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**Is physical activity a potential preventive factor for Vascular dementia? A  
systematic review**

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# Is physical activity a potential preventive factor for Vascular dementia? A systematic review

## Aging & Mental Health

### Abstract

#### Background

Physical exercise has several beneficial effects, including reduced risk for Alzheimer's disease.

Although several studies of potential risk factors for Vascular dementia (VaD) exist, including physical activity, the studies have usually included few participants and there are no meta-analyses addressing this key topic.

#### Methods

The MEDLINE database was searched using the key words "physical exercise" or "activity" or "walking" in combination with "dementia" and "vascular dementia". Potentially relevant studies were assessed and summarised by two of the authors, and longitudinal studies with operationalised definition of physical activity providing risk for VaD in both groups were included in the meta-analysis using pooled estimates from a random effects model.

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#### Results

A total of 24 longitudinal studies, including 1378 patients with VaD, were included in the review. The majority of individual studies did not report significant associations. Five studies fulfilled criteria for meta-analysis, including 10,108 non-demented control subjects and 374 individuals with VaD. The meta-analysis demonstrated a significant association between physical exercise and a reduced risk of developing VaD: OR 0.62 (95%CI 0.42 – 0.92).

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#### Conclusions

We conclude that there is evidence supporting the hypothesis that physical activity is likely to prevent the development of VaD, and should be highlighted as part of secondary prevention programmes in people at risk for cerebrovascular disease.

**Key words:** vascular dementia, physical activity, risk factor, prevention, meta-analysis

## **Is physical activity a potential preventive factor for Vascular dementia? A systematic review**

### **Introduction**

There are twenty-five million people with dementia worldwide (Wimo, Jonsson, & Winblad, 2006). Vascular dementia (VaD) diagnosed clinically accounts for approximately 20%, or 5 million of these individuals, with an estimated 20,000 people a year developing VaD in the UK alone. A further 10-30 % of people have a combination of Alzheimer's disease (AD) and VaD. Despite the high level of need, there are currently no licensed drugs for the treatment or prevention of VaD.

The risk factors for dementia are gradually being elucidated. In addition to age, sex, and genetic factors, a variety of environmental factors such as education, diet, and mental activity seem to be associated with the risk of developing dementia (Blennow, de Leon, & Zetterberg, 2006). The majority of studies have, however, focused on AD, and less is known regarding risk factors for VaD.

The American Centre for Disease Control and Prevention and the American College of Sports Medicine recommend adults to have 30 min or more of moderate-intensity physical activity on five days of the week, due to the strong evidence of an association between physical activity and the primary prevention of type 2 diabetes, cardiovascular disease and premature mortality (Haskell, Lee, Pate, Powell, Blair et al., 2007), and similar recommendations were made for older people (Nelson, Rejeski, Blair, Duncan, Judge et al., 2007). Such an association would suggest that cognitive impairment and dementia due to cerebro-vascular disease might also be prevented by

physical activity. Potential mechanisms for such an effect include reduction of inflammation and increasing trophic factor production and neurogenesis in addition to reduction in cardiovascular disease. Several studies have explored whether regular physical activity would reduce the risk for AD, and in a recent meta-analysis, a beneficial effect of physical activity on the reduced risk for AD was indeed found (Hamer & Chida, 2009).

A few longitudinal studies have explored whether physical activity reduces the risk for VaD. The findings are conflicting. Some studies have supported this hypothesis, whereas others have not found such an association. Most studies have included relatively few subjects with VaD, resulting in low statistical power. No meta-analysis or systematic reviews addressing this topic exist. Accordingly, we performed a systematic review and a meta-analysis by searching the Medline for studies addressing whether regular physical activity is associated with a lower risk for VaD.

Longitudinal studies with operationalised definition of physical activity reporting risk for VaD in both groups were included.

