Risk Profiles of Alzheimer Disease

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ABSTRACT: Alzheimer disease (AD) is a dementing, neurodegenerative disorder that affects approximately 500,000 Canadians and its prevalence is expected to double over the next 30 years. Although several medications may temporarily augment cognitive abilities in AD, there presently exists no proven method to avoid the inevitable clinical deterioration in this devastating condition. The delineation of risk factors for the development of AD offers hope for the advent of effective prevention or interventions that might retard the onset of symptoms. In this article, we provide a comprehensive review of midlife risk factors implicated in the etiopathogenesis of sporadic AD. Although some risk factors are heritable and largely beyond our control, others are determined by lifestyle or environment and are potentially modifiable. In a companion paper, we introduce the concept of an Alzheimer Risk Assessment Clinic for ascertainment and mitigation of these and other putative dementia risk factors in middle-aged adults.

RÉSUMÉ: Profils de risque de la maladie d'Alzheimer. La maladie d'Alzheimer (MA) est une maladie neurodégénérative provoquant une démence, qui touche à peu près 500,000 Canadiens. On s'attend à ce que sa prévalence double au cours des 30 prochaines années. Bien que plusieurs médicaments puissent accroître les capacités cognitives de façon temporaire dans la MA, il n'existe actuellement pas de méthode qui se soit avérée efficace pour éviter la détérioration clinique inexorable observée au cours de cette maladie dévastatrice. La caractérisation de ses facteurs de risque suscite l'espoir qu'une prévention efficace ou des interventions qui retardent le début des symptômes puissent être développées. Nous faisons dans cet article une revue exhaustive des facteurs de risque de l'âge moyen qui sont impliqués dans l'étiopathogenèse de la MA sporadique. Bien que certains facteurs de risque soient transmis de façon héréditaire et donc en dehors de notre contrôle, d'autres sont déterminés par notre style de vie ou par l'environnement et sont potentiellement modifiables. Dans un article qui accompagne celui-ci nous introduisons le concept d'une clinique d'évaluation du risque de la maladie d'Alzheimer et d'autres démences reconnues, pour les identifier et les minimiser chez des adultes d'âge moyen.

1. Introduction

Alzheimer's disease (AD) is a dementing illness characterized by progressive neuronal degeneration, gliosis and the accumulation of intracellular inclusions (neurofibrillary tangles) and extracellular deposits of amyloid (senile plaques) in discrete regions of the basal forebrain, hippocampus, and association cortices[1]. Alzheimer's disease afflicts approximately 5-10% of North Americans over the age of 65 and 30-50% of those who survive to the end of their ninth decade. There are currently ~500,000 Canadians with AD, a number that has more than doubled since 1980 and is expected to rise to over 1.3 million by 2050 as the population ages[2]. Over twice these numbers are projected to suffer from mild cognitive impairment (MCI), a frequent harbinger state of AD featuring cognitive dysfunction (usually memory) that fails to meet dementia criteria. According to estimates of the Alzheimer's Association and the National Institute on Aging, direct and indirect annual costs of caring for individuals with AD in the US exceed $100 billion. Although several medications (cholinesterase inhibitors, NMDA antagonists) may temporarily enhance cognitive abilities in AD, there is presently no proven method to attenuate brain cell attrition and inevitable clinical decline in this disease. In parallel with the intense activity to develop effective neuroprotection for established disease, resources are being mobilized world-wide to delineate risk factors and implement preventive measures in a concerted effort to forestall the anticipated AD epidemic[3,4].

The identification of risk factors for the development of AD offers hope for the advent of effective prevention or interventions that might, at least, delay the onset of symptoms. *Whereas several of these risk factors are heritable and largely beyond our control, others are determined by 'environment' or 'lifestyle' and may be modifiable.* The objective of this article is to review our current understanding of midlife risk factors implicated in the pathogenesis of sporadic AD, with emphasis on potentially modifiable risk where applicable. In a companion article in this issue[5], we introduce the concept of an Alzheimer

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Risk Assessment Clinic (ARAC), a tertiary care facility for dementia risk ascertainment and mitigation recently established at the Jewish General Hospital (McGill University, Montreal).

2. ALZHEIMER DISEASE RISK FACTORS

We find it useful to classify midlife risk factors of sporadic AD in five major categories or profiles: 1) Genetic, 2) Metabolic, 3) Nutritional, 4) Cognitive and 5) Psychological (designated P1-5, respectively). These groupings are not mutually exclusive and individuals may manifest no, one or combinations of risk factors within these domains. The various factors comprising these risk profiles are described below and summarized in the Table.

2.1 Genetic Risk Profile (P1)

Alzheimer disease has a well-defined genetic component in some pedigrees. While certain genetic mutations behave in an autosomal dominant fashion predisposing to early-onset *familial* AD, others serve as modifiers conferring increased risk of *sporadic*, usually late-onset AD. The following are examples of genetic factors implicated in the pathogenesis of AD.

(i) First-degree relatives: Some studies have investigated the relative risk of AD in first-degree relatives of index cases. In a study by Farrer et al[6], relatives of patients with Parkinson disease (PD) were used as a control group. They found that the total lifetime risk of developing dementia was similar among first-degree relatives of patients with AD and those of patients with PD. However, the age-specific risks differed substantially: between the ages of 65 and 80, relatives of patients with AD had a twofold to fourfold increased risk of dementia. Equal risks

were found for parents and siblings and for male and female relatives after adjustment for sex-specific patterns of survivorship. The authors interpreted their results as further supporting the view that a minority of AD cases are caused by a fully penetrant autosomal dominant gene, whereas other, clinically-indistinguishable, cases are of polygenic or multifactorial origin. Twin studies have also been used to assess the heritability of AD. In one such study, Gatz et al[7], found that the concordance rate for AD was 67% among monozygotic pairs and 22% for dizygotic pairs. The heritability of AD was estimated to be 74% with the remaining variance attributable to environmental influences.

(ii) Down's Syndrome: Down's syndrome (DS) is the most common clinical syndrome associated with mental handicap and occurs in about 1 per 1000 live births[8]. Individuals with DS are at an increased risk for developing AD later in life. After the age of 35, nearly all people with DS develop hallmark neuropathological features of AD, *viz.,* senile plaques comprised of β-amyloid and neurofibrillary tangles containing hyper-phosphorylated tau protein[9].

(iii) Amyloid Precursor Protein (APP), Presenilin-1 (PS1), Presenilin-2 (PS2): Familial AD is a rare, early-onset form of the disease (<2% of all AD cases) that is caused most commonly by point mutations in amyloid precursor protein (*APP*) on chromosome 21, presenilin-1 (*PS1*) on chromosome 14, and presenilin-2 (*PS2*) on chromosome 1. While penetrance of *PS2* mutations is variable[10], mutations in *APP* and *PS1* show virtually 100% penetrance[11].

(iv) ApoE: The apolipoprotein E (*APOE*) gene on chromosome 19 is recognized as a major risk factor for the

Table: Alzheimer risk profiles (P1-5)

Genetic Risk Profile (P1)	Metabolic Risk Profile (P2)	Nutritional Risk Profile (P3)	Cognitive Risk Profile (P4)	Psychological Risk Profile (P5)
First-degree relatives	**Vascular Factors**	'Mediterranean' diet	Education	Stress
Down Syndrome	Hypertension	Vitamin C	Cognitive engagement	Depression
Amyloid Precursor Protein (*APP*)	Cerebral Ischemia/Hypoxia	Vitamin E	Social Stimulation	Schizophrenia
Presenilin-1 (*PS1*)	Exercise	Folate	Traumatic brain injury	Personality
Presenilin-2 (*PS2*)	**Endocrine Factors**	Vitamin B6	Parkinson disease	
Apolipoprotein E (*APOE*)	Insulin/glucose	Vitamin B12	Amyotrophic lateral sclerosis	
GSTM3	Lipids	Homocysteine	Progressive supranuclear palsy	
Hfe	Metabolic syndrome	Thiamine (Vitamin B1)	Epilepsy	
TfR2	Sex hormones	Niacin		
ABCA1	Glucocorticoids	Omega-3 fatty acids		
ABCA2	Thyroid hormone	Coffee		
GAPD	Melatonin	Alcohol		
IL-10	**Toxic Factors**			
BDNF (Val66Met)	Medications			
IDE region	Vaccinations			
TOMM40	Illicit drugs			
CLU (*APOJ*)	Workplace/environmental exposures			
PICALM region	Heavy Metals			
	Pesticides/herbicides			
	Inflammatory Factors			
	Cystatin C			
	α_1-Antitrypsin			
	Nonsteroidal anti-inflammatory drugs			

development of late-onset, sporadic AD. Three alleles of this gene, ε2, ε3 and ε4, code for three isoforms of the apoE glycoprotein. Lipoproteins are responsible for transporting cholesterol, triglycerides and other lipids[12]. The three isoforms differ in their affinities for low or high density lipoprotein (LDL, HDL) receptors, their stability, folding characteristics, and their ability to transport cholesterol and phospholipids within the brain[13]. ApoE4 preferentially binds to lower density lipoproteins, while apoE3 binds to higher density lipoproteins[14]. ApoE3 can form homodimers which affects its lipid binding and also reduces its affinity for the LDL receptor[15]. ApoE4 has the lowest stability of all three isoforms and has the greatest propensity to aggregate. Possessing one or two copies of the ε4 variant substantially increases the risk of developing sporadic AD[16,17]. Corder and colleagues[18] were among the first to report a gene dosage effect for AD risk, with odds ratios of 3.2 (95% confidence interval [CI], 2.9-3.5) and 11.6 (8.9-15.4) for carriers of one or two ε4 alleles, respectively, relative to *ε3/ε3* individuals. The deleterious effect of the ε4 allele appears to be more pronounced in women than in men[19,20]. *E*4 carriage may be associated with disadvantages related to sterol homeostasis, membrane repair and other important cellular activities that may impact various central nervous system (CNS) conditions[17]. The latter include augmented tau hyperphosphorylation and the formation of neurofibrillary tangles[21], less efficient clearance of β-amyloid[22], and increased vulnerability to aberrant degradation[23]. Importantly, the potency of various *modifiable* AD determinants (see below) and responsiveness to intervention are often significantly impacted by the presence or absence of the *ε4* allele[17]. The *APOE ε2* allele, on the other hand, appears to be a protective factor against sporadic AD[24].

