

Dementia and Cognitive Impairment

Burden of Disease and Risk Factors

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Dementia is the most common form of neurodegenerative condition and is increasingly frequent as world population ages. It is a leading cause of death and is responsible for considerable morbidity, expressed in the high levels of functional dependence and institutionalization. From a resource management and prevention point of view, it becomes crucial to better characterize the epidemiology of this entity, namely its geographic distribution, its risk factors and impact at a population level. The fact that there are at present no disease-modifying treatments justifies an investment in the identification of modifiable risk factors that may be contemplated in prevention strategies. Recent epidemiological studies increasingly recognize an association between vascular risk factors and cognitive deterioration.

Key-words: dementia; epidemiology; risk factors; burden of illness.

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INTRODUCTION

Dementia should be interpreted as a manifestation of a neurodegenerative process rather than a nosological entity itself. Clinical diagnostic criteria depend largely on non-specific signs and symptoms of cognitive dysfunction and a definite diagnosis usually requires a neuropathological evaluation, and several types of dementia have been defined according to neuropathological features. The available epidemiological studies rely mainly on clinical criteria for diagnosis due to practical reasons, and therefore the potential for misclassification should be taken in account when interpreting the results (1-3). Despite these considerations, dementia is by far the most common neurodegenerative disease and constitutes a burdensome condition, especially at older ages (4). There is a trend for an increase in the overall burden of disease associated with dementia in the next few decades, which is largely determined by the social and demographic changes contributing to population ageing, especially in developing countries undergoing “epidemiological transition” (5, 6). An effort should be made to characterize the epidemiology of dementia and its subtypes worldwide, as this allows the setting up of organized social interventions. Notwithstanding the multidisciplinary commitment and the investment made in research, there are no disease modifying treatments for dementia approved up to date (4), highlighting the importance of defining earlier clinical stages of dementia, identifying modifiable risk factors and implementing preventive strategies.

BURDEN OF DISEASE ASSOCIATED WITH DEMENTIA AND MILD COGNITIVE IMPAIRMENT

Dementia is an increasingly frequent condition, associated with high morbidity and mortality.

Several multicentric studies have been conducted to estimate frequency measures in different regions of the globe, despite the use of distinct methodological approaches. Diagnostic criteria discrepancies between studies are among the most relevant differences to account for when comparing the results.

The EURODEM – Prevalence Research Group study estimated the frequency of dementia subtypes in Europe, using studies conducted in the 1990s in Finland, Denmark, Sweden, the Netherlands, United Kingdom, Italy, Spain and France. Dementia was diagnosed based on DSM-III-R, but the criteria to define Alzheimer's disease (AD) and Vascular Dementia (VaD) varied across centers. The age-standardized prevalences in individuals 65 years and older were 6.4% for dementia (all types), 4.4% for AD and 1.6% for VaD (7). The prevalence of dementia increased continuously with age, reaching 28.5% for individuals aged 90 years and older, with AD being the main contributor to the steep increase observed (7), showing that population ageing will contribute to an increasing burden of AD and presumably other dementia forms (8). The prevalence of dementia was higher in women than in men and this difference was particularly relevant in the older subjects (80-84 years: 11% in men vs 12.6% in women; 85-90 years: 12.8% in men vs 20.2% in women) (7).

The same collaborative study of population-based cohorts estimated age-specific incidence rates. The incidence of dementia increased with age up to 85 years, after which rates increased only in women and reached a plateau in men (9).

Regarding subtypes of dementia, the incidence of AD was higher than the observed for VaD, regardless of age, despite the large heterogeneity in the diagnostic criteria used across study centers (9).

A Delphi consensus study aimed to derive a quantitative estimate of prevalence of dementia around the world, through qualitative assessment of the best available evidence (5). This study was published in 2005 and prevalence was estimated for all regions in the world, for 5-year age groups from 60 to 84 years and for those aged 85 years and older (5). Studies of good methodological quality were frequent in North America, Europe, Japan

and Australia while evidence from well-planned representative epidemiological investigations were scarce in South America, Africa and some regions of Asia. Table 1 illustrates the distribution of prevalence according to 14 World Health Organization (WHO) regions. The number of people estimated to have dementia in 2001 was 24.3 million, worldwide (5).

