Biochimica et Biophysica Acta 1822 (2012) 482-491



Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis



Review

Leisure activities, cognition and dementia

Hui-Xin Wang a,*, Weili Xu a, Jin-Jing Pei b

- ^a Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet and Stockholm University, Gävlegatan 16, 113 30 Stockholm, Sweden
- b KI-Alzheimer Disease Research Center (KI-ADRC), Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Novum, Floor 5, SE-141 57 Huddinge, Sweden

ARTICLE INFO

Article history:
Received 25 May 2011
Received in revised form 1 September 2011
Accepted 2 September 2011
Available online 10 September 2011

Keywords:
Cognitive function
Dementia
Leisure activity
Mental activity
Physical activity
Social activity

ABSTRACT

Accumulated evidence shows that leisure activities have a positive impact on cognitive function and dementia. This review aimed to systematically summarize the current evidence on this topic taking into account the limitations of the studies and biological plausibility for the underlying mechanisms linking cognition, dementia and leisure activities, with special attention on mental, physical and social activities. We included only longitudinal studies, with a follow-up time of at least 2 years, published in English from 1991 to March 2011 on leisure activities and cognition (n = 29) or dementia (n = 23) and provided some evidence from intervention studies on the topic. A protective effect of mental activity on cognitive function has been consistently reported in both observational and interventional studies. The association of mental activity with the risk of dementia was robust in observational studies but inconsistent in clinical trials. The protective effect of physical activity on the risk of cognitive decline and dementia has been reported in most observational studies, but has been less evident in interventional studies. Current evidence concerning the beneficial effect of other types of leisure activities on the risk of dementia is still limited and results are inconsistent. For future studies it is imperative that the assessment of leisure activities is standardized, for example, the frequency, intensity, duration and the type of activity; and also that the cognitive test batteries and the definition of cognitive decline are harmonized/standardized. Further, well designed studies with long follow-up times are necessary. This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

Along with global aging, age related diseases such as cognitive impairment and dementia will increase dramatically in the coming years. Dementia is one of the most common diseases among elderly people. It is a leading cause of disability, institutionalization, and mortality; therefore it has a tremendous impact on both the individual and society. As limited effective treatment alternatives for dementia are currently available, identification of risk or protective factors, especially modifiable factors, could provide potential for preventing the disorder. However, to date, evidence on the modifiable preventive factors for dementia is still limited. Among the proposed protective factors, leisure activities are the most studied.

Leisure activity can be defined as the voluntary use of free time for activities outside the daily routine, it is one of the major components of a healthy lifestyle. After retirement, leisure time constitutes a relatively larger part of the daily life, leisure time activities have emerged

as the most important target for lifestyle changes among older adults because of the potentially beneficial effect on various health outcomes. The effects of exercise on health are perhaps best documented in the primary and secondary prevention of diabetes, all-cause as well as cardiovascular disease (CVD)-cause of mortality. Given that its benefits have been amply demonstrated in cohort studies and randomized clinical trials [1,2], physicians have been prescribing exercise in a similar way to medication. In addition to physical activity, there is increasing evidence showing that other types of leisure activities, such as mental and social activities, also have beneficial effects on a variety of health outcomes, particularly for maintaining functional ability during the aging process and reducing the risk of common age-related chronic diseases [3–5].

In recent decades, increasing attention has been paid to the role of leisure activities as a protective factor against the occurrence of dementia in old age. Despite the cumulative knowledge on the topic, the key question remains: do leisure activities prevent or postpone cognitive decline or dementia? How strong is the evidence? To answer these questions, we performed a systematic critical review to present the evidence from observational studies concerning the impact of leisure activities, specifically mental, physical and social activities, on the risk of dementia and cognitive decline and provided some evidence from intervention studies on the topic.

 $[\]dot{\varpi}$ This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

^{*} Corresponding author. Tel.: +46 8 690 6867; fax: +46 8 690 5954. *E-mail addresses*: huixin.wang@ki.se (H.-X. Wang), weili.xu@ki.se (W. Xu), Jin-Jing.Pei@ki.se (J.-J. Pei).

2. Methods

This systematic review summarized epidemiological studies on leisure activities and dementia according to methods and inclusion criteria developed by our group in a project promoted by the Swedish Council on Technology Assessment in Health Care to summarize the epidemiological evidence in dementia (SBU) [6,7].

Search strategy and inclusion criteria: Studies were identified by searching Medline, Medline plus, and PubMed using terms such as 'cognition', 'cognitive function', 'dementia', and 'Alzheimer's disease (AD)' in combination with 'physical activity', 'exercise', 'intellectual activity', 'mental activity', 'cognitive activity', 'social activity', 'leisure activities', as well as 'social engagement'. Only original papers published in English from 1991 to March 2011 were included in the review. In order to minimize reverse causality, we only included longitudinal studies and cross-sectional studies that collected the exposure information at midlife. All suitable articles were evaluated taking into account their internal validity and classical causal criteria. A final index for each study was calculated by following a three-step procedure: 1) The internal validity of the article was evaluated with a four-grade score taking into account population type, drop-out rate, study design, case ascertainment, diagnostic procedure, exposure assessment, confounding control, presence of bias, and statistical power; 2) Three specific causal criteria (strength of the association, temporality and biological gradient) were examined and graded for each article; 3) Internal validity and causal criteria were then integrated in a four-level index: not acceptable, low, medium and high validity [7]. In this review, only studies with medium and high validity were included to summarize the epidemiological evidence on the topic.

3. Results

3.1. Evidence from observational studies

3.1.1. Physical activity in relation to cognitive function and dementia

We identified 23 observational studies that examined the effect of physical activity on cognitive function (Table 1) and 22 studies on risk of dementia (Table 2). Most of the studies were done in Europe and North America, with the exception of three conducted in China, two in Australia, and one in Japan.

The study populations varied: while most studies were population-based studies carried out in specific geographic areas, a number of studies included a nation-wide sample covering several geographic areas with a large number of participants [8–11], others included specific populations such as a national birth cohort [12], men [13–15], male twin pairs [16], women [17], female nurses [18], and Catholic nuns, priests, and brothers [19]. The follow-up time varied from 2 to 40 years.

Some of the studies investigated the effect of 'physical activity' as a type of activity, some studied the individual physical activity items, and some examined a summary score of leisure activities that included different items of physical activity, ranging from intense physical activities (e.g. aerobic exercise) to light physical movement (e.g. walking). The assessment of physical activity varies between the studies, ranging from the frequency and duration of participating in predefined specific physical activity items to self reported participation. In addition, some studies calculated total kilocalories (energy) per week expended in leisure activities, taking into account the amount, duration, as well as intensity [17,18,20]. While most studies on the topic focused on late life, several studies investigated the effect of midlife physical activity on cognitive function or dementia [12,16,21–23].

Substantial variation was observed in the assessment of cognitive function, ranging from global cognitive tests [24], specific cognitive domain tests [22,25–27], large neuropsychological batteries testing multiple cognitive domains [19,28,29], and brain volumes [30], to global and regional specific measures of neuropathology [31]. The definitions of cognitive impairment also varied from cognitive decline, cognitive

impairment, mild cognitive impairment (MCI) to amnestic MCI (aMCI). Most studies on dementia focused on all types of dementia and AD as outcomes. Although the diagnostic criteria for dementia were different, they are generally comparable across studies.

All observational studies suffer from methodological limitations. Despite the limitations presented in each of the studies, researchers consistently tried to control for potential confounders and verified the possible effects of the limitations on the reported results. In spite of differences in study design, population, location, assessment and categorization of exposures, definition of outcomes and length of follow-up a protective effect of regular physical activity in middle age or late life was reported in 16 out of 23 (70%) on the risk of cognitive decline/impairment and 16 out of 22 (73%) studies on the risk of dementia, including one study that even found a dose–response effect [8].

A recently published meta-analysis of 15 prospective studies that followed-up 33816 subjects without dementia for 1–12 years also reported that physical activity had a moderate protective effect against cognitive decline. Subjects who performed high levels of physical activity reduced the risk of cognitive decline by 38% (HR=0.62, 95% CI: 0.54–0.70). Even low-to-moderate level exercise showed a significant protective effect, reduced the risk by 35% (HR=0.65, 95% CI: 0.57–0.75) [32].

3.1.2. Mental activity in relation to cognitive function and dementia

We identified 9 observational studies that investigated the effect of mental activity on the risk of cognitive decline/impairment (Table 1) and 9 studies on the risk of dementia (Table 2). Most of the studies were conducted in North America and Europe, with the exception of one conducted in China. Almost all studies were population-based and carried out in specific geographic areas, except for one that included a nation-wide sample [21], one that recruited members of the World War II veteran male twin pairs [16], and another study that enrolled Catholic nuns, priests, and brothers [19]. The follow-up times of these studies are quite similar, with the mean ranging from 4 to 6 years, except for one study that investigated the effect of midlife activities 20 years before the cognitive assessment [21], and another that examined such activities from a life course perspective, e.g. during childhood, young adulthood, middle age, and old age on cognitive. The follow-up time of the studies concerning the effect of mental activity on the risk of dementia varied from 4 to 40 years.

