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Physical activity and risk of cognitive decline: a meta-analysis of prospective studies

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Abstract. Sofi F, Valecchi D, Bacci D, Abbate R, Gensini GF, Casini A, Macchi C (Centro S. Maria agli Ulivi, Onlus IRCCS; Thrombosis Centre, University of Florence; Azienda Ospedaliero-Universitaria Careggi, Florence, Italy) Physical activity and risk of cognitive decline: a meta-analysis of prospective studies. *J Intern Med* 2010; doi: 10.1111/j.1365-2796.2010.02281.x.

Objective. The relationship between physical activity and cognitive function is intriguing but controversial. We performed a systematic meta-analysis of all the available prospective studies that investigated the association between physical activity and risk of cognitive decline in nondemented subjects.

Methods. We conducted an electronic literature search through MedLine, Embase, Google Scholar, Web of Science, The Cochrane Library and bibliographies of retrieved articles up to January 2010. Studies were included if they analysed prospectively the association between physical activity and cognitive decline in nondemented subjects.

Results. After the review process, 15 prospective studies (12 cohorts) were included in the final analysis. These studies included 33 816 nondemented subjects followed for 1–12 years. A total of 3210 patients showed cognitive decline during the follow-up. The cumulative analysis for all the studies under a random-effects model showed that subjects who performed a high level of physical activity were significantly protected (−38%) against cognitive decline during the follow-up (hazard ratio (HR) 0.62, 95% confidence interval (CI) 0.54–0.70; $P < 0.00001$). Furthermore, even analysis of low-to-moderate level exercise also showed a significant protection (−35%) against cognitive impairment (HR 0.65, 95% CI 0.57–0.75; $P < 0.00001$).

Conclusion. This is the first meta-analysis to evaluate the role of physical activity on cognitive decline amongst nondemented subjects. The present results suggest a significant and consistent protection for all levels of physical activity against the occurrence of cognitive decline.

Keywords: cognitive decline, dementia, exercise, physical activity.

Introduction

It is unquestionable that physical activity has positive effects on health; indeed, over the last few decades, a large body of evidence has shown that physical activity helps to reduce the risk of cardiovascular and cerebrovascular diseases, diabetes, obesity, hypertension and some cancers [1]. Moreover, it has been demonstrated that an active lifestyle impacts on all causes of mortality. With ageing, some cognitive functions such as attention, memory and concentration decline, becoming slower and inefficient, as for some physical functions such as walking and balance. These manifestations are the result of neural cell loss in the frontal, parietal and temporal lobes [2] and strongly depend on an ipofunction of the monoaminergic and cholinergic pathways [3]. Many of these cognitive changes are evident and can cause mild disability, even if a state of dementia is not reached.

Cognitve decline is heterogeneous, depending on various factors. Many studies have shown an inverse relation between physical activity and the risk of developing cognitive decline [4, 5], but the cause of the association has not been clearly established. Individuals who remain active throughout life, especially during middle age, generally have better cognitive performance during later life, so preserving their cognitive functions for longer. Recent evidence suggests that in addition to reducing vascular risk factors, physical activity may increase directly the production of neurotrophic factors in the brain [6].

The results of a recent meta-analysis showed that physical exercise is able to reduce the incidence of neurodegenerative diseases; in particular, dementia and Alzheimer's disease [7]. By contrast, few and conflicting data are available on the possible protective role of physical activity on the occurrence of cognitive decline, independent of the onset of neurodegenerative disease [8–18].

Therefore, the aim of this study was to conduct a meta-analysis of all the available prospective cohort studies that investigated the association between physical activity and cognitive decline in nondemented subjects.

Methods

Selection of studies

Studies that investigated the possible association between physical activity and cognitive decline in nondemented adults were identified through a computerized search of all electronic databases: MedLine (source: *PubMed*, 1966 to January 2010), Embase (1980 to January 2010), Web of Science, The Cochrane Library (source: *The Cochrane Central Register of Controlled Trials*, 2009, issue 1), Clinicaltrials.org and Google Scholar. Relevant keywords relating to physical activity as Medical Subject Heading terms and text words ('*physical activity*' or '*physical exercise*' or '*exercise*', or '*fitness*' or '*training*') were used in combination with words relating to cognitive impairment ('*cognitive decline*' or '*cognitive function'*, or '*cognitive impairment*' or '*cognitive loss*', or '*dementia*', or '*cognition*' or '*memory*'). We limited the search strategy to prospective cohort epidemiological studies, with no language restrictions, supplemented by manually reviewing the reference list of all retrieved articles.

