Dementia—Now a Worldwide Problem With Most Cases in Low and Middle Income Countries and Falling Age Specific Incidence in More Developed Countries

By far the most important risk factor for the development of dementia is age itself, with the risk of dementia doubling every 5 years, extending into the ninth decade of life.\(^1\) Until recently, dementia was thought to be predominantly a problem of more developed countries because of their greater proportion of older people. Many European and Scandinavian countries have already experienced considerable population aging because of increased longevity and falling fertility rates. For example, in 2016 in the United Kingdom, 18% were over the age of 65 years and 2.4% over the age of 85 years. In contrast, in other developed countries, such as the United States of America, Australia, New Zealand, and Canada, population aging is not as pronounced, mainly because of the large migration intakes that have distorted age structures by bringing younger people into their communities and increasing fertility rates. In Australia in 2016, 15% of the population was aged over 65 years and 2.0% over the age of 85 years. In these relatively young developed countries, population aging will be more dramatic as proportionate migration intakes decrease, such that by 2050 Australia will have a population of 6.8% aged over 85 years.

However, the situation is more complex and uneven in other parts of the world, where ageing has occurred over 2 generations rather than 2 centuries. The number of people with dementia worldwide in 2015 was just under 50 million, with two-thirds of all cases living in low- and middle-income countries.\(^2\) Countries such as South Korea have experienced very rapid aging, with 9% over the age of 65 years in 2004, rising to 13% in 2015. China still has relatively low numbers of older people, but falling fertility rates and increased longevity have increased the number of people over the age of 65 years from 4% in 1990 to 10% in 2016; 25% are expected to be over the age of 65 years by 2050.\(^3\) Already there are over 9 million people with dementia in China, and this is dramatically increasing. It is important to emphasize that it is the population in advanced years that drive the numbers of people with dementia because of the exponential increased prevalence with age. Of concern is the observation that in low- and middle-income countries, 60% of the total cost of care is provided by informal care, whereas this is only 40% in high income countries.\(^3\)

Underscoring is a major problem for determining the impact of dementia. In Australia, case ascertainment has recently increased, such that dementia now represents the second commonest cause of death, allowing for multiple contributory causes of death. Of the total number of deaths, dementia is thought to be an underlying cause in 48% of cases and an associated cause in 52%.\(^4\) The median age of death at 88.6 years is substantially greater for dementia than the other common forms of death, and highlights the fact that the major driver of the number of cases of dementia is age itself.\(^5\)

Dementia prevalence and incidence may not be stable over time, and there is some evidence of up to a 20% reduction in age-specific rates in many countries over the last 20 years. In the United Kingdom, The Netherlands, France, United States, and Spain, there is some evidence of decreased age-specific incidence and prevalence.\(^5\) Possible associations with these decreased rates include increased education and decreased cardiovascular risk factors (especially smoking and hypertension).\(^6\) Of particular note is that these reductions have not been associated with the introduction of any dementia-specific prevention strategies. In a world where dementia will be a major problem in all countries, and especially low and middle-income countries, affordable interventions that are easy to adopt are required.

**Diagnosis in Dementia—The Premature Adoption of Technology**

Traditionally, the diagnosis of dementia has relied on clinical criteria with the use of imaging and blood tests to detect so-called reversible forms of dementia. The diagnosis of dementia has relied on the presence of a decline in memory and other cognitive domains severe enough to affect personal or occupational functioning.\(^6\) Specific forms of dementia are often diagnosed in individual patients based on clinical criteria supported by imaging.

More recently, there has been the promulgation of so-called "research criteria for dementia" based on biomarkers and modern neuroimaging.\(^7\) These criteria, although described to be only used for research purposes, are now often suggested for routine clinical purposes. As well, the recently developed *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria allows not only the determination of disease conditions for major neurocognitive
disorders (used synonymously with the term dementia) but also the ability to make formal pathologic diagnoses in predementia states, such as minor neurocognitive disorder.6 However, there are problems with these new approaches. The most common form of dementia in very old people, where the vast majority of cases is found, is probably mixed dementia. Careful neuropathologic studies have revealed considerable overlap of 5 common age-related neuropathologic processes, many of which are found in noncognitively impaired individuals. These include Alzheimer type pathology (neocortical neurofibrillary tangles and neuritic plaques), microvascular infarcts, neocortical Lewy bodies, hippocampal sclerosis, and generalized brain atrophy.7 The commonest form of neuropathology found in people with late life dementia who, during life, appear to have Alzheimer type dementia was one of mixed disease. Defining a single disease entity, Alzheimer disease, may be less and less relevant as people age. This is further supported by the observation that with increasing age the neuropathologic lesions of Alzheimer disease become less able to discriminate between people with and without dementia.8

