An active and socially integrated lifestyle in late life might protect against dementia

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The recent availability of longitudinal data on the possible association of different lifestyles with dementia and Alzheimer's disease (AD) allow some preliminary conclusions on this topic. This review systematically analyses the published longitudinal studies exploring the effect of social network, physical leisure, and non-physical activity on cognition and dementia and then summarises the current evidence taking into account the limitations of the studies and the biological plausibility. For all three lifestyle components (social, mental, and physical), a beneficial effect on cognition and a protective effect against dementia are suggested. The three components seem to have common pathways, rather than specific mechanisms, which might converge within three major aetiological hypotheses for dementia and AD: the cognitive reserve hypothesis, the vascular hypothesis, and the stress hypothesis. Taking into account the accumulated evidence and the biological plausibility of these hypotheses, we conclude that an active and socially integrated lifestyle in late life protects against dementia and AD. Further research is necessary to better define the mechanisms of these associations and better delineate preventive and therapeutic strategies.

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It is a common belief that maintenance of an active life helps old people to preserve their physical and mental health. Many clinicians have observed that an old patient's capacity to cope with disease can be negatively affected by unfamiliar environments, such as hospitals. For decades psychologists have studied the effect of an engaged lifestyle on cognitive decline,[1] and developed the disuse hypothesis.[2] Sociologists have examined the effect of social network on cognitive ability and suggested that social isolation accelerates cognitive decline in ageing.[3] In addition, many studies have shown that social network, leisure activities, and physical exercise prolong life, improve physical health in general, and decrease the occurrence of specific diseases such as cardiovascular disease.

This background has led to the hypothesis that both social network and leisure activity are implicated in the development of dementia and Alzheimer's disease (AD). During the past 5 years, sufficient results from longitudinal studies have been published to allow some conclusions to be made. This review assesses the published longitudinal studies of lifestyles and cognition and dementia, and summarises the current evidence, taking into account the limitations of the studies and biological plausibility.

Lifestyle effects on survival and health

There is a large amount of epidemiological data on the health benefits of social integration and social support. And there is more evidence of the effects of leisure activities on health and survival, especially physical activities and physical exercise.

Social networks

In a review paper, House and colleagues[4] concluded that even after controlling for baseline health status, people with both a small quantity and a low quality of social relations have an increased risk of death. In a comprehensive review on the effects of social environment on health and ageing, Seeman and Crimmins[5] more recently stated that there is clear evidence for the hypothesis of a generally health-promoting effect of social relationships. The beneficial effect seems to be widespread and life-long from childhood to middle and old age. The evidence is mainly from studies with mortality as the outcome.[6–8] Overall, socially isolated people have two to four times increased risk of all-cause mortality compared with those with extended ties to friends and relatives and in the community.[6,9] In addition, with physical function as an indicator of general health status, several studies have reported an association between limited social ties and physical decline.[10]

The effects of social network on morbidity have most commonly been studied in relation to cardiovascular disease, especially coronary heart disease (CHD) and stroke.[11–14] Authors of a systematic review of psychosocial factors in the aetiology and prognosis of CHD concluded that prospective cohort studies provide strong evidence of an independent aetiological and prognostic role of social support for CHD.[12] According to Berkman and colleagues[15] and Seeman,[16] emotional support could have a major role in determining a favourable prognosis after CHD and stroke.

Leisure activity

Survival is the most common measure of benefits from non-physical activity. In a Swedish study in 1996, people attending cultural events, reading books or periodicals, and

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Table 1. Observational longitudinal studies of the association between social network and cognition

Study, Country	Ref	n	Age at baseline (years)	Social networks at baseline	Follow-up (years)	Cognitive assessment	Control factors	Reported associations
Bassuk et al, USA	31	2812	>65	Social engagement index (marital status, contacts, attendance of church, recreational activities)	3, 6, 12	Global cognitive functioning (Short Portable Mental Status Questionnaire)	Eth, Inc, PMF, Depr, CVD, Smok, Alc, PA, ES	Social disengagement with cognitive decline
Hultsch et al, Canada	32	250	58–65	Social activities; new-information-processing activities; physical activity	6	Decline in cognitive functioning (memory, comprehension, and speed)	CD, IADL, SH, Med, Pers	No association of social activities with cognition
Seeman et al, USA	33	1189	70–79	Social ties; emotional support; instrumental support	7·5	Neuropsychological battery (language, memory, conceptualisation, visuospatial ability)	Eth, Inc, CD, Dep, SEB, PA	Emotional support (but not social ties) with better cognitive function
Bosma et al, Netherlands	34	830	49–81	Physical exercise, mental and social activities	3	Specific tests for memory, verbal fluency; global cognitive test (MMSE)	Cog	Low participation in any activity with cognitive decline
Aartsen et al, Netherlands	35	2076	55–85	Everyday activity, including social, experiential, and developmental activities	6	Specific tests for memory, fluid intelligence, and speed, global cognitive test (MMSE)	PF	No association of any activity with cognition, but information-processing speed with developmental activity
Menec, Canada	36	1292	67–95	Social, mental, and productive activities; number of leisure activities	6	Combined physical and mental function index	ADL, IADL, Cog, SH, Morb, LS	Greater overall activity, and social and productive activities with better function
Zunzunegui et al, Spain	37	964	>65	Social relations (social network, social integration, and social engagement)	4	Global cognitive functioning (scale including memory and orientation items)	Dep, BP, PF	Poor social relations, low participation in social activities, and social disengagement with cognitive decline

