Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence

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Background. The association between physical activity and risk of neurodegenerative diseases is not well established. We therefore aimed to quantify this association using meta-analytical techniques.

Method. We searched Medline, the Cochrane Database of Systematic Reviews and Web of Science databases from 1990 to 2007 for prospective epidemiological studies of physical activity and incident dementia, Alzheimer's and Parkinson's disease. We excluded studies of physical activity and cognitive decline without diagnosis of a neurodegenerative disease. Information on study design, participant characteristics, measurement of exposure and outcome variables, adjustment for potential confounding, and estimates of associations was abstracted independently by the two investigators.

Results. We included 16 prospective studies in the overall analysis, which incorporated 163797 non-demented participants at baseline with 3219 cases at follow-up. We calculated pooled relative risk (RR) using a random effects model. The RR of dementia in the highest physical activity category compared with the lowest was 0.72 [95% confidence interval (CI) 0.60–0.86, $p < 0.001$], for Alzheimer's, 0.55 (95% CI 0.36–0.84, $p = 0.006$), and for Parkinson's 0.82 (95% CI 0.57–1.18, $p = 0.28$).

Conclusions. Our results suggest that physical activity is inversely associated with risk of dementia. Future studies should examine the optimal dose of physical activity to induce protection, which presently remains unclear.

Introduction

Neurodegenerative diseases result from deterioration of neurons, which over time lead to neurodegeneration and disabilities. Despite neurodegenerative diseases presenting a major health problem in ageing communities, modifiable risk factors such as diet and exercise have gained relatively little attention. Physical activity is known to prevent a number of chronic diseases including cardiovascular disease, hypertension, type II diabetes, and certain cancers (O'Donovan *et al.* in press). The association between physical activity and neurodegenerative diseases is, however, less well established. Randomized controlled trials have demonstrated that fitness training has a robust effect on improving certain cognitive processes (Colcombe & Kramer, 2003), which may be important for future risk of dementia (Linn *et al.* 1995; Small *et al.* 2000). Research that attempts to examine the risk of neurodegenerative disease is, however, often prone to biases attributable to pre-existing mental or cognitive dysfunction that may influence physical activity behaviours. Various cardiovascular risk factors might also contribute to the development of neurodegenerative disease (Kivipelto *et al.* 2005; Rosendorff *et al.* 2007), thus confounding possible associations with physical activity. Using a prospective epidemiological design it is possible to examine the cumulative effects of physical activity over several years. We therefore sought to review evidence from prospective epidemiological studies of physical activity and neurodegenerative disease risk.

Method

Study selection and data extraction

We adhered to the guidelines for reporting meta-analysis of observational studies in epidemiology (Stroup *et al.* 2000). We searched Medline, the Cochrane Database of Systematic Reviews and Web of Science databases from 1990 to 2007 using the key words *physical activity* or *exercise* in combination with

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Table 1. *Cohort studies of physical activity and neurodegenerative disease risk*