Most of the studies used the term 'mental activity' to describe a number of different mental activities such as reading, playing games, and studying. They subsequently analyzed participation in any one of these mental activities or a summary composite score. The assessment of mental activity is similar among the studies; typically it is the frequency of participation in predefined or self-reported mental activity items. While most studies on the topic focused on late life mental activity, one study investigated midlife activity [16].

Variations were also observed in the measures of cognitive function, ranging from specific cognitive domains [19,27,28,33] to global cognitive function [20,21,25,34]. One study even assessed global and regional specific measures of neuropathology [31]. There was a variety of targeted outcomes including cognitive decline, cognitive impairment, MCI, and aMCI. Most of the studies on dementia included all types of dementia, and several studies included also AD [11,19,31,35]. One study investigated all types of dementia, AD, and VaD [33]. All studies controlled for potential confounders and showed a protective effect of mental activity against cognitive decline, cognitive impairment, dementia, AD, or VaD regardless the differences in study design, population, location, definition of the outcomes, the length of follow-up, and the time window of the exposure assessed during the life course.

3.1.3. Social and other types of leisure activities in relation to cognitive function and dementia

The influence of social and other types of leisure activities on the risk of cognitive decline/impairment and dementia has been investigated

Table 1Evidence on the association between leisure activities and cognition.

Reference	Location	Pop.	Age	F-up year	Assessment of activities	Outcomes	Covariates	Results	Activity type
Albert et al. [29]	3 cities in USA	1192	70- 79	2.5	PA: freq. and energy expended in daily activities around the house, e.g. yard work	Sum of language, memory, conceptualization, visuospatial ability	Demographic, psychosoc., phys. variables	CD: higher levels PA (p<0.05)	PA
Carmelli et al. [13]	California, USA	566 men	65– 86	6	PA PA	CD: lost >1 quartile of the sum rank of visual retention, controlled oral word association, and digit symbol substitution tests	Age, educ., health	CD: PA (p<0.05)	PA
Broe et al. [74]	Sydney, Australia	327	75– 96	3	Freq. of gardening, yard work, sports, exercise, walking	Constructional ability memory verbal fluency	Age, sex, educ.	Walking associated with poorer construc. ability	PA
Bassuk et al. [24]	New Haven, USA	2812	65+	12	SE: spouse, contact friends, religious membership, services, n. recreational SA	CD	Demographic, cogn., income, health, PA, depr. lifestyle	CD: $OR = 2.4$, 1.1–4.9 for SE	SA
aurin et al. [8]	10 provinces in Canada	4615	65+	5	PA: freq. and intensity of exercise	CI	Age, sex, educ.	CI: OR = 0.6, 0.4–0.8 for high levels vs. no PA. A dose–response assoc.	PA
Ho et al. [75]	Hong Kong, China	2030	70+	3	Exercise	CI	Demographic, gait time, CVD residence	CI: RR = 2 for no exercise women	PA
schuit et al. [14]	Zutphen, Netherlands	347 men	74.6	3	Sum: freq. duration of walking, sport bicycling, hobbies, gardening, odd jobs	CD: >3 points decline on MMSE	Age, educ., alco., smoking, cogn.	CD: $OR = 2.0$, 0.9–4.8 for PA 1 h/day vs. the rest. APOE ε 4 carriers: $OR = 3.7$, 1.1–12.6	PA
affe et al. [17]	4 places in USA	5925 women	65+	8	PA: n. of blocks walked; kilocalories expended in recreation, walking, climbing stairs	CD: >=3-point decline on MMSE	Age, educ., comorbidity, smoking, estrogen, function	CD: OR = 0.7, 0.5-0.8 for blocks walked; OR = 0.7, 0.6-0.9 kcal in highest vs. lowest quartiles	PA
Aartsen et al. [28]	3 places in Netherlands	2076	55- 85	6	SA: church, org. Experiential: trips, museum, theater, cinema, restaurant. Developmental: study, sports	Immediate recall learning fluid intelligence processing speed MMSE	Age, sex, educ., health	Cognition: none of the activities	PA MA SA other
Vilson et al. [19]	A number of places in USA	801 nuns, priests, brothers	65+	4.5	CA: freq. TV, radio, reading, games, puzzles, museum. PA: n. of minutes in walking, jogging, running, gardening, dancing, other sports	Global cognition working memory perceptual speed	Age, sex, educ., cogn.	Reduced decline in glo bal cognition 47%, working memory 60%, perceptual speed 30% for 1-point increment in CA	PA MA
Richards et al.	Across UK	1919 British birth cohort	35	18	Checklist of 25 sports and recreational activities	Verbal memory, memory decline	Sex, educ., SES, IQ at 15 years, health, distress	Verbal memory at 43 years: all activities. Memory decline from 43 to 53 years: PA	PA other
Verghese et al. [33]	NY, USA	469	75– 85	5.1	Sum of freq. in 6 predefined CA	Buschke selective reminding test and Fuld object-memory evaluation	0	Two tests: annual rate of decline reduced by 0.043 and 0.006 points for 1-point incr. in CA score (p<0.05)	MA
Wilson et al. [20]	Chicago, USA	4392	65+	5.3	CA: freq. TV, radio, reading, games, crosswords; museum	CD	Age, sex, race, educ. cogn., depr. symp. health	CD: A 19% decrease for 1-point increase in CA score (p<0.001)	MA
Barnes et al. [38]	Chicago, USA	3899	65+	5.3	SE: religious services, museum, activities, work	CD:	Demographic, SES, CA, PA, depr. symp., health	CD: reduced by 91% for high level (90th percentile) vs. low (10th) of SE, p<0.001	SA
Lytle et al. [76]	Pennsylvania, USA	929	65+	2	Composite exercise level: combination of type, duration, and freq	CD: MMSE score ≥3 points (90th percentile)	Age, sex, educ., self-rated health	CD: $OR = 0.5$, $0.2-0.95$ for high- and $OR = 0.6$, $0.4-0.997$ for low level vs. no exercise	PA