All associations were controlled for age, gender, and education. Eth=ethnicity; Inc=income; CVD= cardiovascular disease; PMF=physical and mental function; dep=depression; smok=smoking; alc=alcohol; PA=physical acivities; ES=emotional support; CD=chronic diseases; IADL=instrumental activity daily living; SH= subjective health; med= medication; pers=personality; SEB=self-efficacy believe; cog= cognitive function; PF= physical function; morb=morbidity; LS=life satisfaction; BP=blood pressure.

playing music or singing in a choir survived longer than those who did not participate in such activities;[17] a similar positive effect was observed in a US study, in which survival was longer in people participating in social and productive activities.[18] This beneficial effect was similar to and independent of the effect of fitness activity, which suggests that mechanisms other than increased cardiopulmonary fitness might be involved. Similar results have been reported more recently from another Swedish study, where greater survival was detected in people engaged in solitary activity, such as reading of books or newspapers or solving of crossword puzzles.[19]

Physical activity

By 1995 the American Centers for Disease Control and Prevention and the American College of Sports Medicine already encouraged US adults to have 30 min or more of moderate-intensity physical activity on most, preferably all, days of the week.[20] This recommendation was on the basis of an extensive review of research on mortality in general and cardiovascular disease in particular. Physical activity decreases the risk of cardiovascular disease and improves survival after a cardiovascular event.[21] This positive effect has been shown in men and women[22,23] as well as in middle age and old age.[24] Light to moderate exercise can have a similar beneficial effect to vigorous physical activity.[25–27] The evidence for a protective effect against stroke is less strong.[21] Beneficial effects of physical exercise have been reported in several diseases—such as hypertension, diabetes mellitus, obesity, osteoporosis, and depression.[21,28–30]

Lifestyle effects on cognition

Research on different lifestyles and cognition is important for understanding and better defining their possible effects on dementia. We present here a systematic review of the observational studies and a summary of the randomised clinical trials.

Observational studies

Several cross-sectional studies have showed that cognitive ability is strongly related to social ties and various activities. These studies were excluded because of the lack of correct temporal relation between cause and effect.

Table 2. Observational longitudinal studies of the association between non-physical leisure activities and cognition

Study, Country	Ref	n	Age at baseline (years)	Non-physical activities	Follow-up (years)	Cognitive assessment	Control factors	Reported associations
Gold et al, Canada*	38	316 men	64·7 (mean at follow-up)	Engaged lifestyle (SES, locus of control and intellectual activities)	40	Intelligence (verbal, nonverbal, mechanical tasks)	SRH, pers, paternal SES	Engaged lifestyle with maintenance of verbal intelligence
Hultsch et al, Canada	32	250	55–86	Social activities; new-information-processing activities; physical activity	6	Decline in cognitive function (memory, comprehension, and speed)	CD, IADL, SH, med, pers	Intellectually challenging activities with lower probability of cognitive decline, but also higher cognition with higher activity
Bosma et al, Netherlands	34	830	49–81	Physical exercise, mental, and social activities (hours per week)	3	Specific tests for memory, and verbal fluency; global cognitive test (MMSE)	Cog	All three activities with lower probability of cognitive decline, but also higher cognition with higher activity
Aartsen et al, Netherlands	35	2076	55–85	Everyday activity, including social, experiential, and developmental activities	6	Specific tests for memory, fluid intelligence, and speed; global cognitive test (MMSE)	PF	No association of any activity with cognition, but information-processing speed with developmental activity
Menec, Canada	36	1292	67–95	Social, mental, and productive activities; number of leisure activities	6	Combined physical and mental function index	ADL, IADL, cog, SH, morb, LS	Greater overall activity, and social and productive activities with better function
Richards et al, UK	39	1919	36	Spare-time activity (activities with high social and mental component); physical exercise	7	Verbal memory	SES, IQ, SH, dep	Spare-time activity and physical exercise with better memory performance in midlife

All associations were controlled for age, gender, and education. SES=socioeconomic status. Additional control was performed for SRH=self reported health; pers=personality; CD=chronic diseases; IADL=instrumental activity daily living; SH=subjective health; med=drug use; cog=cognitive function; PF=physical function; morb=morbidity, LS=life satisfaction; dep=depression. *Confirmed by Arbuckle et al (reference 40) with a follow-up of 45 years.

