EDITORIAL

Machine-learning derived heart and brain age are independently associated with cognition

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Alzheimer's disease and related dementias (ADRDs) have debilitating effects on affected individuals including reduced quality of life, cognitive and verbal decline, reduced mobility and eventual death. Globally, ADRDs is the sixth largest cause of mortality and morbidity.[1] Indeed, the prevalence of ADRDs is projected to increase alongside increased longevity in the general population. Thus, the health and economic burden from ADRDs are substantial and represent a major public health challenge globally.[1] Specific treatment options for ADRDs are limited and attention must be placed on greater understanding of disease pathophysiology and prevention of ADRD.

Cardiovascular risk factors and cerebrovascular pathology are key contributors to ADRD. Hence, early identification and management of these conditions, especially in people who are at high risk of ADRD, could help to prevent onset and delay progression of a common and frequently debilitating condition.

Machine learning (ML) applications are a subtype of artificial intelligence that can help to identify people who are at greatest risk of healthcare conditions and use of ML algorithms show great promise to help improve outcomes in increasing number of healthcare settings. Recently, ML has been shown to significantly improve the dynamic stroke risk prediction, compared the common clinical risk scores[2]. Thus, ML could similarly have the potential to identify people who are at greatest risk of ADRD, and who may benefit from targeted interventions to reduce the onset and progression of the condition.

In the current issue of the Journal, Iakunchykova and colleagues[3] applied ML algorithms to analyse electrocardiograms (ECGs) and estimate heart delta age (HDA) for almost 8000 people aged 40 to 85 years in the Tromsø Study who did not have a diagnosis of dementia at baseline. HAD is the difference between ECG-predicted age and chronological age, which is an independent predictor of cardiovascular disease, although its impact on ADRD is less well established.[4, 5]

The authors demonstrate that HDA is significantly associated with traditional cardiovascular risk factors, as well as a number of measures of cognitive function that are particularly sensitive to early changes in cognition, including word tests, digit symbol coding and finger tapping test scores.

Moreover, digit symbol coding and finger tapping test of the non-dominant hand remained significantly associated with HDA after adjustment for traditional cardiovascular risk factors. The authors also estimated brain derived age (BDA) by applying ML algorithm which they had previously developed for 1693 participants in the Tromsø Study, who also had MRI brain scans.[6] BDA is defined as the MRI-predicted age minus chronological age at the time of MRI and correlations were observed between BDA and HDA. Importantly, only 13-15% of the total effects of HDA on tapping test scores of cognition were mediated by BDA, although these effects were in the same direction. This led the authors to conclude that high HDA and BDA cumulatively impact on cognitive performance.

Taken together, these data suggest that HDA estimated from a simple 12-lead ECG has a strong association with cognitive performance, and could be used to identify people who are at greatest risk of ADRD. HAD could therefore represent a simple, non-expensive marker to identify people who may benefit from interventions to delay the onset or slow the progression of ADRD. This could include, for example, blood pressure and glycaemic control, smoking cessation, reduced alcohol intake and weight management which are all vascular risk factors associated with the development of ADRD. ECG-derived HDA could also help to improve understanding of the pathophysiology of ADRD which is crucial to help support the development more targeted therapies to improve outcomes for people with ADRD.

There has been more recognition of the brain-heart interactions over recent years, including ADRD and other neurological conditions such as stroke and epilepsy. The interactions appear to be bidirectional. For example, a pooled analysis that included 30,465 adults showed that the rate of decline in global cognition, memory and executive function was significantly faster over the years for people with myocardial infarction event, compared to those without.[7]

Iakunchykova and colleagues[3] also support the more general concept that ML analysis of ECGs shows promise to help identify people who are at increased risk of neurological conditions and guide the application of interventions to mitigate this risk. For example, the application of ML ECG analysis to classify people who are at highest risk of AF also shows great promise, and is being evaluated in people after stroke and the general population to identify those who would benefit from AF screening and anticoagulation to prevent AF-related stroke, if AF is detected.[8]

The next step is to assess whether application of ML ECG analysis can be used to improve understanding of disease pathophysiology and guide interventions that may delay the onset or slow the progression of ADRD. If demonstrated to be effective in this context then ML ECG analysis could represent a simple, non-invasive way to help reduce the substantial global burden of ADRD for individuals and society.

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