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Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors

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Abstract

Despite mortality due to communicable diseases, poverty, and human conflicts, dementia incidence is destined to increase in the developing world in tandem with the ageing population. Current data from developing countries suggest that age-adjusted dementia prevalence estimates in 65 year olds are high (≥5%) in certain Asian and Latin American countries, but consistently low (1–3%) in India and sub-Saharan Africa; Alzheimer's disease accounts for 60% whereas vascular dementia accounts for ~30% of the prevalence. Early-onset familial forms of dementia with single-gene defects occur in Latin America, Asia, and Africa. Illiteracy remains a risk factor for dementia. The *APOE* ε4 allele does not influence dementia progression in sub-Saharan Africans. Vascular factors, such as hypertension and type 2 diabetes, are likely to increase the burden of dementia. Use of traditional diets and medicinal plant extracts might aid prevention and treatment. Dementia costs in developing countries are estimated to be US$73 billion yearly, but care demands social protection, which seems scarce in these regions.

Introduction

Older people with dementia exist in nearly every country in the world. Dementia rates are predicted to increase at an alarming rate in the least developed and developing regions of the world despite mortality resulting from malnutrition, poverty, war, and infectious diseases. WHO projections suggest that by 2025, about three-quarters of the estimated 1.2 billion people aged 60 years and older will reside in developing countries.[1] Thus, by 2040, if growth in the older population continues, and there are no changes in mortality or burden reduction by preventive measures, 71% of 81.1 million dementia cases will be in the developing world.[2] About 4.6 million new cases of dementia are added every year, with the highest growth projections in China and its south Asian neighbours. These projections might be confounded by temporal changes due to shorter survival after dementia,[3] lack of education and awareness, inadequate diagnostic assessment,[4] and variability in costs of care of the elderly with dementia,[5] all of which could lead to under-accounting of the dementia

burden.[6] In China, for example, 49% of patients with dementia were classified as normally ageing and only 21% had adequate access to diagnostic assessment,[7] compared with 20% and more than 70%, respectively, in Europe.[8]

There are no known curative or preventive measures for most types of dementia. Diet and lifestyle could influence risk, and studies suggest that midlife history of disorders that affect the vascular system, such as hypertension, type 2 diabetes, and obesity, increase the risk for dementia including Alzheimer's disease (AD).[9–12] Increased trends in demographic transition and urbanisation within many developing countries are predicted to lead to lifestyle changes.[13] Delaying of onset, by modifying risk or lifestyle, decreases the prevalence and public health burden of dementia; a delay in onset of 1 year would translate to almost a million fewer prevalent cases in the USA.[14] However, this in turn might increase demands on health services and costs for older populations.[15]

We review published prevalence estimates and modifying factors for brain ageing-related dementias in developing regions of the world, as defined by the United Nations.[16] Our report is limited to ageing-related neurodegenerative and vascular dementias and does not address dementia secondary to retroviruses (eg, HIV) or other infectious agents, recognising that these might assume importance in younger adults or in specific regions. Other reviews have focussed on these issues,[15,17,18] but we take particular note of genetic and environmental factors,[18,19] in addition to the problems encountered in accounting for differences in dementia occurrence between developed and developing countries. Although more data from developing countries are needed, several comparative dementia prevalence and risk-factor assessment projects, which use similar designs, survey methods, and investigators, have been invaluable resources to allow examination of phenotypic variations in dementias in populations living in very different cultures and environments.[18,20–22]

Dementia screening

Neuropsychometric assessment seems to be the best method to screen individuals in most developing countries.[23] At the outset, the lack of standardisation of screening tools has to be recognised as a major issue in the estimation of the true burden.[20] Standardisation might not be readily achieved because of diversity of language, culture, and levels of literacy. In certain communities, more than 80% of elderly people do not read or write.[24] The mini mental state examination (MMSE) has been translated into many languages, but its use might be limited even as an initial screening tool. Independent back translations and consistent informant assessments are therefore mandated. Neuropsychological test batteries with components relatively free of cultural and linguistic factors (eg, verbal tests of delayed recall and of language) have been developed,[25] but experience suggests that assessments must be consistent with the culture and language of the population under study, and local normative data for test performance need to be compiled.[26]

To achieve universal standardisation and to chart the epidemiological transition and its effect on older people, the 10/66 Dementia Research Group centres have initiated evidence-based procedures for use in different catchment areas worldwide.[27] These include cross-culturally validated assessments for dementia subtype diagnosis, other mental and physical health diagnoses, anthropometry, demographics, non-communicable disease risk factors, disability and functioning, health-service utilisation, care arrangements, and caregiver strain. Nested within the population-based studies is a randomised controlled trial of caregiver intervention for people with dementia and their families.[27] The surveys include ascertainment of other mental disorders, vascular disease, chronic obstructive pulmonary disease, and arthritis.[27] Documentation of specific functional decline can be a challenge, because in some cultures, elderly individuals might have a restricted range of activities

available to them, or family members might take over these activities. However, a history of cognitive decline can generally be combined with psychometric testing to support the diagnosis. Determination of the correct age of individuals who do not possess formal documentation of birth is another factor that could hamper comparisons, although methods on how accuracy might be achieved have been recognised.[28,29]

Dementia prevalence and incidence

Since the Delphi study projections,[2] several large-scale dementia prevalence studies have been done.[30–39] Dementia prevalence estimates vary widely within developing countries (table 1). This variation might indicate differences in population age structure, genetics, and lifestyle, but could also be due to difficulty in standardising dementia assessment and reduced survival after diagnosis.[15] The mean age-adjusted prevalence estimate for dementia among people aged 65 years and older living in developing countries, derived from data published within the past 10 years, was calculated to be 5.3% (95% CI 3.9–6.5; table 1). This estimate was obtained by determining the original sample sizes and numbers of dementia cases reported to be 65 years and older in individual studies per country, and re-calculating mean estimates and variation by use of SPSS 15.0, according to the method by Yang.[59]