van Gelder et al. [15]	Finland, Italy, the Netherlands	295 men MMSE score>18	70+	10	PA: daily duration (min/day), mean intensity, changes in duration and intensity	CD	Cogn., ADL, demographic, lifestyle, depr., vasc. factors	CD: 1.7 points decline (p<0.001) for decrease PA duration >60 min/day vs. maintained; 1.8 to 3.5 times more for lowest intensity vs. other quartiles	PA
Weuve et al. [18]	11 states in USA	16,466 female nurses	70- 81	2	Energy expenditures of running, jogging, walking, hiking, sports, bicycling, dance, exercise; walking pace; stairs climbed	Cognition memory attention category fluency	Age, SES, educ., alco., smoking, health, APOE, vasc. factors	Higher level of PA related to less decline (p<0.001) on all tests except category fluency	PA
Newson and Kemps [26]	Adelaide, Australia	755	77.4	6	Sum of freq. of household maintenance, domestic chores, SA, service	Processing speed picture naming incidental recall	Age, sensory function	Activity was a sign. predictor of cognitive change in speed, picture naming, and incidental recall.	SA other
Sturman et al. [77]	Chicago, USA	4055	65+	6.4	PA index: time spend in walking, jogging, yard work, dancing, exercise, bicycling, swimming, bowling	CD: sum of immediate memory, delayed recall, MMSE, symbol digit modalities test	Age, sex, race, educ.	No sign. associations	PA
Verghese et al. [25]	NY, USA	437	75+	5.6	CA: time spend on reading, writing, crossword puzzles, games, discussions, music. PA: tennis, golf, swimming, bicycling, dancing, exercises, walking, climbing stairs, babysitting	aMCI	Age, educ., sex, illnesses	aMCI: HR = 0.95, 0.9-0.99 for one-point increment in CA, not PA	PA MA
Ghisletta et al. [27]	French speaking region, Switzerland	529	80- 85	6.4	Media: radio, TV, reading. CA: games, crossword puzzles. Manual: gardening, craft. PA: walking, exercise. SA: restaurants, trips; religious	Perceptual speed verbal fluency performance	Age, sex, SES, hearing, vision, health	Increased media and CA lessened decline in perceptual speed, not other functions	PA MA SA other
Wang et al. [34]	Chongqing, China	5437	55+	4	CA: time spend on games, reading, writing, painting. PA: traveling, fishing, gardening, walking. SA: music, dancing, TV, radio, visit friends	CI	Demographic, occup., health, ADL, lifestyle, depr. cogn., activities	CI: RR = 0.97, 0.9–1.0 for playing games, RR = 0.9, 0.8–1.0 for reading, RR = 0.96, 0.9–0.99 for composite CA, RR = 1.1, 1.07–1.12 for watching TV	PA MA SA
Wilson et al. [31]	Chicago, USA	775	65+	5	Freq. reading, games, library, play during childhood, young, middle age, or current	MCI CD Neuropathology	Age, sex, educ. SES, vasc., factor, CA, SA, PA, cogn.	CA associated with reduced MCI and less rapid CD, not neuropathology	MA
Angevaren et al. [78]	The Netherlands	1904	45– 75	5	Average time spent on walking, odd jobs, bicycling, housekeeping, gardening, walking, bicycling	Processing speed	Age, educ, sex, vasc. factors, PA, cogn.	Processing speed: β = 0.06, p<0.05 for changes in intensity on PA	PA
Chang et al. [22]	Reykjavik, Iceland	4761	51	26	The hours per week in sports, exercise during their adult life	Processing speed memory executive function	Age, BP, BMI, cholesterol, smoking, heart rate, educ., depr. APOE	PA related to all measures, p for trend <0.0001 for all	PA
Etgen et al. [79]	Bavaria, Germany	3903	55+	2	PA: n. days per week walking, hiking, bicycling, swimming, gardening, etc.	CI	Age, sex, vasc. factors, kidney disease, depression	CI: OR = 0.6, 0.4–0.9 for moderate, OR = 0.5, 0.4–0.8 for high PA level	PA
Erickson et al. [30]	Pittsburgh, USA	299	78	9	PA: number of blocks walked over a week	CI Brain volumes		Greater PA predicted greater volumes. CI: OR = 3.2, p<0.07 for less PA	PA
Scarmeas et al. [80]	NY, USA	357	65+	5.2	PA: time spend on vigorous, moderate, light activities	CD	Age, sex, educ., ethn. APOE, CDR, smoking, comorbidity	CD: not related to PA	PA
Kåreholt et al. [21]	Sweden	1643 national- wide sample	46– 75	20	MA: reading, hobby, instrument, singing. PA: dancing, sports, gardening. SA: visiting. SC: movies, theater, study. Political: appeal, speech. Organizations	MMSE	Age, sex, educ., f-u, mobility, distress, alco. employment, SES, smoking	Cognition: β = 0.17, p < 0.01 for political, β = 0.11, p < 0.05 for MA. PA in women.	PA MA other

Abbreviations: AD: Alzheimer's disease; BP: blood pressure; BMI: body mass index; MCI: mild cognitive impairment; aMCI: amnestic mild cognitive impairment; MMSE: Mini-Mental State Examination; PA: physical activity; MA: mental activity; SA: social activity; SE: social engagement; SC: social cultural activity; Ind.: individual activity; Other: other type of activities rather than PA, MA and SA; CD: cognitive decline; CI: cognitive impairment; VaD: vascular dementia; CVD: cardiovascular disease; HR: hazard ratio; OR: odds ratio; ADL: activity of daily living.

 Table 2

 Evidence on the association between leisure activities and dementia.

Reference	Country	Pop.	Age	F-up year	Assessment of activities	Outcomes	Covariates	Results	Activity typ
Li et al. [81]	Beijing, China	739	60+	3	Limitation in indoor PA	Dementia	Age	Dementia: RR = 8.7, p<0.05 for limited indoor PA	PA
0	Gironde, France	2040	65+	3	Sports, gymnastics, traveling, visit friends, child care, clubs, associations, reading, TV, games, gardening, odd jobs, knitting	Dementia	Age, cogn. performances	Dementia: Traveling (RR = 0.5, 0.2–0.9), odd jobs/knitting (RR = 0.5, 0.3–0.9), gardening (RR = 0.5, 0.3–1.0). A dose-response pattern	Ind.
oshitake et al. [83]	Kyushu, Japan	828	65+	7	PA: daily exercise during leisure time or moderate to rigorous PA at work	AD	Age, sex, BP, alco., stroke, diab. dementia scale	AD: $RR = 0.2, 0.1-0.7$ for PA	PA
	91 areas in France	3675	65+	4.3	Leisure activities: gardening, traveling, odd jobs or knitting	Dementia	Educ., cogn., depr. symp., alco., soc. network, marital status	Dementia: RR = 2.4, 1.1–5.3 for none vs. 3 activities	Ind.
0	Stockholm, Sweden	1203	75+	3	SE: marital status, living arrangement, contacts with friends	Dementia	Age, sex, ADL, educ., BP, cogn., VD, depr. symp.	Dementia: RR = 1.9, 1.2–3.1 for single living alone vs. married. RR = 1.6, 1.0–2.6 for no friends	SA
	10 provinces in Canada	4615	65+	5	PA: freq. intensity of exercise	Dementia, AD	Age, sex, educ.	Dementia: OR = 0.6, 0.4–0.98. AD: OR = 0.5, 0.3–0.9 for high levels vs. no PA	PA
	3 cities in USA	1172	65+	7	CA: reading, games, studying. PA: walking, excursion, physical conditioning. SA: visiting friends, movies, restaurants, clubs, work, church, synagogues	Dementia	Cogn., health, cerebrovasc. dis., depr.	Dementia: RR = 0.8, 0.6–0.9 for high level CA RR = 0.8, 0.7–0.97 PA RR = 0.85, 0.8–0.9 SA	PA MA SA
9	10 provinces in Canada	4615	65+	5	Engagement in regular exercise with yes or no answers	AD	Age, sex, educ.	AD: $RR = 0.7$, 0.5–0.96 for regularly PA	PA
	Stockholm, Sweden	732	75+	6	Freq. regular participation in mental, social, recreational, productive, and physical activities	Dementia	Age, educ., sex, cogn. comorbid., depr. symp., ADL, activities	Dementia: RR = 0.5, 0.3-0.9 for CA, similar for SA and productive, but not PA (RR = 0.4, 0.1-1.3)	PA MA SA other
Vilson et al. [35]	Chicago, USA	842	65+	4.2	CA: freq. TV, radio, reading, games, crosswords, puzzles, museum. PA: times, minutes in walking, jogging, running, gardening, dancing, exercise, golf, bowling, bicycle, riding, swim.	AD	Age, sex, race, educ., APOE $\epsilon 4$, race and $\epsilon 4$ interaction, f-u time	AD: OR = 0.4, 0.2–0.7 for 1-point increment in CA score, but not PA	РА МА
	A number of places in USA	801 nuns, priests, brothers	65+	4.5	CA: freq. TV, radio, reading, games, crosswords, puzzles, museum. PA: times, minutes in walking, jogging, running, gardening, dancing, exercise, golf, bowling, bicycle, riding, swimming	AD	Age, sex, educ., APOE, med. conditions	AD: HR = 0.7, 0.5–0.9 for 1-point increment in CA score, not PA	PA MA
crowe et al. [36]	Sweden	107 national- wide twins	75+	20	Freq. participation in 11 intellectual-cultural, self- improvement, and domestic activity before the age of 40	Dementia AD	Sex, educ., zygosity	AD: OR = 0.5, 0.3–1.0 Dementia: OR = 0.6, 0.4–1.0 for greater number of activities. AD: greater intellectual-cultural for women not men	Ind. Other
/erghese et al. [33]	NY, USA	469	75–85	5.1		Dementia			PA MA

