

PHYSICAL ACTIVITY AND COGNITIVE FUNCTION OF LONG DISTANCE WALKERS: STUDYING FOUR DAYS MARCHES PARTICIPANTS

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ABSTRACT

Objective: Studies show physical activity to be beneficial for cognitive function. However, studies usually included individuals who were not particularly inclined to exercise. Following research among master athletes, we examined associations between physical activity and cognitive function in participants of the International Nijmegen Four Days Marches. These individuals are also inclined to exercise. On 4 consecutive days > 40,000 participants walk a daily distance of 30-50 km on (120-200 km or 75-125 miles in total).

Method: Four Days Marches participants and less active or inactive control participants from the Nijmegen Exercise Study were examined. Self-reported current and lifelong physical activities were quantified in Metabolic Equivalent of Task minutes/day and training walking speed was estimated in km/h. Cognitive functioning in the domains of working memory, executive function, and visuospatial short-term memory was assessed using the validated Brain Aging Monitor.

Results: Data from 521 participants (mean age 54.7, standard deviation 12.9) showed neither positive associations between lifelong physical activity and working memory, executive function, and visuospatial short-term memory nor positive associations between current physical activity and cognitive functioning in these domains (P-values > 0.05). However, a positive association between training walking speed and working memory was revealed (age adjusted Beta = 0.18, P-value < 0.01).

Conclusion: Walking speed but not lifelong and current physical activity levels were associated with cognitive function. Therefore, walking speed deserves more attention in research aimed at unravelling associations between physical activity and cognitive function.

INTRODUCTION

A growing body of animal and human studies suggests that physical activity ~~like 'cognitive or brain reserve'~~ has a positive effect on the brain and on cognitive function (1). Animal studies showed that physical activity increased proliferation and survival of neurons in the dentate gyrus of the adult mouse hippocampus (1). Studies conducted in older humans showed physical activity to be associated with increased grey and white matter of the prefrontal and temporal cortices (2), a reduced likelihood of cortical atrophy (3), as well as biomarkers of Alzheimer's disease in cognitively normal older adults (4). Furthermore, a randomised controlled trial demonstrated that a home-based intervention programme of self-chosen physical activity, improved cognitive function, but the effect was rather small (5). Finally, a recent comprehensive review suggested that approximately one third of the cases of Alzheimer's disease worldwide might be attributable to potentially modifiable risk factors including physical inactivity (6).

Many of the hitherto conducted studies that examined the relationship between physical activity patterns and cognitive function, included individuals who were not particularly inclined to exercise extensively. Usually, these were people from the general older population. Previously, many older people were shown not to exercise frequently owing to a variety of reasons (7). This underlines the importance of complementary research among individuals who are highly motivated to being physically active, both extensively and over a longer period of time. Previously, several of such studies have been conducted. These studies examined veteran athletes' hippocampal blood flow (8) and cognitive function (9).

The present study aimed to expand on these previous findings from individuals who were inclined to exercise. We therefore set out to investigate associations of physical activity patterns with cognitive function among (senior) participants of the International Nijmegen

Four Days Marches and among physically inactive or less active controls (i.e. friends and relatives). The Nijmegen Four Days Marches (<http://4daagse.nl/en/>) are the largest walking event worldwide. Every year in July, > 40,000 civilian participants from 70 nationalities together with conscripts from the UK, the US, and several European countries, walk a daily distance of 30, 40 or 50 km on four consecutive days (thus 120-200 km or 75-125 miles in total). Approximately 15,000 senior people aged 60 years and older participate in this long distance walking event. Many of them have participated more than once and walk hundreds of miles all year round in preparation of the upcoming Nijmegen Four Days Marches. Thus many (senior) participants of the Nijmegen Four Days Marches are habitual exercisers who are inclined to do prolonged aerobic walking exercises.

Specifically, we examined associations of current and lifelong physical activity as well as walking speed with cognitive function. We examined both current and lifelong physical activity because lifelong physical activity might exert stronger effects on cognitive function than short term physical exercise (10). Furthermore, we also examined ~~walking speed because relatively less attention has been paid to~~ the association between walking speed and cognitive function. Walking speed may be both directly and indirectly linked to cognitive function in later life through the health of the brain itself and that of various other organs ~~on which the brain relies~~. Previous studies reported walking speed to be predictive of survival (11), as well as larger left prefrontal regions of the brain (12). and to be indicative of fitness of multiple organs and the brain, e.g. better pulmonary function and greater muscle strength (13) (11).

We predicted a stronger association between lifelong physical activity and cognitive function than between current physical activity and cognitive function. Furthermore, we predicted a positive association between walking speed and cognitive function.

