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

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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 or, less often, discuss the effects of risk factors that might offer some protection against AD. 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First, at one time it seemed that epidemiologic studies in dementia would be superseded by advances in laboratory molecular genetics.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). 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...
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. 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.

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. 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 pre-morbid (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. At presentation, these individuals often show a greater degree of brain pathology than those who do not have similar support or advantageous socioeconomic circumstances. 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.

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 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. 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 (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
schizophrenia, and the affective psychoses. Systematic questions posed by trained interviewers (who did not need to be clinicians) contained elements of each definition to determine the presence of a symptom or sign of disorder, its severity, and its duration. The PSE did not deal adequately with the dementias and Copeland and colleagues addressed this deficiency by applying the PSE format to dementia diagnosis, leading to the development of the Geriatric Mental State (GMS) Examination. As with the PSE, computer-based algorithms provided classifications of the mental disorders of late life, each of which could be validated against clinical examinations that included data from a clinical history, from informants, and, where indicated, from a limited neurologic examination.

These semistructured interviews represented a major improvement on previous attempts at case finding in epidemiologic studies of dementia. Although most often used in a single interview, the interviews could be used in 2 or more phases in longitudinal studies of dementia incidence. During this early phase of development of diagnostic criteria for AD for use in epidemiologic studies, great care was taken to distinguish between dementias of presumed vascular origin and dementia without evidence of cerebrovascular disease. A simple checklist had been devised from criteria listed in standard textbooks and provided a total score to represent the presence of cortical infarcts. In large part, this approach was based on the idea that detection of large cortical infarcts supported a diagnosis of multi-infarct dementia and allowed for minor cerebrovascular involvement with some AD features but, if there was no evidence of cerebrovascular disease, then an AD diagnosis was likely. The diagnosis of AD was, therefore, made largely by exclusion of other causes of dementia, principally vascular dementias.

In the United States, dementia researchers developed a second approach that is now popular in European studies, probably because it makes better use of the wide range of possible data sources relevant to a dementia diagnosis. The US approach accepted that, in the absence of valid and reliable diagnostic biomarkers to detect the presence of dementia or any of its subtypes, and faced by variations between clinicians in the detection and recording of diagnostic features, a consensus group drawn from relevant disciplines (eg, psychiatry, neurology, clinical psychology, neuroimaging, neuropathology) could achieve agreement on diagnostic classification in the absence of gold standard biomarkers. This approach allowed for variation in mental state over time and the presence of vascular lesions, and provided a counterbalance to the tendency for the application of diagnostic procedures to become idiosyncratic when reliance was placed solely on a single individual repeatedly applying the same criteria to data sets of uneven quality. The US approach was particularly notable for its clear recommendations that certain cognitive deficits were more often found in early AD (eg, dyspraxia) than in other dementias. Advantages of the prevailing US approach included the opportunity to examine relationships between acute cerebrovascular events as triggers for the gradual onset of dementia of the Alzheimer type, whereas, at that time, the European approach would most likely have categorized any subsequent dementia as cerebrovascular in origin. The consensus approach also identified opportunities to improve dementia diagnoses using biomarkers.

The US consensus diagnostic approach seems also to deal appropriately with the contribution of individual differences in the capacity to cope with or adjust for the presence of dementia pathology. This last is not a trivial point: the capacity of an individual to cope with a dementia disorder may depend on personal attributes loosely labeled resilience, but more precisely may be understood as aspects of intelligence, a socially engaged lifestyle, and a preference for mentally effortful recreational pursuits. The idea that an individual possesses a quantifiable cognitive reserve to mitigate the effects of neuropathology (arising from dementia or brain damage incurred through stroke or trauma) is widely discussed and is supported by the repeated observation that there is not a direct relationship between the degree of brain pathology and the severity of clinical features of dementia. From an epidemiologic perspective, the positive contributions of cognitive reserve that could buffer the effects of AD neuropathology suggest a basic distinction between those factors that increase AD risk and those that decrease it, perhaps through neuroprotective mechanisms.

