World dementia

One approach does not fit all

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Abstract

Objective

To highlight the broad global diversity in the diagnosis, management, and research of dementia in different regions of the world.

Methods

A critical review of the limited literature from the global South compared with advances that have emerged from key studies in the West and observations from the authors' experiences.

Results

The last several decades have witnessed major advances in dementia research and include an understanding of epidemiologic trends in the global burden of disease, the development of biomarkers for Alzheimer disease, the identification of novel therapeutic targets, and the recognition of the role of protective life-course experiential factors. For the effective translation of these research advances into societies, a "world approach" to dementia is vital. Developing societies substantially differ from Western countries in their attitudes toward dementia, as well as their clinical manifestations and risk factor profiles, marked by lower education and socioeconomic status, a higher cardiovascular disease burden, and genetic variability. Emerging evidence emphasizes the interaction among ethnicity, genetics, epigenetics, environment, culture, and neurobiology in influencing manifestations of dementia. Therefore, the investigation of dementia in diverse settings, including a more global perspective, is crucial for a comprehensive understanding of the condition as well as the identification of novel solutions.

Conclusions

A world approach to dementia provides an opportunity to understand, manage, coordinate, and begin to prevent dementia through an integrated approach based on firm scientific evidence.

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Glossary

AD = Alzheimer disease; **DSM-5** = *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*; **HIC** = high-income countries; **LMIC** = low- and middle- income countries.

With increasing longevity, the burden of dementia is escalating globally, with variable socioeconomic consequences across different countries.[1] Simultaneously, our understanding of this condition has tremendously increased. Research in the field of dementia has mainly focused on the development of biomarkers to identify preclinical stages of Alzheimer disease (AD) and advances in the understanding of the neurobiological basis of AD as well as the identification of novel therapeutic strategies. However, major challenges remain in effectively translating scientific advances into benefits for diverse communities across the globe.

Why "world" dementia?

Diversity characterizes the world we live in; although economic differences between societies are the most striking, variabilities in ethnic, lifestyle, and sociocultural factors are equally prominent. Globalization, immigration, and migration are also realities, as many societies become increasingly multiethnic and multicultural, with high degrees of variability in their socioeconomic status and lifestyles. We discuss the importance of recognizing how diversity in the world influences the expression of dementia and the need to understand the global heterogeneity of dementia. This will enable a more comprehensive understanding of the disease to ensure prevention and management strategies may be effective across cultures.

Methods

A critical review of the dementia research literature from the global South was conducted, including both epidemiologic studies and clinical investigations, as the published research from these areas of the world is scant. The global South refers to developing countries that are characterized by large inequalities in living standards, life expectancy, and access to resources because of differential economic and social changes. We reviewed studies from these low-income countries that reported the prevalence, incidence, and disease burden of dementia as well as studies that included systematic efforts to address the challenges in diagnosis and care in diverse settings. We also reviewed studies that reported patterns of risk and protective factors for dementia in the global South and the limited cross-cultural collaborative studies conducted to date. These findings were compared to advances that have emerged from key studies conducted in high-income countries (HIC), and the differences were assessed. The findings were also systematically compared to identify areas of research that may benefit from incorporating a more diverse approach to meet the challenges of dementia. This information was coupled with the authors' experiences to identify the potential avenues and opportunities that have emerged to advance dementia research using a more diverse world approach.

Results

Table 1 demonstrates key differences in the dementia burden, diagnosis, risk, and protective factors between low- and middle- income countries (LMIC) and HIC.

Challenges related to diagnosis

The conventional definition of dementia is cognitive impairment that interferes with self-sufficiency. The DSM-5 defines major neurocognitive disorder (previously dementia) based on the presence of a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing and a functional criterion to reflect a loss of independence in daily living.[2] However, one of the main challenges that arises in the diagnosis of dementia in many LMIC is reaching individuals with dementia because of the low awareness in society. Most patients evaluated in hospitals are in a more advanced stage than in the West.[3] This issue is compounded by the fact that fewer specialized health care services exist for dementia diagnosis and care. Skilled personnel and resources are lacking for the development of adequate, dedicated services for patients with cognitive disorders.

In the clinical setting, several challenges arise in the use of neuropsychological tests for diagnosis. Most neuropsychological tests have been developed for educated, predominantly English-speaking Western populations and are not suitable for use in other cultures.[4] Illiteracy remains widely prevalent in developing countries[5] and complicates the adaptation of these diagnostic tests. The development of educationally fair and psychometrically sound adaptations of cognitive tests represents the major activities initiated in many countries to diagnose dementia.[6–10] The development of culture-free cognitive tests continues to be a challenge. However, possibilities remain as all major cognitive domains, with the exception of language, may be tested in animals. Languages are also very diverse in their structures with significant differences in their phonology, grammar, lexicon, and semantics, and the adaptation of tests to detect language impairments and compare findings across cultures is a complex process. Furthermore, multilingualism is a characteristic of many societies, and the more natural integration of multilingualism into the context of cognitive testing remains a difficult task.