We identified 15 observational longitudinal studies, which were all done in Europe and in North America,[31–44] except one from China (tables 1–3).[45] With the exception of two investigations that included a large sample of volunteers,[32,38] all are population-based studies from well known cohort surveys focused on ageing. The initial cohort of the MacArthur Studies of Successful Aging comprised high-functioning older adults, which could limit the generalisability of the findings.[33,41]

The definition of different activities and social network varies largely not only in the measurements used but also in the conceptual level of investigation. Some studies used simple quantitative assessment, such as number of social ties, number of activities, and time devoted to activities. Other studies took into account underlying dimensions and possible mechanisms by examining emotional or structural support, social integration, and social engagement; new information processing activities, cognitive activity score, experiential activities, and developmental activities; or specific aerobic exercises. With the available information, it is not possible to identify the effect of a specific mental or physical activity; therefore, generalisations are made about broad categories. Large variation is also present in the assessment of cognitive performance, ranging from very short global cognitive tests[31] to large neuropsychological batteries testing multiple cognitive domains.[32,33] Most of the studies examined the association between the lifestyle assessed at baseline and cognitive performance at follow-up; only six studies related the lifestyle to cognitive decline. Less variation is present in the length of follow-up (6–7 years in most studies). Only one study had a follow-up of less than 3 years,[41] and one study examined results derived from three follow-ups expanding the observational period to 12 years. In only two studies did researchers assess midlife activity in relation to cognitive ability after 65 years of age.[38,40]

All studies controlled for demographics including education, but only a few included other indicators of socioeconomic status, which could have a confounding role. Whether education sufficiently controls for the socioeconomic status is unclear, especially in these elderly cohorts where social mobility was common.[46] All studies controlled for baseline cognitive performance and for health status, mostly measured with functional scales or self-assessment or reported diseases. Few studies explicitly controlled for depression,[31,33,37,44] and only two for personality.[32,38]

As commonly happens in epidemiological research, none of the reported studies were totally free of methodological problems. Although each study has some limitations, the researchers consistently tried to verify the possible effect of such limitations on their results. In summary, the findings from these studies can be regarded as internally valid.

Randomised controlled trials

There are no randomised controlled trials that test the hypothesis that a rich social network decreases age-related cognitive decline.

Cognitive training

Numerous cognitive training interventions have been done under laboratory or small-scale clinical conditions. In general,

Table 3. Observational longitudinal studies of associations between physical activity and cognition

Study, Country	Ref	n	Age at baseline (years)	Lifestyle measure	Follow-up (years)	Cognitive assessment	Control factors	Reported associations
Albert et al, USA	41	1011	70–79	Physical activity	2–3	Neuropsychological battery (language, memory, conceptualisation, visuo-spatial ability)	Eth, inc, CD, dep, PF, SN, ES	Strenuous physical activity with preservation of cognitive function
Carmelli et al, USA	42	566	65–86	Self reported physical activity	6	Decline in short-term memory, verbal fluency, and visuospatial ability	SRH	Low physical activity with cognitive decline
Hultsch et al, Canada	32	250	55–86	Social activities, new-information-processing activities; physical activity	6	Decline in cognitive function (memory, comprehension and speed)	CD, IADL, SH, med, pers	No association of physical activity with cognition
Yaffe et al, USA	43	5925	>65	Physical activities of low, medium, or high intensity	6–8	Decline in a global cognitive measure (MMSE)	Morb, PF, smok, oestr	Moderate and strenuous physical activity with a decreased cognitive decline
Schuit et al, Netherlands	44	347	Mean= 74·6	Daily time of physical activity (medium or high intensity)	3	Decline in a global cognitive measure (MMSE)	PMF, dep, SH, SRH, smok, alc	Low daily physical activity with higher cognitive decline, only in people with APOE e4
Ho et al, China	45	2030	>70	Self reported physical activity (yes *vs* no)	3	Global cognitive test (CAPE)	PMF, dep	No exercise with cognitive impairment
Bosma et al, Netherlands	34	830	49–81	Physical exercise, mental and social activities (hours per week)	3	Specific tests for memory, and verbal fluency; global cognitive test (MMSE)	cog	All three activities with lower cognitive decline, but also higher cognition with higher activity
Richards et al, UK	39	1919	36	Spare-time activity (high social and mental component); physical exercise	7	Verbal memory performance	SES, IQ, SH, dep	Spare-time activity and physical exercise with better memory performance in midlife

All associations were controlled for age, gender, and education. Eth=ethnicity; inc=income; dep=depression; ES=emotional support; CD=chronic diseases; SRH=self-reported health; IADL= instrumental activity daily living; SH=subjective health; med=medication use; pers=personality; PF=physical function; morb=morbidity; smok=smoking; oestr=oestrogen use; cog=cognition; SN=social network; PMF=physical and mental function, alc=alcohol.

these studies showed that cognitive training helps normal elderly individuals to do better on the specific task for which they were trained than untrained individuals.[47,48] Although some studies showed that this improvement can be retained for months,[49] no one has proven that the improvement in any of the domains can be transferred to real-world situations. In other words, is it possible to improve memory function in daily life with appropriate memory training? To answer this question a large randomised clinical trial (ACTIVE) was initiated in the USA in 1998.[50] The first, recently published, results show a clear and durable beneficial effect from cognitive training on the targeted cognitive abilities, but no effects on everyday function.[51]