(v) GSTM3, hfe and TfR2: There is a fairly wide consensus implicating oxidative stress (free radical damage) in the pathogenesis of AD[25,26]. *Glutathione-S-transferase M3 (GSTM3)* is a brain-specific enzyme that accumulates in senile plaques and neurofibrillary tangles[27]. A polymorphism (rs7483) of this gene has been linked to the development of sporadic AD, possibly by diminishing brain antioxidant defenses within affected individuals[28]. The *Hfe* gene codes for a protein that is expressed in brain and is involved in tissue iron homeostasis. Two common mutations of this gene (C282Y and H63D) are responsible for hereditary hemochromatosis (HH), a systemic iron-overload disorder. Several research groups[29-31], but not others[32], garnered evidence that heterozygosity at these loci may predispose to sporadic AD, possibly by augmenting brain iron deposition. *Transferrin C2:* Transferrin plays a central role in the distribution of body iron and excessive deposits of this redox-active metal in affected brain is characteristic of AD, PD and other aging-related neurodegenerative conditions[25]. The transferrin *TfC2 allele*[33] reportedly occurs with greater frequency in patients with sporadic AD compared to non-demented controls 34 and may further accelerate the clinical appearance of the disease in *APOE* ε4-positive subjects[35].

(vi) Other genes: Other genetic modifiers that may predispose to the development or earlier expression of sporadic AD include variants of the *ABCA1*[36] and *ABCA2*[37] genes, alterations in multiple *GAPD* gene family members[38], polymorphisms of the *IL-10* gene promoter[39], the Val66Met polymorphism of the *BDNF* gene[40], and a variable 276 kb region harbouring the *IDE*

gene[41]. More recently, variants of the *TOMM40* gene, which codes for a channel-forming subunit of a mitochondrial outer membrane protein translocase, have been implicated as fairly robust modifiers of the age of onset of sporadic AD in *APOE* ε3-positive subjects[42]. A genome-wide association study involving over 16,000 individuals also disclosed a significant association of sporadic AD with the *CLU (APOJ)* gene and a region 5' of the *PICALM* gene, two loci not previously suspected to be affiliated with the disease[43]. This listing of potential genetic risk factors is incomplete but suffices to illustrate the remarkable diversity of heritable influences implicated in the expression of 'sporadic' AD.

2.2 Metabolic Risk Profile (P2)

The 'Metabolic' AD risk category comprises a broad range of proven and suspected physiological and biochemical vulnerabilities which may be further organized within (i) Vascular, (ii) Endocrine, (iii) Toxic and (iv) Inflammatory sub-domains.

2.2.1 Vascular Factors

Several risk factors for heart disease in old age have also emerged as important risk factors for dementia and AD[44].

(i) Hypertension: There is fairly robust evidence linking midlife hypertension to the development of dementia in later life. Kivipelto et al[45] found that individuals with raised systolic blood pressure (>160 mm Hg) at midlife had a significantly higher risk of AD later in life, whereas diastolic blood pressure did not significantly impact future AD risk. Enhanced cardiovascular disease may, in part, mediate the augmented AD risk conferred by midlife systolic hypertension. Hypertension is associated with a greater prevalence of silent brain infarction[46], brain atrophy, cerebrovascular atherosclerosis and increased burden of subcortical white matter lesions commonly found in AD[47]. Hypertension may also directly contribute to cerebrovascular permeability, protein extravasation, and formation of neurofibrillary pathology in the brains of patients with AD[48].

Epidemiological studies have suggested that use of blood pressure lowering medications in patients with cardiovascular disease may mitigate the risk of dementia or cognitive decline later in the senium[49,50].

(ii) Cerebral Ischemia/Hypoxia: Cerebral ischemia may promote AD-type changes in the aging brain. The risk of developing AD, and not merely vascular dementia, is significantly increased in individuals with stroke or transient ischemic attacks[51]. Ischemia-related AD pathology may complicate atherosclerotic, congophilic (amyloid) and immune-mediated cerebrovascular disease. Cerebral hypoxia accruing from sleep apnea has been linked to AD[52,53] and, intriguingly, the *APOE* ε4 allele is purportedly over-represented in subjects with this respiratory disorder[54-57]. Among other possible mechanisms, hypoxia is believed to facilitate AD pathogenesis though increased gene expression of β-site APP cleavage enzyme 1 (BACE1), which results in increased β-amyloid production[58].

(iii) Exercise: The benefits of physical activity at all ages as a pivotal component of healthy lifestyle choice are well established. With regard to cognitive health, several longitudinal cohort and cross-sectional observational studies suggest that

regular leisure exercise may decrease the risk of developing dementia in late-life[59-61]. This protective effect against cognitive decline may be mediated through several mechanisms. One possibility is by reducing other vascular morbidities, such as hypertension, diabetes, hypercholesterolemia and obesity[45]. Some studies suggest that neurobiological pathways may be involved more directly, including enhanced neurotrophic factor gene expression, promotion of neuroplasticity, alleviation of brain amyloid burden, increased cognitive reserve and possible benefits of associated psychosocial factors[62]. The *APOE* status may interact with physical activity to differentially protect against dementia. In one study, Rovio et al[62] found that the decrease in risk of dementia associated with physical activity was more pronounced among *APOE* ε4 carriers than non-carriers. This effect may be due to inefficient neural repair mechanisms in *APOE* ε4 carriers, which renders them more dependent on lifestyle-related factors (e.g. exercise) to protect them against dementia and AD[62,63]. These findings are encouraging because they highlight the possible influence of positive lifestyle choices in individuals with genetic susceptibility to AD[17].

While many studies have found positive correlations between physical activity and decreased risk of dementia, the intensity, frequency, duration and type of exercise that are most beneficial have not been elucidated. Rolland et al[64] summarized the somewhat arbitrary measures used to evaluate physical activity. For instance, Rovio et al[65] found that "leisure-time physical activity that lasts at least 20-30 minutes and causes breathlessness and sweating" at least twice a week reduced the risk of AD. Andel et al[59], on the other hand, chose to grade the intensity and not the duration or frequency of the exercise and found that light exercise such as gardening or walking and particularly regular exercise involving sports were associated with reduced odds of dementia compared with minimal exercise. The variable measures used in these studies render it difficult to offer specific recommendations about physical activity to the general public in terms of AD risk prevention. However, given the positive effects of exercise on general health promotion and the many significant associations found between reduced risk of dementia and even light physical activity, age-appropriate levels of physical fitness should be widely encouraged.

2.2.2 Endocrine Factors

(i) Insulin/glucose: Several longitudinal studies have noted an association between midlife diabetes and late-life dementia[66-68]. In addition to diabetes, impaired insulin responsiveness and insulin resistance have also been independently linked to dementia. Insulin-resistance syndrome is characterized by obesity, heart disease, impaired fasting glucose, impaired glucose tolerance, high blood pressure, abnormal cholesterol levels, and kidney damage, and is a frequent harbinger of type-2 diabetes[69]. This syndrome is associated with both AD and vascular dementia[70], suggesting a mechanism involving diabetic microvascular disease[71]. Impaired acute insulin response (AIR) is another form of impaired glycemic control. Acute insulin response is more strongly associated with clinical AD than the previous syndrome[70] and may increase AD risk via interactions between insulin and β-amyloid degrading enzymes within the brain[72]. Of note, *APOE* ε4-positive individuals with type-2

diabetes have about twice the risk of developing AD, compared to those without diabetes[73].

(ii) Lipids: Several studies have observed an association between high serum cholesterol levels and an increased risk of developing AD[74,75]. Kivipelto et al[75] demonstrated that elevated levels of total cholesterol level at midlife significantly enhanced the risk of developing AD independently of *APOE* ε4 allele status and the presence of systolic hypertension. *Lipid Lowering Agents:* Recognition of midlife hypercholesterolemia as a risk factor for AD[45] prompted interest in the potential use of lipid-lowering agents in reducing the risk of the disease. An initial case-control study suggested that lipid-lowering agents may confer cognitive benefits in individuals younger than 80 years of age[76]; however, subsequent studies including one randomized controlled trial (RCT)[77] have failed to replicate this finding[78,79].

(iii) Metabolic syndrome: Metabolic syndrome (MetS) refers to a constellation of risk factors for cardiovascular disease and type-2 diabetes including central obesity, elevated plasma glucose, high blood pressure, atherogenic dyslipidemia, a prothrombotic state, and a pro-inflammatory state[80]. While these factors are known to be particularly detrimental to dementia risk in elderly persons[81], some studies have linked midlife MetS components with increased risk of late-life dementia[44,50]. In a retrospective study, Whitmer et al[50] demonstrated that multiple cardiovascular risk factors, specifically smoking, hypertension and high cholesterol, substantially increased the risk of late-life dementia in a dose-dependent manner.

(iv) Sex hormones: Between 1980 and 2000, several studies suggested that estrogen replacement therapy may improve cognitive performance[82,83] and enhance the positive effects of acetylcholinesterase inhibitors in menopausal women with AD[84]. This view was tempered after the Women's Health Initiative Memory Study (WHIMS), which contained a sample size of over 7,000 women, failed to replicate this finding[85], although the generalizability of this study has been challenged on methodological grounds[86]. Some studies have indicated a possible gene-environment interaction between estrogen and the *APOE* ε4 allele. Notably, Yaffe et al[87] found that estrogen replacement therapy was correlated with less cognitive decline only in women lacking the ε4 allele. Mortensen and Høgh[20] found that the *APOE* ε4-positive women exhibited significantly steeper declines on several cognitive tests between ages 70 and 80 than did non-carriers. The *APOE* ε4 allele was associated with age-related deterioration of cognitive functions in women only, suggesting that the allele may have a sex-specific impact on risk of cognitive decline. Currently, prescribing estrogen to postmenopausal women is not recommended as a means of reducing the risk of developing AD[88]. In men, some evidence suggests that higher levels of free testosterone may confer protection against AD[89].

