The Journal of Nutrition, Health & Aging©
Volume 12, Number 8, 2008

PREVENTION OF PROGRESSION TO DEMENTIA IN THE ELDERLY: RATIONALE AND PROPOSAL FOR A HEALTH-PROMOTING MEMORY CONSULTATION (AN IANA TASK FORCE)

S. GILLETTE-GUYONNET[1,2], G. ABELLAN VAN KAN[1], S. ANDRIEU[2,3], J.P. AQUINO[4], C. ARBUS[5], J.P. BECQ[5], C. BERR[6], S. BISMUTH[7], B. CHAMONTIN[8], T. DANTOINE[9], J.F. DARTIGUES[10], B. DUBOIS[11], B. FRAYSSE[12], T. HERGUETA[11], H. HANAIRE[13], C. JEANDEL[14], S. LAGLEYRE[12], F. LALA[1], F. NOURHASHEMI[1,2], P.J. OUSSET[1,2], F. PORTET[15], P. RITZ[16], P. ROBERT[17], Y. ROLLAND[1,2], C. SANZ[1], M. SOTO[1], J. TOUCHON[15], B. VELLAS[1,2]

1. Gérontopôle, Pôle Gériatrie Gérontologie, Hôpital La Grave-Casselardit, Toulouse; 2. Inserm U558, Toulouse; 3. Département Epidémiologie et Santé Publique, Faculté de Médecine, Toulouse; 4. Clinique de la Porte Verte, Versailles; 5. Médecine Générale, Toulouse; 6. Inserm E0361, Hôpital La Colombière, Montpellier; 7. Médecine Générale, Toulouse; 8. Médecine Interne et Hypertension Artérielle, Hôpital Rangueil, Toulouse; 9. Hôpital Dupuytren, Limoges; 10. ISPED, Inserm U593, Université Victor Segalène, Bordeaux; 11. Centre de Neuropsychologie, Pavillon Paul Castaigne, Hôpital Salpétrière, Paris; 12. Hôpital Purpan, Toulouse; 13. Diabétologie, Maladies Métaboliques, Nutrition, Hôpital Rangueil, Toulouse; 14. Centre de Prévention et de Traitement des Maladies liées au Vieillissement, Centre Antonin Balmès, Montpellier; 15. Département de Neurologie, Hôpital Gui de Chauliac, Montpellier; 16. Service de Médecine B, CHU Angers; 17. CMRR, Inserm JE 2441 Neurobiologie et Psychopathologie, Nice

Abstract: Alzheimer's disease (AD) is the most frequent form of dementia and according to the most recent estimation it affects nearly 27 million people in the world. The onset of the disease is generally insidious. It is becoming increasingly evident that the underlying pathophysiological mechanisms are active long before the appearance of the clinical symptoms of the disease. In the current context, it is important to develop strategies to delay the onset of cognitive decline. Delaying the onset by 5 years would reduce the prevalence by half at term, and a delay of 10 years would reduce it by three-quarters. The effectiveness of currently suggested preventive approaches remains to be confirmed, but certain strategies could be applied straight away to at-risk subjects. We propose that a health-promoting memory consultation should be set up for elderly persons who have attended a specialized memory consultation and in whom the diagnosis of dementia and of AD in particular, has not been established by standardized tools. Through this consultation, they would be offered full multidimensional investigation of all aspects of their health status, follow-up could be organized, general practitioners in private practice could be made more conscious of this population and the elderly could be made more aware of the risk factors to which they are exposed. The development of an information policy for the elderly would meet a present need. In our reflection, we must take into account the question of how to give this preventive consultation its due place in the healthcare pathway of the elderly person in order to ensure coordinated follow-up with all the other health professionals involved. The principle of the health-promoting memory consultation is undergoing validation in a large French multicentre preventive trial in 1200 frail elderly persons aged 70 years followed for three years, the Multidomain Alzheimer Preventive Trial (MAPT).

The ageing of the population which affects all developed countries is leading to an increase in age-related diseases, led by the dementias, notably Alzheimer's disease (AD). At the present time, AD accounts for 70% of prevalent dementias. Its incidence is increasing markedly and according to current predictions the number of persons affected will double every twenty years (1). In their recently published study, Brookmeyer et al. (1) estimated the number of Alzheimer patients worldwide in 2006 to be 26.6 million (ranging between 11.4 to 59.4 million according to the geographical area considered). Their forecast for the future indicates that this number could be multiplied by four by 2050 and reach 106.8 million (variation of 47.2 to 221.2 million), affecting one in 85 persons. In Europe, the prevalence estimated at 7.21 million in 2006 could reach 16.51 million in 2050. The prevalence rate of the disease at ages 65, 75 and 85 years has been estimated at 0.9%, 4.2% and 14.7%, respectively. In France, the figures obtained at the 10-year follow-up of the French Paquid cohort showed that the prevalence of AD in subjects aged 75 and over was estimated at 17.8% (2). Various population studies have estimated the prevalence of AD according to age and sex (3). Extrapolation of these data to the 2004 census gives an estimated figure in France of 766 000 persons with dementia aged over 75 years, of whom over two-thirds are women (618 000) and persons aged over 85 years (394 000). The Eurodem data make it possible to advance figures for each age group, with a mean annual incidence rate which shows a marked increase from 2 per 1000 persons between the ages of 65 and 69 years to 70 per 1000 after 90 years (4). In metropolitan France, the number of new cases of dementia each year is estimated at 225 000 (Paquid data) (5). In persons aged over 85 years, prevalence ranges from 15 to 40% while annual incidence ranges between 60 and 100 person-years (6).

The onset of AD is generally insidious. It appears increasingly evident that the underlying pathophysiological mechanisms are active long before the appearance of the clinical symptoms of the disease. Disease progression does not consist only of memory loss; it also affects the physical condition and independence of the patient, as well as the health of the caregiver. In the absence of curative treatments,

Received June 2, 2008
Accepted for publication June 9, 2008

prevention appears to open up interesting perspectives. Projections of epidemiological data show us that while the prevalence of AD is 5% after 65 years and 25% after 85 years, delaying the onset of the clinical phase of the disease by just one year reduces its prevalence by 25%, and a 5-year delay in onset would decrease the prevalence in the population by 50% after 50 years of application of preventive measures (7). There are also economic consequences, as the monthly cost of a patient with AD increases with the severity of the disease. A 10% decrease in the prevalence of AD according to projections in the United States based on a delay of one extra year between the stage of mild cognitive impairment and clinical AD would correspond to 210 000 fewer patients in one year and a saving of 10 billion dollars (7). It is extremely fortunate for AD prevention that the strategies known to reduce the risk of cardiovascular disease and cancer can also be applied to reduce the risk of AD (8).

Specialized consultations for memory disorders (memory consultations and memory resources and research consultations) were created in France in 2002. The multidisciplinary consultations aim to establish the diagnosis and to set up long-term follow-up via a multidisciplinary approach. More and more elderly persons are now attending these specialized consultations. However, it is frequently observed that in certain individuals with memory complaints, standard neuropsychological tests do not reveal a progressive disorder. In these cases, follow-up and interventions are very rarely proposed. These specialized consultations give us the opportunity of offering multidimensional follow-up and preventive interventions to patients at high risk of developing dementia (elderly persons who express a subjective memory complaint, the frail elderly who have for example incapacities in instrumental activities of daily living or who have a slow walking speed, and those with both vascular and metabolic risk factors). This offer of management could form part of health-promoting memory consultations, whose aim would be to prevent progression to dementia, especially AD, in elderly persons.

In the present work, we discuss the rationale of these consultations and their content. This type of management must be organized around the treating physician, who is familiar with the sufferer in their own environment.

Alzheimer disease in the elderly: is progression accessible to prevention?

