

Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease



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Summary

Background Physical activity may help maintain cognitive function and decrease dementia risk, but epidemiological findings remain controversial. The aim of our study was to investigate the association between leisure-time physical activity at midlife and the subsequent development of dementia and Alzheimer's disease (AD).

Methods Participants were randomly selected from the survivors of a population-based cohort previously surveyed in 1972, 1977, 1982, or 1987. 1449 persons (72.5%) age 65–79 years participated in the re-examination in 1998 (mean follow-up, 21 years). 117 persons had dementia and 76 had AD. Multiple logistic regression methods were used to analyse the association between leisure-time physical activity and dementia or AD.

Findings Leisure-time physical activity at midlife at least twice a week was associated with a reduced risk of dementia and AD (odds ratio [OR] 0.48 [95% CI 0.25–0.91] and 0.38 [0.17–0.85], respectively), even after adjustments for age, sex, education, follow-up time, locomotor disorders, *APOE* genotype, vascular disorders, smoking, and alcohol drinking. The associations were more pronounced among the *APOE* ε4 carriers.

Interpretation Leisure-time physical activity at midlife is associated with a decreased risk of dementia and AD later in life. Regular physical activity may reduce the risk or delay the onset of dementia and AD, especially among genetically susceptible individuals.

Introduction

Recent studies have shown that a large proportion of the population undertakes less physical activity than is necessary to maintain good health.¹ At the same time, the proportion of old people is increasing, and age-related diseases, such as dementia and Alzheimer's disease (AD), are becoming major public health problems. Interventions that could postpone the onset of AD even modestly would have a major effect on public health.²

Current data, epidemiological and experimental, suggest that physical exercise may promote brain health, and prevent or slow cognitive decline and development of dementia; however, results are conflicting.^{3–7} Prospective epidemiological studies have previously been done in cohorts of elderly people (baseline age >65 years), but had relatively short follow-up times (3–7 years), making them prone to biases attributable to subclinical dementia and other factors.^{5–12} The aim of our study was to investigate whether leisure-time physical activity at midlife is associated with a decreased risk of dementia and AD later in life. We also investigated whether sex or the *APOE* ε4 allele modify this association.

Methods

Participants

The participants of the Cardiovascular risk factors, Aging and Incidence of Dementia (CAIDE) study were the survivors of four separate, independent, population-based random samples examined within the framework

of the North Karelia Project and the FINMONICA study. These surveys assessed the cardiovascular risk factors in two eastern provinces of Finland: North Karelia and Kuopio. The study design has been described in detail elsewhere.^{13,14}

Having being investigated once at midlife (either in 1972, 1977, 1982, or 1987), 2000 randomly selected individuals, age 65–79 years by the end of 1997, were invited for a re-examination during 1998 (figure 1). 1449 people (72.5%) participated in the re-examination; 900 (62.1%) were women and 549 (37.9%) were men. The mean age (SD) at midlife examination was 50.6 (6.0) years (range 39–64), and was 71.6 (4.1) years (range 65–79) at re-examination. Mean duration of follow-up was 21 years (SD 4.9). The study was approved by the local ethics committee, and written informed consent was obtained from all participants.

Midlife examination

The survey methods used during the baseline (midlife) visit were carefully standardised and complied with international recommendations. They followed the WHO MONICA protocols of 1982 and 1987 and were similar to the methods used in 1972 and 1977. In brief, the baseline survey procedures included a self-administered questionnaire on health behaviour, health status, and medical history. Participants' blood pressure, height, and weight were measured, and body-mass index (BMI) was calculated. A venous blood sample was taken to determine serum cholesterol concentrations.¹³ In addition, the presence of various