Surprisingly, countries in Latin America, such as Venezuela and Argentina, bear a higher burden of over 5% prevalence of dementia (figure). By contrast, a systematic analysis of six Indian studies suggests low prevalence (2–3%) of all dementias, with marginally fewer cases in urban compared with rural areas and in the northern versus southern states.[33] Pooled analysis of 25 Chinese studies by Dong and colleagues,[30] comprising a total population of more than 76 000, suggested that the overall prevalence of dementia was 3.1%, indicating a significant rise from 1980 to 2004. However, a recent survey of over 34 807 Han Chinese residents aged at least 55 years in 79 rural and 58 urban communities of four distant areas reported a crude prevalence estimate of 5.0%, and 6.8% after adjustment for negative screening.[31] Higher prevalence was apparent in northern regions compared with the south, but no difference was evident among urban and rural Chinese residents.[7] In the Upper Assiut region along the Nile, age-adjusted dementia prevalence in people aged 65 years and older was 5.9%.[51] In the Yoruba (Niger-Kordofanian people) of Nigeria, dementia prevalence was low (2.3%) compared with an African American population in Indiana, USA (8.2%).[52] Among Arabs living in Wadi Ara, a community south of Haifa in Israel, the crude prevalence estimate for all dementias was 21% in those aged over 60 years.[50,74] Consanguinity among families was suggested as a reason for this high prevalence.[74,75] Studies from developing countries in Eastern Europe have assessed some risk factors, but prevalence or incidence data in these communities are unknown.[62]

The variations in prevalence within developing countries seem close to those found in the recently completed 10/66 survey of 14 960 residents aged over 65 years in 11 sites in seven low-income and middle-income countries (China, India, Cuba, Dominican Republic, Venezuela, Mexico, and Peru).[20] Prevalence of dementia according to the Diagnostic and Statistical Manual of Mental Disorders (4th edition) varied widely, from less than 1% in the least developed countries, such as India and rural Peru, to 6.4% in Cuba. The 10/66 study also found that informants in the least developed countries were less likely to report cognitive decline and social impairment,[20] suggesting possible underestimation of prevalence estimates in some locations.

Few incidence estimates are available to substantiate prevalence figures for those aged 65 years and older. Compared with developed countries, relatively lower annual incidence estimates of 1–2% are reported in certain countries, such as Brazil, Nigeria, India, and

Taiwan.[41,46,63,76] In a Brazilian community, incidence was determined to be 13.8 per 1000 person-years.[76] In a comparative study, the Yoruba in Nigeria were found to be half as likely to develop dementia as African Americans in Indiana, USA; age-standardised annual incidence was 1.4% in the Yoruba versus 3.2% in African Americans.[63] Among residents aged 60 years and older in Beijing, China, an incidence of 0.9% was determined at follow-up versus the original prevalence of 2.5%. AD was the most common type of dementia in both prevalent and incident cases.[77]

Subtypes of dementia

Alzheimer's disease

Late-onset AD is the most common subtype of age-related dementia, even in developing countries; 60% of all cases of dementia fulfilled the US National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria.[78] Total population projections suggest that 3.1 million people in China could have AD. Although unusually high prevalence was apparent in some countries, the mean AD prevalence was estimated to be 3.4% (95% CI 1.6–5.0), which is slightly lower than in developed countries. Age-adjusted low prevalence (<1.5%) was reported in sub-Saharan Africa (Nigeria) and India (table 1). The mean estimate was obtained by retrieving the original sample sizes and numbers of probable AD cases in individual studies per country and re-calculating the rate and variation by use of SPSS 15.0, according to the method by Yang.[59] Autopsy studies done in some developing countries have confirmed that the neuropathological changes associated with AD are qualitatively similar to those in patients in developed countries;[79–81] however, more work is needed, particularly given that reported AD cases could also have cerebrovascular changes.[30,31,33]

Consistent with the prevalence estimates, the incidence of AD for those aged 65 years and older was 7.7 per 1000 person-years in Brazil,[76] and 3.24 per 1000 person-years in India.[82] The annual incidence of AD in the Yoruba was determined to be 1.2%, substantially lower than the incidence of 2.5% in African Americans from Indiana.[63]

Vascular dementia

Vascular dementia (VaD) is recognised as the second most prevalent type of dementia. Neuroimaging is not routinely available in developing countries, which influences the accuracy of VaD detection and the confirmation of cases of mixed dementia. Analysis of data from 12 centres[30–36,39,43,44] for which imaging findings were available indicates that 26% of cases of dementia fulfilled the US National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS–AIREN) criteria for VaD.[83] The mean estimate was obtained by determining the screened samples and numbers of reported VaD cases in individual studies per country and calculating the mean and variation in the same way as for AD prevalence. Prevalence estimates of VaD in developing countries range from 0.6% to 2.1% in those aged over 65 years (table 1). A third of 4.5 million Chinese patients with dementia are predicted to have VaD.[31] With the exception of some Latin American and Asian countries,[84] VaD prevalence in developing countries seems to be low. VaD might be more common among the Chinese and Malays, whereas AD is common in Indians and Eurasians.[85] Subcortical VaD caused by small-artery disease,[6] associated with hypertensive disease, seems to be a common (73%) cause of VaD.[64] In several countries in Asia and Latin America, up to 10% of dementia cases are diagnosed with mixed dementia.[30,40] Up to 30% of Chinese people in urban areas develop post-stroke cognitive impairment or delayed dementia after stroke.[86–88]

