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ORIGINAL ARTICLE

Physical activity and dementia: Long-term follow-up study of adult twins

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Introduction. Physical activity is associated with a decreased occurrence of dementia. In twins, we investigated the effect of persistent physical activity in adulthood on mortality due to dementia.

Materials and methods. Physical activity was queried in 1975 and 1981 from the members of the older Finnish Twin Cohort ($n = 21,791$), who were aged 24–60 years at the end of 1981. The subjects were divided into three categories according to the persistence of their vigorous physical activity. Dementia deaths were followed up to the end of 2011.

Results. During the 29-year follow-up, 353 subjects died of dementia. In individual-based analyses the age- and sex-adjusted hazard ratio (HR) was 0.65 (95% CI 0.43–0.98) for subjects partaking in vigorous physical activities in both 1975 and 1981 compared to those who were inactive in both years. No significant change was observed after adjusting for potential confounding factors. The corresponding HR for within-pair comparisons of the less active twin versus the more active co-twin was 0.48 (95% CI 0.17–1.32). The results for analyses of the volume of physical activity were inconclusive.

Conclusions. Persistent vigorous leisure-time physical activity protects from dementia, and the effect appears to remain after taking into account childhood environment.

Key words: Cognition, cognitive decline, dementia, exercise, physical activity, twins

Introduction

An association between decreased physical activity and increased risk of dementia has been found in many observational prospective studies (1–17), but conflicting evidence has also been published (18–21). However, the questionnaire methods used for assessing physical activity have varied in these studies. Overall it appears that no association between physical activity and dementia was observed in studies in which the number of different physical activities, or an index constructed from it, has been the measure of physical activity (18–21); whereas the associations have been positive in studies in which the recording of physical activity has been more comprehensive (for example METs, hours

Key messages

- Persistent vigorous physical activity was associated with lower dementia mortality in the Finnish Twin Cohort.
- Effect size estimates from the pairwise analysis were consistent with the individual-based analyses, but the small number of discordant pairs needs to be taken into account.
- No dose-response was observed in the association of physical activity and lower dementia mortality in old age.

or frequency per week, walking miles). A recent comprehensive review suggests that all levels of physical activity protect from cognitive decline (22). While research in this matter has focused on the volume of physical activity measured in duration and frequency of physical activity, METs or walking distances (2–7,9,11,12,15,23), some studies have been conducted from the perspective of how vigorous the physical activity has been (1,10,13,14,24). From both of these perspectives physical activity, even a low-to-moderate degree in a majority of the studies, has associated with lower occurrence of dementia and cognitive decline.

It is known that neuropathological changes of Alzheimer's disease start to accumulate already 10–15 years before the onset of clinical symptoms (25). Thus, when assessing the effect of physical activity on dementia incidence in old age, it is logical to focus on long-term persistent physical activity in middle age. This kind of perspective renders the bias of incipient dementia less likely. Also other cardiovascular risk factors precisely in midlife have been associated with lower dementia incidence in old age (26–29). In the earlier literature on physical activity and dementia, the age at the time of measuring physical activity has been over 70 in a few studies (3,5,6,8,9,15–18), close to retirement age in many studies (1,2,4,7,20,23), and in middle age (approximately from 40 years to 60 years) in fewer studies (10–14,21,24,30). Most of the studies both in middle age and in old age have found an association between physical activity and lower dementia incidence (1–17), excluding the ones with a questionable measure of physical activity as mentioned earlier (18–21). In the studies in which physical

activity was measured in older age, the time interval between measuring physical activity and the decline in cognition varied from 4 years to 8 years (1–5,7–9,15–20,23), except for one in which the follow-up was substantially longer, reaching 9–15 years (6). The studies in which physical activity was measured in middle age also had longer follow-ups: from 15 years to 31 years (10–14,21,24,30), usually showing an association between baseline physical activity and future dementia. Large variation in cohort sizes is seen as well in earlier observational prospective studies on physical activity and cognitive decline. Some are small with fewer than a thousand participants (3,8,18,21,23), while many have had some thousands of subjects (1,2,4,5,7,9–11,13–17,19,20,24,30). There are two larger cohorts of over 10,000 subjects (6,12). Most observational studies have been prospective (1–21,23,24,30).