A relation can be established between the specific lesions - senile plaques and neurofibrillary degeneration (NFD) - and clinical expression of AD. It should however be noted that only the distribution and extent of NFD are correlated with the type and gravity of the symptoms, respectively. The preferential involvement of certain cortical regions (parietotemporal regions) and of certain neuromediator systems (the cholinergic and glutamatergic systems) is as yet unexplained. The lesions develop slowly and progressively. The senile plaques are diffusely distributed; on the other hand, the distribution of NFD follows a precise course, involving first the entorrhinal cortex and the hippocampal-amygdala region, then the temporoparietal and frontal cortex, before finally affecting most of the cortical and subcortical zones. Compensatory processes (complementary memory systems, activation of neurotransmitters and of other neuronal networks) ensuring maintenance of cognitive reserve make it possible to prevent clinical expression of the lesions at the beginning of the disease and so delay the appearance of disease symptoms (9). AD may thus develop in three phases: an asymptomatic phase of unknown duration, a pre-dementia phase during which the first signs of moderate cognitive decline appear, and a dementia phase.

The term of mild cognitive impairment (MCI) has been proposed to describe subjects who present moderate but significant cognitive alteration which may worsen within two years. Clinical criteria for the definition of MCI have been proposed by Petersen et al. (10): a memory complaint confirmed by those close to the patient, objective memory impairment, normal general cognitive function, intact activities of daily living and absence of dementia. This concept is particularly important as the conversion rate of MCI to dementia is high (11-12). Lehrner et al. (13) observed an annual conversion rate to AD of 6.5% in a population of elderly persons with memory complaints. The conversion rate was particularly high - about 20% - in subjects with amnestic MCI, whereas it was 3% in subjects with a subjective memory complaint but in whom no memory deficit was revealed by neuropsychological tests. Numerous studies have also suggested that memory complaints could be an early indicator of cognitive deterioration which is at a stage still undetectable by standard neuropsychological tools (14-18). The prevalence of memory complaints – defined as everyday memory problems – in the aged ranges between 25 and 50% (19). It is very dependent on the evaluation tools and on the definition used to characterize the complaint. Evaluation of the complaint can be summarized in a simple question « do you think that you have a problem with your memory ? » (20), or specific tools may be used (21). Memory complaints are closely associated with depressive symptoms. Correlations have also been found between memory complaints and changes in brain morphology, in particular left hippocampal volume (22) or white-matter lesions (23). Moreover, memory complaint may be a risk factor for cognitive decline (14,17, 24-26), AD or dementia (27-35). A memory complaint spontaneously expressed to the general practitioner or during the memory consultation could be an even more reliable predictor of future cognitive decline than a complaint which did not result in a consultation (29). The Paquid study, carried out in the general population in persons aged 65 years and over at inclusion, has in fact shown that elderly persons who express a memory complaint to their general practitioner have a higher risk of developing dementia than normal subjects who do not express a complaint, whether their cognitive performances are normal (RR=3.26, p=0.05) or

abnormal (RR=6.09, p=0.001) (29). Particular attention should be paid to the oldest old, in whom dementia is often underdiagnosed. The Three City study showed that of the 201 subjects with dementia at inclusion, only 19% of those aged over 80 years had been referred to a specialist, compared with 55% of subjects aged 65 to 74 years (36). These results show that after the age of 80 years 4 out of 5 patients do not have access to officially recommended diagnostic procedures, either because they have not used the healthcare system or because they have not mentioned cognitive complaints to their physician (3). It is also possible that the neuropsychological tools available for diagnosis are less effective in the oldest old.

The current diagnostic criteria for AD are based on a probabilistic diagnosis established from the clinical criteria of the DSM-IV (37) and NINCDS-ADRDA (38) at the dementia stage of the disease. Early identification of AD, before the dementia stage, is of major importance for the therapeutic management of these patients, in particular since the advent of medications which act on the formation of amyloid plaques, and for increased understanding of the mechanisms of this disease and the discovery of new therapeutic targets (39). At the present time, the main obstacle to early identification of the disease arises from the fact that the diagnosis is dependent on a stage of progression, the dementia syndrome, and is not based on features identifying the disease process itself. Researchers and clinicians together call for a diagnosis which is not dependent on progression. With this aim in mind, a group of international experts (40) has proposed a body of criteria in order to diagnose AD without obligatory reference to the dementia aspect of the disease. These criteria are based on clinical identification of specific memory disturbances suggesting hippocampal dysfunction (10,41-42), and on abnormality of at least one of the following biomarkers:

- hippocampal atrophy shown by magnetic resonance imaging (MRI) (43, 44),
- characteristic abnormalities on functional imaging investigations (45-48), or
- presence of specific markers in cerebrospinal fluid (49-51).

Risk factors and protective factors

The search for modifiable risk factors is a major challenge for epidemiological research on the etiology of AD. At the present time, this field is dominated by research on lifestyle factors, in particular vascular risk factors (hypertension, diabetes, lipid disorders), and studies on nutrition have increased. Other approaches are also being explored, such as the role of the patient's medical history or exposure to certain environmental factors. Increasing attention is being paid, not to the characteristics of the subjects in the years preceding diagnosis, but in a more global manner to the subject's entire life and in particular to the midlife period towards the age of 50 years (52, 53).

Sociodemographic and lifestyle factors

A low educational level is often associated with an increased risk of developing AD in cohort studies (54). Subjects with a high educational level may have a greater cognitive reserve capacity, allowing later expression of the disease (55). It would seem, moreover, that the effect of educational level is manifested well before the disease is diagnosed, with an increased risk of conversion to the MCI stage for normal subjects with a low educational level (56).

A role of certain lifestyle factors has been suggested, including tobacco consumption (57, 58) as a risk factor and moderate alcohol consumption [59, 60], physical exercise (61), a broad spectrum of relationships or social activities (52, 53) or the practice of intellectual or other activities (52, 53, 62-64) as potentially protective factors.

Recent longitudinal studies carried out in the general population aged 65 years or older have reported an inverse association between regular and sustained physical activity and the onset of cognitive decline or dementia (65-70). However, interventional studies are uncommon and rarely select a cognitive outcome to study the efficacy of standardized physical activity.

Numerous studies have suggested the protective role of varied social contacts and activities, whether intellectual or not (for example reading, games, dancing, gardening, do-it-yourself, travelling, learning a language) on the decline of cognitive function, MCI or the onset of dementia (52, 53, 63, 64, 71). However, we should not underestimate the fact that there may be a behavioral change in subjects in the predementia phase (72) which could lead to overestimation of the effect of these factors. It is still difficult to quantify social activities and social networks in epidemiological studies. Marital status could be a good marker of the size of the social network, as is shown by studies which have revealed an increased risk of AD in persons who live alone or who have never married (4, 73, 74). Similarly, the feeling of solitude defined as perceived isolation or the feeling of being unconnected to other people has recently been associated with increased risk of AD (75). Here again, there are few interventional studies. The long-term efficacy of a standardized cognitive training programme, in particular on the targeted domains, and on independence in instrumental activities of daily living has been demonstrated in a single randomized trial in 2832 elderly persons aged 65 to 94 years (62, 76). The programme offered included memory training sessions, training in reasoning (problem-solving ability) or speed of information processing according to the randomized groups.

Frailty factors

Frailty is a new concept which is becoming increasingly important and has arisen both from the clinical care given to elderly persons and from research on ageing. In the 80s, frailty was associated with incapacity, chronic disease, extreme age or the need to call upon geriatric services. At the present time, frailty is dissociated from the other concepts (77). The term of

« frailty » is often used with reference to vulnerable aged persons, who are not capable of withstanding stresses such as disturbances in their environment, injury or acute diseases. These stresses risk leading to a vicious circle in which the elderly person does not succeed in recovering and regaining his or her previous state of health. Physical and/or psychosocial handicaps seem to be the main factors of frailty in aged subjects.