Physical training

The possible beneficial effect on cognition from physical training has been assessed in several small, randomised controlled studies.[48] Churchill and colleagues[48] concluded in their review that the results of short-term trials of physical exercise are equivocal. The authors hypothesised that as high levels of fitness are achieved after years, brief periods of exercise cannot have beneficial effects on a wide array of cognitive process, but rather they can be effective in a subset of cognitive domains that are more sensitive to age-related decrements. This hypothesis is essentially derived from two studies. In a randomised controlled intervention, Kramer and colleagues[52] observed substantial improvements on cognitive tasks requiring executive control in people who received aerobic training compared with anaerobically trained people. This finding was confirmed in a subsequent meta-analysis.[53]

Effect of social network and leisure activity on dementia risk

13 studies of the possible association between social network, physical and cognitive activity, and dementia were found.[54–66]

Observational studies

Tables 4–6 summarise the methodological features and major results of all longitudinal observational studies on this topic.[54–66] No cross-sectional studies are taken into account. Case-control studies with retrospective and unbalanced assessment of the investigated lifestyle are not included,[67–70] because the imprecision introduced is likely to be large and to lead to a differential misclassification of the studied variables. Only one case-control study is taken into account,[63] because the information on activity participation was collected before dementia onset.

Of the 13 studies, only one—done in Japan—was done outside Europe or North America. With the exception of one investigation,[63] all studies are embedded in large longitudinal, population-based studies on ageing and all included the non-demented people identified in the initial

Table 4. Observational longitudinal studies of the association between social network and dementia

Study, Country	Ref	n	Age at baseline (years)	Social network	Follow-up (years)	Control factors	Reported associations*
Bickel and Cooper, Germany	54	422	>65	Social relations, social support, marital status	5–8		Being single or widow with increased risk of dementia†
Fabrigoule et al, France	55	2040	>65	Cultural, productive, and social activities (reported), sport	3	Alc, cog, PF, soc	Travelling, odd jobs, knitting, or gardening with decreased risk of dementia; no association with sport
Helmer et al, France	56	3675	>65	Marital status, social network (social ties and satisfaction feeling), number of activities	5	Alc, dep, SN, LA	Never married with increased risk of dementia and AD; no association with social network and leisure activities
Fratiglioni et al, Sweden	57	1203	>75	Marital status, living arrangement, social ties and satisfaction feeling, social network index	3	Cog, dep, ADL, VD, BP	Single, living alone, or no-satisfaction feeling with increased dementia; poor and limited social network with increased dementia
Scarmeas et al, USA	58	1172	>65	13 selected activities (physical, cultural, recreational, and social); leisure activity score; three factor scores: intellectual, physical, and social	1–7 (mean 2·9)	Occ, PF, dep, VD, hyp, dia	Single activity and factor scores (intellectual, physical and social) with decreased risk of AD; higher leisure activity score with decreased risk
Wang et al, Sweden	59	732	>75	Mental, social, recreational, productive, and physical activities (reported); frequency of participation	6	PF, cog, morb, dep	Frequent engagement in mental, social, and productive activities was inversely related to dementia incidence

All associations were controlled for age, gender, and education. Alc=alcohol; cog=cognition; PF=physical functioning; soc=social class; dep=depression; SN=social network; LA=leisure activity; ADL=activity of daily living; VD=vascular diseases; BP=blood pressure; occ=occupation; hyp=hypertension; dia=diabetes; morb=morbidity. *Dementia diagnosed according to DSM III R criteria, AD diagnosed according to NINCDS-ADRDA criteria. †Diagnosed according to ICD 9 criteria.

cohort. Special populations were included in two studies: twin pairs from a national registry in one survey[63] and catholic clergy members in the other.[60] In all studies baseline was the time of participation in the different activities, except in one where activity during middle-age was explored.[63] As with the studies on cognition, the reports on dementia also vary in the assessment of lifestyles. Social network was assessed from simple categorisation according to marital status[54,56] to more comprehensive indices including all social ties.[56,57] Other studies only took into account engagement in social activities.[58,59] Two studies additionally incorporated a subjective assessment of the social network expressed as feelings of satisfaction.[56,57] The non-physical activities were variously assessed and grouped: some researchers registered all the reported leisure activities;[55,59,63] whereas others collected information only on a selection of common activities with a high mental component.[60–62] Both methods can be criticised. There was little variation in the diagnostic criteria used to define dementia and dementia types. Five studies focused on dementia, three only on AD, and five on both.