Region-specific estimates for the incidence of dementia in individuals aged 60 years and over was also obtained through the Delphi consensus study, ranging from 10.5/1000 person-years for North America and 8.8/1000 person-years for Western Europe, to 4.3/1000 person-years for India and South Asia and 3.5/1000 person-years for Africa.

According to these estimates, the number of individuals diagnosed with dementia will double every 20 years, reaching 81.1 million by 2040; by this time, 71% of the

Table 1 - World Health Organization (WHO) mean estimates for prevalence of dementia, according to world region and age-group (5).

WHO region	Prevalence of dementia (%)					
	60-64 yrs	65-69 yrs	70-74 yrs	75-80 yrs	80-84 yrs	≥ 85 yrs
EURO A	0.9	1.5	3.6	6.0	12.2	24.8
EURO B	0.9	1.3	3.2	5.8	12.2	24.7
EURO C	0.9	1.3	3.2	5.8	11.8	24.5
AMRO A	0.8	1.7	3.3	6.5	12.8	30.1
AMRO B	0.8	1.7	3.4	7.6	14.8	33.2
AMRO D	0.7	1.5	2.8	6.2	11.1	28.1
EMRO B	0.9	1.8	3.5	6.6	13.9	23.5
EMRO D	1.2	1.9	3.9	6.6	13.9	23.5
WPRO A	0.6	1.4	2.6	4.7	10.4	22.1
WPRO B	0.6	1.8	3.7	7.0	14.4	26.2
SEARO B	1.0	1.7	3.4	5.7	10.8	17.6
SEARO D	0.4	0.9	1.8	3.7	7.2	14.4
AFRO D	0.3	0.6	1.3	2.3	4.3	9.7
AFRO E	0.5	1.0	1.9	3.8	7.0	14.9

EURO - Europe; AMRO - The Americas; EMRO - North Africa and the Middle East; WPRO - Western Pacific; SEARO - South Asia; AFRO - Africa; A-E: Patterns of child and adult mortality (from lowest, A, to highest, E).

estimated cases will occur in the developing world (6). The WHO projections suggest that by 2025 about three-quarters of the estimated 1.2 billion people aged 60 years and older will live in developing countries (6), reflecting demographic and epidemiological transitions promoting population ageing. At present, countries in Latin America such as Venezuela and Argentina already bear an important burden of over 5% prevalence of dementia. This contrasts with the lowest estimates for sub-Saharan Africa and India (6), although shorter survival after dementia in these countries, lack of awareness and social support systems as well as inadequate diagnostic assessment, may have led to an underestimation of the frequency of dementia in these settings (6).

Dementia is characterized by major cognitive and functional impairment and is a chronic and progressive disorder, leading to high levels of dependence in the advanced stages of the disease. The age-standardized Disability-Adjusted Life Years (DALYs) for AD and other dementias in 2004 was 260/100,000 in the United States of America, 259/100,000 in the UK, 269/100,000 in Australia and 247/100,000 in Japan (10). These estimates were strikingly lower in most African and South American countries; for example 135/100,000 in Angola, 120/100,000 in Mozambique, 184/100,000 in Colombia or 187/100,000 in Mexico. According to the WHO baseline scenario projections for 2030, Alzheimer's disease and other dementias will become the third leading cause of DALYs in high-income countries (8).

