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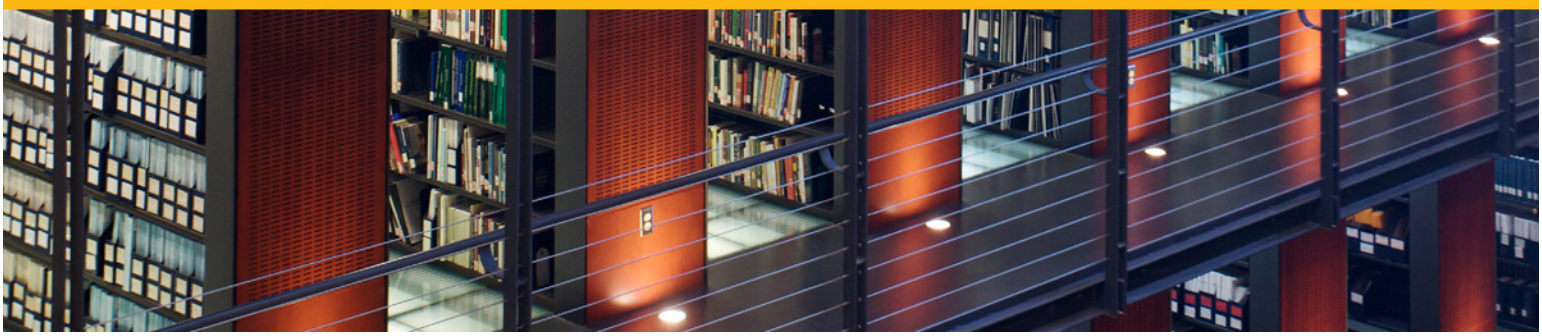

Late-Onset Alzheimer's Disease and Related Dementias

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Late-Onset Alzheimer's Disease and Related Dementias
(Background Paper)

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LATE-ONSET ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

1 INTRODUCTION

Some memory loss can be associated with healthy aging, or normal aging. Dementia, however, refers to a progressive condition that robs a person of much more than the occasional ability to recall events, names or ideas. The most common type of dementia is Alzheimer's disease (AD).

This paper offers an overview of dementia, including its discovery, prevalence, causes, risk factors and costs. It also discusses dementia-related research initiatives supported by the federal government, and presents parliamentary committee studies, parliamentary debate and proposed legislation on dementia.

While the paper offers some information on early-onset AD, its focus is the late-onset form of the disease.

2 IDENTIFICATION OF ALZHEIMER'S DISEASE[1]

In the majority of individuals with AD (93%–95%), the disease occurs after the age of 65. In the remaining cases, the average age of onset is 50.[2] The latter form of AD is referred to as early-onset AD, and it is this form that was first described in 1906 by Alois Alzheimer, a German psychiatrist. A 52-year-old female patient presented with symptoms affecting language, memory, behaviours and ability to think and reason. This symptomology resembled the dementia observed in much older patients, referred to as "senility" at the time. Physically the patient was normal. Over the following five years the patient declined steadily, first cognitively, then physically. Eventually, the deterioration led to an inability to feed, toilet or get around on her own.

Dr. Alzheimer was convinced that he had identified a new illness, since dementia-like symptoms had until that time been described only in elderly patients. After the patient's death, he examined samples of her brain tissue under a microscope and was the first to describe lesions that have been known as "plaques and tangles" for many years. He also noted the pronounced atrophy of the brain tissue.

For several years following Dr. Alzheimer's findings, the disease did not generate much research or medical interest, probably because of the rarity of the condition and the tendency to label it as a form of senility. There was little effort in the scientific community to link the senility seen in old age and the early-onset dementia described by Alzheimer. Some people believed that dementia was a normal consequence of advanced age not observed very often, since few people survived much past the age of 65. Other people believed senility to be an illness rather than a consequence of aging, but maintained that it was separate from the early-onset dementia. During those years, the theory for the cause of senile dementia in either scenario was reduced or impaired blood flow in the brain.

In the 1960s, researchers examined brain tissue samples of deceased elderly patients with and without overt signs of dementia. They found that the patients with senile dementia had the lesions described by Alzheimer in 1906. Thus senile dementia was given the name "Alzheimer's disease." Today we know that the majority of dementia cases, about 63%, are AD. However, several other types of dementia have been described, the next most common being vascular dementia.[3]

3 AGE-RELATED FORGETFULNESS, MILD COGNITIVE DECLINE AND ALZHEIMER'S DISEASE

Some cognitive impairment can accompany normal aging, such as transient forgetfulness. However, this forgetfulness, or age-associated memory impairment, generally does not negatively impact a person's daily activities. For example, this category of memory loss could include temporarily forgetting the name of an acquaintance, misplacing household items, not being able to find the right word to use in conversation, and not remembering an item that a person has gone out to purchase. This level of forgetfulness is common with advanced age and is not necessarily indicative of greater cognitive decline.[4]

Mild cognitive impairment (MCI), however, is severe enough to leave those who suffer from it aware of the change in their cognitive capacity. Therefore, they worry about their memory loss, although it does not usually prevent independent living. MCI can involve the same symptoms as general forgetfulness, but on a more frequent basis. In addition, the afflicted person may start to forget important dates and events and to have difficulty retaining new information. The cause or causes of MCI are not well understood, but the risk factors are believed to be similar to those for AD. People with MCI are at increased risk for AD; however, many cases of MCI do not degenerate further, and some individuals even show improvement over time.[5]

