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Review of modifiable lifestyle and environmental factors in dementia studies

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2. TABLE OF CONTRIBUTIONS

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3. TABLE OF ABBREVIATIONS

AD: Alzheimer's Disease
 APOE: Apolipoprotein E
 HR: Hazard Ratio
 LEF: Lifestyle and Environmental Factors
 MCI: Mild Cognitive Impairment
 OR: Odds Ratio
 RCT: Randomised Controlled Trial
 RR: Relative Risk
 VaD: Vascular Dementia

4. ABSTRACT

4.1. BACKGROUND

Lifestyle and environmental factors (LEF) are modifiable risk factors for cognitive decline and dementia. A comprehensive description of LEF and their quantification criteria is an important preliminary step towards the elucidation of causes and mechanisms underlying the onset and progression of dementia.

4.2. AIM

To present a systematic review of modifiable LEF associated with dementia in longitudinal and case-control studies, and their quantification criteria.

4.3. MATERIALS

A systematic review of articles published between 2003 and 2013, written in English, listed in the public library PubMed was conducted, with keywords ‘lifestyle’ and ‘dementia’ or ‘environmental factors’ and ‘dementia’ in either the title or the abstract.

Population-based cohort studies (Atherosclerosis Risk in Communities (ARIC) Study, Cardiovascular Health Study (CHS), Framingham Heart Study (FHS), Rotterdam Study) with keyword ‘dementia’ in either the title or the abstract were also reviewed.

4.4. RESULTS

Longitudinal observational studies (N=28) included a total of 83,281 subjects with 9.5 years’ median follow-up. Case-control studies (N=11) included a total of 20,377 subjects, randomised controlled trials (N=6) a total of 6,910 subjects, with 5 years’ median follow-up.

4.5. CONCLUSIONS

General consensus emerged on the protective role of higher level of education, cognitively-stimulating activities, physical activity and healthy diet against dementia. Conversely, smoking at midlife emerged as a risk factor. However, studies varied largely in the definition of LEF, in the quantification criteria (frequency, intensity of activity, tracked history thereof) and the choice of confounders in statistical analyses.

Standardisation of LEF quantification questionnaires is needed. Promising objective measurement techniques based on ambulatory monitoring are emerging.

5. INTRODUCTION

As a consequence of the ageing population worldwide, increasing costs to society arise from late-life conditions such as cognitive decline and dementia (Justin *et al.*, 2013). Dementia is a public health problem, with an estimated incidence of 26.6 million cases worldwide (Blumenthal *et al.*, 2013), with a projection of over 81 million cases by 2040 (Ferri *et al.*, 2005). Few recent studies, however, have suggested that the prevalence of dementia might be subject to change over time, and that in higher income countries, both its prevalence and incidence might have decreased over the past two decades (Matthews *et al.*, 2013; Schrijvers *et al.*, 2012; Qiu *et al.*, 2013) owing to an improved prevention of vascular morbidity and higher levels of education (Matthews *et al.*, 2013). However, at the present time, an effective curative treatment for the most frequent causes of dementia is not available.

Alzheimer's disease (AD) accounts for the largest number of dementia cases in the older population (Wilson *et al.*, 2011). In 1997 it was estimated that in North America and Western Europe together, approximately 70% of dementia cases were caused by AD, and 15% by vascular dementia (VaD) (Whitehouse *et al.*, 1997). In a more recent study on the prevalence of dementia in the United States (Plassman *et al.*, 2007), AD accounted for 69.9% of all dementia syndromes, while VaD accounted for 17.4%.

5.1. VASCULAR RISK FACTORS FOR DEMENTIA

A number of vascular risk factors have been associated with cognitive decline and dementia, including hypertension, obesity, smoking, diabetes and hyperlipidaemia (Alonso *et al.*, 2009; Elias *et al.*, 2012; Reitz *et al.*, 2007; Tolppanen *et al.*, 2012).

There is also emerging evidence implicating heart disease as a risk factor, which suggests (Blumenthal *et al.*, 2013) that vascular risk factors could also indirectly contribute to the overall risk of cognitive decline and dementia by promoting cardiac disease. In particular, coronary artery disease, atrial fibrillation, left-ventricular valvular disease and heart failure have been associated with the risk of dementia (Justin *et al.*, 2013).

5.2. PROTECTIVE FACTORS AGAINST DEMENTIA

Protective factors against dementia have also been suggested. The concept of *cognitive reserve* was introduced over two decades ago by (Katzman *et al.*, 1988), to indicate the ability of the brain to tolerate the pathological burden of age- and disease-related changes without obvious clinical evidence (Fratiglioni and Wang, 2007). According to this hypothesis, the greater the reserve, the more severe pathological changes are needed to cause clinically manifest impairment (Liu *et al.*, 2012).

5.3. MODIFIABLE RISK FACTORS

A substantial research effort has been devoted to the identification of modifiable lifestyle and environmental factors (LEF) that could be targeted in a multi-domain intervention plan to delay the onset and progression of dementia. This is the aim of a series of randomised controlled studies (RCTs) that are currently ongoing (Mangialasche *et al.*, 2012; Paillard-Borg *et al.*, 2012; Vemuri and Mormino, 2013; Yaffe and Hoang, 2013).

On a prognostic perspective, LEF are investigated to identify individuals at increased risk of late-life cognitive impairment and dementia (Kivipelto *et al.*, 2013). To this end, a comprehensive identification of LEF, and the standardisation of quantification criteria are an important preliminary step.