Although dementia is a leading cause of death, it is often underrecognized as a terminal illness (11). The European collaborative study of dementia evaluated the prognosis of this condition, assessing the time to institutionalization and the mortality (12). Jagger et al (12) described that prevalent cases had over twice the risk of death compared to noncases in four years, despite the imprecision of the estimates [Relative Risk (RR): 2.38; 95% confidence interval (95%CI), 0.18-32.45] and the use of a sample with a mixture of cases having been diagnosed close to the baseline evaluation or longer ago. Subjects with dementia were also more likely to reside in institutional care at baseline than controls, independently of age and gender (12). Mitchell et al (11) described a mortality of 54.8% over an 18-month period in a group of nursing home residents with advanced dementia; in addition, 40.7% of patients underwent at least one burdensome intervention (hospitalization, emergency room visit, parenteral therapy or tube feeding) in the last three months of life, illustrating the morbidity associated to this degenerative condition.

The social and economical repercussions of the above mentioned trends and projections are thus immense and constitute an alert for the need to stimulate organized social interventions whilst, at the same time, investing in research focusing on prevention strategies and disease-modifying treatments may contribute to reduce the morbidity and mortality burden.

Evidence on the epidemiology of mild cognitive impairment (MCI) is beginning to emerge, but there is a considerable heterogeneity in the frequency estimates presented in the literature, also reflecting the lack of operational diagnostic criteria.

Incidence estimates are scarce; the most robust were obtained in a three-year follow up of a Finnish population aged 60-76 years at baseline, which yielded an incidence rate of 25.9/1,000 person-years (13). Prevalence estimates in studies that include currently accepted MCI criteria range from 12% to 18%, among non-demented individuals aged 65 years and over (14-16).

Regarding the four MCI clinical subtypes, Busse et al (17) describe a higher prevalence of single domain MCI in comparison with multiple domain MCI (11.6% vs 7.6%) and the nonamnestic MCI type was as frequent as amnestic MCI (9.2% vs 10.0%), when applying the original criteria (using a cutoff of 1.0 standard deviation from the neuropsychological tests scores). In another population-based study, Lopez et al (15) reported a similar overall MCI prevalence (19%), but inverse findings regarding MCI subtype frequencies, with multiple domain MCI being more prevalent than single domain MCI (16% vs 6%). This may be partly due to differences in the neuropsychological instruments used and cognitive domains assessed, choice of different cutoffs in neuropsychological instruments and socio-cultural characteristics of the subjects evaluated, as acknowledged by Petersen et al (18).

BURDEN OF DISEASE ASSOCIATED WITH DEMENTIA AND COGNITIVE IMPAIRMENT IN PORTUGAL

In addition to population ageing (19), Portugal presents a high prevalence of illiteracy and low formal education levels (19), which are well established risk factors for dementia (20). The prevalence of this condition is therefore expected to be high in this setting, although epidemiological data on dementia are scarce.

In 1994, Garcia et al (21) estimated the number of individuals with dementia in Portugal, according to the EURODEM and the 1991 Censos data. The total number of subjects estimated to have dementia was 92,470, corresponding to a prevalence of 1.7%, and approximately half of these patients (n=48,706) would have AD under the study assumptions (21).

In 2003, Nunes et al (22) conducted a population-based longitudinal study in rural and urban northern Portuguese populations, aged 55-79 years, aiming to estimate the frequency measures and patterns of cognitive impairment with dementia and no dementia (CIND). The global prevalence of dementia at baseline was 2.7% (CI95%: 1.9-3.8%), with a rural/urban prevalence rate of 2.1 (22). The overall incidence of dementia, defined according to the DSM-IV criteria, was 6.8/1,000 person-years (23). This was higher in the rural area of Arouca (9.1/1,000 person-years) than in the urban setting of São João da Madeira (3.9/1,000 person-years) (23).

After excluding individuals who tested positive for

dementia according to the Mini Mental State Examination (MMSE) or Blessed Dementia Scale score, cutoff points for CIND were set at one standard deviation below the mean of the MMSE, according to educational level. CIND was further defined in the presence of various categories of impairment identified either on clinical examination or neuropsychological testing (22). The overall prevalence of CIND was 12.3% (95%CI: 10.4-14.4%), higher in the rural population when compared to the urban: 16.8% (95%CI: 14.3-19.8%) versus 12.0% (95%CI: 9.3-15.4%) (22).