Two investigators (FS, DV) assessed all potentially relevant articles for eligibility. The decision to include or exclude studies was hierarchical and made on the basis of the following: (i) the study title; (ii) the study abstract; and (iii) the complete study manuscript. In the event of conflicting opinions between investigators, disagreement was resolved through discussion.

Eligible studies were included if they met all of the following criteria: (i) a prospective cohort design; (ii) the association between physical activity and cognitive function as the primary or secondary outcome; (iii) nondemented subjects evaluated at baseline; (iv) clear definitions of methods used to assess cognitive performance and cognitive decline; (v) reported data on physical activity levels in relation to cognitive function; and (vi) reported estimates of association between physical activity and cognitive decline. Accordingly, studies were excluded if: (i) the design was cross-sectional, case control or interventional; (ii) outcomes other than those of interest for the meta-analysis were considered; (iii) patients with dementia or cognitive decline at baseline were included in the study; (iv) the association between physical activity and cognitive decline was not reported; or (v) estimates of the association between physical activity and the decline in cognitive function were not presented (Data S1).

The outcome of interest for the current meta-analysis was cognitive decline or cognitive impairment, defined as decline in cognitive functioning tests at follow-up examination (see Table 1 for further information about tests used to measure cognitive function).

Data extraction

All data were reviewed and separately extracted by two independent investigators (FS and DV) using a standardized form. The following patient characteristics were recorded: data and study cohort, country of the study cohort, baseline year, number of subjects at baseline, gender of the cohort, years of follow-up, age of the study cohort at baseline, definition of outcome of interest, methods used to assess cognitive function and physical activity, hazard ratio (HR) and confidence interval (CI) values for risk of cognitive decline, and adjustment for confounding factors in multivariate models.

Statistical analysis

We used Review Manager (RevMan; version 5.0.23 for Macintosh; Copenhagen, Denmark) to pool results from the individual studies.

Pooled results are reported as HR and are presented with 95% CI with two-sided *P* values using a random-effects model (DerSimonian and Laird method). $P < 0.05$ was considered to be statistically significant. When available, we used the results of the original studies from multivariate models with the most

Table 1 *Study characteristics*

Source, y *(Cohort)*	Country, (baseline y)	Subjects, *n*	Gender	F-up, y	Age, year	Outcome, (*n*) *(Definition)*	Assessment of cognitive performance	Assessment of physical activity	Physical activity categories	RR (95% CI)	Adjustment
Ho *et al.*, 2001 [8]	China (1991)	519	M	3	≥70	Cognitive impairment (35) *(CAPE <8 points)*	Information/orientation part of the Clifton Assessment Procedure for the elderly (CAPE)	Questionnaire *(Categories based on engagement in a not-otherwise specified exercise)*	No Yes	1.00 0.53 (0.25–1.11)	Age, education
Ho *et al.*, 2001 [8]	China (1991)	469	F	3	≥70	Cognitive impairment (104) *(CAPE <8 points)*	Information/orientation part of the Clifton Assessment Procedure for the elderly (CAPE)	Questionnaire *(Categories based on engagement in a not-otherwise specified exercise)*	No Yes	1.00 0.53 (0.31–0.83)	Age, education
Laurin *et al.*, 2001 [9] *(Canadian Study of Health and Aging)*	Canada (1991)	1831	M	5	≥65	Cognitive impairment-No Dementia (179) *(According to WHO ICDs)*	MMSE and clinical evaluation	Questionnaire *(Categories based on frequency and intensity of exercises)*	None Low Moderate High	1.00 0.65 (0.30–1.38) 0.84 (0.53–1.34) 0.68 (0.39–1.20)	Age, education, smoking, alcohol, NSAIDs, functional ability in basic and DALYs, self-rated health, chronic conditions
Laurin *et al.*, 2001 [9] *(Canadian Study of Health and Aging)*	Canada (1991)	2784	F	5	≥65	Cognitive impairment-No Dementia (257) *(According to WHO ICDs)*	MMSE and clinical evaluation	Questionnaire *(Categories based on frequency and intensity of exercises)*	None Low Moderate High	1.00 0.69 (0.41–1.16) 0.55 (0.36–0.82) 0.47 (0.25–0.90)	Age, education, smoking, alcohol, NSAIDs, functional ability in basic and DALYs, self-rated health, chronic conditions