Source	Country/Cohort	Sex	Age at baseline/ Follow-up (years)	Cases/N	Assessment of physical activity	Assessment of outcome	Adjustments
Sumic *et al.* (2007)	USA/ Oregon brain Aging Study	♂♀	⩾85 4.7	38/66	Self-reported, time/week (low: ⩽4 h/week; high: ⩾4 h/week)	D/CI: MMSE <24 and CDR=0.5	Age, education, ApoE4 genotype, cognitive function
Larson *et al.* (2006)	USA/ Adult Changes in Thought Study	♂♀	⩾65 6.2	158/1740	Self-reported, frequency/ week >15 min (regular exercisers >3/week)	AD/D: CASI <86, and clinical assessment based on DSM-IV criteria	Age, gender
Wang *et al.* (2006)	China	♂♀	⩾55 4.7	593/5437	Self-reported frequency/ week (daily; weekly; monthly)	CI: MSSE<24	Age, gender, education, occupation, medical conditions, smoking, alcohol, depressive symptoms, baseline cognitive function, other activities
Logroscino *et al.* (2006)	USA/ Harvard Alumni	♂	67.6 9	101/10 714	Self-reported, frequency/ duration: quintiles EE (<1000 to >3000 kcal/week)	PD: self-report and mortality data	Age, smoking, tea, coffee, history of CVD, cancer
Chen *et al.* (2005)	USA/Health Professionals Follow-up	♂♀	40–75 12–14	387/125 828	Self-reported, frequency/ duration: quintiles MET h/week	PD: self-report with confirmed medical record	Age, smoking, energy, caffeine, lactose and alcohol intake, BMI
Rovio *et al.* (2005)	Finland/CAIDE study	♂♀	39–64 21	193/1449	Self-reported, frequency/week ('active' ⩾2/week)	AD/D: clinical assessment based on DSM-IV criteria	Age, gender, education, follow-up time, locomotion disorders, ApoE4 genotype, BMI, BP, cholesterol, disease history, smoking, alcohol
Podewils *et al.* (2005)	USA/CHS study	♂♀	⩾65 5.4	480/3375	Self-reported, frequency/ duration: quintiles EE (<248 to >1657 kcal/week)	AD/D: 3MS <80, phone interview, medical records, medical diagnosis	Age, education, gender, ethnicity, ApoE4 genotype, baseline 3MS, white matter grade score, impairment of activities, social support/network

Abbott et al. (2004)	USA/Honolulu-Asia Aging Study	♂	71–93 7	158/2257	Self-reported walking distance/day (<0.25 to >2 miles/day)	AD/D: CASI <74, clinical assessment based on DSM-IV	Age, education, ApoE4 genotype, cognitive and physical performance, BMI, disease history, cholesterol
Verghese et al. (2003)	USA/Bronx Aging Study	♂♀	75–85 5.1	124/469	Self-reported, frequency (scale according to activity days/week)	AD/D: neurophysiological tests, worsening of scores on the Blessed test, DSM-IV criteria	Age, gender, education, disease history, baseline cognitive function
Yamada et al. (2003)	Japan/Adult Health study	♂♀	30–70 25–30	114/1774	Self-reported, frequency including leisure and occupational activity	AD/D: CASI screen, clinical assessment based on DSM-IV	Age, gender, education
Wang et al. (2006)	Sweden/ Kungsholmen Project	♂♀	≥75 6.4	123/1375	Self-reported, frequency (none, <weekly, daily–weekly)	D: MMSE screen, clinical assessment based on DSM-IV	Age, gender, education, baseline MMSE, depressive symptoms, disease history, physical functioning
Wilson et al. (2002)	USA/Chicago Health and Aging Project	♂♀	≥75 4.1	139/842	Self-reported, frequency/ duration (high: >5 h/week)	AD: clinical diagnosis	Age, gender, ethnicity, ApoE4 genotype
Laurin et al. (2001)	Canada/Canadian Study of Health and Aging	♂♀	≥65 5	285/4615	Self-reported, frequency/ intensity (high level ∼ ≥3 /week vigorous)	D/AD: 3MS <77, clinical assessment based on DSM-IV	Age, gender, education, smoking, alcohol, anti-inflammatory drugs, physical functioning, self-rated health, disease history
Ho et al. (2001)	China	♂♀	≥70 3	139/988	Practise exercise (yes/no)	CI: CAPE <7	Age, education
Fabrigoule et al. (1995)	France	♂♀	≥65 3	84/2040	Sports participation (yes/no)	AD/D: MMSE, clinical assessment based on DSM-III	Age, social class, cognitive and physical ability
Yoshitake et al. (1995)	Japan/The Hisayama Study	♂♀	≥65 7	103/828	Physically active defined as daily exercisers or heavily active at work	AD: MMSE <21, clinical assessment based on DSM-III	Age, gender, BP, stroke, diabetes, alcohol

EE, Energy expenditure; MET, metabolic equivalent tasks; AD, Alzheimer's disease; CI, cognitive impairment; D, dementia; PD, Parkinson's disease; MMSE, Mini Mental State Examination; 3MS, Modified Mini Mental State Examination; CDR, Clinical Dementia Rating Scale; CASI, Cognitive Ability Screening Instrument; CAPE, Clifton Assessment Procedures for the Elderly; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; ApoE4, apolipoprotein allele 4; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease.