METHODS

The Nijmegen Exercise Study

The Nijmegen Exercise Study (NES) is a cohort study. Its primary aim is to examine the effects of physical activity on health and disease characteristics (14). For that goal, it enrolls participants of the International Nijmegen Four Days Marches. To obtain a sufficient number of physically less active and inactive control participants, relatives and friends who did not participate in the Nijmegen Four Days Marches were also approached to participate. Between 15 June and 1 September 2014, NES study participants were invited to fill out an online questionnaire to assess demographic characteristics, physical activity parameters and relevant covariates (see section below entitled “Covariates”) directly followed by an invitation to perform the online puzzle games of the Brain Aging Monitor - Cognitive Assessment (BAMCOG) (15, 16). The BAMCOG was previously shown to have convergent validity with widely used neuropsychological tests (see section below entitled “Cognitive Function”). For the present analysis, we excluded NES study participants who had a history of stroke or transient ischemic attack, central nervous system disorders or disorders that might compromise cognitive function (multiple sclerosis, meningioma, dyspraxia, ADHD, or Parkinson's disease), vision problems (glaucoma or macular degeneration), or >3 units of alcohol consumption per day, as all of these conditions might interfere with BAMCOG performance, as well as participants whose questionnaires were incompletely filled out. The study was conducted in accordance with the Declaration of Helsinki. The Committee on

Research Involving Human Participants (CMO) of the region Arnhem and Nijmegen, the Netherlands, approved the study. All participants provided informed consent.

Physical activity parameters

We assessed NES study participants' current physical activity levels ~~in the past month~~ using the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH). The SQUASH was previously shown to be substantially correlated with objective measures of physical activity (17). Using the SQUASH, we assessed the minutes per day of walking, cycling, carrying out household chores, gardening, doing odd jobs and sports activities (17). Based on Ainsworth's Compendium of Physical Activities (18), we then assigned Metabolic Equivalent of Task (MET) values to these specific activities as measured with the SQUASH. Subsequently, MET minutes per day were calculated by multiplying the minutes of current physical activity with the accompanying MET values.

Furthermore, we also assessed NES study participants' lifelong physical activity levels for four different age phases: 18-29 years, 30-49 years, 50-64 years, and ≥ 65 years of age (19). For these lifelong physical activity, participants were asked to rate the intensity of these activities on a 3-point scale (low, moderate, or high). Subsequently, we assigned MET values of 2.5 METs for activities with low perceived intensity, 4.5 METs for activities with moderate perceived intensity, and 8.5 METs for activities with high perceived intensity. MET minutes per day were then also calculated for lifelong physical activity by multiplying the minutes of physical activity with accompanying MET values. Thus, it was ensured that a NES study participant who engaged in various sports activities on a highly regular basis, but who did *not* participate in the Four Days Marches could receive approximately the same grading in terms of an active lifestyle as a NES study participant who actually participated in the Four Days Marches and who walked all year round.

Finally, we asked Nijmegen Four Days Marches participants to rate their average training walking speed during their walks in preparation for the Nijmegen Four Days Marches in km/h. A substantial correlation was observed between self-rated training walking speed and average walking speed in km/h during the Four Days Marches as inferred from starting and finishing times in a side study of the NES study ($N = 78$, $r = 0.58$, $P < 0.01$).

Cognitive Function

Cognitive function was assessed using the Brain Aging Monitor - Cognitive Assessment (BAMCOG), which consists of online puzzle games that assess the performance in three cognitive domains: working memory, executive function, and visuospatial short-term memory (15, 16). Previously, the BAMCOG was shown to have convergent validity with neuropsychological tests (Table 1 provides an overview of the puzzle games and associations with specific neuropsychological tests). Every game had successive levels of increasing difficulty and each level consisted of three trials. Advancing to the next level required successful completion of at least two of the three trials in the current level. In each game, cognitive function was measured as the highest level that a participant had attained. Prior to commencement of each game, participants were given concise instructions followed by a practice trial in order to familiarise them with the game.

Covariates

Demographic covariates were assessed including sex, age, and educational level (low to intermediate vs. high). Furthermore, we assessed Body Mass Index (BMI), hours per day of 'cognitive stimulating activities' (i.e. reading newspapers and magazines, making brain

teasers, and watching informative television programs), smoking status (never, ever, or yes current smoker), number of units of alcohol consumed per day, and hours of sleep per day.