The cognitive changes in AD are much more profound than those seen in age-related forgetfulness and MCI. As well, it is often the family and friends of people suffering from AD who first notice the cognitive decline, while the person affected may be unaware of the changes. Unlike persons affected by forgetfulness or MCI, who may temporarily forget items, names, ideas or words, people with AD forget what an item may be for, where it should be stored or that they know a certain person. They often lose the sense of time, exhibit odd or inappropriate behaviours and emotions, cannot learn new information and are easily disoriented. Patients with AD progressively degenerate until they lose all ability to walk, dress, bathe and even swallow.[6]

4 THE PLAQUES AND TANGLES OF ALZHEIMER'S DISEASE[7]

The brain lesions first described by Alois Alzheimer over a century ago have been extensively researched over the past few decades. These lesions include surface deposits of a protein called "amyloid-β," referred to as "plaques," as well as deposits inside the brain cells of a twisted protein called "tau," referred to as "tangles." Upon autopsy, most, but not all, brains of AD patients have been found to have both plaques and tangles. These lesions have also been located in the brains of some

cognitively intact seniors. As a result, while researchers largely agree that plaques and tangles play a role in the development of AD, their exact role remains unclear.

The early hypothesis was that these deposits were the cause of AD, but the observation that they do not form in all AD cases and that some non-AD patients have significant deposits has led researchers to examine alternative hypotheses. In addition, the reason for the aggregation of these proteins in the brain has also been elusive. Some researchers speculate that plaques and/or tangles may protect against AD. This hypothesis would explain both the presence and absence of plaques and tangles in AD and healthy patients. However, research has not been conducted to test this hypothesis or to suggest a threshold at which the deposits lose their ability to protect against the disease.

5 THE BURDEN OF THE DISEASE

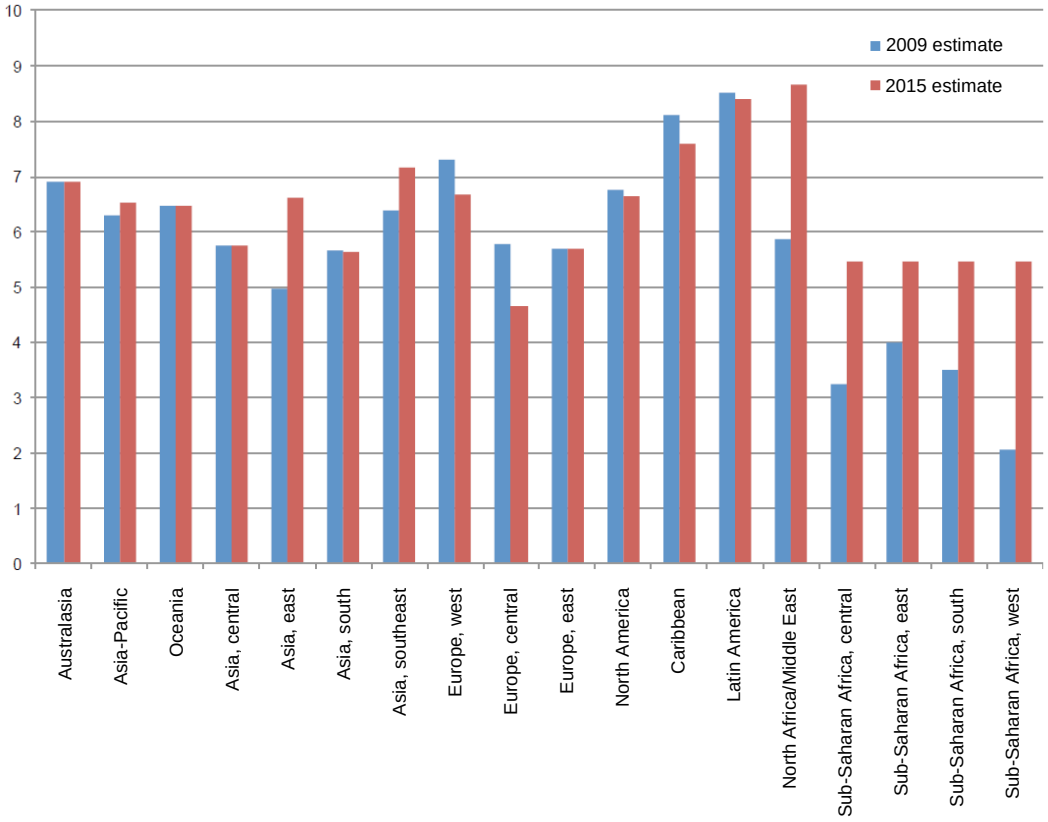
5.1 PREVALENCE AND INCIDENCE

"Prevalence" of AD refers to the number of individuals living with AD at a particular time and is measured as a proportion of the population. "Incidence" of AD refers to the number of new cases in a given period, usually per year, as a proportion of the population. It is important to note that neither prevalence nor incidence can be measured as simply the absolute number of affected individuals within a population. That is because the total number of cases can increase with changes in the total population base, the proportion of the population aged over 65 or the survivability of the condition, without necessarily changing the prevalence or incidence rate.