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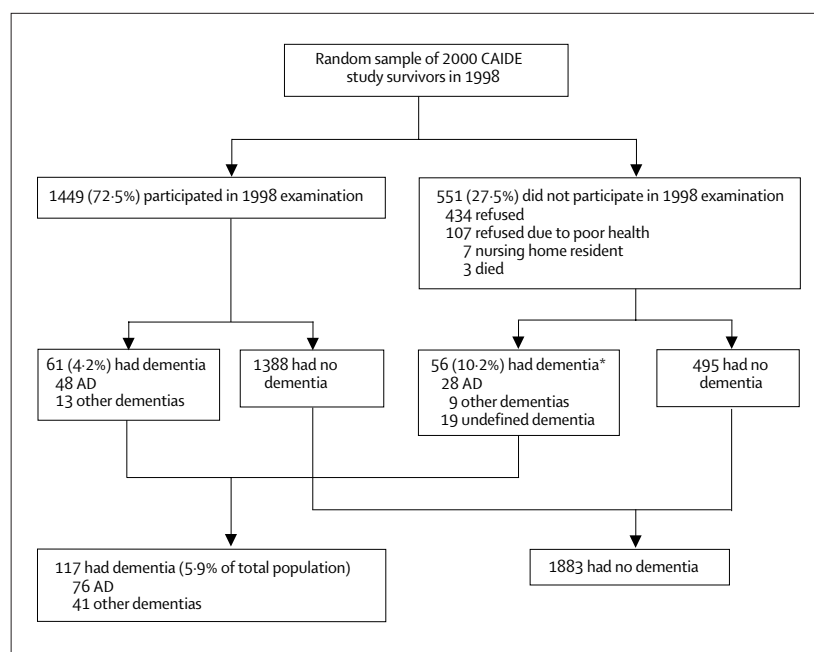


Figure 1: Formation of the study population

Percentages of participants and non-participants in the examination in 1998 are indicated. *Dementia diagnoses from patient records of the local hospitals and primary health-care centres.

locomotor disorders was determined. Participants were categorised as having a locomotor disorder if at least one of following was present: rheumatoid arthritis, arthritis, arthropathy, or arthralgia of the joints of the extremities or the back.

Leisure-time physical activity was assessed on the questionnaire as follows: "How often do you participate in leisure-time physical activity that lasts at least 20–30 mins and causes breathlessness and sweating?" The six response categories were as follows: (1) daily ($n=201$), (2) 2–3 times a week ($n=580$), (3) once a week ($n=421$), (4) 2–3 times a month ($n=250$), (5) a few times a year ($n=404$), and (6) not at all ($n=79$). A trend test for physical activity including these original categories was of borderline significance ($p=0.086$). For the current analyses, these categories were dichotomised as follows: "active" people were defined as those who participated in leisure-time physical activity at least twice a week ($n=781$), and "sedentary" people were defined as those who participated in leisure-time physical activity less than twice a week ($n=1154$). The cut-off for this dichotomisation was based on earlier^{1,15} and more conservative¹⁶ recommendations for health-promoting physical activity. Dichotomisation is also used in other studies on physical activity and dementia, AD, cognitive decline or memory decline.^{6,8,10,17} Our preliminary analyses also showed that the dichotomisation best distinguished participants who developed dementia from those who did not. Data on the midlife physical activity were available for 1935 of 2000 participants who formed the study population. Only two of those with missing data on physical activity had dementia, and none of them had AD.

Re-examination

During the re-examination in 1998, the survey methods we used were identical to those applied in the previous surveys. Furthermore, the participants were studied for their *APOE* genotypes by use of PCR and *HhaI* digestion.¹⁸ Cognitive status was determined, and participants who scored 24 or less on the mini-mental state examination¹⁹ at the screening phase ($n=294$) were referred for further examinations, including thorough neurological and cardiovascular examinations and a detailed neuropsychological examination. 61 participants were diagnosed as having dementia according to the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) criteria,²⁰ of whom 48 fulfilled the diagnostic criteria of AD according to National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.²¹ The dementia diagnoses of non-participants were derived from patients' records of the local hospitals and primary healthcare centres. The total number of dementia cases increased to 117 (5.9% of the population) when these diagnoses were also taken into account. The analyses concerning AD we restricted to AD diagnoses at re-examination ($n=48$) to ensure diagnostic accuracy, but we repeated the analyses by including non-participants and AD cases identified by register linkage only ($n=76$; figure 1).