Concerning the relative weight of dementia subtypes in Portugal, these authors reported a similar prevalence of both AD and VaD in the Northern region, highlighting the fact that the latter may be more prevalent in our country than in the rest of Europe (22). The high impact of cardiovascular risk factors and cerebrovascular disease in the country may partially explain these results.

The World Health Organization reported an age-standardized Disability-Adjusted Life Years (DALYs) of 254/100.000 for Portugal, concerning the year 2004. This estimate is comparable to those for the United Kingdom and the United States of America in the same year (10), showing that dementia is a major public health issue also in Portugal.

RISK FACTORS FOR MCI AND DEMENTIA

MCI and progression to dementia

Few studies addressed the determinants of MCI. Tervo et al (13) identified older age, low educational level, Apolipoprotein (APOE) ϵ 4 allele carrier state and treated hypertension as the most prominent variables associated with a higher risk of MCI (13). In the longitudinal Cardiovascular Health Study Cognition Study low educational level, cortical atrophy, magnetic resonance imaging-identified infarcts and depression were found to be the main risk factors for MCI. In the Portuguese survey by Nunes et al (22), the highest prevalence of CIND was observed in rural elderly individuals. Cumulative vascular risk factors accounted for 31.4% of the CIND cases, followed by depression (18.4%) and cerebrovascular disease (14.2%) (22).

There has been intense research and debate regarding the progression of MCI to AD, although no consensus exists as to whether the former should be viewed as an entity with multiple etiological explanations or only a marker for identification of patients with prodromal AD. Overall, the conversion rate from MCI to dementia in clinical samples is reported to range between 10% and 20%, regardless of age, considering follow-up periods of one to three years (24). Different subtypes of MCI may be associated with the development of specific forms of dementia; amnesic subtypes of MCI were shown to be associated with a higher risk of AD (4); in the study by Busse et al (17), progression to non-AD dementia was more frequent in non-amnesic MCI and for all other types of MCI the most common form of dementia diagnosed at follow-up was AD. A correct characterization of the cognitive domains

affected may therefore help to determine outcome, and in fact deficits in verbal memory and psychomotor speed/executive function abilities were shown to strongly predict conversion to AD in a prospective study conducted by Tabert et al (25) in an MCI group of individuals.

Predictors of progression to AD in individuals with MCI have been identified: APOE ϵ 4 allele carrier state (26) and reduced hippocampal volumes derived from magnetic resonance images (27) are the two main risk factor identified.

Cerebral spinal fluid markers, Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) patterns of metabolism and molecular imaging techniques are among other variables currently being assessed in what is considered to be an expanding field of research (28, 29).

Dementia

Family history is a major non-modifiable risk factor for AD, reflecting the contribution of genetic determinants. In the rare familial forms of AD with onset before the age of 60, point mutations in the amyloid precursor protein (APP, chromosome 21), the presenilin 1 (PS1, chromosome 14) and the presenilin 2 (PS2, chromosome 1) genes cause autosomal dominant transmission of the disease. In non-familial AD, which constitutes the vast majority of cases, the major genetic risk factor identified are related with the APOE ϵ 4 gene polymorphism (30).

Aging and female gender are two additional well-established non-modifiable risk factors for AD (4, 31), independently from education (31). This gender difference was initially suggested to be associated with postmenopausal estrogen deficiency, but the large prospective Women's Health Initiative Memory Study (WHIMS) confirmed that hormone replacement therapy (HRT) provided no benefit for global cognition among women aged 65 years or older (32); in fact, women assigned to HRT had a slightly but significantly lower average cognitive function compared with those assigned to placebo (33).