It is also important to note that statistics provided in this paper pertain to dementia in general, in line with available statistics. While dementia can be diagnosed with a high degree of confidence, the exact type of dementia may not be apparent. The two primary types of dementia, AD and vascular dementia, may not be distinguished for many patients. For example, the Alzheimer Society of Canada refers to AD and related dementias.

According to Alzheimer's Disease International, the worldwide prevalence of dementia among people aged 60 and older varies significantly from region to region – between 4.6% and 8.7% (see Figure 1). Within North America, the prevalence is estimated at about 6.6%. In Canada, about 747,000 people were living with dementia or other cognitive impairment in 2011, a prevalence of almost 15% in those 65 years of age and older.[8] Applying these prevalence data to the known population produces an estimate of 47 million people worldwide over 60 years of age with dementia, up from an estimated 36 million reported in 2012.[9]

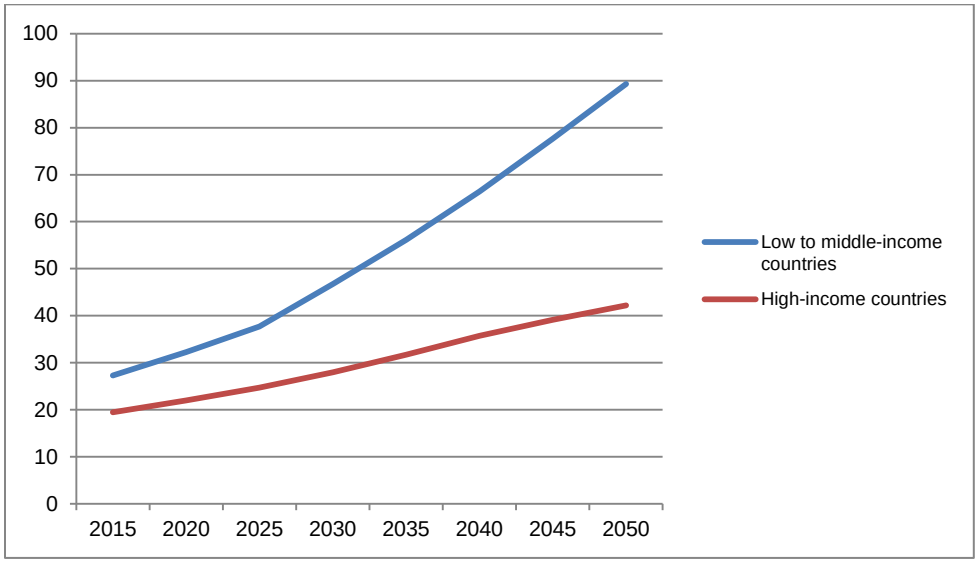
Figure 1 – Estimated Prevalence of Dementia for Individuals Aged 60 and Over



Source: Alzheimer's Disease International, *World Alzheimer Report 2015: The Global Impact of Dementia – An Analysis of Prevalence, Incidence, Cost and Trends*, London, 2015, p. 22.

The number of people over age 60 with dementia is expected to nearly double every 20 years, to 75 million by 2030 and 132 million by 2050 (see Figure 2). The total number of people over 60 is projected to grow between now and 2050 by 56% in high-income countries (which include Canada), and considerably faster in all other countries, namely by 138% in upper middle-income countries, 185% in lower middle-income countries and 239% in low-income countries.[10] Accordingly, low- and middle-income countries will experience a larger increase in the number of people suffering from dementia than will high-income countries.

Figure 2 – Number of People with Dementia in High-Income and Low- to Middle-Income Countries (millions)



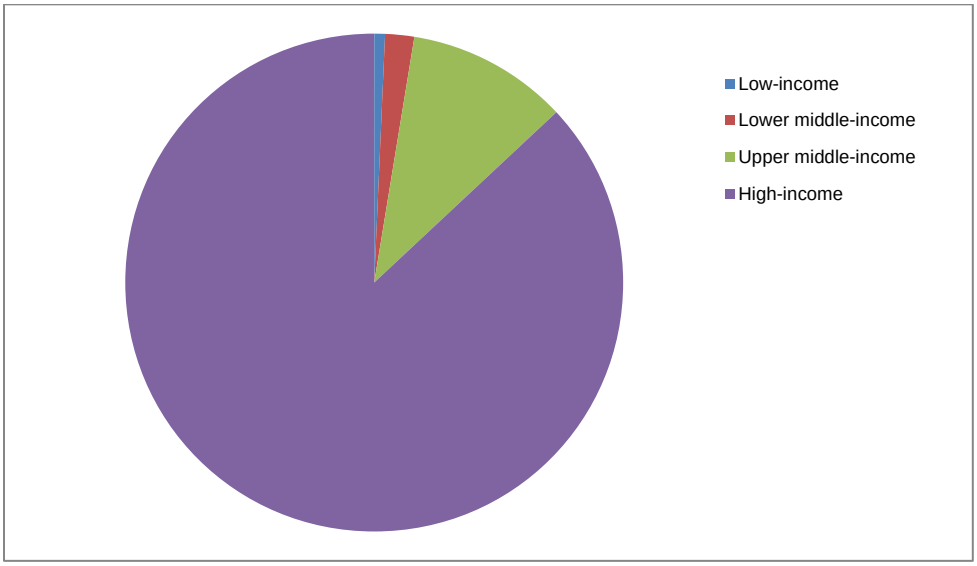
Source: Figure prepared by the author using data obtained from the *World Alzheimer Report 2015: The Global Impact of Dementia – An Analysis of Prevalence, Incidence, Cost and Trends*, London, 2015, Figure 2.4, p. 23.