Statistical Analyses

Demographic and background characteristics of the NES study participants were summarised using descriptive statistics. Spearman's correlation coefficients were calculated between performance in the cognitive domains as measured with the BAMCOG puzzle games and demographic and background characteristics. Differences between participants with 'low' 'moderate' and 'high' tertiles of current and lifelong physical exercise on demographic and background characteristics were examined with χ^2 -analysis and ANOVA. Associations between self-reported training walking speed and demographic and background characteristics were examined with Pearson's correlations.

Associations between performance in the cognitive domains (dependent variables) and current and lifelong physical exercise as well as training walking speed (independent variables) were examined with multiple linear regression analysis and standardized regression coefficients (Betas) were calculated. To take the possibility into account that there might be non-linear associations between physical activity and cognitive function, MET minutes of current and lifelong physical activity were classified into tertiles (current physical activity: 'low' ≤ 17 MET minutes, 'moderate' = 18-40 MET minutes and 'high' ≥ 41 MET minutes; lifelong physical activity: 'low' ≤ 90 MET minutes, 'moderate' = 91-206 MET minutes and 'high' = ≥ 207 MET minutes). Tertiles of MET minutes of current and lifelong physical activity were represented by dummy variables. Self-reported training walking speed was classified into ordinal categories ('low' ≤ 5.1 km/h, 'moderate' = 5.2-5.7 km/h, and 'high' ≥ 5.8 km/h). Regression models were adjusted for the above described covariates if they were associated with cognitive function or with the physical activity parameters at the bivariate

level (P-values < 0.05), but were only retained in final multivariate models if they remained significant. To control for the false positive rate, the interpretation of P-values of individual independent variables was guided by inspecting the P-values of the overall ANOVA F-test of each regression model.

In line with previous studies in which associations between physical activity and cognitive function were examined in later life, the analyses were then repeated for senior NES study participants aged > 60. Furthermore, two sensitivity analyses were conducted. First, as diabetes mellitus was previously found to be associated with worse cognitive function (20), the above analyses were repeated without NES study participants who reported to have been diagnosed with type 2 diabetes. Second, because depression was also found to be associated with worse cognitive function (21), we also repeated the above analyses without NES study participants who reported to suffer from depression. In the final models, findings were considered statistically significant if associated P-values were ≤ 0.05 . All statistical analyses were performed with SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp).

RESULTS

Study population

There were 4221 NES study participants of whom 619 had cognitive data collected with the online puzzle games of the BAMCOG. After excluding 98 participants, data were available for a total of 521 eligible participants of whom 209 were > 60 years (Figure 1). Participants who were included in the present analysis were slightly younger than NES study participants who had no BAMCOG data or who were excluded: Mean age = 54.7, Standard Deviation = 12.9 vs. Mean age = 57.5, Standard Deviation = 13.0, independent t-test: t (df 4219) = -4.66, $P < 0.01$). Percentage of women was not different between the two groups (48.8% vs. 45.4%, χ^2 (df 1) = 2.13, $P = 0.145$). Among the included participants, the number of women and men was comparable and there was ample spread in NES study participants' demographic and background characteristics (Table 2). Of the NES study participants, 121 (23%) had never participated in the Four Days Marches, 141 (27%) had 1-3 times participated, 108 (21%) 4-7 times, 93 (18%) 8-15 times, and 58 (11%) ≥ 16 times.

Cognitive performance

The median performance on the BAMCOG puzzle games was 5 (interquartile range 4-7) for the game measuring working memory, 2 (interquartile range 1-3) for the game measuring executive function (planning), and 2 (interquartile range 1-3) for the game measuring visuospatial short-term memory. Performance on the BAMCOG puzzle games was found to have a negative association with age. Educational level was positively associated with working memory and visuospatial short-term memory. BMI was negatively associated with working memory and so was alcohol consumption. Female sex was associated with better visuospatial short-term memory, whereas smoking status and cognitive stimulating activities

were negatively associated with executive function and visuospatial short-term memory. No associations were observed between sleep and cognitive function (see Table 3).