However, the prevalence of vascular cognitive impairment that involves all domains of cognitive function and causes of vascular injury is likely to be greater than that of VaD.[89]

Other subtypes of dementia

Prevalence data on other types of neurodegenerative dementia are limited. Single case reports and dementia prevalence studies do record causes of dementia other than AD (table 1). The first autopsy-confirmed case report of dementia with Lewy bodies in sub-Saharan Africa was reported in a Nigerian patient.[90] Cases of dementia with Lewy bodies and Parkinson's disease with dementia have been reported in India,[91] Sri Lanka,[49] Taiwan,[92] and China.[30,93] Frontotemporal lobar degeneration, which involves a range of disorders associated with and without microtubule-associated Tau protein accumulation, does exist in developing countries but has rarely been described.[30,92,94] Several cases of primary progressive aphasia with slow progressive deterioration of linguistic processes have been reported in Brazil.[95] The Chamorros of Guam are affected by amyotrophic lateral sclerosis (ALS) and Parkinson's dementia complex (PDC), both of which are associated with pathological changes that resemble the neurofibrillary tangles found in AD.[96] However, Guam has experienced rapid modernisation since World War II, and the incidence of ALS and PDC has declined.[65] Recent studies indicate that the prevalence of dementia is approximately 12% among Chamorros aged 65 years or over (8.8% Guam dementia [clinically resembles AD], 1.5% PDC, and 1.3% VaD). Prion diseases, including sporadic, dominantly inherited, or transmitted cases of Creutzfeldt-Jakob disease, have also been described.[66] The 129M susceptibility allele of the prion protein gene is found at high frequencies in Eurasian populations.[67]

Familial forms of dementia

Worldwide prevalence of early-onset dementias, generally defined as occurring before 65 years of age, is expected to be much higher than the global prevalence of early-onset AD at approximately 5.3 per 100 000 population.[97] Most monogenic and complex disorders, including familial AD, Parkinson's disease with dementia, frontotemporal lobar degeneration, Huntington's disease, and small-vessel diseases of the brain, have been described in developing countries, but their frequencies are unknown (figure). Indigenous African and Asian families have been found with early-onset (33–45 years) AD caused by mutations in the amyloid precursor protein and presenilin genes.[68,92,98,99] In Medellin, Colombia, the E280A mutation in the presenilin 1 gene (*PSEN1*) causes severe AD in a large kindred.[100] Over 200 families with early-onset AD have also been identified among Caribbean Hispanics originating from the Dominican Republic and Puerto Rico.[101] In 10% of these families, at least one family member had onset of dementia before the age of 55 years and almost half showed an association with a previously unreported presenilin mutation.[101]

Many families with early-onset VaD of small-vessel-disease type, in the form of cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL),[89] have been described in Asia, Africa, and Latin America.[69,70,102] The trinucleotide repeat (CAG, GCC expansion) diseases, of which Huntington's disease is an example, are an important cause of disability and dementia in sub-Saharan Africa,[103] Asia,[92,104] and Latin America.[105] In Maracaibo, Venezuela, the estimated prevalence of Huntington's disease in the state of Zulia is about 720 in 100 000 inhabitants, compared with 5–10 per 100 000 reported worldwide.[71] Of note, environmental factors have been shown to influence the phenotypic expression of these dominant genes.[72,106]

Behavioural and psychological symptoms of dementia

Behavioural and psychological symptoms of dementia (BPSDs) are common among people with dementia in developing countries, although there seem to be marked regional variants.[22,107] Several factors, including methods of reporting and cultural taboos, might account for the variations. However, at least one BPSD was reported in 70% of participants from 17 developing countries, and at least one case-level AGECAT psychiatric syndrome was shown by nearly half of those with dementia.[27] Depression syndromes are most commonly followed by anxiety neurosis and schizophreniform or paranoid psychosis. Almost 80% of patients with AD in a Brazilian study had one or more BSPDs.[108] Apathy was present in more than half (53%), followed by depression (38%), sleep alterations (38%), and anxiety (25%), whereas the most frequent neuropsychiatric symptoms in the cognitively impaired (but not demented) group were anxiety and sleep alterations, followed by depression.[108] In India, patients with AD rather than VaD have significantly more delusions, hallucinations, anxieties, phobias, and caregiver distress with longitudinal patterns similar to those reported in developed countries.[91] Poor cognitive performance was associated with significantly higher rates of depression in the Yoruba.[109] Despite substantial socioeconomic and cultural differences between the Yoruba and African Americans, prevalence estimates of both mild and severe depression are generally similar in the two population samples.[109] Although patterns of behavioural disturbances might vary,[108,110] BPSDs seem to be common in developing and developed countries.

Early stages of dementia and mild cognitive impairment

The transition or prodromal stage between normal ageing and dementia or mild cognitive impairment (MCI) is a heterogeneous entity. Diagnostic criteria and standardisation of MCI are evolving, which makes direct comparisons among studies more difficult, possibly due to the stronger influence of illiteracy and socioeconomic factors, than in similar studies when dementia is diagnosed. Patients and families in developing countries are also less likely to admit or report cognitive difficulties because of prevailing cultural attitudes; identification of MCI in these countries therefore requires the presence of additional factors, such as infection and vascular comorbidites and poor nutrition. A small number of studies suggest that conversion rates of MCI or cognitive impairment with no dementia seem to be low in developing countries,[111,112] but they report similar prevalences of impairment to those in developed countries. An Indian cross-sectional study reported that, in individuals aged 50 years and older, overall prevalence of MCI was 14.9% (95% CI 12.2–18.0) and that multiple-domain MCI was the most prevalent (8.85%) and was associated with increasing age, hypertension, and diabetes mellitus.[113] In Brazil, prevalence of cognitive functional impairment was 16–19%.[114] Higher age, low education, epilepsy, and depression were associated with increased risk, as were being female, widowhood, low social class, and head trauma. Stroke and diabetes were also associated with MCI within communities in Brazil, Puerto Rico, and Malaysia.[114,115]