	Active (n=515)	Sedentary (n=736)	p
Demographics			
Age at midlife (years)	50.8 (6.1)	49.5 (5.8)	<0.001
Age at re-examination (years)	71.5 (4.0)	70.9 (3.9)	0.08
Follow-up time (years)	20.7 (5.0)	21.3 (4.7)	0.02
Education (years)	8.7 (3.6)	8.7 (3.4)	0.96
Men : women	228 (44.3%) : 287 (55.7%)	265 (36.0%) : 471 (64.0%)	0.003
<i>APOE</i> $\epsilon 4$ carriers	171 (33.2%)	267 (36.3%)	0.26
Midlife measurements			
Systolic blood pressure (mm Hg)	144.0 (19.2)	143.8 (20.3)	0.42
Diastolic blood pressure (mm Hg)	89.3 (10.3)	89.2 (11.3)	0.93
Body-mass index (kg/m ²)	26.5 (3.7)	26.4 (3.6)	0.75
Total serum cholesterol (mmol/L)	6.7 (1.2)	6.7 (1.2)	0.98
History of locomotor disorders	150 (29.1%)	215 (29.2%)	0.97
Re-examination measurements (late-life)			
Dementia	15 (2.9%)	38 (5.2%)	0.05
Alzheimer's disease*	10/510 (2.0%)	31/729 (4.3%)	0.026
History of diabetes mellitus	40 (7.8%)	37 (5.0%)	0.047
History of stroke	32 (6.2%)	61 (8.3%)	0.17
History of myocardial infarction	79 (15.3%)	98 (13.3%)	0.31
Smokers	234 (45.4%)	325 (44.2%)	0.65
Alcohol drinkers	380 (73.8%)	532 (72.3%)	0.56

Data in brackets are means (SD) or percentages (%). The t test was used for means (SD) and the χ^2 test was used for percentages (%). The active group comprises people who participated in leisure-time physical activity at least two times per week at midlife. The sedentary group comprises people who participated in leisure-time physical activity less than two times per week at midlife. *Only Alzheimer's disease diagnoses from the re-examination were included (total sample $n=1239$).

Table 1: Sociodemographic and clinical characteristics of the participants according to the midlife leisure time physical activity

The main analyses were restricted to participants with no missing data on outcome, physical activity, or any of the covariates. The total number of participants in the analyses for dementia was 1251 (61 cases), and 1239 for AD (48 cases). We also analysed the whole sample ($n=1935$, including dementia and AD cases identified by register linkage) for which the number of individuals with dementia was 115 (two patients with dementia had missing data on physical activity), and those with AD was 76 (no missing data).

Statistical analyses

Differences among the participants according to their midlife leisure-time physical activity categories (active vs sedentary) were analysed with the χ^2 test and Student's t test as appropriate. The association between midlife leisure-time physical activity and the subsequent development of dementia and AD was investigated with multiple logistic regression analyses, with the sedentary group as the reference category. First, analyses were adjusted for potential confounders for the relation between physical activity and dementia: socio-demographic variables (age at re-examination, sex, education), follow-up time, and locomotor disorders (which may limit participation in leisure-time physical activity; model 1). Second, we adjusted in addition for vascular risk factors at midlife (BMI, total serum cholesterol, systolic blood pressure), history of vascular disorders at re-examination (myocardial infarction, stroke, diabetes), and *APOE* $\epsilon 4$ carrier status (carriers vs non-carriers; model 2). Finally, we investigated whether other lifestyle factors modify the association between physical activity and dementia, and made additional adjustments for smoking status (ever smokers vs never smokers) and alcohol drinking reported at re-examination (yes vs no; model 3).

We also did stratified analyses to assess the effect of *APOE* $\epsilon 4$ carrier status on the relation between leisure-time physical activity and the risk of dementia and AD. The putative multiplicative interaction between leisure-time physical activity and *APOE* $\epsilon 4$ carrier status was then analysed by including an interaction term in the model. The interaction between leisure-time physical activity and sex was analysed in a similar manner. In medical epidemiology, a corroborated view is that risk factors that act independently have an additive effect.²² This means that when no causal interaction exists, the total effect of risk factors is equal to the sum of the effects of the separate risk factors. This implies that there is an interaction as a departure from additivity, often called additive interaction, when the total effect of risk factors are smaller (antagonism) or larger (synergism) than the sum of the separate effects.²² Therefore, besides multiplicative interaction, we also calculated additive interactions by using relative excess risk from interaction (RERI) as a measure.²² We chose RERI because it shows the size of the interaction in a

way that is comparable to an interaction term, which makes it easy to compare the results from multiplicative and additive interactions. The calculation of RERI takes into account the distributional differences between risk and odds.²³ SEs for the additive interaction were calculated with the delta method.²⁴ If there is no additive interaction, then RERI is equal to zero. In this case, if RERI is greater than zero, then there is a larger difference among the *APOE* carriers. The level of significance was $p<0.05$ in all analyses. The analyses were done by use of SPSS for Windows, release 12.0.