(v) Glucocorticoids: Elevated levels of circulating and salivary glucocorticoids have been reported in patients with AD. Moreover, clinical and experimental observations suggest that glucocorticoids may adversely affect hippocampal function and cognition in humans[90-93]. Green et al[94] reported that gluco-corticoid administration increases the formation of the β-amyloid peptide by augmenting the steady-state levels of amyloid precursor protein (APP) and β-APP cleaving enzymes.

They also found that glucocorticoids increase tau accumulation, potentially exacerbating neurofibrillary tangle formation.

(vi) Thyroid hormone: One study disclosed a possible link between hyperthyroidism and increased AD risk. The Rotterdam Study found that participants aged 55 years and over with suppressed levels of thyroid stimulating hormone (TSH) were about three times more likely to develop dementia and AD[95].

(vii) Melatonin: Melatonin, an indoleamine secreted by the pineal gland, is a potent free radical scavenger[96]. Melatonin inhibits β-amyloid generation and fibrillization[97] and attenuates tau hyperphosphorylation[98]. As such, the hormone may confer cytoprotection in AD-affected neural tissues.

2.2.3 Toxic Factors

Toxic substances derived both *exogenously* (from the environment) and *endogenously* (metabolic by-products) have been implicated in the development of AD and other dementias. Exogenous toxins are considered here; endogenous toxins, such as homocysteine, are discussed below.

(i) Medications: Benzodiazepines: The relationship of benzodiazepine use in elderly and midlife populations and cognition was investigated by several groups with conflicting results. A systematic review[99] of six prospective studies concluded that exposure to benzodiazepines at any time was associated with an enhanced risk of cognitive decline in three of the studies, decreased risk in two, and was unchanged in one study.

The roles of lipid-lowering agents and non-steroidal anti-inflammatory medications as potential modifiers of AD are discussed in Sections 2.2.2 and 2.2.4, respectively.

(ii) Vaccinations: Viral infection and attendant immunological changes have been implicated in the development of AD. There is evidence suggesting that vaccination against diphtheria, tetanus, poliomyelitis or influenza is associated with a lower risk of AD than no vaccination[100,101].

(iii) Illicit drugs: Illicit drug use may increase the risk of AD. Methamphetamine abuse, in particular, has been linked to long-term neuronal damage[102], which may curtail cognitive reserve and increase susceptibility to AD later in life. The relationship to other illicit drugs is less well understood and remains difficult to analyze in a systematic fashion.

(iv) Workplace/environmental exposures:

Heavy Metals: Exposure to heavy metals has been associated with cognitive deficits and AD. In a recent study[103], retained cumulative dose of iron resulting from previous environmental exposure was associated with lower test scores in seven cognitive domains. Some studies have linked aluminum exposure in drinking water to increased risk of AD[104], though this topic remains controversial. Inorganic mercury has also been identified as one of the potential exogenous risk factors for AD. The main source of inorganic mercury in developed countries is dental amalgam[105]. The putative role of heavy metals in AD has lead to the experimental use of chelating agents as a potential therapy for the disease[106].

Pesticides/herbicides: In a longitudinal population based study in Manitoba, Canada, occupational exposure to fumigants or defoliants significantly increased the incidence of AD[100]. Other studies also found an association between occupational exposure to pesticides, low cognitive performance, and an increased risk of developing AD[107,108]. Although 'level 1' evidence linking workplace toxins to AD may never materialize, the use of protective clothing under such circumstances to limit the potential risk of cognitive decline in later life would seem prudent[88].

2.2.4 Inflammatory Factors

Animal models and human neuropathological studies have implicated neuroinflammation in the pathogenesis of AD. Markers of inflammation, including reactive microglia, chemokines, pro-inflammatory cytokines and deposits of C-reactive protein, have been found in and around amyloid plaques and may contribute to the neurodegenerative process in AD brain[109,110]. Some have argued further that peripheral inflammatory processes, e.g. incurred by chronic infections or rampant atherosclerosis, may also play a role in the etiopathogenesis of AD in genetically predisposed persons[111].

(i) Cystatin C: Experimental, genetic and clinical research suggests that increased activity of cystatin C, an endogenous cysteine protease inhibitor, in the brain may protect against the development of AD, possibly by binding and preventing the aggregation of β-amyloid[112]. Sundelöf and colleagues[113] reported a decline in serum cystatin C preceding clinically manifest AD in elderly men free of dementia at baseline, suggesting that cystatin C measurement may prognosticate AD risk in elderly individuals.

(ii) α1-Antitrypsin: Levels of α1-antitrypsin, a protease inhibitor and acute phase reactant, are elevated in AD plasma and affected brain parenchyma. Novel heme oxygenase-1 suppressor (HOS) activity ascribed to this protein may curtail heme oxygenase-1-dependent derangement of cerebral iron homeostasis and thereby afford some protection against the disease[114].

(iii) Nonsteroidal anti-inflammatory drugs (NSAIDs): Several recent surveys have investigated the possible role of NSAID use in decreasing the risk of AD[115,116]. Most reviews concluded that NSAIDs are beneficial in lowering the risk of dementia and AD. However, other randomized controlled trials failed to find an association between NSAID exposure and a decreased risk of AD[117,118]. Nonsteroidal anti-inflammatory drugs use may even be associated with increased neuritic plaque formation[119]. It has been suggested that these discrepancies may be due to the timing, type, and/or dosage of NSAIDs used[120]. Therefore, there is currently insufficient evidence to recommend prescribing NSAIDs for the specific intention of reducing the risk of dementia or AD[88].

2.3 Nutritional Risk Profile (P3)

(i) "Mediterranean" diet: The Mediterranean-type diet has been associated with numerous health benefits, including reduced risk of cardiovascular disease, cancer[121] and mortality[122]. The diet comprises a high intake of plant foods (fruits, vegetables, legumes, nuts, and cereals), fish and olive oil, and low consumption of meat, poultry and high-fat milk products. The diet has recently been linked to a reduced risk of late-life cognitive decline[123,124], MCI, AD, and conversion from

584

MCI to AD[125]. It is the opinion of some that the Mediterranean-type diet should not be recommended as a matter of policy for AD prevention until stringent (level 1), generalizable data becomes available in support of this intervention[123]. While such evidence would be welcome, we feel that the potential benefits of this diet, to the extent that we currently understand them, should be discussed with all persons actively inquiring about personal dementia risk and strategies for its mitigation.

(ii) Vitamins C and E: Oxidative stress and free radical damage have been heavily implicated in the etiopathogenesis of MCI and AD[26,126]. The results of several epidemiological surveys suggested that increased consumption of the antioxidants vitamin E and vitamin C via the diet (mainly fruits and vegetables) or nutraceutical supplementation may lower the risk of developing AD[127-129]. Other studies, however, have failed to corroborate these associations[130,131] and treatment with vitamin E did not forestall conversion from MCI to AD in a large industry-sponsored multi-centre trial[132].

(iii) Folate, vitamin B_6, vitamin B_{12} and homocysteine: Low blood levels of folic acid[133,134] and increased plasma homocysteine have been posited as risk factors for the development of AD and dementia. Plasma homocysteine may augment AD risk independently or by accelerating vascular risk factors such as coronary artery disease, carotid atherosclerosis, and clinical stroke[111,135]. In a recent Swedish study, serum levels of homocysteine and holotranscobalamin (the active component of vitamin B_{12}) were, respectively, positively and negatively correlated with risk of incident AD after adjusting for age, sex, education, smoking, blood pressure, body-mass index, stroke, mini-mental state examination scores and *APOE* ε4 allele status[136]. Plasma homocysteine levels can be lowered by supplementation with folic acid, vitamin B_{12} and vitamin B_6[137-139] and may therefore constitute an attractive target in AD prevention. Indeed, a recent RCT found that treatment with homocysteine-lowering B vitamins slowed the rate of brain atrophy in elderly individuals with MCI. An accelerated rate of atrophy was associated with lower final cognitive test scores[140]. Another study[141] also found that three-year folic acid supplementation in men and women aged 50-70 years with elevated plasma total homocysteine was associated with improved performance in memory, sensorimotor speed, complex speed, information processing speed and word fluency, compared to a placebo group. However, several other studies failed to reproduce these positive results. For example, it was disappointing that in a two-year, double-blind, placebo-controlled RCT involving 276 healthy seniors, homocysteine suppression with daily folate (1000 micrograms), vitamin B_{12} (500 micrograms) and vitamin B_6 (10 mg) engendered no discernible benefits on multiple tests of cognition[138]. Nor did daily supplementation with of B[12] (400 micrograms), folic acid (2 mg) and B_6 (25 mg) over two years improve cognitive function in hypertensive men aged 75 and older[142]. Similarly, in a meta-analysis of trials identified via the Cochrane Dementia and Cognitive Improvement Specialized Register Group, there were no salutary effects of 750 micrograms of folic acid per day on measures of cognition or mood in older healthy women and in patients with different forms of dementia[143]. Overall, clinical trials of B vitamin supplements involving patients with already

adequate B_{12} and folate status have proven negative, while cognitive function may be preserved or improved by such treatment in subjects recruited with suboptimal or borderline folic acid or B_{12} status[141,144].

Fortification of flour with folic acid was introduced in Canada in 1998 as a measure to prevent congenital birth defects. While some data suggest that this public health measure may have contributed to a reduction in the incidence of stroke in this country[145], no comparable information is available regarding the potential impact of this policy on the incidence of AD. Notwithstanding evidence that responsiveness to cholinesterase inhibitors in patients with established AD may be improved by administration of folic acid[132], further studies will be required before folate, vitamin B_6 or B_{12} can be advocated with confidence as a form of primary AD prevention.