Risk factors for dementia

Age and sex

Exposure early in life to deleterious conditions related to poverty, including infectious diseases, malnutrition, and prenatal stress, might influence the ageing process and reduce longevity for people in developing countries.[116,117] Despite these realities, increasing age is the most consistent risk factor for dementia worldwide (table 2). Age was also a strong risk factor,[30,51] with dementia prevalence of 2–11%, in those aged under 65 years. Nearly all studies in Latin America, Africa, and Asia confirm that women are marginally more likely to develop dementia and AD, particularly in very old age,[76] on the basis of the greater

expected numbers of ageing women,[1] whereas VaD was slightly more prevalent in men (table 2).

Early-life negative events and physical attributes

Recent studies suggest that various genetic and environmental factors, including early-life brain development, body growth, socioeconomic conditions, environmental enrichment, head injury, and cognitive reserve, are likely to contribute to dementia risk.[120,127] These factors have not been specifically investigated, but people in developing countries have a greater likelihood of early-life negative risks. Life expectancy at birth is much lower than in developed countries because of higher infant and maternal mortality and greater prevalence of infectious diseases. However, differences between developing and developed countries are substantially reduced in those who have reached the age of 65 years.[128] In addition, older people in an area with high early-life mortality are not necessarily protected from dementia. In fact, such individuals continue to be at higher risk of death.[129] Nevertheless, physical characteristics, such as leg length and head circumference, might be markers of early-life stressors,[118,119,130] which result in reduced cognitive reserve. Significant negative early-life events might also increase the risk of AD among survivors.[131]

Literacy and education

On the one hand, illiteracy or low educational achievement has been shown to be a robust risk factor for dementia.[120] On the other hand, intellectually stimulating, socially engaging, or physical activities might lower the risk of dementia.[121] The situation is not different in developing countries, where surveys have consistently identified low education as a risk factor for dementia (table 2).[85] However, in some communities, level of education, indexed by years of primary schooling, might not necessarily contribute to low prevalence.[18] Low literacy is often linked to poverty or lower socioeconomic status, which is also associated with poorer health, lower access to health care, and increased risk of dementia (table 2).[35,76,132]

Genetic association studies and risk genes

Several groups in Asia and Latin America have done genetic association studies, spanning more than 127 polymorphisms across at least 69 different putative AD susceptibility genes.[133] Genetic traits with autosomal recessive features are being explored in communities with high consanguinity. For example, studies in Wadi Ara have shown clustering of AD in families, and association with a new haplotype of the angiotensin-converting enzyme.[134,135] The association of AD with at least two genes, apolipoprotein E (*APOE*) and neuronal sortilin-related receptor (*SORL1*),[133,136,137] seems to be affected by ethnicity, age, sex, medical history, and geographical location. The *APOE* ε4 allele does not increase risk in sub-Saharan Africans and is only weakly associated with AD in Caribbean Hispanics and African Caribbean people of Jamaican origin.[101,136,138] *APOE* ε4 is a risk factor for AD among women but not men in Venezuela.[139] However, frequencies of the *APOE* ε4 allele are reported to be relatively increased in healthy Africans and some non-Africans: for example, 14–41% in indigenous people from Central African Republic, East Africa, Southern Africa, Malaysia, Australia, and Papua New Guinea,[122,123,140] compared with 8–12% in Caucasians and Japanese.[136] By contrast, certain groups have low frequencies of the *APOE* ε4 allele: 3–4% in the Wadi Ara Arabs in Israel, Oman, and Algeria,[134] and 7% in North Indians and Taiwanese people.[92,141]

Comparative analysis showed that the *APOE* ε4 allele was a risk factor for AD in African Americans, but not in Yoruba Nigerians,[124,142] or in population samples from the Vihiga and Nyeri districts of Kenya,[29] or Kingston, Jamaica.[143] There was also a lack of association

of *APOE* genotypes with risk for dementia after adjusting for sex, age at diagnosis, and education,[68,122,124] and in communities with high consanguinity.[134]

Early-onset familial AD in developed countries has not been reported to be modified by the *APOE* ε4 allele. However, patients with early-onset AD carrying the *APOE* ε4 allele in the Colombian kindred with the E280A presenilin mutation were twice as likely to develop disease at an earlier age than those without the *APOE* ε4 allele.[144] Low education and rural residence also influenced the age of onset in these patients.[144] The *APOE* ε4 allele was strongly associated with late-onset familial AD among Caribbean Hispanics from the Dominican Republic and Puerto Rico,[101] but not in Guamanians with dementia.[65] The risk of ALS, PDC, and AD in Guam seems to be associated with genetic variants within the Tau gene, one of which increases the risk for progressive supranuclear palsy.[145]

The *SORL1* gene, which might influence homoeostasis of the amyloid precursor protein, is thought to be the second most important gene to modify late-onset AD in multiple and ethnically diverse populations.[137] Association of risk with this gene was found in Wadi Ara Arabs, among whom there is high consanguinity, as well as in Caribbean Hispanics[137] and Han Chinese.[146] Allelic heterogeneity in *SORL1* is suggested by the novel single-nucleotide polymorphisms that have been found to be associated with the gene.[133]

Stroke and vascular disease risk factors

Stroke is an increasing burden in developing countries,[147,148] and a major cause of mortality and long-term disability.[149] Accumulating evidence suggests that stroke injury and vascular factors increase risk for AD and other dementias.[10,89,150–155] Vascular factors, such as hypertension,[9] dyslipidaemia,[156,157] hyperinsulinaemia and type 2 diabetes,[158,159] obesity,[160] subclinical atherosclerosis,[161] and arrhythmias,[162] are associated with greater risk of cognitive impairment and dementia. Studies in Latin America also show that metabolic syndrome doubles the risk of cognitive impairment,[163] and is significantly associated with functional dependence, depression, and low quality of life.[164] Factors that decrease vascular function, such as tobacco use, which is common in countries such as China,[165] might further influence cognition in old age.

