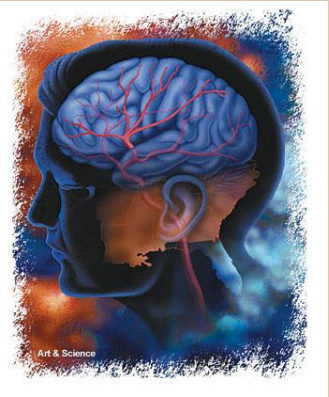
Metabolic Disease and Dementia

The onset of disease in middle age increases risk



Cardiometabolic diseases including diabetes, heart disease, and stroke are a growing challenge in our society. Since people live longer, it is more likely that they will have more than one condition. Up to 30% of our older population now have two or more cardiometabolic diseases which have been associated with negative health outcomes. How does having more than one problem affect our risk for dementia? What about the timing of the onset of these diseases? Does this matter? This study looked at the link between multiple cardiometabolic diseases, the timing of the onset of the disease, and the overall risk.

Abstract

- Aims: Cardiometabolic diseases (CMDs), including diabetes, heart disease, and stroke, are established risk factors for dementia, but their combined impact has been investigated only recently. This study aimed to examine the association between mid- and late-life cardiometabolic multimorbidity and dementia and explore the role of genetic background in this association.
- Methods and results: Within the Swedish Twin Registry, 17 913 dementia-free individuals aged ≥60 were followed for 18 years. CMDs [including age of onset in mid (60) or late (≥60) life] and dementia were ascertained from medical records. Cardiometabolic multimorbidity was defined as having ≥2 CMDs. Cox regression was used to estimate the CMD–dementia association in (i) a classical cohort study design and (ii) a co-twin study design involving 356 monozygotic and dizygotic pairs. By comparing the strength of the association in the two designs, the contribution of genetic background was estimated. At baseline, 3,312 (18.5%) participants had 1 CMD and 839 (4.7%) had ≥2 CMDs. Over the follow-up period, 3,020 participants developed dementia. In the classic cohort design, the hazard ratio (95% confidence interval) of dementia was 1.42 (1.27–1.58) for 1 CMD and 2.10 (1.73–2.57) for ≥2 CMDs. Dementia risk was stronger with mid-life as opposed to late-life CMDs. In the co-twin design, the CMD–dementia association was attenuated among monozygotic [0.99 (0.50–1.98)] but not dizygotic [1.55 (1.15–2.09)] twins, suggesting that the association was in part due to genetic factors common to both CMDs and dementia.
- Conclusion: Cardiometabolic multimorbidity, particularly in mid-life, is associated with an increased risk of dementia. Genetic background may underpin this association.

This study shows that having multiple cardiometabolic diseases (CMD) increased the risk of dementia, especially if these conditions develop in mid-life (< age 60). The risk of dementia, both Alzheimer's and vascular dementia increased by 42% for each additional cardiometabolic condition. The risk of dementia decreased by 11% for each additional decade of age at the onset of the first CMD. For individuals with CMD multimorbidity, the risk of dementia decreased by 16% for each additional decade of older age at the development of their second CMD. Together, these results suggest that the earlier these risky conditions develop, the more damaging they may be to cognitive health. C*ardiometabolic multimorbidity was related to a 50% increased risk of Alzheimer's disease and more than double the risk of Vascular dementia. This suggests that both neurodegenerative and vascular mechanisms may be involved in the development of dementia in people with CMDs.*

There are several potential mechanisms for these findings. Chronically elevated glucose in type 2 diabetes contributes to oxidative stress which contributes to both cerebral atherosclerosis and neurodegeneration. It can lead directly to neuronal death through its toxic effect on the myelin sheath. Cerebral insulin resistance (coined type 3 diabetes), has been linked to tau hyperphosphorylation and increased generation of amyloid-β which are found in Alzheimer's patients. Chronic cerebral hypoperfusion from stroke or reduced cardiac output from heart disease can alter cerebral blood flow velocity, leading to the development of vascular brain lesions. Cerebral hypoperfusion could also trigger brain hypoxia (low oxygen), which can promote the deposition of amyloid-β. Endothelial dysfunction characterizes CMDs and can disrupt the integrity of the blood-brain barrier, leading to impaired amyloid-β clearance. Inflammation is seen with many

of these conditions, which plays a well-established role in the pathogenesis of these conditions and may accelerate the progression of both neurodegenerative and vascular brain pathologies.

My takeaway from this paper is that the length of time one has cardiometabolic disease matters. This infers that we should identify risk factors for these conditions earlier in life, and when present, we should treat them aggressively to avoid the long-term effects on the brain from exposure to elevated glucose, lipids, and overall inflammation. This has the potential to reduce oxidative stress, deposition of amyloid-β, and improve clearance of amyloid-β, all of which should reduce our risk of Alzheimer's dementia. A healthy vascular environment reduces our risk of heart disease but also vascular dementia.

What can we do to reduce our risk? Don't smoke. Keep blood pressure in range. Control lipids, blood glucose, and insulin levels. Exercise regularly (helps with all of these). We may still develop some of these cardiometabolic diseases, but the later this happens the better it is for our brains.

Abigail Dove, Jie Guo, Anna Marseglia, Johan Fastbom, Davide Liborio Vetrano, Laura Fratiglioni, Nancy L Pedersen, Weili Xu, Cardiometabolic multimorbidity and incident dementia: the Swedish twin registry, European Heart Journal, 2022;, ehac744, https://doi.org/10.1093/eurheartj/ehac744.