A substantial number of studies related to LEF in dementia have been published, including review studies. However, the definition and quantification criteria of LEF vary largely across studies (Fratiglioni *et al.*, 2004). To the present date no studies have been published which focus on LEF categorisation and quantification.

5.4. AIM

This study aims to present a systematic review of modifiable LEF that have been associated with dementia in longitudinal and case-control studies, and to review their quantification criteria.

6. Materials

In this systematic review, articles published between 2003 and 2013, written in English, and listed in the public library PubMed, with the keywords ‘lifestyle’ and ‘dementia’ or ‘environmental factors’ and ‘dementia’ appearing in either the title or the abstract, were considered. Articles that were referenced in review papers matching the inclusion criteria were also considered.

Furthermore, articles published from population-based cohort studies such as the Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), the Framingham Heart Study (FHS), and the Rotterdam Study, with keyword ‘dementia’ in either the title or the abstract, were also reviewed.

7. Results

Longitudinal observational studies (N=28) included a total of 83,281 subjects (median: 1456, inter-quartile range: 1110-3137) with median follow-up of 9.5 years (inter-quartile range: 6-21 years). Case-control studies (N=11) included a total of 20,377 subjects (median: 410, inter-quartile range: 314-801), and randomized controlled trials (N=6, all ongoing) a total of 6910 subjects (median: 690, inter-quartile range: 160-1680), with median follow-up of 5 years (inter-quartile range: 1-5). Of the 45 studies, most were from centres within the EU (N=24), or the USA (N=13), others were from Australia (N=4), China (N=1), Japan (N=1), India (N=1), Turkey (N=1).

7.1. STATISTICAL ANALYSIS

In the reviewed studies, descriptive statistics were calculated using either parametric or non-parametric tests as deemed appropriate based on the relative frequency distributions of factors. Logarithmic variable transformation was performed in (de Bruijn *et al.*, 2013) in the presence of highly skewed distribution of physical activity data.

The proportion comparison of risk factors was done using the χ^2 test.

The strength of association between putative risk factors and dementia (dichotomous outcome) was expressed either in the form of odds ratios (OR), or hazard ratios (HR) or relative risk (RR), with the associated two-sided 95% confidence intervals (CI). Crude ORs were calculated from univariate frequency tables, whereas adjusted ORs were calculated from multiple logistic regression.

Hazard ratios (HR) were calculated from the Cox regression model for proportional hazards, using empirical thresholds to separate risk groups (high risk vs. low risk) and the follow-up time as underlying time scale.

Relative risks (RR) were calculated as the ratio of the probability of the event occurring (dementia) in an exposed group (e.g. heavy smokers) to the probability of the event occurring in the non-exposed group (e.g. non-smokers).

Putative predictors were included in multivariable regression models following a stepwise criterion with inclusion significance level of 0.05 (i.e. predictors with $p < 0.05$ were included in the model) and exclusion level of 0.1 (predictors with $p > 0.1$ were excluded).

For continuous outcomes such as cognitive performance scores, the association of baseline factors with the outcome was assessed by general linear models (GLMs) adjusted for confounders (such as age and sex).

7.2. LEF IN OBSERVATIONAL AND CASE-CONTROL STUDIES

In this section, LEF from longitudinal cohort studies and cross-sectional case-control studies are presented. In the reviewed studies, LEF information was obtained either by questionnaire or personal interview. In some studies, information on participants' socioeconomic status was complemented with information collected from the Public Register.

In the following paragraphs, LEF are grouped in seven macroscopic categories: 1) social engagement, 2) education and socioeconomic status, 3) physical and leisure activity, 4) dietary habits, alcohol, coffee and tea consumption, 5) smoking, 6) living arrangements and marital status, 7) environmental pollution.

For each category, individual factors from relevant studies are reported, together with relevant findings on the association of LEF with the risk of dementia and AD. Results from individual studies are summarised in Tables 1 – 3. At the end of this section, a comprehensive summary of LEF and quantification criteria is given in Table 4.

7.3. SOCIAL ENGAGEMENT

Social engagement is generally referred to those activities that involve social interaction of the subject with others, regardless of the level of cognitive engagement. Studies generally agreed that higher engagement in social activities may be a protective factor against dementia (Tables 1 – 3).

In (Lipnicki *et al.*, 2013) social activity was defined as the average number of current face-to-face contacts with friends or relatives per month; categorised as low if below an arbitrary fixed threshold of five.

Paillard-Borg and colleagues (Paillard-Borg *et al.*, 2012) introduced the concept of *social network*, which included living arrangements, parenthood, friendship, frequency and satisfaction with contact with children and friends. Church attendance was considered (Norton *et al.*, 2012), in addition to social interaction. A *latent class analysis* method was used to identify behavioural classes and their association with the risk of dementia in a cohort of generally healthy subjects without functional impairment at baseline. The method identified four distinct behavioural patterns, in which lifestyle – assessed through smoking, alcohol consumption, dietary habits, exercise, and social interaction – and religious status were coupled in various combinations. The class of subjects with an unhealthy diet, low levels of physical exercise, social engagement, and frequent church attendance (termed “unhealthy-religious”) was identified as the one with higher risk of developing dementia over a mean follow-up of 6.3 years.

In (Seidler *et al.*, 2003) factors defining a *psychosocial network* were grouped into two classes: social ties (marital status, number of people living in the same household, number of confidants, number of close relatives) and social activities (sports, cultural activities, club membership). The psychosocial network was assessed at three different stages (age 30, age 50, and 10 years before examination). The odds ratio of dementia for subjects who had either high psychosocial ties or engaged in high social activities (OR: 0.4; 95% CI: 0.2, 0.6) and for subjects who had both high psychosocial ties and engaged in high social activities (OR: 0.1; 95% CI: 0.04, 0.5) suggested a protective role of engagement.