The length of follow-up is a crucial issue, as limited leisure activity and poor social network might represent a manifestation of early dementia rather than a premorbid risk factor. All studies had at least 3 years between the assessment of the lifestyles and dementia diagnosis, except one investigation with follow-up ranging from 1 year to 7 years.[58] However, even an interval of 5–6 years may not completely exclude the possibility that early cognitive disturbances affected the initiative, the mood, and the interest of those people who will later develop dementia. Worse ability in specific cognitive domains has been reported among people who later develop dementia 7 years,[71,72] and even 10 years,[73] later; however, this is mainly limited to episodic memory and clearly did not affect daily life. In addition, all the studies of the effect of lifestyle on dementia were adjusted for cognitive ability at baseline, and most of the studies repeated the analyses in the subgroup of cognitively unaffected people.[58–62] Finally, Verghese and colleagues[62] took advantage of 21 years of follow-up to examine the effect of cognitive and physical activity after excluding all people who received a dementia diagnosis at any point during the first 9 years; the protective effect was confirmed in all four analyses.

Control for relevant variables is the second crucial issue, as many factors may influence, or relate to, a person's lifestyle; such factors might also be associated with dementia. Age and gender are two of these factors. Education is especially relevant when other indicators of socioeconomical status are missing.[46,74,75] Other relevant factors include depression, chronic diseases, and physical disability, which may decrease an individual's possibility or wish to participate in social interactions or to engage themselves in leisure activities. All studies controlled for demographics and education, and most of the studies controlled for physical function and health status, but only seven studies controlled for depression or depressive symptoms.[56–62]

In summary, with the exclusion of studies controlling only for demographics, all other investigations have solid internal validity.

Randomised controlled trials

There are no randomised controlled trials exploring the suggested protective effect of social network or physical and

Table 5. Observational longitudinal studies of the association between non-physical leisure activity and dementia

Study, Country	Ref	n	Age at baseline (years)	Activity	Follow-up (years)	Control factors	Reported associations*
Fabrigoule et al, France	55	2040	>65	Cultural, productive, and social activities (reported); sport	3	Alc, cog; PF, Soc	Travelling, odds jobs, knitting, or gardening with lower dementia risk; no association with sport
Scarmeas et al, USA	58	1172	>65	13 selected activities (physical, cultural, recreational and social); leisure activity score; three factor scores	1–7 (mean 2·9)	Occ, PF, dep, VD, hyp, dia	Single activity and factor scores (intellectual, physical, and social) with decreased risk of AD; higher leisure activity score with lower risk of AD
Wang et al, Sweden	59	732	>65	Mental, social, recreational, productive, and physical activities (reported); frequency of participation	6	PF, cog, morb, dep	Frequent engagement in mental, social, and productive activities with decreased dementia risk
Wilson et al, USA	60	801	>65	Cognitive activity score (participation and frequency to seven mental activities); physical activity (time)	Mean 4·5	SRH, dep,cog, PF	Higher cognitive activity score with lower AD risk
Wilson et al, USA	61	842	Mean 76 (SD 6·3)	Cognitive activity score (frequency of seven information processing activities); physical activity score (time in seven activities)	4	Eth, APOE, dep, occ, PMF	Higher cognitive activity score with lower AD risk
Verghese et al, USA	62	469	>75	Six cognitive activities and eleven physical activities; cognitive and physical activity scores (time)	Median 5·1	CD, dep, PMF	Reading and playing board games and musical instruments with a low risk of dementia and AD; cognitive-activity score with reduced risk of both
Crowe et al, Sweden	63	107	>75	Intellectual-cultural, self-improvement, and domestic activity	Middle adulthood		Overall activity with decreased dementia risk

Exposure assessed during midlife. All associations were controlled for age, gender, and education. Alc=alcohol; cog=cognition; PF=physical functioning; soc= social class; occ= occupation; dep=depression; VD=vascular diseases; hyp=hypertension; dia=diabetes; morb=morbidity; SRH=self-reported health status; eth=ethnicity; PMF=physical and mental functioning; CD=chronic diseases. *Dementia diagnosed according to DSM III R criteria, AD diagnosed according to NINCDS-ADRDA criteria.

non-physical activities on dementia. Recently, a randomised controlled trial in patients with AD showed that exercise training combined with education for carers on behavioural management improved physical health and depression in the patients with dementia.[76]

Current evidence

Most of the evidence is from observational studies (figure 1). A higher risk of cognitive decline or lower cognitive performance was observed in five of seven studies of social networks and six of seven studies of non-physical activity (mostly cognitively stimulating activity). Physical activity, including both exercise and daily physical activity, was inversely related to cognition in seven of eight studies. It is difficult to estimate the extent of publication bias, but owing to the debate raised by the topic of lifestyle and cognition, especially in psychology,[77–79] even articles reporting negative results might have had a good chance of being published.

Three of six studies that investigated dementia as the outcome reported an association between social network and dementia.[57–59] Two studies showed an association with marital status.[54,55] Six of seven reported an association between mental activity and dementia,[58–63] which was confirmed also for AD in four studies.[58–62] Six of nine studies reported an association of physical activity with dementia, confirmed also for AD.[55,58,62,64–66] Because of the differences in the definition of the exposures, it is not possible to verify the extent of the potentially large publication bias.

In summary, all three lifestyle components (social, mental, and physical) seem to have a beneficial effect on cognition and a protective effect against dementia.

