* 569-579.

Barnes, L.L., & Bennett, D.A. (2014). Alzheimer's Disease in African Americans: Risk Factors and Challenges for the Future. *Health Aff*, *33,* 580-586.

Bateman, C., Xiong, T.L.S., Benzinger, A.M., Fagan, A., Buckles, V., Oliver, A.,…Morris, J.C. et al. (2012). Clinical and biomarker changes in dominantly inherited Alzheimer's Disease. *N Engl J Med*, *367,* 795-804.

Braak, H., Thal, D.R., Ghebremedhin, E., & Tredici, K.D. (2011). Stages of the pathologic process in Alzheimer Disease: Age categories from 1 to 100 years. *J Neuropathol Exp Neurol, 70,* 960-969.

Brown, B.M., Peiffer, J.J., Taddei, K., Lui, J.K., Laws, S.M., Gupta, V.B.,…Martins, R.N. (2013). Physical activity and amyloid-B plasma and brain levels: results from the Australian Imaging, Biomarkers and Lifestyle Study of Ageing. *Mol Psychiatry*, *18,* 875-881.

Bureau UC. Census 2000. US Census Bureau; Washington, D.C.

Buschke, H. (1973). Selective reminding for analysis of memory and learning. *J Verb Learn Verb Behav, 12, 543-550.*

Cass, S.P. (2017). Alzheimer's Disease and Exercise: A Literature Review. *Curr Sports Med Rep*, *16,* 19-22.

Colcombe, S.J., Erickson, K.I., Raz, N., Webb, A.G., Cohen, N.J. McAuley, E., & Kramer, A.F. (2003). Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci*, *58,* 176-180.

Coray, T.W. & Rogers, J. (2012). Inflammation in Alzheimer Disease-A Brief Review of the Basic Science and Clinical Litearture. *Cold Spring Harb Perspect Med*, *2,* a006346.

Cotman, C.W., Berchtold, N.C., & Christie, L.A. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci*, *30,* 462-472.

Deeny, S.P., Poeppel, D., Zimmerman, J.B., Roth, S.M., Brandauer, J., Witkowski, S.,…(2008). Exercise, APOE, and working memory: MEG and behavioral evidence for benefit of exercise in e4 carriers. *Biol Psychol, 78,* 179-187.

Dodrill, C. (1978). A neuropsychological battery for epilepsy. *Epilepsia*, *19*, 611-623.

Egan, M.F., Kojima, M., Callicott, J.H., Holdberg, T.E., Kolachana, B.S., Bertolino,A…Weinberger, D.R. (2003). The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell*, *112,* 257-269.

Egan, B.M., Zhao, Y., & Axon, R.N. (2010). US trends in prevalence, awareness, treament, and control of hypertension, 1988-2008. *JAMA*, *303,* 2043-2050.

Elder, G.A., Gama Sosa, M.A., & Gasperi, R.D. (2010). Trasgenic mouse models of Alzheimer's Disease. *Mt Sinai J Med*, *77,* 69-81.

Erickson, K.I., Prakash, R.S., Voss, M.W., Chaddock, L., Heo, S., McLaren, M.,…Kramer, A.F. (2010). Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. *J Neurosci, 30,* 5368-5375.

Erickson, K.I., Voss, M.W., Prakash, R.S., Basak, C., Szabo, A. Chaddock, K.,… Kramer, A.F. Exercise training increases size of hippocampus and improves memory (2011). *PNAS, 108,* 3017-3022.

Feairheller, D.L., Diaz, K.M., Sturgeon, K.M., Williamson, S.T., & Brown, M.D. (2011). Racial differences in the time-course oxidative stress responses to acute exercise. *J Exerc Physiol Online*, *14,* 49-59.

Flicker, L. (2010). Modifiable lifestyle factors for Alzheimer's Disease. *J Alzheimers Dis, 20,* 803-811.

Friedland, R.P., Fritsch, T., Smyth, K.A., Koss, E., Lerner, A.J. Chen, C.H.,...Debanne, S.M. (2001). Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. *PNAS*, *98,* 3440-3445.

Goldstein, F.C., Zhao, L., Steenland, K., & Levey, A.I. (2001). Inflammation and cognitive functioning in African Americans and Caucasians. *Int J Geriatr Psychiatry, 30,* 934-941.

Green, R.C., Cupples, L.A., Go, R., Benke, K.S., Edeki, T., Griffith, P.A.,…MIRAGE Study Group (2002). Risk of dementia among white and African American relatives of patients with Alzheimer's disease. *JAMA*, *287,* 329-336.

Hallal, P.C., Anderson, L.B., Bull, F.C., Guthold, R., Haskell, W., & Ekelund, U. (2012). Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet, 380,* 247-257.