Despite these fundamental problems that decrease the association between the presence of dementia and Alzheimer type pathology, there is still considerable momentum behind the “Alzheimerization” of dementia, a process where the vast majority of cases of dementia are attributed to Alzheimer disease, with associated attempts to diagnose dementia before routine case-finding, using biomarkers and imaging associated with specific pathology. The use of biomarkers and neuroimaging has been touted as beneficial in this regard, but the evidence in support of this approach is limited.9 A call to use standardized methodology for diagnostic test accuracy studies in the area of dementia10 is often unheeded and focus remains on identifying associations rather than clinical utility, and then advocating for the use of these biomarkers in routine clinical practice.11 When the discordance between properly conducted diagnostic test accuracy studies (eg, using Cochrane methodology) and other reviews using nonsanadardized methodology is raised,12 advocates point out “what ultimately determines the true value of a diagnostic test is whether clinicians request it or not.”13 These requests for diagnostic tests include many where Cochrane diagnostic test accuracy reviews have not found clinical utility, (eg, plasma and cerebrospinal fluid amyloid beta,14 postmortem emission tomography imaging with the 11C-labeled Pittsburgh compound-B,15 99mTc-DPTA postmortem emission tomodiography,16 cerebrospinal fluid tau, and the cerebrospinal fluid tau/Abeta ratio).17 It is important to emphasize that these reviews are based on the mere ability to diagnose dementia reliably at an earlier time point. They do not address the even more important issue, which is the lack of an effective intervention that could be used at an earlier time point to alter the progress of dementia.

Management of People With Dementia—Pharmacologic Agents of Modest Efficacy and Plenty of Evidence for Nonpharmacologic Interventions

There are few effective pharmacologic strategies for management of dementia and Alzheimer disease. The cholinesterase inhibitors have been shown to be efficacious for mild to moderate disease severity.18 However, from the time of their initial release, the average treatment effect on patients has been found to be modest and it was difficult to determine the effect, if any, of these agents on functional ability and the postponement of entry into residential care.19 No existing data can justify the use of these agents for treatment of patients with mild cognitive impairment, not only because they produce no observable benefit but also because of the relatively high rates of adverse events.20 Memantine has been shown to have a small beneficial effect on patients with moderate to severe Alzheimer disease.21 The enthusiasm for the use of medications has often exceeded what could be gleaned from the available evidence. Disturbingly, there have been reports of the years of major benefits from some medications that could not be replicated (eg, tacrine24 and Donepezil25). These reports in high profile journals are an indication of how much enthusiasm and hope has been present by all parties for new pharmacologic interventions. Interventions based on the amyloid hypothesis have been vigorously pursued and although effective at removing amyloid protein from the brain, they have not resulted in any clinical improvement,26 and in 1 trial of a gamma secretase inhibitor, semagacestat, irreversible worsening.27 On the other hand, there are many nonpharmacologic strategies that have important benefits for people with dementia but that are yet to be adopted into routine clinical practice. The enthusiasm for nonevidence-based diagnostic practice and for pharmacologic agents where the evidence is of either for modest or no benefits, is juxtaposed against strong evidence of real benefits for nonpharmacologic interventions. These include cognitive rehabilitation,28 cognitive stimulation29 psychological treatments for depression and anxiety,30 case management approaches to home support,31 and psychosocial interventions for reducing antipsychotic medication in care home residents.32 There are also beneficial interventions directed at caregivers of people with dementia, including cognitive reframing33 and telephone counseling.34 These interventions are distinguished by an investment in training people to better manage and care for people with dementia, without the need for major technological advances.

Conclusions

The world is aging rapidly due to increased longevity and decreased fertility. Much of the world will have sizeable proportions of older people, who will be at risk of dementia. Most of the people with dementia will live in low- and middle-income countries. Despite a considerable investment in neuroimaging and biomarkers to aid in the diagnosis of dementia at an earlier stage, there is as yet insufficient evidence to justify the routine clinical use of such technologies. Currently available pharmaceutical interventions have only modest benefits and only in established dementia. There is considerable evidence for nonpharmacologic interventions in the care and management of people with dementia, and these interventions have received insufficient funding for their widespread adoption into routine clinical practice. These interventions may have great applicability to practice in low and middle income countries where the majority of people with dementia will live.

References