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## Methods

### *Search strategy*

Medline was searched on 17/09/2008 using key words: physical exercise or activity or walking in combination with dementia and vascular dementia. In addition, the reference lists of the reviewed articles were searched. The number of hits were: dementia and: -exercise (458), -activity (1397), -walking (353); vascular dementia and: -exercise (38), -activity(88), -walking(28). Only papers published in English were included, and those that were a clinical trial, naturalistic study, meta-analysis,

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clinical trials, systematic review, comparative study or a twin study. We identified 436 papers fulfilling these criteria. After limiting the search to those including persons older than 18, eliminating studies not focused on the incidence or prevalence of dementia there remained 46 studies conducted and published after June 1990 which were considered further for inclusion. The 46 papers were read, and their reference lists were used for a more elaborate literature search. Taking into account our inclusion criteria (see below) and after searching for additional key studies by hand, we had a final list of 24 papers. The search was repeated on May 30<sup>th</sup> 2009, but no additional papers were added to the list.

### ***Criteria for inclusion in meta-analysis***

- 1-Paper based on an original study
- 2-Case selection included total dementia or vascular dementia or vascular cognitive impairment.
- 3-Longitudinal, prospective study
- 4-Having a control group.
- 5-Diagnosis of dementia and VaD were based on operational criteria
- 6-Operationalised definition of exercise at baseline
- 7-A temporal relationship between exercise and dementia could be observed
- 8-A reported odds ratio (OR) or relative risk and standard error measuring the association between physical activity and VaD or provision of enough data to allow for their calculation.

### ***Data collection and analysis***

References retrieved by the search strategy were examined by two reviewers (FS, DAa) in order to discard those which were not eligible for the review. The full text of remaining references was retrieved and the inclusion criteria were applied to these independently by the same two reviewers. Disagreements were resolved by discussion between the two reviewers and consultation with a third reviewer (CB).

### *Data analysis*

The summary data and statistics required for each study was summarized in tables. For the meta-analysis, as the outcomes were binary, ie VaD or no dementia, the odds ratio was used to measure the treatment effect across two groups: low and high physical activity. Studies reporting RRs were also included as the RR was thought a good approximation to the OR in this analysis. An inverse-variance weighted estimate of the typical treatment effect across trials was calculated. The pooled estimate from a fixed-effects model is presented and a test for heterogeneity using a standard chi-square statistic and I-squared were performed. If, however, there was evidence of heterogeneity of the treatment effect between trials then a random-effects model would be used. Evidence of possible publication bias was examined via a funnel plot. All analyses were performed using the Review Manager Version 5.0 and Stata Intercooled Version 9.2.

### **Results**

Of the 24 studies (including 1,378 individuals with VaD) considered for final inclusion, 5 papers (374 with VaD, 10,108 without dementia) fulfilled all criteria for inclusion in the meta-analysis: (Abbott, White, Ross, Masaki, Curb et al., 2004; Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001; Podewils, Guallar,

Kuller, Fried, Lopez et al., 2005; Ravaglia, Forti, Lucicesare, Pisacane, Rietti et al., 2008; Yoshitake, Kiyohara, Kato, Ohmura, Iwamoto et al., 1995). In addition, two studies provided results of the association between physical activity and development of VaD, but did not provide specific data related to the VaD group (Taaffe, Irie, Masaki, Abbott, Petrovitch et al., 2008; Yamada, Kasagi, Sasaki, Masunari, Mimori et al., 2003).

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Characteristics of the studies included in the meta-analysis are shown in table 1. In only one of the studies (Ravaglia et al., 2008) a significant association between physical activity and risk for VaD was found. However, the number of people with VaD was low, 54 or lower in four of the five studies, and thus the statistical power to detect an effect was low.

The diagnosis of VaD was made according to consensus criteria, after a screening measure, based on informant-based history, neuropsychological testing, clinical assessment by a physician, laboratory tests and neuroimaging. In one study (Yoshitake, Kiyohara, Kato, Ohmura, Iwamoto et al., 1995), a neuropathological diagnosis was available for most cases. The definition and classification of physical activity differed between the studies, although was based on the current level of physical activity at time of baseline assessment, i.e. while being free from dementia.