Alzheimer's Disease International's incidence estimates project 9.9 million new cases of dementia in 2015. Age-specific prevalence is expected to remain constant, or possibly decline slightly in high-income countries.[11]

5.2 Economic Cost

The economic impact of AD and related dementias includes direct costs, such as those for medical and social services, as well as the indirect cost of lost wages for informal caregivers. In its calculations, the Alzheimer Society of Canada includes additional indirect costs due to lost productivity (see below). Although most people with dementia live in low- and middle-income countries, 90% of the costs incurred for AD are in high-income countries (see Figure 3).

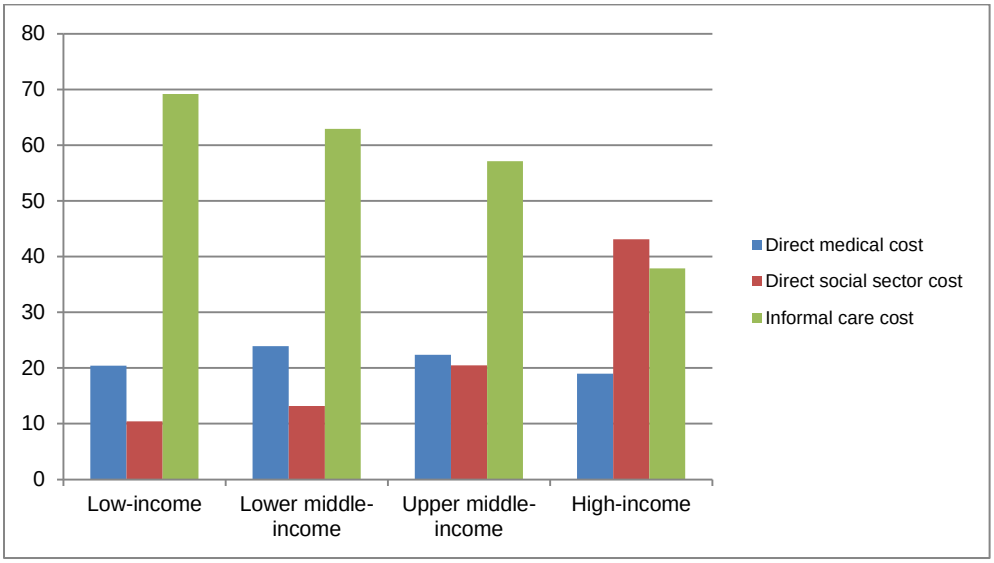
Figure 3 – Proportion of Direct Costs Linked to Dementia Care by Country Income Level



Source: Figure prepared by the author using data obtained from the *World Alzheimer Report 2015: The Global Impact of Dementia – An Analysis of Prevalence, Incidence, Cost and Trends*, London, 2015, "Table 6.11: Costs of dementia in 2015 (billion US$), by 2015 World Bank country iincome level, according to different approaches to costing informal care based on different caregiver inputs," p. 64.

In 2015, the direct cost of dementia worldwide was calculated to be US$818 billion (C$1,105 billion), up from US$604 billion (C$816 billion) in 2010,[12] an increase of over 35% in just five years. By 2030, the global direct cost of dementia is projected to reach US$2 trillion. The breakdown of the worldwide cost of dementia includes direct costs of medical care (20%) and social services (40%), as well as the indirect costs of informal care (40%). Examined by country income level, the bulk of the costs in low- to middle-income countries are associated with informal, unpaid care, while in high-income countries, the social sector costs account for about the same amount as the indirect costs of informal care (see Figure 4).

Figure 4 – Percentage Distribution of Total Dementia Cost by Country Income Level



Source: Figure prepared by the author using data obtained from the *World Alzheimer Report 2015: The Global Impact of Dementia – An Analysis of Prevalence, Incidence, Cost and Trends*, London, 2015, "Table 6.6, Sub-category costs of dementia in 2010 and 2015 (billion US$, and percent of total costs), by country income level based on current World Bank country classification," p. 60.

In 2015, Alzheimer's Disease International calculated the average annual cost per person with dementia to be about US$17,500. [13]This amount has increased by 3.1% on average each year since 2010. The per person cost of care ranges from a low of US$872 in South Asia to a high of US$56,218 in North America, which does not include indirect costs.[14]

In a 2010 report, the Alzheimer Society of Canada projected that the cumulative direct health costs of dementia would increase from C$8 billion in 2008 to C$93 billion in 2038.[15] When it included indirect costs in the calculation, the Society estimated the total annual economic burden of dementia in Canada of both the direct and indirect costs (i.e., reduced labour productivity of the patient as well as that of informal caregivers) at C$15 billion in 2008. This total annual economic burden was projected to more than double every decade to reach C$153 billion by 2038. Those estimates have since increased. According to a 2012 report from the Society, the annual economic burden had risen to C$33 billion, and the cumulative estimate for both direct and indirect costs for 2040 was C$293 billion, well ahead of the 2010 projection.[16]

Given the projected increase in costs associated with AD and dementia in general, accurately determining the causes and risk factors linked to developing AD – and therefore how the disease could be prevented, postponed or better managed – is essential in order to contain expenses.

