Tipping the scales towards routine APOE genotyping

Ross Dunne – Consultant old age psychiatrist at Greater Manchester Mental Health NHS Foundation Trust and honorary senior lecturer at the Geoffrey Jefferson Brain Research Centre, University of Manchester
Elizabeth Coulthard – Associate Professor in Dementia Neurology at the University of Bristol and consultant neurologist at North Bristol NHS Trust

Summary sentence – Personalised Alzheimer's disease prevention and treatment will rely on APOE genotyping, but this well-validated predictor is rarely used in routine care.

Preventing or delaying dementia due to Alzheimer's disease (AD) requires personalised risk reduction plans[1]. Obesity is a risk factor for dementia, but the "obesity paradox" suggests that higher mid-life BMI is a risk factor for later dementia, whereas lower BMI seems protective in later life. This is partially explained by the long AD prodrome itself *causing* weight loss[2], but heterogeneity between studies perhaps implies additional mechanisms.

Here, Shinohara al (*citation*) examine the role of APOE in the "obesity paradox"[2]. They analyse the comprehensive NACC dataset to investigate the role of APOE and obesity in AD risk, building on their previous studies evaluating APOE and diabetes. This study generates testable hypotheses about the possible interaction of APOE and obesity, dichotomising BMI into "Obese" (n=434) and "non-Obese" (n=2737) for the purposes of interpretability, and measuring cognitive decline, and, in a subset, neuropathology. The authors suggest that obesity is linked to faster cognitive decline in older cognitively normal individuals without APOE4, possibly by provoking vascular disease. However, obesity is linked to *less* cognitive decline in both impaired and cognitive normal individuals with APOE4.

While large cohorts are an invaluable infrastructure to test and generate hypotheses, there are limitations. This study does not fully exploit established techniques of causal inference, such as directed acyclic graphs (DAGs), mendelian randomisation and more[3]. These techniques open the door to elucidating the mechanistic relationships between APOE and AD and their modifiers. The obesity "paradox" has similarities to the long debated "low birth-weight paradox" where low birth-weight children born to smoking mothers have a lower infant mortality rate than the low birth-weight children of non-smokers. There, the problem is a "lurking" unmeasured variable, confounding low birth weight's position as a

mediator between smoking and infant mortality. In non-smoking mothers, profound developmental abnormalities explain low birth weight, and thus increase mortality[4]. Well-conducted studies using causal inference methods can unpick these relationships[5].

Nevertheless, the differential impact of obesity according to APOE status demonstrated here potentially supports APOE genotyping to stratify AD-dementia prognostication and clinical trials of preventive-interventions. In our view, no current prognostic model for AD is complete without APOE genotype, because APOE4/4 represents the same increase in risk of incident AD as an additional ten years of ageing after age 50[6]. While fluid biomarkers can hugely increase the precision of diagnosis and prognosis in the preclinical or prodromal phases of AD, APOE can be tested across the life-course with implications for cognition from midlife onwards.

APOE testing is often not clinically routine, and the UK National Institute of Health and Care Excellence (NICE) guidelines specifically advise against it. Yet, APOE genotype could be a vital clinical tool. In addition to personalised prognostication and tailored interventions, it is a major risk predictor in the development of Amyloid-related Imaging Abnormalities (ARIA), side effects of emerging monoclonal antibodies[7]. Genotyping has been demonstrated to be acceptable to both patients and clinicians[8]. Therefore, routine clinical testing of APOE AD prevention and treatment should be reconsidered, perhaps initially in people with memory impairment.

1. Frisoni, G. B. *et al.* Dementia prevention in memory clinics: recommendations from the European task force for brain health services. *The Lancet Regional Health - Europe* **26**, 100576 (2023).
2. Pegueroles, J. *et al.* Obesity and Alzheimer's disease, does the obesity paradox really exist? A magnetic resonance imaging study. *Oncotarget* **9**, 34691–34698 (2018).
3. Hernán, M. & Robins, J. M. *Causal inference*. (Chapman & Hall/CRC, 2021).
4. Hernandez-Diaz, S., Schisterman, E. F. & Hernan, M. A. The Birth Weight 'Paradox' Uncovered? *American Journal of Epidemiology* **164**, 1115–1120 (2006).

5. McElreath, R. *Statistical rethinking: a Bayesian course with examples in R and Stan*. (Chapman & Hall/CRC, 2020).
6. Jack, C. R. *et al.* Associations of Amyloid, Tau, and Neurodegeneration Biomarker Profiles With Rates of Memory Decline Among Individuals Without Dementia. *JAMA* **321**, 2316 (2019).
7. Honig, L. S. *et al.* ARIA in patients treated with lecanemab (BAN2401) in a phase 2 study in early Alzheimer's disease. *Alzheimer's & Dementia : Translational Research & Clinical Interventions* **9**, (2023).
8. Roberts, J. S. & Green, R. C. Disclosing APOE genotype to individuals at risk for Alzheimer's disease. (2021).