In their studies, Fried and collaborators contributed to the determination of the principal characteristics of frailty: weakness, low endurance, reduced physical activity, slow walking speed and involuntary weight loss (78, 79). These authors also demonstrated that the frail elderly had a higher risk of falls, developing functional limitations and impaired mobility, hospitalization and death within three years. More recently, Buchman et al. (80) showed that elderly persons defined as frail according to Fried's criteria were at greater risk of AD. There is, moreover, increasingly strong evidence linking walking speed and cognitive decline (81-83). In particular, Alfaro-Acha et al. (83) showed an increased risk of cognitive decline in the elderly subjects who took the most time to walk a distance of 2.4 meters (results of the EPESE study of 2070 subjects aged 65 years and over followed for 7 years). Lastly, some authors have also suggested that weight loss may precede the diagnosis of AD (84-87). Low BMI may be an early sign of disease onset (88). A study of 918 clergymen followed for 5.5 years showed that an annual loss of one BMI unit was associated with a 35% increase in the risk of AD (89).

Other multidomain approaches have been developed to define frailty and have led to the development of a frailty index. These take into account the level of dependence (90, 91) or the deficits identified during clincal examination such as sensory disturbances, urinary problems or cardiovascular risk (91). Incontinence in particular is a known factor of social isolation and depression (92) and it is also frequently reported in elderly persons with cognitive and functional decline (93). It is important to take problems of sight and hearing into account, as they can lead to restriction of social and intellectual activities which in themselves accelerate the trajectory of aging. According to the findings of the French Acoudem study, the risk of developing cognitive disturbances was twice as high in elderly persons with hearing difficulties (94). The findings of the Blue Mountains Eye Study (3509 subjects aged 50 years and over) also showed that persons with moderate to severe visual or hearing impairment had lower MMSE scores (95). The data of the SOF study (Study of Osteoporotic Fractures), concerning 6112 women aged 69 years and over, found that visual impairment on inclusion was associated with cognitive and functional decline during follow-up. The presence of both visual and hearing impairment increased these risks (96). Near vision impairment was also associated with cognitive decline in 2140 subjects aged 65 years and over followed for 7 years in the EPESE study (97). Lastly, some works have suggested a possible association between cognitive impairment and age-related macular degeneration in elderly subjects (98-100).

Changes on the scale of instrumental activities of daily living (IADL) (101) could identify the frail elderly, in particular those with mild cognitive impairment, as shown by Nourhashemi et al. (102). The IADL assesses the subject's ability to carry out certain complex tasks of daily living (using the telephone, shopping, preparing meals, doing housework and washing, taking medication, managing paperwork and using transport). These authors studied the EPIDOS cohort (EPIDémiologie de l'Ostéoporose), a population of 7500 women volunteers, aged over 75, living at home and free of dementia. Dependence evaluated with the IADL scale was found to be independently associated with numerous characteristics of the frailty syndrome such as isolated memory deficit, vision and hearing impairments, fear of falling and perceived poor health. With the present state of knowledge and in the absence of validated evaluation tools, walking speed appears to be the most pertinent marker of frailty in these subjects according to the recent conclusions of a group of experts (77).

Nutritional factors

Current epidemiological data are in favour of a protective role of certain micronutrients (group B vitamins related to homocystein metabolism, the antioxidant vitamins C and E, flavonoids, polyunsatured omega-3 fatty acids) and macro-nutrients (fish) in the prevention of cognitive decline and dementia (103). Some disagreements exist however between the studies, mainly arising from methodological problems (confounding factors taken into account, mode of collection of nutritional data, forms and doses of the vitamins used in randomized controlled studies). At the present time, it is still difficult to propose specific recommendations for the prevention of AD (103). Moreover, recent findings show that subjects with AD already have inadequate nutrient intakes (calcium, iron, zinc, vitamin A, omega-3 and omega-6 unsaturated fatty acids) in the early stages of the disease (104). Epidemiological analysis of the relations between nutrient consumption and cognitive decline is complex and it is highly unlikely that a single component plays a major role. We need to pursue studies which will improve our knowledge of the biochemical mechanisms underlying the pathophysiological processes and will identify potential therapeutic agents, and which in a public health perspective will examine food groups and dietary patterns. A recently published paper, based on the findings of the French Three Cities study, suggested that a diet with little variety may increase the risk of dementia (105). In this work, daily consumption of fruits and vegetables was associated with reduced risk of dementia. Weekly consumption of fish was associated with reduced risk of AD and dementia only in ApoE epsilon 4 noncarriers. Regular consumption of oil or fish rich in omega-3 fatty acids was associated with reduced risk of dementia, whereas regular consumption of oils rich in omega-6 fatty acids increased this risk. Another study has shown decreased risk of AD in subjects with a diet similar to the Mediterranean diet (106). The outcome of patients with AD

once the diagnostic has been established also appears to be better in patients whose diet is similar to the Mediterranean diet (107).

All these works highlight the need to consider the interactions between micro- and macronutrients in future studies. The impact of classic social determinants of diet, such as regional cultures, social status and educational level, must of course be taken into account. Communication and nutritional advice will benefit from being adapted to dietary habits and to the patient's stage in the cycle of ageing (108-110).

Vascular risk factors

The relation between blood pressure and dementia is a complex one. Depending on the period of life considered, the effects of blood pressure and of hypertensive treatment differ (111). Nearly all studies report an association between high blood pressure 20 to 30 years before cognitive evaluation and later decline in cognitive function or onset of dementia. In studies where blood pressure was measured at a later period, results are contradictory depending on whether cognitive decline or dementia incidence are examined. One study performed in subjects aged over 75 years found an increased risk of AD in both subjects with the highest systolic values and in those with the lowest values in relation to the median tertile (112). In the same cohort, blood pressure declined during the 3 years preceding the diagnosis of dementia (113). The results of randomized studies with protocols whose primary aim was not to study the effect of blood pressure on dementia or cognitive decline are still too limited. The first randomized Syst-Eur trial with an antihypertensive medication (nitrendipin) showed decreased incidence of dementia in elderly subjects with isolated systolic hypertension (114). The Progress study (115) reported a significantly reduced risk of cognitive decline in subjects treated with perindropil or indapamid. No significant effect on the MMSE score or on change in this score was found in subjects with arterial hypertension treated with candesartan (116).

Longitudinal studies show that diabetes affects cognitive decline or the onset of dementia. In 2006, a review of the literature (117) summed up studies involving nearly 110 000 subjects: the risk of dementia was multiplied 1.5 to 2-fold in diabetic patients compared with non-diabetic patients after adjustment for other cardiovascular risk factors. In addition, studies of the relation between diabetes and cognitive function have revealed a dose-effect relationship (increased duration of disease or more severe disturbances of glycoregulation resulted in poorer cognitive performances) and an improvement in cognitive function when glycemic balance was also improved (118-120). The pathophysiological explications are multiple. On the one hand, like the other complications of diabetes, chronic hyperglycemia could have damaging effects on the brain in particular via the polyol and hexosamine pathways, via imbalance of the production and degradation of free radicals, or via advanced glycation of functional and structural proteins (121-124). On the other hand, as suggested by Suzanne Craft and collaborators'' work, cognitive alterations are potentially due to the effects of insulin resistance and peripheral hyperinsulinemia via an increased level of free fatty acids and of inflammation markers such as TNF-alpha (125-126). The consequences are low insulin levels in the brain and increased beta amyloid deposits, both of which lead to deterioration of cognitive performances. Treatments which correct the insulin deficiency of the brain, such as inhaled insulin, or which increase sensitivity to insulin, such as PPAR-gamma nuclear receptor analogues, may improve cognitive function (127-128). Furthermore, recent studies report an increased risk of cognitive decline (129-131) and AD (132) in elderly subjects with metabolic syndrome.