7.4. EDUCATION AND SOCIOECONOMIC STATUS

Education level was one of the most extensively utilised LEF. With very few exceptions, higher education level was a protective factor against dementia (Tables 1 – 3).

Socioeconomic status was generally reported in terms of type of job (including manual vs. intellectual, responsibility role, social demand), income level, and early-life financial and social conditions.

Socioeconomic variables from the public records were collected in (Whalley *et al.*, 2013) about the occupation of the head of the household, the number of residents per room and record of parental death. The loss of either parent before age 11 was associated with higher risk of dementia later in life.

Indicators of early life socioeconomic level of the household were used by Wilson and colleagues (Wilson *et al.*, 2005). These included parental education, the county of birth and literacy rate (with data from the US Census). In Ngandu *et al.* 2007, income level and occupation were considered.

Andel and colleagues (Andel *et al.*, 2005) took into account job complexity with respect to data (*e.g.* synthesis, analysis, computation), people (*e.g.* supervise, instruct, persuade, serve) and things (*e.g.* manipulate, operate, handle). Complexity of working with people was associated with reduced risk of dementia (OR: 0.86; 95% CI: 0.76, 0.98) and AD alone (OR: 0.83; 95% CI: 0.70, 0.98).

In Smyth *et al.*, 2004, 122 AD cases and 235 control subjects were compared across four decades of life (20s, 30s, 40s, and 50s). Mental (physical) occupational demands were significantly lower (higher) for AD subjects with respect to the control.

7.5. PHYSICAL AND LEISURE ACTIVITY

The association of physical and leisure activities with dementia was reported in numerous studies. Results generally agreed that moderate physical and cognitively stimulating activities are associated with a reduced risk of dementia or delayed onset of the disease (Tables 1 – 3).

In a few studies (Kivipelto *et al.*, 2006; Larson *et al.*, 2006; Ngandu *et al.* 2007; Norton *et al.*, 2012) a dichotomic distinction between physically active and sedentary lifestyle was adopted, whereas others identified specific activities within this macroscopic category (Lipnicki *et al.*, 2013; Verghese *et al.*, 2003). Frequency of participation was generally recorded as daily, weekly, monthly, or annually

In Lipnicki *et al.*, 2013, physical activity was quantified as the sum of current participation across a set of listed activities including bicycling, yoga, and walking. An increased risk of incident mild cognitive impairment (MCI) or dementia was found in men performing increased level of physical activity. This result contrasts with nearly unanimous consensus by

other studies reviewed in this work, which suggest moderate physical activity as a protective factor against dementia. For example, in (Paillard-Borg *et al.*, 2012) age at onset of dementia was significantly older (mean 17 months) in subjects with the highest level of participation in physical and social activity compared to the inactive. In (Simons *et al.*, 2006), daily gardening predicted a 36% lower risk of dementia. Daily walking predicted a 38% lower risk in men, but there was no significant prediction in women.

However, recently de Bruijn *et al.*, 2013, examined the association between physical activity and risk of dementia by stratifying the follow-up observation time using a cut-off threshold of 4 years.

This association between physical activity and dementia was confined to the follow-up period of the first 4 years (HR: 0.82; 95% CI: 0.71, 0.95) and became inconsistent for the longer follow-up (HR: 1.04; 95% CI: 0.93, 1.16), suggesting either the presence of a reverse causality or a short term effect of late-life physical activity.

In Gelber *et al.*, 2012, physical activity was quantified by the number of hours spent daily in sedentary, mild, moderate, and heavy physical engagement. Subjects that were less physically active were found at higher risk of VaD but not AD.

In Karp *et al.*, 2006, a mental, social and physical component score was estimated for each activity reported by participants. Reduced relative risks of dementia were found in subjects with higher mental, physical and social score. The most beneficial effect was observed in subjects with high scores in all or in two of the components (RR of dementia = 0.53; 95% CI: 0.36 – 0.78), suggesting that a broad spectrum of activities may be more beneficial than engaging in a single type of activity.

In Crowe *et al.*, 2003, leisure activities practised regularly before the age of 40 were studied. These included reading, listening to the radio, watching television, social visits, cultural activities, hobbies, home and family, clubs and organisations, studies, gardening, and sports. Participation in a greater overall number of leisure activities was associated with lower risk of AD and dementia.

In Verghese *et al.*, 2003, both cognitive and physical activities included individually as well as socially engaging activities. A one-point increment in the cognitive-activity score was significantly associated with a reduced risk of dementia (HR: 0.93; 95% CI: 0.90, 0.97), whereas physical activity was not.

In Fritsch *et al.*, 2005, mental leisure activities involving “novelty seeking” were studied. Participants were asked to indicate how often (never, sometimes, often) they would participate in each of the activities of a predefined set (*e.g.* learn a new skill, pick up a new hobby, learn a new subject, tackle a challenging problem) from the age of 20 to the age of 60 (control group members) and from the age of 20 to 5 years prior to the time of onset of AD (cases). Greater participation in novelty-seeking activities was associated with reduced odds of AD (OR: 0.248; 97.5% CI: 0.139, 0.443).

In Tripathi *et al.*, 2012, participation in cognitively-stimulating activities (reading, solving puzzles) was protective against dementia (OR: 0.35; 95% CI: 0.17, 0.71).