6 CAUSES OF AND RISK FACTORS FOR ALZHEIMER'S DISEASE[17]

Because nothing that will predict AD with 100% certainty has been identified to date, the "cause" of AD is not known. Instead, factors that can increase or decrease the risk of developing AD have been determined. These factors can be categorized as either modifiable (meaning that a person has some control over them) or non-modifiable (meaning that the conditions are beyond a person's control).

6.1 NON-MODIFIABLE FACTORS

6.1.1 AGE[18]

Advanced age is recognized as the single most important risk factor for AD. As mentioned above, over 90% of people suffering from AD are older than 65, and the risk of AD increases after the age of 65, particularly between the ages of 75 and 85. While age itself is a non-modifiable risk factor, it may be considered a reflection of the accumulation of damage inflicted by modifiable risk factors. Those risk factors are described below.

6.1.2 GENETICS[19]

The dementia that was described by Alzheimer was early-onset AD, which is now known to have a stronger genetic component than late-onset AD. Three genes have been identified in the development of early-onset AD: presenilin 1 (PSEN1), presenilin 2 (PSEN2) and amyloid precursor protein gene (APP). The protein products of each of these three genes affect the amyloid-β protein balance in the brain.

With respect to late-onset AD, the gene for apolipoprotein E (APOE), found on chromosome 19, has been determined to affect the development of the disease, depending on the version of the gene. Specifically, one version of the APOE gene, denoted as the APOEε4 allele, increases an individual's chance of developing AD, while another version, called the APOEε2 allele, appears to offer some protection against developing AD. The risk of developing AD is two to four times higher for a person who carries the ε4 allele on only one number 19 chromosome and 10 to 15 times higher for someone who carries the ε4 allele on both number 19 chromosomes. While it is not necessary to be an ε4 carrier to develop AD, individuals who are carriers tend to develop the condition at an earlier age. Like PSEN1, PSEN2 and APP, the product of the APOE gene also appears to play a role in amyloid-β protein balance, although the exact mechanism by which each of these genes works is quite different.

Numerous other genes that appear to affect a person's risk of developing AD have been identified. However, they increase or decrease the risk of developing AD by only 0.10 to 0.15 times, which is almost insignificant compared to the increased risk of 2 to 15 times attributed to APOEε4.

It is important to note that no genetic variant has been determined to be either necessary or sufficient for the development of AD. That is, people with the genes described here may not develop AD, while others without any of these genes can still develop the condition.

6.1.3 Strokes, Mild Cognitive Impairment and Brain Trauma

Conditions that compromise brain health are associated with an increased risk of AD. Strokes[20] (regardless of severity), existing cognitive impairment[21] and head trauma producing brain injury[22] have been shown to accompany an increased rate of AD. Sometimes these risk factors are listed as "modifiable" because the risk of strokes and MCI can be reduced through medication and lifestyle (see below), while brain trauma can be prevented to some extent by modifying lifestyle and using safety equipment.

6.1.4 Other

There has been some discussion about whether gender or ethnicity may be risk factors for AD, but research has not demonstrated any links. It has been suggested that an increased rate of AD among women or among certain ethnic groups may be attributable to other risk factors. For example, historically, women have lived longer than men, which could make age the primary risk factor. As well, diabetes – a modifiable risk factor related to obesity, healthy eating and metabolic syndrome – described below, is more prevalent among women than among men.[23] Socio-economic level, which can affect all of the modifiable risk factors described below, may be linked to increased rates of AD among some ethnic groups within certain populations or countries. There is also some evidence to suggest that the risk of developing AD associated with the presence of the APOE gene varies for different ethnic groups.[24]

6.2 Modifiable Factors

Research has revealed that several modifiable factors, many of which are interconnected, have an impact on the risk of developing AD. In general, a healthy lifestyle with effectively managed medical conditions is believed to reduce the risk of developing this dementia. There is evidence that the rate of brain cell regeneration increases with exercise and intellectual stimulation and decreases with stress, depression and anxiety.[25] This link may explain, at least in part, why a healthy, active lifestyle appears to reduce the risk of developing AD.

6.2.1 Chronic Disease

Several chronic conditions, if not properly managed, are believed to increase the risk of developing AD. These conditions include high blood pressure, diabetes, high cholesterol and chronic inflammation.[26] This association has been drawn primarily from observational studies, although interventional (clinical) trials have begun. Early results suggest that proper management of these conditions may either protect against developing AD or slow its progression.[27]

6.2.2 Obesity and Metabolic Syndrome

The chronic conditions listed above often accompany obesity. In fact, obesity is a risk factor for a collection of conditions referred to as metabolic syndrome or metabolic disorder. Criteria for diagnosing this syndrome include impaired insulin response or glucose metabolism, as identified by existing type 2 diabetes, high fasting glucose or impaired glucose tolerance.[28] In addition, at least some of the following symptoms must be present: reduced high-density lipoprotein (HDL or "good") cholesterol or increased total serum cholesterol, high blood pressure, increased abdominal (waist) circumference, and urinary excretion of albumin.[29]

Obesity, as a consequence of poor diet and physical inactivity, is the primary cause of metabolic syndrome. However, while the syndrome affects a large proportion of obese individuals, people of normal weight are also susceptible. This is because insulin resistance is a secondary cause of metabolic syndrome. In addition to being a risk factor for developing AD, metabolic syndrome, if not appropriately treated, is predictive of cardiovascular disease, which includes heart disease and stroke.