(iv) Thiamine: Thiamine (Vitamin B_1) is involved in the presynaptic release and metabolism of acetylcholine[146,147] and its deficiency is associated with memory and cognitive deficits (Wernicke-Korsakoff syndrome)[148]. Thiamine deficiency has been linked to AD in some studies[146,149], but not others[150,151].

(v) Niacin: Niacin participates in DNA synthesis and stability[152] and exhibits antioxidant activity in brain mitochondria[153]. Supplemental intake of niacin has been associated with slower rates of cognitive decline and development of AD[154], although this relationship remains to be systematically tested.

(vi) Omega-3 fatty acids: Omega-3 fatty acids, such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and linolenic acid (LA), are essential for optimal functioning of cell and organellar membranes and, in brain, facilitate intercellular communication and the growth, maintenance and regeneration of neurites[155,156]. An investigation at the University of Guelph[157] found 30-40% lower circulating levels of DHA in individuals with AD and other forms of cognitive dysfunction relative to cognitively-healthy subjects. Moreover, large observational studies support the notion that fish consumption, a major source of omega-3 fatty acids, may substantially diminish the risk of AD and other dementias[132].

(vii) Coffee: Several studies have found that coffee consumption at midlife is associated with a decreased risk of dementia/AD later in life[158,159]. In a recent study, Eskelinena et al[160] found that the lowest risk category constituted those who drank three to five cups per day.

(viii) Alcohol: In the French PAQUID study, consumption of moderate quantities of red wine (250-500 mL/day) was associated with a lower risk of AD (RR, 0.53) and all-cause dementia (RR, 0.56)[161]. Similarly, in the Canadian Study of Health and Aging[60], a reduced risk of AD (OR, 0.49) was noted in persons consuming wine on a weekly or more frequent basis. The report of the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia concluded that "although there is insufficient evidence to make a firm recommendation for the primary prevention of dementia, physicians might choose to advise their patients about the potential advantages of moderate consumption of wine[88]".

2.4 Cognitive Risk Profile (P4)

Robust mental activity may forestall dementia by increasing cognitive reserve, operationally defined as the extent of brain deterioration a person can sustain before signs of cognitive impairment become manifest[162]. Factors considered to augment cognitive reserve include years of formal education, cognitive exercises and social interaction.

(i) Education: Years of formal education exert a fairly strong and reproducible impact on AD incidence[163]. In case-control studies, education years are often significantly lower in the AD groups than cognitively-normal individuals matched for age and other demographic and clinical variables. Although education may enhance cognitive reserve directly by influencing neural growth and synaptogenesis (plasticity) during critical periods, 'confounding' effects of genetic variation (which may impact scholastic achievement and AD risk independently) and socioeconomic status may be contributory[164].

(ii) Cognitive engagement: Participation in cognitive exercises and leisure intellectual activities has been associated with a reduced risk of developing AD. Cognitively stimulating leisure activities include reading, playing a musical instrument, doing crossword puzzles, writing for pleasure, etc[61,165]. Valenzuela and Sachdev[166] conducted a meta-analysis that included over 29,000 subjects from 22 longitudinal cohort studies to evaluate the effect of education levels, occupational complexity and mentally stimulating lifestyle pursuits on brain reserve and dementia. They found that participating in mentally stimulating leisure activities was associated with an overall risk reduction of 50% for dementia (OR 0.50, 95% CI, 0.42–0.61). A recent systematic review of leisure cognitive activities and their role in preventing dementia included thirteen observational studies, most of which were of cohort design[167]. No randomized controlled trials met inclusion criteria for the review. The authors concluded that while there is strong evidence supporting the notion that active engagement in leisure cognitive leisure activities during mid- or late life may mitigate the risk of AD and dementia, there are insufficient data to infer a direct causal relationship. They also noted that while certain cognitive activities appeared to be more favourable than others, proof of this assertion will require more rigourous analysis. Positive findings in the aforecited studies have provided impetus to the field of cognitive training aimed at maintaining or enhancing neuropsychological skills such as memory, reaction time, reasoning ability and attention. A randomized controlled trial[168] evaluated the effectiveness and durability of cognitive training interventions in improving targeted cognitive abilities in persons aged 65 to 94 years. The investigators found significant improvement in the areas of speed, reasoning and memory training immediately after the intervention period, as well as two years later in participants who received booster training. Valenzuela et al[169] performed a systematic review of randomized clinical trials with longitudinal follow-up to examine whether cognitive exercises can prevent the onset of dementia. They found that cognitive exercise training in healthy older individuals engenders strong and persistent protective effects on longitudinal neuropsychological performance. While the generalizability of this skill training to overall cognitive enhancement has been questioned by some[170,171], more recent controlled trials have shown that there is some transfer among brain training skills[172]. The application of cognitive enhancement has also fuelled the popularity of electronic gaming devices that incorporate brain-training programs. One research group conducted an RCT and found that brain plasticity-based computer games[172] may enhance cognitive function. Others have attained similar positive results using virtual reality training programs[173]. Overall, while brain-training computer games currently are too novel a phenomenon to guage their long-term contribution to AD risk reduction, they remain a promising area for research. Midlife individuals are encouraged to make use of these "brain-training" programs, as long as they do not replace all other forms of cognitive engagement (due to the aforementioned dispute over the generalizability of skills).

(iii) Social Stimulation: Social engagement, e.g. playing board games and participating in group discussions, has been implicated as an independent protective factor against AD, whereas loneliness, defined as the feeling of being disconnected from others, may increase risk of late-life dementia and rates of cognitive decline in the elderly[174]. Associations of AD with marital status have also been reported, with never-married individuals shouldering greater risk[175].

(iv) Traumatic brain injury: There is considerable evidence linking acute and chronic (repeated) traumatic brain injury (TBI) to cognitive decline and the development of dementia (pugilistica) and AD[176-181]. The latter may be proportional to the severity of head injury[176] and exacerbated in individuals harbouring *APOE* ε4 alleles[132]. Neuroinflammation, excitotoxicity, oxidative stress, caspase activation, ischemia, microhemorrhages, axonal shear injury, β-amyloid deposition and tau hyperphosphorylation are among the many mechanisms postulated to mediate the deleterious effects of TBI on AD risk[132]. Although acute traumatic brain damage is often accidental, chronic TBI accruing from participation in contact sports, such as boxing, ice hockey, American football, rugby, soccer and the martial arts, can be prevented by abstention or optimal use of protective headgear and adherence to safety guidelines[182,183].

(v) Parkinson's disease: Idiopathic Parkinson's disease (PD) is a degenerative disorder of the basal ganglia featuring resting tremor, bradykinesia, rigidity, postural instability, autonomic insufficiency and several pre-motor phenomena[184]. Parkinson's disease patients are almost twice as likely to develop dementia than control subjects[185], with earlier onset of the movement disorder (e.g ages 50-54) conferring greater dementia risk[186]. The dementia in this population may represent spread of Lewy body pathology (α-synucleinopathy) to cortical regions[187] and/or concomitant AD. In support of the latter formulation, diminished cerebrospinal fluid (CSF) concentrations of β-amyloid$_{1-42}$, an established biomarker of sporadic AD[188], was recently shown to be an independent predictor of cognitive decline in PD subjects[132].

(vi) Amyotrophic lateral sclerosis: Amyotrophic lateral sclerosis (ALS) is a fatal, aging-related neurodegenerative disorder characterized by progressive upper and lower motor neuron loss and weakness of skeletal muscles of the head, neck, trunk and limbs. Dementia is more frequent in ALS than in age-matched control subjects and may represent fronto-temporal lobe dementia (tauopathy) or co-existing AD[132].

(vi) Progressive supranuclear palsy: Progressive supranuclear palsy (PSP) is a rare neurodegenerative disease of the extrapyramidal motor system characterized by parkinsonism and supranuclear pareses of gaze. The histopathology of PSP features neurofibrillary tangles, glial tau inclusions, neuronal loss and gliosis[189]. Although tau pathology is common to both PSP and AD, there is no clinical or neuropathological evidence that AD is over-represented among individuals with PSP. Progressive supranuclear palsy patients carrying *APOE* ε4 alleles exhibit higher burdens of AD pathology, but this may be commensurate with findings in the general population[189].

(vii) Epilepsy: There is no definitive evidence that patients with chronic, intractable epilepsy are at an increased risk for developing AD later in life. However, cognitively intact individuals with epilepsy demonstrate enhanced APP expression and accelerated accretion of senile plaques in AD-prone neural tissues[190]. Chronic microglial activation and interleukin-1β secretion may promote brain amyloid deposition in epileptic persons[191,192], particularly in those individuals carrying an *APOE* ε4 allele[193].

(viii) Down's syndrome: The role of Down's syndrome as a predisposing factor for sporadic AD is discussed in section 2.1 (Genetic Risk Profile).

(ix) Human immunodeficiency virus (HIV): The availability of highly active retroviral therapy for HIV-infected patients suggests that in the future, there will be large numbers of long-term HIV survivors with AD brought on by advancing age[194]. HIV infected individuals are susceptible to HIV-associated neurocognitive disorders (HAND), such as the subcortical dementing illness known as the AIDS dementia complex. Some studies have raised the possibility that the presence of HAND may place individuals at higher risk for AD[195]. Indeed, a recent report indicated that CSF amyloid concentrations in HAND are similar to those seen in AD, suggesting that these neurological disorders may share common pathophysiological mechanisms[196].

2.5 Psychological Risk Profile (P5)

(i) Stress: Prolonged psychological stress has been associated with memory loss and hippocampal atrophy and may predispose to AD. Chronic stress engenders hypercortisolemia and augmented circulating and salivary cortisol levels have been reported in sporadic AD. As discussed above, adrenal glucocorticoids may be directly toxic to hippocampal neurons and may enhance tau hyperphosphorylation and the deposition of β-amyloid[132].

(ii) Depression: Several studies have shown an association between a history of depression and subsequent dementia, particularly AD. Other studies have also indicated a link between late-life depression and cognitive impairment. There remains considerable controversy whether late-life depression is a true risk factor for AD, an early or prodromal symptom of the illness, a psychological reaction to incipient memory failure or is altogether unrelated to dementia[197-200].