In three studies, trained interviewers used a standardised interview (Ravaglia et al., 2008; Yoshitake, Kiyohara, Kato, Ohmura, Iwamoto et al., 1995; Podewils, Guallar, Kuller, Fried, Lopez et al., 2005), one used a clinical interview (Abbott et al., 2004) and one combined questions from two questionnaires (Laurin et al., 2001). One study rated the level of physical activity during leisure period and work, defining the physically active group as those including daily exercise during the leisure period or

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at least moderate severe activity during work (Yoshitake, Kiyohara, Kato, Ohmura, Iwamoto et al., 1995). Two reported the estimated daily energy expenditure, but reported on tertiles (Ravaglia et al., 2008) or quartiles (Podewils et al., 2005). One study used the average walking distance per week (Abbott et al., 2004), whereas one classified into groups based on the number of times and the intensity of physical activities per week (Laurin et al., 2001), both studies divided physical activity into four categories. To compare among studies, two groups were created, low and high physical activity, by collapsing the two lowest and highest groups from the three studies with four categories, and by categorising the two highest tertiles in the high group and the lowest tertile in the low group in the fourth study. The fixed-effects meta-analysis demonstrated a significant association between physical exercise and the risk of developing VaD: OR 0.72 (95%CI 0.58 – 0.90). However, evidence of heterogeneity was found, with  $I^2=66.4%$  ( $p=.03$ ). We therefore re-analysed using a random effects model and the pooled OR remained statistically significant (0.62, 0.42 – 0.92). (Figure 1). Due to the small number of studies, quantitative analyses to identify sources of heterogeneity, such as subgroup analyses, were not performed. Although there was a low number of studies, visual analysis of the funnel plot indicated some evidence of publication bias, with potentially a lack of smaller studies observing effects that were positive or close to null. In neither of the two studies reporting on the association between VaD and physical activity but without reporting data was a significant association between VaD and physical activity found (table 2).

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Twelve studies reported the association of physical exercise and the development of dementia, not excluding VaD, but did not report a specific association with VaD: (Andel, Crowe, Pedersen, Fratiglioni, Johansson et al., 2008; Broe, Creasey, Jorm, Bennett, Casey et al., 1998; Carlson, Helms, Steffens, Burke, Potter et al., 2008;

Crowe, Andel, Pedersen, Johansson, & Gatz, 2003; Fabrigoule, Letenneur, Dartigues, Zarrouk, Commenges et al., 1995; Larson, Wang, Bowen, McCormick, Teri et al., 2006; Li, Shen, Chen, Zhau, Li et al., 1991; McCallum, Simons, Simons, & Friedlander, 2007; Rovio, Kareholt, Helkala, Viitanen, Winblad et al., 2005; Rovio, Kareholt, Viitanen, Winblad, Tuomilehto et al., 2007; Scarmeas, Levy, Tang, Manly, & Stern, 2001; Verghese, Lipton, Katz, Hall, Derby et al., 2003; Wang, Karp, Winblad, & Fratiglioni, 2002) (table 3). In five of these, a statistically significant protective effect of physical exercise on the risk of total dementia found, although in one study, this effect was found only in men (Fabrigoule et al., 1995; McCallum, Simons, Simons, & Friedlander, 2007). In seven studies, no significant effect between physical activity and risk for dementia was found.

Finally, five studies reported on the association between physical exercise and cognitive decline, not excluding vascular cognitive impairment, but in these studies, a diagnosis of dementia was not made: (Lautenschlager, Cox, Flicker, Foster, van Bockxmeer et al., 2008; Lytle, Vander Bilt, Pandav, Dodge, & Ganguli, 2004; Middleton, Kirkland, & Rockwood, 2008; Sumic, Michael, Carlson, Howieson, & Kaye, 2007; Verghese, LeValley, Derby, Kuslansky, Katz et al., 2006) Four of these studies reported that cognition was positively associated with physical activity. In two of these, the effect was significant in women only. In one study, no such association was found (Verghese et al., 2006). In a report from the Canadian Study of Health and Aging, which was also the basis for one of the studies included in the meta-analysis (Laurin et al., 2001), a subgroup of people with “Cognitive Impairment, No Dementia” (CIND) were classified as vascular CIND (Middleton, Kirkland, & Rockwood, 2008). In women, physical activity was associated with a lower risk for vascular CIND, but no effect on vascular or total CIND was found in men. Physical

activity was classified based on the number and intensity of various physical activities performed during a week, and groups were collapsed into “moderate-high” exercise (three or more times per week, at least as intense as walking) or “low” (all other physical activity).