Role of the funding source

No funding source had a role in the preparation of this article or the decision to submit it for publication. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Individuals who participated in leisure-time physical activity at least twice a week at midlife (active group) were somewhat older and had shorter follow-up than those in the sedentary group (table 1). Other sociodemographic and clinical characteristics did not differ significantly between the two activity groups. The proportions of participants with dementia and AD later in life was lower in the active group.

The active group had lower odds of dementia later in life compared with the sedentary group after controlling for demographic variables, follow-up time, and locomotor disorders (model 1; table 2). This association remained significant after further adjustments for midlife vascular risk factors, history of vascular disorders at re-examination, and *APOE* $\epsilon 4$ carrier status (model 2), and for smoking and alcohol drinking (model 3). In this final model, participants in the active group had 52% lower odds of dementia compared with the sedentary group (table 2). The results from the analyses of the whole sample (including those who did not participate in the re-examination) were similar to the results from the main analyses (results not shown).

	Odds ratio (95% CI) for active vs sedentary group	
	Dementia (n=1251)	Alzheimer's disease (n=1239)
Crude model	0.55 (0.30–1.01)	0.45 (0.22–0.93)
Model 1	0.45 (0.24–0.85)	0.34 (0.15–0.74)
Model 2	0.46 (0.24–0.88)	0.34 (0.15–0.77)
Model 3	0.47 (0.25–0.90)	0.35 (0.16–0.80)

Model 1 was adjusted for age at re-examination, sex, education, follow-up time, and locomotor disorders. Model 2 was adjusted for the same variables as model 1 with the addition of *APOE* $\epsilon 4$ genotype, midlife body-mass index, systolic blood pressure, cholesterol, and history of myocardial infarction, stroke, and diabetes mellitus. Model 3 was adjusted for the same variables as model 2 with the addition of smoking status and alcohol drinking. The analyses included participants with no missing data on the outcome, physical activity, or any of the covariates (including 61 cases with dementia and 48 with Alzheimer's disease).

Table 2: Association between midlife leisure-time physical activity and odds of dementia and Alzheimer's disease later in life

	Odds ratio (95% CI) for active vs sedentary group
Dementia	
<i>APOE</i> $\epsilon 4$ carriers (n=438)	
Model 1	0.39 (0.16–0.98)
Model 2	0.38 (0.15–0.99)
Model 3	0.41 (0.16–1.06)
<i>APOE</i> $\epsilon 4$ non-carriers (n=813)	
Model 1	0.55 (0.23–1.32)
Model 2	0.59 (0.24–1.43)
Model 3	0.60 (0.25–1.47)
Alzheimer's disease	
<i>APOE</i> $\epsilon 4$ carriers (n=433)	
Model 1	0.23 (0.07–0.73)
Model 2	0.23 (0.07–0.74)
Model 3	0.24 (0.07–0.79)
<i>APOE</i> $\epsilon 4$ non-carriers (n=806)	
Model 1	0.54 (0.19–1.50)
Model 2	0.59 (0.21–1.69)
Model 3	0.61 (0.21–1.80)

Model 1 was adjusted for age at re-examination, sex, education, follow-up time, and history of locomotor disorders. Model 2 was adjusted for the same variables as model 1 with the addition of midlife body mass index, systolic blood pressure, cholesterol, and history of myocardial infarction, stroke, and diabetes mellitus. Model 3 was adjusted for the same variables as model 2 with the addition of smoking status and alcohol drinking.