Abbott et al. [87]	Hawaii, USA	2257 Japanese men	71-93	4.7	Freq. participation in 6 predefined CA and 11 PA. One point = 1 activity for 1 day per week Average amount of distance walked per day	Dementia	Age, educ., sex, med. illnesses, cogn. APOE €4, cogn, declines in PA	Dementia: RR = 0.9, 0.9–0.96 AD: RR = 0.9, 0.9–0.98 for 1-point increment in CA score but not PA Dementia: HR = 1.9, 1.1–3.3 for men walked <0.25 mile vs.>2 miles AD: HR = 2.2 walked	PA
Podewils et al. [10]	4 communities in USA	3375	65+	6	Energy expenditure of walking, household chores, mowing, raking, gardening, hiking, jogging, biking, exercise, cycling, dancing, aerobics, bowling, golfing, swimming	Dementia AD VaD	since mid-age Age, sex, race, APOE, educ., ADL, cogn., social support, white-matter grade	least vs. most Dementia: RR = 0.5, 0.3–0.8 for $>$ 3 PA vs. 0–1. More marked in ϵ 4 noncarriers, absent in carriers. Similar for AD and VaD	PA
Rovio et al. [23]	2 cities in Finland	1449	65-79	21	Freq. PA that lasts at least 20–30 min and causes breathlessness and sweating. Active: at least twice a week, sedentary: <twice a="" td="" week<=""><td>Dementia AD</td><td>Age, sex, educ., f-u, locomotor disorders, APOE, vasc. factors</td><td>Dementia: $OR = 0.5$, $0.2-0.9$. AD: $OR = 0.4$, $0.2-0.9$ for midlife PA at least twice a week. More pronounced among $\varepsilon 4$ carriers</td><td>PA</td></twice>	Dementia AD	Age, sex, educ., f-u, locomotor disorders, APOE, vasc. factors	Dementia: $OR = 0.5$, $0.2-0.9$. AD: $OR = 0.4$, $0.2-0.9$ for midlife PA at least twice a week. More pronounced among $\varepsilon 4$ carriers	PA
Simons et al. [88]	Dubbo, Australia	2805	60+	16	PA: walking, gardening, sports	Dementia	Age, sex, marital status, educ., stroke, ADL	Dementia: $HR = 0.6$, $0.4-0.8$ for daily gardening, $RR = 0.6$, $0.4-0.9$ for daily walking among men	PA
Larson et al. [89]	Seattle, USA	1740	65+	6.2	Number of days per week of exercises for ≤15 min. Freq. exercise calculated by the times per week	Dementia	Age, sex	Dementia: RR = 0.6, 0.4–0.9 exercised >2 times/week vs. less	PA
Karp et al. [3]	Stockholm, Sweden	732	75+	6	Freq. of regularly participation in cognitive, social, physical activities	Dementia	Age, educ., sex, cogn., ADL, comorbidity, depr. symp.,	Dementia: RR = 0.7, 0.5–1.0 for high CA, RR = 0.6, 0.4–0.9 PA, RR = 0.7, 0.5–1.0 SA	PA MA SA
Saczynski et al. [37]	Hawaii, USA	Midlife: 1748 Late-life: 2513 Japanese- American men	45-60 71-86		SE: sum of marital status, living arrangement, social, political, community groups, social events, have a confidant	Dementia	Age, educ., stroke, CHD, disability, APOE, cogn., depr.	Dementia: RR = 2.3, 1.2–4.7 for late-life SE. HR = 1.9, 1.1–3.1 for decreased SE from mid- to late life vs. highest quartile at both periods	SA
Wilson et al. [19]	Chicago, USA	775	65+	5	Freq. of childhood, young adulthood, middle age, current: reading, games, library	AD	Age, sex, educ., SES, vasc. burden, CA, SA, PA, cogn.	AD: RR = 0.6, 0.4-0.8 for frequent current CA	MA
Kivipelto et al. [90]	Two cities in Finland	1449		21	PA that last at least 20–30 min each time and causing sweating and breathlessness	Dementia	Age, educ., sex, f-u time, vasc. factors	Dementia: $OR = 2.0$, 1.1–3.9 for no PA, especially among $\varepsilon 4$ carriers	PA
Carlson et al. [16]	42 states in USA	147 world war II veteran white male twins	44.7	20- 40	Novel CA: reading, courses, extra work; Intermediate: home activities, visiting, club, hobbies; Passive: TV, radio; movies, theater, art, music. PA: sports, outdoor activities, gardening, exercise	Dementia	Occupation, zygosity, APOE	Dementia: $OR = 0.7$, $0.6-0.9$ for greater midlife CA, not PA. Robust in mono-zygotic twins for CA and SA. More evident in $\varepsilon 4$ carriers	PA MA
Taaffe et al. [91]	Hawaii, USA	2263 Japanese- American men	71-92	6.1	PA: sum of time spend (in basal, sedentary, slight, moderate, heavy activities) * weight (oxygen consumption)	Dementia AD	Age, educ., APOE, cogn.	Dementia: HR = 0.5, 0.3–0.9 for high PA vs. least in men with low physical function, not with high function	PA
Akbaraly et al. [11]	Three cities in French	5698	65+	4	Time, freq. in stimulating activities; social support activities; PA; passive leisure activities	Dementia AD	Vasc. factors, depr. symp., phys. func., activities	Dementia: HR = 0.5, 0.3–0.8; AD: HR = 0.4, 0.2–0.7 for stimulating, not other activities	PA MA SA
Scarmeas et al. [92]	NY, USA	1880	65+	5.4	PA: time spend on aerobic, dancing, jogging, handball, bicycling, swimming, hiking, tennis, walking, dancing, calisthenics, golfing, bowling, gardening, horse riding	AD	Cohort, age, sex, ethnicity, educ., APOE, health, depr., activities	AD: HR = 0.8, 0.5–1.04 for some PA; HR = 0.7, 0.5–0.95 for much activity. p for trend: 0.03	PA
Chang et al. [22]	Reykjavik, Iceland	4761	51	26	Time spend in sports or exercised during their adult life in winter and summer	Dementia	Age, sex, educ., BMI, vasc. factors APOE, health, heart rate	Dementia: OR = 0.6, 0.4–0.9 for > 5 h PA	PA
Hughes et al. [93]	Pennsylvania, USA	942	65+	6	Reading, hobbies, games, crafts, crosswords, jigsaw, musical instruments, bridge, gardening, baking, painting	Dementia	Age, sex, educ., depr. symp., IADL, PA, health, recruitment status	Dementia: $HR = 0.9$, 0.8–0.99 for greater number of activities	Ind.
Scarmeas et al. [80]	NY, USA	357	65+	5.2	The typical time spend in vigorous, moderate and light activities. PA: min *times* coefficient in 3 categories: no PA, some, much	AD	Age, education, sex, ethnicity, APOE, smoking, co-morbidity, baseline CDR	Exercise may affect not only risk for AD but also subsequent disease duration: more PA is associated with prolonged survival in AD	PA

Abbreviations: AD: Alzheimer's disease; BP: blood pressure; BMI: body mass index; MCI: mild cognitive impairment; aMCI: amnestic mild cognitive impairment; MMSE: Mini-Mental State Examination; PA: physical activity; MA: mental activity; SA: social activity; SE: social engagement; Ind.: individual activity; Other: other type of activities rather than PA, MA and SA; CD: cognitive decline; CI: cognitive impairment; VaD: vascular dementia; CVD: cardiovascular disease; HR: hazard ratio; OR: odds ratio; ADL: activity of daily living.

less. We identified only 6 studies on social activity and 5 on other activity types or individual activity items on cognition (Table 1) and the same number of studies on dementia (Table 2). These studies were carried out in the USA, the Netherlands, Australia, Switzerland, and China. All studies are population-based investigations in cognition studies, with the exception of in dementia studies one study included twin pairs [36], and another included Japanese-American men [37]. The follow-up time ranged from 4 to 12 years in cognition studies and 3 to 7 years in dementia studies.

Three of the 6 studies investigated the effect of 'social activity' as a type of activity that included a number of individual social activities and were summed up into a composite score. One study investigated the effects of individual social activity items [34], and another two examined social engagement's effect [24,38] on cognition. One study examined the effect of productive and recreational activities on risk of dementia, and 4 studies investigated the influence of individual leisure activity items or the number of leisure activities on risk of dementia.

The outcome measures of cognitive function ranged from specific cognitive domains [26–28] to general global cognitive function [24,34,38]. Most of the studies on dementia targeted all types of dementia as outcome, only one study also included AD [36]. Potential confounders were considered in all these studies.

The results from these studies are inconsistent. Three of the 6 studies reported a protective effect [24,26,38] of social activity on the risk of cognitive decline/impairment, and the other three did not find a significant effect [27,28,34]. There are limited studies on other types of leisure activities in relation to cognitive function, and results were inconclusive and the effect was domain specific. For example, one study reported that participation in political activity, but not social-cultural and organizational activities, was related to better cognition [21], and another found that increased media activity, such as reading, watching TV and listening to radio, may lessen decline in perceptual speed, but not in verbal fluency or performance, whereas no significant effect of social and religious activities on any of the cognitive domains was found [27]. A protective effect of social engagement/activity, productive activity, and individual activities, such as traveling, gardening, odd jobs or knitting, and having a larger number of leisure activities on the risk of dementia was reported. One study even reported a dose-response effect of the number of leisure activities on the risk of dementia. In contrast, two studies did not find a significant protective effect of late life social support activity [11] or midlife social engagement [37] on the risk of dementia. However, the later study did find a protective effect of late life social engagement on the risk of dementia [37].

3.2. Evidence from randomized controlled trials

Although the observational studies have several advantages such as a large number of participants, acquisition of information about many factors, and following the participants for many years some for decades, a major limitation of such studies is that findings can only establish the presence of an association between a designated factor and a clinical outcome, but they do not provide proof of causality. Uncertainty remains about the potential influence of unidentified factors, and whether an intervention directed at a particular factor would necessarily change the outcome in clinically significant ways. Intervention studies in humans would be considered to be the "gold standard" for the proof of a factor's impact on an outcome.