6.2.3 Unhealthy Lifestyle

6.2.3.1 Smoking[30]

Several lifestyle choices have been shown to increase the risk of developing AD, as they have been for many other chronic diseases. Current smoking has been shown to increase the risk of developing AD by 45%, while the impact of past smoking is not as clear. There are different mechanisms by which smoking is believed to increase the chance of developing AD. The first mechanism is the well-established link between cardiovascular disease/atherosclerosis and smoking. The second is the increase in the level of the amino acid homocysteine in the blood – known to be a risk factor for AD – caused by smoking. The final mechanism is the oxidative stress that occurs with the generation of free radicals[31] that is produced by smoking; it is associated with excitotoxicity[32] and can bring about brain-cell death.

6.2.3.2 Alcohol Consumption

Excessive alcohol consumption is generally considered to be a risk factor for developing AD.[33] Use of alcohol, like smoking, boosts the production of free radicals, causing oxidative stress, and may in this way increase the risk of developing AD.[34]

Determining whether alcohol use is a risk factor for AD is considered difficult for several reasons, including the problem of differentiating between alcoholic dementia and AD and the unreliableness of self-reported alcohol use. As well, alcohol abusers have a higher rate of other risky lifestyle behaviours than do low to moderate alcohol users, suggesting that an increased risk of AD may be attributable to other factors.

Alternatively, some stakeholders have suggested that non-drinkers of alcohol may be at an increased risk of developing AD, while moderate alcohol consumption may protect against AD.[35]

6.2.3.3 Physical Inactivity

Physical exercise has been promoted as a defence against developing AD. Physical inactivity may increase the risk of obesity or the risk of high blood pressure, cardiovascular disease, type 2 diabetes, etc., which are all elements of metabolic syndrome. As well, physical activity may stimulate the growth of new brain cells, improve mood and help to combat depression and stress.[36]

6.2.3.4 Poor Diet

A poor diet can also contribute to the risk of developing AD, although this is largely through the interconnectivity of diet and the development of type 2 diabetes, obesity and metabolic syndrome leading to cardiovascular disease. Some stakeholders suggest that a diet high in antioxidants (which is consistent with a healthy diet of fruits, vegetables, nuts, fish, poultry, eggs, etc.[37]) can help to reduce oxidative stress.

6.2.4 Poor Mental Health

Unhealthy psychological conditions such as depression, stress and anxiety are associated with an increased risk of AD. Research suggests that mental stress, depression and anxiety can decrease the brain's capacity to generate new cells[38] possibly because these states cause an increased production of free radicals, which can produce oxidative stress.[39]

6.2.5 Poor Intellectual Health

The concept of "brain reserve" has been coined to help explain the observation that individuals with higher levels of education are less likely to develop AD than individuals with lower levels of education.[40] In fact, education is one of several proxy, or indirect, measures of brain reserve. Others include "idea density" in writing (such as the complexity of sentence structure), intellectual complexity of occupation and intellectual ability. Activities that keep the brain active, such as maintaining social networks, reading, playing board games, etc., can increase brain reserve and decrease the risk of depression and anxiety. Therefore, these activities are believed to protect against AD or at least slow its progression. Like physical activity, intellectual activity may also help to increase new brain cell growth.[41]

7 CURRENT TREATMENT AND ONGOING RESEARCH

There is no cure for AD, and no therapies have been proven effective at stopping the progression of the disease. Therapeutic options are limited to a few pharmaceuticals that may slow the progression of the disease in its early stages and to existing psycho-active medications that help to manage some of the behavioural symptoms.

One class of drugs approved for early-stage AD treatment is cholinesterase inhibitors. These drugs help to promote the transmission of nerve impulses across synapses by inhibiting the breakdown of the neurotransmitter acetylcholine. These

drugs are no longer effective when the production of acetylcholine becomes very low as a result of the destruction of brain cells that produce it, which is essentially in the advanced stage of the disease. Another drug, memantine, prevents brain nerve cells from being overstimulated when AD causes brain cells to become leaky and secrete large amounts of the neurotransmitter glutamate.[42]

Sometimes other drugs are prescribed to address specific symptoms – which can include physical or verbal aggression, delusions and sleeping problems – that become problematic in AD.[43]

Research is ongoing worldwide to find a cure or an effective treatment to better manage this degenerative condition. On 11 December 2013, Canada signed the G8 Dementia Summit Declaration.[44] The declaration was designed as an international response to dementia and focuses on promoting dementia research and facilitating the sharing of results. Canada was selected along with France to co-host, in September 2014, the second Global Dementia Legacy Event, which addressed partnerships between academia and the pharmaceutical, medical device and information technology industries.[45]

In Canada, the Dementia Research Strategy of the Canadian Institutes of Health Research (CIHR) comprises the international collaboration described above and work done through the Canadian Consortium on Neurodegeneration in Aging.[46] The consortium promotes research in prevention, treatment and quality of life.[47] In 2013–2014, CIHR invested C$37.8 million in dementia research.[48] Its total budget for research grants that year was C$718 million.[49]

Researchers are pursuing potential treatments that target some of the issues described above. Areas of research include strategies either to prevent the accumulation of tau and beta-amyloid proteins from forming plaques and tangles, or to cause the breakdown of existing plaques and tangles; effective treatments to combat the chronic inflammation associated with AD; and improved understanding of the insulin resistance or impaired glucose metabolism associated with AD.[50]

8 PARLIAMENTARY INITIATIVES

The federal role in health care is largely limited to research and the provision of services to various groups, including First Nations on reserves, the armed forces, veterans, federal inmates and refugees. However, the federal government does have an interest in containing the cost of health care delivery, because it transfers funds to the provinces and territories, which have the primary responsibility for health care service delivery, in the form of the Canada Health Transfer (CHT). In general terms, the CHT is the federal contribution to the publicly funded health care system.

