

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'étiopathogénèse 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.

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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 cortices¹. 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 ages². 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 issue⁵, 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 al⁶, 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 al⁷, 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 births⁸. 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 hyperphosphorylated tau protein⁹.

(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 variable¹⁰, mutations in APP and PS1 show virtually 100% penetrance¹¹.

(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	
TJR2	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, $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$, code for three isoforms of the apoE glycoprotein. Lipoproteins are responsible for transporting cholesterol, triglycerides and other lipids¹². 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 brain¹³. ApoE4 preferentially binds to lower density lipoproteins, while apoE3 binds to higher density lipoproteins¹⁴. ApoE3 can form homodimers which affects its lipid binding and also reduces its affinity for the LDL receptor¹⁵. ApoE4 has the lowest stability of all three isoforms and has the greatest propensity to aggregate. Possessing one or two copies of the $\epsilon 4$ variant substantially increases the risk of developing sporadic AD^{16,17}. Corder and colleagues¹⁸ 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 $\epsilon 4$ alleles, respectively, relative to $\epsilon 3/\epsilon 3$ individuals. The deleterious effect of the $\epsilon 4$ allele appears to be more pronounced in women than in men^{19,20}. *E4* 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) conditions¹⁷. The latter include augmented tau hyperphosphorylation and the formation of neurofibrillary tangles²¹, less efficient clearance of β -amyloid²², and increased vulnerability to aberrant degradation²³. 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 $\epsilon 4$ allele¹⁷. The *APOE* $\epsilon 2$ allele, on the other hand, appears to be a protective factor against sporadic AD²⁴.

(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 tangles²⁷. A polymorphism (rs7483) of this gene has been linked to the development of sporadic AD, possibly by diminishing brain antioxidant defenses within affected individuals²⁸. 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 groups²⁹⁻³¹, but not others³², 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 conditions²⁵. The transferrin *TfC2 allele*³³ reportedly occurs with greater frequency in patients with sporadic AD compared to non-demented controls³⁴ and may further accelerate the clinical appearance of the disease in *APOE* $\epsilon 4$ -positive subjects³⁵.

(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 members³⁸, polymorphisms of the *IL-10* gene promoter³⁹, the Val66Met polymorphism of the *BDNF* gene⁴⁰, and a variable 276 kb region harbouring the *IDE*

gene⁴¹. 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* $\epsilon 3$ -positive subjects⁴². 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 disease⁴³. 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 AD⁴⁴.

(i) *Hypertension*: There is fairly robust evidence linking midlife hypertension to the development of dementia in later life. Kivipelto et al⁴⁵ 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 infarction⁴⁶, brain atrophy, cerebrovascular atherosclerosis and increased burden of subcortical white matter lesions commonly found in AD⁴⁷. Hypertension may also directly contribute to cerebrovascular permeability, protein extravasation, and formation of neurofibrillary pathology in the brains of patients with AD⁴⁸.

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 attacks⁵¹. 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* $\epsilon 4$ allele is purportedly over-represented in subjects with this respiratory disorder⁵⁴⁻⁵⁷. Among other possible mechanisms, hypoxia is believed to facilitate AD pathogenesis through increased gene expression of β -site APP cleavage enzyme 1 (BACE1), which results in increased β -amyloid production⁵⁸.

(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-life⁵⁹⁻⁶¹. 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 obesity⁴⁵. 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 factors⁶². The *APOE* status may interact with physical activity to differentially protect against dementia. In one study, Rovio et al⁶² found that the decrease in risk of dementia associated with physical activity was more pronounced among *APOE* ϵ 4 carriers than non-carriers. This effect may be due to inefficient neural repair mechanisms in *APOE* ϵ 4 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 AD¹⁷.