Studies on cholesterol levels, decline of cognitive function and dementias are also contradictory (133). High cholesterol levels in middle age may be the most strongly associated with increased risk of AD. Randomized trials of various statins against placebo have so far yielded negative results (134-136).

The implication of vascular factors is also suggested by the results of studies showing a positive relation between obesity and the risk of dementia onset (137-140). The various vascular risk factors must be simultaneously assessed in order to establish scores for dementia risk, as for cardiovascular disorders. This approach has been proposed by Kivipelto et al. [141]. Their aim was to develop a simple method of dementia risk prediction in the elderly based on their vascular risk profile 20 years earlier. Their work was based on the CAIDE (Cardiovascular Risk Factors, Aging and Dementia) study data and concerned 1409 subjects who were first seen in 1977 (mean age 50 years, range 39 to 64 years) and seen again 20 years later in 1998 (mean age 71 years, range 65 to 80 years) to identify dementia. The score which was used, which had a sensitivity of 77% and a specificity of 63%, included age, educational level, hypertension, high cholesterol levels and obesity but not physical activity or apolipoprotein E4.

Mood disturbances, sleep disturbances and other disorders

A review of the literature and a recent meta-analysis suggest that depression could be an independent risk factor for AD (142). A study carried out in 281 subjects aged 65 years and over, with little or no cognitive impairment (evaluated with the Short Portable Mental Status Questionnaire: 4 or less errors) showed however that depressive symptoms are neither prodromal nor predictive of cognitive decline, but that these two states develop concurrently (143).

An association between sleep disturbances (less effective sleep, difficulty in falling asleep, more frequent daytime naps, sleep apnea syndrome) and cognitive decline has been found in several studies (144-148). Among patients with sleep disturbances, the risk of cognitive decline may be greater in ApoE epsilon 4 carriers (149). Sleep disturbances may also be associated with poorer physical performance in elderly women (150). Some studies have underlined the possible association

between various heart diseases, in particular atrial fibrillation (151), heart failure (152-154) and coronary artery disease (155), and cognitive impairment or AD.

Lastly, other factors (head injuries, aluminium content of drinking water, anesthetics…) have been suggested but their association with AD is based on debatable findings.

The search for potentially modifiable risk factors is a major public health challenge in AD. Our present state of knowledge is inadequate and calls for new projects to be proposed in order to evaluate the impact of factors associated with lifestyle or modified by medical treatments (antihypertensives, management of diabetes).

The health-promoting memory consultation: what population should be targeted and what evaluations should be proposed ?

An increasing number of elderly persons attend memory consultations because of memory complaints. In some, dementia or MCI may be diagnosed during the consultation, but in others the complaint may be subjective. This subjective complaint is not necessarily accompanied by objective assessment of impairment of memory or cognitive performance, and so follow-up or interventions are rarely offered. These specialized consultations give us the opportunity to offer follow-up and multidimensional preventive interventions to patients at high risk of developing dementia, in particular dementia of Alzheimer type (the frail elderly with slow walking speed or limitations in instrumental activities of daily living; elderly persons with a high metabolic and vascular risk; elderly persons who express a memory complaint or who present mild cognitive impairment). Follow-up consultations may be proposed on a annual basis, or on a six-monthly basis for elderly persons with mild cognitive impairment. Such management could be included as part of the creation of a health-promoting memory consultation. This initiative would make it possible overall to carry out full multidimensional investigation of the elderly person's state of health, to organize follow-up and management of the medical problems identified in collaboration with the general practitioners in private practice, to increase the awareness of these physicians of this population, to make the elderly more conscious of the risk factors to which they are exposed, and to undertake effective long-term preventive action. The frequency of the evaluations proposed during follow-up will depend on the initial global evaluation and on the patient's age. Health-promoting memory consultations should also provide an opportunity to make the elderly more aware of the benefit of certain eating habits (according to the recommendations of the National Plan for Nutrition and Health), of a healthy lifestyle (physical exercise in particular) and of correction of vascular risk factors, which are all parameters that can contribute to the prevention of AD. Education will be a major element in the management of the elderly. Moreover, diagnosis of AD during follow-up will be simplified if the physician is already in possession of a previous neuropsychological evaluation. Preventive interventions directed at modifiable environmental factors are of particular value and should be developed in order to promote healthy ageing. The impact of such actions will be even greater if they are started early. Multidisciplinary management associating the general practitioner, the geriatrician and the neurologist is probably one of the keys to optimal preventive management in the elderly.

Based on the data of the literature, we suggest that the following information should be collected and the following evaluations included in the health-promoting memory consultation:

- sociodemographic information (age, sex, living arrangements, marital status, educational level, professional activities)
- general clinical examination (cardiopulmonary, abdominal, neurological investigations, examination of the limbs, incontinence)
- medical history and concomitant diseases
- polymedication
- sight testing (questioning, test of visual acuity, Amsler grid)
- hearing tests (questioning, hearing handicap inventory for the elderly- screening version (HHIE-S), audiometry)
- assessment of gait and balance disturbances (one-leg balance test, falls) and of frailty (Short Physical Performance Battery, SPPB)
- evaluation of independence (Instrumental Activities of Daily Living (IADL))
- evaluation of nutritional status (Mini Nutritional Assessment, MNA)
- evaluation of depression (history, Geriatric Depression Scale (GDS)-15 items)
- evaluations of metabolic status and cardiovascular risk.

Cognitive function is evaluated during the specialized memory consultation and so it is not included in the initial health-promoting memory consultation. It may be proposed during follow-up and should include evaluations of:

- the memory complaint (visual analogic scales)
- memory deficit (5-word test)
- visual constructive apraxia (clock-drawing test)
- as well as global cognitive evaluation (MMSE).

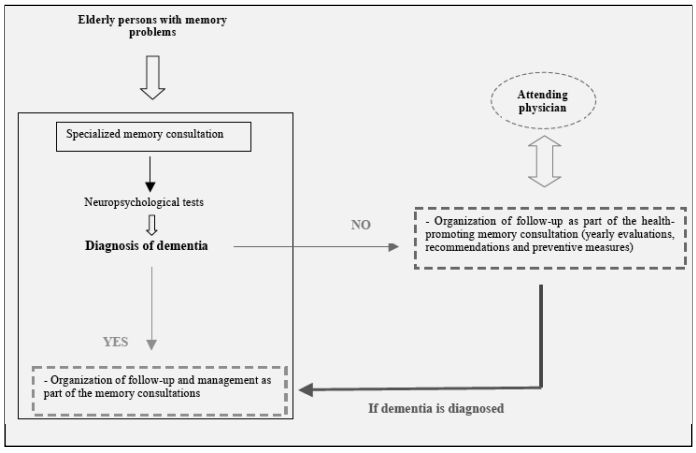
The expert group discussed the usefulness of including apolipoprotein E epsilon4 allele genotyping in the consultation, but this proposal was not retained. Numerous teams have confirmed that the apolipoprotein E epsilon4 allele is two to four times more frequent in Alzheimer patients than in the general population, whereas the epsilon2 allele seems to have a protective effect. The apolipoprotein E epsilon4 allele is thus an important risk factor for AD. However, at the individual level, the presence of an epsilon4 genotype is insufficient to affirm the diagnosis since not all persons possessing this allele

develop AD. Such an approach thus cannot ignore the ethical questions raised by an attitude which would be equivalent to imposing a diagnosis of AD on the persons concerned and on their families, whereas in the present state of our knowledge the justification for treatment, at least on a medical level, is still insufficient.