Current therapies for AD are mainly symptomatic, focusing on treating cognitive or behavioral symptoms and disease-modifying treatments are the main target of molecular research, especially focused on amyloid deposition (34), hyperphosphorylated tau protein (35) and oxidative stress (36). In parallel, epidemiological research has tried to identify modifiable risk factors for the development of dementia, since there are at present no approved disease-modifying treatments and primary prevention could play a crucial role in controlling the outburst of dementia. Education level was the first modifiable exposure shown to be inversely associated with the risk of dementia (4). Lifestyles and habits have also received considerable attention, and, among these, some of the traditional determinants of cardiovascular disease have been described as important risk factors for dementia and AD, in addition to VaD. Timing of exposure is an extremely important aspect to consider, especially because neurodegenerative conditions are chronic and progressive, with pathological changes developing over years before

Table 2 - Cohort studies assessing the relation between midlife exposure to vascular risk factors and the risk of dementia.

Vascular risk factor	1 st author Year Country	Type of study Sample characteristics	Outcome(s)	Results *	Control of confounding
	Whitmer (38) 2005 USA	Retrospective cohort Members of the Kaiser Permanent Medical Care Program of Northern California Baseline population: 8845 Mean age at baseline: 41 years Follow-up (mean): 34 years	Dementia (ICD-9)	Hypertension vs no hypertension: HR=1.24 (1.22-1.66)	Age at start of case ascertainment, race, education, sex
	Kivipelto (39) 2005 Finland	Prospective cohort Participants from the CAIDE study Baseline population: 1985 Follow-up (mean): 21 years Completeness of follow-up: 73%	Dementia (DSM-IV) and Alzheimer's disease (NINCDS-ADRA)	SBP ^a >140 vs <140 mmHg: OR=1.97 (1.03-3.77)	BMI, total cholesterol level, age, sex, education, follow-up time
	Launer (37) 2000 USA	Prospective cohort Participants from the Honolulu Heart Program (Japanese-American men) Baseline population: 3703 Follow-up (mean): 20 years	Alzheimer's disease and vascular dementia (DSM-III)	DBP ^b 90-94 vs 80-89 mmHg: OR=3.8 (1.6-8.7) DBP ^b ≥95 vs 80-89 mmHg: OR=4.3 (1.7-10.8) SBP ^a ≥160 vs 110-139 mmHg: OR=4.8 (2.0-11.0)	Age, education, apolipoprotein epsilon allele, smoking, alcohol intake
Hypertension	Kilander(40) 1998 Sweden	Prospective cohort Men residing in Uppsala (born in 1920-1924) Baseline population: 999 Follow-up (mean): 20 years	MMSE and Trail-Making Test scores	DBP ^b (mmHg), Cognitive Score, Mean (SD): ≤ 70, + 0.17 (0.71) 75-80, ± 0.00 (0.82) 85-90, + 0.04 (0.7) 95-100, ± 0.00 (0.89) ≥ 105, - 0.33 (0.82)	Age, educational and occupational levels
	Kivipelto (39) 2005 Finland	Prospective cohort Participants from the CAIDE study Baseline population: 1985 Follow-up (mean): 21 years Completeness of follow-up: 73%	Dementia (DSM-IV) and Alzheimer's disease (NINCDS-ADRA)	Total cholesterol >251 vs <251 mg/dl: OR=2.09 (1.16-3.77)	SBP, BMI, age, sex, education, follow-up time
	Whitmer (38) 2005 USA	Retrospective cohort Members of the Kaiser Permanent Medical Care Program of Northern California Baseline population: 8845 Mean age at baseline: 41 years Follow-up (mean): 34 years	Dementia (ICD-9)	Total cholesterol ≥240 vs <240 mg/dl: HR=1.42 (1.22-1.66)	Age at start of case ascertainment, race, education, sex
Cholesterol	Schnaider Beerli (41) 2004 Israel	Prospective cohort Members of the Israeli Ischemic Heart Disease project (men) Mean age at baseline: 47 years Follow-up (mean): 35 years Completeness of follow-up: 72.6%	Dementia (DSM-IV)	Diabetes vs no diabetes: OR=2.83 (1.40-5.71)	Age, area of birth, socioeconomic status, mean cholesterol, mean HDL cholesterol, mean DBP and SBP, BMI, smoking

CAIDE – Cardiovascular Risk Factors, Aging and Dementia; ICD – International Classification of Diseases; DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-III – Diagnostic and Statistical Manual of Mental Disorders, Third Edition; NINCDS-ADRA – National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; DBP – diastolic blood pressure; SBP – systolic blood pressure; BMI – body mass index; MMSE – Mini Mental State Examination; OR – odds ratio; HR – hazard ratio; * results are presented as OR or HR (95% confidence interval); † p<0.05.