Table 3: Association between midlife leisure-time physical activity and odds of dementia and Alzheimer's disease by *APOE* $\epsilon 4$ allele status

Socioeconomic factors and depressive symptoms may affect an individual's ability or desire to participate in leisure-time physical activity. Therefore, we did additional analyses to control for midlife depressive symptoms (measured with Beck Depression Scale), income, and marital status; however, these covariates did not correlate with physical activity and did not modify the association between physical activity and AD (results not shown). Physical activity was associated with an inverse tendency for the odds of dementia in men (model 3: odds ratio [OR] 0.56, 95% CI 0.22–1.43) and women (model 3: 0.44, 0.18–1.09), although confidence intervals were somewhat wider because of the smaller sample size. There was no evidence for a significant multiplicative interaction between sex and physical activity for the odds of dementia ($p=0.878$).

Physical activity at midlife reduced the risk of AD in all models (crude model and models 1–3; table 2): active individuals had approximately 60% lower odds of AD than sedentary individuals. Results from the analyses in

which non-participants (diagnoses derived exclusively from medical records) were also included were similar to the main analyses that included only AD cases diagnosed in re-examination (results not shown). Physical activity seemed to have similar effect both among men (model 3: OR 0.31, 95% CI 0.09–1.12) and women (model 3: 0.43, 0.14–1.28), and the multiplicative interaction term between sex and physical activity for the odds of AD was not significant ($p=0.583$).

Among *APOE* $\epsilon 4$ carriers, the inverse association between midlife physical activity and the subsequent risk of dementia was significant in models 1 and 2, and remained of borderline significance after full adjustments (table 3). Among *APOE* $\epsilon 4$ non-carriers, the association was not significant. Since the stratified analyses indicated that the effect of physical activity might be more pronounced among *APOE* $\epsilon 4$ carriers, we did further analyses that included all possible groupings of the physical activity and *APOE* $\epsilon 4$ allele status interaction term in the logistic regression model. Compared with sedentary *APOE* $\epsilon 4$ carriers, physically active $\epsilon 4$ carriers had an OR of 0.38 (95% CI 0.15–0.97) for dementia, sedentary $\epsilon 4$ non-carriers had an OR of 0.38 (0.19–0.77), and active $\epsilon 4$ non-carriers had an OR of 0.23 (0.10–0.55) after adjustments. Nevertheless, the multiplicative interaction term between the *APOE* $\epsilon 4$ allele and midlife leisure-time physical activity was not significant ($p=0.516$) after adjustment. The additive interaction term between physical activity and the *APOE* $\epsilon 4$ allele was of borderline significance (RERI=0.45, $p=0.062$), which supported the findings of the stratified analyses (ie, that *APOE* $\epsilon 4$ carrier status may modify the association between physical activity and subsequent development of dementia).

Among the *APOE* $\epsilon 4$ carriers, the association between physical activity and AD was significant in all models (table 3), whereas among *APOE* $\epsilon 4$ non-carriers, it was not significant. All possible groupings of physical activity and *APOE* $\epsilon 4$ allele status interaction were also analysed in relation to AD. Compared with the sedentary *APOE* $\epsilon 4$ carrier group, the active *APOE* $\epsilon 4$ carriers had an OR of 0.18 (95% CI 0.05–0.67), the sedentary *APOE* $\epsilon 4$ non-carriers had an OR of 0.30 (0.13–0.71), and the active *APOE* $\epsilon 4$ non-carriers had an OR of 0.22 (0.08–0.60). There was a weak tendency towards a multiplicative interaction between physical activity and the *APOE* $\epsilon 4$ allele status for the development of AD ($p=0.12$, after adjustments), and the additive interaction term was significant in the model (RERI=0.73, $p=0.020$), which indicated that *APOE* $\epsilon 4$ may modify the association between physical activity and the odds of AD.