dementia, *Alzheimer's disease*, *Parkinson's disease*, and *cognition* and also examined the reference lists of the retrieved articles. We limited the current systematic review to prospective cohort epidemiological studies in an attempt to eliminate selection and recall bias. Criteria for inclusion were as follows: (1) English-language full-length publication in a peer-reviewed journal; (2) prospective cohort studies in non-demented men and women at baseline, with a diagnosis of dementia or cognitive impairment at follow-up; and (3) measures of physical activity (frequency/time/type) at baseline. Information on participants and study characteristics, measurement of exposure and outcome, adjustment for potential confounders, and hazard ratio (HR) or relative risks (RRs) with 95% confidence intervals (CIs) was abstracted by one author (M.H.) and verified by another (Y.C.). Assessment of quality was made based on the validity and accuracy of the physical activity exposure measure and adjustment for potential confounding. Quality and validity were assessed independently by both reviewers and any discrepancies were resolved by discussion.

Statistical analysis

We used random effects modelling to meta-analyse the data, which allows for heterogeneity between studies (Dersimonian & Laird, 1986). HR or RR was used as a measure of the association between physical activity and risk of neurodegenerative disease. For the present analyses we assumed RRs to be a valid approximation of HRs, thereby enabling the use of one consistent measure throughout. In each case we extracted a RR for the highest *versus* the lowest reported physical activity group (referent group). RRs or HRs were transformed by taking their natural logarithms and standard errors were calculated from ln RR or ln HR and corresponding 95% CIs. In all analyses we used RRs from multivariate models with the most complete adjustment for potential confounders. If HR or RR was not presented we calculated RR and 95% CI from the study data with the use of the number of participants (N) and the number of cases (A) in both exposed (1, physically active) and unexposed groups (0, sedentary): $RR = (A1/N1$ divided by $A0/N0)$ and $95\% \ CI = \exp[\ln RR \pm 1.96 \sqrt{(1/A1 + 1/A0)}]$. We used the Q-test for homogeneity between studies, which tests whether the between-study variability in effect sizes exceeds that expected from corresponding within-study variability. To detect publication biases we explored heterogeneity in funnel plots and the degree of asymmetry by using Begg's asymmetry method (Begg & Berlin, 1989). Data for dementia, Alzheimer's and Parkinson's outcomes were analysed separately. We also performed sensitivity analyses based on gender and quality of studies. All analyses were performed on a Macintosh G4 using a meta-analysis program (Masui, 2003).
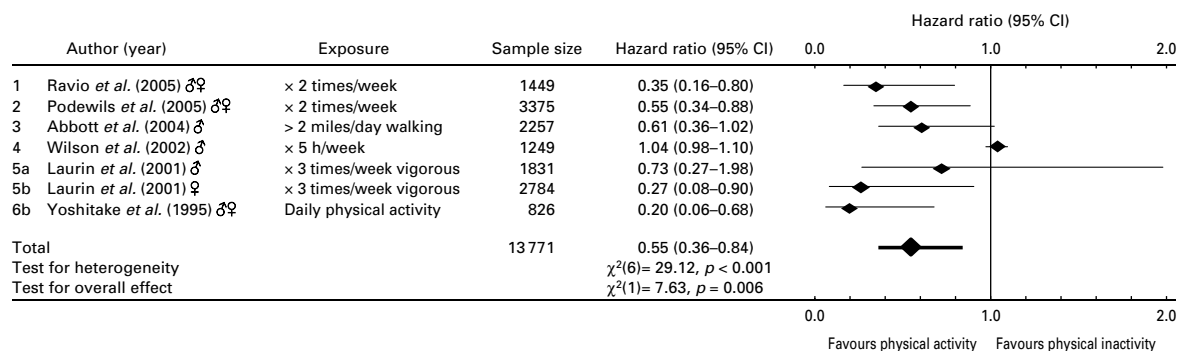
Results