Table 1 (*Continued*)

Source, y (*Cohort*)	Country, (baseline y)	Subjects, *n*	Gender	F-up, y	Age, year	Outcome, (*n*) (*Definition*)	Assessment of cognitive performance	Assessment of physical activity	Physical activity categories	RR (95% CI)	Adjustment
Schuit *et al.*, 2001 [10] *(The Zutphen Elderly Study)*	The Netherlands (1990)	347	M	3	Mean: 74.6	Cognitive decline (47) *(≥3 decline on MMSE)*	MMSE	Questionnaire *(Frequency and duration of exercise and then converted in minutes/day)*	≤30 min day^{-1} 31–60 min day^{-1} >60 min day^{-1}	1.00 0.56 (0.19–1.67) 0.50 (0.18–1.43)	Age, education, alcohol, smoking, cognitive function at baseline, disabilities ADL, self-reported health, history of MI, angina, TIA, diabetes, CVD
Yaffe *et al.*, 2001 [5] *(Study of Osteoporotic Fractures)*	US (1986)	5925	F	Mean: 7.5	≥65	Cognitive decline (1178) *(≥3-point decline on MMSE)*	MMSE	Questionnaire *(Quartiles based on frequency and duration of exercises converted into kilocalories expended per week)*	1st quartile 2nd quartile 3rd quartile 4th quartile	1.00 0.90 (0.74–1.09) 0.78 (0.64–0.96) 0.74 (0.60–0.90)	Age, education, health status, functional limitation, depression score, stroke, diabetes, hypertension, MI, smoking, oestrogen use
Pignatti *et al.*, 2002 [11]	Italy	1201	F	12	70–75	Cognitive decline (104) *(≥1-point decline on MSQ)*	MSQ	Questionnaire *(Categories based on type, frequency and intensity of exercises)*	Low High	1.00 0.27 (0.09–0.83)	MSQ at baseline
Lytle *et al.*, 2004 [12] *[Monongahela Valley Independent Elders Survey (MoVIES)]*	US (1987)	1146	M/F	2–4	≥65	Cognitive decline (110) *(≥3-point decline on MMSE)*	MMSE	Questionnaire *(Categories based on type, frequency and duration of exercises)*	None Low High	1.00 0.63 (0.39–0.99) 0.45 (0.22–0.95)	Age, gender, education, previous level of cognitive function, self-rated health status

Table 1 (*Continued*)

Source, y (*Cohort*)	Country, (baseline y)	Subjects, *n*	Gender	F-up, y	Age, year	Outcome, (*n*) (*Definition*)	Assessment of cognitive performance	Assessment of physical activity	Physical activity categories	RR (95% CI)	Adjustment
Flicker *et al.*, 2005 [13] (*Health in Men Study*)	Australia (1996)	618	M	Mean: 4.8	≥65	Cognitive Impairment (111) (*MMSE score <24 points*)	MMSE	Self-reported (*Categories based on frequency and intensity of exercises*)	Nonvigorous Vigorous	1.00 0.50 (0.25–0.99)	Age, education, treatment of hypertension, diabetes, consumption of full-cream milk, alcohol
Singh-Manoux *et al.*, 2005 [14] (*Whitehall II Study*)	UK (1985)	10 308	M/F	11	35–55	Cognitive function (*Lowest cognitive-functioning quintile*)	Cognitive test battery (20-word free-recall test of short-term memory; Alice-Heim 4-I test; Mill Hill Vocabulary Scale; Phonemic fluency; Semantic fluency) (*Alice-Heim 4-I test*)	Self-administered questionnaire (*Categories based on frequency and duration of exercises reported as hours per week*)	Low level Medium level High level	1.00 0.81 (0.65–1.02) 0.61 (0.48–0.78)	Age, gender, education, employment grade, self-rated health, blood pressure, cholesterol, smoking, mental health, social network index score, Mill Hill Vocabulary Scale
Sumic *et al.*, 2007 [15] (*The Oregon Brain Aging Study*)	US (1989)	39	M	Mean: 4.7	≥85	Cognitive Impairment (23) (*MMSE score <24 points*)	MMSE	Self-administered questionnaire (*Hours per week of exercises*)	≤4 h $week^{-1}$ >4 h $week^{-1}$	1.00 0.91 (0.25–3.40)	Age, education, ApoE4, delayed recall test
Sumic *et al.*, 2007 [15] (*The Oregon Brain Aging Study*)	US (1989)	27	F	Mean: 4.7	≥85	Cognitive Impairment (15) (*MMSE score <24 points*)	MMSE	Self-administered questionnaire (*Hours per week of exercises*)	≤4 h $week^{-1}$ >4 h $week^{-1}$	1.00 0.12 (0.03–0.41)	Age, education, ApoE4, delayed recall test