Physical Activity

Tertiles of 'low' 'moderate' and 'high' current physical activity reflected median METmins/day of 11 (interquartile range 7-14), 25 (interquartile range 20-33) and 85 (interquartile range 54-137). Tertiles of 'low' 'moderate' and 'high' levels of lifelong physical activity reflected median METmins/day of 39 (interquartile range 10-65), 143 (interquartile range 116-172), and 320 (interquartile range 246-428). Tertiles of current physical activity were significantly different with regard to higher educational level (low: 62%, moderate: 50%, and high: 39%, χ^2 (df 2) = 19.3, $P < .001$), hours of sleep per day (low: Mean = 7.0, Standard Deviation = 0.78; moderate: Mean = 7.3, Standard Deviation = 0.77 and high: Mean = 7.1, Standard Deviation = 0.83, F [df 2,518] = 4.86, $P = .008$), and BMI (low: Mean = 25.7, Standard Deviation = 3.8; moderate: Mean = 24.9, Standard Deviation = 3.9; high: Mean = 24.7, Standard Deviation = 3.1, F [2, 518] = 3.91, $P = 0.02$). Tertiles of lifelong physical exercise were significantly different with regard to BMI (low: Mean = 25.0, Standard Deviation = 3.8; moderate: Mean = 25.7, Standard Deviation = 3.6; high: Mean = 24.7, Standard Deviation = 3.3, F [df 2, 518] = 3.28, $P = .039$). Self-reported training walking speed was negatively associated with age ($r = -0.19$, $P < 0.001$), sleep per day ($r = -0.14$, $P = 0.004$), BMI ($r = -0.12$, $P = 0.017$), and female sex ($r = -0.15$, $P = 0.003$) with current physical activity ($r = 0.12$, $P = 0.016$) and with lifelong physical exercise ($r = 0.15$, $P = 0.004$).

Associations between physical activity and cognitive function

~~When studying all participants in~~ Regression analyses adjusted for confounding variables, (Table 4) demonstrated that neither current nor lifelong physical activity were positively

associated with cognitive function. By contrast, training walking speed was found to be associated with working memory also after controlling for age (Beta = 0.18, P = 0.004, N = 249). The magnitude of the association between training walking speed and working memory was in between that of the association of working memory with age (Beta = -0.23, P = 0.000), and that of the association of working memory with educational level (Beta = 0.15, P = 0.006). Similar results were obtained when restricting the analyses to participants aged > 60 years. Sensitivity analyses in which participants with type 2 diabetes (N = 16) and depression (N = 34) were excluded, did not substantially alter the findings.

DISCUSSION

Contrary to our predictions, we did not find associations of lifelong and current physical activity with cognitive function in this sample of Four Days Marches participants of whom many were inclined to exercise extensively.

There are several possible explanations why we did not find associations between extent of physical activity and cognitive function. First, a restriction of range in levels of physical activity in the sense that there were only active participants was unlikely. The lowest tertiles of current and lifelong physical activity seemed to reflect lower activity levels. Theoretically, the absence of associations of lifelong and current physical activity with cognitive function could also have been caused by a limited sample size and associated suboptimal statistical power. Yet, our sample had sufficient power to detect a medium effect size in a regression analysis with eight predictors (22). Moreover, our findings did not change when we restricted the analysis to individuals > 60 years or after excluding participants with depression or type 2 diabetes in sensitivity analyses. In sum, we believe that the absence of associations was a robust finding.

Although we did not prove a direct association of lifelong and current physical activity with cognitive function, it is possible that physical exercise exerted an indirect effect. Our findings provided some support for this notion. On the one hand, better performance on the working memory task was associated with a lower BMI. On the other hand, a lower BMI was associated with higher levels of physical activity. Clearly, more research is needed to examine potential indirect positive effects of physical activity on cognitive function through improvement of multiple physical fitness parameters. The associations of alcohol consumption with working memory, and of smoking status with executive function and visuospatial short-term memory suggest yet another possibility. Perhaps physical activity

would only exert beneficial effects on cognitive function in individuals who did not smoke or who consumed only limited amounts of alcohol. Clearly, more ~~follow-up~~ research in this group of individuals is therefore warranted.

At the same time, our findings demonstrated a positive association between ~~faster~~ self-reported training walking speed during walks in preparation for the Nijmegen Four Days Marches and ~~better~~ working memory. This finding is consistent with positive associations between training walking speed and cognitive function that were previously found among individuals who were older than the participants of this study and who were also not particularly inclined to exercise extensively (23, 24). The finding is also consistent with a range of positive associations of walking speed with survival (11), better pulmonary function and greater muscle strength (13), as well as larger left prefrontal regions of the brain (12). Together, all these findings are in support of the notion that walking speed may be both directly linked to cognitive function in later life through the health of the brain itself and also indirectly linked through the health of other organs ~~on which the brain relies~~. The present association between faster training walking speed during *preparation* for the Nijmegen Four Days Marches and better working memory was also consistent with our own previous preliminary findings from a pilot study. In a small sample of seventy older Nijmegen Four Days Marches participants aged ≥ 60 years, we found a positive association between training walking speed during *participation* in the Nijmegen Four Days Marches and performance on the Cognitive Impairment Test (CIT) (25), which is a validated measure of global cognitive function (26). The presently found association between ~~faster~~ training walking speed during preparation for the Nijmegen Four Days Marches and ~~better~~ working memory was also relevant. It was almost as strong as the association between age and working memory. Furthermore, the association was as strong as the association between education and working memory. Education has been shown to exert a positive effect on cognitive function that is

consistent with the 'cognitive or brain reserve' hypothesis (27, 28). However, at the same time, more research should be conducted to know if walking speed is associated with better functioning in specific cognitive domains such as working memory as was found in the present study as opposed to global cognitive function or other specific cognitive functions.