Hence, overall, observational prospective studies in this field points in the direction that physical activity, especially in middle age, is beneficial for cognitively healthier aging. A positive effect of physical activity on cognition has also been reported in randomized controlled trials (31,32). However, the evidence of an association between physical activity and dementia is currently considered insufficient to draw firm conclusions on a causal relationship (33).

One difficulty of observational longitudinal studies is that both early childhood experiences and genetics are involved in determining the physical activity level of an individual (34,35). Therefore it is not clear whether it is physical activity alone, childhood exposures and experiences, or the genotype behind the physical activity that is responsible for the reported association between physical activity and better cognition during old age in longitudinal observational studies. The twin study approach offers a unique way to investigate the effect of physical activity on later life dementia incidence while taking into account the effect of childhood environment and genetics. In the present study we investigated the effect of long-term vigorous physical activity on mortality due to dementia later in life in the Finnish Twin Cohort.

Materials and methods

Study cohort

The study cohort in this study was the older Finnish Twin Cohort, a nationwide sample of same-sex twin pairs born before 1958 with both co-twins alive in 1967. The study participants were selected from the Central Population Registry of Finland in 1974 with permission from the National Board of Health. A more comprehensive description of the cohort is found elsewhere (36). Four surveys of the entire cohort have been carried out (37), and this study uses data from the first two surveys (1975 and 1981). The baseline questionnaire was mailed to the subjects in 1975. Among those whose addresses could be identified (93.5%) the response rate was 87.6%. A follow-up questionnaire was mailed in 1981 irrespective of the response in 1975. The response rate among those responding in 1975 and alive in 1981 was 90.7%. The total number of twin pairs in the beginning of the prospective follow-up in 1975 was 13,888. The total number of twins who answered the questions about physical activity on both questionnaires (1975 and 1981) was 21,791. Of these twins a total of 20,413 had also answered all of the questions concerning our covariates (see below). An earlier statement from the ethical committee of the Hospital District of Southwest Finland covers our current study (ETMK 77/1801/2013, 21.5.2013). The study was conducted according to good clinical and scientific practice and guidelines and the declaration of Helsinki. All of the participants gave their informed consent by providing questionnaire responses.

The participants were provided regular feedback on the purpose and conduct of the study and were informed that they may withdraw from the study at any time.

Physical activity and covariate assessment

The questionnaires mailed in 1975 and 1981 were very similar and included identical questions about physical activity during leisure time and during the journey from and to work, among many other questions. In the current study we investigated the effect of physical activity on dementia mortality using participation in vigorous physical activity as an indicator of physical activity. Subjects' participation in vigorous physical activity was categorized based on their answer to the following question: On average, is your leisure-time physical activity as strenuous as: 1) walking, 2) alternately walking and jogging, 3) jogging (light running), 4) running. The subject was categorized as a partaker in vigorous activity if answering 2, 3, or 4. This classification was also used in our previous study (38). For the present study the cohort was further categorized based on the persistence of and changes in their vigorous physical activity. Three subgroups were created: no vigorous physical activity in both 1981 and 1975, persistent vigorous activity in both 1975 and 1981, and those who demonstrated a change (i.e. decreased physical activity from vigorous activity in 1975 to no vigorous activity in 1981 or vice versa). Although we cannot demonstrate without question that the 'no vigorous activity' group has not done some vigorous physical activity between the time points, or that the 'persistent vigorous activity' group would have been vigorously active for the whole of the 6-year period, the report of vigorous physical activity at both time points reflects the subject's abilities and interest in physical activity in a long time period and in many cases likely from an even longer period of time than six years. The measurement of physical activity at two time points increases the validity of the protective factor and is regarded as having a persistent level of the health habit also in our earlier studies on the same cohort (38).