Table 1 (*Continued*)

Source, y *(Cohort)*	Country, (baseline y)	Subjects, *n*	Gender	F-up, y	Age, year	Outcome, (*n*) *(Definition)*	Assessment of cognitive performance	Assessment of physical activity	Physical activity categories	RR (95% CI)	Adjustment
Middleton *et al.*, 2008 [16] *(Canadian Study of Health and Aging)*	Canada (1991)	4683	M/F	5	≥65	Cognitive Impairment-No Dementia (454)	mMMSE	Self-administered questionnaire *(Categories based on frequency and intensity of exercises)*	Low Moderate-High	1.00 0.73 (0.59–0.91)	Age, gender, education, NSAIDs, vascular risk factor index
Niti *et al.*, 2008 [17] *(Singapore Longitudinal Aging Study)*	Singapore (2004)	1635	M/F	1–2	≥55	Cognitive decline (490) *(≥1-point decline on MMSE)*	MMSE	Questionnaire *(Categories based on frequency and intensity of exercises)*	Low Medium High	1.00 0.60 (0.45–0.79) 0.62 (0.46–0.84)	Age, gender, education, number of medical illness, hypertension, diabetes, cardiac diseases, stroke, smoking, alcohol, functional disability, depression, APOE-ε4 status, baseline MMSE
Etgen *et al.*, 2010 [18] *(The INVADE Study)*	Germany (2001)	3485	M/F	2	>55	Cognitive impairment (207) *(6CIT score >7)*	6CIT *(Short Blessed Test)*	Questionnaire *(Days per week of strenuous activities)*	No Moderate High	1.00 0.44 (0.24–0.83) 0.46 (0.25–0.85)	Age, gender, BMI, baseline 6CIT score, depression, alcohol, diabetes, IHD and/or stroke, hyperlipidemia, hypertension, chronic kidney disease, smoking habit

CAPE, Clifton assessment procedure for the elderly; MMSE, mini-mental state examination; MSQ, mental status questionnaire; mMMSE, modified mini-mental state examination; APOE, apolipoprotein E; NSAIDs, nonsteroidal anti-inflammatory drugs; IHD, ischemic heart disease.

complete adjustment for potential confounders; the confounding variables included in this analysis are shown in Table 1.

The primary aim of the present meta-analysis was to evaluate whether high levels of physical activity were associated with significant protection against cognitive decline at follow-up. Thus, for studies reporting low levels of physical activity, instead of high, in relation to cognitive decline, we recalculated the HR using conventional procedures. Statistical heterogeneity was evaluated using the I^2 statistic, which assesses the appropriateness of pooling the individual study results. The I^2 value provides an estimate of the amount of variance across studies because of the heterogeneity rather than chance. Where I^2 was greater than 50%, heterogeneity was considered to be high. Moreover, to further investigate the heterogeneity across studies, we performed sensitivity analyses by dividing studies into groups according to their main characteristics. Subgroup analyses were then performed according to gender, mean sample size of the study populations (less than/at least 3500), mean duration of follow-up (less than/at least 5 years) and method used to evaluate cognitive function (mini-mental state examination (MMSE)/other). Publication bias was appraised by visual inspection of the funnel plot of effect size against standard error and, analytically, by the Egger's test.