7.6. DIETARY HABITS, ALCOHOL, COFFEE AND TEA CONSUMPTION

Dietary habits have been studied in relationship with vascular risk factors such as hypertension, diabetes and hyperlipidaemia, which are known risk factors for dementia. Protective factors such as antioxidants and polyunsaturated fatty acids have also been studied.

Devore and co-workers (Devore *et al.*, 2010) studied the association of dietary antioxidants with long-term risk of dementia. After adjusting for potential confounders, higher intake of vitamin E at baseline was associated with lower long-term risk of dementia (HR: 0.75; 95% CI: 0.59, 0.95). Conversely, dietary intake levels of vitamin C, β -carotene, and flavonoids were not associated with the risk of dementia.

In a previous study on the same population, Devore and colleagues (Devore *et al.*, 2009) found no association between the consumption of ω -3 polyunsaturated fatty acids and the risk of dementia.

In Norton *et al.*, 2012, a dichotomised classification ('high'/'low') of diet based on the median value of the Dietary Approaches to Stop Hypertension (DASH) ('high' = above median) and alcohol consumption (2 or more alcoholic beverages per week) was used; however this classification was not directly associated with the risk of dementia.

Lipnicki and colleagues (Lipnicki *et al.*, 2013) found no association between the frequency of alcohol consumption – quantified as 'at least monthly or less' or 'not at all' in the year preceding the interview – and the risk of either MCI or dementia.

Eskelinen and colleagues (Eskelinen *et al.*, 2009) found lower risk of later-life dementia and AD in coffee drinkers at mid-life compared with those consuming very limited quantities or not drinking coffee at all. The lowest risk was found in those who drank 3 – 5 cups per day. Tea drinking was not associated with either dementia or AD. These results conflict with those of Ritchie *et al.*, 2007, in which no relation was found between caffeine consumption and dementia risk over 4 years.

In Mehlig *et al.*, 2008, alcohol consumption was divided into 'never', 'past (not during last 10 years)', 'past (not during last year)', 'monthly', 'weekly', 'several times/week', 'daily'. Wine consumption was found to be protective for dementia (HR = 0.6; 95% CI = 0.4, 0.8). In contrast, consumption of spirits at baseline was associated with increased risk of dementia (HR = 1.5; 95% CI = 1.0, 2.2). This result is consistent with that of Simons *et al.*, 2006, in which alcohol intake predicted a 34% lower risk of dementia. Also Takahashi *et al.*, 2011, found current alcohol consumption associated with a decreased risk of VaD (OR: 0.48; 95% CI: 0.31, 0.74). A review study on the association between mild (not exceeding 2 wine glasses per day) and moderate (up to 4 wine glasses per day) alcohol consumption and risk of dementia by Letenneur (Letenneur, 2004) presented consistent results, supporting the hypothesis of a protective role of mild–moderate alcohol consumption on the risk of incident dementia and AD.

Laitinen and colleagues (Laitinen *et al.*, 2006) found that a moderate intake of unsaturated fats at mid-life was protective, whereas a moderate intake of saturated fats could increase the risk of dementia and AD, especially among APOE ϵ 4 carriers. In Yamada *et al.*, 2003, consumption frequency of fish, meat, tofu, and milk were categorised in 'less than twice a week', 'two to four times a week', or 'almost daily'. VaD prevalence increased significantly with age and lower milk intake. In Tripathi *et al.*, 2012, daily fruit consumption (OR: 0.28; 95% CI: 0.12, 0.65), salad (OR: 0.30; 95% CI: 0.14, 0.67), and refined vegetable oil consumption (OR: 0.22; 95% CI: 0.07, 0.66) were protective against dementia, whereas saturated fatty acids and pickles were risk factors.

7.7. SMOKING

Habitual smoking was generally included in the statistical analysis as categorical ('never', 'past', 'current') confounder. However, some studies also assessed smoking as a risk factor. In a large cohort study by Rusanen and co-workers (Rusanen *et al.*, 2012) on 21,123 participants with a mean follow-up of 23 years, subjects smoking more than 2 packets per day

in mid-life had a higher risk of dementia (HR: 2.14; 95% CI: 1.65, 2.78), AD (HR: 2.57; 95% CI: 1.63, 4.03), and VaD (HR: 2.72; 95% CI: 1.20, 6.18) compared to non-smokers. In a prospective study by Rusanen *et al.*, 2010, on 1,449 participants with a mean follow-up of 21 years, smoking in mid-life increased the odds ratio of dementia (OR: 4.93; 95% CI: 1.51, 16.11) and AD (OR: 6.56; 95% CI: 1.80, 23.94) only among APOE ϵ 4 carriers. The latter result contrasts with another population-based cohort study by Reitz *et al.*, 2007, in which smoke was a risk factor for dementia (HR: 1.47; 95% CI: 1.18, 1.86) and AD (HR: 1.56; 95% CI: 1.21, 2.02), only among APOE ϵ 4 non-carriers.

Moreover, Reitz *et al.*, 2007, found no association between current smoking and risk of VaD, or between past smoking and risk of AD, or VaD.

In Anstey *et al.*, 2007, the association of smoking with dementia was studied in a meta-analysis of 19 prospective studies including a total of 26,374 participants (mean age 74 years) who were followed up for 2 – 30 years to detect the onset of dementia. Current smokers at baseline had a higher risk of AD (RR: 1.79; 95% CI: 1.43, 2.23) and VaD (RR: 1.78; 95% CI: 1.28, 2.47) than those who had never smoked. Compared with former smokers, current smokers at baseline showed an increased risk of AD (RR: 1.70, 95% CI: 1.25, 2.31), but the groups were not different with respect to the risk of VaD.

