Physical Activity and Cognition in the Northern Manhattan Study

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Abstract

Background: To test the hypothesis that leisure time physical activity (PA) is associated with cognitive status. Methods: We assessed cognition using the Mini-Mental Status Examination (MMSE) at enrollment and using the modified Telephone Interview for Cognitive Status (TICS-m) administered annually since 2001 in the Northern Manhattan Study. Baseline measures of leisure time PA were collected via in-person questionnaires. Total PA was categorized into 3 groups based on the metabolic equivalent (MET) score, a composite of total reported intensity and time. We used linear regression models to examine the association of PA with MMSE, and generalized estimating equations for change in TICS-m over time. Results: There were 3,298 stroke-free participants with MMSE data (mean MMSE 26.0 ± 3.8) and 2,279 with TICS-m scores available. Compared to no PA, those with the upper quartile of MET scores had greater baseline MMSE scores (adjusted β = 0.4, p = 0.01) but no association with change in TICS-m over time. There were interactions (p < 0.05) between PA and both insurance and education; compared to no PA, those in the upper quartile of MET scores had a greater MMSE score only among those with Medicaid/no insurance (adjusted β = 0.83, p = 0.0005) and those who did not complete high school (adjusted β = 0.68, p = 0.001). Conclusions: Increased levels of PA were associated with better baseline MMSE, particularly among those with socioeconomic disadvantages, but not with cognitive decline.

Introduction

As the population continues to age, the public health impact of neurodegenerative conditions that present with cognitive impairment or dementia will be particularly high [1]. Several identified risk factors for cognitive impairment have shed light on the pathogenesis of the underlying causes, particularly on a genetic and molecular basis [2]. Physical activity (PA) is one useful target for prevention since individuals at risk may modify their behavior with little potential for adverse events or need for medications, and the added benefit of protection against other diseases of aging.

Several investigators [3–9], and a recent meta-analysis [10], have documented a dose-response association between baseline measures of PA and subsequent cognitive performance or risk of dementia; prior studies have demonstrated a protective effect on only vascular dementia,
or on Alzheimer disease alone [11, 12]. Not all groups, however, have documented an association between cognitive function and PA, particularly among older individuals [6, 13, 14]. Randomized clinical trials of PA programs have shown conflicting results [15–17]. A recent National Institutes of Health State-of-the-Science Conference Statement argued that there was probably a ‘decreased risk’ of cognitive decline with PA, though the data available was ‘low quality’ [18, 19]. A recent Cochrane database review indicated insufficient evidence to support the effect of PA on cognition in older people [20]. Several unanswered questions remain. Few studies have used the same population to examine cognitive performance at baseline and changes over time. The populations studied have also varied, ranging from participants enrolled in middle adulthood to those over the age of 65 years; these studies have rarely enrolled participants with low socioeconomic status or educational achievement, or populations with a large proportion of Hispanics. Furthermore, few studies have examined whether the effect of PA could be modified by sociodemographics. We aimed to examine the independent association between measures of PA and cognitive performance at enrollment and over time and to examine whether baseline factors modified these associations. We hypothesized that total PA would be associated with higher Mini-Mental Status Examination (MMSE) performance at baseline, and a slower decline over repeated measures of the modified Telephone Interview for Cognitive Status (TICS-m).

Methods

Recruitment of the Cohort

The Northern Manhattan Study (NOMAS) is a population-based prospective cohort study designed to evaluate the effects of medical, socioeconomic, and other risk factors on the incidence of stroke and other vascular outcomes in a stroke-free racially/ethnically diverse community cohort. The methods of participant recruitment, evaluation, and follow-up have been previously reported [21]. A total of 3,298 participants were recruited between 1993 and 2001, and participants were followed annually by telephone.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Institutional Review Boards at Columbia University Medical Center and the University of Miami Miller School of Medicine. All participants provided written informed consent.

Cohort Evaluation

Data regarding baseline status and risk factors were collected through interviews of participants. Race-ethnicity was determined by self-identification. Standardized questions were asked regarding the following conditions: hypertension, diabetes, hypercholesterolemia, cigarette smoking, and cardiac conditions. Depression was defined based on a Hamilton Depression Rating Scale score >10 or a history of antidepressant use. Insurance status was defined as having no insurance or Medicaid versus having private insurance or Medicare [22]. Educational achievement was assessed via the self-reported grade at which school was completed and classified as completing high school versus not. We did not collect information regarding household income.

Cognitive performance at baseline was measured using the MMSE in English or a validated Spanish translation administered by trained bilingual research assistants.

Starting in 2001, a mean of 4.7 years after the initial MMSE, the TICS-m was administered to participants during annual telephone follow-up [23]. The TICS-m was designed to assess cognitive performance across multiple domains and includes calculations, delayed 10-word recall, language, and attention. It was administered over the phone at each annual follow-up and required 10 min on average to complete. Incomplete TICS-m tests were not used in the statistical analysis as only the total score is valid.