**THE GEOGRAPHY OF DEMENTIA**

Shared environmental exposures and nongenetic transmission of disease are closely related to detection of spatial proximity. Observational studies of this type often assume that risk of disease is greater if people at increased risk are closely related in space and time. The basic approach in spatial epidemiology is to examine maps of disease distributions and/or secular trends in the incidence of a disease. Beyond this basic idea lies a major problem of testing a statistical hypothesis. The typical aim is to identify clusters of disease, but these aims rarely extend to explicit causal inferences being drawn with
confidence from the data. However, in terms of public understanding of disease risk, maps provide an accessible method of presenting otherwise difficult-to-understand scientific evidence in support of a particular estimation of disease risk.

The prevailing research strategy in the epidemiology of LOAD is to study multiple risk factors in samples at risk of LOAD on grounds of age and the presence or absence of specific risk factors (eg, family history of dementia). Population samples are usually drawn from well-defined areas with known demographics. It is especially helpful if exposures to dementia risk or neuroprotective factors have already been established in the population. A good example of this approach is provided by studies that explored the possible benefits and timing of nonsteroidal antiinflammatory agents (NSAIDs) in the prevention of AD.24 Table 1 is adapted from population-based cross-sectional studies at 11 study sites10 and summarizes current estimates of the prevalence of dementia adjusted for differences in the age and sex distribution of local populations. This type of study is an excellent example of the research methods required in spatial epidemiology to understand how dementia might present at different sites, how diagnostic practices might influence findings, and how levels of dementia-related disability are important. The investigators needed to devise methods to adjust for survival differences, socioeconomic factors, and variations in education and health service provision between geographic regions to obtain reliable estimates of dementia prevalence in each study locality.

International studies also support the proposal that dementia prevalence varies between geographic regions, and encourages the view that environmental exposures contribute to dementia.25 Among these studies, comparisons between African Americans living in Indianapolis (IN) and the indigenous Yoruba living in and around Ibadan in Nigeria provide compelling evidence that these international differences between populations are not spurious and require explanation.26,27 The Ibadan-Indianapolis studies stimulated useful discussion about the genetic structure of African American and native Nigerian populations and how intergenerational continuities of poverty and poor diet could have affected African Americans to a greater extent than native Nigerians, and stimulated a search for sources of geographic difference in dementia risk. The heuristic value of these comparisons has several possible explanations:

a. More stressful urban life of African Americans
b. Lower intensity and shorter duration of formal schooling among rural African Americans28
c. Exposure in urban United States to pollutant neurotoxins (eg, atmospheric lead)
d. A Western diet that is calorie rich and nutrient poor
e. An increased risk of abnormal age-related glucose metabolism and type II diabetes
f. Greater use of alcohol and tobacco among African Americans
g. Better diet of native Nigerians, with fewer calories, more fresh fruit and vegetables, little red meat, and more fish
h. Differences in intracerebral cholesterol metabolism between Nigerians and African Americans.29

Scottish studies on the geographic distribution of EOAD support the view that EOAD distribution is nonrandom.30–33 Clusters of cases were found in areas of Scotland associated with coal mining at the time of birth of EOAD cases. Kinship analyses of these clusters34,35 suggested that genetic relatedness did not explain these areas of high EOAD density.

To understand environments within which an individual develops and loses cognitive competencies, it is helpful to apply research methods that can distinguish between different components of

### Table 1
Prevalence of dementia by geographic region and in comparison with prevalence estimates from a meta-analysis of European sites

<table>
<thead>
<tr>
<th>Study Sites</th>
<th>Standardized Prevalence (%)</th>
<th>SMR (EURODEM)</th>
</tr>
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<tbody>
<tr>
<td>Latin America (urban)</td>
<td>4.6</td>
<td>80 (70–91)</td>
</tr>
<tr>
<td>Latin America (rural)</td>
<td>1.5</td>
<td>27 (16–41)</td>
</tr>
<tr>
<td>China (urban)</td>
<td>3.0</td>
<td>57 (36–86)</td>
</tr>
<tr>
<td>China (rural)</td>
<td>2.4</td>
<td>56 (32–91)</td>
</tr>
<tr>
<td>India (urban)</td>
<td>0.9</td>
<td>22 (7–41)</td>
</tr>
<tr>
<td>India (rural)</td>
<td>0.8</td>
<td>18 (5–34)</td>
</tr>
</tbody>
</table>

Abbreviations: EURODEM, European Community Concerted Action on the Epidemiology of Dementia; SMR, standardized morbidity ratio.