We identified 1866 studies in the literature search, of which 16 studies met inclusion criteria (see Table 1). We did not include cohort studies that examined physical activity and cognitive decline without diagnosis of a neurodegenerative disease, although these studies are displayed in Table 2. The included studies incorporated 163797 participants with 3219 cases (2731 dementia/Alzheimer's, 488 Parkinson's) at follow-up. Two studies were performed in men only, whereas the remainder were mixed cohorts. For dementia and Alzheimer's disease outcomes we identified five high-quality studies (Laurin *et al.* 2001; Wilson *et al.* 2002; Abbott *et al.* 2004; Podewils *et al.* 2005; Rovio *et al.* 2005) that had used an adequate and valid assessment of physical activity and adjusted for relevant confounders, including age, education, vascular risk factors, existing medical conditions, and the apolipoprotein allele 4 (ApoE4) genotype. The two studies that examined risk of Parkinson's disease were also both considered to be high quality (Chen *et al.* 2005; Logroscino *et al.* 2006).

Figures 1–3 show the associations between physical activity and Alzheimer's disease, dementia and Parkinson's disease respectively. The pooled RR of overall dementia in the highest physical activity category compared with the lowest was 0.72 (95% CI 0.60–0.86, $p < 0.001$), for Alzheimer's 0.55 (95% CI 0.36–0.84, $p = 0.006$), and for Parkinson's 0.82 (95% CI 0.57–1.18, $p = 0.28$). There was significant heterogeneity for the association between physical activity and dementia [$\chi^2 (13) = 46.66$, $p < 0.001$] and Alzheimer's [$\chi^2 (6) = 29.12$, $p < 0.001$], but not for Parkinson's [$\chi^2 (2) = 3.09$, $p = 0.21$]. We found no evidence of publication biases in any analyses using Begg's asymmetry method (p's > 0.1). To further explore the heterogeneity issue we performed sensitivity analyses based on gender and study quality. In studies that presented separate gender effects, the RR was more robust for men [0.72, 95% CI 0.57–0.90, $p = 0.004$; $\chi^2 (3) = 0.99$, $p = 0.80$] than for women [0.46, 95% CI 0.18–1.14, $p = 0.09$; $\chi^2 (2) = 9.95$, $p = 0.007$] in relation to risk of dementia. There was also a more robust effect in high-quality studies [0.61, 95% CI 0.46–0.82, $p = 0.001$; $\chi^2 (10) = 43.96$, $p < 0.001$] compared with lower quality studies [0.75, 95% CI 0.60–0.93, $p = 0.01$; $\chi^2 (9) = 33.99$, $p < 0.001$] in relation to dementia and Alzheimer's risk, although

Table 2. *Cohort studies of physical activity and cognitive decline* (*excluded from analyses*)

Study	Country/Cohort	N/follow-up (years)	Findings
Sturman *et al.* (2005)	USA/Chicago Health and Aging Project	4055♂♀ 6.4	Each additional physical activity (h/week) was associated with slower rate of cognitive decline although not significant in fully adjusted model
Singh-Manoux *et al.* (2005)	UK/Whitehall II Study	6236♂♀ 11	Low physical activity associated with poorer performance on test of fluid intelligence
Weuve *et al.* (2004)	USA/Nurse's Health Study	16 466♀ 1.8	Women in highest physical activity quintiles had lower cognitive decline after adjustments
van Gelder *et al.* (2004)	Finland, Italy and Netherlands Elderly Study	295♂ 10	Men who reduced activity (>60 min/day) and remained sedentary had greatest cognitive decline over follow-up
Lytle *et al.* (2004)	USA/Pittsburgh study, community sample	1146♂♀ 2	High activity (>30 min, 3 times/week) protective against cognitive decline (decline ≥3 MMSE points)
Richards *et al.* (2003)	British 1946 birth cohort study	1919♂♀ 10	Physical activity at age of 36 years associated with slower decline in memory at follow-up
Yaffee *et al.* (2001)	USA Study of Osteoporotic Fractures	5925♀ 6–8	Women in highest quartile of walking (175 blocks/week) 35% less likely to experience cognitive decline (decline ≥3 MMSE points)
Schuit *et al.* (2001)	Netherlands Aging Study	347♂ 3	Greater than 60 min/day exercise associated with a twofold reduction in risk of cognitive decline (decline ≥3 MMSE points)
Albert *et al.* (1995)	USA/MacArthur Studies	1192♂♀ 2–2.5	Structural equation modelling identified strenuous activity as a direct predictor of cognitive decline
Broe *et al.* (1998)	Sydney Older Persons Study	327♂♀ 3	No associations between physical activities and decline in MMSE scores