Table 2 (cont.) - Cohort studies assessing the relation between midlife exposure to vascular risk factors and the risk of dementia.

Vascular risk factor	1 st author Year Country	Type of study Sample characteristics	Outcome(s)	Results *	Control of confounding
BMI	Kivipelto (39) 2005 Finland	Prospective cohort Participants from the CAIDE study Baseline population: 1985 Follow-up (mean): 21 years Completeness of follow-up: 73%	Dementia (DSM-IV) and Alzheimer's disease (NINCDS- ADDA)	BMI>30 vs <30 kg/m ² : OR=2.09 (1.16-3.77)	SBP, total cholesterol level, age, sex, education, follow-up time
	Whitmer (38) 2005 USA	Retrospective cohort Members of the Kaiser Permanente Medical Care Program of Northern California Baseline population: 8845 Mean age at baseline: 41 years Follow-up (mean): 34 years	Dementia (ICD-9)	Diabetes vs no diabetes: HR=1.46 (1.19-1.79)	Age at start of case ascertainment, race, education, sex
Diabetes	Schnaider Beeri (41) 2004 Israel	Prospective cohort Members of the Israeli Ischemic Heart Disease project (men) Mean age at baseline: 47 years Follow-up (mean): 35 years Completeness of follow-up: 72.6%	Dementia (DSM-IV)	Diabetes vs no diabetes: OR=2.83 (1.40-5.71)	Age, area of birth, socioeconomic status, mean cholesterol, mean HDL cholesterol, mean DBP and SBP, BMI, smoking

CAIDE - Cardiovascular Risk Factors, Aging and Dementia; ICD - International Classification of Diseases; DSM-IV - Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-III - Diagnostic and Statistical Manual of Mental Disorders, Third Edition; NINCDS-ADDA - National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; DBP - diastolic blood pressure; SBP - systolic blood pressure; BMI - body mass index; MMSE - Mini Mental State Examination; OR - odds ratio; HR - hazard ratio; *results are presented as OR or HR (95% confidence interval).

symptoms and deficits are experienced; the same generally happens for conditions emerging as a consequence of vascular risk factors, and it is thus reasonable to assume that exposure patterns in midlife may contribute to determine the risk of dementia at an older age (37), even though the latency period is essentially unknown. Table 2 summarizes some of the available epidemiological evidence associating midlife exposure to cardiovascular risk factors and a higher risk of dementia at an older age.

The prospective studies with shorter follow-up periods and assessing the independent role of individual risk factors and the occurrence of AD later in life have shown an association between hypertension (42), diabetes (43, 44), high cholesterol (45) and a higher risk of AD, although the level of evidence is stronger for the first two (46). Clustering of cardiovascular risk factors have been reported to increase the risk of dementia in an additive manner so that individuals with hypertension, obesity and high total cholesterol in midlife have a risk of dementia and AD six times higher than those with no vascular risk factors (39). Supporting these results, the metabolic syndrome has also been shown to be independently associated with AD (47).

Gene-environmental interactions probably exert an important role in determining the risk of dementia and in fact, diabetic patients who are also APOE ϵ 4 carriers have been described to have a higher risk of AD, supporting this hypothesis (48).

