Short Communication

Physical activity is associated with higher cognitive function among adults at risk for Alzheimer's disease

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A B S T R A C T

Objective: We evaluated the specific association between physical activity and cognitive function among a national sample of the broader U.S. adult population with a family history of Alzheimer's disease.
Methods: Data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) were used to identify 219 older adults, ages 60–85, with a family history of Alzheimer's disease. The Digit Symbol Substitution Test (DSST) was used to assess cognitive function, with physical activity assessed via a validated questionnaire.
Results: In an unadjusted model, older adults, who had at least one blood relative with Alzheimer's disease, had greater cognitive function when meeting MVPA guidelines in comparison to their inactive counterparts (β = 9.6; 95% CI: 4.6–14.7; P = 0.001). After adjustments, results were attenuated, but still statistically significant (8.5; 95% CI: 4.0–13.0; P = 0.001).
Conclusion: In this national sample of individuals at risk for Alzheimer's disease, meeting physical activity guidelines was associated with higher cognitive function.

1. Introduction

Old age is the most substantive predictor of Alzheimer's disease. Following age, family history is the next strongest predictor.[1] Genetic influence is profound among individuals diagnosed with both early-onset (< 60 years old) and late-onset (> 60) Alzheimer's disease. The gene responsible for the genesis of b-amyloid plaques characteristic of Alzheimer's disease, has been identified on chromosome 21 [2,3]. Genome wide association studies (GWASs) have discovered evidence for three critical genes associated with early-onset Alzheimer's disease, and one gene implicated in later onset pathogenesis. In GWASs, nearly one million genetic variants, or single nucleotide polymorphisms, are tested for Alzheimer's risk. Moreover, over 200 mutations, within Amyloid B protein precursor (APP), Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2), have been found to contribute to early-onset pathogenesis.[1] Late-onset Alzheimer's may be influenced by mutation of the apolipoprotein gene (APOE), which is normally a key player in lipid metabolism, but is associated with reduced clearance of b-amyloid proteins in Alzheimer's patients.[4] There is an extensive and growing body of research suggesting genetic mutations span multiple chromosomes.[1] The multitude of genetic biomarkers found in Alzheimer's suggest a cohort with any familial predisposition to the disease may be at a high risk for

cognitive dysfunction. Our specific aim for this study was to assess the plausibility for physical activity to mediate potential cognitive decline among older adults with expected susceptibility to Alzheimer's disease. Such an investigation is important as adults at risk for Alzheimer's disease tend to be less active than their counterparts.[5]

Beyond a genetic predisposition for Alzheimer's Disease, lifestyle risk factors have also been emphasized in previous research, indicating low-education, obesity, depression, hypertension, diabetes, smoking, and sedentary behaviors may also contribute to the development of Alzheimer's.[6] In addition to genetic predisposition to dementia, such environmental and lifestyle factors may also be shared among families, which may also contribute to cognitive dysfunction risk.[7,8] The first trial finding positive statistical significance, with respect to exercise and cognition among older adults having some degree of objective and subjective cognitive dysfunction, suggested the benefits of physical activity may be long-lasting.[9] Other work also demonstrates favorable effects of physical activity on cognitive function.[10,11] Exercise is thought to induce neurological changes within cerebral structures. Angiogenesis, or new blood vessel proliferation, is promoted, as well as neurogenesis, or formation and fortitude of neural networks.[12–14] Additional neurotropic mechanisms moderated by physical activity include increases in brain-derived neurotropic factor, specifically within

the hippocampus, as well as enhanced neurotransmitter activity and global neuroplasticity.[15,16] The formation of Amyloid-b plaques is also reduced with habitual exercise engagement.[16] Thus, there is plausibility for an association between physical activity and cognitive function, among both the broader population and those at risk for Alzheimer's disease. To evaluate this possibility, the specific purpose of this brief report was to evaluate the association between physical activity and cognitive function among older adults with a family history of Alzheimer's disease, which, to our knowledge, has not been evaluated in the literature.

2. Methods

2.1. Design

Data from the 1999–2002 National Health and Nutrition Examination Survey (NHANES) were used. Study procedures were approved by the National Center for Health Statistics ethics review board, with informed consent obtained prior to data collection.

The NHANES is an ongoing survey conducted by the Centers for Disease Control and Prevention that uses a representative sample of non-institutionalized United States civilians selected by a complex, multistage, stratified, clustered probability design. The multistage design consists of 4 stages, including the identification of counties, segments (city blocks), random selection of households within the segments, and random selection of individuals within the households. Further information on NHANES methodology and data collection is available on the NHANES website (http://www.cdc.gov/nchs/nhanes.htm).