(iii) Schizophrenia: Deterioration in several cognitive domains occurs among other "negative" symptoms of chronic schizophrenia and this may be associated with atrophic changes within the brain. However, there is currently no convincing evidence of enhanced rates of AD among elderly schizophrenics, suggesting that midlife schizophrenia may not be a significant risk factor of the disease [201-204].

(iv) Personality: Personality consists of the psychological qualities that bring continuity to an individual across situations and time. The popular 'five-factor model' of personality encompasses the dimensions of neuroticism, openness to experience, conscientiousness, agreeableness and extra-version[205]. *Neuroticism*, a.k.a. distress proneness, a measure of an individual's tendency to experience negative emotions such as anxiety and anger, has been linked to excessive AD risk and accelerated cognitive decline[206]. On the other hand, conscientiousness, a tendency toward self-discipline and goal-direction, may diminish the risk of AD, MCI and cognitive decline[207].

In patients with various medical conditions, high levels of spirituality and religiosity have been associated with lower morbidity and mortality and enhanced quality of life[208], ascribed to bolstered immune profiles[209], lower rates of depression[210] and increased optimism and hope[211]. In a longitudinal study, higher levels of spirituality and private religious practices were associated with slower disease progression in patients with probable Alzheimer dementia[212].

CONCLUSIONS

In recent years, governments and private health foundations in industrialized countries have begun to implement systematic and multi-faceted strategies in a concerted effort to stem the impending AD epidemic. At the forefront of this campaign is recognition of the necessity to marry development of neuroprotective and disease-modifying pharmaceuticals (and possibly vaccines) with effective risk management and disease prevention. Considerable evidence amassed over the last decade has implicated a host of risk factors in the etiopathogenesis of sporadic AD. In this review, factors potentially predisposing to AD are classified according to five 'risk profiles': Genetic, Metabolic, Nutritional, Cognitive and Psychological. It is understood that these categories are not mutually-exclusive and persons may manifest multiple predisposing factors representing more than one risk domain. Importantly, while certain vulnerabilities are inherited and fixed, others are at least partly environmentally-determined and potentially modifiable by diet, lifestyle or medications. Examples of the latter include midlife hypertension, hyperlipidemia, dysregulated glucose/insulin homeostasis, inadequate intellectual or social engagement, high chronic anxiety and work- or sport-related TBI. Although the *APOE* ε4 allele is an 'uncontrollable' genetic factor that predisposes to the development of sporadic AD in its own right, its presence or absence impacts the strength or 'gain' of the association of various *modifiable* risk factors with the disease[17]. Disclosure of *APOE* ε4 status to middle-aged, cognitively-intact individuals concerned about AD risk has thus far proved to be psychologically and socially well-tolerated and may spur the adoption of lifestyle and dietary behaviors which serve to mitigate AD risk[132]. These considerations recently prompted us to re-visit the prospect that *presymptomatic APOE* testing might one day be deemed medically appropriate and ethical for the

purpose of AD risk ascertainment and prevention in individuals actively seeking such information[213].

If the current literature offers any indication, we may anticipate with confidence the rapid further accrual of new data defining novel susceptibility factors and preventive strategies for the management of sporadic AD. Fortunately, large-scale programs like "Prevent Alzheimer's Disease by 2020" in the US[4] and priority funding in this area by the Canadian Institutes of Health Research[214] have been deployed to confront this formidable health threat on our continent. As our populations age – and commensurate with the inexorable drive towards 'personalized medicine' and unprecedented access to biomedical information – it is fairly certain that an informed public will inquire increasingly about personal estimates of AD risk. To address these concerns directly, an Alzheimer Risk Assessment Clinic was established in Montreal in 2009 as described in a companion article in this issue of the *Journal*[5].

REFERENCES

1. Selkoe DJ. The molecular pathology of Alzheimer's disease. Neuron. 1991;6(4):487-98.
2. Rising tide: The impact of dementia on Canadian society: Alzheimer Society of Canada, 2010. http://www.alzheimer.ca.
3. Khachaturian ZS. A roadmap for the prevention of dementia II: Leon Thal Symposium 2008. Alzheimer Dement. 2009;5(2):85-92.
4. Khachaturian ZS, Khachaturian AS. Prevent Alzheimer's disease by 2020: a national strategic goal. Alzheimer Dement. 2009;5(2):81-4.
5. Schipper HM, Liberman A, Kelner N, et al. ARAC - The Montreal Jewish General Hospital Alzheimer Risk Assessment Clinic. Can J Neurol Sci. 2011;38(4):600-11.
6. Farrer LA, O'Sullivan DM, Cupples LA, Growdon JH, Myers RH. Assessment of genetic risk for Alzheimer's disease among first-degree relatives. Ann Neurol. 2004;25(5):485-93.
7. Gatz M, Pedersen NL, Berg S, et al. Heritability for Alzheimer's disease: the study of dementia in Swedish twins. J Gerontol. 1997;52A(2):M117-25.
8. Mann DMA. Alzheimer's disease and Down's syndrome. Histopathology. 1983;13:125-37.
9. Lott IT, Osann K, Doran E, Nelson L. Down syndrome and Alzheimer disease: response to donepezil. Arch Neurol. 2002;59(7):1133-6.
10. Rogaev EI, Sherrington R, Rogaeva EA, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. Nature. 1995;376(6543):775-8.
11. Rogaeva E, Tandon A, George-Hyslop PHS. Genetic markers in the diagnosis of Alzheimer's disease. J Alzheimers Dis. 2001;3(3):293.
12. Li WH, Tanimura M, Luo CC, Datta S, Chan L. The apolipoprotein multigene family: biosynthesis, structure, structure–function relationships, and evolution. J Lipid Res. 1988;29(3):245-71.
13. Zhong N, Weisgraber KH. Understanding the association of Apolipoprotein E4 with Alzheimer disease: clues from its structure. J Biol Chem. 2009;284:6027-31.
14. Weisgraber K. Apolipoprotein E distribution among human plasma lipoproteins: role of the cysteine-arginine interchange at residue 112. J Lipid Res. 1990;31:1503-11.
15. Weisgraber KH, Shinto LH. Identification of the disulfide-linked homodimer of apolipoprotein E3 in plasma. Impact on receptor binding activity. J Biol Chem. 1991;266:12029-34.
16. Hsiung G-YR, Sadovnick AD. Genetics and dementia: risk factors, diagnosis, and management. Alzheimers Dementia. 2007;3(4):418-27.
17. Schipper HM. Apolipoprotein E: Implications for AD neurobiology, epidemiology and risk assessment. Neurobiol Aging. doi:10. 1016/j.neurobiolaging.2009.04.021
18. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993;261(5123):921-3.
19. Fleisher A, Grundman M, Clifford RJ, et al. Sex, apolipoprotein E {varepsilon}4 status, and hippocampal volume in mild cognitive impairment. Arch Neurol. 2005;62(6):953-7.
20. Mortensen EL, Høgh P. A gender difference in the association between APOE genotype and age-related cognitive decline. Neurology. 2001;57:89-95.
21. Harris FM, Brecht WJ, Xu Q, et al. Carboxyl-terminal-truncated apolipoprotein E4 causes Alzheimer's disease-like neuro-degeneration and behavioral deficits in transgenic mice. Proc Natl Acad Sci. 2003;100(19):10966-71.
22. Bennett DA, Wilson RS, Schneider JA, et al. Apolipoprotein E {epsilon} 4 allele, AD pathology, and the clinical expression of Alzheimer's disease. Neurology. 2003;60(2):246-52.
23. Acharya P, Segall ML, Zaiou M, et al. Comparison of the stabilities and unfolding pathways of human apolipoprotein E isoforms by differential scanning calorimetry and circular dichroism. Biochim Biophys Acta. 2002;1584(1):9-19.
24. Raber J, Huang Y, Ashford J. ApoE genotype accounts for a vast majority of AD risk and AD pathology. Neurobiol Aging. 2004;25:641-50.
25. Moreira P, Honda K, Liu Q, et al. Oxidative stress: the old enemy in Alzheimer's disease pathophysiology. Curr Alzheimer Res. 2005;2(4):403-8.
26. Schipper HM. Brain iron deposition and the free radical-mitochondrial theory of ageing. Ageing Res Rev. 2004;3:265-301.
27. Tchaikovskaya T, Fraifeld V, Urphanishvili T, Andorfer JH, Davies P, Listowsky I. Glutathione S-transferase hGSTM3 and ageing-associated neurodegeneration: relationship to Alzheimer's disease. Mech Ageing Dev. 2005;126(2):309-15.
28. Maes OC, Schipper HM, Chong G, Chertkow HM, Wang E. A GSTM3 polymorphism associated with an etiopathogenetic mechanism in Alzheimer disease. Neurobiol Aging. 2010;31(1):34-45.
29. Moalem S, Percy ME, Andrews DF, et al. Are hereditary hemochromatosis mutations involved in Alzheimer disease? Am J Medical Genet. 2000;93(1):58-86.
30. Sampietro M, Caputo L, Casatta A, et al. The hemochromatosis gene affects the age of onset of sporadic Alzheimer's disease. Neurobiol Aging. 2001;22(4):563-8.
31. Pulliam JF, Jennings CD, Kryscio RJ, et al. Association of HFE mutations with neurodegeneration and oxidative stress in Alzheimer's disease and correlation with APOE. Am J Medical Genet. 2003;119B(1):48-53.
32. Berlin D, Chong G, Chertkow H, Bergman H, Phillips NA, Schipper HM. Evaluation of HFE (hemochromatosis) mutations as genetic modifiers in sporadic AD and MCI. Neurobiol Aging. 2004;25(4):465-74.
33. Zatta P, Messori L, Mauri P, et al. The C2 variant of human serum transferrin retains the iron binding properties of the native protein. Biochim Biophys Acta. 2005;1741(3):264-70.
34. Zambenedetti P, Bellis GD, Biunno I, Musicco M, Zattac P. Transferrin C2 variant does confer a risk for Alzheimer's disease in caucasians. J Alzheimers Dis. 2003; 5(6):423-7.