3.2.1. The effect of physical activity on cognitive function

A number of randomized controlled trials (RCT) have been carried out to examine whether physical activity improves cognitive function or prevents cognitive decline. To date, the evidence is intriguing but controversial. A recent RCT examined the effects of aerobic exercise on cognitive function in 152 participants aged 70–80 years with MCI [39]. The participants were randomly assigned to a moderate-intensity walking program; taking a daily B vitamin pill; or to a placebo control

group for one year. No effects for walking interventions at 6 or 12 months, but there were trends for effects in improving memory in men, and memory and attention in women with better adherence.

However, a study that included 138 participants aged 50 years and above with memory complaints showed promising results [40]. A 24-week home-based program of physical activity modestly improved cognition relative to controls. Participants in the intervention group improved 0.73 points (95% confidence interval (CI): -1.27 to 0.03) on the cognitive test scores and the control group (usual care) remained unchanged (0.04, 95% CI: -0.46 to 0.88) after 18 months of the intervention. In a recently published RCT that included 33 adults aged 55 to 85 years with aMCI [41], aerobic exercise had sex-specific effects on cognition. The high-intensity aerobic group exercised at 75–85% of heart rate reserve for 45–60 min per day, 4 days per week for 6 months. The control group carried out stretching exercise but maintained their heart rate at or below 50% of their heart rate reserve. For women, aerobic exercise improved performance on multiple tests of executive function, but for men the effect was only found on Trails B performance.

Particularly intriguing are the exercise intervention studies that looked at effects on not only cognition but also the underlying brain structure and activity. A previous study reported that a 6-month aerobic training (1 h, 3 times per week) in persons aged 60–79 years increased brain volume in both gray and white matter regions [42], and that increases in cardiovascular fitness (walking for 40–45 min per session, 3 times per week for 6-month) in 29 high-functioning, community dwelling older adults aged 58 to 77 years resulted in increased functioning of the attentional network and greater neural activity in regions associated with attention control and less activity in the anterior cingulate cortex [43]. These results provide a strong biological basis for the role of aerobic fitness in maintaining and enhancing the health of central nervous system and cognitive functioning [42] and in improving the plasticity of the aging human brain [43].

A number of meta-analyses have also been carried out to examine whether aerobic fitness training enhances cognitive function. The analysis from 18 intervention studies published between 1966 and 2001 in healthy but sedentary older adults [44] showed that most fitness training had robust but selective benefits for cognition, with the largest fitness-induced benefits occurring for executive-control processes. These results are in line with a recently published meta-analytic review of 29 randomized controlled trials carried out between 1966 and 2009 [45]. Individuals who were randomly assigned to receive aerobic exercise training demonstrated modest improvements in attention and processing speed (g=0.16, p=0.003), executive function (g=0.12, p=0.02), and memory (g=0.13, p=0.03). In addition, similar training effects on cognitive performance (effect sizes = 0.57, 95% CI: 0.43–1.17) were found in a meta-analysis in elderly persons with cognitive impairment and dementia [46].

3.2.2. The effect of physical activity on risk of dementia

Basic science and observational evidence on humans strongly supports the hypothesis that increased physical activity prevents the onset of dementia. There is now increasing amounts of trial evidence to support this hypothesis in terms of cognitive benefits in healthy older people as well as in people at risk for dementia [32,40,47]. However, to date there are no RCTs confirm that increased physical activity prevents dementia.

3.2.3. The effect of mental activity on cognitive function

Clinical research has evaluated cognitive training in normal aging, MCI, and in people with dementia [47]. Consistent with the findings from observational studies, the analysis of 7 randomized clinical trials in healthy older adults showed that cognitive exercise interventions had an average effect size of 0.6 on neuropsychological performance [48]. The effect size was similar for RCTs with longer (greater than 2 years) and shorter follow-up periods. However, the quality of reporting of the trials was generally low. The overall findings to date indicate

that multi-domain cognitive training has the potential to improve cognitive function in healthy older adults and slow decline in affected individuals [49]. However, more controlled studies are needed to establish a protocol of recommendations regarding the systemization of exercise necessary to produce benefits on cognitive function in people with MCI [40,47,50].

3.2.4. The effect of mental activity on risk of dementia

The potential impact of mental activity/cognitive training on older adults has been a topic of increasing interest. Three recent meta-analyses of clinical trials yielded different results. The lack of randomized clinical trials and methodological issues for clinical evidence makes it difficult to draw any conclusion on whether cognitive training programs for older adults can reduce the risk of dementia.

3.2.5. The effect of social and other types of activity on cognitive function and dementia

To our knowledge, there is no RCT to date that has focused on the effects of social and other types of activity in improving cognitive function or preventing dementia.

4. Discussion

We conducted this review to systematically summarize the influence of leisure activities on the risk of dementia and cognitive decline. The evidence to-date indicates that leisure activities, especially mental and physical activities may protect against cognitive decline and dementia. However, the beneficial effect of physical activity on the risk of dementia needs to be confirmed in well designed randomized clinical trials. Although other types of leisure activities may play a protective role on the risk of dementia and cognitive decline, the evidence to date is insufficient to allow us to draw any firm conclusions. This is in line with the conclusion from the 2010 NIH panel's review of the state of the evidence on dementia prevention that ongoing studies on physical activity and cognitive engagement may provide new insights into the prevention or delay of cognitive decline or Alzheimer's disease [51].

The discrepancies found in the effects of different leisure activities on the risk of dementia or cognitive decline might be interpreted by the variation in: 1) selection of study population, age and sex of the participants, and age of exposure assessment; 2) duration of follow-up; 3) assessment of exposure: the type, the frequency, and the intensity of the activities; 4) assessment of outcomes: cognitive test batteries used for cognitive assessment; and 5) competitive risk of mortality.

Although most of the observational studies included only participants without a dementia diagnosis or cognitive impairment at baseline, some included people with an MMSE score >18 [15]. The youngest age of the participants varied from 55 to 75+. It is well known that the incidence of dementia increases with age, the older the cohort studied, the more likely it is that the cognitive decline observed represents prodromal dementia, therefore, decreased leisure activities may be a consequence or a symptom of preclinical dementia. In the timing of exposure assessment, age is also a key issue. Most of the studies assessed leisure activities in late life, although some studies did assess midlife leisure activities, only one study assessed the life course leisure activities and examined their effect on cognitive function in late life [31].

Due to biological, social, and other differences between the sexes, the effect of leisure activities on risk of dementia and cognitive decline may vary between men and women. Although there is no conclusive evidence, sex differences have been observed in dementia occurrence, risk factors, and outcomes [52–54].

It is generally accepted that mild memory disturbance is one of the first symptoms of dementia, and that a more global pattern of low cognitive performance emerges closer to the diagnosis of dementia [55]. Cognitive changes may predate clinical diagnosis by at least

10 years [56] and can be present as much as 20 years before diagnosis [57]. Different follow-up times (varied greatly from 2 to 40 years) may explain the different results from various studies.

The assessment and analytic strategy of leisure activities varied from study to study. Some studies collected information on activities with only "yes" or "no" answers, some with more detailed information, and others calculated a composite activity score. The categorization of leisure activities also varies across the studies, with the exception of mental activity. Different types of activities or individual activity items often comprise different components of physical, mental, and social activities which likely have differing effects on the functioning of the brain.

Diagnosis of dementia is generally comparable across the studies, although some selected all types of dementia as the outcome, others used AD or VaD. However, the definition of cognitive decline varied greatly. Some studies studied incident MCI or cognitive impairment without dementia, others used arbitrary categorization of decline on general cognition, specific domains of cognition, and some studied changes in brain volumes or neuropathology. The discrepancy between the outcome measures of dementia and cognition might be explained by the large gap (10–20 years) between the first cognitive changes and clinical diagnosis of dementia. At older ages dementias are often characterized by a mixture of AD and cerebrovascular pathology [58], which might influence the type of cognitive symptoms experienced already in the preclinical stage of dementia. Further, it may also be explained by the fact that competitive risk of mortality increases with age and mild cognitive symptoms are related to elevated mortality [59].

The variation between the results from observational and intervention studies might be due to: 1) the disparity in type, duration and intensity of the leisure activities; 2) the time point in the life course that exposure was measured, 3) the length of follow-up, 4) the selection of study population: cognitively normal, old adults with MCI, patients with a dementia diagnosis; 5) the age and sex of the participants. The magnitude of the influence of leisure activities is determined not only by the type of activity, but also the intensity and the duration of the exposure, and the time period in the life course. The population selected for intervention included older adults with good cognitive function, those with MCI or memory complains, and those with dementia.

