Spatial Distribution and Secular Trends in the Epidemiology of Alzheimer's Disease

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KEYWORDS

• Geography • Secular trends • Diagnosis • Nutrition
• Vascular risk • Stroke • Fetal origins of adult disease
• Life-course methods

Key Points: Alzheimer's Disease Epidemiology

1. There is nonrandom distribution of dementia incidence in space and time.
2. International comparisons are needed to estimate the current and future dementia burden in developed and developing countries.
3. In developed countries, there is some evidence that dementia incidence is decreasing, and this may be attributable to public health measures to reduce vascular disease and/or greater personal resources to buffer the effects of dementia.
4. Nutritional epidemiology is relevant to understanding how and why dementia incidence might vary in space and time. This is true of folate/vitamin B_{12} metabolism and, possibly, dietary fish oil.
5. A life-course approach to understanding how and when risk factors increase susceptibility to vascular disease is relevant to late-life dementia. This approach may identify epigenetic pathways that involve both environmental and molecular genetic factors.

There are many excellent recent reviews on the epidemiology of Alzheimer's disease (AD). Almost all evaluate evidence for the role of specific factors that increase the risk of AD[1] or, less often, discuss the effects of risk factors that might offer some protection against AD.[2] This article does not examine these issues but focuses on trends in the spatial and secular incidence of AD that have remained neglected by reviewers. Related questions arising from the genetic epidemiology of AD, although relevant when international comparisons are considered, are in their infancy and are outside the scope of this review. However, 2 points are relevant and are listed here for completeness.

First, at one time it seemed that epidemiologic studies in dementia would be superseded by advances in laboratory molecular genetics. Supported by identification of genetic mutations in early onset AD (EOAD), claims were made that the causes of AD, irrespective of age at onset, were genetic and that these would soon be remediable. So far, among many putative associations only *APOE*ε4 has remained a well-established genetic susceptibility factor for late-onset AD (LOAD).[3] Molecular genetic research programs can deploy large-scale detection techniques using genome-wide association study methods. These powerful methods detect many genes each of small effect and results so far are

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promising. However, convincing replication of findings in LOAD remains elusive and, at least for some time, a considered combination of molecular genetic and epidemiologic methods will continue to be used to unravel the complex multifactorial causes of AD.[4] To date, no evidence relevant to understanding genetic sources of differences between geographic areas has been presented.

Second, epidemiologic data cannot be assumed to be transferable across cultures or to be stable within 1 culture over time. However, what seems like a major potential source of error can become a strength and it is here that spatial epidemiology is most helpful. Apparent inconsistencies in cross-cultural epidemiologic observational data provide clues to the complex multifactorial nature of the dementias. When well-defined populations differ significantly from others in patterns of AD incidence, their genetic structures and environmental exposures become topics of intense scrutiny. The best-known example is found among the Chamarro people of the Pacific Island of Guam who suffer from a complex syndrome with features of Parkinson disease, AD, and motor neuron disease (the Parkinson-dementia complex of Guam) but for whom there is no clear-cut evidence for either a genetic or environmental cause.[5]

DEMENTIA DIAGNOSIS AND CLASSIFICATION

Secular trends and spatial distributions of AD are relevant to understanding how multiple causal factors might influence life-course pathways toward AD.[6] To become a case of dementia, an individual must cross thresholds of loss of cognitive performance and activities of daily living, and should show worsening progression from a premorbid (ie, original) level of mental performance. These thresholds are open to individual variation. People of higher socioeconomic status who have strong family support and who can retain sufficient mental flexibility to compensate for early deficits attributable to the presence of brain pathology present to health services later in the course of their dementia.[7] At presentation, these individuals often show a greater degree of brain pathology than those who do not have similar support or advantageous socioeconomic circumstances.[8] Therefore, it follows that, when there are improvements in the material well-being of a society, when measures are in place to enhance family and community support, the apparent incidence of dementia might decline. Accurate dementia case ascertainment should continue to rely on prospective longitudinal studies with access to a wide range of data sources relevant to both hospital-treated cases and those who remain in the community and do not enter the hospital system.

These considerations weaken the preconception that a simple mechanistic model of dementia onset, with gold standard criteria for case recognition, suffices for all individuals with dementia. In turn, acceptance of sources of individual variation indicates that, in some instances, certain putative risk factors for dementia identified in observational studies might not be determinants of dementia but consequences of case-finding methodology. A good example of the steps needed to identify and allow for these effects was provided by a ground-breaking cross-cultural study.[9–11]

During the second half of the last century, consistent measures of the incidence and prevalence of late-onset dementias were gradually established. Using harmonized diagnostic criteria and acceptable survey methods, findings from pioneering European studies in Scandinavia, the United Kingdom, Italy, and Holland[12–15] were used to inform public policy and social and biomedical research. Within the broad grouping of the late-onset dementias, and encouraged by progress in neurochemical studies, governments and the pharmaceutical industry began to focus on AD almost to the exclusion of other forms of dementia. The public and press became aware of AD as a major cause of disability and premature death that was seriously underreported and had remained a neglected research topic. Opinion leaders emphasized that the burgeoning epidemic of AD would become the single greatest threat to the maintenance of health care and living standards of old people, with great potential to jeopardize the capacity of developed countries to maintain satisfactory standards of health care and social support for all sections of society.[16] Urgent concern about the implications of a silent dementia epidemic is, with hindsight, now recognized as the first tangible benefit of more than 25 years of intense epidemiologic research in dementia.

Although broadly similar estimates of the incidence and prevalence of AD are now widely accepted, there are some caveats. The first is that research methods have differed between localities and over time. Specifically, European investigators pioneered diagnostic procedures based on standardized psychiatric interviews and were greatly influenced by the success of the UK-US diagnostic project for which an interview-based method[17] (The Present State Examination [PSE]) amenable to the application of computerized diagnostic algorithms was developed. The PSE was founded on precise definitions of psychopathology that would discriminate most efficiently between functional psychoses, specifically