7.8. LIVING ARRANGEMENTS AND MARITAL STATUS

Only a limited number of studies analysed the independent association of living arrangements and marital status with dementia, others included these factors such as being members of a social network. In Lipnicki *et al.*, 2013, marriage reduced the risk of incident mild cognitive impairment or dementia.

7.9. ENVIRONMENTAL POLLUTION

Very few of the reviewed studies considered environmental pollution. In a case-control study by Harmanci *et al.*, 2003, exposure to occupational low frequency (below 300 Hz) electromagnetic field was classified as high (average exposure greater than 10 mG or intermittent exposure greater than 100 mG, medium (average exposure of 2 – 10 mG or intermittent exposure greater than 10 mG), or low (any exposure below the medium level) according to the criteria defined in Sobel *et al.*, 1995.

Subjects with occupations which according to Sobel *et al.*, 1995, caused medium to high exposure to electromagnetic fields (seamstress, dressmaker, and tailor) were found to be at increased risk of AD (OR: 4.02; 95% CI: 1.02, 15.78) compared to those with other occupations. The use of electricity for residential heating was also associated with AD (OR: 2.77; 95% CI: 1.12, 6.85).

Evidence from epidemiological studies has also suggested that workers chronically exposed to lead may be at higher risk of dementia. However, large-sample longitudinal studies, following subjects up from their early life, are awaited to confirm this hypothesis (Landrigan *et al.*, 2005; Sofrizzi *et al.*, 2006).

7.10. CHOICE OF CONFOUNDERS

Studies varied largely in the choice of confounders used in the statistical analysis of protective/risk factors for dementia. Most studies adjusted their statistical models for age, gender and education (either intended as continuous variable (number of years of education) or categorical variable (level achieved)).

Some studies adjusted for the presence of APOE $\epsilon 4$ allele (Abbott *et al.*, 2004; de Bruijn *et al.*, 2013; Devore *et al.*, 2009; Devore *et al.*, 2010; Eskelinen *et al.*, 2009; Gelber *et al.*, 2012; Norton *et al.*, 2012; Shadlen *et al.*, 2006; Tripathi *et al.*, 2012; Whalley *et al.*, 2013). Relatively few studies adjusted for socioeconomic status (Gelber *et al.*, 2012; Ngandu *et al.*, 2007), vascular risk factors (de Bruijn *et al.*, 2013; Devore *et al.*, 2009; Eskelinen *et al.*, 2009; Gelber *et al.*, 2012; Laitinen *et al.*, 2006; Rusanen *et al.*, 2011; Shadlen *et al.*, 2006; Verghese *et al.*, 2003), baseline cognitive score (Ritchie *et al.*, 2007; Verghese *et al.*, 2003), alcohol consumption (Devore *et al.*, 2009; Devore *et al.*, 2010; Karp *et al.*, 2004; Rusanen *et al.*, 2011), smoking (Devore *et al.*, 2009; Devore *et al.*, 2010; Seidler *et al.*, 2004). Only one study adjusted for the education level of parents (Seidler *et al.*, 2004).

7.11. LEF IN RANDOMISED CONTROLLED TRIALS

Evidence from longitudinal cohort studies and cross-sectional case-control studies supports the association between higher engagement in mental activity in the early, middle and late life stages and a significant reduction in dementia incidence. A protective role against dementia syndromes of healthy diets has also been shown (Solfrizzi *et al.*, 2008).

However, the multifactorial nature of the mechanisms likely involved in the development and progression of dementia challenges both observational and cross-sectional studies. To this end, the importance of randomised controlled trials (RCTs) in identifying risk and protective factors has been highlighted in numerous studies (Mangialasche *et al.*, 2012; Nash 2007; Panza *et al.*, 2008; Polidori and Pientka, 2012; Solfrizzi *et al.*, 2008; Valenzuela and Sachdev, 2006).

At the time of writing, six RCTs designed to provide new insights into the prevention of dementia are ongoing (Table 5). In Europe, three multidomain RCTs are focusing on the management of vascular risk factors and vascular diseases by implementing nutritional, physical and cognitive training.

In Blumenthal *et al.*, 2013, the independent effects of diet (low-fat dairy products; fruits and vegetables; reduced fat and cholesterol) and aerobic exercise (walking, bicycling) are currently being studied in a sample of men and women aged 55 or over, with cardiovascular disease or its risk factors. In Cyarto *et al.*, 2012, a moderate home-based physical activity programme is being administered to a population of older adults with subjective memory complaints. As part of the protocol, participants undergo regular assessment of physical activity including cardiovascular endurance examination, based on a short walk test in which the distance walked and the heart rate are recorded. To objectively measure weekly physical activity, participants also undergo periodic seven-day continuous monitoring of gait by plantar sensors.

8. Discussion

8.1. LEF ASSOCIATION WITH DEMENTIA: INTERPRETATION OF FINDINGS

From this review a general consensus emerged on the protective role of higher levels of education and cognitively-stimulating activities, physical activity and healthy diet against dementia.

Although contradictory results have been reported, fairly robust evidence links mid-life hypertension to the development of dementia in later life (Bilbul and Schipper, 2011; Justin *et al.*, 2013). Several hypotheses have been formulated on the pathophysiological links between hypertension and dementia. Hypertension has been suggested as the cause of vascular alterations leading to lacunar and cortical infarcts (Bilbul and Schipper, 2011; Justin *et al.*,

2013), cerebrovascular disease, and the accumulation of β -amyloid mediated by cerebral hypoperfusion secondary to endothelial dysfunction (Noboru and Okamura, 2012).