Smoking is presently recognized as an environmental risk factor for dementia (49). Although it was initially suggested that it could reduce the risk of AD (50), recent prospective studies show that smokers have a significantly increased risk of dementia, including AD (51, 52), especially among the APOE ϵ 4 carriers (53). A meta-analysis based on 19 prospective studies yielded a combined RR of 1.79 (95% CI: 1.43 to 2.23) for incident AD in current smokers in comparison with never smokers, 1.78 (95% CI: 1.28 to 2.47) for incident vascular dementia, and 1.27 (95% CI: 1.02 to 1.60) for any dementia (54). Compared with those who never smoked, current smokers at baseline also showed greater yearly declines in Mini-Mental State Examination scores over the follow-up period (β =-0.13, 95% CI: -0.18 to 0.08) (54).

Regarding alcohol consumption, evidence suggests that light and moderate intakes may have beneficial effects on cognitive health, in comparison to abstinence or heavy drinking. These conclusions are mostly based on prospective studies with follow-up periods ranging from 2 to 8 years, which describe a reduced risk of dementia and AD in alcohol drinkers in late life (55). Adding to these data, the prospective study by Anttila et al (56) also assessed MCI as an outcome, in parallel with dementia. This 23-year follow-up study confirmed a U-shaped relation between alcohol consumption in midlife and mild cognitive impairment at older age (56). No U-shaped relation was observed (56), but the APOE genotype seemed to modify the risk of dementia, as higher RR estimates were obtained for APOE ϵ 4 carriers with concomitant higher alcohol intakes (56).

The role of physical activity in cognitive health has only recently been addressed. Two studies assessing leisure-time physical activity in midlife in relation to later risk of dementia suggest that higher levels of activity are associated with a lower risk of AD and dementia (57, 58). There are at present no formal recommendations on the type, intensity, frequency and duration of exercise that most effectively reduced the risk of dementia later in life (59).

The potential effect of diet on the prevention of dementia and cognitive decline further extends this research field (60) and has received considerable attention. Much research to date has focused on specific nutrients. High intake of antioxidants has been suggested as a potentially protective measure against neurodegeneration, since free radicals and oxidative damage have been implicated in age-related brain disease. Dietary and supplemental intake of vitamin C and E has been associated with a lower risk of AD (61, 62), and high midlife exposure to fruits and vegetables has been described to decrease the risk of dementia (63). Nevertheless, other authors reported no significant association between these two variables and the occurrence of dementia (64). Randomized controlled trials of folate, vitamin B6 and B12 supplementation have shown no protective cognitive effects (65, 66). Regarding macronutrients, dietary fat has been the most thoroughly investigated. In a longitudinal study with a follow up of 21 years, Laitinen et al (67) described an association between moderate intake of total and unsaturated fats and a reduced risk of AD and dementia when compared with to a low consumption. Conversely, moderate saturated fat intake was described to be associated with an increased risk of dementia; further studies with shorter follow-up periods reported similar findings (68, 69). Despite the fact that some reports support an association between at least some dietary habits and cognitive health on a long term, the IANA (International Academy of Nutrition & Aging) task force on nutrition and cognitive decline with aging stresses the need for further meta-analysis and prospective studies with a robust follow-up, accounting for confounding factors and standard social determinants of food habits, before specific recommendations can be made (60).

In keeping with the trend of investigating the role of modifiable risk factors and dietary habits in chronic diseases, caffeine has been investigated as a molecule with the potential to promote neuroprotection, in particular in Parkinson's disease and dementia. A Portuguese cohort study aiming to quantify the association between caffeine dietary intake and cognitive decline strongly suggested a protective effect in women (70). In addition, a recent meta-analysis also suggested a protective effect of caffeine in cognitive deterioration, with a summary relative risk for the association between caffeine intake and different measures of cognitive impairment/decline of 0.84 (95%CI: 0.72-0.99; $I^2=42.6\%$) (71).

CONCLUSIONS

Dementia and cognitive impairment without dementia are relevant entities, both from a clinical and a social point of view. It is of paramount importance to better understand their impact on populations and the distribution of their determinants, in order to promote preventive strategies. Vascular risk factors have become an increasingly well established determinant for VaD, as well as for AD. Health policies focused on the modification of life-styles are warranted for better prevention and control the epidemic of dementia.

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