MMSE, Mini Mental State Examination.

	Author (year)	Exposure	Sample size	Hazard ratio (95% CI)
1	Ravio *et al.* (2005) ♂♀	× 2 times/week	1449	0.35 (0.16–0.80)
2	Podewils *et al.* (2005) ♂♀	× 2 times/week	3375	0.55 (0.34–0.88)
3	Abbott *et al.* (2004) ♂	> 2 miles/day walking	2257	0.61 (0.36–1.02)
4	Wilson *et al.* (2002) ♂	× 5 h/week	1249	1.04 (0.98–1.10)
5a	Laurin *et al.* (2001) ♂	× 3 times/week vigorous	1831	0.73 (0.27–1.98)
5b	Laurin *et al.* (2001) ♀	× 3 times/week vigorous	2784	0.27 (0.08–0.90)
6b	Yoshitake *et al.* (1995) ♂♀	Daily physical activity	826	0.20 (0.06–0.68)
	Total		13 771	0.55 (0.36–0.84)

Test for heterogeneity $\chi^2(6) = 29.12$, $p < 0.001$
Test for overall effect $\chi^2(1) = 7.63$, $p = 0.006$

Favours physical activity   Favours physical inactivity

Fig. 1. The association between physical activity and Alzheimer's disease in prospective cohorts.

heterogeneity was displayed in both. In two studies that examined gene interactions with the ApoE4 genotype, one observed more pronounced associations of physical activity and dementia among ApoE ε4 carriers (Rovio *et al.* 2005) whereas in a different cohort the effects were absent in the carriers (Podewils *et al.* 2005).