2.2. Participants

In the present study, participants who answered *yes* (N = 219) to the following question were considered to have a blood relative with Alzheimer's disease: "*Including living and deceased, were any of your biological, that is, blood relatives including grandparents, parents, brothers, or sisters, ever told by a health professional that they had Alzheimer's disease*?"

2.3. Cognitive function

The Digit Symbol Substitution Test (DSST) was used to assess cognitive function. The DSST, a component of the Wechsler Adult Intelligence Test and a test of visuospatial and motor speed-of-processing, has a considerable executive function component and is frequently used as a sensitive measure of frontal lobe executive functions.[17] The DSST was used to assess participant cognitive function tasks of pairing (each digit 1–9 has a symbol it is associated with) and free recall (allowing participants to draw more figures in the limited time due to remembering pairs). Participants were asked to draw as many symbols as possible that were paired with numbers within 2 min. Following the standard scoring method, one point is given for each correctly drawn and matched symbol, and one point is subtracted for each incorrectly drawn and matched symbol, with a maximum score of 133.

2.4. Physical activity

As described elsewhere,[18] participants were asked open-ended questions about participation in leisure-time physical activity over the past 30 days. Data was coded into 48 activities, including 16 sports-related activities, 14 exercise-related activities, and 18 recreational-related activities. For each of activity, Metabolic Equivalent of Task (MET)-min-month was calculated by multiplying the number of days, by the mean duration, by the respective MET level (MET-min-month = days*duration*MET level). Those at or above 2000 MET-min-month (equivalent to 150 min/week) were defined as physically active.

As described elsewhere,[18] this self-reported physical activity measure has demonstrated evidence of convergent validity by associating with accelerometer-assessed physical activity.

2.5. Covariates

For all models, covariates included: *age*; *gender*; *race-ethnicity* (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other); self-reported current *smoking* (yes/no), *energy intake* (kcals; continuous), physician-diagnosed *hypertension* (yes/no), physician-diagnosed *diabetes* (yes/no), *C-reactive protein* (mg/dL; continuous) and *weight status* (overweight/obese [measured body mass index 25 kg/m^2 or higher] vs. normal weight).

Participants were classified as smokers if they self-reported smoking every day or some days; otherwise, classified as non-smoker. Previous research demonstrates evidence of validity for self-reported smoking assessment.[19] Energy intake (kcal) was assessed from the mobile examination center interview and the follow-up telephone interview, with the average of these values used; if data was missing from the telephone interview, only energy intake obtained from the MEC interview was used. C-reactive protein was assessed from a blood sample, using latex-enhanced nephelometry.

2.6. Analysis

All statistical analyses, computed in Stata (v. 12), accounted for the complex survey design employed in NHANES. A weighted multivariable linear regression model was used to examine the association of meeting physical activity guidelines ($\geq$2000 MET-min-month) and cognitive function (outcome variable). Statistical significance was established as an alpha < 0.05.

3. Results

Characteristics of the study variables are shown in Table 1. In an unadjusted model, participants meeting MVPA guidelines had greater cognitive function when compared to their inactive counterparts (β = 9.6; 95% CI: 4.6–14.7; P = 0.001). After adjustments, results were similar ($\beta_{adjusted}$ = 8.5; 95% CI: 4.0–13.0; P = 0.001).

These findings suggest that meeting MVPA guidelines among those with a family history of Alzheimer's disease (N = 219) had greater cognitive function when compared to those not meeting MVPA guidelines. We also employed a sensitivity analysis evaluating whether meeting MVPA guidelines was associated with cognition among those without a family history of Alzheimer's disease (N = 2107). In this subpopulation, and in the adjusted model, meeting MVPA guidelines was positively associated with cognitive function (β = 5.60; 95% CI: 3.92–7.29; P < 0.001). This association, however, was of a smaller

Table 1
Weighted characteristics of the study variables among a national sample of older adults with a family history of Alzheimer's disease, 1999–2002 NHANES (N = 219).

Variable	Point Estimate	95% CI
DSST, mean	47.7	44.1–51.2
Age, mean years	69.8	68.9–71.1
Energy intake, mean kcals	1781	1678–1884
C-reactive protein, mean mg/dL	0.57	0.41–0.73
% overweight/obese	69.6	
Gender, % Female	58.1	
Race-Ethnicity, %		
Non-Hispanic white	86.4	
Current Smoker, %	11.2	
Meeting MVPA Guidelines, %	37.5	
Hypertensive, %	55.9	
Diabetic, %	11.3	

DSST, Digit Symbol Substitution Test; MVPA, Moderate-to-vigorous physical activity.