## Discussion

In addition to the many well-known beneficial effects of physical exercise, this systematic review demonstrates a significant reduced risk for VaD in people who are more physically active compared to people who are less physically active using meta-analysis technique. Since most studies have low statistical power due to a low number of people with VaD, a meta-analysis is more suited to address this important question. The usefulness of meta-analysis is highlighted by the fact that only one of the five studies included in the meta-analysis reported a positive effect which reached significance (Ravaglia et al., 2008).

Physical activity is a complex behaviour that is indeed difficult to assess. A poor assessment method of physical activity will dilute the estimated associations because of misclassification of individuals (Andersen, 2004). Two of the studies included used weekly energy expenditures, whereas in the other studies, the daily walking distance, the number of times performing physical activity per week, or frequency and intensity of physical activity at work or during leisure periods were reported. Since the cohorts were evenly divided in four, three, or two groups based on the level of physical activity, (that is ranking from the lowest to the highest level), we think that combining these categories is reasonable. However, we did not make any attempt to identify a

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dose-relationship, or a minimal cut-off level of physical exercise needed to have a positive effect on the risk of VaD.

The quality of the studies varied, and there were several factors that varied among the studies and which might have influenced the findings. All studies were naturalistic longitudinal studies, and factors other than physical exercise may differ between the groups. Potential confounders such as smoking, diet, diabetes, cholesterol levels, and cardiovascular disease may have influenced the findings in the meta-analysis. Finally, different criteria for VaD differ were used. The criteria for VaD differ regarding which patients are included as VaD or not when applied to the same persons (Wiederkehr, Simard, Fortin, & van Reekum, 2008), and thus the choice of VaD criteria might influence the findings.

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The first attempt to test the hypothesis that physical exercise can prevent cognitive decline and possibly dementia in a randomised trial of persons at high risk was recently reported (Lautenschlager et al., 2008). People who had subjective and objective cognitive impairment but did not meet criteria for dementia were randomised to a 24-week home-based program of physical activity or an education and usual care group. After 18 months, 12 months after the intervention, difference on some of the cognitive outcome measures favouring the physical activity group was found (Lautenschlager et al., 2008). The findings from this study support the hypothesis that physical exercise can improve cognitive functioning in people at risk for dementia, suggesting that physical exercise may in fact protect against the development of dementia, including VaD or delay age at onset.

The time between baseline assessment of physical exercise and diagnosis of VaD was rather short, varying between 4 and 7 years. Since dementia is a gradual process, subtle cognitive impairment might be present already at baseline and possibly influence the level of physical activity. In some studies therefore, adjustment for baseline cognitive performance was attempted. On the other hand, the relatively short duration of some studies, could actually be a "positive" finding, since it implies that change can be achieved after a relatively short timeframe of physical activity. Provided that the preventive effect can be sustained over longer period of time, this may make secondary prevention more achievable. Another limitation is that the threshold for classifying physical activity differed among studies. In the meta-analysis, these were selected a priori based on best judgement of the reviewers and may not have been the optimal thresholds. There was heterogeneity between the studies. The small number of studies included in the meta-analysis precluded sensitivity analyses to explore the causes of heterogeneity. Since all included studies were population-based, potential sources of heterogeneity are the use of two different criteria for VaD, and, probably most importantly, different methods to define and classify physical activity.