Results

Study identification and selection

Our search strategy yielded 58 articles (Fig. 1). Of these, we first excluded 17 articles because they had a cross-sectional, case–control or interventional design. The selected articles were then carefully reviewed, and a further 14 articles were excluded because the reported outcome was incidence of dementia or Alzheimer's disease, i.e. not the outcome of interest. Subsequently, 12 papers were excluded because they did not report estimates of the association between physical activity and decline in cognitive function. The reasons for exclusion in all cases are reported as supplementary information.

Thus, 15 prospective studies [5, 8–18] were included in the analysis. Of these, three conducted analyses separately for men and women and so were entered into the final analysis each as a single paper. The number of participants included in the studies varied from 27 to 10 308, with a follow-up time ranging from 1 to 12 years. A total of 33 816 nondemented sub-

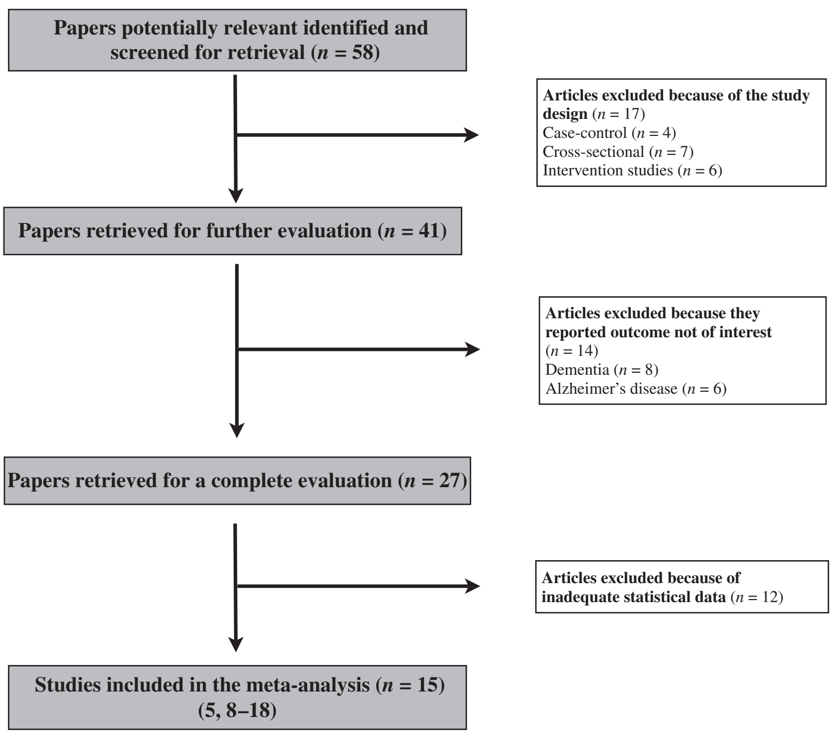

Fig. 1 *Flow chart of search strategy.*

jects were included in the analysis. During the follow-up period, 3210 incident cases of cognitive decline were reported.

Characteristics of the studies included in the meta-analysis are summarized in Table 1. The included studies were conducted all over the world, including China, Singapore, USA, Canada and Europe. All of the studies included only elderly subjects (>65 years) with the exception of the study by Singh-Manoux *et al.*, [14] that investigated younger subjects too. With regard to the methods used to assess cognitive functioning at baseline, most of the studies used the MMSE. In addition, the definition of cognitive decline at follow-up varied substantially in terms of points of decline for cognitive tests used to measure cognitive function.

Meta-analysis

Meta-analytic pooling under a random-effects model showed that subjects who performed physical activity at baseline had a significantly reduced risk of cognitive decline during follow-up. Indeed, by grouping studies according to the different levels of physical activity, subjects who reported performing a high level of activity had a 38% reduced risk of cognitive decline with respect to those who reported being sedentary (HR 0.62, 95% CI 0.54–0.70; $P < 0.00001$) (Fig. 2). We found no significant heterogeneity amongst the studies ($I^2 = 17\%$; $P = 0.26$).