Several limitations need to be mentioned. Although we employed similar search strategies used in other systematic reviews, we might have overlooked or missed some relevant studies in the existing literature. Further, we could not rule out the influence of publication bias. However, given the increasing interest and debate on the topic of leisure activities and dementia, even studies reporting negative results might have had a good chance of being published. Moreover, although we included only longitudinal studies, the possibility of reverse causation remains a major limitation for the observational studies of cognition and dementia.

The precise mechanism through which leisure activities impact cognition is still unclear, but there are a number of proposed hypotheses. One of them is cognitive reserve, where the life experience, such as leisure activities, may influence neural processing and synaptic organization by permitting neurological processes to become more efficient, adaptive, and plastic thus allowing some people to cope with progressing dementia pathology better than others [60,61]. Although environments that involve diverse cognitive stimuli may be the most conducive in increasing cognitive reserve, physiological benefits of physical activity have been related to changes in hormone levels, improved cerebral blood flow, and an increased number of neuronal synapses and brain volume and plasticity [42,43]. Social activities may offer a stimulating social environment that involves not only dealing with complex and challenging social issues, but also physical movement and information processing. In addition, more prominent cerebral blood flow (CBF) deficits were related to all the three types of activities in patients with early AD, but not in the healthy controls [62].

Leisure activities may also have beneficial effects through psychological and behavioral pathways by lowering stress [36], having a better diet and healthier lifestyle, promoting psychological well-being [63,64], and lowering inflammation [65], consequently reducing the risk of developing cognitive decline, dementia or various diseases (e.g. cardio-vascular diseases, diabetes) that are associated with cognitive decline and dementia [66–68]. Moreover, evidence from experimental, neuro-pathological, and epidemiological studies supports both a direct and indirect effect of severe atherosclerosis on dementia and AD in old people [69–73].

In summary, a protective effect of mental activity on cognitive decline has been consistently reported in both observational and interventional studies, but the effect on the risk of dementia or AD remains inconsistent from the later studies. Most of the observational studies provided evidence of the protective role of physical activity on the risk of cognitive decline/impairment and dementia, but this finding is less evident in intervention studies. The evidence of other types of leisure activities on the risk of dementia and cognitive decline to date is insufficient to allow us to draw any firm conclusions. Standardized assessments on frequency, intensity, and duration of predefined individual activity items as well as on the type of activities as well as universal test batteries on cognitive function are warranted. Well designed studies with large sample size and long follow-up time confirming the potential protective effect of other types of leisure activities on cognitive function and dementia would lead to significant public health benefits because currently no efficient treatment for dementia and cognitive impairment is available.

Acknowledgements

Thanks to Professor Laura Fratiglioni for her intellectual and practical support and Helen Long for her excellent English edition. This research was supported by grants from the Swedish Council for Working Life and Social Research, the Swedish Brain Power, the Gamla Tjänarinnor Foundation, the Söderström-Königska Foundation, and the Centre for Health Care Science and the board of research at Karolinska Institutet.

References

- [1] R.S. Taylor, A. Brown, S. Ebrahim, J. Jolliffe, H. Noorani, K. Rees, B. Skidmore, J.A. Stone, D.R. Thompson, N. Oldridge, Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials, Am. J. Med. 116 (2004) 682–692.
- [2] J.E. Manson, D.M. Nathan, A.S. Krolewski, M.J. Stampfer, W.C. Willett, C.H. Hennekens, A prospective study of exercise and incidence of diabetes among US male physicians, JAMA 268 (1992) 63–67.
- [3] A. Karp, S. Paillard-Borg, H.X. Wang, M. Silverstein, B. Winblad, L. Fratiglioni, Mental, physical and social components in leisure activities equally contribute to decrease dementia risk, Dement. Geriatr. Cogn. Disord. 21 (2006) 65–73.
- [4] S. Paillard-Borg, H. Wang, B. Winblad, L. Fratiglioni, Pattern of participation in leisure activities among older people in relation to their health conditions and contextual factors: a survey in a Swedish urban area, Ageing Soc. 29 (2009) 803–821.
- [5] H.X. Wang, A. Karp, B. Winblad, L. Fratiglioni, Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project, Am. J. Epidemiol. 155 (2002) 1081–1087.
- [6] Demenssjukdomar: En systematisk litteraturöversikt, Stockholm, 2006.
- [7] L. Fratiglioni, H.X. Wang, Brain reserve hypothesis in dementia, J. Alzheimers Dis. 12 (2007) 11–22.
- [8] D. Laurin, R. Verreault, J. Lindsay, K. MacPherson, K. Rockwood, Physical activity and risk of cognitive impairment and dementia in elderly persons, Arch. Neurol. 58 (2001) 498–504.
- [9] J. Lindsay, D. Laurin, R. Verreault, R. Hebert, B. Helliwell, G.B. Hill, I. McDowell, Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging, Am. J. Epidemiol. 156 (2002) 445–453.
- [10] L.J. Podewils, E. Guallar, L.H. Kuller, L.P. Fried, O.L. Lopez, M. Carlson, C.G. Lyketsos, Physical activity, APOE genotype, and dementia risk: findings from the Cardiovascular Health Cognition Study, Am. J. Epidemiol. 161 (2005) 639–651.
- [11] T.N. Akbaraly, F. Portet, S. Fustinoni, J.F. Dartigues, S. Artero, O. Rouaud, J. Touchon, K. Ritchie, C. Berr, Leisure activities and the risk of dementia in the elderly: results from the Three-City Study, Neurology 73 (2009) 854–861.
- [12] M. Richards, R. Hardy, M.E. Wadsworth, Does active leisure protect cognition? Evidence from a national birth cohort, Soc. Sci. Med. 56 (2003) 785–792.