In some cultures, tests adapted for education alone may not be adequate. Low levels of education are often associated with high levels of occupational complexity (e.g., individuals such

Table 1 Comparison of dementia burden, diagnosis, risk, and protective factors between low- and middle-income and high-income countries

	Low and middle-income countries	High-income countries
Epidemiology		
Prevalence of dementia[12,46]	Variable (2.7%–8.0%)	Uniform (6.3%–7.2%)
Secular trends in prevalence and incidence[19,47]	Limited studies: Increasing trends	Systematic studies: Stable or declining
Burden of global dementia (2010–2050)[46]	57.7%–70.5%	42.3%–29.5%
Diagnostic challenges		
Awareness[48]	Low	High
Specialized services[48]	Scarce	Larger number
Neuropsychological tests[4]	Few standardized tests; illiteracy and linguistic diversity remain challenges	Wide range of validated tests, predominantly for educated English-speaking societies
Biomarkers	Limited access	In wider use
Risk and protective factors		
Etiologies[12,49]	Vascular dementia remains common, as does Alzheimer disease; infections and nutritional deficiencies occur frequently	Predominantly neurodegenerative, vascular dementia is less common
Demographic factors		
Educational status[5]	Low	High
Socioeconomic conditions	Low	High
Rural background[50]	50%–70%	20%–40%
Occupation	Predominantly agrarian	Industrialized
Bilingualism[51–53]	Frequent in autochthonous populations in many countries	Encountered among immigrants in many countries
Pollution levels[54]	High	Low
Cardiovascular risk[12]	High burden	Decreasing burden
Genetic factors[29]	Limited studies	Several genetic risk factors identified through large consortia

as craftsmen who may have low literacy but high expertise in complex skills). They will need to be assessed in a different approach from an illiterate, manual, unskilled laborer; moreover, tests that detect the early breakdown of cognitive domains, such as complex perceptual motor and visuospatial skills that are not acquired through formal education, will need to be developed. Cultural differences also significantly influence cognitive domains, such as semantic memory and social cognition. Semantic memory derives from our understanding of the concepts of the world around us and therefore differs between regions. Similarly, belief systems and social behavior are culture- and context-driven and vary across communities. Therefore, the evaluation of these cognitive domains requires tests developed or adapted to the individual cultures. The same biological pathology that causes cognitive decline may be differentially expressed in different social, cultural, and economic contexts. More challengingly, the recent criteria for the diagnosis of AD dementia advocate the use of imaging and CSF biomarkers to improve diagnostic accuracy.[11] Although basic CT scan imaging is accessible in several urban areas of LMIC,[12] the availability of advanced biomarkers is limited to few research centers, thus contributing to challenges in the modernized era of AD dementia diagnosis. Our reliance on biomarkers may also require review, given the overlap between individuals with and those without cognitive impairment.[13]

The functional impairment required to diagnose dementia may also have a different meaning for an elderly man living alone in a Western society, driving and able to do his own banking but beginning to decline, compared with a man living in a more traditional society as part of an extended family. The man living in the West is likely to promptly seek medical attention with fairly immediate consequences for his self-

sufficiency and future. In contrast, the man in a traditional society would be accepted and cared for as a revered member of the extended family, with his increasing dependence on them considered a part of aging. The social consequences of failing powers are received very differently in different societies; e.g., in some societies, they are accepted as a sign of aging, whereas in other societies, they are considered a stigma.

Societies in LMIC are in a state of transition, with a shift in demography and urbanization and a gradual weakening of joint family systems. Recent studies that explored caregiver burden in LMIC report high levels of strain among caregivers, typically women.[14] Institutionalized care is not widely available, and cultural differences exist in caregiver burden, with higher levels of anxiety reported among caregivers in developing countries.[15] The need for caregiver education and support programs to reduce the burden is increasingly emphasized.