In addition, the volume of physical activity was measured by the MET index. The MET index is based on structured questions on leisure physical activity (monthly frequency, mean duration, and mean intensity of the sessions) and the reported physical activity during the journey to and from work (39). The MET index was calculated by estimating the MET score (metabolic equivalent, i.e. multiple of metabolic resting energy expenditure) and by multiplying it with the duration and frequency of the physical activity. Thus, the MET index was reported as a sum-score of MET hours per day. For example, 1 MET h/day corresponded to approximately 30 minutes of walking every other day. The MET index was validated in a previous study (40).

In this study, education, binge drinking, body mass index (BMI), smoking status, and hypertension were derived from the questionnaires and used as covariates. Education was represented by years of schooling in 1981 and asked about in nine categories (41,42). Binge drinking was used as a dichotomized variable depending on whether the person had reported regular excess drinking on single occasions. Excess drinking was defined as drinking more than five bottles of beer, more than one bottle of wine, or more than half a bottle of spirits on a single occasion at least monthly (43). BMI was computed from self-reported weight and height (kilograms per meters squared). Smoking status was a four-category covariate based on information on smoking in the 1981 questionnaire. The categories were as follows: 1) never smoked, 2) occasional smoking, 3) former smokers, 4) current cigarette smokers (44). Hypertension was used as a two-category covariate based on having a diagnosis of hypertension and regularly using anti-hypertensive medication.

The prevalence of hypertension, diabetes, coronary artery disease, and pulmonary diseases in different groups according to the persistence of vigorous physical activity at baseline in 1981 are shown in the results. The person was regarded having diabetes if he or she reported having physician-diagnosed diabetes in the 1981 questionnaire. The person was regarded as having coronary artery disease if he or she reported having physician-diagnosed angina pectoris or myocardial infarct in the 1981 questionnaire. And the person was regarded as having pulmonary disease if he or she reported having physician-diagnosed chronic bronchitis, emphysema, or asthma. The validity of self-reported physician-diagnosed chronic disease such as coronary artery disease, hypertension, diabetes, and asthma has been proven to be good in the Finnish population (45–47).

Zygosity was determined by a validated questionnaire that has been used in other large cohort studies (48). The 2-fold ratio of dizygotic to monozygotic twins reflects the high frequency of dizygotic twinning in the 1960s in Finland (49).

Because chronic diseases can affect the ability to exercise, the analyses were also performed in a subgroup of healthy subjects. We excluded persons who had chronic diseases, such as diabetes, coronary artery disease, chronic pulmonary obstructive disease, and malignant cancer at baseline (1981) based on data from the questionnaires and the medical registries on long-term medication use (maintained by the Social Insurance Institution of Finland) and cancer incidence (Finnish Cancer Registry). The exclusion criteria are described in detail elsewhere (38).

Dementia mortality assessment

Data on emigration and exact dates of death were obtained from the Causes of Deaths Register available from Statistics Finland. Dementia death was defined according to appropriate versions of the International Classification of Diseases (ICD). In ICD8 (deaths between 1970 and 1986) the following diagnoses were counted as a dementia death: Dementia senilis et praeseniilis (ICD 290 category), Senilis (ICD 290,00), Morbus Alzheimer (ICD 290,01), Morbus Pick (ICD 290,11), Praeseniilis alia sive NUD (ICD 290,19), Senilitas, psychosi non indicata (ICD 794), Marasmus senilis (ICD 794,00), and Senilitas alia sive NUD (ICD 794,09). In ICD9 (years 1987 to 1995) the following diagnoses were categorized as a dementia death: Dementia senilis et praeseniilis (ICD 290 category, ICD 2900A), Morbus Alzheimer (ICD 3310A), Morbus Pick (ICD 3311A), Dementia e multis infarctibus (ICD 4378A), and Senilitas, psychosi non indicata (ICD 797). In the most recent period (years 1996 to 2011, International Statistical Classification of Deaths (ICD10) the following diagnoses were considered to be a dementia death: Dementia vascularis (F01), Dementia non specificata (F03), Morbus Alzheimer (G30), and Senilitas (R54).