Similarly, when low-to-moderate levels of physical activity were taken into consideration, the significant protection against cognitive decline during follow-up was still observed (HR 0.65, 95% CI 0.57–0.75; $P < 0.00001$), and with no significant heterogeneity amongst the studies ($I^2 = 33\%$; $P = 0.10$) (Fig. 3).

Sensitivity analyses

To investigate the possible differences across studies, we performed sensitivity analyses by grouping studies according to various characteristics such as gender of the study population, study size (mean size of the study sample was 3500), length of follow-up (mean duration was 5 years) and method used to determine cognitive function (MMSE/other). Smaller studies, including only women, and with a shorter duration of follow-up, showed a tendency towards a higher estimate of association in terms of significant reduced risk of cognitive decline, compared with larger studies, in men, and with a longer follow-up period (Table 2).

Publication bias

Funnel plots of effect size versus standard error to investigate possible publication bias were broadly symmetrical, suggesting the absence of publication bias for both high and moderate levels of physical activity ($P > 0.05$ for both levels, Egger's test) (Figs 4 and 5).

Discussion

This is the first meta-analysis that aimed to investigate the association between physical activity and cognitive decline in nondemented subjects. The overall analysis of 15 cohort prospective studies investigating 30 331 nondemented subjects followed for a period of 1–12 years and 3003 incident cases of cognitive decline showed that physically active individuals at baseline have a significantly reduced risk of developing cognitive decline during follow-up. Indeed, the cumulative analysis demonstrated a 38% reduced risk of cognitive decline in subjects with high

Study or Subgroup	Weight	Risk ratio IV, Random, 95% CI
Ho *et al.*, (M)	2.7%	0.53 [0.25, 1.12]
Ho *et al.*, (F)	5.8%	0.53 [0.32, 0.87]
Laurin *et al.*, (M)	4.6%	0.68 [0.39, 1.19]
Laurin *et al.*, (F)	3.6%	0.47 [0.25, 0.89]
Schuit *et al.*,	1.4%	0.50 [0.18, 1.41]
Yaffe *et al.*,	20.5%	0.74 [0.60, 0.91]
Pignatti *et al.*,	1.3%	0.27 [0.09, 0.82]
Lytle *et al.*,	2.8%	0.45 [0.22, 0.94]
Flicker *et al.*,	3.2%	0.50 [0.25, 1.00]
Singh–Manoux *et al.*,	16.7%	0.61 [0.48, 0.78]
Sumic *et al.*, (M)	0.9%	0.91 [0.25, 3.36]
Sumic *et al.*, (F)	0.9%	0.12 [0.03, 0.44]
Middleton *et al.*,	19.1%	0.73 [0.59, 0.91]
Niti *et al.*,	12.6%	0.62 [0.46, 0.84]
Etgen *et al.*,	3.9%	0.46 [0.25, 0.85]
Total (95% CI)	**100.0%**	**0.62 [0.54, 0.70]**

Heterogeneity: $Tau^2 = 0.01$; $\chi^2 = 16.94$, df = 14 ($P = 0.26$); $I^2 = 17\%$
Test for overall effect: $Z = 7.49$ ($P < 0.00001$)

