Mechanisms and implications of the relationship between weight and dementia risk

Authors’ response to the letter: BMI is unlikely to be a plausible intervention target for reducing the incidence of dementia.

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Word count: max 453 words (10 references)
In the comments to our study [1] Davies, Korologou-Linden & Anderson [2] suggest that weight reduction is unlikely to be a plausible intervention target for reducing the incidence of dementia. Although we did not claim a causal link between obesity and dementia risk, the relationship reported in our study is observational, based on a longitudinal analysis of a large representative population sample of English adults 50 and older [3], and our findings are not in isolation [4]. One meta-analysis found that midlife obesity was associated with an increased dementia risk (RR = 1.91 [1.4, 2.62]) across populations from both the United States and China [5].

While obesity is a complex issue, with a high degree of genetic heritability [6], substantial reductions in caloric intake, increases in physical activity and tailored psychological interventions could be beneficial for many health outcomes. As we have seen from one of the first randomised controlled trial ‘CALERIE: Comprehensive Assessment of the Long-Term Effects of Reducing Intake of Energy’, cutting caloric intake by 15% for two years decreased systemic oxidative stress [7], which has also been tied to age-related neurological conditions, such as dementia and Alzheimer's disease (AD).

Moreover, the link between obesity and dementia is supported by underlying biological mechanisms, that are part of the hallmarks of the cardiometabolic profile (e.g., diabetes, hyperinsulinaemia and raised glycosylated haemoglobin levels) [8] and associated inflammatory response [9]. Some evidence indicates that these mechanisms are also influenced by the hormonal changes occurring after midlife, with increased levels of estrogen and sex hormone-binding globulin affecting dementia risk [10]. Therefore, weight reduction may well be a plausible intervention target for reducing the incidence of dementia; though, we acknowledge that more research is needed with more attention given to the type of dementia investigated (e.g., dementia, vascular dementia or AD) and the specific periods across midlife when obesity is particularly detrimental.
The argument that the rise in obesity is inconsistent with the fall in Alzheimer's disease incidence assumes that adiposity acts independently of these cardiometabolic processes, but we also need to consider the current challenges in diagnosing Alzheimer disease. The Mendelian randomization studies are important but are based on diagnosed Alzheimer's disease which may underestimate true population prevalence.

Irrespective of the arguments made around causality, weight loss interventions are certainly needed, considering the sharp increase in the levels of obesity in recent years, and their long-term consequences. However, such interventions should not be considered in isolation, but within the appropriate economic and political context driving the relevant policy infrastructure. Public health efforts to prevent and manage health issues related to body weight should be strengthened for healthy ageing. At the same time, the relationship between obesity and dementia, in particular, is worthy of future study.

**Conflict of interest:** None declared.
References:


2. Davies, Korologou-Linden & Anderson, BMI is unlikely to be a plausible intervention target for reducing the incidence of dementia Int J Epidemiol, 2021 (citation to be linked).


