Title

Time trends in neuropathology give clues to dementia risk reduction

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Standfirst

A new study sheds light on declining dementia incidence by examining time trends in neuropathology in two large US autopsy cohorts. A reduction in vascular pathologies while neurodegenerative pathologies remained similar over time suggest that improvements in both cardiovascular health and cognitive reserve have helped reduce dementia risk.

Refers to Grodstein, F. et al. Trends in Postmortem Neurodegenerative and Cerebrovascular Neuropathologies Over 25 Years. *JAMA Neurol*. https://doi.org/10.1001/jamaneurol.2022.5416 (2023).

Dementia incidence has declined in high-income countries in recent decades[1]. The main hypothesized drivers include increased levels of education and improved prevention and treatment of cardiovascular disease. Although a number of long-running cohort studies have been able to compare rates of clinical dementia across generations, long-running autopsy cohorts that examine the neuropathologies associated with dementia are extremely rare. Therefore to date there has been minimal evidence as to if and how levels of neurodegenerative and vascular pathologies have changed across time. Such evidence is important to inform our understanding of the observed dementia trends and the scope for further population-level dementia risk reduction.

A recent study by Francine Grodstein and colleagues compared neuropathological and clinical outcomes across birth cohorts by estimating their age-standardised prevalence to account for differences in age at death[2]. Data came from two long-running autopsy cohorts: the Religious Orders Study (ROS) from across the US, and the Rush Memory and Aging Project (MAP) from Chicago, Illinois (the combined cohort is referred to as ROSMAP). 1554 participants born between 1905 and 1930 contributed data to the analysis, and were divided into four birth cohorts balancing size and age range.

The results show a reduction across each birth cohort in moderate or severe atherosclerosis and arteriolosclerosis. A trend of reduced chronic gross infarcts across birth cohorts did not continue in the latest one, whereas chronic microinfarcts increased in the latest two birth cohorts. In contrast to these patterns in vascular pathologies, the prevalence of a pathologic diagnosis of Alzheimer's disease (AD) and the study's bespoke global measure of AD pathology remained steady across birth cohorts. However, beneath this there was variation in their metrics of amyloid burden and tau tangle density, with amyloid rising then falling across birth cohorts, and tau tangle density increasing across birth cohorts. Other included neurodegenerative pathologies (LATE-NC stage 2+ and neocortical Lewy bodies) remained

similar over time. Clinical AD dementia showed a slight decline across birth cohorts, but this was not statistically significant.

The authors conclude that the reductions in atherosclerotic vessel disease reflect improvements in cardiovascular health, while the more nuanced pattern of chronic gross and micro- infarcts may reflect reduced stroke incidence and increased post-stroke survival. In contrast, given the relatively static levels of neurodegenerative disease they suggest that the reduction in dementia risk across time has been courtesy of vascular and resilience pathways. In particular they note that the increase in tau tangle density, the pathology with the strongest link to dementia, adds weight to the argument that levels of cognitive reserve have improved over time.

The clear strength of this study is the size and duration of the ROSMAP cohorts, with detailed clinical and neuropathological assessment consistent across time. This puts ROSMAP in a unique position to analyse birth cohort trends in neuropathology. The main limitations reflect the representativeness of the sample compared to the US population in terms of age, education, socio-economic status, race/ethnicity and health.

Although there was overlap in four of the six age strata used to standardise to the overall age distribution, this was not the case for the oldest (98+ years) and youngest (<82 years) age strata, over-represented in the first two and last two birth cohorts respectively (eFigure in the Supplemental material)[2]. This may have influenced age-standardised prevalence estimates, and would benefit from a sensitivity analysis restricted to the overlapping age strata (82-97 years) or propensity score matching to reduce epoch differences.

The study looked at important neurodegenerative and vascular pathologies as individual outcomes, however we know that in older age groups the majority of those with dementia have multiple co-occurring pathologies, as shown by ROSMAP and other studies[3]. It would be interesting to also see how the frequency of combinations may have changed across birth cohorts, as well as outcomes such as cortical atrophy.

The “conditions in which people are born, grow, work, live, and age, and the wider forces and systems shaping [them]”[4], known as the social determinants of health, have a profound impact on neurological health[5]. The evidence of birth cohort trends in dementia and neuropathology remind us of the relevance of birth year and the historical and social context in which people lived[6]. The decline in dementia risk has likely been an ‘off-target’ effect of improvements across time in social determinants (including education) and the prevention and management of cardiovascular disease.

However, despite the improvements seen across these generations there is no room for complacency, as recent evidence from nationally representative US studies demonstrate. The Health and Retirement Study showed a decline in dementia prevalence between 2000 and 2012 (with an average increase of one year’s education contributing), however there was an increase in the prevalence of cardiovascular risks including hypertension, obesity and diabetes[7]. A study using the National Health and Nutrition Examination Survey (NHANES) looking at trends in cardiovascular disease between 1999 and 2016 showed that declines in prevalence occurred almost exclusively in the top 20% of earners[8]. While some

dementia risks are declining others are on the rise, and reductions in cardiovascular disease burden have not been shared equitably across the population.

This new study[2] aids in the understanding of the recent decline in dementia incidence, and supports the hypotheses that benefits are from improved vascular health and higher cognitive reserve, despite no reduction in neurodegenerative disease. These findings need replicating in the rare studies able to do so. Even in high-income countries the outlook for a continued decline in dementia risk is uncertain if not bleak, with rising levels of risk factors, and widening social and health inequalities. Yet many low and middle-income countries face much larger forecasted increases in dementia prevalence due to population growth, ageing and increases in cardiovascular risk factors[9]. More than ever there is a need for governments to prioritise population-level approaches to dementia risk reduction[10], which can bring multiple health (and environmental) benefits.

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Competing interests
The authors declare no competing interests.