The shift from infectious diseases to non-communicable but modifiable chronic disorders has resulted from gradual adoption of a Western lifestyle that includes excessive caloric intake, unhealthy diet, and decreased physical activity.[160,165–170] This trend is expected to contribute to the global burden of AD.[171,172] Vascular disease-controlling medications, such as antihypertensives and statins, might not be protective.[173,174] The most cost-effective way to prevent dementia might be through dietary or lifestyle interventions in communities at variable risk of cardiovascular disease,[175] such as the Yoruba,[176] northern Indians,[177] Venezuelans,[178] and Wadi Ara Arabs.[179]

Dietary factors

Studies examining nutritional risk, which often rely on self-reports, are fraught with difficulties and should be cautiously interpreted. Observational data suggest that the low risk of dementia in some developing countries can be attributed to the type of diet.[180] Diets rich in fruits, vegetables, and fibre improve human well-being and significantly reduce development of the pathological processes that are characteristic of neurodegenerative disorders.[181] Chinese studies suggest that regular tea drinking might be protective against AD.[182] The low incidence of dementia in the Yoruba Nigerians is consistent with their traditional low calorie and low fat diet consisting of grains, yam tubers (*Dioscorea rotundata*), vegetables, and some fish.[176] Among Indonesians, there is a 30% lower risk of impairment with higher consumption of mucuna tempe,[73] which has a high fibre content.[183]

By contrast, eating tofu has been associated with worsening memory, independent of age, sex, and education, among Indonesians,[73] which concurs with the association of tofu consumption in midlife and cognitive impairment and brain atrophy in elderly Japanese Americans.[184] Salivary phytooestrogens (genistein and daidizein) are associated with a higher risk of dementia, particularly in Javanese people aged over 68 years.[73] The interaction between ageing and staple diets containing potential toxins might explain the dementia prevalence in certain locations such as Guam, where preparing or eating cycad fruit during young adulthood is associated with late-life dementia and PDC.[145]

Use of herbs and medicinal plants for dementia

Developing countries tend to retain traditional herbal medical practices and thus offer an invaluable resource for new anti-dementia therapies.[185] However, the usefulness of such a resource relies on documented evidence of the effects. One of the largest long-term controlled clinical trials in progress on dementia prevention is based on the Asian traditional tree medicine *Gingko biloba*.[186] Preliminary data have indicated significant effects on dementia progression,[187] but the most recent Cochrane analysis concluded that evidence of predictable and clinically significant benefit of *G biloba* and standardised extract (EGb 761) for people with dementia is inconsistent and unconvincing.[188] Huperzine A, originally isolated from *Huperzia serrata*, a type of moss used in traditional Chinese medicine (also known as *qiang ceng ta*),[189] has been marketed in China as a new drug for AD treatment, and its derivative, ZT-1, is being developed as a new anti-AD drug.[190,191] A plethora of pharmacognostic practices, including those for cognitive care, still exist in countries such as Africa, South America, India, and in other aboriginal cultures.[185] Other relevant phytotherapeutics from developing countries, including combinations of traditional Chinese medicinal herbs (*yi-gan san* and *ba wei di huang wan*), sage (*Salvia officinalis* and *Salvia lavandulaefolia*), and lemon balm (*Melissa officinalis*), which have shown positive benefits on behavioural symptoms and cognition, need to be explored in wider studies.[192,193]

Several species of medicinal plants have activities in vitro or in vivo that are relevant to dementia (eg, anti-cholinesterase, anti-amyloid, anti-inflammatory, anti-oxidant, neuroprotective, and memory enhancing). The most frequently reported are blueberry, cannabis, club moss, curcumin, garlic, ginseng, green tea, pomegranate, and rhubarb.[170,181,194,195] The dementia drug rivastigmine is a synthetic chemical analogue of physostigmine (from the Calabar bean, *Physostigma venenosum*), and galantamine is the main alkaloid in daffodil and snowdrop bulbs.[196] Initiatives thus need to continue to protect, assess, and standardise traditional herbal medicines used in developing countries.

Mortality and dementia

Dementia modifies survival and increases the risk of death. A study among Shanghai residents indicated that the mortality risk ratios for AD and VaD, particularly in those over 75 years of age, were similar to the mortality risk ratio for cancer.[125] In another Chinese study, the risk for death in patients with dementia was reported to be three times higher than in the whole cohort, although not related to a specific cause.[84] In Brazilians, dementia was determined to be the most significant predictor of death, followed by age, history of stroke, complaints of visual impairment, heart failure, and severe arterial hypertension.[197] In Ballabgarh, India, the median survival time after onset of dementia symptoms was determined to be 3.3 years for patients with dementia and 2.7 years for patients with AD compared with 5.0–9.3 years in developed countries.[46] Dementia was also associated with increased mortality in Nigerians and African Americans (relative risk ratio, compared with the population studies, was 2.83 versus 2.05).[198,199]