Development of an information policy for the elderly would respond to current needs; recent findings have shown that elderly persons feel less concerned by dementia than younger ones, and that they have poor awareness of risk factors (156). The health-promoting memory consultation is being validated as part of a large French multicentre preventive study of 1200 frail elderly personnes aged 70 years and followed for three years in the Multidomain Alzheimer Preventive Trial study (MAPT). This study aims to examine the efficacy of isolated omega-3 fatty acid supplementation, of multidomain interventions (nutritional advice, cognitive training, physical exercise, social activities) either isolated or in association, on the evolution of cognitive function. As part of the study, the health-promoting memory consultation will be carried out every year in the elderly persons receiving the multidomain intervention.

Table 1

Proposal for introducing the health-promoting memory



consultation in the healthcare pathway of the elderly person

Acknowledgments: We wish to thank Laboratoires Novartis for enabling the meeting of the Task Force.

References

1. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimer's Dement 2007;3:186-191.
2. Ramaroson H, Helmer C, Barberger-Gateau P, Letenneur L, Dartigues JF. Prevalence de la démence et de la maladie d'Alzheimer chez les personnes de 75 ans et plus: données réactualisées de la cohorte Paquid. Rev Neurol 2003;159:405-411.
3. Gallez C. Rapport sur la maladie d'Alzheimer et les maladies apparentées. OPEPS 2005.
4. Fratiglioni L, Launer LJ, Andersen K, Breteler MM, Copeland JR, Dartigues JF, Lobo A, Martinez-Lage J, Soininen H, Hofman A. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurology 2000;54:S10-S15.
5. Commenges D, Joly P, Letenneur L, Dartigues JF. Incidence and mortality of Alzheimer's disease or dementia using an illness-death model. Stat Med 2004;23:199-210.
6. Ankri J, Poupard M. Prevalence and incidence of dementia among the very old. Review of the literature. Rev Epidémiol Santé Publique 2003;51:349 -360.
7. Brookmeyer R, Gray S. Methods for projecting the incidence and prevalence of chronic disease in ageing populations: application to Alzheimer's disease. Stat Med 2000;19:1481-1493.
8. Rapport J. Ménard. 8 Novembre 2007. Source: http://www.premier-ministre.gouv.fr/IMG/pdf/plan_2008_2012.pdf
9. Smith GE, Pankratz VS, Negash S, Machulda MM, Petersen RC, Boeve BF, Knopman DS, Lucas JA, Ferman TJ, Graff-Radford N, Ivnik RJ. A plateau in pre-Alzheimer memory decline. Evidence for compensatory mechanisms ? Neurology 2007;69:133-139.
10. Petersen RC, Smith GE, Ivnik RJ, Kokmen E, Tangalos EG. Memory function in very early Alzheimer's disease. Neurology 1994;44:867-872.
11. Schmidtke K, Hermeneit S. High rate of conversion to Alzheimer's disease in a cohort of amnestic MCI patients. Int Psychogeriatr 2008;20:96-108.
12. Maioli F, Coveri M, Pagni P, Chiandetti C, Marchetti C, Ciarrocchi R, Ruggero C, Nativio V, Onesti A, D'Anastasio C, Pedone V. Conversion of mild cognitive impairment to dementia in elderly subjects: a preliminary study in a memory and cognitive disorder unit. Arch Gerontol Geriatr 2007;44 Suppl 1:233-241.
13. Lehrner J, Gufler R, Guttmann G, Maly J, Gleiss A, Auff E, Dal-Bianco P. Annual conversion to Alzheimer disease among patients with memory complaints attending an outpatient memory clinic: the influence of amnestic mild cognitive impairment and the predictive value of neuropsychological testing. Wien Klin Wochenschr 2005;117:629-635.
14. Dufouil C, Fuhrer R, Alperovitch A. Subjective cognitive complaints and cognitive decline: consequence or predictor? The epidemiology of vascular aging study. J Am Geriatr Soc 2005;53:616-621.
15. Barnes LL, Schneider JA, Boyle PA, Bienias JL, Bennett DA. Memory complaints are related to Alzheimer disease pathology in older persons. Neurology 2006;67:1581-1585.
16. Saykin AJ, Wishart HA, Rabin LA, Santulli RB, Flashman LA, West JD, McHugh TL, Mamourian AC. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology 2006;67:834-842.
17. Dik MG, Jonker C, Comijs HC, Bouter LM, Twisk JW, van Kamp GJ, Deeg DJ. Memory complaints and APOE-epsilon4 accelerate cognitive decline in cognitively normal elderly. Neurology 2001;57:2217-2222.
18. Coley N, Ousset PJ, Andrieu S, Matheix Fortunet H, Vellas B. Memory complaints to the general practitioner: data from the GuidAge study. J Nutr Health Aging 2008;12:66S-72S.
19. Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry 2000;15:983-991.
20. Bassett SS, Folstein MF. Memory complaint, memory performance and psychiatric diagnosis: a community study. J Geriatr Psychiatry Neurol 1993;6:105-111.
21. Jonker C, Launer LJ, Hooijer C, Lindeboom J. Memory complaints and memory impairment in older individuals. J Am Geriatr Soc 1996;44:44-49.
22. van der Flier WM, van Buchem MA, Weverling-Rijnsburger AW, Mutsaers ER, Bollen EL, Admiraal-Behloul F, Westendorp RG, Middelkoop HA. Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. J Neurol 2004;251:671-675.
23. Minett TS, Dean JL, Firbank M, English P, O'Brien JT. Subjective memory complaints, white-matter lesions, depressive symptoms, and cognition in elderly patients. Am J Geriatr Psychiatry 2005;13:665-671.
24. Reid LM, Maclullich AM. Subjective memory complaints and cognitive impairment in older people. Dement Geriatr Cogn Disord 2006;22,5-6:471-485.
25. Jorm AF, Masaki KH, Davis DG, Hardman J, Nelson J, Markesbery WR, Petrovitch H, Ross GW, White LR. Memory complaints in nondemented men predict future pathologic diagnosis of Alzheimer disease. Neurology 2004;63:1960-1961.
26. Schofield PW, Marder K, Dooneief G, Jacobs DM, Sano M, Stern Y. Association of subjective memory complaints with subsequent cognitive decline in community-dwelling elderly individuals with baseline cognitive impairment. Am J Psychiatry 1997;154:609-615.
27. Tobiansky R, Blizard R, Livingston G, Mann A. The Gospel Oak Study stage IV: the clinical relevance of subjective memory impairment in older people. Psychol Med 1995;25:779-786.
28. Schmand B, Jonker C, Hooijer C, Lindeboom J. Subjective memory complaints may announce dementia. Neurology 1996;46:121-125.
29. Dartigues JF, Fabrigoule C, Letenneur L, Amieva H, Thiessard F, Orgogozo JM. Epidemiology of memory disorders. Therapie 1997;52:503-506.
30. St John P, Montgomery P. Are cognitively intact seniors with subjective memory loss more likely to develop dementia ? Int J Geriatr Psychiatry 2002;17:814-820.
31. Palmer K, Backman L, Winblad B, Fratiglioni L. Detection of Alzheimer's disease and dementia in the preclinical phase: population based cohort study. BMJ 2003;326(7383):245.
32. Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. A prospective study of