- [13] D. Carmelli, G.E. Swan, A. LaRue, P.J. Eslinger, Correlates of change in cognitive function in survivors from the Western Collaborative Group Study, Neuroepidemiology 16 (1997) 285–295.
- [14] A.J. Schuit, E.J. Feskens, L.J. Launer, D. Kromhout, Physical activity and cognitive decline, the role of the apolipoprotein e4 allele, Med. Sci. Sports Exerc. 33 (2001) 772–777.
- [15] B.M. van Gelder, M.A. Tijhuis, S. Kalmijn, S. Giampaoli, A. Nissinen, D. Kromhout, Physical activity in relation to cognitive decline in elderly men: the FINE Study, Neurology 63 (2004) 2316–2321.
- [16] M.C. Carlson, M.J. Helms, D.C. Steffens, J.R. Burke, G.G. Potter, B.L. Plassman, Midlife activity predicts risk of dementia in older male twin pairs, Alzheimers Dement. 4 (2008) 324–331
- [17] K. Yaffe, D. Barnes, M. Nevitt, L.Y. Lui, K. Covinsky, A prospective study of physical activity and cognitive decline in elderly women: women who walk, Arch. Intern. Med. 161 (2001) 1703–1708.
- [18] J. Weuve, J.H. Kang, J.E. Manson, M.M. Breteler, J.H. Ware, F. Grodstein, Physical activity, including walking, and cognitive function in older women, JAMA 292 (2004) 1454–1461
- [19] R.S. Wilson, C.F. Mendes De Leon, L.L. Barnes, J.A. Schneider, J.L. Bienias, D.A. Evans, D.A. Bennett, Participation in cognitively stimulating activities and risk of incident Alzheimer disease, JAMA 287 (2002) 742–748.
- [20] R.S. Wilson, D.A. Bennett, J.L. Bienias, C.F. Mendes de Leon, M.C. Morris, D.A. Evans, Cognitive activity and cognitive decline in a biracial community population, Neurology 61 (2003) 812–816.
- [21] I. Kareholt, C. Lennartsson, M. Gatz, M.G. Parker, Baseline leisure time activity and cognition more than two decades later, Int. J. Geriatr. Psychiatry. 26 (2011) 65–74.
- [22] M. Chang, P.V. Jonsson, J. Snaedal, S. Bjornsson, J.S. Saczynski, T. Aspelund, G. Eiriksdottir, M.K. Jonsdottir, O.L. Lopez, T.B. Harris, V. Gudnason, L.J. Launer, The effect of midlife physical activity on cognitive function among older adults: AGES—Reykjavik Study, J. Gerontol. A Biol. Sci. Med. Sci. 65 (2010) 1369–1374.
- [23] S. Rovio, I. Kareholt, E.L. Helkala, M. Viitanen, B. Winblad, J. Tuomilehto, H. Soininen, A. Nissinen, M. Kivipelto, Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease, Lancet Neurol. 4 (2005) 705–711.
- [24] S.S. Bassuk, T.A. Glass, L.F. Berkman, Social disengagement and incident cognitive decline in community-dwelling elderly persons, Ann. Intern. Med. 131 (1999) 165–173.
- [25] J. Verghese, A. LeValley, C. Derby, G. Kuslansky, M. Katz, C. Hall, H. Buschke, R.B. Lipton, Leisure activities and the risk of amnestic mild cognitive impairment in the elderly, Neurology 66 (2006) 821–827.
- [26] R.S. Newson, E.B. Kemps, General lifestyle activities as a predictor of current cognition and cognitive change in older adults: a cross-sectional and longitudinal examination, J. Gerontol. B Psychol. Sci. Soc. Sci. 60 (2005) P113–P120.
- [27] P. Ghisletta, J.F. Bickel, M. Lovden, Does activity engagement protect against cognitive decline in old age? Methodological and analytical considerations, J. Gerontol. B Psychol. Sci. Soc. Sci. 61 (2006) P253–P261.
- [28] M.J. Aartsen, C.H. Smits, T. van Tilburg, K.C. Knipscheer, D.J. Deeg, Activity in older adults: cause or consequence of cognitive functioning? A longitudinal study on everyday activities and cognitive performance in older adults, J. Gerontol. B Psychol. Sci. Soc. Sci. 57 (2002) P153–P162.
- [29] M.S. Albert, K. Jones, C.R. Savage, L. Berkman, T. Seeman, D. Blazer, J.W. Rowe, Predictors of cognitive change in older persons: MacArthur studies of successful aging, Psychol. Aging 10 (1995) 578–589.
- [30] K.I. Erickson, C.A. Raji, O.L. Lopez, J.T. Becker, C. Rosano, A.B. Newman, H.M. Gach, P.M. Thompson, A.J. Ho, L.H. Kuller, Physical activity predicts gray matter volume in late adulthood: the Cardiovascular Health Study, Neurology 75 (2010) 1415–1422.
- [31] R.S. Wilson, P.A. Scherr, J.A. Schneider, Y. Tang, D.A. Bennett, Relation of cognitive activity to risk of developing Alzheimer disease, Neurology 69 (2007) 1911–1920.
- [32] F. Sofi, D. Valecchi, D. Bacci, R. Abbate, G.F. Gensini, A. Casini, C. Macchi, Physical activity and risk of cognitive decline: a meta-analysis of prospective studies, J. Intern. Med. 269 (2011) 107–117.
- [33] J. Verghese, R.B. Lipton, M.J. Katz, C.B. Hall, C.A. Derby, G. Kuslansky, A.F. Ambrose, M. Sliwinski, H. Buschke, Leisure activities and the risk of dementia in the elderly, N. Engl. J. Med. 348 (2003) 2508–2516.
- [34] J.Y. Wang, D.H. Zhou, J. Li, M. Zhang, J. Deng, M. Tang, C. Gao, Y. Lian, M. Chen, Leisure activity and risk of cognitive impairment: the Chongqing aging study, Neurology 66 (2006) 911–913.
- [35] R.S. Wilson, D.A. Bennett, J.L. Bienias, N.T. Aggarwal, C.F. Mendes De Leon, M.C. Morris, J.A. Schneider, D.A. Evans, Cognitive activity and incident AD in a population-based sample of older persons, Neurology 59 (2002) 1910–1914.
- [36] M. Crowe, R. Andel, N.L. Pedersen, B. Johansson, M. Gatz, Does participation in leisure activities lead to reduced risk of Alzheimer's disease? A prospective study of Swedish twins, J. Gerontol. B Psychol. Sci. Soc. Sci. 58 (2003) P249–P255.
- [37] J.S. Saczynski, L.A. Pfeifer, K. Masaki, E.S.C. Korf, D. Laurin, L. White, L.J. Launer, The effect of social engagement on incident dementia, Am. J. Epidemiol. 163 (2006) 433–440.
- [38] L.L. Barnes, C.F. Mendes de Leon, R.S. Wilson, J.L. Bienias, D.A. Evans, Social resources and cognitive decline in a population of older African Americans and whites, Neurology 63 (2004) 2322–2326.
- [39] J.G. van Uffelen, M.J. Chinapaw, W. van Mechelen, M. Hopman-Rock, Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial, Br. J. Sports Med. 42 (2008) 344–351.
- [40] N.T. Lautenschlager, K.L. Cox, L. Flicker, J.K. Foster, F.M. van Bockxmeer, J. Xiao, K.R. Greenop, O.P. Almeida, Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial, JAMA 300 (2008) 1027–1037.

- [41] L.D. Baker, L.L. Frank, K. Foster-Schubert, P.S. Green, C.W. Wilkinson, A. McTiernan, S.R. Plymate, M.A. Fishel, G.S. Watson, B.A. Cholerton, G.E. Duncan, P.D. Mehta, S. Craft, Effects of aerobic exercise on mild cognitive impairment: a controlled trial, Arch. Neurol. 67 (2010) 71–79
- [42] S.J. Colcombe, K.I. Erickson, P.E. Scalf, J.S. Kim, R. Prakash, E. McAuley, S. Elavsky, D.X. Marquez, L. Hu, A.F. Kramer, Aerobic exercise training increases brain volume in aging humans, J. Gerontol. Med. Sci. 61A (2006).
- [43] S.J. Colcombe, A.F. Kramer, K.I. Erickson, P. Scalf, E. McAuley, N.J. Cohen, A. Webb, G.J. Jerome, D.X. Marquez, S. Elavsky, Cardiovascular fitness, cortical plasticity, and aging, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 3316–3321.
- [44] S. Colcombe, A.F. Kramer, Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol. Sci. 14 (2003) 125–130.
- [45] P.J. Smith, J.A. Blumenthal, B.M. Hoffman, H. Cooper, T.A. Strauman, K. Welsh-Bohmer, J.N. Browndyke, A. Sherwood, Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials, Psychosom. Med. 72 (2010) 239–252
- [46] P. Heyn, B.C. Abreu, K.J. Ottenbacher, The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis, Arch. Phys. Med. Rehabil. 85 (2004) 1694–1704.
- [47] J.G. van Uffelen, A.P.M.J. Chin, M. Hopman-Rock, W. van Mechelen, The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review, Clin. J. Sport Med. 18 (2008) 486–500.
- [48] M. Valenzuela, P. Sachdev, Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials with longitudinal follow-up, Am. J. Geriatr. Psychiatry 17 (2009) 179–187.
- [49] N. Gates, M. Valenzuela, Cognitive exercise and its role in cognitive function in older adults, Curr. Psychiatry Rep. 12 (2010) 20–27.
- [50] F. Sofi, A. Capalbo, F. Cesari, R. Abbate, G.F. Gensini, Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies, Eur. J. Cardiovasc. Prev. Rehabil. 15 (2008) 247–257.
- [51] M.L. Daviglus, C.C. Bell, W. Berrettini, P.E. Bowen, E.S. Connolly Jr., N.J. Cox, J.M. Dunbar-Jacob, E.C. Granieri, G. Hunt, K. McGarry, D. Patel, A.L. Potosky, E. Sanders-Bush, D. Silberberg, M. Trevisan, National Institutes of Health State-of-the-Science Conference statement: preventing Alzheimer disease and cognitive decline, Ann. Intern. Med. 153 (2010) 176–181.
- [52] N.A. Azad, M. Al Bugami, I. Loy-English, Gender differences in dementia risk factors, Gend. Med. 4 (2007) 120–129.
- [53] M. Musicco, Gender differences in the occurrence of Alzheimer's disease, Funct. Neurol. 24 (2009) 89–92.
- [54] E. Sinforiani, A. Citterio, C. Zucchella, G. Bono, S. Corbetta, P. Merlo, M. Mauri, Impact of gender differences on the outcome of Alzheimer's disease, Dement. Geriatr. Cogn. Disord. 30 (2010) 147–154.
- [55] S. Sacuiu, D. Gustafson, B. Johansson, V. Thorvaldsson, S. Berg, M. Sjogren, X. Guo, S. Ostling, I. Skoog, The pattern of cognitive symptoms predicts time to dementia onset, Alzheimers Dement. 5 (2009) 199–206.
- [56] M.F. Elias, A. Beiser, P.A. Wolf, R. Au, R.F. White, R.B. D'Agostino, The preclinical phase of Alzheimer disease: a 22-year prospective study of the Framingham Cohort, Arch. Neurol. 57 (2000) 808–813.
- [57] A. LaRue, L.F. Jarvik, Reflections of biological changes in the psychological performance of the aged, Age 3 (1980) 29–32.
- [58] D.A. Snowdon, L.H. Greiner, J.A. Mortimer, K.P. Riley, P.A. Greiner, W.R. Markesbery, Brain infarction and the clinical expression of Alzheimer disease. The Nun Study, IAMA 277 (1997) 813–817.
- [59] A. Borjesson-Hanson, D. Gustafson, I. Skoog, Five-year mortality in relation to dementia and cognitive function in 95-year-olds, Neurology 69 (2007) 2069–2075.
- [60] A.F. Kramer, L. Bherer, S.J. Colcombe, W. Dong, W.T. Greenough, Environmental influences on cognitive and brain plasticity during aging, J. Gerontol. A Biol. Sci. Med. Sci. 59 (2004) M940–M957.
- [61] Y. Stern, What is cognitive reserve? Theory and research application of the reserve concept, J. Int. Neuropsychol. Soc. 8 (2002) 448–460.
- [62] N. Scarmeas, E. Zarahn, K.E. Anderson, C.G. Habeck, J. Hilton, J. Flynn, K.S. Marder, K.L. Bell, H.A. Sackeim, R.L. Van Heertum, J.R. Moeller, Y. Stern, Association of life activities with cerebral blood flow in Alzheimer disease: implications for the cognitive reserve hypothesis, Arch. Neurol. 60 (2003) 359–365.
- [63] H.X. Wang, M.A. Mittleman, C. Leineweber, K. Orth-Gomer, Depressive symptoms, social isolation, and progression of coronary artery atherosclerosis: the Stockholm Female Coronary Angiography Study, Psychother. Psychosom. 75 (2006) 96–102.
- [64] H.X. Wang, C. Leineweber, R. Kirkeeide, B. Svane, K. Schenck-Gustafsson, T. Theorell, K. Orth-Gomer, Psychosocial stress and atherosclerosis: family and work stress accelerate progression of coronary disease in women. The Stockholm Female Coronary Angiography Study, J. Intern. Med. 261 (2007) 245–254.
- [65] T. Seeman, Social ties and health: the benefits of social integration, Ann. Epidemiol. 6 (1996) 442–451.
- [66] R.M. Sapolsky, L.C. Krey, B.S. McEwen, The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis, Endocr. Rev. 7 (1986) 284–301.
- [67] J.K. Belanoff, K. Gross, A. Yager, A.F. Schatzberg, Corticosteroids and cognition, J. Psychiatr. Res. 35 (2001) 127–145.

