Commentary: Searching for risks for Alzheimer’s disease

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The search for risk factors for Alzheimer’s disease is notoriously problematic, both for genetic and acquired risk. Why is it so difficult to look for risks? The study published by Tyas et al. exemplifies many of these difficulties, but also shows why we should persist.

The range of studies which have informed possible risks for dementia varies from studies of very rare families with autosomal dominant patterns of Alzheimer’s disease through case-controlled studies and prospective observational cohort studies to randomized control trials of interventions (such as the WISDOM trial of hormone replacement therapy and dementia in the United Kingdom). The study presented in this edition is a prospective cohort study. Tyas et al. present data from a longitudinal study of people aged 65 and above, with collection from the non-demented at outset of putative risk factors for dementia. Increasing age and lower education were associated with increased risk, as expected. At 5-year follow-up 36 of those who had developed Alzheimer’s disease were compared with 658 individuals who were cognitively intact, out of an original 1763. Self-report of fumigant/defoliant occupational exposure, migraine and self-reported memory loss were associated with increased risk, and vaccinations and occupational exposure to noise were associated with reduced risk. Important findings which are different from earlier reports include lack of an influence of family history of dementia, and lack of protective effect for non-steroid anti-inflammatory drugs (NSAID) and smoking.

The difficulties in interpreting the findings of this study relate to the very nature of the outcome measured, which risk factors are measured and how, as well as whether, these risks could be risks or merely markers of the process (and at what stage in the life course), response rates and the analytical approach to the study design used.

In this study, and many others, Alzheimer’s disease is measured rather than dementia. Alzheimer’s disease is identified in life by first fulfilling criteria for dementia, and then examining the characteristics of the dementing process with attention to co-morbidity and other possible causes of dementia. Whether Alzheimer’s is diagnosed will, to some extent, depend on the zeal with which other possible factors are pursued, such as imaging for vascular and white matter changes and post-mortem confirmation. Post-mortem studies of selected populations in specialized settings suggest high accuracy of pre-mortem diagnostic processes, but post-mortem series from population-based studies reveal that the neuropathology underlying dementia is, in many cases and most particularly in the older age groups, a mixed picture. Searching for pure Alzheimer’s disease in this study led to the rejection from analysis of 74 individuals with cognitive impairment who were not considered to have Alzheimer’s disease (i.e. a group twice as large as the AD incident group). Such search for pure AD is probably better limited to younger age groups, where it is rather easier to identify. Despite the exclusion criteria the Alzheimer’s disease category is likely to represent a mixed group which is likely to dilute associations rather than create them. Much of the Alzheimer’s research endeavour and funding is predicated on the ability to identify a very specific disorder, but justified because of the expected increase in incidence and prevalence in the older age groups. Studies in the older age groups therefore might be better addressing the larger picture of cognitive decline in older age, akin to hypertension which has many possible underlying mechanisms, rather than a specific pathologically defined entity which cannot actually be measured during life as yet. At a practical level most studies report on both cognitive decline and Alzheimer’s disease, but the biomedical research community remains rather more comfortable with dichotomous outcomes than continuous ones despite the bulk of evidence that this is a false dichotomy.

Many studies of dementia, most particularly the earlier case control studies, have examined risk cross-sectionally—a particular problem for dementia in that for any questionnaire risk collection the data have to be collected from an informant for both cases and controls. The prospective nature of the Manitoba study sidesteps this issue, as well as the potentially biased reporting of risk. Five years is a reasonably long period, and the reporting of risk by the subsequently demented is less likely to be affected by pre-diagnostic changes than if shorter follow-up periods are used. Prospective studies have been important in testing the hypotheses generated by the case-control studies, and in many cases have reached reduced or null findings, such as family history of dementia, head injury and smoking. Risks can include those indicating early changes, and those which might be genuine risks. The risks reported here fall into both these categories—illustrated by occupational exposure and self-reported memory loss. Each of these has quite different implications. For the former it might be the pursuit of more specific occupational cohort studies, and a search for plausible biological mechanisms, for the latter additional evidence is provided for the question which could be used to identify individuals accurately at an early enough stage in any pathological process to alter subsequent natural history. It should be emphasized that this provides only a tiny fragment of the necessary evidence.

The method of risk information collection does have problems, in that it is difficult to interpret the exact meaning of specific responses. In occupational exposure the following questions would be important. How accurate and complete are
the data, how much and at what life stage and over what period of time did exposure occur? Although it has been shown that self-report of important medical conditions is relatively well-reported, how does this relate to underlying pathophysiological status? These are issues which have been well rehearsed in all epidemiological studies. The Manitoba study cannot answer these as practical issues prohibit this, and therefore these findings can only act as signposts for other research. Self-report of migraine is likely to be more accurate, although under-reporting can occur in headache. A major contribution of longitudinal studies to date has been that of the role of vascular disease in risk for dementia and Alzheimer’s disease. There is increasing evidence that migraine is associated with increased risk for vascular events, and therefore this finding does fit into an emerging picture. This will merit more detailed biological studies, since the vascular consequences of migraine in the brain are likely to be different from those of other identified risks such as carotid artery narrowing.

This study, as do most population-based longitudinal studies in older people, suffers from considerable drop-out and incomplete interviews. It is very important to know that the findings are not merely a function of the design, and are robust. The impact of such design features, and of drop-out can be explored through complex analysis, in which the impact of drop-out and death are assessed, or can be assessed through simpler sensitivity analysis. This study emphasizes the difficulty of even relatively large cohort studies in the small size of the incident group and lack of power, with multiple testing. For the significant findings the proportion of controls exposed is very small, and the population attributable risks similarly so. Combining studies and recognizing in the analysis that each study has measured risk in a different, and inevitably imperfect, way can be a useful way forward (such as the EURODEM studies).

Which studies are not worth doing? It is generally accepted that further case-control studies examining acquired risk have made their contribution but remain a cornerstone for genetic association studies, if sufficiently powered. Cohort studies continue to have a contribution to make in terms of hypothesis generation. There are many studies of this kind which will provide data over the next few years. A limited number are similar in design to the Manitoba study, but several more targeted younger cohorts with more detailed measurement of biological factors are moving into late middle age. These cohorts, which are measuring baseline cognition, can incorporate those possible risk factors identified by current cohort studies of older populations (thus carrying hypotheses across generations). Specifically targeted studies must then follow to piece together the jigsaw before a coherent picture emerges which might impact on healthy ageing. The reason for urgency is the likely emergence of interventions which may have considerable cost policy and social implications but do not take into account the narrow nature of most research evidence.

References

1. General Practice Framework. GP RS, MRC Epidemiology and Medical Care Unit, Wilson Institute of Preventative Medicine, Charterhouse Square, London EC1M 6BQ (Contact: J Jordan or M Vicker) or www.gpfr.qmw.ac.uk