Assessment of PA

PA was measured using an in-person questionnaire adapted from the National Health Interview Survey of the National Center for Health Statistics at enrollment, when the MMSE was also obtained [24]. This questionnaire records the duration and frequency of various leisure time/recreational activities for the 2 weeks prior to the interview. Participants were then asked if they had engaged in any PA in the preceding 2 weeks, and those who answered ‘no’ were coded as physically inactive. For each activity, the participants were asked the duration of activity and the number of times they engaged in this same activity, and if this level of activity was typical of other weeks. If the duration of activity was less than 10 min, it was coded as ‘no activity’. This questionnaire has been previously reported as reliable and valid in this population [25] and correlates with the body mass index (BMI) and activities of daily living. Objective measures of physical fitness correlate well with PA questionnaires [26].

Questionnaires were correlated with validated compendia of PA that outline the intensity of multiple leisure time PA measured in metabolic equivalents (MET) [27]. Total activity was summarized via the MET score, whereby the MET for each individual activity is multiplied by the frequency per week and the duration. Total energy expenditure was estimated by accounting for the participant’s weight [21].

Statistical Analysis

Baseline demographics by PA categories were compared using the χ2 test for categorical variables and the Kruskal-Wallis test for continuous variables. We fitted: (1) linear regression models with MMSE as the outcome to calculate parameter estimates (β) and 95% CI, and (2) generalized estimating equations with identity link to calculate parameter estimates (β) and 95% CI for change in TICS-m scores over time.

The MET score was our primary exposure of interest and was categorized into 3 groups: (1) no PA (MET score = 0) as the reference (41%), (2) intermediate PA (MET score ≤ 14), and (3) high PA (MET score >14). In secondary analyses, PA was assessed as: (1) any versus none, and (2) total energy expenditure in increments of 500 kcal/week.
Unadjusted and adjusted models were constructed with hypothesized confounders: demographics (age, sex, race-ethnicity, medical insurance, and education) and vascular risk factors (dyslipidemia, current tobacco use, moderate alcohol use, hypertension, depression, and diabetes). We tested for interactions between PA and baseline sociodemographic factors (age, sex, race-ethnicity, education, medical insurance), and stratified models were carried out only when the p value for the interaction term was <0.05. Final models were checked for improvements of fit using the likelihood ratio test (LRT) or the Wald test as appropriate. All analyses were conducted using SAS version 9.2 (Cary, N.C., USA).

Results

Description of the Cohort

The entire NOMAS cohort (n = 3,298) contributed data on PA and MMSE at enrollment. The demographics of the cohort are presented in Table 1. The mean MMSE at baseline was 26 (median 27, interquartile range 24–29), with a lower value among those who did not complete high school (median 25, interquartile range 22–28) versus those who did (median 28, interquartile range 27–29), and those with Medicaid or no insurance (median 26, interquartile range 23–28) compared to their counterparts (median 28, interquartile range 26–29). The TICS-m was obtained annually in 2,279 participants after a mean follow-up of 4.7 years from baseline, and 1,969 participants had at least 2 measures (median 4; minimum 1 and maximum 9). Since we were primarily interested in the effect of PA on cognition in a community-based sample, we excluded 44 participants with stroke prior to the first TICS-m, as well as those with TICS-m administered after a stroke (n = 60). The main...
reason for not obtaining TICS-m scores was death before the first TICS was administered \( (n = 525) \). Participants who did not have a TICS-m study were more likely to be younger, women, and Hispanic compared to white; participants were also less likely to have been smokers or have diabetes or coronary artery disease compared to the rest of the cohort.

### Association of PA and MMSE Using Linear Regression

PA was associated with the MMSE at enrollment (LRT with 2 d.f., \( p = 0.007 \)). In analyses adjusting for age, sex, race-ethnicity, insurance, and education (model 1), and further adjusting for vascular disease risk factors (model 2), those engaging in intermediate and high total PA had higher MMSE scores than those who were physically inactive (table 2). Total activity in kilocalories per week was only associated with MMSE in univariate analyses.

We found evidence that the effect of PA on MMSE differed by sociodemographics: health insurance status (LRT with 2 d.f., \( p \) interaction = 0.03) and educational achievement (LRT with 2 d.f., \( p \) interaction = 0.02). Compared to those who were inactive, those in the high PA group had higher MMSE scores if they had Medicaid or no insurance (adjusted \( \beta = 0.83 \), standard error 0.24, \( p = 0.0005 \)) or if they did not complete high school (adjusted \( \beta = 0.68 \), standard error 0.21, \( p = 0.001 \)). We found no associations among those with Medicare/private insurance or among those who completed high school.