Data analysis

The data were analyzed using the Cox proportional hazard regression model in Stata. The proportional hazards assumptions were assessed by visual inspection of the 'log-log' curves using *stphplot* and according to whether the necessary assumptions were met. The persistently inactive group was used as a reference group in analyses of the persistence of vigorous physical activity. We also evaluated the volume of physical activity; the cohort was divided into five quintiles according to their MET index as in our previous studies (39,50). The most inactive group was used as a reference group. Follow-up began on the date of the subject's response in 1981 and continued until the subject emigrated, died, or the follow-up period ended (31 December 2011). For both analyses, twinship was taken into account by adding a family covariate into the model.

Both individual and pairwise analyses were performed. The number of individuals in the cohort was 21,791, but the number of pairs was 8,988. In pairwise analyses, the mortality due to dementia was compared within the pair, with the hazard ratio (HR) defining the risk estimate within the pair. The informative pairs are those discordant for physical activity that are also discordant for dementia mortality. The results were initially adjusted for age and sex. The length of education was added to the model because it was estimated to be the most influential in the matter of interest. Finally, all potential confounding factors (heavy use of alcohol, BMI, smoking, hypertension) were added into the model. Due to missing data for some of the confounding factors, the number of subjects in the full model with all confounding factors was decreased. The analyses were also performed in a model among healthy subjects at baseline. Furthermore, we performed an interaction analysis in which we observed no interaction between the physical activity groups by gender or zygosity.

Results

A total of 21,791 participants were followed from 1981 to 2011. Before the follow-up phase, subjects' engagement in leisure-time physical activity was queried at two different time points 6 years apart during adulthood, in 1975 and 1981. During the 29-year follow-up 353 persons died of dementia, and the first dementia death occurred in 1983. Table I shows the baseline characteristics of the participants, who were divided into subgroups according to their vigorous physical activity levels in 1975 and 1981. The group who took part in vigorous physical activities in both 1975 and 1981 had lower BMI, were more educated, had less hypertension, and were less likely to be current smokers in 1981; however, more subjects in the persistently active group were binge drinkers.

Individual analyses showed that the subjects who engaged in physical activity more strenuous than walking at both time points had a significantly lower age- and sex-adjusted HR (0.65, 95% CI 0.43–0.98, $P = 0.041$) for developing dementia during follow-up (Table II) than subjects who did not engage in strenuous physical activity. After adjusting the model for all of the confounding factors, the persistently vigorously physically active group retained a significantly lower risk of developing dementia (HR 0.61, 95% CI 0.40–0.95, $P = 0.027$).

When restricting the analysis to subjects who were healthy at baseline, very similar point estimates were obtained, but with wider confidence intervals because the sample size was smaller compared to the whole cohort. The risk of dying of dementia was lower for those who engaged in vigorous physical activities persistently during adulthood (HR 0.64, 95% CI 0.33–1.23, $P = 0.18$), with a similar result in the final adjusted model (HR 0.61, 95% CI 0.31–1.20, $P = 0.15$). In a subgroup of subjects younger than 60 years in 1981 (19,501 subjects) the results obtained were very similar to those of the whole subgroup, except that in this subgroup the protective effect of physical activity against dementia was greater but the confidence intervals were wider due to the smaller number of the subjects (Table II). The hazard ratio for developing dementia was 0.49 (95% CI 0.26–0.94, $P = 0.032$) in the final model in the individual analysis.

Pairwise analyses showed that the members of twin pairs who engaged in vigorous physical activity at both time points had a markedly lower HR (0.48) for developing dementia compared to the inactive co-twin. However, the analysis lacked statistical power and was not significant ($P = 0.15$). Therefore, of the 8,988 twin pairs, only 217 were discordant for dementia death, and of these only 20 were discordant for both dementia death and physical activity. After adjusting for all confounding factors the

Table I. Baseline characteristics of the 21,791 individuals according to the persistence of vigorous exercise in 1975 and 1981.^{a,b}