* SMR is obtained by applying estimates derived from pooled European surveys (EURODEM) to the samples recruited at each of the listed study sites. An SMR of 100 implies that the observed number of dementia cases agrees with the number expected in that sample using EURODEM estimates; an SMR less than 100 implies that the prevalence is lower than would be expected in a European sample with the same age and sex distribution.

the environment that are relevant to cognitive maturation and decline. This distinction can be achieved by arranging environmental influences in a hierarchy based on the size of their effects at different points in the life course and judgments about the relative importance of specific timing of exposures (critical periods). These methods of life-course research in aging research and in the epidemiology of diseases of late life (including the dementias) are in the first phase of construction. Life-course theory has the potential to draw together apparently diverse contributions identified in epidemiologic studies concerning the causes of late-onset dementias including AD. The application of life-course methodology to different geographic settings has the potential to show how childhood experiences can modify the risk of late-onset dementia.6

**SECULAR TRENDS IN THE INCIDENCE OF DEMENTIA**

Dementia was recognized in antiquity but was not considered a major public health problem until the latter part of the twentieth century. Until about 1975, most senile dementia was attributed to hardening of the arteries of the brain, and the diagnosis of AD was reserved for rare forms of early onset (presenile) dementia that were often familial. The discovery of neurochemical abnormalities in AD consolidated the view, put forward from about 1955, that Alzheimer neuropathology accounted for more than 50% of senile dementia. Eventually, this view prevailed over the idea that cerebrovascular disease was more important largely because, at the time, it seemed that, in a manner akin to Parkinson disease, if AD could become a neurotransmitter deficiency disorder, then it could potentially become treatable using therapies that replaced or mimicked the transmitter deficiency. This change did not obviate the inclusion of risk factors for vascular disease among studies of causes of dementia in AD and, as discussed later, the vascularization of AD has proceeded steadily for 3 decades since the discovery of the cholinergic deficit in AD.

Community-based studies have consistently shown that the neuropathologic findings among those dying with a clinical dementia syndrome were typically mixed, with features of both AD and cerebrovascular disease neuropathology.36 Rather than claiming that clinical dementia can be confidently attributed to either AD or cerebrovascular disease, many now argue that these 2 types of pathology are frequently detectable in the aged brain and that the rate of progress to dementia is determined by factors (some genetic, some environmental) that differ between individuals, to the net effect that both types of pathology contribute additively to the dementia syndrome.

These observations are relevant to understanding secular trends in the incidence of dementia. If it were accepted that vascular risk factors are implicated among the causes of AD, then it is reasonable to hypothesize that reduction of exposure to vascular risk (eg, public health measures to limit tobacco smoking, encouragement to exercise, and to be moderate in dietary habits and alcohol intake) should lead to a reduction in AD incidence. To date, there are few reports that investigate this proposal. However, in a landmark study, Rocca and colleagues37 describe 4 observational studies, including their own, that together approximate to a US national picture of changes in AD incidence. The studies came from Rochester, Minnesota (1975–1994)37; the Chicago Health and Aging Project (1997–2008)38,39, Indianapolis (1992 and 2001)40, and the National Health and Retirement Study (1993 and 2002).41 The 4 studies present different approaches to the detection of trends in dementia incidence, each providing data relevant to identification and management of those at risk of dementia through description of factors that seemed influential in modifying that risk over time. Their aims included recognition of determinants of elements of social and health care of the elderly that would inform health planning in the twenty-first century.