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Several intervention studies have assessed the effect of physical exercise on cognition in healthy elderly and various clinical groups such as depressed persons or individuals with cardiovascular disease, and positive effects have been reported (Colcombe & Kramer, 2003). The effect of physical exercise on people with cognitive impairment and dementia has also been studied, and several meta-analyses have reported positive effects on cognition (Colcombe & Kramer, 2003) and also on brain atrophy (Burns, Cronk, Anderson, Donnelly, Thomas et al., 2008), although a recent Cochrane analysis concluded that there was insufficient evidence to say whether or not physical

activity programs are beneficial for people with dementia (Forbes, Forbes, Morgan, Markle-Reid, Wood et al., 2008). One might expect a gradual decrease in VaD risk over time related to improved treatment and higher uptake of treatment for cardiovascular risk factors which will complement physical activity. The fact that the only significant finding was reported in the most recent study is in support of this hypothesis. However, no intervention studies have yet focused on people with cognitive impairment thought to be caused by vascular factors. On the basis of the findings in this meta-analysis we recommend that intervention studies using physical activity for people with vascular risk factors with and without cognitive impairment should be conducted.

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The recent recommendations for physical activity (Haskell et al., 2007) state that as an alternative to the minimum of 30 minutes on five days each week adults could do vigorous-intensity activity for a minimum of 20 minutes on three days each week. Furthermore, because of the dose-response relationship between physical activity and health persons may benefit more by exceeding the minimum recommended amounts of physical activity. Whether this applies in the primary prevention of VaD is not yet known. Data from one cohort study showed that walking corresponding to the amount required meeting the current guidelines was associated to 34% reduction in risk of cognitive impairment (Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001).

The amount of physical activity a person does is influenced by many environmental and social factors, not just personal choice. Indeed, in order to achieve the recommended goals of physical activity these and medical factors should be addressed collectively. The potential is huge; the majority of adults in Westernised countries do not meet the minimum recommendation of physical activity (Anderssen,

Engeland, Sogaard, Nystad, Graff-Iversen et al., 2008). Most adults contact their GP at least once a year, and GPs are in dialogue with groups it is normally difficult to get health information out to. Interestingly, advising patients in consultations leads to a 12-50% increase in activity level 6 months after the consultation, and increased frequency and intensity through repeated contact over several months yields a further increase in activity level (Aittasalo, Miilunpalo, Kukkonen-Harjula, & Pasanen, 2006). To achieve change at population levels however evidence on major environmental and social initiatives are required.

### ***Conflict of interest***

No conflict of interest.

### ***Funding***

The project was funded by the UK Alzheimer's Society, who took part in formulating the research question, but had no influence on the choice of design, data collection, data analysis or decision to publish.

### ***Description of author roles***

CB designed the study and supervised data collection, performed the meta-analysis, and critically revised the paper. DAa participated in the literature search and compiling of the data, and wrote the manuscript.

FS collected data and assisted with writing the paper.

SA assisted in writing the paper, including a critical revision of the final version.

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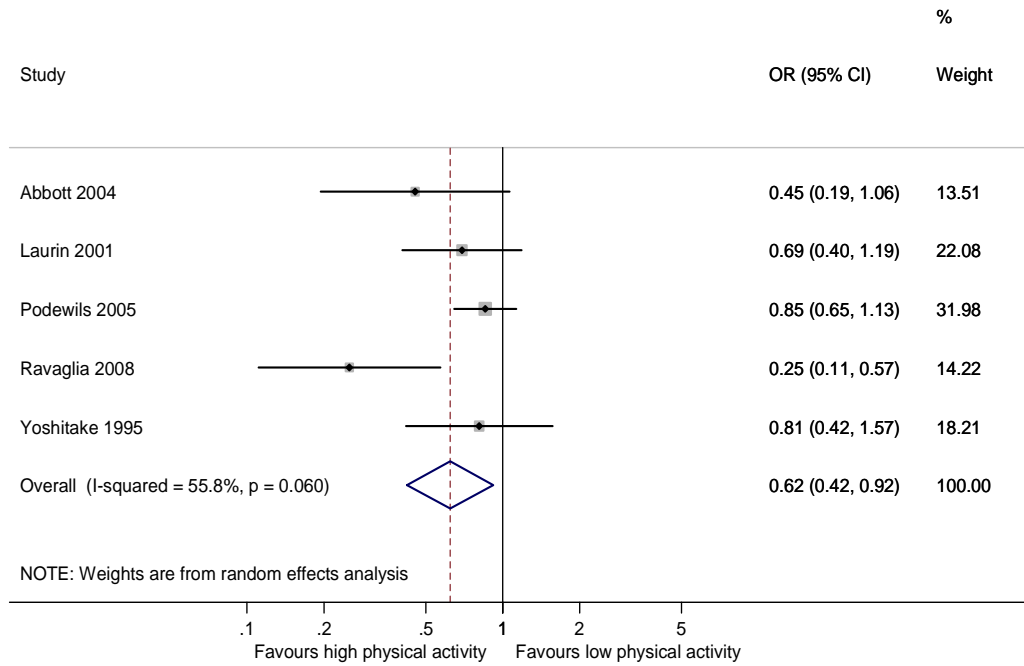