Discussion

The present meta-analysis of prospective cohort studies suggests that physical activity reduces the risk of dementia and Alzheimer's disease by 28% and 45% respectively. Physical activity was not associated with a significant reduction in risk of
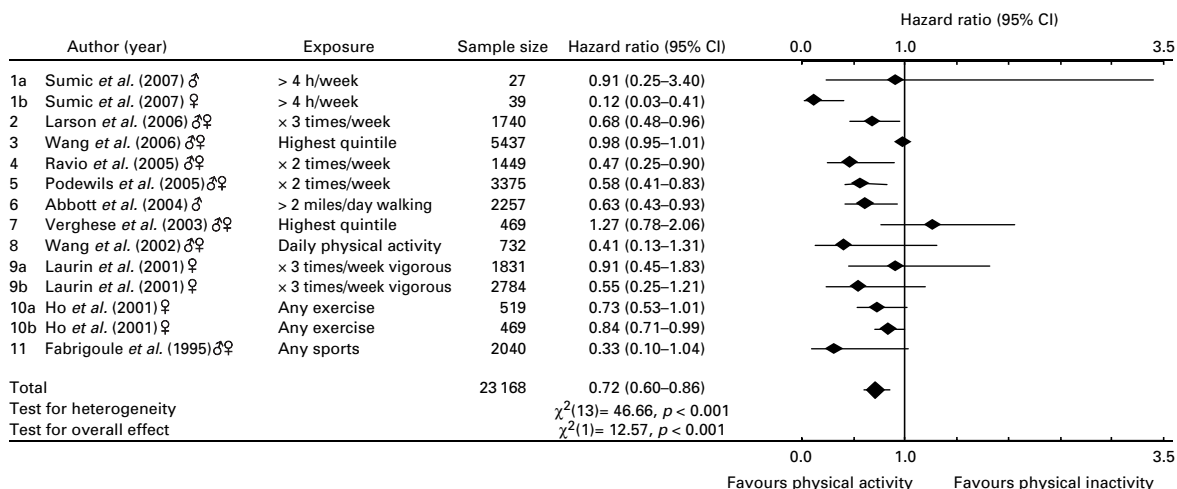
	Author (year)	Exposure	Sample size	Hazard ratio (95% CI)
1a	Sumic *et al.* (2007) ♂	> 4 h/week	27	0.91 (0.25–3.40)
1b	Sumic *et al.* (2007) ♀	> 4 h/week	39	0.12 (0.03–0.41)
2	Larson *et al.* (2006) ♂♀	× 3 times/week	1740	0.68 (0.48–0.96)
3	Wang *et al.* (2006) ♂♀	Highest quintile	5437	0.98 (0.95–1.01)
4	Ravio *et al.* (2005) ♂♀	× 2 times/week	1449	0.47 (0.25–0.90)
5	Podewils *et al.* (2005)♂♀	× 2 times/week	3375	0.58 (0.41–0.83)
6	Abbott *et al.* (2004) ♂	> 2 miles/day walking	2257	0.63 (0.43–0.93)
7	Verghese *et al.* (2003) ♂♀	Highest quintile	469	1.27 (0.78–2.06)
8	Wang *et al.* (2002) ♂♀	Daily physical activity	732	0.41 (0.13–1.31)
9a	Laurin *et al.* (2001) ♀	× 3 times/week vigorous	1831	0.91 (0.45–1.83)
9b	Laurin *et al.* (2001) ♀	× 3 times/week vigorous	2784	0.55 (0.25–1.21)
10a	Ho *et al.* (2001) ♀	Any exercise	519	0.73 (0.53–1.01)
10b	Ho *et al.* (2001) ♀	Any exercise	469	0.84 (0.71–0.99)
11	Fabrigoule *et al.* (1995)♂♀	Any sports	2040	0.33 (0.10–1.04)
	Total		23 168	0.72 (0.60–0.86)
	Test for heterogeneity		$\chi^2(13)= 46.66, p < 0.001$	
	Test for overall effect		$\chi^2(1)= 12.57, p < 0.001$	

Fig. 2. The association between physical activity and dementia in prospective cohorts.

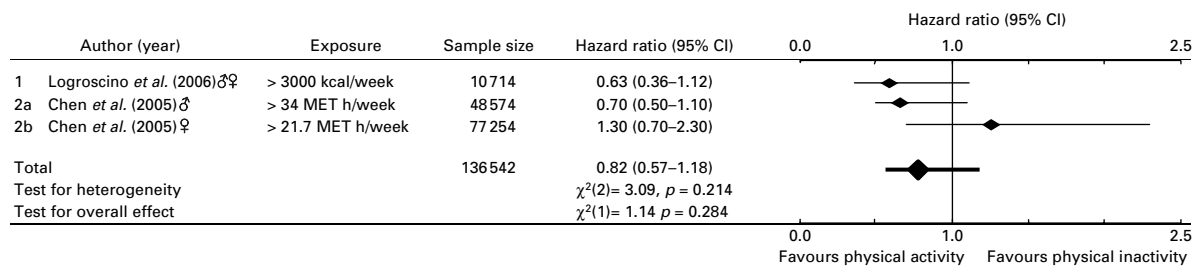|	Author (year)	Exposure	Sample size	Hazard ratio (95% CI)
1	Logroscino *et al.* (2006)♂♀	> 3000 kcal/week	10 714	0.63 (0.36–1.12)
2a	Chen *et al.* (2005)♂	> 34 MET h/week	48 574	0.70 (0.50–1.10)
2b	Chen *et al.* (2005)♀	> 21.7 MET h/week	77 254	1.30 (0.70–2.30)
	Total		136 542	0.82 (0.57–1.18)
	Test for heterogeneity		$\chi^2(2)= 3.09, p = 0.214$	
	Test for overall effect		$\chi^2(1)= 1.14\ p = 0.284$	

Fig. 3. The association between physical activity and Parkinson's disease in prospective cohorts.