Costs of dementia

Current projections indicate that the burden of disease, expressed as WHO-designated disability-adjusted life-years (DALYs), is unequally distributed between middle-income and low-income countries (table 3).[16,200] However, if dementia prevalence in developing countries is assumed to increase substantially due to demographic transition, the DALYs per number of patients with dementia who are 65 years and older are similar between regions.[5] To estimate the total costs, we modelled the societal worldwide costs as well as region-specific and country-specific costs by combining prevalence estimates,[5] country-specific, and region-specific data on gross domestic product per person, and average wage with results from previously published cost-of-illness studies in several key countries from which detailed data about direct costs and informal care costs were available.[201] From this model, total costs of dementia in developing countries are estimated to be US$72.6 billion yearly (table 3). By use of the lower Delphi estimates,[2] costs for Africa would be US$2.9 billion. [201] Cost estimates do not provide any information about the cost distribution among those who actually pay or how large a proportion of the total resources are required for a particular disorder.[202] In developed countries, long-term institutional care constitutes the main cost, [203,204] whereas in developing countries, informal care, usually at home,[205] is invariably the only method of care.[206,207]

The cost model estimates that approximately 75% of the global costs occurred in middle-income countries, where 46% of patients with dementia worldwide reside,[201] but informal care costs, which are increasing in developing countries,[13,208] were proportionally greater (1.0 of 1.8 billion or 56% of total) in the least developed countries.[201] For example, in Argentina and Brazil,[209,210] the expenses (medical and non-medical) borne by families of people with dementia were considered to be very high. Similarly, in China, non-medical costs increased with severity of cognitive decline and increases in BPSDs, and daily 24-hour care was needed for those with a MMSE score below 11 and BPSDs.[211] In Turkey, informal care was estimated (by use of a replacement cost approach) to be the major cost driver, although the amount of informal care time was lower than in other studies.[206] The dominance of informal care was evident in South Korea, where these costs constituted 55% of societal costs,[212] but in India, the amount of informal care was similar to that in middle-income countries.[213] By contrast, the costs of home care (including informal care) with nursing care in Taiwan were less than for institutional care, particularly for patients with severe dementia if a replacement cost approach was used.[214,215] The weakness of such projections is that they rely on extrapolation of data from middle-income countries,[216] and require information about true prevalence, and the conceptualisation, quantification, and actual costs of informal care.[201] Definitions of care activities, particularly in terms of instrumental activities of daily living and supervision versus normal family activities, also pose difficulties in the estimations of overall cost.

Dementia awareness, care, and services

Understanding the burden and costs of dementia is crucial to guide future health care and socioeconomic policy.[27] Policymakers need evidence to prioritise and plan appropriately for the rapidly growing numbers of older people with dementia and other chronic diseases. Low public awareness, under-diagnosis, and under-treatment could be addressed by national mobilisation strategies to increase awareness and specialised training for heath professionals and authorities through mass media, scientific reports, and special activities, and by the setting up of open clinics in communities. For example, through such efforts, the mean proportion of patients with AD in China treated with acetylcholinesterase inhibitors and memantine increased from 12.1% (range 0.2–29.1%) in 2001 to 19.6% (range 2.3–41.1%) in

2007.[217] The variation among the Chinese districts mainly depended on the levels of economic development and medical insurance cover.[7]

Social protection is hard to define, but is a major concern in most developing countries. This might be complicated by a lack of carers due to urban and economic migration, conflict, and HIV/AIDS. The circumstances of those with dementia in each centre of the 10/66 study, surveyed by use of an adapted version of the Client Service Inventory Report,[27] highlight the vulnerabilities of dependent older people living in these regions.[218] For people with dementia, the state does not provide long-term care; consequently, the family, particularly the patients' offspring, plays a vital part. An estimate of the worldwide costs of dementia used an average of 1.6 hours of informal personal care per day for all people with dementia.[201] However, this figure is exceeded in most 10/66 study centres. In all Latin American centres other than Mexico, a sixth to a quarter of people with dementia have no children locally available to provide care. Even in rural China and in India, 5–10% lack this fundamental support.[218] Children can provide food, shelter, personal care, and income for their parents through cash transfers (particularly important in India, Dominican Republic, rural Peru, Mexico, and China because of very low pension coverage). In all 10/66 centres, living with children is the norm, and three-generation households (including children under 16 years) are common.[205] Nevertheless, around a fifth of people with dementia (10–37% by centre) live alone or with a spouse only, and hence can be considered vulnerable.[207,218] Current research indicates that a worryingly high proportion of people with dementia lack the basic necessities for life (ie, food), particularly in parts of Latin America, and in India, where social protection is most insecure.[4,205,207,209,210,218,219]

International agreements, plans, and policy guidelines have called for an end to age discrimination and a focus on reducing disadvantage linked to poverty and the consequences of ill health.[1] Ensuring social protection, allowing access to good quality age-appropriate health care, and addressing the problem of disability are key concerns. Thus, levels of caregiver strain, including that contributed by behavioural disturbances and stress, are as high as in developed countries despite extended family networks and home care.[207] Moreover, dependency is strongly linked to poverty, and imposes additional economic strain on families.[207] The Ibadan project in Nigeria has advocated periodic home visits, and empowerment of caregivers through regular meetings to make caring for individuals with dementia easier and more adaptable.[220]

Conclusions

The prevalence of dementia, particularly that of AD, is increasing in the developing countries of Asia and Latin America. However, reliable age-adjusted estimates indicate a low prevalence of dementia in India and sub-Saharan Africa. Difficulties in definition, ascertainment of decline in intellectual ability, and assessment of patients mean that meagre information on MCI is available in developing countries.[20] Illiteracy and depressive illness remain strong risks for dementia. Further research is needed to examine why the *APOE* ε4 allele does not seem to influence AD progression in sub-Saharan Africa. Increasing frequency of vascular disease and global trends in modernisation will add to the burden of AD within developing countries. Harmonisation of screening methods worldwide could help to define risks and to devise novel approaches for dementia prevention. The impact of dementia in developing countries deserves further epidemiological and implementation research to enable early detection, widespread adequate treatment, and caregiver support. Such efforts will no doubt promote greater awareness, refine the policy agenda, and lead to a call for concerted action.