An association of diabetes mellitus with dementia has also been hypothesised, mediated by cerebral microvessel dysfunction and oxidative stress (Justin *et al.*, 2013; Noboru and Okamura, 2012). Oxidative stress and inflammation are also caused by cigarette smoking (Yaffe and Hoang, 2013).

By mitigating the risk of vascular morbidities such as hypertension, diabetes, hypercholesterolaemia and obesity, leisure activities involving moderate physical activity may act as a protecting factor against dementia (Bilbul and Schipper, 2011; Yaffe and Hoang, 2013). On the other hand, cognitively-engaging activities, especially those developed from an early stage of life such as scholarly education, promote synaptogenesis in adult life, thereby increasing cognitive reserve (Fratiglioni and Wang, 2007; Liu *et al.*, 2012; Ngandu *et al.* 2007; Yaffe and Hoang, 2013) and resulting in a more limited amyloid burden in the brain (Landau *et al.* 2012).

Favourable socioeconomic factors, such as comfortable living since the earliest stages of life, more rewarding occupations and social recognition, could also play a neuroprotective role against cognitive decline (Smyth *et al.*, 2004; Wilson *et al.*, 2005).

8.2. VARIABILITY IN LEF INCLUSION AND QUANTIFICATION CRITERIA

The studies included in this systematic review varied largely in: *i*) the definition of LEF; *ii*) the quantification criteria; *iii*) the use of confounders in statistical analysis.

8.2.1. Definition of LEF

Differences were found in the conceptual definition of LEF, especially those related to the physical, leisure and social activities, socioeconomic status and living arrangements. As leisure activities may involve physical activity and/or social engagement, and/or cognitive engagement, different categorisations were adopted by different studies, either grouping or separating leisure, social, and cognitively-engaging activities. Similarly, socioeconomic factors were intended in some studies as referring to the individual only, whereas in others also the family, household and community were considered. Furthermore, living arrangements were in some cases intended as marital status; in others as number of household members (in a categorical sense: one or more than one individual).

However, direct comparison of the different approaches to determine the strongest predictive factors of dementia is hampered by the large difference either in the quantification of LEF (weighting criteria, discussed below) or in the choice of confounders.

8.2.2. Quantification criteria

The quantification criteria of individual factors varied in measuring the intensity or frequency of activity participation, or in the accuracy in tracking the subject's past history. In particular, early-life factors such as childhood hardship, poor living arrangements in early-life, parental death in early life, parental education were considered only in few studies.

As the role of LEF in determining the risk of dementia in late-life is likely to develop over the earlier life span (Cadar *et al.*, 2012; Fratiglioni and Wang, 2007), the accurate tracking of LEF in the subject's early life is a fundamental point, which could add substantial information to the analysis.

Furthermore, the reviewed studies generally differed in the way they calculated the score indices, which were used in the statistical analysis. This, in principle, introduces further between-study variability, by assigning different weights to the original LEFs.

8.2.3. Choice of confounders in statistical analysis

Most studies adjusted their statistical models for age, gender and education. However, very few adjusted for genetic factors (APOE ϵ 4 allele), baseline cognitive score (Mini-Mental State Examination (MMSE) score), vascular risk factors (obesity, diabetes, hypertension), depression, or physical function. Socioeconomic factors (income, occupation, parental education level), as well as subjective habits (smoking, alcohol consumption) were also rarely included. No single study included all the above confounders.

8.3. FUTURE PERSPECTIVE FOR OBJECTIVE QUANTIFICATION OF LEF

In the observational and case-control studies reviewed, LEF information was generally obtained by questionnaires or interview. Objective quantification of LEF was only found in one RCT (Cole *et al.*, 2009), in which the gait pattern of subjects was periodically monitored for seven continuous days by plantar sensors. Wearable sensors have also been successfully employed in gait analysis in Parkinson's disease (Hausdorff, 2005) and AD (Sheridan *et al.*, 2013), as well as in studies of sleep disorder associated with AD (Lim *et al.*, 2013).

Recent advances in technology have brought about the opportunity to record physiological signals (heart rate, body temperature, haemoglobin oxygen saturation); biomechanical signals (body posture and movement); and environmental signals (temperature, light, sound, pollutants) using lightweight non-obtrusive devices with long battery capacity. Often, multiple signals are acquired by a single device (sensor fusion).

Whilst these technologies are not viable for older or severely cognitively-impaired subjects, they could be considered for younger or middle-aged individuals.

Evidence from epidemiological studies has shown a stronger association of mid-life vascular risk factors with dementia than that measured at late life, which has led to the hypothesis that mid-life risk factors may be a better measure of later life risk of developing dementia (Tolppanen *et al.*, 2012; Qiu *et al.*, 2005). This perspective may offer a favourable condition for the exploitation of wearable technologies, resulting in more quantitative and objective measurements of LEF, as well as an increased amount of information, which could potentially contribute to the early detection of symptoms of cognitive decline.

Moreover, in the rapidly evolving world of technologies, strenuous and continuous effort is devoted to improve *wearability* of sensors and recording capacity (Bassett, 2012; Chan *et al.*, 2012; Patel *et al.*, 2012). This will likely increase the potential of ambulatory monitoring for the older and cognitively more impaired population.

8.4. STUDY LIMITATIONS

This systematic review focused on LEF in dementia studies. Numerous studies have been published on cognitive decline preceding dementia, and in particular on mild cognitive impairment (MCI), which have also addressed the role of LEF. However, whilst individuals with MCI are at increased risk of progression to dementia, not all eventually will. Due to space limitations, in this systematic review, these studies were not included.