588

35. Van Rensburg SJ, Potocnik FCV, Villiers JNPd, Kotze MJ, Taljaard JJF. Earlier age of onset of Alzheimer's disease in patients with both the transferrin C2 and apolipoprotein Epsilon 4 alleles. Ann NY Acad. Sci. 2000;903:200-3.

36. Katzov H, Chalmers K, Palmgren J, et al. Genetic variants of ABCA1 modify Alzheimer disease risk and quantitative traits related to beta-amyloid metabolism. Hum Mutat. 2004;23(4): 358-67.

37. Mace S, Cousin E, Ricard S, et al. ABCA2 is a strong genetic risk factor for early-onset Alzheimer's disease. Neurobiol Dis. 2005; 18(1):119-25.

38. Li Y, Nowotny P, Holmans P, et al. Association of late-onset Alzheimer's disease with genetic variation in multiple members of the GAPD gene family. Proc Natl Acad Sci USA. 2004;101 (44):15688-93.

39. Lio D, Licastro F, Scola L, et al. Interleukin-10 promoter polymorphism in sporadic Alzheimer's disease. Genes Immun. 2003;4(3):234-8.

40. Feher A, Juhasz A, Rimanoczy A, Kalman J, Janka Z. Association between BDNF Val66Met polymorphism and Alzheimer disease, dementia with Lewy bodies, and Pick disease. Alzheimer Dis Assoc Disord. 2009;23(3):224-8.

41. Ertekin-Taner N, Allen M, Fadale D, et al. Genetic variants in a haplotype block spanning IDE are significantly associated with plasma Abeta42 levels and risk for Alzheimer disease. Hum Mutat. 2004;23(4):334-42.

42. Roses AD, Lutz MW, Amrine-Madsen H, et al. A TOMM40 variable-length polymorphism predicts the age of late-onset Alzheimer's disease. Pharmacogenomics J. 2009.

43. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet. 2009;41(10): 1088-93.

44. 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(9):735-41.

45. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. Brit Med J. 2001;322:1447-51.

46. Vermeer S, Koudstaal P, Oudkerk M, Hofman A, Breteler M. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke. 2002;33: 1179-80.

47. Waldstein SR, Siegel EL, Lefkowitz D, et al. Stress-induced blood pressure reactivity and silent cerebrovascular disease. Stroke. 2004;(35):1294-8.

48. Petrovitch H, White LR, Izmiriliand G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. Neurobiol Aging. 2000;21(1):57-62.

49. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. Arch Intern Med. 2003;163(9):1069-75.

50. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. Neurology. 2005;64(2):277-81.

51. Kalaria RN. The role of cerebral ischemia in Alzheimer's disease. Neurobiol Aging. 2000;21:321-30.

52. Kadotani H, Kadotani T, Young T, et al. Association between apolipoprotein E {epsilon}4 and sleep-disordered breathing in adults. J Am Med Assoc. 2001;285(22):2888-90.

53. Guo X, Waern M, Sjögren K, et al. Midlife respiratory function and incidence of Alzheimer's disease: A 29-year longitudinal study in women. Neurobiol Aging. 2007;28(3):343-50.

54. Cosentino FII, Bosco P, Drago V, et al. The APOE [epsilon]4 allele increases the risk of impaired spatial working memory in obstructive sleep apnea. Sleep Medicine. 2008;9(8):831-9.

55. Gottlieb DJ, DeStefano AL, Foley DJ, et al. APOE ε4 is associated with obstructive sleep apnea/hypopnea. Neurology. 2004;63(4): 664-8.

56. Gozal D, Capdevila OS, Kheirandish-Gozal L, Crabtree VM. APOE ε4 allele, cognitive dysfunction, and obstructive sleep apnea in children. Neurology. 2007;69(3):243-9.

57. O'Hara R, Luzon A, Hubbard J, Zeitzer JM. Sleep apnea, apolipoprotein epsilon 4 allele, and TBI: mechanism for cognitive dysfunction and development of dementia. J Rehabil Res Dev. 2009;46(6):837-50.

58. Sun X, He G, Qing H, et al. Hypoxia facilitates Alzheimer's disease pathogenesis by up-regulating BACE1 gene expression. Proc Natl Acad Sci. 2006;103(49):18727-32.

59. Andel R, Crowe M, Pedersen NL, Fratiglioni L, Johansson B, Gatz M. Physical exercise at midlife and risk of dementia three decades later: A population-based study of Swedish twins. J Gerontol. 2008;63(A):62-6.

60. Lindsay J, Laurin D, Verreault R, et al. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am J Epidemiol. 2002;156(5):445-53.

61. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. N Engl J Med. 2003;348(25):2508-16.

62. Rovio S, Kareholt I, Helkala E, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurology. 2005;4(11):705-11.

63. Mahley RW, Rall Jr. SC. Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Gen. 2000;1: 507-37.

64. Rolland Y, Abellan van Kan G, Vellas B. Physical activity and Alzheimer's disease: from prevention to therapeutic perspectives. J Am Medical Direc Assoc. 2008;9(6):390-405.

65. Rovio S, Kåreholt I, Helkala E-L, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. Lancet Neurol. 2005;4(11):705-11.

66. Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MMB. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia. 1996;39(11):1392-7.

67. Curb JD, Rodriguez BL, Abbott RD, et al. Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance. Neurology. 1999;52(5):971-5.

68. Xu W, Qiu C, Gatz M, Pedersen NL, Johansson B, Fratiglioni L. Mid- and late-life diabetes in relation to the risk of dementia. Diabetes. 2009;58(1):71-7.

69. Martins IJ, Hone E, Foster JK, et al. Apolipoprotein E, cholesterol metabolism, diabetes, and the convergence of risk factors for Alzheimer's disease and cardiovascular disease. Mol Psychiatry. 2006;11(8):721-36.

70. Ronnemaa E, Zethelius B, Sundelof J, et al. Impaired insulin secretion increases the risk of Alzheimer disease. Neurology. 2008;71(14): 1065-71.

71. Knopman DS. Go to the head of the class to avoid vascular dementia and skip diabetes and obesity. Neurology. 2008;71(14): 1046-7.

72. Craft S, Watson G. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol. 2004;3:169-78.

73. Peila R, Rodriguez BL, Launer LJ. Type 2 Diabetes, APOE gene, and the risk for dementia and related pathologies. Diabetes. 2002;51(4):1256-62.

74. Jarvik GP, Wijsman EM, Kukull WA, et al. Interactions of apolipoprotein E genotype, total cholesterol level, age, and sex in prediction of Alzheimer's disease: A case-control study. Neurology. 1995;45(6):1092-6.

75. Kivipelto M, Helkala EL, Laakso MP, et al. Apolipoprotein E ε4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent risk factors for late-life Alzheimer disease. Ann Int Med. 2002;137(3):149-55.

76. Rockwood K, Kirkland S, Hogan DB, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurology. 2002;59:223-7.

77. Feldman HH, Doody RS, Kivipelto M, et al. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease. Neurology. 2010;74(12):956-64.

78. Zandi PP, Sparks DL, Khachaturian AS, et al. Do statins reduce risk of incident dementia and Alzheimer disease? Arch Gen Psychiatry. 2005;62:217-24.

79. Li G, Higdon R, Kukull WA, et al. Statin therapy and risk of dementia in the elderly: a community-based prospective cohort study. Neurology. 2004;63:1624-8.

80. Milionis H, Florentin M, Giannopoulos S. Metabolic syndrome and Alzheimer's disease: a link to a vascular hypothesis? CNS Spectr. 2008;13(7):606-13.

81. Vanhanen M, Koivisto K, Moilanen L, et al. Association of metabolic syndrome with Alzheimer disease: a population-based study. Neurology. 2006;67(5):843-7.

82. Yaffe K, Sawaya G, Lieberburg I, Grady D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. J Am Med Assoc. 1998;279:688-95.

83. Kawas C. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Obstet Gynecol Surv. 1997;52 (11):694.

84. Tang MX. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Obstet Gynecol Surv. 1997;52 (1):37.

85. Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. J Am Med Assoc. 2004;291 (24):2947-58.

86. Sherwin BB. Estrogen and memory in women: how can we reconcile the findings? Horm Behav. 2005;47(3):371-5.

87. Yaffe K, Haan M, Byers A, Tangen C, Kuller L. Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. Neurology. 2000;54(10):1949-54.

88. Patterson C, Feightner J, Garcia A, MacKnight C. Primary prevention of dementia. Alzheimer's Dementia. 2007;3(4): 348-54.

89. Moffat SD, Zonderman AB, Metter EJ, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology. 2004;62(2): 188-93.

90. Balldin J, Gottfries CG, Karlsson I, Lindstedt G, Langstrom G, Walinder J. Dexamethasone suppression test and serum prolactin in dementia disorders. Br J Psychiatry. 1983;143:277-81.

91. Sapolsky RM. Is this relevant to the human? In: Sapolsky RM, editor. Stress, the aging brain, and the mechanisms of neuron death. Cambridge: MIT Press; 1992. p. 305-39.

92. Souza-Talarico JN, Chaves EC, Lupien SJ, Nitrini R, Caramelli P. Relationship between cortisol levels and memory performance may be modulated by the presence or absence of cognitive impairment: evidence from healthy elderly, mild cognitive impairment and Alzheimer's disease subjects. J Alzheimers Dis. 2009;19(3):839-48.

93. Spar JE, Gerner R. Does the dexamethasone suppression test distinguish dementia from depression? Am J Psychiatry. 1982; 139(2):238-40.

94. Green KN, Billings LM, Roozendaal B, McGaugh JL, LaFerla FM. Glucocorticoids increase amyloid-β and tau pathology in a mouse model of Alzheimer's disease. J Neurosci. 2006;26(35): 9047-56.

95. van Osch LADM, Hogervorst E, Combrinck M, Smith AD. Low thyroid-stimulating hormone as an independent risk factor for Alzheimer Disease. Neurology. 2004;62:1967-71.