Search strategy and selection criteria

First-hand information on cognitive screening and several relevant references were provided by the World Federation of Neurology Dementia Research Group members and co-authors. A systematic literature search of PubMed and Medline was also done with combinations of search terms, including “developing countries” and “dementia”, with topic headings including “Alzheimer's disease”, “prevalence”, “incidence”, “cognitive impairment”, “mortality”, “risk factors”, “vascular dementia”, “Asia”, “Africa”, “Latin America”, “care”, and “costs”. PubMed was searched for relevant articles in any language (all understood by co-authors) until May, 2008. Searches were also done in the Cochrane database, EMBASE, Dare, NHS-EED, HTA, Applied Social Sciences Index and Abstracts, Social Services Abstracts, Sociological Abstracts, PsycINFO, and Social Sciences Citation Index with combinations of similar search terms. Some publications, particularly conference proceedings, were found through Google searches. The bibliography was derived from a total of 520 articles that were screened for relevance to this Review. The full list of search terms is available from the authors on request.

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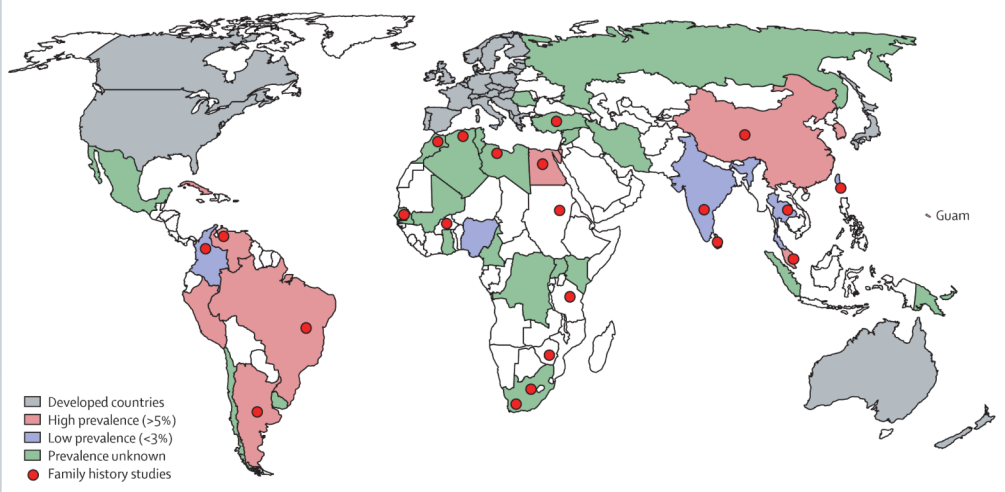

Figure. Sporadic and familial dementias in developing countries

Red-shaded countries have prevalence or incidence estimates of all dementias that have been determined to be similar (>5%) to those in developed countries (grey-shaded countries). Blue-shaded countries have significantly lower prevalence (<3%) of dementia. Sample sizes for the estimates in the various studies were between 700 and 3200 individuals. Green-shaded areas show countries where there are published cases of dementia or subtypes (AD or VaD), where risk factors have been examined but prevalence or incidence are unknown. Reliable information was not available for countries without shading. Red spots show locations of families with neurodegenerative and vascular disorders causing dementia including AD, Parkinson's disease, Lewy body disease, frontotemporal lobar degeneration, Huntington's disease, amyotrophic lateral sclerosis, and CADASIL. Information on dementia prevalence and types was derived from many sources.[22,29,31,35,37–39,41,45,46,49–52,58,62–73]

Table 1

AD and VaD prevalence and key risk factors in developing countries

	Year	Criteria	Sample size (n)	Age (years)	Prevalence (95% CI)			Causes of other dementias
					All dementia	AD	VaD	
Asia								
China[30]*	2007	DSM-III, ICD-10	87 761	>65	3.1% (2.8–3.5)	2.0% (1.5–3.1)	0.9% (0.7–1.1)	Mixed, PDD, DLB, FTD
China (Beijing, Xian, Shanghai, Chengdu)[31]	2005	DSM-IV	34 807	>65	5.0%	3.5% (3.0–3.9)	1.1% (0.9–1.1)	Mixed, PDD, DLB
Taiwan[40-43]†	1995-1998	DSM-IIIR, DSM-IV	7149	>65	3.2% (1.5–4.9)	1.9% (1.2–2.5)	0.7% (0.1–1.3)	Mixed
South Korea[3,32,44]‡	1994-2005	DSM-III, DSM-IV	7096	>65	10.1% (7.3–12.9)	5.2% (3.5–6.8)	2.1% (1.2–2.9)	Mixed
Thailand[45]	2001	DSM-III	4048	>60	3.4% (2.8–4.0)	..	..	..
India[33,34,46-48]§	1996-2006	DSM-III, DSM-IV	14 767	>65	2.7% (1.4–4.0)	1.3% (0.8–1.8)	1.1% (0.2–1.9)	Mixed, PDD, DLB, PSD
Sri Lanka[49]	2003	DSM-IV	703	>65	3.98% (2.6–5.7)	2.85%	0.6%	Mixed
Israel (Wadi Ara)[50]¶	2002	DSM-IV	823	>65	21.1%	20.5%	6.0%	Mixed
Africa								
Egypt[51]	1998	DSM-IV	1366	>65	5.93%	2.86%	1.25%	Mixed
Nigeria[52]//	1995	DSM-III, ICD-10	2494	>65	2.3% (1.2 -3.4)	1.4% (0.62–2.2)	0.72%	Mixed, DLB
Latin America**								
Cuba[53]	1999	DSM-IV	799	>60	8.2% (6.3–10.4)	5.1% (3.6–6.6)	1.9% (1.0–3.0)	Mixed, alcohol dementia
Argentina[54]	1999	DSM-IV	1900	>65	11.5%	..	..	Age
Brazil[35–37,55]††	2002-2008	DSM-IIIR, DSM-IV	7513	>65	5.3% (1.5–8.9)	2.7% (0.1–5.2)	0.9% (0.06–1.78)	Mixed, PDD
Chile[56]	1997	DSM-IIIR	2213	>65	4.3% (3.5–5.3)	..	..	..
Colombia[57,58]	2000	DSM-IV	1611	>65 and >75	1.8% (1.2–2.7) and 3.4% (1.2–5.6)	..	..	..
Peru[38]	2007	DSM-IV	1532	>65	6.7% (5.5–8.0)	..	..	..
Venezuela[39]	2002	DSM-IV	2438	>55 and >65	8.0% (7.0–9.2) and 10.3% (8.3–13.0)	4.0% (3.3–4.8)	2.1% (1.6–2.7)	Mixed