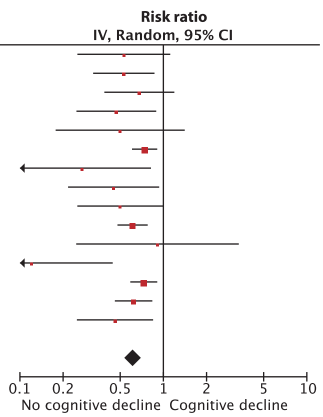

Fig. 2 *Forest plot of studies investigating a high level of physical activity.*

Study or Subgroup	Weight	Risk ratio IV, Random, 95% CI
Ho *et al.*, (M)	3.0%	0.53 [0.25, 1.12]
Ho *et al.*, (F)	5.9%	0.53 [0.32, 0.87]
Laurin *et al.*, (M)	6.4%	0.84 [0.53, 1.34]
Laurin *et al.*, (F)	7.6%	0.55 [0.36, 0.83]
Schuit *et al.*,	1.5%	0.56 [0.19, 1.66]
Yaffe *et al.*,	16.0%	0.78 [0.64, 0.96]
Pignatti *et al.*,	1.4%	0.27 [0.09, 0.82]
Lytle *et al.*,	6.4%	0.63 [0.40, 1.00]
Flicker *et al.*,	3.4%	0.50 [0.25, 1.00]
Singh-Manoux *et al.*,	14.8%	0.81 [0.65, 1.01]
Sumic *et al.*, (M)	1.1%	0.91 [0.25, 3.36]
Sumic *et al.*, (F)	1.1%	0.12 [0.03, 0.44]
Middleton *et al.*,	15.2%	0.73 [0.59, 0.91]
Niti *et al.*,	12.1%	0.60 [0.45, 0.80]
Etgen *et al.*,	4.1%	0.44 [0.24, 0.82]
Total (95% CI)	**100.0%**	**0.65 [0.57, 0.75]**

Heterogeneity: $Tau^2 = 0.02$; $\chi^2 = 20.93$, df = 14 ($P = 0.10$); $I^2 = 33\%$
Test for overall effect: $Z = 6.17$ ($P < 0.00001$)

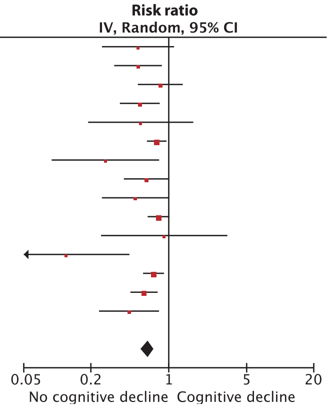

Fig. 3 *Forest plot of studies investigating a low-to-moderate level of physical activity.*

Table 2 *Subgroup analyses*

	Studies, *n*	High level of physical activity	Moderate level of physical activity
Gender			
Males	10	0.63 (0.56–0.72)	0.70 (0.62–0.79)
Females	10	0.60 (0.51–0.71)	0.63 (0.54–0.75)
Sample size			
<3500 subjects	12	0.53 (0.45–0.64)	0.57 (0.48–0.67)
≥3500 subjects	3	0.70 (0.62–0.79)	0.77 (0.68–0.87)
Duration of follow-up			
<5 years	9	0.54 (0.44–0.65)	0.55 (0.46–0.66)
≥5 years	6	0.67 (0.59–0.77)	0.74 (0.65–0.85)
Method used to determine cognitive function			
MMSE	10	0.64 (0.54–0.75)	0.67 (0.57–0.78)
Others	5	0.56 (0.46–0.68)	0.57 (0.50–0.80)

MMSE, mini-mental state examination

levels of physical exercise, compared to sedentary subjects. Moreover, low-to-moderate levels of physical activity similarly resulted in a significantly reduced risk of deterioration of cognitive performance (–35%).

To date, few studies have investigated the relationship between an active lifestyle and cognitive performance in mentally healthy subjects, and results have been conflicting [8–18]. Recent data, including some from longitudinal studies and randomized trials, reported a significant association between physical activity during leisure time and a reduced risk of cognitive impairment at follow-up [4, 9], whereas other studies reported no significant benefit of physical activity on the decline in cognitive function [10, 19]. Recently, Hamer & Chida [7] conducted a meta-analysis to investigate the role of physical activity on the occurrence of neurodegenerative diseases in nondemented subjects. In the overall analysis, they found that physical activity is able to decrease the risk of neurodegenerative diseases such as clinical dementia and Alzheimer's disease, but they did not take into account cognitive decline as a clinical outcome. By contrast, the present meta-analysis is the first, to the best of our knowledge, that included only cognitive decline as the clinical outcome. The choice to study healthy subjects in relation to the decline in cognitive functions was based on the hypothesis that physical activity may help cognitive performance during ageing, by preventing disability rather than a specific disease. Cognitive decline can, in fact, occur as a part of the ageing processes of the brain, without leading to dementia but resulting in a poorer quality of life. Nonetheless, the diagnosis of dementia is based on a number of parameters other than the worsening of