### Association of PA and TICS-m

The results of GEE models examining the association of PA with TICS-m over time are outlined in table 3. In summary, we found that PA was associated with TICS-m at the first measurement, but not with changes over time. In univariate analyses, 1 year of aging was associated with a decline in TICS-m of 0.01 per year (\( p < 0.0001 \)). Compared to those who were inactive, those with high PA had a trend towards greater TICS-m on the first assessment (adjusted \( \beta = 0.55 \) points, \( p = 0.06 \)). We did not find an association between PA and change in TICS-m performance over time (\( \chi^2 \) with 2 d.f., \( p = 0.83 \)). We found no interaction with insurance status, educational attainment, or baseline MMSE.

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Discussion

In our study we found that more leisure time PA was independently associated with better cognitive performance in a cross-sectional manner, but not over time. In further analyses we found that the associations between leisure time PA and performance on the MMSE were apparent only among those of lower socioeconomic status: i.e. those who did not complete high school or who had Medicaid or no insurance. PA remains an attractive target for preventing cognitive decline because it is relatively low risk, does not require medications or medical follow-up, and can be inexpensive. The mechanisms by which PA may influence the MMSE are several and can be categorized by vascular dependent and independent effects. PA modulates the effect and levels of stroke risk factors such as hypertension and diabetes [28], thereby potentially reducing the burden of subclinical cerebrovascular disease. PA may also lower the risk of subclinical cerebrovascular disease independently of its effects on modifiable stroke risk factors [22]. Extensive literature has demonstrated the protective effects of PA on the brain, including neurogenesis, angiogenesis, hippocampal size and levels of brain-derived neurotrophic factor [29], and neuronal connectivity [30]. We did not find an association with cognitive scores over time, counter to other studies [17]. Our results may differ for several reasons. We used the TICS-m as a global cognitive screening measure which may lack sensitivity for subtle changes in domains that have been previously associated with PA, such as cognitive speed and executive function. Further, we do not have information on prevalent or incident dementia in this sample, though the prevalence of dementia was less than 5% in a subsample of patients who underwent a full neuropsychological battery. The mean age of our participants was 71.5 years, which is younger than in most dementia studies, and our average of 4 years of follow-up may not have been long enough to detect an association. Close to one third of the sample died or had an incident cardiovascular event, the latter potentially a competing factor in cognitive decline. In our study we did not collect information on PA in earlier adulthood, which could be more protective [31]. Further, our data are observational and differed from randomized clinical trials of healthy participants, or those with mild cognitive impairment [15] or Alzheimer disease [32, 33]. Interestingly trials of PA in patients with Alzheimer’s disease have shown improvements in functional impairment and depression but not necessarily cognitive impairment [34]. Lastly, it is possible that the influence of PA on cognition in later life is relatively weak, particularly in the face of other nonmodifiable risk factors such as age or genetics.

An additional novel finding in our study is that PA was associated with better performance on the MMSE only among those who have Medicaid/no insurance, and those who did not complete high school, while there were no associations among their counterparts. We did not collect information on household income and believe that these two measures could be a proxy for socioeconomic status. It may be that higher MMSE scores among those with better socioeconomic status and more education mitigate the effect of leisure time PA. Possibly only those at higher risk due to other factors would benefit from lifestyle interventions such as exercise. We may have been unable to detect an effect of PA in the upper ranges of the MMSE due to ceiling effects or lack of power.

Our study has important strengths, including an urban population with a large proportion of Hispanics and individuals with Medicaid or no insurance, who have been underrepresented in previous studies. We were able to examine the effects with both cross-sectional and longitudinal analyses to help investigate the concept of cognitive reserve [35]. Our study also has some important weaknesses, however. We did not have available direct measures of physical fitness or activity such actigraphy [36]. Actigraphy, however, only measures activity when the participant wears the device, and habitual activity may not be captured. In our study we did not collect TICS-m until 2001 and it was not measured in the entire cohort mostly due to early deaths. Cardiovascular disease was the main cause of death in our cohort, for which PA would be a protective factor. The missing TICS-m could lead to a nondifferential loss to follow-up, thereby biasing our results towards the null [37]. Overall in our cohort the TICS-m declined over time, and we have previously noted a deleterious effect of renal function on the TICS-m over time [38]; any independent effect of PA is likely to be clinically small if we are underpowered. We followed participants for a limited number of years, and it is possible that over a longer period of time there could be a protective effect of PA. One prior study showed a strong effect of PA when assessed in middle age, suggesting that by the time participants reach the average age in our study the underlying pathologic process leading to cognitive decline may already be underway without overt clinical signs. It is important to note that PA has protective effects against multiple oth-
er conditions associated with aging, including stroke and MI [21, 39], and our findings should not discourage individuals from performing even light-intensity activities. As with any epidemiological study, it is not possible to establish causation and residual confounding may be present. Further studies will be required to clarify these causal pathways.

In our study we found that PA was associated with baseline cognitive status, particularly in older adults with a lower socioeconomic status, but it was not significantly associated with a decline in cognitive performance. This, however, should not dissuade older patients from exercising, but it highlights the importance of continuing to search for modifiable risk factors for cognitive decline.

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Disclosure Statement

The authors report no conflicts of interest.

References