~~There are several strengths of this study. First, our sample consisted of many individuals who were highly motivated to exercise. The present findings therefore complement findings from the vast majority of previously conducted studies, which were usually conducted among individuals who were less inclined to exercise. Second, a strength of the BAMCOG puzzle games were their ecological validity. They were easily accessible to participants who played these puzzle games online at home, while they were challenging enough to capture participants' attention. At the same time, the BAMCOG puzzle games were previously shown to have convergent validity with standard neuropsychological tests. Furthermore, the association between worse performance on the BAMCOG puzzle games with increasing age found in the present study, supports the notion that the BAMCOG may measure age-associated cognitive decline. The associations between the BAMCOG puzzle games of executive function and visuospatial short term memory and smoking status are also in line with a previous finding (29). Other strengths were that we were able to adjust for important covariates which were associated with cognitive function or with the physical activity parameters, and the exclusion of participants who had other CNS disorders.~~

A number of methodological issues should be addressed. Our study was limited by its cross-sectional design. This leaves the question unanswered whether in our sample, training walking speed affected the trajectory of cognitive decline (differential preservation), whether it was associated with enhanced baseline cognitive ability (preserved differentiation) (30), or whether bidirectional effects were at play (23). Assessment of lifelong and current physical activity and training walking speed through self-report could have been distorted by recall and

reporting bias in participants as acknowledged by several researchers (4, 31). However, the SQUASH questionnaire was previously shown to be substantially correlated with objective measures of physical activity (17). Furthermore, self-rated training walking speed was also correlated with walking speed during the Four Days Marches as inferred from starting and finishing times that were available for a subsample of participants. ~~Although recall bias may have occurred with regard to reporting of physical exercise and training walking speed, many people in our sample were highly motivated to exercise. This may have made them less liable to a social desirability bias causing them to overestimate their amounts of physical exercise and training walking speed.~~ Selection bias may have occurred in the sense that participants with BAMCOG data were somewhat younger than those without these data. However, although it is true that cognitive decline often manifests itself with progressing age, our subgroup analysis of individuals of > 60 years did not change the outcomes. We had only cognitive test data available and neuro-imaging data and physical fitness parameters were not collected. Studying the brains and physical fitness of in particular senior Nijmegen Four Days Marches participants could therefore be valuable. Altogether, a longitudinal follow-up study of participants of the Nijmegen Four Days Marches or other people who are inclined to exercise, that also encompasses objective measures of physical activity and fitness as well as and imaging of the brain would be worthwhile to pursue.

Taken together, we conclude that not the amount of current and lifelong physical activity, but rather walking speed seems to be associated with better working memory. Walking speed therefore deserves more attention in research aimed at unravelling associations between physical activity and cognitive function.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

REFERENCES

1. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. *Nat Rev Neurosci*. 2008 Jan;9(1):58-65.
2. Colcombe SJ, Erickson KI, Scalf PE, Kim JS, Prakash R, McAuley E, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci*. 2006 Nov;61(11):1166-70.
3. Colcombe SJ, Erickson KI, Raz N, Webb AG, Cohen NJ, McAuley E, et al. Aerobic fitness reduces brain tissue loss in aging humans. *J Gerontol A Biol Sci Med Sci*. 2003 Feb;58(2):176-80.
4. Liang KY, Mintun MA, Fagan AM, Goate AM, Bugg JM, Holtzman DM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann Neurol*. 2010 Sep;68(3):311-8.
5. Lautenschlager NT, Cox KL, Flicker L, Foster JK, van Bockxmeer FM, Xiao J, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*. 2008 Sep 3;300(9):1027-37.
6. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014 Aug;13(8):788-94.
7. Crombie IK, Irvine L, Williams B, McGinnis AR, Slane PW, Alder EM, et al. Why older people do not participate in leisure time physical activity: a survey of activity levels, beliefs and deterrents. *Age Ageing*. 2004 May;33(3):287-92.
8. Alfini AJ, Weiss LR, Leitner BP, Smith TJ, Hagberg JM, Smith JC. Hippocampal and Cerebral Blood Flow after Exercise Cessation in Master Athletes. *Front Aging Neurosci*. 2016 Aug 5;8:184.
9. Zhao E, Tranovich MJ, DeAngelo R, Kontos AP, Wright VJ. Chronic exercise preserves brain function in masters athletes when compared to sedentary counterparts. *Phys Sportsmed*. 2016;44(1):8-13.
10. Dregan A, Gulliford MC. Leisure-time physical activity over the life course and cognitive functioning in late mid-adult years: a cohort-based investigation. *Psychol Med*. 2013 Nov;43(11):2447-58.
11. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, et al. Gait speed and survival in older adults. *JAMA*. 2011 Jan 5;305(1):50-8.
12. Rosano C, Aizenstein HJ, Studenski S, Newman AB. A regions-of-interest volumetric analysis of mobility limitations in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci*. 2007 Sep;62(9):1048-55.

