How preventable is dementia?

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Dementia, the most feared accompaniment of ageing, already affects more than 900,000 people in the UK with numbers predicted to rise rapidly in line with increasing life expectancy.[1] As the scale of the coming epidemic with its attendant financial implications becomes clear, dementia prevention becomes ever more a priority for governments, and individuals increasingly want to know what they can do to modify their risk.

Evidence linking a variety of potential risk factors for dementia comes predominantly from observational and epidemiological studies alongside some clinical trials, which have been synthesized in a number of comprehensive analyses, the best known of which is the Lancet Commission on Dementia. First published in 2017[2] and revised in 2020,[3] this identifies twelve potentially modifiable risk factors acting at different stages of life that together might explain ~40% of worldwide dementia risk. In early life the principle risk is *low education*. In mid-life (defined as ages 45-65) these are *obesity*, excess *alcohol*, *traumatic brain injury, hearing loss*, and *hypertension*; while in later life *smoking*, *depression*, *social isolation*, *physical inactivity*, *diabetes mellitus* and *air pollution* are implicated.

That such a significant proportion of dementia cases might be modifiable is cause for optimism at a time when therapeutic advances in dementia are few and far between. However, a number of important questions remain. What evidence is there to guide specific targets and interventions? How much modification can reasonably be expected in practice? What aspects of dementia are we preventing? And are there more risk factors to be determined?

When it comes to making recommendations there is a relative lack of randomised controlled trial evidence to allow for targeted advice. In dementia we are some way off the risk calculators (e.g. QRISK®3)[4] developed and validated for stroke/heart attack. Much advice is appropriately centred on reinforcing existing cardiovascular risk modification: monitoring blood pressure in mid-life – perhaps as early as the 30s[5] – with current guidance suggesting aiming for a systolic <130mmHg[3], is perhaps the intervention with the best evidence base. Other advice includes avoiding drinking alcohol to excess; not smoking; maintaining weight within recommended limits; eating a balanced diet; and screening for, and managing, diabetes.[6] There is no good evidence for the use of any specific antihypertensive medications, aspirin or statins[3]. Exercise, and aerobic exercise in particular, appears to have cognitive benefits: as well as influencing cardiovascular risk, there is emerging evidence for

direct effects on brain neurochemistry[7]. Reinforcing those interventions that are beneficial both for cardiovascular and brain health ("*what's good for your heart is good for your brain*") appears to be an important and motivating message which is gaining traction with the public.

A number of risks and recommendations may be more specific to dementia. Remaining cognitively active throughout life seems to be beneficial, but while brain training apps and protocols have variously been reported to improve performance in certain cognitive domains, it is by no means certain that they impact on cognitive decline and dementia[3]. It seems sensible to recommend activities that individuals find enjoyable, mentally stimulating, and which ideally also increase quality of life and promote social interaction – there seems little point in taking up Sudoku if you hate it. There is considerable interest in the relationship between repeated sporting head impacts and later life dementia, particularly given the reported ~4-fold increased risk of neurodegenerative disease in outfield professional footballers.[8] Sporting bodies and the research community are currently grappling with how best to promote the undoubted health and social benefits of sport while minimising head injuries. To what extent relationships between depression, social isolation and dementia are cause or effect is unclear, but addressing mental health and loneliness is clearly an urgent public health priority. While the causal relationship between hearing loss and dementia and the potential mechanisms linking the two continue to be debated[9,10], few would argue that having one's hearing checked and deafness treated is important if only to help prevent isolation and promote engagement with others; there is some evidence that hearing aid use is beneficial.[3]

It is unlikely, however, that even in the best-case scenario reductions in dementia prevalence anywhere near 40% are achievable by addressing these risks alone. Some, notably improving education and air pollution require concerted worldwide governmental action at a scale which seems unlikely to be achievable in the near future. Considerable progress has already been made in reducing smoking and improving blood pressure control in the past few decades which may well responsible for the declining age-related incidence of dementia seen in many Western countries in recent years[11]. Conversely, other risks such as diabetes and obesity are obstinately on the rise despite having been known to influence cardiovascular disease for many years.[12,13] There is some evidence that intensive, supervised multi-modal regimens focussing on diet, exercise, cognitive training and vascular risk monitoring may be beneficial for brain health[14], but how feasible these programmes are outside of clinical trials has yet to be determined. Individuals with multiple risk factors who may be at highest risk are often the ones most difficult to engage with prevention strategies; and the frequent co-occurrence of multiple risk factors may lead to overestimates of the potential for dementia reduction if individual risk estimates are calculated in isolation.

While it may not be important to individuals *how* a given intervention might impact their risk, understanding the impact of risk modification on the pathologies that lead to specific forms of dementia is of vital importance if we are to move towards an era of personalised risk reduction. We do not know, for instance, exactly how hypertension relates to late life cognitive impairment, although there is substantial evidence to suggest this is principally via its effects on cerebrovascular pathology rather than the pathological pathways leading to Alzheimer's disease[5]. Similarly, teasing out the myriad potential reasons and confounds that link air pollution to dementia is a major challenge. As long as "dementia" is the outcome, it is

possible that potentially very modifiable risks for specific forms of dementia may be overlooked. By analogy if one were to carry out an epidemiological study assessing risks factors for "cancer" rather than its specific subtypes, one might not identify human papillomavirus infection or ultraviolet light exposure, despite these now being known to be major risks for (amongst others) cervical and skin cancer respectively. Thus, while the identification of a number of modifiable risk factors for dementia is clearly a major advance, it should be viewed as the first step in identifying how different risks lead to different forms of dementia, which combined with an individual's genetic risk profile may ultimately lead to personalised risk reduction strategies.

Studies estimate that ~70-80% of an individual's risk for developing Alzheimer's disease is genetic[15], and while genetic and environmental factors inevitably interact it is clear that a substantial, and likely the majority, of an individual's risk of developing dementia is not modifiable. Many patients with dementia understandably question whether their life choices have led to the development of their condition; it is vital that by focussing on risk reduction we do not inadvertently create guilt in those who do become affected: as autosomal dominant forms of dementia demonstrate some people are destined to develop dementia however they live their lives. And, akin to cancer, while we should prevent what we can prevent and must continue to research and explore modifiable risk factors, it is equally important that in parallel we continue to develop novel therapies and provide a rational evidence base for their use, and the infrastructure for their deployment.

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