Hozawa, A., Folsom, A.R., Sharrett, A.R., & Chambless, L.E. (2007). Absolute and attributable risks of cardiovascular disease incidence in relation to optimal and borderline risk factors: comparison of African American with white subjects–atherosclerosis risk in communities study. *Arch Intern Med*, *167*, 573–579.

Hinton, L.W. & Levkoff, S. (1999). Constructing Alzheimer's: Narratives of lost identities, confusion, and Loneliness in Old Age. *Cult. Med. Psychiatry*, *23*, 453-475.

Hughes, T.F., & Ganguli, M. (2009). Modifiable midlife risk factors for late-life cognitive impairment and dementia. *Curr Psychiatry Rev*, *5,* 73-92.

Ieraci, A., Madaio, A., Mallei, A., Lee, F.S., & Popoli, M. (2016). Brain-Derived Neurotrophic Factor Val66Met Human Polymorphism Impairs the Beneficial Exercise-Induced Neurobiological Changes in Mice. *Neuropsychopharmacology, 4*1, 3070-3079.

Joseph, R.P., Ainsworth, B.E., Keller, C., & Dodgson, J.E. (2015). Barriers to physical activity among African American women: An integrative review of the literature. *Women Health*, *55,* 679-699.

King, A.C., Castro, C., Wilcox, S., Eyler, A.A., Sallis, J.F., & Brownson, R.C. (2000). Personal and environmental factors associated with physical inactivity among different racial-ethnic groups of U.S. middle-aged and older-aged women. *Health Pyschol*, *19,* 354-364.

Kirchhoff, A.C., Elliott, L., Schlichting, J.A., & Chin, M.H. (2008). Strategies for physical activity maintenance in African American women. *Am J Health Behav*, *32,* 517-524.

Laurin, D., Verreault, R., Linday, J., Macpherson, K., & Rockwood, K. (2001). Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol*, *58,* 498-504.

Liang, K.Y., Mintun, M.A., Fagan, A.M., Goate, A.M., Bugg, J.M., Holtzman, D.M.,…Head, D. (2010) Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann Neurol*, *68,* 311-318.

Logue, M.W., Schu, M.M, Vardarajan, B.N., Buros J, Green, R.C, Go, R.C.,… Borenstein, D.A. (2011). A comprehensive genetic association study of Alzheimer disease in African Americans. *Arch Neurol*, *68*, 1569–79.

Loprinzi, P.D. (2015). Need for Increased Promotion of Physical Activity Among Adults at Risk for Alzheimer's Disease: A Brief Report. *J Phys Act Health*, *12,* 1601-1604.

Nascimento, C.M., Pereira, J.R., Pires de Andrade, L., Garuffi, M., Ayan, C., Kerr,…Stella, F. (2015). Physical exercise improves peripheral BDNF levels and cognitive functions in mild cognitive impairment elderly with different bdnf Val55Met genotypes. *J Alzheimers Dis*, *43,* 81-91.

Nasreddine, Z.S., Phillips, N.A., Bedirian, V., Charbonneau, S. , Whitehead,V., Collin, I.,…H. Chertkow. (1973). The Montreal Cognitive Assessment, MoCA: a brief screening tool. *J Am Geriatr Soc*, *53,* 695-699.

National Center for Health Statistics. Health, United States, 2016: With Chartbook on Long-Term Trends in Health. Hyattsville, MD. 2017.

Nelson, M. E., Rejeski, W. J., Blair, S. N., Duncan, P. W., Judge, J. O., King, A. C.,…Castaneda- Sceppa, C. (2007). Physical activity and public health in older adults: Recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*, *8*, 1435–1445.

Nied, R.J. & Franklin, B. (2002). Promoting and Prescribing Exercise for the Elderly. *Am Fam Physician, 65,* 419-427.

Ogoh, s., Tsukamoto, H., Hirasawa, A., Hasegawa, H., Hirose, N., & Hashimoto, T. (2014). The effect of changes in cerebral blood flow on cognitive function during exercise. *Physiol Rep*, *2,* e12163.

Okonkwo, O.C., Schultz, S.A., Oh, J.M., Larson, J., Edwards, D., Cook, D.,…Sager, M.A. (2014). Physical activity attenuates age-related biomarker alterations in preclinical AD. *Neurology*, *83,* 1753-1760.

Paalani, M., Lee, J.W., Haddard, E., & Tonstad, S. (2011). Determinants of inflammatory markers in a Bi-ethnic population. *Ethn Dis*, *21,* 142-149.

Pereira A. C., Huddleston D. E., Brickman A. M., Sosunov A. A., Hen R., McKhann G. M.,. Small S. A. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci USA*, *104,* 5638-5643.

Perry, V.H. (2004). The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. *Brain Behav Immun*, *18,* 407-413.

Peterson, A.M. & Pedereson, B.K. (1985). The anti-inflammatory effect of exercise. *J Appl Physiol*, *98,* 1154-1162.