Some parliamentary committees have undertaken studies that have addressed AD, although within the larger context of aging or neurological diseases. In June 2012, the House of Commons Standing Committee on Health tabled a report following its study on neurological disorders, entitled *Focussing on the Brain: An Examination of Neurological Diseases in Canada*.[51] One of the five conditions addressed in the study was AD. The report noted that the aging of the population would likely result

in an increased incidence of AD and other age-related conditions. The report called for a pan-Canadian strategy for neurological diseases. Specific recommendations focused on research, surveillance and public awareness.

An earlier study, lasting 2.5 years, was conducted by the Senate Special Committee on Aging, which examined several issues related to aging, including health issues. In April 2009 the committee tabled a final report, entitled *Canada's Aging Population: Seizing the Opportunity*.[52] The report contained 32 recommendations, including recommendations that the federal government, in collaboration with provinces and territories, develop a national caregiving strategy and that it provide funding to the provinces and territories to integrate models of care, including home care services.

As for legislation, Bill C-356, An Act respecting a national strategy for dementia, was introduced in the 41st Parliament. The private member's bill sought to require that the Minister of Health consult with provincial and territorial counterparts for the purpose of developing "a comprehensive national plan to address all aspects of Alzheimer's disease and related dementias."[53] The bill was defeated at second reading.

A private member's motion that addressed the need to establish a pan-Canadian dementia strategy with some of the same elements as those listed in Bill C-356 was unanimously adopted in June 2015.[54]

9 CONCLUSION

The incidence of AD and related dementias is projected to continue to increase in the coming years as the population ages. As in other high-income countries, in Canada, the largest proportion of funds for AD are spent on direct social sector and indirect care expenses, rather than on medical care expenses. This distribution of the economic burden is unlikely to change until there are more therapeutic options for treating, slowing or preventing AD. While research pursues such treatments, focussing at the same time on establishing how the modifiable risk factors, namely unhealthy lifestyles, increase the risk of developing AD and whether adoption of healthy habits can delay the onset of the disease would be a worthwhile endeavour.

NOTES

1. The source of much of the information in this section is José Manuel Martinez Lagé, "100 Years of Alzheimer's Disease (1906–2006)," *Journal of Alzheimer's Disease*, Vol. 9, 2006.
2. Alzheimer Society of Canada, *Rising Tide: The Impact of Dementia on Canadian Society*, 2010, p. 10.
3. Vascular dementia accounts for about 15% of dementia cases, and is caused by impairment of the blood supply to the brain.

   For a description of non-AD dementias, see "Non-Alzheimer's dementia," Series in*The Lancet*, Vol. 386, No. 10004, 24 October 2015.

4. Alzheimer Society of Canada, "Normal aging vs dementia," *About dementia: What is dementia?*

5. Alzheimer's Association, "Mild Cognitive Impairment," *Alzheimer's & Dementia: What Is Dementia?*

6. Alzheimer Society of Canada, "Normal aging vs dementia."

7. The sources of much of the information in this section are Jay Ingram, "Plaques and Tangles" and "A Deadly Progression," in *The End of Memory*, HarperCollins, 2014; and Lars M. Ittner and Jürgen Götz, "The Amyloid-β and tau – a toxic *pas de deux* in Alzheimer's disease," *Nature Reviews Neuroscience*, Vol. 12, February 2011.

8. Alzheimer Society of Canada, "Dementia numbers in Canada," *About dementia: What is dementia?*

9. World Health Organization [WHO] and Alzheimer's Disease International, *Dementia: a public health priority*, Geneva, 2012, pp. 17–18.

   Note that the age cut-off used for international statistics is 60, whereas Canadian statistics report on people over the age of 65. The apparent discrepancy in prevalence rates is explained by the fact that people tend to develop dementia, and AD in particular, after the age of 65. The Canadian prevalence rate also includes all cognitive impairment incidents.

10. These numbers were reached using data in World Bank, *Country and Lending Groups*.

11. Alzheimer's Disease International, *World Alzheimer Report 2015: The Global Impact of Dementia – An Analysis of Prevalence, Incidence, Cost and Trends*, London, 2015, pp. 21–23.

12. Canadian dollar amounts were calculated on 7 December 2015 using Bank of Canada, Daily Currency Converter, at an exchange rate of 1.3508.

13. Alzheimer's Disease International (2015), p. 64.

14. Ibid., p. 61.

15. Alzheimer Society of Canada (2010), pp. 22–23, exhibits 9 and 11.

16. Ibid., exhibit 10. See also Alzheimer Society of Canada, "A new way of looking at the impact of dementia in Canada," September 2012.

17. Alzheimer Society of Canada, "Risk factors," *About dementia: Alzheimer's disease*; and Ingram (2014).

18. Several population-based studies have yielded various conclusions about the increased risk of AD with advancing age. See, for example, L. Fratiglioni et al., "Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group," *Neurology*, Vol. 54, No. 5, Supplement 5, 2000.