13. Buchman AS, Boyle PA, Leurgans SE, Evans DA, Bennett DA. Pulmonary function, muscle strength, and incident mobility disability in elders. *Proc Am Thorac Soc*. 2009 Dec 1;6(7):581-7.
14. Maessen MF, Eijsvogels TM, Verheggen RJ, Hopman MT, Verbeek AL, de Vegt F. Entering a new era of body indices: the feasibility of a body shape index and body roundness index to identify cardiovascular health status. *PLoS One*. 2014 Sep 17;9(9):e107212.
15. Aalbers T, Baars MA, Olde Rikkert MG, Kessels RP. Puzzling with online games (BAM-COG): reliability, validity, and feasibility of an online self-monitor for cognitive performance in aging adults. *J Med Internet Res*. 2013 Dec 3;15(12):e270.
16. Aalbers T, Baars MA, Qin L, de Lange A, Kessels RP, Olde Rikkert MG. Using an eHealth Intervention to Stimulate Health Behavior for the Prevention of Cognitive Decline in Dutch Adults: A Study Protocol for the Brain Aging Monitor. *JMIR Res Protoc*. 2015 Nov 10;4(4):e130.
17. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. *J Clin Epidemiol*. 2003 Dec;56(12):1163-9.
18. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr, Tudor-Locke C, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011 Aug;43(8):1575-81.
19. Maessen MF, Verbeek AL, Bakker EA, Thompson PD, Hopman MT, Eijsvogels TM. Lifelong Exercise Patterns and Cardiovascular Health. *Mayo Clin Proc*. 2016 Jun;91(6):745-54.
20. Koekkoek PS, Kappelle LJ, van den Berg E, Rutten GE, Biessels GJ. Cognitive function in patients with diabetes mellitus: guidance for daily care. *Lancet Neurol*. 2015 Mar;14(3):329-40.
21. Elliott R, Sahakian BJ, McKay AP, Herrod JJ, Robbins TW, Paykel ES. Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance. *Psychol Med*. 1996 Sep;26(5):975-89.
22. Cohen J. A power primer. *Psychol Bull*. 1992 Jul;112(1):155-9.
23. Gale CR, Allert M, Sayer AA, Cooper C, Deary IJ. The dynamic relationship between cognitive function and walking speed: the English Longitudinal Study of Ageing. *Age (Dordr)*. 2014;36(4):9682,014-9682-8. Epub 2014 Jul 5.
24. Rosano C, Simonsick EM, Harris TB, Kritchevsky SB, Brach J, Visser M, et al. Association between physical and cognitive function in healthy elderly: the health, aging and body composition study. *Neuroepidemiology*. 2005;24(1-2):8-14.

25. Wouters H, Eijssvogels TM, Hopman MT. Walking speed and cognition in later life: findings from older participants of the Nijmegen 4 Days Marches. *J Am Geriatr Soc*. 2015 Apr;63(4):820-1.
26. Brooke P, Bullock R. Validation of a 6 item cognitive impairment test with a view to primary care usage. *Int J Geriatr Psychiatry*. 1999 Nov;14(11):936-40.
27. Roe CM, Xiong C, Miller JP, Morris JC. Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology*. 2007 Jan 16;68(3):223-8.
28. Schmand B, Smit JH, Geerlings MI, Lindeboom J. The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. *Psychol Med*. 1997 Nov;27(6):1337-44.
29. Reitz C, den Heijer T, van Duijn C, Hofman A, Breteler MM. Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. *Neurology*. 2007 Sep 4;69(10):998-1005.
30. Bielak AA, Cherbuin N, Bunce D, Anstey KJ. Preserved differentiation between physical activity and cognitive performance across young, middle, and older adulthood over 8 years. *J Gerontol B Psychol Sci Soc Sci*. 2014 Jul;69(4):523-32.
31. Geda YE, Roberts RO, Knopman DS, Christianson TJ, Pankratz VS, Ivnik RJ, et al. Physical exercise, aging, and mild cognitive impairment: a population-based study. *Arch Neurol*. 2010 Jan;67(1):80-6.

