The importance of cognitive ageing for understanding dementia

Archana Singh-Manoux, PhD [1,2,3]

Mika Kivimäki, PhD [2]

* Corresponding author & address:

[1]Centre for Research in Epidemiology & Population Health, INSERM U1018

Hôpital Paul Brousse, Bât 15/16

16 Avenue Paul Vaillant Couturier

94807 VILLEJUIF CEDEX, France

Telephone: +33 (0)1 77 74 74 10   Fax: +33 (0)1 77 74 74 03

Email: Archana.Singh-Manoux@inserm.fr

[2]Department of Epidemiology and Public Health

University College London, UK

[3]Centre de Gérontologie, Hôpital Ste Périne, AP-HP, France

Number of characters in title: 59: Word count: 1644.

Abstract

A third of those over 80 years of age are likely to have dementia, the lack of a cure requires efforts directed at prevention and delaying the age of onset. We argue here for the importance of understanding the cognitive ageing process, seen as the decline in various cognitive functions from adulthood to old age. The impact of age on cognitive function is heterogeneous and the identification of risk factors associated with adverse cognitive ageing profiles would allow well targeted interventions, behavioural or pharmacological, to delay and reduce the population burden of dementia. A shift away from binary outcomes such as dementia assessed at one point in time in elderly populations to research on cognitive ageing using repeated measures of cognitive function and staring earlier in the lifecourse would allow the sources of variability in ageing to be better understood.

An effective treatment or cure for dementia remains elusive,[1] making prevention and delaying the age of onset important in order to meet the public health challenge of an exponential increase in dementia. The 2009 World Alzheimer Report estimates 36 million cases of dementia in 2010 and projects that this number will double every 20 years, with most of the increase coming from low-income countries.[2] Increase in life expectancy feeds the epidemic as the prevalence rises with age, doubling every 4-5 years after the age of 60 so that over a third of those over 80 are likely to have dementia.[3]

Dementia is a syndrome characterised by impairment of multiple cognitive capacities that are severe enough to interfere with daily functioning. The diagnosis is based on clinical rather than neuropathological status. As most cognitive functions decline with age, it is often difficult to establish where normal variation ends and the disease begins. However, there is now quite a lot of evidence from both a clinical and neurodegenerative point of view to suggest that dementia develops over many years, perhaps as long as 20-30 years.[2;4;5] We argue here that attempts to identify risk factors need to take into account the length of the latency period and the insidious onset that characterises dementia. Besides age and genetic predisposition, several environmental and behavioural risk factors have been identified although these results lack consistency and specificity.[6] It is possible that inconsistent findings are a result of the research design used to study cognitive ageing; most studies on risk factors are based on elderly populations who may be free of clinical but not preclinical dementia at the start of follow-up.

Progress on the molecular basis for dementia, the amyloid hypothesis in particular,[7] shows great promise. However, advances in understanding the dementia process are not yet at a stage that would allow biomarkers or changes in brain structure to be incorporated in the diagnostic criteria. Furthermore, the association between neuropathological aspects and clinical aspects in terms of neuropsychological functioning is not straight forward.[4] Autopsies of individuals with 'normal' brain ageing and intact cognition reveal almost as many neurofibrillary tangles and amyloid plaques as are seen in patients with dementia;[8] 20-40% of non-demented individuals have enough neuropathology to warrant a diagnosis of dementia.[5] Both clinical and neuropathological studies suggest that dementia has a long preclinical phase characterized by progressive neuropathological changes and decline in cognitive functioning.[2;6] Population based longitudinal studies can contribute by focussing on causes, the course of cognitive ageing in order to complete the long term clinical picture of dementia. In the section that follows we discuss the research paradigm we propose towards this end.

1. Outcome: cognitive ageing rather than binary outcomes

We argue for the importance of understanding the cognitive ageing process, seen as the decline in various cognitive functions from adulthood to old age. The diagnosis of dementia involves the presence of multiple cognitive deficits, a critical feature of such a diagnosis is "decline from previous functioning".[9] Thus, the cognitive, behavioural and functional data generated in studies is converted to categorical data reflecting poor cognitive status when the outcome of interest ought to be cognitive decline, in the best case scenario over the 20-30 years that it takes for dementia to develop. Research on Mild Cognitive Impairment (MCI), a prodromal phase of dementia,[10] is a step in the right direction but to take it further the focus needs to be on understanding decline in cognitive function that is *dissimilar to age-matched peers*.

Cognitive ageing is characterized by increasing heterogeneity,[11] resulting in age peers becoming more and more dissimilar as people get older due to differences between individuals in the rate of cognitive decline. Framingham data show divergence in cognitive trajectories up to 22 years before the diagnosis of dementia.[12] The long latency period for dementia implies that greater attention needs to be paid to poor cognitive performance compared to age-matched peers starting early in midlife. There are no clinical criteria to operationnalise poor cognitive performance. We propose that for research purposes cognitive performance and decline situated 1.5 standard deviation below the mean or that in the worst decile[13] or quintile[14] be used distinguish individuals *dissimilar to age-matched peers*. Identification of risk factors that gradually shape or abruptly change cognitive ageing trajectories have enormous potential for early detection and prevention of dementia.