Interpretation of the findings

Are these associations causal? Is it possible to interpret these associations as protective effects of an active and integrated lifestyle on cognition and against dementia in old age? The association between baseline lifestyle and cognitive performance at follow-up could have at least three possible explanations. First, the premorbid cognitive capability of an individual to engage in certain activities might mediate or confound the reported associations.[80,81] Indeed, there are no studies that specifically controlled for this potential confounder, but most of the studies controlled for baseline mental function and for education, which should be quite accurate surrogates. Second, social engagement and the participation in physical and non-physical activity might be an indicator of a good lifestyle in general, which could be linked to better overall physical and mental-health status. Indeed, several studies took into account and controlled for health status at baseline. Third, the reduced social network and activity could be determined by the prodromal cognitive and depressive symptoms that have been reported in early phases of the dementia.[71,82] As already discussed, several studies have tried to verify this possibility by controlling for baseline cognition and by examining subpopulations with intact cognition, or by excluding those cases with dementia diagnosis within 9 years of follow-up.[58–62] All these additional analyses confirmed the associations. Interestingly, two studies on cognition have reported a reciprocal or bidirectional relation between cognitive stimulation and cognitive performance.[32,34] However, this mutual association does not exclude the possible beneficial effect of cognitive stimulation, because it may create a self-reinforcing mechanism.[34]

Table 6. Observational longitudinal studies of the association between physical activities and dementia

Study, Country	Ref	N	Age at baseline (years)	Activity	Follow-up (years)	Control factors	Reported associations*
Yoshitake et al, Japan	64	828	>65	Leisure and at work physical activity	7	BP, CVD, alc, dia, cog, haem	Daily physical activity with lower risk of AD
Fabrigoule et al, France	55	2040	>65	Sport	3	Alc, cog, PF, soc	No association
Scarmeas et al, USA	58	1172	>65	13 selected activities (physical, cultural, recreational and social); leisure activity score; three factor scores	1–7, mean 2·9	Occ, PF, dep, VD, hyp, dia	Single activity and factor scores with low risk of AD
Lindsay et al, Canada	65	4615	>65	Regular exercise (not otherwise defined)	5		Regular physical activity with low risk of AD
Laurin et al, Canada	66	4615	>65	Low, moderate, high physical activity level (time and intensity)	5	FA, smo, alc, NSAID, ADL, IADL, SRH, CD	High physical activity with low risks of dementia and AD risk
Wang et al, Sweden	59	732	>75	Physical activities (reported); frequency of participation	6	PF, cog, morb, dep	No association
Wilson et al, USA	60	801	>65	Physical activity (time)	Mean 4·5	SRH, dep, cog, PF	No association
Wilson et al, USA	61	842	Mean 76	Physical activity score (time in seven activities)	4	Eth, APOE, dep, occ, PMF	No association
Verghese et al, USA	62	469	⩾75	11 physical activities; physical activity scores (time)	Median 5·1	CD, dep, PMF	Only dancing with low dementia risk

All associations were controlled for age, gender, and education. BP=blood pressure; CVD=cerebrovascular disease; alc=alcohol; dia=diabetes; cog=cognition; haem=haematocrit; PF=physical function; soc= social class; occ=occupation; dep=depression; VD=vascular disease; hyp=hypertension; FA=family aggregation; smo=smoking; NSAID=non-steroidal anti-inflammatory drugs; ADL=activity of daily living; IADL=instrumental activity of daily living; s-Hlth=subjective health; CD=chronic diseases; morb=morbidity; SRH=reported health; PMF=physical and mental function. *Dementia diagnosed according to DSM III criteria, AD disagnosed according to NINCDS-ADRDA criteria.

Possible mechanisms

How might social network, physical activity, and non-physical activity protect against cognitive decline and dementia? Several single pathways have been suggested, as well as more complex and integrated models, where the effect on health in general is taken into account in addition to cognition and dementia.

Social network

Berkman and colleagues[3] proposed a conceptual model of a cascading causal process beginning with the larger social and cultural context that determines the social network structure and the characteristics of network ties. Social networks affect health by operating through five main mechanisms (social support, social influence, social engagement, person-to-person contact, and access to resources and material goods), which influence different health outcomes through three major pathways: behavioural, psychological, and physiological. A similar model has been proposed by Seeman and Crimmins[5] with a distinction between the final biological pathways and the intermediate mechanisms (psychological and behavioural) through which social network may affect human health.

Mental activity

The engagement hypothesis states that the intellectual capabilities in later life might be preserved by a combination of favourable environmental contexts early in life with higher occupational status and intellectual stimulation during adulthood.[1,40] The use of this model of cognitive ageing has led to the "disuse" hypothesis, which suggests that changes in every day experiences and activity patterns result in disuse and consequent "atrophy" of cognitive processes and skills, expressed in the adage "use it or lose it".[2] The possible beneficial effect of cognitive stimulation presumes the existence of a reserve capacity that can potentially be used. For dementia, the reserve hypothesis was proposed first by Katzman[83] and then developed in more functional terms by Stern and colleagues.[84,85] This hypothesis suggests that there are individual differences in the ability to cope with AD pathology, which could explain the repeated observation of an absence of a direct relation between the degree of brain pathology and the clinical manifestation.[85] The reserve hypothesis is well supported by the consistently replicated finding of an association between low education and increased risk of AD and dementia.[86] Cognitive reserve may be enabled by more efficient use of brain networks or a better ability to recruit alternative brain networks as needed.