Table 1. Overview of the Brain Aging Monitor - Cognitive Assessment Battery (BAMCOG) Online Puzzle Games

Game	Levels	Description	Associated Cognitive Domains	Convergent validity with neuropsychological tests*
The Lost Artefacts	7	Participants are shown a personal list of gems and relics and a waterway. After 1 second, different gems and relics start floating along the waterway. Participants need to select only those gems and relics which they have on their personal lists.	Working Memory	WAIS-III Letter Number Sequencing & Spatial Working Memory
Temple of Wisdom	5	Participants are presented with a scrambled water canal. Their task is to unscramble the canal so that the water flow is no longer obstructed. Clearing the way is done by sliding columns and rows in the correct order so that all pieces of the canal end up connected to one another.	Planning	BADS Zoo Map & Stockings of Cambridge
Nebo's Amulet	8	A pawn creates a visual pattern in a 4x4 matrix. This visual pattern dissolves quickly and upon its complete disappearance, participants have to reproduce an exact copy of the visual pattern.	Visuospatial short-term memory	WMS-III Spatial SpanTask & Spatial Span

* See: Aalbers T, Baars MA, Olde Rikkert MG, Kessels RP. Puzzling with online games (BAM-COG): reliability, validity, and feasibility of an online self-monitor for cognitive performance in aging adults. J Med Internet Res. 2013 Dec 3;15(12):e270.

Table 2 Demographic and Background Characteristics of the Participants

Characteristics	Statistic (N,%, M, SD)	
	All individuals	<i>Individuals > 60 years</i>
N Sex (%)		
Men	267 (51.2)	142 (67.9)
Women	254 (48.8)	67 (32.1)
M Age (years) (SD)	54.7 (12.9)	66.4 (4.7)
N Educational level (%)		
Low to intermediate	259 (49.7)	114 (54.5)
High	262 (50.3)	95 (45.5)
M BMI (kg/m ²) (SD)	25.1 (3.6)	25.2 (3.2)
M Cognitive stimulation (hours/day) (SD)	1.66 (1.28)	2.23 (1.38)
N Smoking status (%)		
Never	266 (51.1)	70 (33.5)
Ever	204 (39.2)	122 (58.4)
Yes current smoker	51 (9.8)	17 (8.1)
N Daily Alcohol Intake (%)		
< 1 unit	276 (53.0)	80 (38.3)
1 unit	182 (34.9)	87 (41.6)
≥ 2 units	63 (12.1)	42 (20.1)
M sleep (hours/day) (SD)	7.1 (0.8)	7.2 (0.79)

Notes: BMI, Body Mass Index

Table 3 Correlation Coefficients between Performance on BAMCOG Puzzle Games and Participants' Characteristics

Characteristics	Working Memory		Executive Function (planning)		Visuospatial short-term memory	
	Spearman's	P	Spearman's	P	Spearman's	P
	<i>r</i>		<i>r</i>		<i>r</i>	
Age (years)	-0.23	<.001	-0.34	<.001	-0.39	<.001
Sex *	0.09	.099	-0.01	.917	0.10	.038
Educational level †	0.15	.006	0.12	.056	0.17	<.001
Sleep (hours/day)	-0.05	.334	-0.09	.158	0.04	.451
Units alcohol intake (n/day)	-0.11	.038	-0.11	.066	-0.07	.142
Cognitive stimulation (hours/day)	-0.08	.148	-0.16	.008	-0.18	<.001
Smoking status ‡	0.01	.925	-0.14	.020	-0.12	.012
BMI (kg/m ²)	-0.16	.003	-0.06	.305	-0.05	.256

* 0, male; 1, female; † 0, low to intermediate; 1, high; ‡ 0, never; 1, ever; 2, yes current smoker

Notes: BAMCOG, Brain Aging Monitor - Cognitive Assessment; BMI, Body Mass Index

Table 4 Performance on BAMCOG Puzzle Games for Different Indicators of Physical Activity: Multiple Regression Analysis

