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Predictors of early-onset cognitive impairment

Dementia is a major global health crisis with an estimated 35 million people diagnosed at present, and that number is projected to triple by 2050. Many more suffer from mild cognitive impairment (MCI), which is recognized as a precursor for many types of dementia (Petersen *et al.*, 2014). At the recent G8 Summit in London, health ministers from participating countries discussed dementia and its treatment and prevention (Fox and Petersen, 2013), and issued a communiqué calling for increased research into the mechanisms of disease, and increased efforts targeted at prevention (G8 Summit, 2013). To that end, the identification of lifestyle factors that may contribute to the development of dementia is crucial. In the current issue of *Brain*, Nyberg and colleagues present data from a longitudinal study in which they reveal the contribution of two such factors—early cardiovascular fitness and cognitive fitness—to the risk of early-onset dementia and MCI (Nyberg *et al.*, 2014).

Longitudinal studies such as these are much needed. In 2010, an NIH ‘State of the Science’ report concluded that there was insufficient evidence to support the use of pharmaceutical agents, dietary supplements or other means for the prevention of cognitive decline or Alzheimer’s disease (NIH State-of-the-Science, 2010). Having reviewed the literature, attendees at the conference concluded that the appropriate longitudinal studies had not been conducted to validate any interventions. Of note, studies that have investigated modifiable lifestyle risk factors for MCI or dementia have typically assessed risk factors in midlife at best, or more often than not, in late life. The relatively few studies that have assessed risk factors acquired before early adulthood have focused on risk of late-onset dementia as their endpoint. For example, the Aberdeen 1921 and 1936 Birth Cohort Studies have access to obstetric and neonatal records of 667 hospital births in 1921, and to the Scottish

Mental Surveys of childhood mental ability test scores for children born in 1921 and in 1936, providing a wealth of information with which to examine early life risk factors for later life cognitive impairment (Whalley *et al.*, 2011). However, these cohorts were not representative of the United Kingdom. Furthermore, the relatively small subsets that were successfully traced and alive and eligible for research were studied from the ages of 77 to 88 years and from 64 to 68 years, respectively, precluding investigation of the contribution of neonatal factors, childhood intelligence, and early-life cognitive abilities to the risk of early-onset dementia.

Early-onset dementia is an understudied condition, with the exception of the rare autosomal dominant mutations that produce early-onset Alzheimer’s disease. However, such cases constitute only a small fraction of all cases of early-onset dementia. Nyberg and colleagues now report the results of a study into the impact of cardiovascular fitness and cognitive performance at age 18 in over 1.1 million Swedish male conscripts examined between 1968 and 2005 (Nyberg *et al.*, 2014). The men were followed for up to 42 years, and performance at the time of enrolment was correlated with the risk of developing MCI and dementia later in life. The study focused on early-onset (before the age of 65 years) of dementia and MCI as endpoints and controlled for many confounding factors.

Nyberg and colleagues (2014) exploited this unique data set to evaluate lifestyle predictors of cognitive decline. They concluded that a combination of low cardiovascular fitness and poor cognitive performance in early adulthood was associated with a nearly 14-fold increase in the risk of early-onset MCI and an 8-fold increased risk of early-onset dementia. Low cardiovascular fitness and poor cognitive performance were also independently

associated with an increased risk of these outcomes, but the estimated risks were lower.

The manuscript by Nyberg *et al.* (2014) is timely and draws attention to the issue of early-onset dementia. With the recent failure of pharmacological treatments for Alzheimer's disease in clinical trials, there is now an increased focus on lifestyle factors that may alter the course of cognitive changes in ageing. Equally compelling data have been obtained regarding lifestyle factors and the risk of developing MCI (Bennett *et al.*, 2014; Roberts *et al.*, 2014). The results of these studies are important because they suggest that a sizeable number of people could develop early-onset disease, and most of these cases will be unrelated to the known genetic mutations for early-onset Alzheimer's disease.

Nyberg and colleagues' data also suggest that factors that are amenable to intervention in early life could help to prevent later cognitive decline. Promoting cardiovascular fitness and cognitive activities in childhood and the teen years may help individuals to achieve optimal performance by early adulthood, which may serve to reduce their risk of early-onset MCI and dementia. Although these preventive strategies seem possible and logical, their implementation may require lifestyle modifications and education at early ages for individuals, and training and education of families, communities and society. In addition, behavioural changes would have to occur in large numbers of individuals for them to have an impact at the population level. Regardless, the success of interventions would not only impact early-onset MCI and dementia, but would also favourably impact late-life cognitive impairment. Barnes and Yaffe (2011) have estimated that a 10–25% reduction in the prevalence of common modifiable risk factors such as type 2 diabetes, onset of hypertension and obesity in midlife, smoking, depression, poor educational attainment, and cognitive inactivity could prevent 1 to 3 million cases of Alzheimer's disease worldwide and 184 000 to 492 000 cases in the United States (Barnes and Yaffe, 2011). Thus, successful prevention strategies before early adulthood could have a tremendous impact in reducing the burden of Alzheimer's disease and other dementias.

The study by Nyberg and colleagues (2014) has a few limitations with regards to methodology. The use of ICD-9 codes to identify MCI cases raises questions about the diagnostic criteria. The authors indicate that they studied the subgroup 'early-onset MCI' to obtain a more exact diagnosis; however, early-onset MCI may be even more heterogeneous and subject to misclassification than MCI in later life. This potential misclassification could result in overestimation of the risk of MCI in the study. On the other hand, as MCI is a relatively recent diagnosis in the medical literature, there is also a possibility that the condition might have been under-diagnosed.

Overall, this is an interesting study that sheds light on early-life risk factors, and the potential for lifestyle modification to reduce

the risk of late-life cognitive impairment. These findings are consistent with previous work in the Nun Study, which revealed the influence of early-life linguistic abilities on the risk of dementia in later life (Snowdon *et al.*, 1996). While factors such as cognitive reserve certainly play a role here, the results of these studies suggest that early lifestyle factors can impact later-life cognitive function.

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