changes in subjective memory complaints and onset of dementia in South Korea. Am J Geriatr Psychiatry 2006;14:949-956.
33. Heun R, Kolsch H, Jessen F. Risk factors and early signs of Alzheimer's disease in a family study sample. Risk of AD. Eur Arch Psychiatry Clin Neurosci 2006;256:28-36.
34. Wang L, van Belle G, Crane PK, Kukull WA, Bowen JD, McCormick WC, Larson EB. Subjective memory deterioration and future dementia in people aged 65 and older. J Am Geriatr Soc 2004;52:2045-2051.
35. Geerlings MI, Jonker C, Bouter LM, Ader HJ, Schmand B. Association between memory complaints and incident Alzheimer's disease in elderly people with normal baseline cognition. Am J Psychiatry 1999;156:531-537.
36. Alperovitch A, Amouyel P, Dartigues JF, Ducimetière P, Mazoyer B, Ritchie K, Tzourio C. Epidemiological studies on aging in France: from the Paquid study to the Three-City study. C R Biol 2002;325:665-672.
37. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (IV-TR), 4th ed. (Text Revision). Washington, DC: 2000.
38. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS–ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-944
39. Greig NH, Lahiri DK, Giacobini E. Editorial: advances in Alzheimer therapy: something old, something new, something borrowed, something blue. Curr Alzheimer Res 2005;2:275-279.
40. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007;6:734-746.
41. Ivanoiu A, Adam S, Van der Linden M, Salmon E, Juillerat AC, Mulligan R, Seron X. Memory evaluation with a new cued recall test in patients with mild cognitive impairment and Alzheimer's disease. J Neurol 2005;252:47-55.
42. Tounsi H, Deweer B, Ergis AM, Van der Linden M, Pillon B, Michon A, Dubois B. Sensitivity to semantic cuing: an index of episodic memory dysfunction in early Alzheimer disease. Alzheimer Dis Assoc Disord 1999;13:38-46.
43. Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, Kuiper M, Steinling M, Wolters EC, Valk J. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992;55:967-972.
44. Jack CR, Petersen RC, Xu YC, Waring SC, O'Brien PC, Tangalos EG, Smith GE, Ivnik RJ, Kokmen E. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. Neurology 1997;49:786-794.
45. Consensus report of the Working Group on "Molecular and Biochemical Markers of Alzheimer's Disease". The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group. Neurobiol Aging 1998;19:109-116.
46. Jagust W, Thisted R, Devous MD, Sr, Van Heertum R, Mayberg H, Jobst K, Smith AD, Borys N. SPECT perfusion imaging in the diagnosis of Alzheimer's disease: a clinical-pathologic study. Neurology 2001;56:950-956.
47. Huang C, Eidelberg D, Habeck C, Moeller J, Svensson L, Tarabula T, Julin P. Imaging markers of mild cognitive impairment: multivariate analysis of CBF SPECT. Neurobiol Aging 2006;28:1062-1069.
48. Borroni B, Anchisi D, Paghera B, Vicini B, Kerrouche N, Garibotto V, Terzi A, Vignolo LA, Di Luca M, Giubbini R, Padovani A, Perani D. Combined 99mTc-ECD SPECT and neuropsychological studies in MCI for the assessment of conversion to AD. Neurobiol Aging 2006;27:24-31.
49. Blennow K, Hampel H. CSF markers for incipient Alzheimer's disease. Lancet Neurol 2003;2:605-613.
50. Andreasen N, Blennow K. CSF biomarkers for mild cognitive impairment and early Alzheimer's disease. Clin Neurol Neurosurg 2005;107:165-173.
51. Parnetti L, Lanari A, Silvestrelli G, Saggese E, Reboldi P. Diagnosing prodromal Alzheimer's disease: role of CSF biochemical markers. Mech Ageing Dev 2006;127:129-132.
52. Fratiglioni L, Paillard-Borg S, Winblad B. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol 2004;3:343-353.
53. Fratiglioni L, Winblad B, von Strauss E. Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project. Physiol Behav 2007;92:98-104.
54. Letenneur L, Launer LJ, Andersen K, Dewey ME, Ott A et al. Education and the risk for Alzheimer's disease: sex makes a difference. EURODEM pooled analyses. EURODEM Incidence Research Group. Am J Epidemiol 2000;151:1064-1071.
55. Letenneur L, Gilleron V, Commenges D, Helmer C, Orgogozo JM, Dartigues JF. Are sex and educational level independent predictors of dementia and Alzheimer's disease ? Incidence data from the Paquid project. J Neurol Neurosurg Psychiatry 1999;66:177-183.
56. Kryscio RJ, Schmitt FA, Salazar JC, Mendiondo MS, Markesbery WR. Risk factors for transitions from normal to mild cognitive impairment and dementia. Neurology 2006;66:828-832.
57. Ott A, Andersen K, Dewey ME, Letenneur L, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A, Launer LJ; EURODEM Incidence Research Group. Effect of smoking on global cognitive function in nondemented elderly. Neurology 2004;62:920-924.
58. Reitz C, den Heijer T, van Duijn C, Hofman A, Breteler MM. Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study. Neurology 2007;69:998-1005.
59. Letenneur L, Larrieu S, Barberger-Gateau P. Alcohol and tobacco consumption as risk factors of dementia: a review of epidemiological studies. Biomed Pharmacother 2004;58:95-99.
60. Savaskan E, Olivieri G, Meier F, Seifritz E, Wirz-Justice A, Muller-Spahn F. Red wine ingredient resveratrol protects from beta-amyloid neurotoxicity. Gerontology 2003;49:380-383.
61. Heyn P, Abreu BC, Ottenbacher KJ. The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil 2004;85:1694-1704.
62. Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, Mann Koepke K, Morris JN, Renbok GW, Unverzagt FW, Stoddard AM, Wright E for the Active Study Group. Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA 2006;296:2805-2814.
63. Fabrigoule C, Letenneur L, Dartigues JF, Zarrouk M, Commenges D, Barberger-Gateau P. Social and leisure activities and risk of dementia: a prospective longitudinal study. J Am Geriatr Soc 1995;43:485-490.
64. Wilson RS, Scherr PA, Schneider JA, Tang Y, Bennett DA. The relation of cognitive activity to risk of developing Alzheimer's disease. Neurology 2007a; 69:1-10.
65. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K. A prospective study of physical activity and cognitive decline in elderly women: women who walk. Arch Intern Med 2001;161:1703-1708.
66. Lytle ME, Vander Bilt J, Pandav RS, Dodge HH, Ganguli M. Exercise level and cognitive decline: the MoVies project. Alzheimer Dis Assoc Disord 2004;18:57-64.
67. Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F. Physical activity, including walking, and cognitive function in older women. JAMA 2004;292:1454-1461.
68. Abbott RD, White LR, Ross GW, Masaki KH, Curb JD, Petrovitch H. Walking and dementia in physically capable elderly men. JAMA 2004;292:1447-1453.
69. Podewils LJ, Guallar E, Kuller LH, Fried LP, Lopez OL, Carlson M, Lyketsos CG. Physical activity, apoE genotype and dementia risk: findings from the Cardiovascular Health Cognition Study. Am J Epidemiol 2005;161:639-651.
70. Larson EB, Wang Li, Bowen J, McCormick WC, Teri L, Crane P, Kukull W. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006;144:73-81.
71. Bialystok E, Craik FIM, Freedman M. Bilingualism as a protection against the onset of symptoms of dementia. Neuropsychologia 2007;45:459-464.
72. Saczynski JS, Pfeifer LA, Masaki K, Korf ES, Laurin D, White L, Launer LJ. The effect of social engagement on incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol 2006;163:433-440.
73. van Gelder BM, Tijhuis M, Kalmijn S, Giampaoli S, Nissinen A, Kromhout D. Marital status and living situation during a 5-year period are associated with a subsequent 10-year cognitive decline in older men: the FINE Study. Neurology 2006;5:735-741.
74. Helmer C, Damon D, Letenneur L, Fabrigoule C, Barberger-Gateau P, Lafont S, Fuhrer R, Antonucci T, Commenges D, Orgogozo JM, Dartigues JF. Marital status and risk of Alzheimer's disease: a French population based cohort study. Neurology 1999;53:1953-1958.
75. Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, Tang YX, Bennett DA. Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry 2007b;64:234-240.
76. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN, Rebok GW, Smith DM, Tennstedt SL, Unverzagt FW, Willis SL for the Active Group Study. Effects of cognitive training interventions with older adults. A randomized controlled trial. JAMA 2002;288:2271-2281.
77. Abellan Van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B on behalf of the geriatric advisory panel. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging 2008;12:29-37.
78. Fried LP, Tangen CM, Waltson J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA for the Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol Biol Sci Med Sci 2001;56 A:M146-M156.
79. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the concepts of disability, frailty and comorbidity: implications for improved targeting and care. J Gerontol Biol Sci Med Sci 2004;59:255-263.
80. Buchman AS, Boyle PA, Wilson RS, Tang YX, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med 2007;69:483-489.
81. Onder G, Penninx BW, Lapuerta P, Fried LP, Ostir GV, Guralnik JM, Pahor M. Change in physical performance over time in older women: the Women's Health and Aging Study. J Gerontol A Biol Sci Med Sci 2002; 57:M289-M293.