Variable	No vigorous activity in 1975 or 1981	Persistent vigorous activity (both 1975 and 1981)	Change (vigorous activity in either 1975 or 1981 but not both)
All, <i>n</i> (%)	8438 (38.7)	7063 (32.4)	6290 (28.9)
Male, <i>n</i> (%)	3216 (31.2)	4222 (41.0)	2858 (27.8)
Female, <i>n</i> (%)	5222 (45.4)	2841 (24.7)	3432 (29.9)
Pairs, <i>n</i> (%)	3331 (37.1)	3026 (33.7)	2631 (29.3)
Monozygotic, <i>n</i> (%)	2476 (38.4)	2165 (33.5)	1814 (28.1)
Dizygotic, <i>n</i> (%)	5289 (38.4)	4436 (32.2)	4040 (29.3)
Age in years at 1981, mean (SD)	46.8 (14.9)	35.2 (9.1)	38.0 (11.4)
School years in 1981, mean (SD)	2.9 (1.7)	4.3 (2.2)	3.6 (2.0)
Heavy users of alcohol 1981, <i>n</i> (%)	1561 (19.2)	2087 (29.8)	1613 (26.1)
BMI in 1975, mean (SD)	24.0 (3.7)	22.4 (2.7)	22.7 (3.2)
BMI in 1981, mean (SD)	24.6 (3.8)	23.1 (2.8)	23.5 (3.3)
Smoking status in 1981, <i>n</i> (%)			
Never smoked	4234 (51.6)	3264 (46.9)	2706 (43.8)
Occasional smoking	188 (2.3)	284 (4.1)	178 (2.9)
Former smoker	1538 (18.7)	1671 (24.0)	1306 (21.2)
Current smoker	2253 (27.4)	1734 (24.9)	1986 (32.2)
Hypertension, <i>n</i> (%)	948 (11.2)	134 (1.9)	291 (4.6)
Coronary artery disease, <i>n</i> (%)	675 (8.0)	114 (1.6)	210 (3.3)
Diabetes, <i>n</i> (%)	286 (3.5)	60 (0.9)	91 (1.5)
Pulmonary disease, <i>n</i> (%)	954 (11.3)	385 (5.5)	481 (7.7) ^b

^aThe study cohort has been divided into three groups according to their physical activity in 1975 and 1981. Vigorous physical activity denotes engaging in physical activity more strenuous than walking.

^bAll the differences between the groups were significant for all the variables ($P < 0.001$).

HR was 0.54 (95% CI 0.15–1.98, $P = 0.35$). For the dizygotic pairs, 14 twin pairs were discordant for both dementia and the persistence of vigorous physical activity. Of these pairs, the inactive twin died of dementia in eight cases, and the active twin had dementia listed as a cause of death in six cases. Only six pairs of monozygotic twins were discordant for both dementia and the persistence of physical activity. Among these pairs there were three cases in which the inactive twin died of dementia and three cases in which the active twin died of dementia. Notably, the number of discordant pairs is not enough to explain such a good HR. Thus, the physically active twins must have remarkably outlived the inactive co-twins, explaining the good HR (in all pairs) when it takes into account also the length of follow-up.

We extensively analyzed the associations between the volume of physical activity in 1975 and 1981 and dementia death. The only significant predictor of dementia death was physical inactivity in 1981 (MET index < 0.6 h/day, i.e. less than 20 minutes of walking every other day; lowest quintile) compared to more

physically active individuals (Table III). The interaction test found no significant difference between genders in the effect of the volume of physical activity in 1981 to dementia mortality later.

Discussion

Our 29-year longitudinal study of the Finnish Twin Cohort showed an association between the persistence of vigorous physical activity and mortality from dementia. Participating in vigorous physical activities at two different time points, in 1975 and 1981, was regarded as persistent level of physical activity. This finding is in line with earlier studies on the subject that suggest that physical activity protects from dementia (22,51–53) and that physical activity in midlife protects from dementia (10–12,14,24). The association between the persistently vigorously physically active and dementia deaths was not only seen in the individual-based analyses, but also supported by the pairwise analyses when the active twins were compared to their inactive co-twins. However,

Table II. Cause-specific mortality due to dementia in 1982–2011 by persistence and level of vigorous physical activity.