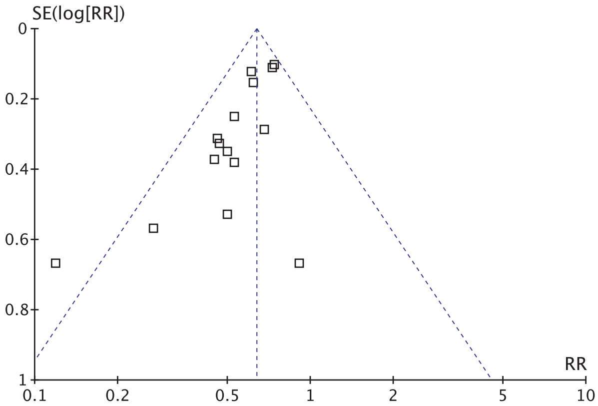

Fig. 4 *Funnel plot for studies investigating a high level of physical activity.*

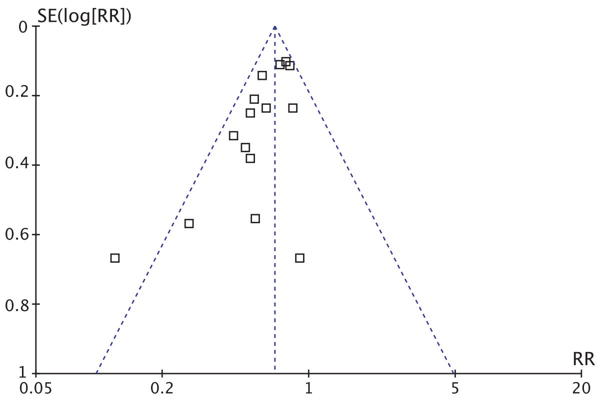

Fig. 5 *Funnel plot for studies investigating a low-to-moderate level of physical activity.*

cognitive performance, and patients referred to as 'nondemented' could show signs of slight cognitive decline as early clinical manifestations of neurodegenerative disease.

Several explanations for the protective effect of physical activity on cognitive functions have been suggested. First, physical exercise helps to maintain cerebrovascular integrity, by sustaining blood flow and the supply of oxygen and nutrients to the brain [20]. Furthermore, physical activity positively influences cardiovascular risk factors, such as diabetes, hypertension, obesity and dyslipidaemia, and reduces the incidence of cardiovascular and cerebrovascular events, with global haemodynamic benefits [21]. Secondly, another possible protective mechanism is the neurotrophic effect of physical exercise. This may stimulate the release of neurotrophins, increasing synapses and dendritic receptors, and promoting neuronal growth and survival [22]. Finally, it has been reported that an active lifestyle is able to prevent stress by reducing cortisol levels, which can positively influence cognitive function [23].

There are a few limitations in this meta-analysis. First, the methods used to investigate cognitive decline and levels of physical activity varied substantially across the included studies. The MMSE test was the most frequently used tool for the diagnosis of cognitive decline, but other tests were used in some studies. This might have resulted in a nonhomogenous definition of cognitive decline amongst the studies. Indeed, the MMSE test with the classical cut-off (>3-point decline at follow-up or a score lower than 24 points) seems to be very suitable for the diagnosis of cognitive decline but is affected by learning bias and is therefore less accurate compared to other neuropsychological tests. By contrast, however, sensitivity analysis showed no significant difference for estimates of association in relation to the different methods used to determine cognitive function. Moreover, with regard to physical activity, data were obtained from questionnaires; thus, bias could be introduced by misinterpretation of the questions and the personal perception of fatigue. In addition, studies differ in the methods used to classify the level of activity, ranging from studies with a simple differentiation of active/not active to others with three or four levels of intensity. Nevertheless, heterogeneity results as well as subgroup analyses did not show any significant differences in risk reduction amongst physically active subjects in terms of the intensity of activity. Indeed, in the overall results, we did not observe a dose–response effect; instead, we found similar estimates of association for both high and low-to-moderate intensity of exercise.

In conclusion, these results highlight the important role of physical activity in the protection of mental functions even in subjects without neurodegenerative disease. These considerations could be important especially because the population is ageing and a good cognitive function is fundamental for individual autonomy and quality of life, even in nondemented subjects. The effect of physical activity does not appear to be dose dependent, but may be stronger in women than in men. However, further studies are needed to determine the optimal type, frequency and intensity of exercise to preserve the integrity of cognitive function.

Conflict of interest statement

No conflict of interest was declared.

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Data S1. Reasons of exclusion.

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