Rocca and colleagues37 commented on improvements in mortality of the national US population that could be associated confidently with interventions to control hypertension, hyperlipidemia, and abnormal glucose metabolism. These reductions in mortality caused by stroke and heart disease seemed sufficient to argue that dementia incidence should have fallen in step with these measures to improve public health. Their findings were largely negative in the Minnesota, Indiana, and Illinois studies but the National Health and Retirement Study provided grounds for cautious optimism. This large national study found (using neuropsychological measures without reliance on detection of dementia caseness) that the proportion of old people who developed cognitive impairment was significantly less in the later-born birth cohorts than in the older individuals. Such improvements over time are considered to be associated with longer duration of education and greater net worth (wealth) of the later-born old people. Rocca and colleagues37 also noted that worsening of national health statistics linked to growing numbers of obese and poorly controlled hypertensive individuals would potentially have countered any improvements in dementia incidence.
and that these effects may be subject to local variations to a greater extent than in the National Health and Retirement Study.

**COULD NUTRITION EXPLAIN VARIATION IN DEMENTIA INCIDENCE?**

Secular trends in dementia incidence could be closely related to the nutritional origins of individual differences in rates of biological aging, how these evolved, and how changing environments could have affected aging. The basis of this inference is that, like many of the cancers and atherosclerotic disorders, AD is an age-dependent condition, and it implicates biological aging as a necessary precondition of the pathogenesis of AD. Theories of biological aging could therefore be relevant to understanding the neurobiology of age-related cognitive decline and AD. This view is supported by stronger associations between cognitive decline and biological measures of aging than with chronological age. However, firm links between inception of AD and rates of biological aging have not been established. For example, there are no associations between AD and other age-dependent conditions (eg, osteoporosis, some cancers, and chronic obstructive pulmonary disease).

Interest in nutritional sources of variation in dementia incidence is related to the possibility that biological aging reflects the accumulation of damage to large bioregulatory molecules that are inefficiently replaced or repaired. This type of age-related damage is attributable to oxidative stress, in which excessive free radicals of oxygen are generated and antioxidant defenses are insufficient to counter their effects. Antioxidant defenses comprise 2 elements: enzymatic (eg, superoxide dismutase) or nonenzymatic circulating micronutrients (eg, vitamin C). This line of reasoning has supported nutritional surveys among those at risk of dementia by reason of increasing age. So far, no convincing epidemiologic evidence has been provided to establish an important role for specific antioxidant micronutrients in the pathogenesis of AD. Issues of reverse causality are sometimes inadequately addressed so that it is not possible to distinguish the pathway from a poor diet to AD from that followed when impaired cognition in early dementia impairs the ability to obtain and prepare a nutritious diet.

However, when dietary patterns are investigated, the overall intake of a diet rich in antioxidants and fish with modest amounts of red meat and red wine (The Mediterranean Diet) seems to have advantages compared with a typical Western diet with more calories, fewer antioxidants, more saturated fats, and greater consumption of beer and spirits. In conjunction with genetic variation in response to specific dietary micronutrients, these nutritional data could provide explanations for the geographic variation in dementia incidence. A major research effort is currently underway to examine the sources of variation between countries and cultures in the incidence of AD. When considered alongside migration studies of the Japanese from Japan, from Hawaii, the northwestern United States, and Brazil, or African Americans from Indianaopolis, there is a strong case to pursue these lines of enquiry because they seem likely to have wider relevance.

The possible role of obesity in midlife has been explored in some surveys, and there are important statistical issues when so many risk factors for vascular disorders are highly intercorrelated in Western societies. Obesity, hypertension, abnormal glucose metabolism, and hyperlipidemia frequently coexist, sometimes in association with a sedentary lifestyle, smoking, and low socioeconomic status. Nevertheless, careful analysis of these factors present in midlife has separated their diverse influences and identified an important role for obesity, in conjunction with the metabolic syndrome, as independent contributors to AD risk.

The importance of diet and intake of specific micronutrients in brain development is well established. A sufficiency of calories and a mixed balanced diet ensures adequate growth and cognitive development that, in conjunction with positive parenting, optimizes child development. These same factors are also important in later life such that malnutrition is a major risk factor for increased disability and disease morbidity among old people. These ill effects also include increased risks of cognitive impairment, so nutritional assessment has become a key component of evaluation in old-age medicine and in the dementia clinic. However, the scientific basis for nutritional interventions to promote retention of cognitive function in late life, or even prevent or delay dementia onset, remains uncertain. Nevertheless, there are 2 pertinent examples from studies on the nutritional epidemiology of dementia that merit comment.