9. CONCLUSIONS

In this systematic review, general consensus emerged on the protective role of higher level of education and cognitively-stimulating activities (promoting cognitive reserve and limiting amyloid burden), physical activity and healthy diet (reducing vascular risk factors) against dementia, whereas the association of dementia with other factors such as smoking and alcohol consumption was controversial.

Studies varied largely in the definition of LEF, in their quantification criteria, and in the choice of confounders in the statistical analysis.

Substantial variability was observed in the definition of socioeconomic variables, as well as in the measurement of frequency and intensity of physical, social and cognitively stimulating activities. Substantial limitations were observed in tracking the subject's past history of participation in the above activities.

Standardisation of LEF-reporting questionnaires is needed to allow direct comparison of results from different studies. Objective measurement techniques based on ambulatory monitoring are emerging, and may represent a substantial step forward both in the standardisation of LEF quantification and in the amount of information which could contribute to a better understanding of the underlying causes and mechanisms implicated in the onset and progression of dementia.

10. TABLES

Table 1. LEF in dementia: summary of longitudinal cohort studies. (Articles published in 2008-2013)

Study: 1 st Author (Year)	Study Site	Study Name	N	Age/ Follow-up [y] (*)	Lifestyle and environmental factors
de Bruijn (2013)	Netherlands	Rotterdam Study	4406	61-97/14	PF: Physical activity (only first 4 y follow-up)
Lipnicki (2013)	Australia	Sydney Memory and Ageing Study	889	70-90/2	PF: marriage; PF: more education(years)
Whalley (2013)	UK	N/R	281	78/10	RF: death of parent before age 11; NA: occupation of head of household, NA: No. residents/room
Gelber (2012)	USA	Honolulu-Asia Aging Study	3468	52/25	RF: lack of physical activity, smoking at midlife
Norton (2012)	USA	Cache County study	2491	73/6	PF: physical exercise, housework, gardening; PF: above Median DASH; NA: attending church
Paillard-Borg (2012)	Sweden	Kungsholmen Project	1375	75-95/9	PF: more leisure activity; PF: more active
Rusanen (2011)	Finland	N/R	21123	50-60/23	RF: heavy smoking (>2 packs/day)
Devore (2010)	Netherlands	Rotterdam Study	5395	55+/9	PF: vitamin E
Rusanen (2010)	Finland	Cardiovascular Risk Factors, Aging and Dementia Study	1449	65-79/21	RF: smoking (only for apolipoprotein ε4 carriers)
Devore (2009)	Netherlands	Rotterdam Study	5395	55+/9	NA: omega-3 polyunsaturated fatty acids
Eskelinen (2009)	Finland	Cardiovascular Risk Factors, Aging and Dementia Study	1409	39-64/21	PF: coffee consumption; NA: tea consumption
Mehlig (2008)	Sweden	Prospective Population Study of Women	1462	38-60/34	NA: alcohol consumption

(*) some studies reported average follow-up, others reported a fixed value, others reported the maximum.

DASH: Dietary Approaches to Stop Hypertension; NA: no association with dementia reported; PF: protective factor for AD or other dementia; RF: risk factor for AD or other dementia. Unless otherwise specified PF and RF refer to all-cause dementia; N/R: not reported.

Table 2. LEF in dementia: summary of longitudinal cohort studies. (Articles published in 2003-2007)

Study: 1 st Author (Year)	Study Site	Study Name	N Age/ Follow-up [y] ^(*)	Lifestyle and environmental factors
Ngandu (2007)	Finland	Cardiovascular Risk Factors, Aging and Dementia Study	1449 39-64/21	RF: education (<5 vs. 6-8 y); RF: job with higher physical demand
Reitz (2007)	Netherlands	Rotterdam Study	6868 55+/7	RF: current smoking at baseline (only APOE ε4 non-carriers)
Ritchie (2007)	France	Three City Study	7017 65+/3	RF: caffeine consumption rate
Karp (2006)	Sweden	N/R	1203 75+/6	PF: higher physical / mental activity score
Kivipelto (2006)	Finland	Cardiovascular Risk Factors, Aging and Dementia Study	1409 39-64/20	PF: physical activity (>2 times/week); RF: education (< 10 y);
Laitinen (2006)	Finland	Cardiovascular Risk Factors, Aging and Dementia Study	1449 39-64/21	RF: saturated fats; PF: polyunsaturated fats;
Larson (2006)	USA	Adult Changes in Thought study	1740 65+/6	PF: physical exercise (>3 times/week)
Shadlen (2006)	USA	Cardiovascular Health Study	2786 65+/6	RF: education (<11 y)
Simons (2006)	Australia	Dubbo Study	2805 60+/16	PF: daily walking, daily gardening
Ravaglia (2005)	Italy	Conselice Study of Brain Aging	1016 65+/4	RF: education (<4 y)
Wilson (2005)	USA	Religious Orders Study	859 75/10	NA: household; NA: community socioeconomic level
Abbott (2004)	USA	Honolulu-Asia Aging Study	2257 71-93/8	PF: walk (>0.25 miles/day)
Karp (2004)	Sweden	Kungsholmen Project	931 75+/3	RF: education (<8 y)
Crowe (2003)	Sweden	N/R	107 75+/20	PF: more leisure activity
Verghese (2003)	USA	Bronx Aging Study	469 75+/5	PF: reading, play music; PF: board games, dance
Yamada (2003)	Japan	Adult Health Study	1773 33+/30	PF: milk intake

^(*) some studies reported average follow-up, others reported a fixed value, others reported the maximum.