Risk and protective factors

Several longitudinal population and cohort studies conducted over the previous several decades have fundamentally contributed to the understanding of the neurobiological basis of dementia. This understanding has enabled a shift in the focus towards the identification of factors that reduce the risk of dementia.[16–18] While advancing age and genetic factors are nonmodifiable risk factors, several experiential factors, including education, exercise, diet, occupation, and activities that are cognitively stimulating and socially engaging, have been recognized as being able to provide resilience against brain pathology and alter the clinical expression of neurodegenerative disease. The prevalence and incidence of dementia appears to be stable or declining in the Western world (table 1).[19] Improved risk factor control, a declining incidence of stroke, and improvements in societal conditions, education, and health care are considered to be responsible for the reduced risk of dementia.[19–21] However, the majority of these studies have been located in developed countries, where cohorts typically consist of homogeneous populations of Caucasian ethnicity, characterized by longer lifespans, a higher socioeconomic status, and individuals from educated and urban backgrounds. Longitudinal studies of more diverse communities that investigate whether these mechanisms play a similar role universally are limited.[22,23]

The profile of risk and protective factors differs between developing and developed countries (table 1). Populations in LMIC are typically characterized by low levels of education, a poor socioeconomic status, childhood malnutrition, and high proportions of individuals living in rural areas, demographic factors that increase the risk of dementia. Poor health conditions, early life risk factors, and the increasing incidence of cardiovascular disease and stroke contribute to the increasing burden of dementia.[3,9,24–26] Furthermore, cognitive impairment as a result of infections, nutritional deficiencies, and head injuries is common in developing countries. The burden of cognitive impairment as a result of HIV infection continues to be high in Sub-Saharan Africa, particularly for individuals in midlife.[27] A lower life expectancy at birth and a high proportion of the population consisting of young or middle-aged adults contribute to the larger numbers of patients with early-onset dementia in developing countries. Early-onset AD dementia is recognized to be substantially different from late-onset dementia in its clinical course.[28] These differences in the dementia profile are likely to differentially affect the societal burden across populations.

While major advances in elucidating the genetic susceptibility to dementia have been made by large consortia, these efforts have predominately been restricted to Caucasian populations.[29] Very little, in comparison, is known regarding the genetic susceptibility to dementia in LMIC, where the genetic variability is enormous. Genetic studies of non-Caucasian populations will provide more widely applicable knowledge regarding the genetic mechanisms and gene–environment interactions that underlie cognitive decline in aging.

Vascular contributions to dementia

Although neurodegenerative diseases, such as AD, account for the most common cause of dementia, vascular disease also considerably contributes to elderly cognitive decline. The increasing burden of cardiovascular risk factors manifests as a commonly associated neuropathologic finding in patients with dementia.[30] The relative contribution of neurodegenerative vs vascular disease to the dementia burden varies between developing and developed economies. The burden of vascular contributions is substantially higher in developing countries as a result of the increasing incidence of vascular risk factors, such as diabetes mellitus, metabolic syndrome, and hypertension, as well as the relatively early age at which they manifest.[12] In the 1900s, 15% of the population lived in cities, compared with half of the current population today. Many urban dwellers live in megacities, where access to fast food is easy, but obtaining adequate exercise is difficult. Pollution has also become an all-pervading problem and is a risk factor for both stroke and dementia. Air pollution, whether it occurs in New Delhi or Beijing, affects the rest of the world because we share the same biosphere.[31–33] Thus, there is a compelling need to investigate dementia as a world problem, addressing both our commonality and diversity.

Research opportunities

Populations are diverse in their profiles of dementia risk and protective factors, and these factors differentially interact in each society to produce distinct patterns of dementia (table 2). An initial direction for research could be to investigate these complex interactions in different settings to provide novel insights into the mechanisms that underlie the development of risk and resilience against dementia. Limited studies have explored this concept to date. Although the protective role of education against the risk of developing dementia has been recognized,[34] this effect has not been proven to be consistent,[35,36] and it has been reported to depend on the interaction with other variables, such as sex or

Table 2 Research priorities to advance the understanding of dementia as a world problem

Research priorities towards a world approach to dementia
1. Investigate interactions among genetic, epigenetic, sociodemographic, and environmental factors in diverse settings to provide novel insights into the mechanisms that underlie dementia.
2. Integrate basic neuroscience methods with the investigation of varied life-course exposures to advance the understanding of the concept of cognitive reserve.
3. Harmonize research efforts meaningfully via the application of advanced imaging and genetic technologies in populations that are evaluated using locally relevant clinical protocols.
4. Target multiple mechanisms because a single approach to reducing the dementia burden may be a reductionist approach.
5. Expand clinical trials to larger populations in the global South to obtain more generalizable findings.
6. Explore how low-cost and effective technology may globally aid the diagnosis and rehabilitation of individuals with dementia.
7. Focus on the joint prevention of stroke and dementia as an effective intervention that may globally reduce the dementia burden.

rural residence.[37,38] Similarly, the role of bilingualism as a protective factor has been shown to vary with its association with other sociodemographic factors, and it has predominantly been identified in nonimmigrant bilingual communities that have high levels of multiple language use as part of their daily lives.[39,40] Furthermore, although a decline in the incidence of dementia was identified in African Americans over a period of 10 years, no difference was identified among Africans in Nigeria when assessed using a similar design, thereby underscoring the importance of investigating the genetic and environmental interactions.[41] These studies also highlight the importance of investigating the interactions between different levels of exposure in diverse contexts to understand the complexity of dementia risk.