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## Is physical activity a potential preventive factor for Vascular dementia? A systematic review

Figure 1. Forest plot of the effect of physical activity on incident VaD



## Is physical activity a potential preventive factor for Vascular dementia? A systematic review

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Table 1. Studies included in the meta-analysis

Study	Selection	Country	VaD criteria	Exercise classification	Duration follow-up, y	Number	Results	Age at baseline, y	Number of cases with physical exercise <sup>5</sup>			
									1	2	3	4
Laurin 2001	Population	Canada	NINDS-AIREN	High exercise: Three or more times , more intense than walking per week Moderate: Three or more, equal intensity to walking Low exercise: all other exercises No exercise	5	ND: 3894 VaD: 54	ns <sup>1</sup>	73.5	1103 23	485 5	1360 18	731 8
Podewill 2005	Population	US	ADDTC	energy expenditure /week (quartiles)	5.4	ND: 2895 VaD: 213	ns <sup>2</sup>	75	715 55	706 58	733 52	740 48
Abbott 2004	Population (men)	US-Hawaii	ADDTC	Distance walked per day (miles) (<0.25; 0.25-1; 1-2; >2)	7.3	ND: 2099 VaD: 30	ns <sup>3</sup>	77	551 10	706 13	406 1	436 6
Ravaglia 2008	Population	Italy	NINDS-AIREN	energy expenditure /week (tertiles)	4	ND: 663 VaD: 27	0.34(0.14-0.82) <sup>4</sup>	73	213 18	223 4		209 5

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Formatert tabell

<u>Yoshitake 1995 Population Japan</u>	<u>NINDS-AIREN</u>	-----	7	<u>ND: 557</u>	<u>Ns (RR 0.81: 0.42-1.57)</u>	73	=	=	-----
		<u>Four categories each for leisure and work<sup>6</sup></u>		<u>VaD: 50</u>			=	=	

- 1) Adjusted for age, sex, education (p=0.46)
- 2) P for trend. Hazard Ratios, comparing the lowest energy expenditure groups with the three others, increasing expenditure: 1.32 (0.89-1.96); 0.99(0.63-1.57); 1.03 (0.64-1.67). Adjusting for age, education, gender, ethnicity, APOE, baseline cognition, MRI, ADL, instrumental ADL, social network, social support
- 3) Comparing the group walking >2 miles/day with the three other groups, adjusted for APOE, baseline cognition, education, physical performance and decline in performance, body mass index, childhood years spent living in Japan, job status, hypertension, diabetes, CHD, total and HDL cholesterol. p-values were 0.8 (<0.25 mile/d), 0.8 (0.25-1 mile/d) and 0.09 (>1-2 mile/d).
- 4) Hazard ratio (HR) for VaD comparing highest and middle tertiles pooled together with lowest tertile, adjusted for confounders (CVD, hypertension, hyperhomocysteinemia, comorbidity, basic ADL skills (Model III)
- 5) Levels of physical activity: 1=minimum, 4=maximum activity
- 6) Physically active group defined as those with daily exercise during the leisure period or moderate to severe activity during work

← - - - - **Formatert:** Punktmerking og nummerering

#### Abbreviations:

ADDC: Alzheimer's Disease Diagnostic and Treatment Centers (Chiu HC et al. Neurology 1992;42:473-80); NINDS-AIREN: National Institute of Neurological and Communicative Disorders and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NINDS-AIREN: National Institute of Neurological and Communicative Disorders and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition; VaD: Vascular dementia; ND: No dementia