Physical activity

Physical activity as well as mental activity may increase cognitive reserves. Kramer and colleagues'[52] hypothesis of a selective improvement in neurocognitive function as a consequence of physical training can be interpreted in terms of cognitive reserve.

Summary

In summary, the three lifestyle components (social, mental, and physical) seem to have common pathways, rather than specific mechanisms. These common pathways are not exclusive, but they might all be relevant and acting at the same time. We believe that most of the common pathways converge into three major aetiological hypotheses for dementia and AD: the cognitive-reserve hypothesis, the vascular hypothesis, and the stress hypothesis.

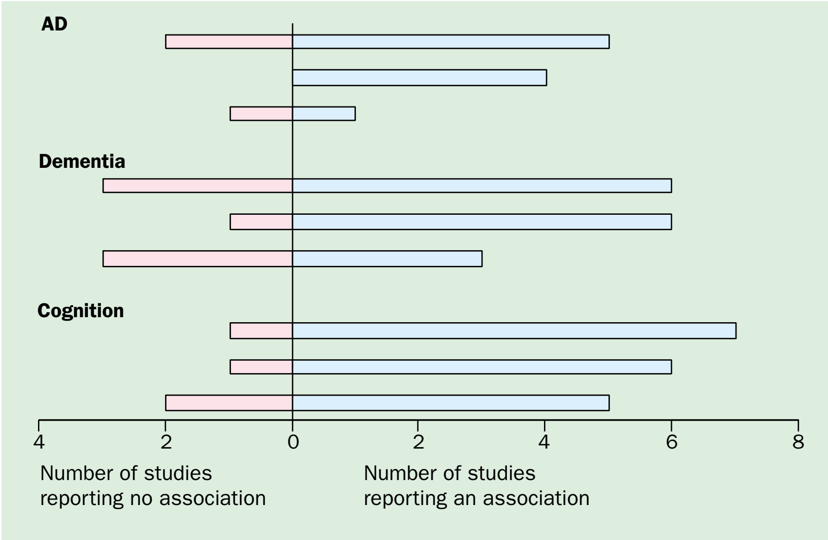

Figure 1. Evidence for protective factors for AD, dementia, and cognition. Top bar=physical activity; middle bar=mental activity; bottom bar=social network.

Biological plausibility

Cognitive-reserve hypothesis

A series of experimental studies support this hypothesis. First, experimental studies in animals, especially rats, have shown that environmentally enriched conditions have the potential to prevent or reduce cognitive deficits in young and even in adult rats,[87,88] and that the deleterious effects of impoverished environment on memory and learning are, at least partly, reversible.[89] Environmentally enriched conditions are a combination of plentiful opportunities for physical activity, learning, and social interaction, which are equivalent to normal conditions in the wild. Second, studies on brain plasticity provide strong support for the functional reserve hypothesis, because independent of the methods or the level (molecular, cellular, structural) the stimuli required to elicit plasticity are thought to be activity-dependent.[90] In the past 5 years, accumulating evidence concerning brain plasticity in adult life has shown the existence of angiogenesis, synaptogenesis, and neurogenesis.[48,91] According to Churchill and colleagues,[48] mental stimulation selectively increases synaptogenesis in adulthood, whereas physical exercise may enhance non-neuronal components of the brain, such as vasculature. More observations have recently shown that at least some regions of the adult brain can respond to environmental stimuli by adding new neurons. This response can be sustained until periods in later life.[88] Neurogenesis has been shown in the adult rodent hippocampus, the olfactory bulb, and the cerebral cortex not only of rodents but also of primates and human beings.[48] Third, even brain-imaging studies in human beings support the view that people with higher reserve—assessed using the surrogates education and occupation—may tolerate more pathology.[85] Finally, numerous studies have shown that, in various cognitive operations, older adults show less specificity than young adults in the regions of the brain that are recruited to do that task. Some researchers interpret this dedifferentiation as a compensatory function.[92]

Vascular hypothesis

Social, mental, and physical stimulation could act via the reported beneficial effects on cardiovascular diseases and stroke. The vascular hypothesis in dementia and AD is supported by several epidemiological studies. Vascular disorders and vascular risk factors are involved in the pathogenesis and progression of AD.[93–98] Evidence from experimental, neuropathological, and epidemiological studies supports both a direct or indirect effect of severe atherosclerosis on dementia and AD in old people.[99–102] As there is substantial clinical and neuropathological overlap between AD and other dementias, the additive or synergistic interactions between vascular factors and AD pathology may be relevant in the production of clinical dementias, including AD.[99,103,104] Cerebrovascular disorders could also promote clinical expressions of dementia and AD in older people.[105–106]

Stress hypothesis

Psychological mechanisms, such as relaxation and stress reduction, might be a third common mechanism. Active individuals with more frequent contacts and integration have more