Parkinson's disease, although this finding should be viewed in light of limited evidence in this area. Further evidence presented in Table 2 also strongly supports the role of physical activity in preventing cognitive decline.

There was a large amount of heterogeneity in our findings that was possibly due to different gender effects although there were limited studies to specifically examine this issue. Possible gender effects might reflect differences in biological responses to exercise in men and women (Day, 2008) that have relevance for cognitive health, although future studies should be conducted to confirm this finding. The higher quality studies demonstrated more robust effects and this may have been partly due to more precise categorization of physical activity exposure. A substantial proportion of the included studies did not accurately define physical activity levels in terms of frequency, duration and intensity, which may be important in relation to risk of neurodegenerative disease. Nevertheless, in studies that examined relative risk of dementia across well-defined physical activity quintiles, a linear dose–response relationship was not consistently demonstrated. For example, Abbott *et al.* (2004) showed a linear reduction in risk

of dementia across quintiles of increasing daily walking distance, although in other reports that assessed physical activity from combined frequency, duration and intensity data, there was weaker evidence for a dose–response relationship (Laurin *et al.* 2001; Podewils *et al.* 2005). Data from the Nurse's Health Study (Weuve *et al.* 2004) have demonstrated that walking for a minimum of 1.5 h per week is associated with better cognitive performance and in a cohort of Dutch men, decreasing activity duration by more than 60 min/day over 10 years resulted in significant cognitive decline (van Gelder *et al.* 2004). The optimal dose of physical activity for risk reduction therefore remains to be accurately defined.

One important factor that is likely to bias the association between physical activity and neurodegenerative disease risk is the presence of subtle cognitive changes at baseline that may influence physical activity and other lifestyle behaviours. Thus studies with short follow-ups and a lack of adjustment for cognitive function at baseline may be particularly vulnerable to such biases. In addition, the timing of physical activity assessment in relation to neurodegeneration might be crucial. For example, it is not clear at what stage in an individual's

life physical activity is most important for future protection.

Physical activity may be protective against cognitive decline and neurodegenerative diseases through a number of possible mechanisms. Regular exercise is likely to promote vascular health by lowering blood pressure, lipids, obesity and inflammatory markers, and improving endothelial function, which are risk factors for dementia and Alzheimer's disease (Kivipelto *et al*. 2005; Rosendorff *et al*. 2007). In particular, cerebral circulation appears to be important for cognitive performance and exercise adaptations may involve improved blood flow and oxygen supply to these areas. Beneficial effects of exercise on reducing amyloid β plaques in the frontel cortex have been demonstrated recently in a transgenic mouse model (Adlard *et al*. 2005; Lazarov *et al*. 2005), which might be mediated through insulin control (Farris *et al*. 2003). Studies of physical activity and cerebrovascular structural abnormalities have reported no association between physical activity levels and white matter lesions (Carmelli *et al*. 1999; Podewils *et al*. 2007), although improvements in aerobic fitness were shown be related to greater white matter integrity in select brain regions (Marks *et al*. 2007). Other mechanisms may involve effects on brain plasticity and cognitive reserve, angiogenesis, neurogenesis, synaptogenesis, and increased levels of neurotrophic factors (Cotman & Berchtold, 2002; Kramer *et al*. 2005; Cotman *et al*. 2007). An emerging theory is that exercise enhances several growth factors, such as brain-derived neurotrophic factor and insulin-like growth factor, which mediate the protective and therapeutic effects of exercise on brain function (Cotman *et al*. 2007). There is evidence to suggest the pro-inflammatory cytokines impair some of the growth factor signalling pathways in the brain, thus anti-inflammatory actions of exercise may be important.

In conclusion, our results suggest that physical activity is protective against future risk of dementia and Alzheimer's disease. However, the optimal dose of physical activity for risk reduction remains to be accurately defined and this should be a focus of future research.

Acknowledgements

Declaration of Interest

None.

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