Characteristics	Working Memory		Executive Function		Visuospatial short-term memory	
	Beta	P-value	Beta	P-value	Beta	P-value
<i>All participants</i>						
	N = 331		N = 266		N = 470	
Current Physical Activity	Beta	P-value	Beta	P-value	Beta	P-value
Low		--		--		--
Moderate	-0.05*	.391	-0.00†	.976	0.00‡	.986
High	-0.01*	.823	-0.06†	.364	0.08‡	.118
Lifelong Physical Activity	Beta	P-value	Beta	P-value	Beta	P-value
Low		--		--		--
Moderate	0.04*	.523	0.02†	.745	-0.10‡	.044
High	0.10*	.111	0.04†	.554	-0.07‡	.166
Walking Speed	Beta	P-value	Beta	P-value	Beta	P-value
	N = 249		N = 202		N = 355	
	0.18§	.004	0.07¶	.293	0.06§	.245
<i>Participants ≥ 60 years</i>						
Current Physical Activity	Beta	P-value	Beta	P-value	Beta	P-value
Low		--		--		--
Moderate	-0.15*	.217	0.00†	.980	-0.02‡	.855
High	-0.00*	.979	-0.20†	.136	0.13‡	.159
Lifelong Physical Activity	Beta	P-value	Beta	P-value	Beta	P-value
Low		--		--		--
Moderate	0.10*	.367	0.01†	.954	-0.12‡	.162
High	0.10*	.372	0.15†	.240	0.02‡	.840
Walking Speed	Beta	P-value	Beta	P-value	Beta	P-value
	N = 101		N = 72		N = 151	
	0.22§	.026	-0.03¶	.807	0.01§	.885

Adjusted for * age, educational level, Body Mass Index; †: age, sleep per day; ‡: age, educational level; §: age ¶: age, sex. Notes: BAMCOG, Brain Aging Monitor - Cognitive Assessment; BMI, Body Mass Index

Figure 1

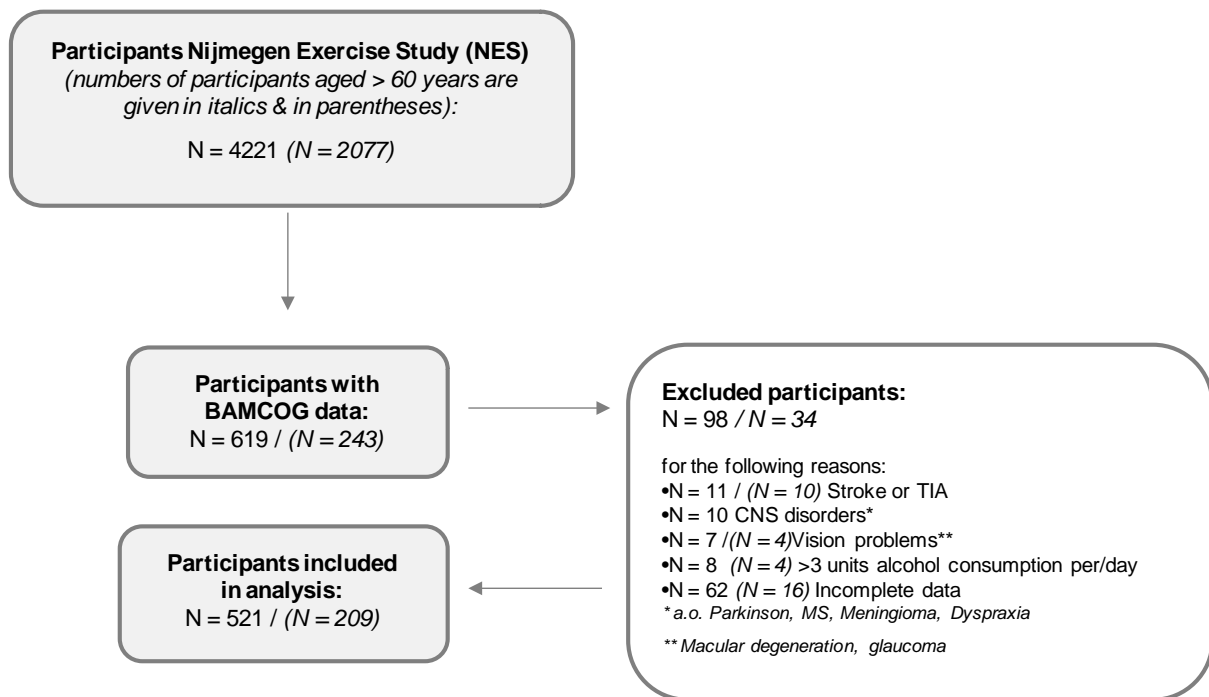


FIGURE LEGENDS

Figure 1 Flowchart of enrolment and inclusion for all participants and participants > 60 years of the Nijmegen Exercise Study (NES)