ADIPOSITY IMPACTS COGNITIVE FUNCTION IN ASIAN POPULATIONS: AN EPIDEMIOLOGICAL AND MENDELIAN RANDOMIZATION STUDY

Theresia Mina[1], Konstadina Griva[1], Yew Yik Weng[1,2], Gervais Wansaicheong[1,3], Ng Hong Kiat[1], Rinkoo Dalan[1,4], Dorrain Low Yan Wen[1], Benjamin Lam Chih Chiang[1,5], Elio Riboli[1,6], Lee Eng Sing[1,7], Joanne Ngeow[1,8], Paul Elliott[1,6], Marie Loh[1,2], Jimmy Lee[1,9], John Chambers[1,6]

[1]Global and Population Health, Nanyang Technological University Lee Kong Chian School of Medicine, Singapore

[2]National Skin Centre, Singapore

[3]Department of Diagnostic Radiology, Tan Tock Seng Hospital (TTSH), Singapore

[4]Department of Endocrinology, TTSH

[5]Khoo Teck Puat Hospital, Singapore

[6]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, United Kingdom

[7]Clinical Research Unit, National Healthcare Group Polyclinic, Singapore

[8]Division of Medical Oncology, National Cancer Centre, Singapore

[9]Research Division, Institute of Mental Health, Singapore

Abstract

Background Obesity and metabolic disease predict future cognitive decline. Asia has a high prevalence of both obesity and metabolic disease, potentially amplifying the future burden of dementia in the region. We aimed to investigate the impact of adiposity and metabolic risk on cognitive function in Asian populations, and the potential mechanisms involved, using an epidemiological analysis and a two-sample Mendelian Randomization (MR) study.

Methods The Health for Life in Singapore (HELIOS) Study is a population-based cohort of South-East Asian men and women in Singapore, aged 30-84 years. We analyzed 8,769 participants with metabolic and cognitive data collected between 2018–2021. Whole-body fat mass was quantified with Dual X-Ray Absorptiometry (DEXA). Cognition was assessed using a computerized cognitive battery. An index of general cognition '***g***' was derived through factor analysis. We tested the relationship of fat mass indices and metabolic measures with '***g***' using regression approaches. We then performed inverse-variance-weighted MR of adiposity and metabolic risk factors on '***g***', using summary statistics for genome-wide association studies of BMI, visceral adipose tissue (VAT), waist-hip-ratio (WHR), blood pressure, HDL cholesterol, triglycerides, fasting glucose, HbA1c, and general cognition.

Findings Participants were 58·9% female, and aged 51·4 (11·3) years. In univariate analysis, all adiposity and metabolic measures were associated with '***g***' at P<0.001. In multivariate analyses, reduced '***g***' was associated with increased visceral fat mass index and lower HDL cholesterol (change in '***g***' per 1SD change in predictor [β]: -0·06, P=3·6x10^{-5} and 0·05, P=2·1x10^{-7} respectively), but not with blood pressure, triglycerides, or glycemic indices. In MR analyses, with a Bonferroni corrected threshold P<0·005, reduced '***g***' was causally linked with genetic variants for greater VAT (β= -0·13; P=1·5x10^{-4}), BMI (β= -0·09; P=6·0x10^{-5}) and WHR (β= -0·10; P=1·5x10^{-4}), but not HDL. MR did not support a causal role for blood pressure, lipid, or glycemic indices on cognition.

Conclusion We show an independent causal relationship of adiposity and cognition in a multi-ethnic Asian population. VAT may have specific etiological role on cognition beyond BMI. Our findings have important implications for future cognitive health and healthy ageing, in the context the rising burden of obesity in the Asia-Pacific region.