- [68] H.X. Wang, A. Karp, A. Herlitz, M. Crowe, I. Kareholt, B. Winblad, L. Fratiglioni, Personality and lifestyle in relation to dementia incidence, Neurology 72 (2009) 253–259.
- [69] L.J. Launer, Demonstrating the case that AD is a vascular disease: epidemiologic evidence, Ageing Res. Rev. 1 (2002) 61–77.
- [70] D.L. Sparks, S.W. Scheff, H. Liu, T.M. Landers, C.M. Coyne, J.C. Hunsaker III, Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension, J. Neurol. Sci. 131 (1995) 162–169.
- [71] H. Petrovitch, L.R. White, G. Izmirilian, G.W. Ross, R.J. Havlik, W. Markesbery, J. Nelson, D.G. Davis, J. Hardman, D.J. Foley, L.J. Launer, Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Honolulu-Asia aging Study, Neurobiol. Aging 21 (2000) 57–62.
- [72] M.M. Esiri, Z. Nagy, M.Z. Smith, L. Barnetson, A.D. Smith, Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease, Lancet 354 (1999) 919–920.
- [73] S.E. Vermeer, N.D. Prins, T. den Heijer, A. Hofman, P.J. Koudstaal, M.M. Breteler, Silent brain infarcts and the risk of dementia and cognitive decline, N. Engl. J. Med. 348 (2003) 1215–1222.
- [74] G.A. Broe, H. Creasey, A.F. Jorm, H.P. Bennett, B. Casey, L.M. Waite, D.A. Grayson, J. Cullen, Health habits and risk of cognitive impairment and dementia in old age: a prospective study on the effects of exercise, smoking and alcohol consumption, Aust. N. Z. J. Public Health 22 (1998) 621–623.
- [75] S.C. Ho, J. Woo, A. Sham, S.G. Chan, A.L. Yu, A 3-year follow-up study of social, lifestyle and health predictors of cognitive impairment in a Chinese older cohort, Int. J. Epidemiol. 30 (2001) 1389–1396.
- [76] M.E. Lytle, J. Vander Bilt, R.S. Pandav, H.H. Dodge, M. Ganguli, Exercise level and cognitive decline: the MoVIES project, Alzheimer Dis. Assoc. Disord. 18 (2004) 57–64.
- [77] M.T. Sturman, M.C. Morris, C.F. Mendes de Leon, J.L. Bienias, R.S. Wilson, D.A. Evans, Physical activity, cognitive activity, and cognitive decline in a biracial community population, Arch. Neurol. 62 (2005) 1750–1754.
- [78] M. Angevaren, L. Vanhees, A.C. Nooyens, C.G. Wendel-Vos, W.M. Verschuren, Physical activity and 5-year cognitive decline in the Doetinchem cohort study, Ann. Epidemiol. 20 (2010) 473–479.
- [79] T. Etgen, D. Sander, U. Huntgeburth, H. Poppert, H. Forstl, H. Bickel, Physical activity and incident cognitive impairment in elderly persons: the INVADE study, Arch. Intern. Med. 170 (2010) 186–193.
- [80] N. Scarmeas, J.A. Luchsinger, A.M. Brickman, S. Cosentino, N. Schupf, M. Xin-Tang, Y. Gu, Y. Stern, Physical activity and Alzheimer disease course, Am. J. Geriatr. Psychiatry 19 (2011) 471–481.
- [81] G. Li, Y.C. Shen, C.H. Chen, Y.W. Zhau, S.R. Li, M. Lu, A three-year follow-up study of age-related dementia in an urban area of Beijing, Acta Psychiatr. Scand. 83 (1991) 99–104.
- [82] C. Fabrigoule, L. Letenneur, J.F. Dartigues, M. Zarrouk, D. Commenges, P. Barberger-Gateau, Social and leisure activities and risk of dementia: a prospective longitudinal study, J. Am. Geriatr. Soc. 43 (1995) 485–490.
- [83] T. Yoshitake, Y. Kiyohara, I. Kato, T. Ohmura, H. Iwamoto, K. Nakayama, S. Ohmori, K. Nomiyama, H. Kawano, K. Ueda, et al., Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study, Neurology 45 (1995) 1161–1168.
- [84] C. Helmer, D. Damon, L. Letenneur, C. Fabrigoule, P. Barberger-Gateau, S. Lafont, R. Fuhrer, T. Antonucci, D. Commenges, J.M. Orgogozo, J.F. Dartigues, Marital status and risk of Alzheimer's disease: a French population-based cohort study, Neurology 53 (1999) 1953–1958.
- [85] L. Fratiglioni, H.X. Wang, K. Ericsson, M. Maytan, B. Winblad, Influence of social network on occurrence of dementia: a community-based longitudinal study, Lancet 355 (2000) 1315–1319.
- [86] N. Scarmeas, G. Levy, M.X. Tang, J. Manly, Y. Stern, Influence of leisure activity on the incidence of Alzheimer's disease, Neurology 57 (2001) 2236–2242.
- [87] R.D. Abbott, L.R. White, G.W. Ross, K.H. Masaki, J.D. Curb, H. Petrovitch, Walking and dementia in physically capable elderly men, JAMA 292 (2004) 1447–1453.
- [88] L.A. Simons, J. Simons, J. McCallum, Y. Friedlander, Lifestyle factors and risk of dementia: Dubbo Study of the elderly, Med. J. Aust. 184 (2006) 68–70.
- [89] E.B. Larson, L. Wang, J.D. Bowen, W.C. McCormick, L. Teri, P. Crane, W. Kukull, Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older, Ann. Intern. Med. 144 (2006) 73–81.
- [90] M. Kivipelto, S. Rovio, T. Ngandu, I. Kareholt, M. Eskelinen, B. Winblad, V. Hachinski, A. Cedazo-Minguez, H. Soininen, J. Tuomilehto, A. Nissinen, Apolipoprotein E epsilon4 magnifies lifestyle risks for dementia: a population-based study, J. Cell Mol. Med. 12 (2008) 2762–2771.
- [91] D.R. Taaffe, F. Irie, K.H. Masaki, R.D. Abbott, H. Petrovitch, G.W. Ross, L.R. White, Physical activity, physical function, and incident dementia in elderly men: the Honolulu-Asia Aging Study, J. Gerontol. A Biol. Sci. Med. Sci. 63 (2008) 529–535.
- 92] N. Scarmeas, J.A. Luchsinger, N. Schupf, A.M. Brickman, S. Cosentino, M.X. Tang, Y. Stern, Physical activity, diet, and risk of Alzheimer disease, JAMA 302 (2009) 627–637.
- [93] T.F. Hughes, C.C. Chang, J. Vander Bilt, M. Ganguli, Engagement in reading and hobbies and risk of incident dementia: the MoVIES project, Am. J. Alzheimers Dis. Other Demen. 25 (2010) 432–438.