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Table 2. Studies reporting on the association between physical exercise and vascular dementia without reporting exact numbers

Study	Selection	Region	VaD criteria	Exercise definition	Follow up time, yrs	Number of cases, ND/VaD	Mean age Years, baseline	Results	Comments
Yamada 2003	Population	Japan	DSMIV	Physical Activity Index <sup>1</sup>	30	1774/38	Midlife	Ns	Data not shown
Taaffe 2008	Population (men)	Pacific	ADDTC	Physical Activity Index <sup>2</sup>	6	2090/31	77	Ns	Data not shown

- 1) Physically active group defined as those with daily exercise during the leisure period or moderate to severe activity during work
- 2) Individuals estimate how many hours they spend sleeping, resting, being sedentary, or engaged in light, moderate, or heavy activity. These numbers are weighted based on estimated oxygen consumption for each activity (Kannel WB, Sorlie P. Arch Intern Med 1979;139:857-61)

### Abbreviations:

ADDTC: Alzheimer's Disease Diagnostic and Treatment Centers (Chiu HC et al. Neurology 1992;42:473-80); NINDS-AIREN: National Institute of Neurological and Communicative Disorders and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NINDS-AIREN: National Institute of Neurological and Communicative Disorders and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition; VaD: Vascular dementia; ND: No dementia. Ns: Not significant

**Slettet:** Yoshitake 1995

**Slettet:** Population

**Slettet:** Japan

**Slettet:** NINDS-AIREN

**Slettet:** Four categories each for leisure and work<sup>1</sup>

**Slettet:** 7

**Slettet:** 557/50

**Slettet:** 73

**Slettet:** ns

**Slettet:** Relative risk 0.81 (0.42-1.57)(unadjusted)

**Slettet:** Index<sup>2</sup>

### Is physical activity a potential preventive factor for Vascular dementia? A systematic review

Table 3. Association between physical exercise and dementia including VaD but not providing VaD-specific results

Study	Selection	Country	Dementia criteria	Exercise definition	Fup time, yrs	Number of cases, ND/Dem	Mean age Years, baseline	Results*	Significance
Fabrigoule 1995	Population	France	HIS	Sports or gymnastic participation, yes/no	3	2043/21	75	RR 0.33(0.10-1.04)	If adjusted for age only
Broe 1998	Population	Australia	DSMIV	Times per month doing active sports, gardening, exercise, walks	3	327/47	81	No significant association (Data not provided)	No
Scarmeas 2001	Population	US	DSMIIR Stroke-rel. Dem.	Walking or physical conditioning last month, yes/no	2.9	1772/207 VaD 35	75	RR 0.80 (0.66-0.97)	Yes
Wang 2002	Population	Sweden	DSMIIR	Swimming, walking, gymnastics (no, less than daily, daily)	6	732/123	81	RR 0.67(0.34-1.33)	No effect
Verghese 2003	Population	US	DSMIIR ADRCC	11 physical activities# (daily, several days/w, once weekly, monthly, occasionally, never)	5	469/124Va D 30	79	Total score: HR 0.99 (0.91-.01)	Frequent vs rare dancing: 0.24 (0.06-0.99)
Crowe 2003	Twin registry	Sweden	NINDS-AIREN	Regularly involved in playing sports before age of 40, yes/no	20+	107/107	57	Data not provided	No

Rovio 2005	Population	Finland	DSMIV	Leisure-time physical activity <sup>1</sup>	21	2000/117	51	OR 0.47(0.25-0.90)	Yes
Larson 2006	Population	US	DSMIV	Days per week doing physical activity <sup>2</sup>	6	1343/158	75	HR 0.62(0.44-0.86)	Yes
McCallum 2007	Population	Australia	Medical records -ICD	Walking, gardening and sporting activity (daily, weekly or less often)	14	2805/285	60+	Gardening: HR 0.64(0.5-0.83) Walking: 1.0(0.78-1.28)	Gardening, but not walking
Rovio 2007	Population	Finland	DSMIV	Work-related or commuting physical activity <sup>3</sup>	21	1158/44	51	Work-related: R 1.45(0.66-3.17) Commuting: OR 0.46 (0.1-2.17)	Neither occupational nor commuting activity
Carlson 2008	Twin registry	US	DSMIIR	13 Physical activities (never-1 to daily-5) <sup>4</sup>	15	147/147	45	OR 0.99 (0.73-1.33)	No
Andel 2008	Twin registry	Sweden	NINDS-AIREN	Exercise from age 25 to 50 <sup>5</sup>	31	2870/264	48	Light: 0.63(0.43-0.91) Regular: 0.34(0.16-0.72) Hard: 0.7(0.40-1,24)	Light and regular, but not hard physical activity