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 al⁶⁴ summarized the somewhat arbitrary measures used to evaluate physical activity. For instance, Rovio et al⁶⁵ 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 al⁵⁹, 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 dementia⁶⁶⁻⁶⁸. 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 diabetes⁶⁹. This syndrome is associated with both AD and vascular dementia⁷⁰, suggesting a mechanism involving diabetic microvascular disease⁷¹. 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 syndrome⁷⁰ and may increase AD risk via interactions between insulin and β -amyloid degrading enzymes within the brain⁷². Of note, *APOE* ϵ 4-positive individuals with type-2

diabetes have about twice the risk of developing AD, compared to those without diabetes⁷³.

(ii) *Lipids*: Several studies have observed an association between high serum cholesterol levels and an increased risk of developing AD^{74,75}. Kivipelto et al⁷⁵ demonstrated that elevated levels of total cholesterol level at midlife significantly enhanced the risk of developing AD independently of *APOE* ϵ 4 allele status and the presence of systolic hypertension. *Lipid Lowering Agents*: Recognition of midlife hypercholesterolemia as a risk factor for AD⁴⁵ 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 age⁷⁶; 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 state⁸⁰. While these factors are known to be particularly detrimental to dementia risk in elderly persons⁸¹, some studies have linked midlife MetS components with increased risk of late-life dementia^{44,50}. In a retrospective study, Whitmer et al⁵⁰ 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 AD⁸⁴. 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 finding⁸⁵, although the generalizability of this study has been challenged on methodological grounds⁸⁶. Some studies have indicated a possible gene-environment interaction between estrogen and the *APOE* ϵ 4 allele. Notably, Yaffe et al⁸⁷ found that estrogen replacement therapy was correlated with less cognitive decline only in women lacking the ϵ 4 allele. Mortensen and Høgh²⁰ found that the *APOE* ϵ 4-positive women exhibited significantly steeper declines on several cognitive tests between ages 70 and 80 than did non-carriers. The *APOE* ϵ 4 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 AD⁸⁸. In men, some evidence suggests that higher levels of free testosterone may confer protection against AD⁸⁹.

(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 humans⁹⁰⁻⁹³. Green et al⁹⁴ reported that glucocorticoid 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 AD⁹⁵.

(vii) *Melatonin*: Melatonin, an indoleamine secreted by the pineal gland, is a potent free radical scavenger⁹⁶. Melatonin inhibits β -amyloid generation and fibrillization⁹⁷ and attenuates tau hyperphosphorylation⁹⁸. 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 review⁹⁹ 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 damage¹⁰², 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 study¹⁰³, 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 AD¹⁰⁴, 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 amalgam¹⁰⁵. The putative role of heavy metals in AD has led to the experimental use of chelating agents as a potential therapy for the disease¹⁰⁶.

Pesticides/herbicides: In a longitudinal population based study in Manitoba, Canada, occupational exposure to fumigants

or defoliants significantly increased the incidence of AD¹⁰⁰. 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 prudent⁸⁸.

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 persons¹¹¹.

(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 -amyloid¹¹². Sundelöf and colleagues¹¹³ 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) *α 1-Antitrypsin*: Levels of α 1-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 disease¹¹⁴.

(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 formation¹¹⁹. It has been suggested that these discrepancies may be due to the timing, type, and/or dosage of NSAIDs used¹²⁰. Therefore, there is currently insufficient evidence to recommend prescribing NSAIDs for the specific intention of reducing the risk of dementia or AD⁸⁸.

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, cancer¹²¹ and mortality¹²². 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

MCI to AD¹²⁵. 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 intervention¹²³. 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 AD¹²⁷⁻¹²⁹. 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 trial¹³².

(iii) *Folate, vitamin B₆, vitamin B₁₂ 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 B₁₂) 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 status¹³⁶. Plasma homocysteine levels can be lowered by supplementation with folic acid, vitamin B₁₂ and vitamin B₆¹³⁷⁻¹³⁹ 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 scores¹⁴⁰. Another study¹⁴¹ 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 B₁₂ (500 micrograms) and vitamin B₆ (10 mg) engendered no discernible benefits on multiple tests of cognition¹³⁸. Nor did daily supplementation with of B₁₂ (400 micrograms), folic acid (2 mg) and B₆ (25 mg) over two years improve cognitive function in hypertensive men aged 75 and older¹⁴². 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 dementia¹⁴³. Overall, clinical trials of B vitamin supplements involving patients with already

adequate B₁₂ 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 B₁₂ 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 country¹⁴⁵, 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 acid¹³², further studies will be required before folate, vitamin B₆ or B₁₂ can be advocated with confidence as a form of primary AD prevention.

