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Vascular risk factors and dementia revisited

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Although dementia is for the most part a disease of the elderly, epidemiological data suggests that the pathological processes leading to the disease start operating many years before the clinical onset.^{1, 2} Hence there is reason to believe that some risk factors begin to exert their impact as early as midlife. In this issue (p.XXX), Alonso et al. present evidence suggesting that exposure to vascular risk factors in midlife is associated with an increased risk of dementia. In 11,151 community participants from the Atherosclerosis Risk in the Communities study, vascular risk factors were measured at a mean age of 56 years, and hospitalizations with a diagnosis of dementia were prospectively recorded over a follow-up period averaging 13 years. Presence of diabetes, hypertension and active smoking in midlife were associated with a significantly increased risk of hospitalization with a diagnosis of dementia. Interestingly, these associations were stronger in individuals aged less than 60 when the vascular risk factors were assessed. The large size and diverse ethnicity of the sample increase the generalizability of the findings, and support the notion that decreasing the risk factor burden in middle-age could reduce the incidence of dementia.

Several studies have previously shown that diabetes,³ hypertension,³ obesity,⁴ and smoking⁵ are associated with an increased risk of dementia, but other groups did not observe such a relation.⁶ Although the positive associations were observed mainly in studies where risk factors were assessed in midlife while most negative studies targeted older populations,⁶ these discrepancies could be ascribed to various other differences between studies in addition to age. By assessing the impact of vascular risk factors in different age groups and at different time points within the same cohort, Alonso et al. provide important evidence that age is indeed an important modulator of the association between vascular risk factors and dementia.

Why vascular risk factors are better predictors of dementia when measured in middle-aged, rather than in older individuals, remains unclear. Exposure to risk factors in midlife probably better reflects the total amount of exposure throughout a lifespan than does a single measure recorded later in life. Risk factor measurements in the elderly may also be modified by concomitant diseases inducing weight loss, cessation of smoking or drop in blood pressure, which could lead to an underestimation of prior exposure. Alternatively, assessing risk factors in older people may introduce a selection bias due to premature death of individuals exposed to these risk factors, thus leading to an under-representation of individuals most sensitive to the risk factor exposure. Furthermore, vascular lesions may play a more important role in triggering the development of clinical dementia in younger individuals (who are not included in studies focusing on elderly people from the outset), while in older individuals the effect of Alzheimer disease pathology or age-related changes such as neuronal loss or reduced synaptic

density may more often overwhelm the effect of vascular disease. Finally, medications could play important modifier effects in the association between vascular risk factors and dementia.

As emphasized by the authors, their findings suggest that a more systematic application of vascular risk factor management guidelines in middle-aged adults might substantially reduce the incidence of dementia. More data from clinical trials is however needed to assess the impact of such interventions in midlife on the occurrence of dementia. Several trials have assessed the impact of antihypertensive treatments on dementia: only one of them,⁷ conducted in individuals aged 65 years or more, demonstrated a significantly lower incidence of dementia in patients randomized to antihypertensive treatment versus placebo. No such data is available for antidiabetic treatment although increasing glycemic control has been related to better cognitive scores.⁸ Important limitations when assessing the effect of vascular risk factor treatments in midlife on dementia risk are that (i) there is overwhelming evidence that these treatments should anyway be prescribed to reduce the burden of vascular disease and (ii) dementia is a late onset disease, thus leading to an important time lag between interventions in midlife and onset of dementia. Strategies to overcome these difficulties could be to incorporate cognitive outcomes in comparative effectiveness trials of validated risk factor management strategies, and to use intermediate endpoints such as longitudinal change in cognitive test scores or brain structure on MRI.

Finally, refining the analysis of the relation between midlife vascular risk factors and dementia could improve our understanding of the underlying mechanisms. Whether this relation is mediated solely by cerebrovascular disease or whether other mechanisms, such as increased inflammation, oxidative stress or metabolic changes, could play a role is unclear. Assessing in greater detail the role of body composition and metabolic characteristics of diabetes, or the impact of interim cerebrovascular events on the association between vascular risk factors and incident dementia, could for instance be helpful.

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