19. The sources of much of the material in this section are Rudolph E. Tanzi, "The Genetics of Alzheimer Disease," *Cold Spring Harbor Perspectives in Medicine*, Vol. 2, 2012; and Matthew C. Schu et al., "The Genetics of Alzheimer's Disease," *Advances in Biological Psychiatry*, Vol. 28, 2012.

20. See, for example, Lawrence S. Honig et al., "Stroke and the Risk of Alzheimer Disease," *JAMA Neurology*, Vol. 60, No. 12, December 2003.

21. See, for example, P.A. Boyle et al., "Mild cognitive impairment: Risk of Alzheimer disease and rate of cognitive decline," *Neurology*, Vol. 67, No. 3, 2006.

22. See, for example, S. Fleminger et al., "Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication," *Journal of Neurological and Neurosurgical Psychiatry*, Vol. 74, 2003.

23. Jack Diamond, *A Report on Alzheimer's Disease and Current Research*, Alzheimer Society of Canada, 2008.

24. Schu (2012), p. 21.

25. Jef Akst, "Brain Gain," *The Scientist*, 1 October 2015.

26. Acute inflammation, if localized, is a healthy response to infection or injury. Chronic inflammation, however, is an unhealthy state associated with many chronic diseases, which brings about tissue damage. While signs of it may be subtle, it can be determined by the persistent appearance of specific proteins in the blood.

27. Perminder S. Sachdev, "Is the Incidence of Dementia Declining?," Alzheimer's Australia, Paper 39, April 2014, p. 8.

28. Variations of these criteria are employed by different medical and governing bodies. Cited here is Scott M. Grundy et al., "Definition of Metabolic Syndrome – Report of the National Heart, Lung, and Blood Institute/American Health Association Conference on Scientific Issues Related to Definition," *Circulation*, 2004, Vol. 109, No. 3.

29. Albumin is a normal blood protein, which is only excreted in the urine when kidney damage has allowed the protein to pass through. Chronic conditions such as diabetes can produce such kidney damage.

30. The source of much of the material in this section is J. McKenzie et al., "Tobacco Use and Dementia," *WHO Tobacco Knowledge Summaries*, WHO and Alzheimer's Disease International, June 2014.

31. Free radicals are highly reactive molecules that are produced during some normal biological reactions and can be beneficial, as well as safely disposed of, in the body. Overproduction of these compounds, however, can be damaging through a process called oxidative stress, which accelerates aging and plays a major role in chronic disease development. Antioxidants, either naturally produced or supplied through food and supplements, can reduce oxidative stress.

32. Excitotoxicity refers to the overstimulation of nerve cells.

33. See, for example, K.J. Anstey et al., "Alcohol consumption as a risk factor for dementia and cognitive decline: Meta-analysis of prospective studies," *American Journal of Geriatric Psychiatry*, Vol. 17, 2009.

34. Lien Ai Pham-Huy, Huan He and Chuong Pham-Huy, "Free Radicals, Antioxidants in Disease and Health," *International Journal of Biomedical Science*, Vol. 4, No. 2, June 2008.

35. Sachdev (2014), p. 9.

36. Akst (2015).

37. Pham-Huy (2008); and Ontario Brain Institute, "The Role of Physical Activity in the Prevention and Management of Alzheimer's Disease – Implications for Ontario," 2013.

38. Akst (2015).

39. Pham-Huy (2008).

40. See, for example, M. Valenzuela and P.S. Sachdev, "Brain reserve and dementia: a systematic review," *Psychological Medicine*, Vol. 36, No. 4, 2006.

41. Akst (2015).

42. Alzheimer Society of Canada, "Drugs approved for Alzheimer's disease," *About dementia: Treatment options*.

43. Alzheimer's Disease International, *Drug treatments*.

44. Government of the United Kingdom, *G8 Dementia Summit Declaration*, 11 December 2013.

45. Canadian Institutes of Health Research [CIHR], Global action against dementia, *Summary Report: Second Global Dementia Legacy Event Harnessing the Power of Discoveries: Maximizing academia–industry synergies*, September 2014.

46. CIHR, *CIHR Dementia Research Strategy*.

47. CIHR, *Components of the CIHR Dementia Research Strategy*.

48. CIHR, "Featured research," *CIHR Dementia Research Strategy*.

49. CIHR, *A Portfolio for Health Innovation: Canadian Institutes of Health Research Annual Report 2013–14*, p. 1.

50. Mayo Clinic, *Alzheimer's treatments: What's on the horizon?*

51. House of Commons, Standing Committee on Health, *Focussing on the Brain: An Examination of Neurological Diseases in Canada*, Report 10, 1st Session, 41st Parliament, June 2012.

52. Senate, Special Committee on Aging, *Canada's Aging Population: Seizing the Opportunity*, Final Report, 2nd Session, 40th Parliament, April 2009.

53. Bill C-356: An Act respecting a National Strategy for Dementia, 1st Session, 41st Parliament (first reading version, 24 November 2011).

54. House of Commons, "Alzheimer's Disease and Other Forms of Dementia," *Debates*, 2nd Session, 41st Parliament, 27 May 2015; and House of Commons, "Alzheimer's Disease and Other Forms of Dementia," *Debates*, 2nd Session, 41st Parliament, 17 June 2015.