It is also becoming increasingly clear that a single approach to reducing the dementia burden may not work, and multiple mechanisms will need to be targeted. A crucial area of research will be to identify the most effective interventions that may globally reduce the dementia burden. Furthermore, as technological advances are reaching different corners of the world, there is a unique opportunity to explore how low-cost and effective technology may aid in the early diagnosis and rehabilitation of individuals with dementia as well as the development of meaningful worldwide collaborative efforts.

Thus, it is vital to harmonize research efforts both across and within populations. A deeper understanding of the genuine similarities and differences will emerge with the use of clinical tools that are relevant for a particular sociodemographic context, along with the appropriate application of the current technology. Efforts to harmonize clinical research methods across countries have been made[6,42]; however, the harmonizing of imaging protocols and genetic studies has predominately been restricted to Caucasian populations.[18,29] Although the application of these advanced genetic and imaging methods to diverse populations in LMIC is the way forward, these technologies must be employed in combination with locally validated clinical protocols that incorporate indigenous sociodemographic life-course experiences to yield novel insights into the causation of dementia and identify protective mechanisms. It is also crucial to harmonize research frameworks across multiple disciplines. The integration of epidemiologic, clinical, basic neuroscience, and sociocultural research frameworks will facilitate advances in understanding the mechanisms that underlie the complexity of dementia.

More recently, efforts are underway to identify the neurobiological mechanisms of cognitive reserve, and research suggests that physical exercise and cognitively stimulating activities induce neuroplasticity that is mediated by alterations in neurotrophic signaling, inflammation, synaptic density, and stress responses.[43] Equivalent studies from cohorts in LMIC, characterized by a rich diversity of these experiential factors, are limited. The integration of neurobiological research methods in varied life-course exposures in diverse contexts is an important research avenue to pursue to facilitate the understanding of the concept of cognitive reserve.

The developing world has a substantial number of individuals who could be participants in clinical trials to evaluate treatment strategies. A few sophisticated centers could recruit patients who would have extensive ongoing testing with a protocol developed and validated for local populations. The protocol could be simplified with the essential monitoring investigations and used for a larger number of patients. Periodically, a statistically valid sample of the patients following the simpler protocol could be examined in the advanced centers to ensure comparability to individuals in the more extensive studies. This approach would accelerate the testing of new drugs, and interpretations in a diverse population would make the findings more generalizable.[44]

Immediate research opportunities include The Global Burden of Disease initiative, which has provided broad comparative data on global dementia. Moreover, a larger proportion of dementia experts could help develop tools to capture more sophisticated data as part of the initiative. As the HIV epidemic subsides, it is leaving an infrastructure that could potentially be used for the management of chronic conditions, including

dementia. A number of longitudinal studies of dementia exist, which calls for partnerships between investigators in developing and developed countries who may be able to provide technological support for sophisticated components of research, such as imaging techniques and genome analyses.

As an actionable goal, based on the evidence that preventing stroke contributes to the prevention of some dementia globally, all major international organizations that address dementia and stroke have committed to a proclamation regarding stroke and potentially preventable dementias.[21] The joint prevention of stroke and dementia, as well as sharing expertise and infrastructure, may confer benefits in savings from the scaling and use of a common approach.[45]

Discussion

While dementia represents a global and increasing problem, its manifestations, identification, and management considerably differ worldwide. Clearly, given this diversity, dementia, more so than other medical disorders, must be understood from a more global/world perspective. Moreover, the inclusion of these perspectives is crucial not only for the comprehensive understanding of the condition but also to identify novel solutions to combat this disabling disorder. We need to learn substantially more regarding the interactive factors in dementia, including ethnicity, genetics, epigenetics, environment, culture, linguistics, economics, and politics. Nevertheless, we have an opportunity to begin preventing stroke and some dementias together by the commitment of all major international organizations that address both diseases through the proclamation,[21] which fits in with the United Nations' resolution on noncommunicable diseases. A major step towards this goal would be to accept and act on the premises of the World Brain Alliance, which states the following:

1. There is no health without brain health.
2. Brain health begins with the mother and the child and their education.
3. Our brains are our future.

By doing this, we can assure that an aging world becomes a better world.

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