Level of physical activity in 1975 and 1981 (<i>n</i>) ^c	Individual analyses ^a			Pairwise analyses ^b		
	Age- and sex-adjusted HR (95% CI)	Age-, sex-, and education-adjusted HR (95% CI)	Final model ^d HR (95% CI)	Age HR (95% CI)	Age- and education-adjusted HR (95% CI)	Final model HR (95% CI)
All (21,791)						
None (8438)	1.00	1.00	1.00	1.00	1.00	1.00
Change (6290)	0.95 (0.72–1.24)	0.96 (0.73–1.26)	0.92 (0.69–1.23)	0.97 (0.45–2.06)	1.22 (0.54–2.75)	1.10 (0.43–2.78)
Persistent (7063)	0.65 (0.43–0.98)	0.67 (0.44–1.01)	0.61 (0.40–0.95)	0.48 (0.17–1.32)	0.62 (0.21–1.79)	0.54 (0.15–1.98)
Healthy (15,795)						
None (4897)	1.00	1.00	1.00	1.00	1.00	1.00
Change (6068)	0.83 (0.51–1.36)	0.81 (0.49–1.34)	0.87 (0.52–1.46)	1.14 (0.27–4.81)	1.54 (0.32–7.32)	1.46 (0.18–11.5)
Persistent (4830)	0.64 (0.33–1.23)	0.61 (0.32–1.19)	0.61 (0.31–1.20)	0.36 (0.06–2.24)	0.48 (0.05–4.36)	1.00 (0.05–19.7)
Age < 60 years in 1981 (19,501)						
None (6626)	1.00	1.00	1.00	1.00	1.00	1.00
Change (5944)	0.73 (0.47–1.13)	0.71 (0.45–1.12)	0.74 (0.46–1.17)	0.87 (0.24–3.21)	1.04 (0.27–3.93)	1.02 (0.23–4.42)
Persistent (6931)	0.52 (0.28–0.96)	0.48 (0.26–0.90)	0.49 (0.26–0.94)	0.31 (0.07–1.28)	0.37 (0.08–1.74)	0.53 (0.10–2.93)

^aIn individual analyses the Cox regression analysis was run comparing individuals in the three different groups.

^bIn the pairwise analyses the members of twin pairs were compared between each other and thus are matched for age, sex, shared childhood experiences, and partially (DZ pairs) or fully (MZ pairs) on genotype.

^cNo vigorous activity in 1975 and 1981 (reference category) versus vigorous physical activity in 1975 and 1981 (persistent), vigorous activity in either 1975 or 1981 but not both (change).

^dThe final model was additionally adjusted for BMI, heavy drinking, hypertension, and smoking.

Table III. Mortality in 1982–2011 due to dementia according to the volume of physical activity.^a

	Individual analyses ^b			Pairwise analyses ^c		
	Age- and sex-adjusted HR (95% CI)	Age-, sex-, and education-adjusted HR (95% CI)	Final model ^d HR (95% CI)	Age HR (95% CI)	Age- and education-adjusted HR (95% CI)	Final model HR (95% CI)
All						
MET QII–V	0.82 (0.65–1.02)	0.83 (0.66–1.04)	0.74 (0.59–0.95)	0.48 (0.25–0.93)	0.47 (0.23–0.97)	0.48 (0.20–1.12)
MET QI	1.00	1.00	1.00	1.00	1.00	1.00
Healthy						
MET QII–V	0.62 (0.40–0.97)	0.61 (0.39–0.96)	0.60 (0.37–0.95)	0.30 (0.08–1.09)	0.26 (0.06–1.06)	0.38 (0.07–2.17)
MET QI	1.00	1.00	1.00	1.00	1.00	1.00

^aVolume of physical activity was defined by MET quintiles (h/day) in 1981 (MET quintile I versus MET QII–V). The MET index was determined according to the intensity, duration, and frequency of physical activity based on the information from questionnaires. The MET indices were then divided into five quintiles. The MET index of quintile I (QI) was 0–0.59 hours per day (h/day) and the MET index of quintiles II–V was 0.6–30.1 h/day. For example 1 MET h/day corresponds to about 30 minutes of walking every other day.

^bIn individual analyses the Cox regression analysis was run comparing individuals in the three different groups.

^cIn the pairwise analyses the twins were compared regarding the level of physical activity and, thus, are matched based on age, sex, shared childhood experiences, and partially (DZ pairs) or fully (MZ pairs) on genotype.