We also investigated whether those who did not participate in the 1998 re-examination differed from those who were assessed (table 4). Non-participants were significantly older, had fewer years of education, and had higher blood pressure, BMI, and serum cholesterol concentrations at midlife than participants at re-

	Participants (n=1449)	Non-participants (n=551)	p
Age (years)	50.4 (6.0)	51.1 (6.0)	0.016
Education (years)	8.6 (3.4)	7.6 (3.0)	<0.001
Systolic blood pressure (mm Hg)	144.5 (20.1)	149.8 (21.2)	<0.001
Diastolic blood pressure (mm Hg)	89.3 (11.0)	91.6 (11.1)	<0.001
Serum cholesterol (mmol/L)	6.7 (1.2)	7.0 (1.3)	<0.001
Body-mass index (kg/m ²)	26.6 (3.7)	27.2 (4.6)	0.002
Smokers	623 (43.0%)	264 (47.9%)	0.05

Data in brackets are means (SD) or percentages (%). The t test was used for means (SD) and the χ^2 test was used for percentages (%).

Table 4: Characteristics of participants and non-participants in the 1998 re-examination

examination. Non-participants were also more likely to be smokers than were participants.

Discussion

This study shows that leisure-time physical activity at midlife is related to a decreased risk of dementia and AD. Individuals participating at least twice a week in a leisure-time physical activity had 50% lower odds of dementia compared with sedentary persons. The association was somewhat stronger for AD than for overall dementia; those in the active group had 60% lower odds of AD compared to those in sedentary group, even after adjusting for a wide array of potential confounding factors. The *APOE* $\epsilon 4$ allele status seemed to modify the associations between physical activity and dementia or AD as physical activity had more pronounced effects against dementia or AD among the *APOE* $\epsilon 4$ carriers.

Some short-term longitudinal cohort studies have suggested that an inverse association may exist between regular and high intensity leisure-time physical activity,^{5,6,11} or some specific form of physical activity, such as dancing¹⁰ or walking,⁷ and the risk of dementia or AD, whereas others have not found any association.^{12,25–28} Most studies that have investigated the association between physical activity and dementia have focused on other leisure-time activities and risk factors, and various methods have been used to assess and group physical activity. As far as we are aware, our study is one of the first to investigate the long-term association between midlife leisure-time physical activity and the subsequent risk of dementia and AD. Our study confirms the findings of a retrospective study that suggested that patients with AD were less active in midlife compared with non-demented individuals.²⁹ Those findings are also in agreement with some recent studies reporting that physical activity may be associated with better cognitive function³⁰ or protect against cognitive or memory decline,^{17,31} even after controlling for baseline cognitive function. A study from Japan found no association between physical activity and dementia during a follow-up of 20 years.²⁸ However, that study combined leisure-time and occupational physical activity into a single category. Manual work, which usually includes more physical activity and may be associated with lower level of education, has been associated with an increased risk of dementia.³² Thus, the inclusion of occupational physical activity into the physical activity definition may partly explain the non-significant results of that study, but also other factors, such as genetic, demographic, and lifestyle characteristics (eg, different basic level of physical activity) of the populations may account for the different results.

Our study cohort comprised a large, representative, and prospective population-based cohort. Midlife risk factors are of great interest given that AD changes in the

brain may start to develop decades before the manifestation of symptomatic dementia.³³ In studies with shorter follow-up and in which the assessment of physical activity is only done in old age, subclinical dementia may have affected the individuals' observed physical activity. This kind of bias is unlikely to have occurred in our study, in which activity assessment was done at midlife, on average 21 years before the diagnosis of dementia. However, the possibility of a reverse causation and residual confounding cannot totally be ruled out.³⁴

There are several possible pathways through which physical activity could protect against dementia and AD.³ First, the effect could be mediated through various vascular risk factors (eg, hypertension, hypercholesterolaemia, diabetes, overweight) that have been found to contribute to the development of dementia and AD.^{35,36} Physical activity is important in promoting overall and vascular health.³⁷ In our analyses, the association between physical activity and dementia or AD remained significant after adjusting for various vascular risk factors and disorders, indicating that physical activity has an independent role. However, other vascular mechanisms, such as subclinical atherosclerosis and endothelial dysfunction, might be important mediators. There may also be several neurobiological mechanisms linking leisure-time physical activity to dementia and AD. Recent studies have indicated that physical activity affects several gene transcripts and neurotrophic factors that are relevant for the maintenance of cognitive functions,^{38,39} and that exercise may promote brain plasticity.^{40,41} Exercise may even alleviate amyloid burden in the brain, as suggested by a recent study in a transgenic mouse model of AD.⁴² Physical activity has also been suggested to increase cognitive reserve.⁴³