82. Duff K, Mold JW, Roberts MM. Walking speed and global cognition: results from the OKLAHOMA Study. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2008;15:31-9.
83. Alfaro Acha A, Al Snih S, Raji MA, Markides KS, Ottenbacher KJ. Does 8-foot walk time predict cognitive decline in older Mexican Americans? J Am Geriatr Soc 2007;55:245-251.
84. Barrett-Connor E, Edelstein SL, Corey-Bloom J, Wiederholt WC. Weight loss precedes dementia in community-dwelling older adults. J Am Geriatr Soc 1996;44:1147-1152.
85. Stewart R, Masaki K, Xue QL, Peila R, Petrovitch H, White LR, Launer LJ. A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study. Arch Neurol 2005;62:55-60.
86. Johnson DK, Wilkins CH, Morris JC. Accelerated weight loss may precede diagnosis in Alzheimer disease. Arch Neurol 2006;63:1312-1317.
87. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, McGovern P, Folsom AR; Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42-48.
88. Nourhashemi F, Deschamps V, Larrieu S, Letenneur L, Dartigues JF, Barberger-Gateau P. Body mass index and incidence of dementia: the PAQUID study. Neurology 2003;60:117-119.
89. Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA. Change in body mass index and risk of incident Alzheimer disease. Neurology 2005;65:892-897.
90. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hebert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. Lancet 1999; 353:205-206.
91. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K. Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatrics 2002;2:1.
92. Markland AD, Goode PS, Burgio KL, Redden DT, Richter HE, Sawyer P, Allman RM. Correlates of urinary, fecal and dual incontinence in older African-American and white men and women. J Am Geriatr Soc 2008;56:285-290.
93. Huang AJ, Brown JS, Thom DH, Fink HA, Yaffe K, Study of Osteoporotic Fractures Research Group. Urinary incontinence in older community-dwelling women: the role of cognitive and physical function decline. Obstet Gynecol 2007;109:909-916.
94. Pouchain D, Dupuy C, San Jullian M, Dumas S, Vogel MG, Hamdaoui J, Vergnon L pour le GRAP. La presbyacousie est-elle un facteur de risque de démence ? Etude Acoudem. Revue de Gériatrie 2007;32:439-445.
95. Tay T, Wang JJ, Kifley A, Lindley R, Newall P, Mitchell P. Sensory and cognitive association in older persons: findings from an older Australian population. Gerontology 2006;52:386-394.
96. Lin MY, Gutierrez PR, Stone KL, Yaffe K, Ensrud KE, Fink HA, Sarkisian CA, Coleman AL, Mangione CM. Study of osteoporotic fractures research group. Vision impairment and combined vision hearing impairment predict cognitive and functional decline in older women. J Am Geriatr Soc 2004;52:1996-2002.
97. Reyes Ortiz CA, Kuo YF, DiNuzzo AR, Raji MA, Markides KS. Near vision impairment predicts cognitive decline: data from the Hispanic Established Populations for Epidemiologic Studies of the Elderly. J Am Geriatr Soc 2005;53:681-686.
98. Pham TQ, Kifley A, Mitchell P, Wang JJ. Relation of age-related macular degeneration and cognitive impairment in an older population. Gerontology 2006;52:353-358.
99. Clemons TE, Rankin MW, McBee WL. Age-Related Eye Disease Study Research Group. Cognitive impairment in the Age-Related Eye Disease Study: AREDS report no. 16. Arch Ophthalmol. 2006;124:537-543.
100. Wong TY, Klein R, Nieto FJ, Moraes SA, Mosley TH, Couper DJ, Klein BE, Boland LL, Hubbard LD, Sharrett AR. Is early age-related maculopathy related to cognitive function? The Atherosclerosis Risk in Communities Study. Am J Ophthalmol 2002;134:828-835.
101. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-186.
102. Nourhashemi F, Andrieu S, Gillette-Guyonnet S, Vellas B, Albarède JL, Grandjean H. Instrumental activities of daily living as a potential marker of frailty: a study of 7364 community-dwelling elderly women (the EPIDOS study). J Gerontol A Biol Sci Med Sci 2001;56:M448-M453.
103. Gillette-Guyonnet S, Abellan Van Kan G, Andrieu S, Barberger Gateau P, Berr C, Bonnefoy M, Dartigues JF, de Groot L, Ferry M, Galan P, Hercberg S, Jeandel C, Morris MC, Nourhashemi F, Payette H, Poulain JP, Portet F, Roussel AM, Ritz P, Rolland Y, Vellas B. IANA task force on nutrition and cognitive decline with aging. J Nutr Health Aging 2007;11:132-152.
104. Schatenstein B, Kergoat MJ, Reid I. Poor nutrient intakes during 1-year follow-up with community-dwelling older adults with early-stage Alzheimer dementia compared to cognitively intact matched controls. J Am Diet Assoc 2007;107:2091-2099.
105. Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, dartigues JF, Alperovitch A. Dietary pattern and risk of dementia in the Three City cohort study. Neurology 2007;69:1921-1930.
106. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol 2006;59:912-921.
107. Scarmeas N, Luchsinger JA, Mayeux R, Stern Y. Mediterranean diet and Alzheimer disease mortality. Neurology 2007;69:1084-1093.
108. Poulain JP, Tibère L. Évolutions des représentations nutritionnelles des jeunes seniors: 1966/1998. Cahiers de Nutrition et de Diététique 2000;35:40-46.
109. Poulain JP. Les tendances actuelles du comportement alimentaire. In: Appfelbaum M, Romon M, Abrégé de Nutrition, Masson. 2005a.
110. Poulain JP. Sociologies de l'alimentation, les mangeurs et l'espace social alimentaire. PUF, Collection Quadrige. 2005b.
111. Qiu C, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. Lancet Neurol 2005;4:487-499.
112. Qiu C, Winblad B, Viitanen M, Fratiglioni L. Pulse pressure and risk of Alzheimer disease in persons aged 75 years and older: a community-based, longitudinal study. Stroke 2003;34:594-599.
113. Qiu C, von Strauss E, Winblad B, Fratiglioni L. Decline in blood pressure over time and risk of dementia: a longitudinal study from the Kungsholmen project. Stroke 2004;35:1810-1815.
114. Forette F, Seux ML, Staessen JA, Thijs L, Birkenhäger WH, Babarskiene MR, Babeanu S, Bossini A, Gil-Extremera B, Girerd X, Laks T, Lilov E, Moisseyev V, Tuomilehto J, Vanhanen H, Webster J, Yodfat Y, Fagard R. Prevention of dementia in randomised double-blind placebo controlled systolic hypertension in Europe (Syst-Eur) trial. Lancet 1998;352:1347-1351.
115. Tzourio C, Anderson C, Chapman N, Woodward M, Neal B, MacMahon S, Chalmers J; PROGRESS Collaborative Group. Effects of blood pressure lowering with perindropil and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med 2003;163:1069-1075.
116. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A; SCOPE Study Group. The study of cognition and prognosis in the elderly (Scope): principal results of a randomized double-blind intervention trial. J Hypertens 2003;21:875-886.
117. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet 2006;5:64-74.
118. Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology 2004;63:658-663.
119. Ryan CM, Freed MI, Rood JA, Cobitz AR, Waterhouse BR, Strachan MW. Improving metabolic control leads to better working memory in adults with type 2 diabetes. Diabetes Care 2006 29:345-351.
120. Logroscino G, Kang JH, Grodstein F. Prospective study of type 2 diabetes and cognitive decline in women aged 70-81 years. BMJ 2004; 328(7439):548.
121. Leszek J, Malyszczak K, Bartys A, Staniszewska M, Gamian A. Analysis of serum of patients with Alzheimer's disease for the level of advanced glycation end products. Am J Alzheimers Dis Other Demen 2006;21:360-365.
122. Riederer P, Hoyer S. From benefit to damage. Glutamate and advanced glycation end products in Alzheimer brain. J Neural Transm 2006;113:1671-1677.
123. Sasaki N, Fukatsu R, Tsuzuki K, Hayashi Y, Yoshida T, Fujii N, Koike T, Wakayama I, Yanagihara R, Garruto R, Amano N, Makita Z. Advanced glycation end products in Alzheimer's disease and other neurodegenerative diseases. Am J Pathol 1998;153:1149-1155.
124. Sato T, Shimogaito N, Wu X, Kikuchi S, Yamagishi S, Takeuchi M. Toxic advanced glycation end products (TAGE) theory in Alzheimer's disease. Am J Alzheimers Dis Other Demen 2006;21:197-208.
125. Craft, S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. Curr Alzheimer Res 2007;4:147-152.
126. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004;3:169-178.
127. Risner ME, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM, Zvartau-Hind ME, Hosford DA, Roses AD; Rosiglitazone in Alzheimer's Disease Study Group. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J 2006;6:246-254.
128. Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, Fishel MA, Kulstad JJ, Green PS, Cook DG, Kahn SE, Keeling ML, Craft S. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. Am J Geriatr Psychiatry 2005;13:950-958.
129. Yaffe K. Metabolic syndrome and cognitive decline. Curr Alzheimer Res 2007a; 4:123-126.
130. Yaffe K, Haan M, Blackwell T, Cherkasova E, Whitmer RA, West N. Metabolic syndrome and cognitive decline in elderly Latinos: findings from the Sacramento Area Latino Study of Aging study. J Am Geriatr Soc 2007b;55:758-762.
131. Yaffe K. Metabolic syndrome and cognitive disorders: is the sum greater than its parts ? Alzheimer Dis Assoc Disord 2007;21:167-171.
132. Vanhanen M, Koivisto K, Moilanen L, Helkala EL, Hänninen T, Soininen H, Kervinen K, Kesäniemi YA, Laakso M, Kuusisto J. Association of metabolic syndrome with Alzheimer's disease: a population based study. Neurology 2006;67:843-847.
133. Schobab LA, Hsiung GY, Feldman HH. Cholesterol in Alzheimer's disease. Lancet