^dThe final model was additionally adjusted for BMI, heavy drinking, hypertension, and smoking.

the pairwise result lacked statistical power. Thus, the result seems to remain after taking into account childhood environment and genetic background. Unfortunately, due to the small number of monozygotic pairs discordant for both dementia and physical activity, we cannot exclude the possibility of genetic confounding. The results are in line with one earlier comprehensive twin study on the subject (24), but contradictory to another twin study in which the measure of physical activity may have been less accurate (21). For clarification by vigorous physical activity we mean that the person has reported participation in physical activity as strenuous as or more strenuous than ‘alternately walking and jogging’ (more intensive than normal walking) which reflects the person’s ability and interest to participate in vigorous physical activity.

However, in extensive analyses of the volume of physical activity in 1975 and 1981, only physical inactivity in 1981 was a significant predictor of dementia death. This is not coherent with the majority of earlier literature on the subject (22) in which the volume of physical activity, even low-to-moderate intensity, protects from dementia. It may be that our relatively crude end-point measure was not powerful enough to show the underlying association in this context. On the other hand, the tendency to participate in vigorous physical activity could be connected with early childhood exposure to physical activity and might reflect the subject’s physical and cognitive abilities acquired at young age (54–56).

Physically active persons may differ from sedentary persons in additional lifestyle choices. However, the results did not change much after controlling for BMI, length of education, heavy alcohol consumption, smoking, or hypertension. Because chronic disease can affect a person’s ability to participate in physical activity we analyzed a subgroup of healthy individuals. The results in this subgroup were similar to those of the whole cohort. Also, when we restricted the analysis to those who were younger than 60 years in 1981, the results were rather similar.

We did not find an effect of gender on the association we found between the persistence of physical activity and dementia in later years. Previous studies have implied that the association between physical activity and better cognition in old age may be stronger among women (12,22,30), whereas others have presented evidence to the contrary (52).

Current evidence indicates that low-to-moderate-intensity exercise is sufficient to lower the risk from dementia, without a further reduction in risk with greater levels of physical activity (22). The results of this study are in line with this previous finding. In our study, only the sedentary quintile with regard to the amount of physical activity carried an increased risk of dementia death.

Our study had many strengths. Physical activity was measured at multiple (two) time points. The follow-up period was very long and the cohort large, comprising 21,791 subjects. The twin design is undoubtedly an asset, allowing us to control for familial confounding factors, even though the number of pairs discordant for physical activity remained low. Our nationwide cohort comprised a large proportion of all the same-sex twins born before 1958 in Finland with both co-twins still alive in 1967 and can be considered a good representation of Finnish people. In addition, the outcome measurements were collected from the Finnish Causes of Deaths Register and can be considered very reliable. The overall mortality of the twin cohort is comparable to that of the general population (37).

Our study also had limitations. Despite the large cohort, the number of pairs discordant for both physical activity and dementia deaths remained low. In addition, a number of study participants were quite young when physical activity was first queried. To evaluate truly the physical activity in midlife the follow-up should be dated a bit later in the study participants’ life span. Moreover, the outcome measure, dementia mortality, is a crude indicator when dealing with small numbers of twin pairs discordant for physical activity, as its sensitivity for detecting all dementia cases may be low. Furthermore, our data on physical activity and covariates, BMI, heavy alcohol consumption, smoking, and hypertension, are based on questionnaires, which may be a source of bias. However, self-reported hypertension (45–47), BMI (57), and smoking (58) have been shown to be quite reliable in the Finnish population. Moreover, the subjects filled out the questionnaires in early midlife or midlife instead of old age, rendering the recall bias smaller, and sources of misclassification are unlikely to be related to dementia many years later.

In conclusion, our study adds to earlier evidence that physical activity protects against dementia later in life, even after taking into account childhood environment. Our findings indicate that long-term participation in vigorous leisure-time physical activity is associated with reduced risk of dementia later in life, yet some of the results regarding the volume of physical activity were contradictory. The exact amount and intensity of physical activity needed to protect from cognitive decline later and whether there is a dose-response relationship between physical activity and cognition should be examined further.

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