Developing countries defined according to United Nations definition.[16] Age-adjusted prevalence estimates and variation for people aged 65 years and older were calculated from the original published sample sizes and numbers of cases using SPSS 15.0.[59]

*Systematic analysis of 25 studies in 1980–2004 with sample range of 906–15 910 people.

†Mean estimates for four studies from 1995 to 1998; incidence estimates substantiate the prevalence in these communities (see main text).

‡Mean estimates determined for seven studies from 1994 to 2005. Although South Korea and Taiwan are included here as developing UN Asian regions, the International Monetary Fund regard these countries as advanced economies.

§Mean and variation analysis from six rural and urban studies.

¶Annual incidence of AD among cognitively impaired but not demented patients was 4.4%.

//A small study needing confirmation, which used the cognitive screening interview for dementia to screen a hospital-based sample in Jos, revealed an overall dementia prevalence of 6.4% (95% CI 3.8–9.9%), with age, female sex, and body mass index (≤18.5 kg/m2) as major risk factors.[60]

**In Uruguay, prevalence figures were 0.5% for 60–69 year olds and 4.4% for 70–79 year olds.[61]

††Combined prevalence estimates from four Brazilian studies. DLB=Dementia with Lewy bodies. DSM=Diagnostic and Statistical Manual of Mental Disorders. FTD=frontotemporal dementia. ICD-10=International Classification of Diseases, 10th edition. Mixed=mixed AD and VaD. PDD=Parkinson's disease with dementia. PSD=post-stroke dementia. ..=not determined.

Table 2

Comparison of risk factors for dementia, AD, and VaD, in developed and developing world regions

	Developed regions (North America, Europe, Japan)	Asia (China, Guam, India, South Korea, Taiwan*)	Africa (Egypt, Nigeria, Kenya, South Africa)	Latin America (Argentina, Brazil, Venezuela)
Increasing age	Positive	Positive	Positive	Positive
Female sex	Positive	Positive	Unclear	Unclear
Family history	Positive	Positive	..	Positive
Head injury	Positive	..	..	Positive
Genes (*APOE* ε4 allele)	Positive	Positive	No risk	Unclear
Illiteracy or lack of education	Positive	Positive	Positive	Positive
MCI or cognitive impairment without dementia	Positive	Positive	..	Positive
Urban living	Unclear	Unclear	Negative	Positive
Low socioeconomic status or poverty	Unclear	Positive	..	Positive
Occupation as housewife	Negative	Positive	Unclear	Positive
Depressive illness	Positive	Positive	Positive	Positive
Vascular disease†	Positive	Positive	Positive	Unclear
Low fibre diet	Unclear	Positive	Positive	..
Smoking	Positive	Positive	..	Unclear

*In a 3-year incidence study, lower education, history of consistent unemployment, limited physical activity, and stroke history were identified as risk factors for dementia.[84]

†Hypertension and diabetes were the most common risk factors associated with cases of AD and VaD. Studies in South Koreans and Jamaican Caribbeans established that smaller head circumference and shorter leg length were risk factors for dementia.[118,119] Summary compiled from previously published studies.[15,18,19,29–31,33–35,37–39,41,42,45–52,54,56,62,65,73,76,101,109,113,115,120–126] MCI=Mild cognitive impairment. ..=not determined.

Table 3

Burden of AD and other types of dementia in terms of DALYs and cost of illness estimates in different world regions

	DALYs			Costs (2005 US$)			
	Total (×103)	Per 100 000 persons	Per 1000 people with dementia*	Direct (×109)	Informal care (×109)	Illness (×109)	Per dementia patient
Developed regions	4741	395	350	168.1	74.7	242.8	17 964
Developing regions							
Middle income (less developed)	5597	107	354	42.3	30.3	72.6	4588
Low income (least developed)	422	57	363	0.8	1.0	1.8	1521

Data on DALYs were derived from WHO.[200]

*Prevalence and cost estimates were derived from previous estimates by creating a model that accounts for prevalence estimates, country-specific, and region-specific data on gross domestic product per person, and average wage with cost-of-illness for key countries within each region from which detailed data about direct costs and informal care costs were available.[5,201] Regions are designated according to United Nations definitions.[16]