96. Reiter RJ, Carneiro RC, Oh CS. Melatonin in relation to cellular antioxidative defense mechanisms. Horm Metab Res. 1997;29 (8):363-72.

97. Cheng Y, Feng Z, Zhang Q-Z, Zhang J-T. Beneficial effects of melatonin in experimental models of Alzheimer disease. Acta Pharmacol Sin. 2006;27 (2):129-39.

98. Wang J, Wang Z. Role of melatonin in Alzheimer-like neurodegeneration. Acta Pharmacol Sin. 2006;27(1):41-9.

99. Verdoux H, Lagnaoui R, Begaud B. Is benzodiazepine use a risk factor for cognitive decline and dementia? a literature review of epidemiological studies. Psychol Med. 2005;35:307-15.

100. Tyas SL, Manfreda J, Strain LA, Montgomery PR. Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. Int J Epidemiol. 2001;30:590-7.

101. Verreault R, Laurin D, Lindsay J, De Serres G. Past exposure to vaccines and subsequent risk of Alzheimer's disease. Can Med Assoc J. 2001;165(11):1495-8.

102. Ernst T, Chang L, Leonido–Yee M, Speck O. Evidence for long-term neurotoxicity associated with methamphetamine abuse: A 1H MRS study. Neurology. 2000;54:1344-9.

103. Shih RA, Glass TA, Bandeen-Roche K, et al. Environmental lead exposure and cognitive function in community-dwelling older adults. Neurology. 2006;67:1556-62.

104. Flaten TP. Aluminium as a risk factor in Alzheimer's disease, with emphasis on drinking water. Brain Res Bull. 2001;55(2):187-96.

105. Mutter J, Naumann J, Sadaghiani C, Schneider R, Walach H. Alzheimer Disease: mercury as pathogenetic factor and apolipoprotein E as a moderator. Neuroendocrinol Lett. 2004; 25(5):331-9.

106. Bush AI. Metal complexing agents as therapies for Alzheimer's disease. Neurobiol Aging. 2002;23:1031-8.

107. Baldi I, Lebailly P, Mohammed-Brahim B, Letenneur L, Dartigues J-F, Brochard P. Neurodegenerative diseases and exposure to pesticides in the elderly Am J Epidemiol. 2003;157:409-14.

108. Gauthier E, Fortier I, Courchesne F, Pepin P, Mortimer J, Gauvreau D. Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study. Environ Res. 2001;86 (1):37-45.

109. Finch C, Morgan T. Systemic inflammation, infection, APOE alleles, and Alzheimer disease: a position paper. Curr Alzheimer Res. 2007;4(2):185-9.

110. McGeer E, McGeer P. The importance of inflammatory mechanisms in Alzheimer's disease. Exp Gerontol. 1998;33(5): 371-8.

111. Breteler MMB. Vascular risk factors for Alzheimer's disease: An epidemiologic perspective. Neurobiol Aging. 2000;21(2): 153-60.

112. Mi W, Pawlik M, Sastre M, et al. Cystatin C inhibits amyloid-beta deposition in Alzheimer's disease mouse models. Nature Gen. 2007;39:1440-2.

113. Sundelöf J, Ärnlöv J, Ingelsson E, et al. Serum cystatin C and the risk of Alzheimer disease in elderly men. Neurology. 2008;71: 1072-9.

114. Maes OC, Kravitz S, Mawal Y, et al. Characterization of alpha(1)-antitrypsin as a heme oxygenase-1 suppressor in Alzheimer plasma. Neurobiol Dis. 2006;24:89-100.

115. Etminan M, Gill S, Samii A. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and metaanalysis of observational studies. Brit Med J. 2003;327(7404):128.

116. Szekely CA, Thorne JE, Zandi PP, et al. Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. Neuroepidemiol. 2004;23:159-69.

117. Klegeris A, McGeer P. Non-steroidal anti-inflammatory drugs (NSAIDs) and other antiinflammatory agents in the treatment of neurodegenerative disease. Curr Alzheimer Res. 2005;2:355-65.

118. Lyketsos CG, Breintner JC, Green RC, et al. Naproxen and celcoxiben do not prevent AD in early results from a randomized clinical trial. Neurology. 2007;68(21):1800-8.

119. Sonnen JA, Larson EB, Walker RL, et al. Nonsteroidal anti-inflammatory drugs are associated with increased neuritic plaques. Neurology. 2010;75(13):1203-10.

120. Breitner J. NSAIDs and Alzheimer's disease: how far to generalize from trials? Lancet Neurol. 2003;2:527.

121. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008 Sep 11;337:a1344.doi:10.1136/bmj.a1344.

122. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003;348(26):2599-608.

123. Feart C, Samieri C, Barberger-Gateau P. Mediterranean diet and cognitive function in older adults. Curr Opin Clin Nutr Metab Care. 2010;13(1):14-8.

124. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Ann Neurol. 2006;59(6):912-21.

125. Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Mediterranean diet and mild cognitive impairment. Arch Neurol. 2009;66(2):216-25.

126. Moreira PI, Honda K, Liu Q, et al. . Oxidative stress: the old enemy in Alzheimer's disease pathophysiology. Curr Alzheimer Res. 2005;2(4):403-8.

127. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol. 2004;61(1):82-8.

128. Engelhart MJ, Geerlings MI, Ruitenberg A, et al. Dietary Intake of Antioxidants and Risk of Alzheimer Disease. J Am Med Assoc. 2002;287(24):3223-9.

129. Sano M, Ernesto C, Thomas R, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. N Engl J Med. 1997;336(17):1216-22.

130. Laurin D, Masaki KH, Foley DJ, White LR, Launer LJ. Midlife dietary intake of antioxidants and risk of late-life incident dementia: The Honolulu-Asia Aging Study. Am J Epidemiol. 2004;159(10):959-67.

131. Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. J Am Med Assoc. 2002;287(24):3230-7.

132. Petersen RC, Thomas RG, Grundman M, et al. Donepezil and vitamin E in the treatment of mild cognitive impairment. N Engl J Med. 2005;352:2379-88.

133. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, Vitamin B12, and Serum Total Homocysteine Levels in Confirmed Alzheimer Disease. Arch Neurol. 1998;55(11):1449-55.

134. Wang H-X, Wahlin A, Basun H, Fastbom J, Winblad B, Fratiglioni L. Vitamin B12 and folate in relation to the development of Alzheimer's disease. Neurology. 2001;56(9):1188-94.

135. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med. 2002; 346:476-83.

136. Hooshmand B, Solomon A, Kareholt I, et al. Homocysteine and holotranscobalamin and the risk of Alzheimer disease: A longitudinal study. Neurology. 2010;75(16):1408-14.

137. Wald DS, Bishop L, Wald NJ, et al. Randomized trial of folic acid supplementation and serum homocysteine levels. Arch Intern Med. 2001;161(5):695-700.

138. McMahon JA, Green TJ, Skeaff CM, Knight RG, Mann JI, Williams SM. A controlled trial of homocysteine lowering and cognitive performance. N Engl J Med. 2006;354(26):2764-72.

139. Tucker KL, Olson B, Bakun P, Dallal GE, Selhub J, Rosenberg IH. Breakfast cereal fortified with folic acid, vitamin B-6, and vitamin B-12 increases vitamin concentrations and reduces homocysteine concentrations: a randomized trial. Am J Clin Nutr. 2004;79(5):805-11.

140. Smith AD, Smith SM, de Jager CA, et al. Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PLoS1. 2010;5(9):e12244.

141. Durga J, van Boxtel MPJ, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet. 2007;369(9557):208-16.

142. Ford AH, Flicker L, Alfonso H, et al. Vitamins B(12), B(6), and folic acid for cognition in older men. Neurology. 2010;75(17):1540-7.

143. Malouf M, Grimley EJ, Areosa SA. Folic acid with or without vitamin B12 for cognition and dementia. Cochrane Database Syst Rev. 2003(4):CD004514.

144. Kang JH, Cook N, Manson J, Buring JE, Albert CM, Grodstein F. A trial of B vitamins and cognitive function among women at high risk of cardiovascular disease. Amer J Clin Nutr. 2008;88(6):1602-10.

145. Yang Q, Botto LD, Erickson JD, et al. Improvement in stroke mortality in Canada and the United States, 1990 to 2002. Circulation. 2006;113(10):1335-43.

146. Blass JP, Gleason P, Brush D, DiPonte P, Thaler H. Thiamine and Alzheimer's disease: a pilot study. Arch Neurol. 1988;45(8):833-5.

147. Gehlert DR, Morey WA, Wamsley JK. Alterations in muscarinic cholinergic receptor densities induced by thiamine deficiency: Autoradiographic detection of changes in high- and low-affinity agonist binding. J Neurosci Res. 1985;13(3):443-52.

148. Kril JJ. Neuropathology of thiamine deficiency disorders. Metabol Brain Dis 1996;11(1):9-17.

149. Mimori Y, Katsuoka H, Nakamura S. Thiamine therapy in Alzheimer's disease. Metabol Brain Dis. 1996;11(1):89-94.

150. Nolan KA, Black RS, Sheu KFR, Langberg J, Blass JP. A trial of thiamine in Alzheimer's disease. Arch Neurol. 1991;48(1):81-3.

151. Meador K, Loring D, Nichols M, et al. Preliminary findings of high-dose thiamine in dementia of Alzheimer's type. J Geriatr Psychiatry Neurol. 1993;6(4):222-9.

152. Hageman GJ, Stierum RH. Niacin, poly(ADP-ribose) polymerase-1 and genomic stability. Mutat Res Fund Molec Mech Mutag. 2001;475(1-2):45-56.

153. Melo SS, Arantes MR, Meirelles MS, Jordão Jr AA, Vannucchi H. Lipid peroxidation in nicotinamide-deficient and nicotinamide-supplemented rats with streptozotocin-induced diabetes. Acta Diabetol. 2000;37(1):33-9.

154. Morris MC, Evans DA, Bienias JL, et al. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. J Neurol Neurosurg Psychiatry. 2004;75(8):1093-9.