Neurol 2005;4:841-852.
134. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.
135. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott DJ, Sweeney BJ, Twomey C, Westendorp RG; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (Prosper): a randomised controlled trial. Lancet 2002;360:1623-1630.
136. Sparks DL, Sabbagh MN, Connor DJ, Lopez J, Launer LJ et al. Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. Arch Neurol 2005;62:753-757.
137. Whitmer RA, Gunderson EP, Quesenberry CP Jr, Zhou J, Yaffe K.Body mass index in midlife and risk of Alzheimer disease and vascular dementia. Curr Alzheimer Res 2007;4:103-109.
138. Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005;330 (7504):1360.
139. Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. Arch Intern Med 2003;163:1524-1528.
140. Hayden KM, Zandi PP, Lyketsos CG, Khachaturian AS, Bastian LA, Charoonruk G, Tschanz JT, Norton MC, Pieper CF, Munger RG, Breitner JC, Welsh-Bohmer KA; Cache County Investigators. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. Alzheimer Dis Assoc Disord 2006;20:93-100.
141. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. Lancet Neurol 2006;5:735-741.
142. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 2006;63:530-538.
143. Han L, McCusker J, Abrahamowicz M, Cole M, Capek R. The temporal relationship between depression symptoms and cognitive functioning in older medical patients - prospective or concurrent? J Gerontol A Biol Sci Med Sci 2006;61:1319-1323.
144. Yaffe K, Blackwell T, Barnes DR, Ancoli-Israel S, Stone KL, Study of Osteoporotic Fractures Group. Cognitive decline is associated with sleep disturbance in older community dwelling women. Neurology 2006;66 (suppl.2): A5.
145. Tworoger SS, Lee S, Schernhammer ES, Grodstein F. The association of self-reported sleep duration, difficulty sleeping and snoring with cognitive function in older women. Alzheimer Diss Assoc Disord 2006;20: 41-48.
146. Blackwell T, Yaffe K, Ancoli-Israel S, Schneider JL, Cauley JA, Hillier TA, Fink HA, Stone KL, Study of Osteoporotic Fractures Group. Poor sleep is associated with impaired cognitive function in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 2006;61:405-410.
147. Yaffe K, Blackwell T, Barnes DR, Ancoli-Israel S, Stone KL, Study of Osteoporotic Fractures Group. Preclinical cognitive decline and subsequent sleep disturbance in older women. Neurology 2007b;69:237-242.
148. Alchanatis M, Zias N, Deligiorgis N, Liappas I, Chroneou A, Soldatos C, Roussos C. Comparison of cognitive performance among different age groups in patients with obstructive sleep apnea. Sleep Breath 2008;12:17-24.
149. Spira AP, Blackwell T, Stone KL, Redline S, Cauley JA, Ancoli-Israel S, Yaffe K. Sleep-disordered breathing and cognition in older women. J Am Geriatr Soc 2008;56:45-50.
150. Goldman SE, Stone KL, Ancoli-Israel S, Blackwell T, Ewing SK, Boudreau R, Cauley JA, Hall M, Mattehws KA, Newman AB. Poor sleep is associated with poorer physical performance and greater functional limitations in older women. Sleep 2007;30:1317-1324.
151. Forti P, Maioli F, Pisacane N, Rietti E, Montesi F, Ravaglia G. Atrial fibrillation and risk of dementia in non-demented elderly subjects with and without mild cognitive impairment. Neurol Res 2006;28:625-629.
152. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. Arch Intern Med 2006;166:1003-1008.
153. de la Torre JC. How do heart disease and stroke become risk factors for Alzheimer's disease? Neurol Res 2006;28:637-644.
154. Polidori MC, Mariani E, Mecocci P, Nelles G. Congestive heart failure and Alzheimer's disease. Neurol Res 2006;28:588-594.
155. Beeri MS, Rapp M, Silverman JM, Schmeidler J, Grossman HT, Fallon JT, Purohit DP, Perl DP, Siddiqui A, Lesser G, Rosendorff C, Haroutunian V. Coronary artery disease is associated with Alzheimer disease neuropathology in APOE4 carriers. Neurology 2006;66:1399-1404.
156. Yeo LH, Horan MA, Jones M, Pendleton N. Perceptions of risk and prevention of dementia in the healthy elderly. Dement Geriatr Cogn Disord 2007;23:368-371.