2. Exposure: examine risk factor trajectories over the lifecourse

Better understanding of risk factors, in terms of specificity, will come from adoption of a lifecourse approach where risk factors are assessed prior to the beginning of the dementia process.[10;11] There might be critical periods (childhood, adolescence, early adulthood, midlife, etc.) of exposure that late life measures of risk factors cannot assess, as is the case with obesity. Obesity in midlife is a risk factor for dementia but at older ages it is low body weight that is associated with dementia as incipient dementia and comorbidity are often accompanied by metabolic and behavioural changes that lower weight.[15] If the latency period of dementia is several decades then research on older individuals includes those who may be at an advanced stage in the latency period and neuropathological changes accompanying dementia could alter

the levels of these risk factors. The likelihood of protopathic bias in results from these studies necessitates closer attention to risk factor levels earlier in the lifecourse.

Cardiovascular risk factors have been shown to be associated with poor cognitive function in middle-aged adults[13-15] and also with dementia in later life.[16] Repeat assessments of these risk factors are necessary as measures at one point in time often provide an imprecise estimate of their long-term impact. Trajectories or repeated assessments of risk factors may not only improve risk stratification but also allow the examination of competing hypotheses of the exposure-disease association: cumulative risk, risk trajectories or critical period models and the timing of changes in risk factors before disease onset. If the atherosclerotic degenerative process is important for dementia then the estimation of total cumulative exposure to risk factors or the specific trajectories of risk factors that are harmful can only be undertaken using a longitudinal design.

3.   Investigate socioeconomic context

Socioeconomic factors, education or occupation, have been shown to be associated with higher cognitive scores and reduce the risk of dementia,[17] suggesting that there are continuities between cognitive ageing and dementia. The burden of dementia is also socially variable; those with greater education show less severe cognitive decline.[18] Socioeconomic factors are seen to be a proxies for cognitive reserve, defined as the ability of individuals to tolerate progressive brain pathology without manifestation of clinical cognitive symptoms.[19] Most individuals finish education early in the lifecourse and it is unclear if experiences over the adult lifecourse or later life measures of social circumstances can alter levels of cognitive reserve. Plasticity in cognitive reserve would have tremendous implications for understanding cognitive ageing. For now it remains a "black box" and further research is required to understand the mechanisms by which it influences cognitive ageing trajectories. Most research on the risk factors for dementia typically controls for a range of confounders including socioeconomic factors. We argue that socioeconomic factors are not just methodological confounds and their role as modifiers of cognitive ageing needs further attention.

4.   Assess population impact of risk factors

The population-perspective, rooted in prevention and tied to the prevalence of putative risk factors, attempts to identify risk factors that would reduce disease burden at the level of the population. Much of the current research in dementia focuses on identifying

individuals at the highest risk, either from established risk factors or through research on 'new' risk factors. This approach misses opportunities for large-scale prevention of common risk factors and consequently their impact at the level of the population. The major advantage of a population perspective is that a focus on "a large number of people at a small risk may give rise to more cases of disease than the small number who are at high risk".[20]

The heritability estimate of dementia [21] is no different to that of heart disease and there is no reason why lessons learnt from one cannot be applied to the other. Secular decline in mortality from heart disease in recent years is the result of identification of risk factors likely to impact population burden of the disease rather than subgroups of individuals at particularly high risk. Adoption of a similar approach for dementia implies focussing on the risk factors that are highly prevalent at the population level as their impact is likely be to substantial even if the associated relative risk is small at the individual level.

New research agenda for the future

The shift away from binary outcomes measured at one point in time to an analysis of cognitive change using repeated measures of cognition brings substantial methodological challenges: What are the specific aspects of cognition that ought to be measured? How to ensure sound psychometric properties for cognitive tests? How to deal with learning and practice effects that plague repeat cognitive testing? What are the optimal statistical methods to analyse change, account for non-response in longitudinal analysis? Despite these challenges, the benefit of the focus on cognitive ageing is that the identification of risk factors for unfavourable ageing trajectories will help establish early therapeutic interventions. This has obvious advantages over treating individuals with dementia where neuropathological changes might well be too far advanced to be reversible.

The dementia epidemic requires strategic choices in setting research priorities to allow rapid translation into advances in clinical care. We recommend adoption of an extended time window for study of both cognitive ageing and risk factors in order to identify sub-clinical disease processes and novel risk factors at the earliest possible stages of life. This approach contrasts with the focus elderly populations and attempts to contribute to the development of a better health-care delivery with earlier and more effective interventions in more accurately identified risk groups.

Acknowledgements

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