155. Bourre JM. Dietary omega-3 Fatty acids and Psychiatry: mood, behaviour, stress, depression, dementia and aging. J Nutr Health Aging. 2005;9(1):31-8.

156. Bourre JM. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 2: macronutrients. J Nutr Health Aging. 2006;10(5):386-99.

157. Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. Lipids. 2000;35(12):1305-12.

158. Maia L, dev Mendonça A. Does caffeine intake protect from Alzheimer's disease? Eur J Neurol. 2002;9:377-82.

159. Quintana JLB, Allam MF, Del Castillo AS, Navajas RF-C. Alzheimer's disease and coffee: a quantitative review. Neurol Res. 2007;29(1):91-5(5).

160. Eskelinena MH, Ngandua T, Tuomilehto J, Soininen H, Kivipelto M. Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study. J Alzheimers Dis. 2009;16:85-91.

161. Larrieu S, Letenneur L, Helmer C, Dartigues JF, Barberger-Gateau P. Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort. J Nutr Health Aging. 2004;8(3):150-4.

162. Mortimer J. Brain reserve and the clinical expression of Alzheimer's disease. Geriatrics. 1997;52(Suppl 2):S50-53.

163. Stern Y, Gurland B, Tatemichi TK, Tang MX, Wilder D, Mayeux R. Influence of education and occupation on the incidence of Alzheimer's disease. J Am Med Assoc. 1994;271(13):1004-10.

164. Crowe M, Andel R, Pedersen NL, Johansson B, Gatz M. Does participation in leisure activities lead to reduced risk of Alzheimer's disease? a prospective study of Swedish twins. J Gerontol. 2003;58(5):P249-55.

165. Scarmeas N, Levy G, Tang MX, Manly J, Stern Y. Influence of leisure activity on the incidence of Alzheimer's disease. Neurology. 2001;57(12):2236-42.

166. Valenzuela MJ, Sachdev P. Brain reserve and dementia: a systematic review. Psychol Med. 2006;36(04):441-54.

167. Stern C, Munn Z. Cognitive leisure activities and their role in preventing dementia: a systematic review. Int J Evid Based Healthc. 2010;8(1):2-17.

168. Ball K, Berch DB, Helmers KF, et al., for the ASG. Effects of Cognitive Training Interventions With Older Adults. J Am Med Assoc. 2002;288(18):2271-81.

169. Valenzuela M, Sachdev P. Can cognitive exercise prevent the onset of dementia? Systematic review of randomized clinical trials

with longitudinal follow-up. Am J Geriat Psychiatry. 2009;17 (3):179-87.

170. Neely AS, Bäckman L. Effects of multifactorial memory training in old age: generalizability across tasks and individuals. J Gerontol. 1995;50B(3):P134-40.

171. Verhaeghen P, Marcoen A, Goossens L. Improving memory performance in the aged through mnemonic training: a meta-analytic study. Psychol Aging. 1992;7(2):242-51.

172. Mahncke HW, Connor BB, Appelman J, et al. Memory enhancement in healthy older adults using a brain plasticity-based training program: A randomized, controlled study. Proc Natl Acad Sci. 2006;103(33):12523-8.

173. Optale G, Urgesi C, Busato V, et al. Controlling memory impairment in elderly adults using virtual reality memory training: A randomized controlled pilot study. Neurorehabil Neural Repair 2010;24(4):348-57.

174. Wilson RS, Krueger KR, Arnold SE, et al. Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry. 2007;64(2):234-40.

175. Helmer C, Damon D, Letenneur L, et al. Marital status and risk of Alzheimer's disease: a French population-based cohort study. Neurology. 1999;53(9):1953-8.

176. Guo Z, Cupples LA, Kurz A, et al. Head injury and the risk of AD in the MIRAGE study. Neurology. 2000;54(6):1316-23.

177. Jordan BD, Relkin NR, Ravdin LD, Jacobs AR, Bennett A, Gandy S. Apolipoprotein E epsilon4 associated with chronic traumatic brain injury in boxing. J Am Med Assoc. 1997;278(2):136-40.

178. Mayeux R, Ottman R, Maestre G, et al. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology. 1995;45(3 Pt 1):555-7.

179. Plassman BL, Havlik RJ, Steffens DC, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology. 2000;55(8):1158-66.

180. Szczygielski J, Mautes A, Steudel WI, Falkai P, Bayer TA, Wirths O. Traumatic brain injury: cause or risk of Alzheimer's disease? A review of experimental studies. J Neural Transm. 2005;112 (11):1547-64.

181. Wilson M, Montgomery H. Impact of genetic factors on outcome from brain injury. Br J Anaesth. 2007;99(1):43-8.

182. McCrory P, Zazryn T, Cameron P. The evidence for chronic traumatic encephalopathy in boxing. Sports Med. 2007;37(6): 467-76.

183. Rabadi MH, Jordan BD. The cumulative effect of repetitive concussion in sports. Clin J Sport Med. 2001;11(3):194-8.

184. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology. 1967;17:427-42.

185. Marder K, Tang M-X, Cote L, Stern Y, Mayeux R. The frequency and associated risk factors for dementia in patients with Parkinson's disease. Arch Neurol. 1995;52(7):695-701.

186. Breteler MMB, Groot RFM, Romunde LKJ, Hofman A. Risk of dementia in patients with Parkinson's disease, epilepsy, and severe head trauma: a register-based follow-up study. Am J Epidemiol. 1995;142(12).

187. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain. 2010;133(6): 1755-62.

188. Schipper HM. The role of biologic markers in the diagnosis of Alzheimer's disease Alzheimers Dementia. 2007;3:325-32.

189. Tsuboi Y, Josephs KA, Cookson N, Dickson aDW. APOE E4 is a determinant for Alzheimer type pathology in progressive supranuclear palsy. Neurology. 2003;60:240-5.

190. Mackenzie IRA, Miller LA. Senile plaques in temporal lobe epilepsy. Acta Neuropathol. 1994;87:504-10.

191. Griffin WST, Mrak RE. Interleukin-1 in the genesis and progression of and risk for development of neuronal degeneration in Alzheimer's disease. J Leukocyte Biol. 2002;72:233-8.

192. Sheng J, Boop F, Mrak R, Griffin W. Increased neuronal beta-amyloid precursor protein expression in human temporal lobe epilepsy: association with IL-1 alpha immunoreactivity. J Neurochem. 1994;63:1872-9.

193. Gouras GK, Relkin NR, Sweeney D, Munoz DG, Mackenzie IR, Gandy SE. Increased apolipoprotein E epsilon 4 in epilepsy with senile plaques. Ann Neurol. 1997 Mar;41(3):402-4.

194. Alisky JM. The coming problem of HIV-associated Alzheimer's disease. Med Hypoth. 2007;69(5):1140-3.

195. Guillemin GJ, Brew BJ. Chronic HIV infection leads to an Alzheimer's disease like illness: involvement of the kynurenine pathway. Internat Cong Ser. 2007;1304:324-34.

196. Clifford DB, Fagan AM, Holtzman DM, et al. CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease. J Neurol. 2009;73(23):1982-7.

197. Butters MA, Young JB, Lopez O, et al. Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialog Clin Neurosci 2008;10:345-57.

198. 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(5):530-8.

199. Chen P, Ganguli M, Mulsant B, DeKosky S. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. Arch Gen Psychiatry. 1999; 56(3):261-6.

200. Zalsman G, Aizenberg D, Sigler M, Nahshony E, Karp L, Weizman A. Increased risk for dementia in elderly psychiatric inpatients with late-onset major depression. J Nerv Mental Dis. 2000;188 (4):242-3.

201. Baldessarini R, Hegarty J, Bird E, Benes F. Meta-analysis of postmortem studies of Alzheimer's disease-like neuropathology in schizophrenia. Am J Psychiatry. 1997;154:861-3.

202. Harrison P, Weinberger D. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry. 2005;10:40-68.

203. Jellinger KA, Gabriel E. No increased incidence of Alzheimer's disease in elderly schizophrenics. Acta Neuropathol. 1999;97: 165-9.

204. Thibaut F, Coron B, Hannequin D, et al. No association of apolipoprotein epsilon 4 allele with schizophrenia even in cognitively impaired patients. Schizophr Res. 1998;30(2): 149-53.

205. Digman JM. Personality structure: Emergence of the five-factor model. Ann Rev Psychiatry. 1990;41(1):417-40.

206. Wilson RS, Evans DA, Bienias JL, Mendes de Leon CF, Schneider JA, Bennett DA. Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology. 2003;61: 1479-85.

207. Wilson RS, Schneider JA, Arnold SE, Bienias JL, Bennett DA. Conscientiousness and the incidence of Alzheimer disease and mild cognitive impairment. Arch Gen Psychiatry. 2007;64(10): 1204-12.

208. Dominick K, Ahern F, Gold C, Heller D. Relationship of health-related quality of life to health care utilization and mortality among older adults. Aging Clin Exp Res. 2002 Dec;14(6): 499-508.

209. Koenig H, Cohen H, George L, Hays J, Larson D, Blazer D. Attendance at religious services, interleukin-6, and other biological parameters of immune function in older adults. Int J Psychiatry Med. 1997;27(3):233-50.

210. Koenig H, Cohen H, Blazer D, et al. Religious coping and depression among elderly, hospitalized medically ill men. Am J Psychiatry. 1992;149:1693-700.

211. Idler E, Kasl S. Religion among disabled and nondisabled persons II: attendance at religious services as a predictor of the course of disability. J Gerontol. 1997;52B(6):S306-16.

212. Kaufman Y, Anaki D, Binns M, Freedman M. Cognitive decline in Alzheimer disease: Impact of spirituality, religiosity, and QOL. Neurology. 2007;68:1509-14.

213. Schipper HM. Presymptomatic apolipoprotein E genotyping for AD risk assessment and prevention. Alzheimer Dement, 2011, [in press].

214. Beaudet A. Message from the president. Annual Meeting of Chairs and Scientific Officers. Ottawa, ON, Canada: Canadian Institutes for Health Research, 2010.