(iv) *Thiamine*: Thiamine (Vitamin B₁) 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 stability¹⁵² and exhibits antioxidant activity in brain mitochondria¹⁵³. Supplemental intake of niacin has been associated with slower rates of cognitive decline and development of AD¹⁵⁴, 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 Guelph¹⁵⁷ 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 dementias¹³².

(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 al¹⁶⁰ 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 Aging⁶⁰, 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 wine⁸⁸".

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 manifest¹⁶². 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 incidence¹⁶³. 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 contributory¹⁶⁴.

(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 Sachdev¹⁶⁶ 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 design¹⁶⁷. 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 rigorous analysis. Positive findings in the aforesaid 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 trial¹⁶⁸ 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 al¹⁶⁹ 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 skills¹⁷². 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 games¹⁷² may enhance cognitive function. Others have attained similar positive results using virtual reality training programs¹⁷³. Overall, while brain-training computer games currently are too novel a phenomenon to gauge 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 elderly¹⁷⁴. Associations of AD with marital status have also been reported, with never-married individuals shouldering greater risk¹⁷⁵.

(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 AD¹⁷⁶⁻¹⁸¹. The latter may be proportional to the severity of head injury¹⁷⁶ and exacerbated in individuals harbouring *APOE* $\epsilon 4$ alleles¹³². 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 risk¹³². 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 phenomena¹⁸⁴. Parkinson's disease patients are almost twice as likely to develop dementia than control subjects¹⁸⁵, with earlier onset of the movement disorder (e.g. ages 50-54) conferring greater dementia risk¹⁸⁶. The dementia in this population may represent spread of Lewy body pathology (α -synucleinopathy) to cortical regions¹⁸⁷ and/or concomitant AD. In support of the latter formulation, diminished cerebrospinal fluid (CSF) concentrations of β -amyloid₁₋₄₂, an established biomarker of sporadic AD¹⁸⁸, was recently shown to be an independent predictor of cognitive decline in PD subjects¹³².

(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 AD¹³².

(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 gliosis¹⁸⁹. 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* $\epsilon 4$ alleles exhibit higher burdens of AD pathology, but this may be commensurate with findings in the general population¹⁸⁹.

(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 tissues¹⁹⁰. Chronic microglial activation and interleukin-1 β secretion may promote brain amyloid deposition in epileptic persons^{191,192}, particularly in those individuals carrying an *APOE* $\epsilon 4$ allele¹⁹³.

(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 age¹⁹⁴. 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 AD¹⁹⁵. 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 mechanisms¹⁹⁶.

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 -amyloid¹³².

(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 dementia¹⁹⁷⁻²⁰⁰.

(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 disease²⁰¹⁻²⁰⁴.

(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 extraversion²⁰⁵. *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 decline²⁰⁶. On the other hand, conscientiousness, a tendency toward self-discipline and goal-direction, may diminish the risk of AD, MCI and cognitive decline²⁰⁷.

In patients with various medical conditions, high levels of spirituality and religiosity have been associated with lower morbidity and mortality and enhanced quality of life²⁰⁸, ascribed to bolstered immune profiles²⁰⁹, lower rates of depression²¹⁰ and increased optimism and hope²¹¹. In a longitudinal study, higher levels of spirituality and private religious practices were associated with slower disease progression in patients with probable Alzheimer dementia²¹².

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* $\epsilon 4$ 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 disease¹⁷. Disclosure of *APOE* $\epsilon 4$ 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 risk¹³². 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 information²¹³.

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 US⁴ and priority funding in this area by the Canadian Institutes of Health Research²¹⁴ 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.

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