NA: no association with dementia reported; PF: protective factor for AD or other dementia; RF: risk factor for AD or other dementia. Unless otherwise specified PF and RF refer to all-cause dementia; N/R: not reported.

Table 3. LEF in dementia: summary of case-control studies.

Study: 1 st (Year)	Author	Study Site	Study Name	N Age	Lifestyle and environmental factors
Tripathi (2012)		India	N/R	300 66	RF: lack of physical activity; RF: lack of socialisation; RF: low education, RF: rural living; RF: saturated fatty acids, PF: polyunsaturated fats, fruits
Takahashi (2011)		USA	N/R	410 82	PF(for VaD): current alcohol consumption
Gatz (2006)		USA	HARMONY Study	14165 65+	RF: education(<8 y)
Andel (2005)		USA	HARMONY Study	778 59+	PF: complex work with people
Fritsch (2005)		USA	N/R	809 68+	PF: novelty-seeking leisure
Lam (2005)		China	N/R	154 75	RF: poor education
Tognoni (2005)		Italy	N/R	2366 65+	RF: low education (years), NA: alcohol consumption, smoking
Seidler (2004)		Germany	N/R	360 65+	PF: high challenge/control work/high social demand work
Smyth (2004)		USA	N/R	357 60+	RF: low mental and high physical demanding job
Harmanci (2003)		Turkey	N/R	254 70+	PF: university/college degree; RF: exposure to electromagnetic field at work
Seidler (2003)		Germany	N/R	424 65+	PF: psychosocial network

NA: no association with dementia reported; NR: not reported; PF: protective factor for AD or other dementia; RF: risk factor for AD or other dementia; N/R: not reported.

Table 4. Summary of modifiable LEF and quantification criteria in dementia studies

Factor	Category	Description	Quantification	Protective / Risk Factor
Lifestyle	Cognitive engagement (leisure)	Reading, writing, playing games (computer, cards, puzzles), volunteer work	Frequency of participation, past history	PF
	Social engagement	Visit relatives/friends, travel, club/association membership, cultural activities	Frequency of participation, no. social ties	PF
	Education	Level (primary, secondary, vocational, high school, university, college)	No. years (or categorical: above/below threshold)	PF (higher level)
	Occupation	job type (office, managerial, business, manual labour), self-satisfaction, complexity (data/things/people)	Categorical	PF (manager/business/control/co-ordination)
	Socioeconomic status	Demographic information (Public Register), social and financial status	(middle, older life) income, parental education, parental death at young age	PF (higher level)
	Physical activity	Aerobic exercise (walking, cycling, house-keeping)	Duration/frequency, past history	PF
		Anaerobic exercise (strength and resistance training)	Duration/frequency, past history	PF
		Housekeeping, gardening		PF
	Diet	Vitamins B, C, D, E	Quantity	PF
		Polyunsaturated omega-3 fatty acids	Quantity	PF
		Serum cholesterol	Quantity	RF (high level)
		Alcohol consumption	Categorical (past, present), quantity/frequency	Controversial
		Smoking	Categorical (past, present), quantity/frequency	Most agree is RF
	Habits	Alcohol consumption	Categorical (past, present), quantity/frequency	Most agree moderate quantity is PF
		Drinking coffee	Categorical (past, present), quantity/frequency	Controversial
		Drinking tea	Categorical (past, present), quantity/frequency	NA
	Marital status		Categorical (married/ single/ widowed/divorced)	RF (single/living alone)
	Living arrangement	No. people in household, type of house (size, facilities)	Categorical (house type), quantitative (household size)	RF (crowded house at early-life)
Environmental	Pollution	Electromagnetic exposure at work, electrical heating at home	Categorical (above, below threshold)	RF
	Location		Categorical (urban / rural)	RF (rural) ^(*)

^(*) only one study

NA: no association with dementia reported; PF: protective factor; RF: risk factor

Table 5. Modifiable LEF in dementia: summary of (ongoing) randomized controlled trials.

First (Year)	Author	Study Name	Study Site(s)	No. Participants (Age)	Objectives	Intervention Duration (post-treatment follow-up)
Anstey (2013)		Body Brain Life (BBL)	Australia	180 (50–60)	To assess efficacy of online intervention to reduce the risk of AD in middle-aged adults at risk. (Subjects were dementia-free at the time of participation).	12 weeks (6 months)
Kivipelto (2013)		Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)	Finland	1200 (60–77)	To investigate the extent to which a multi-domain intervention can prevent/delay cognitive impairment in elderly at increased risk of cognitive decline	2 years (5 years)
Cyarto (2012)		Australian Imaging Biomarkers and Lifestyle Flagship Study of Aging (AIBL)	Australia	156 (>= 60)	To determine whether a 24-month physical activity program can delay the progression of white matter changes on magnetic resonance imaging	2 years (not reported)
Blumenthal (2013)		ENLIGHTEN	USA	160 (>= 55)	To examine the independent effects of exercise and diet on neurocognitive function among individuals at risk for dementia	6 months (1 year)
Richard (2009)		The Prevention of Dementia by Intensive Vascular Care (PreDIVA)	Netherlands	3534 (70–80)	To assess whether nurse-led intensive vascular care in primary care decreases the incidence of dementia and reduces disability	6 years (6 years)
Gillette-Guyonnet (2009)		The Multidomain Alzheimer Preventive Trial (MAPT)	France	1680 (>= 70)	To evaluate the efficacy of a multi-domain intervention (nutritional, physical, and cognitive training) and omega 3 treatment in the prevention of cognitive decline in frail elderly persons aged 70 years or over	3 years (5 years)

AD: Alzheimer's disease

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