**Homocysteine**

A good case can be made that homocysteine (HCY) increases the risk of cognitive decline and AD. The evidence from observational studies, with 1 exception, shows that increased plasma HCY concentrations are linked to increased dementia risk. Intervention studies intended to lower HCY concentrations have not, so far,
provided evidence that this strategy can reduce dementia risk.\textsuperscript{52} Folate deficiency at the time of conception has been linked to hypomethylation of noncoding DNA that regulates the expression of genes critical to specific times during neurodevelopment. Plausibly, abnormal DNA methylation could modify the risk of adult disease.\textsuperscript{52} This points to several possible pathways, all involving folate/homocysteine metabolism, that could increase dementia risk\textsuperscript{6} and, when dietary availability of folate varies between localities or over time, might explain geographic and/or secular variation in dementia incidence.

**Docosohexanoic Acid and Eicosohexanoic Acid**

The dietary intake of marine oils rich in the omega 3 essential fatty acids docosohexanoic acid (DHA) and eicosopentanoic acid (EPA) are linked to improved health, with claims of specific benefits for respiratory function, cardiovascular disease, and inflammatory disorders.\textsuperscript{53} The benefits for central nervous system function include greater intellectual development and retention of cognitive function in late life among breast-fed infants (human breast milk is replete with DHA and EPA, whereas formula feed prepared from cows’ milk is not) and in epidemiologic studies of cognitive aging and dementia. Intervention studies testing cognitive benefits of DHA and EPA supplementation have not supported these claims.\textsuperscript{54} Nevertheless, studies that compare dementia incidence between Asian communities with high dietary fish oil intake and those with predominantly inland (pastoral) dietary habits, where oily fish is unavailable, are currently underway.

**SYNTHESIS**

A diet deficient in essential micronutrients (eg, specific vitamins or antioxidants) might increase AD risk and could explain why specific locations or birth epochs could be associated with increased

![Fig. 1. A life-course approach to the epidemiology of AD showing the timing of major influences on cognitive development, the acquisition of unhealthy behaviors, and major dietary factors that increase dementia risk in late life and others that may protect against or slow the onset of dementia. NAI, non-accidental injury. (Adapted from Whalley LJ, Dick FD, McNeill G. A life-course approach to the aetiology of late-onset dementias. Lancet Neurol 2006;5(1):88; with permission.)](image-url)
AD incidence. However, no consensus has been reached on these topics. There remains insufficient convincing data from randomized controlled trials to show that dietary supplementation is linked to better retention of cognitive abilities in late life or the prevention/delay of dementia onset.

Data on geographic distribution of dementia are strongly suggestive of risk factors common to dementia and stroke. When taken together with observations of associations between vascular risk factors and both inception and survival in dementia, the role of vascular risk factors in the pathophysiology of AD is further strengthened and becomes worthy of enquiry. The life-course approach to understanding how factors that increase susceptibility to late-life vascular disease provides a useful model, illustrated in Fig. 1, which represents a provisional synthesis of epidemiologic observations in dementia. It has some potential to identify time points when the risk of dementia might be lessened and draws attention to the possibility that control of vascular risk factors in midlife might reduce AD risk.

In this article, some of the main concepts and the implications of nonrandom spatial distribution and secular trends of dementia are reviewed and advanced as the basis for further discussion. The most important are (1) the strength of evidence for international differences in dementia distribution; (2) the need to investigate and monitor changes over time in dementia incidence, partly because of covariation with reductions in vascular disease but also because, as societies become more affluent, so their dementia risk might increase; (3) the need to model the pathophysiology of AD to inform how dementia risk might be reduced and to identify the precise timing and nature of possible beneficial interventions.

REFERENCES

Epidemiology of Alzheimer’s Disease