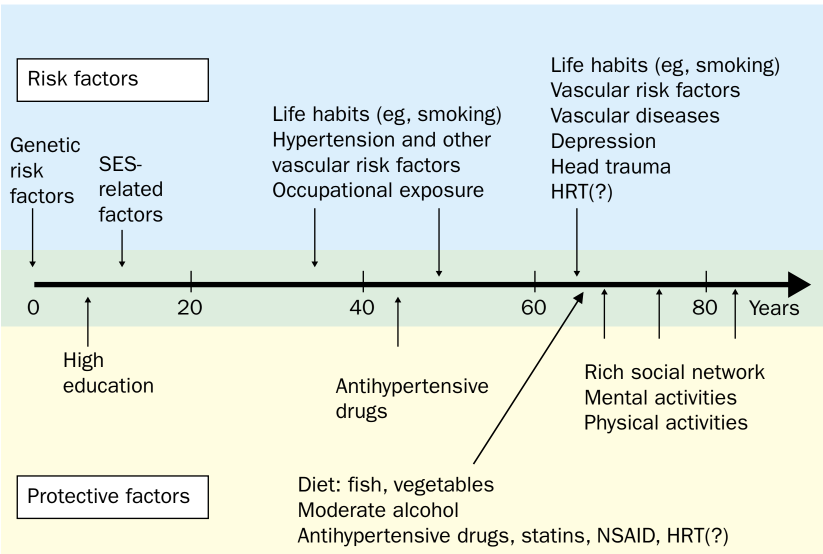

Figure 2. The timeline of risk factors and protective factors for dementia. Time for each factor is identified from the available studies. SES=socioeconomic status.

opportunities to engage with others, leading to positive emotional states such as self-esteem, social competence, and adequate mood, which lead to lower stress. Stress has recently been related to AD—a higher susceptibility to distress led to two times the risk of the disease.[107] The hippocampal region of the brain is involved in the response to stress.[108,109] According to the glucocorticoid cascade hypothesis,[110] the corticosterone hypersecretion caused by stress downregulates the hippocampal corticosteroid receptors, which in turn dampens the feed-back inhibition of the adrenocortical axis leading to further hypersecretion, that finally causes permanent loss of hippocampal neurons. In addition, associations between high concentrations of cortisol, impaired cognitive function, and hippocampal atrophy have been found in several studies of people with dementia, major depression, post-traumatic stress disorder, and Cushing's disease.[111,112] Thus, stress adaptation failure has been suggested to play a part in the pathogenesis of dementia.[113–115] Indeed, changes in the hippocampus as well as learning and memory deficits in animals and human beings have been associated with chronic stressful experience.[107]

Conclusions

In the past 30 years extensive research has increased our knowledge of the aetiology of AD and other dementing disorders. Several hypotheses have already emerged from the epidemiological research. This review provides enough evidence to support the hypothesis that and active and socially integrated lifestyle in late life seems to protect against AD and dementia. This hypothesis can be easily integrated in a general model of dementia occurrence that takes into account the effect of different risk and protective factors acting at different times during the life course of an individual (figure 2). The reported times are derived from the available studies of each specific factor.[86] Genetic predisposition and accumulation of exposure to risk factors, only partly mitigated by protective factors, greatly increase the risk of dementia in late life. This risk may still be modulated in old age by psychosocial factors.

We have no data to help disentangle whether the social, mental, and physical stimulation in late life can decrease the lifetime risk of disease or merely postpone the onset of dementia. Independent of the final mechanism, this hypothesis opens new perspectives for prevention of and even treatment for AD and dementia.

Search strategy and selection criteria

Studies were identified by searches of MEDLINE, MEDLINE plus, and PubMed with the terms "cognition", "dementia", and "Alzheimer's disease" in combination with "social network", "social relations", "leisure activity", "physical activity"; or "cognitive training", and "physical training". Studies were also identified from relevant articles. Only papers published in English were included; abstracts or congress proceedings were not taken into account.

Many questions remain for future research. Some address the role of possible confounders: Can the background personality or the premorbid intelligence explain the reported associations? Is it important to maintain an active lifestyle during the whole life span or only during old age? Can a change in the lifestyle play a major part? Can other lifestyles be relevant? What is the role of genetic risk factors? Are these associations valid in populations with different sociocultural environments?

Other questions address the underlying mechanisms: Is the cognitive stimulation the common factor for all the investigated lifestyles? Which is the most relevant component: physical, cognitive, or social? How do they interact? Might social network act through psychological pathways, such as emotional support, feeling of integration, and meaning in life? Is there a direct effect of physical activity on the brain, such as improvement of cerebral blood flow? Answers to these questions will help us to better define the target populations for future specific interventions, and consequently to better delineate preventive and therapeutic strategies.

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Authors' contribution

LF wrote the review and helped in all other parts of its preparation. SPB did the reference search, selected the articles, and made the first draft of the tables. BW helped to determine the structure and in the writing of the paper.

Conflict of interest

We have no conflicts of interest.

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