Pickard, J.G., Inoue, M., Chadiha, L.A., & Johnson, S. (2012). The relationship of social support of African American Caregivers Help-Seeking for Emotional problems. *Soc Serv Rev, 85,* 246-265.

Piepmeier, A.T., & Etnier, J.L. (2015). Brain-derived neurotrophic factor (BDNF) as a potential mechanism of the effects of acute exercise on cognitive performance. *J Sport Health Sci, 4,* 14-23.

Possin, K.L., Laluz, V.R., Alcana, O.Z., Miller, B.L., & Kramer, J.H. (2011). Distinct Neuroanatomical Substrates and Cognitive Mechanisms of Figure Copy Performance in Alzheimer's Disease and Behavioral Variant Frontotemporal Dementia. *Neuropsychologia*, *49,* 43-48.

Querido, J.S. & Sheel, A.W. (2007). Regulation of cerebral blood flow during exercise. *Sports Med*, *37,* 765-782.

Resnicow, K., McCarty, F., Blissett, D., Wang, T., Heitzler, C., & Lee, R. E. (2003). Validity of a Modified CHAMPS Physical Activity Questionnaire among African-Americans. *Med Sci Sports Exerc, 35*, 1537-1545.

Rovio, S., Kareholt, I., Helkala, E.L., Viitanen, M., Winblad, B., Tuomilehto, J.,…Kivipelto, M (2005). Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurology*, *4,* 705-711.

Serrano-Pozo, A., Frosch, M.P., Masliah, E., & Hyman, B.T (2011). Neuropathological Alterations in Alzheimer Disease. *Cold Spring Harb Perspect Med*, *1,* a006189.

Sharma, M., Sergent, L., & Stacy, R. (2005). Predictors of leisure-time physical activity among African American women. *Am J Health Behav*, *29,* 352-359.

Silverberg, N.B., Ryna, L.M., Carrillo, M.C., Sperling, R., Peterson, R.C., Psoner, H.B.,…Ferman, T.J. (2013). Assessment of cognition in early dementia. *Alzheimers Dement*, *7,* e60-376.

Spreen, O. & Strauss, E. (1998). *A compendium of neuropsychological tests. 2nd ed.* New York: Oxford University Press.

Steenland, K.,Goldstein, F.C., Levey,A., & Wharton, W. (2015). A Meta-Analysis of Alzheimer's Disease Incidence and Prevalence Comparing African-Americans and Caucasians. *J Alzheimers Dis*, *50*, 71-76.

Stewart, A.L., Mills, K.M., King, A.C., Haskell, W.L., Gillis, D., Ritter, P.L. (2001). CHAMPS Physical Activity Questionnaire for Older Adults: outcomes for interventions. *Med. Sci. Sports Exerc.,33,* 1126-1141.

Stillman, C.M., Lopez, O.L., Becker, J.T., Kuller, L.H., Mehta, P.D., Russell, P.T., & Erickson, K.I. (2017). Physical activity predicts reduced plasma B amyloid in the Cardiovascular Health Study. *Ann Clin Transl Neurol*, *4,* 284-291.

Stroop, J. (1935). Studies of interference in serial verbal reactions. *J Exp Psychology*, *18,* 643-662.

Tang, H., Mao, X., Xie, L., Greenberg, D.A., & Jin, K. (2013). Expression level of vascular endothelial growth factor in hippocampus is associated with cognitive impairment in patients with Alzheimer's disease. *Neruobiol Aging*, *34,* 1412-1415.

Taylor R. J., Chatters L. M., & Levin J. S. (2004) *Religion in the lives of African Americans: Social, psychological, and health perspectives.* Thousand Oaks, CA: Sage Publications.

U.S. Department of Health and Human Services. (2008). Physical activity guidelines advisory committee report. Washington, DC: U.S. Department of Health and Human Services. Retrieved from: https://health.gov/paguidelines/pdf/paguide.pdf

Vandenberg, S.G. & Kuse, A.R. (1978). Mental rotations, a group test of three-dimensional spatial visualization. *Percept Mot Skills*, *47,* 599-604.

Voss, M.W., Nagamatsu, L.S., Liu-Ambrose, T., & Kramer, A.F. (2011). Exercise, brain, and cognition across the life span. *J Appl Physiol*, *111,* 1505-1513.

Whitmer, R.A., Sidney, S., Shelby, J., Johnson, S.C., & Yaffe, K. (2005). Midlife cardiovascular factors and risk of dementia in later life. *Neurology*, *64,* 277-281.

Woods, J.A., Wilund, K.R., Martin, S.A., & Kistler, B.M. (2012). Exercise, Inflammation and Aging. *Aging Dis*, *3,* 130-140.

Xu, J., & Qiu, C. (2018). Worldwide economic costs and societal burden of dementia. *Biomarkers for Preclinical Alzheimer's Disease*, *137,* 3-13.