\*Results after adjustment for maximum number of potential confounders

**Abbreviations:**

ADDTC: Alzheimer's Disease Diagnostic and Treatment Centers (Chiu HC et al. Neurology 1992;42:473-80); NINDS-AIREN: National Institute of Neurological and Communicative Disorders and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; NINDS-AIREN: National Institute of Neurological and Communicative Disorders and Association Internationale pour la Recherche et l'Enseignement en Neurosciences; Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition; ND: No dementia HIS: Hachinski Ischemia Scale; ICD : International Classification of Diseases, 9<sup>th</sup> edition, Clinical Modification (World Health Organisation and US National Center for Health Statistics) and 10<sup>th</sup> edition, Australian modification; Q: Questionnaire; VaD: Vascular dementia; ND: No dementia

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# tennis or golf, swimming, bicycling, dancing, group exercises, team games such as bowling, walking for exercise, climbing more than two flights of stairs, housework, babysitting)

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- 1) Participating in leisure-time physical activity that lasts at least 20-30 mins and causes breathlessness and sweating (Daily, 2-3 times a week, once a week, 2-3 times a month, a few times a year, not at all. Dichotomized into "active": at least twice week or "sedentary" people (less than twice a week)
- 2) Number of days last year, for at least 15 minutes, doing walking, hiking, bicycling, aerobics, swimming, weight training or stretching, or other exercise. "Regularly" defined as at least 3 times a week.

3) "How physically heavy is your work?" Original four categories dichotomized into sedentary work and physical work. Daily commuting physical activity: minutes per day walking, bicycling, other physical activity when going to or from work (not at all (sedentary), 59 min or less (moderately active), at least 60 min (active)

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4) No details of physical activities provided

5) Hardly any exercise-0; light exercise such as walking or light gardening-1; regular exercise involving sports-2; hard physical training-3 (Results from case-control analysis)

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Table 4. Studies of the association between physical exercise and cognitive decline

Study	Selection	Country, Ethnicity	Cognition	Exercise definition	Follow up time, yrs	Number of cases,	Mean age, baseline	Results	Significant effect
Lytle 2004	Population	US	MMSE	Q: frequency and type, aerobic/anaerobic	2	929	77	Risk for 3+ decline: OR=0.39(0.19 – 0.78)	Yes
Verghese 2006	Population	US	aMCI	Participation in 10 physical activities	5-6	346	79	HR 0.985(0.967-1.008)	No
Sumic 2007	Volunteers 85+	US	MMSE CDR	Q: walking distance, h/w in light phys activ	4.7	66	88.5	High(>4 hrs/w): Women: 88% decrease	Yes, but women only
Middleton 2008	Population	Canada	VCI-ND	Validated Q: high 3+/w equal to walking	5	4846	73	OR 0.59 (0.40-0.88)	Yes, but women only
Lautenschlager 2008	RCT adults w memory problems	Australia	ADAS cog	Home-based program for physical activity	1.5	138	69	Modest improvement Difference: -1.3 points (-2.38 to -0.22)	Yes

aMCI: Mild Cognitive Impairment, Amnestic type; MMSE: Mini-Mental State Examination; CDR: Clinical Dementia Rating Scale, ADAS-cog: Alzheimer's Disease Assessment Cognitive subscale; VCI-ND: Vascular cognitive impairment, not demented  
HR: Hazard ratio; OR: Odds ratio



Study	Selection	Country, Ethnicity	Dementia criteria	Exercise definition	Fup time, yrs	Number of cases, ND/Dem	Me ag Yea base
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