Finally, participating in leisure-time physical activity may be associated with other lifestyle and socioeconomic factors⁴⁴ associated with the risk of dementia. In our study, adjustments for several sociodemographic and vascular factors did not explain the investigated association, but we still cannot totally exclude some residual confounding. It would have been interesting to have data about other socioeconomic factors, general intellectual ability, and personality traits at midlife to be able to further elucidate these complex associations and the potential residual confounding and selection biases (those with higher cognitive ability might have been more likely to participate in leisure-time physical activity, and this ability in general might protect against dementia). Interestingly, the study by Richards and coworkers,¹⁷ with data about baseline cognition, several socioeconomic factors, and non-physical types of leisure-time activities, did not indicate that these factors would explain the association between physical activity and better memory function.

The effects of physical activity against dementia and AD were more pronounced among *APOE* $\epsilon 4$ carriers

than non-carriers. A similar interaction has been reported previously for cognitive decline.⁴⁵ One explanation for the possible effect modification of *APOE* genotype may be that those individuals carrying the *APOE* $\epsilon 4$ allele have less effective neural protection and repair mechanisms, and are thus more dependent on lifestyle-related factors to protect them against dementia and AD.⁴⁶ These findings provide an optimistic outlook for persons with genetic susceptibility; it may be possible to reduce the risk of dementia by adopting positive lifestyle options. Such findings have recently been reported from the Finnish Diabetes Prevention Study in which individuals with high-risk genotypes for type 2 diabetes benefited most from lifestyle interventions.⁴⁷ The interplay of genes and environment in the aetiology of AD needs to be further investigated in other large cohort studies.

Our results may be somewhat compromised by survival bias. It has been shown previously that physical inactivity is associated with increased mortality.⁴⁸ Thus, if we assume that among the deceased there were more sedentary persons and that they were also more likely to have dementia, then our results would represent an underestimation of the true protective effect associated with physical activity.

Only individuals who scored 24 or less on the mini-mental state examination in the screening phase underwent the exhaustive examinations needed for the diagnosis of dementia and its subtypes. Some dementia cases may have been lost because of this cut-off, and this may have resulted in underestimation of the prevalence of dementia among the participants. Healthcare-seeking behaviour and diagnostic bias can lead to somewhat biased results if the entire sample is included in the analyses. However, the dementia cases detected in the study and those ascertained from the registries were similar in their midlife physical activity as well as in other characteristics. If the analyses were restricted only to participants in the re-examination, the results were similar to the main analyses that also included non-participants. Furthermore, when we compared non-participants and participants in re-examination, we found that non-participants were older, less educated, and had more vascular risk factors than participants at midlife examination. According to earlier studies, individuals with cognitive impairment are less likely to participate in studies of this type.⁴⁹ It is also known that medical records often underestimate dementia diagnoses. Thus, if anything, possible non-participation bias can be considered to have underestimated the observed associations rather than the opposite.

A further limitation in most large studies concerning physical activity is the reliability of physical activity data. Even though the exact level of physical activity could not be quantified accurately, the ranking of individuals into different categories as done in our study is possible. Having several follow-up measurements would have

allowed us to assess changes occurring in physical activity during follow-up and its relation to dementia. Future studies are needed to more thoroughly assess how various types of leisure-time physical activity, intensities, and frequencies can influence the risk of dementia and AD.

Our results indicate that regular leisure-time physical activity at midlife may be protective against dementia and AD later in life. These findings may have wide implications for preventive health care; if an individual adopts an active lifestyle in youth and at midlife, this may increase their probability of enjoying both physically and cognitively vital years later in life.

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Authors' contributions

SR and MK were the principal investigators. SR analysed the data and drafted the paper. MK and IK assisted in analyses and writing. MK and E-LH did the diagnosing of dementia. MK, E-LH, AN, JT, and HS contributed to the conception and design of the study. JT and AN were involved in the baseline surveys for the study. SR, IK, E-LH, MV, BW, HS, JT, AN, and MK took part in planning the study, interpreting the data, and commented on the article. MK is the guarantor.

Conflicts of interest

We have no conflicts of interest.

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