F1 - The Causal Role of Adiponectin and Triglycerides in Ischemic Heart Diseases Using a Separate Sample Mendelian Randomization Analysis from Publicly Available Data

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(i) Training Programme
Details of Training Activities: The training programme primarily focused on learning a new technique in Mendelian randomization studies using summary statistics from genome wide association studies. The programme consisted of multiple components. First, I was in an academic attachment to Professor Debbie A Lawlor at the Bristol Medical School: Population Health Sciences. I was supervised by Prof Lawlor via weekly in person meetings and regular email exchanges. I also conducted collaborative projects with other Integrative Epidemiology Unit (IEU) members at the University of Bristol, principally with Dr J Bowden and Dr MC Borges. Second, I attended a short course in Mendelian randomization where I learnt how to implement cutting edge methods in Mendelian randomization which are more robust to violation of assumptions in Mendelian randomization. Lastly, I took the opportunity to attend several seminars from different groups/ institutions such as emulation of randomized controlled trials from Mendelian randomization by Dr Brian Ferrence, and evaluation of environmental impact on mental health using twin status by Dr Claire Haworth.

Benefits of Training: The training has significantly refined my skills in conducting Mendelian randomization, in particular the part on 2 sample Mendelian randomization and the relevant statistical approaches. The training opportunity has also fostered potential long term collaborations between the University of Hong Kong (HKU) and the University of Bristol, and has important implications for my research career using Mendelian randomization. I also focused on how short course was being conducted by the Bristol group, which I eventually adopted some of the approaches back in my own HKU course.

Learning Experience: The learning experience, which included the academic attachment, the short course, and the seminars I attended, was very rewarding. Regular discussion with Prof Lawlor and other IEU members also enriched my thoughts in how causes of diseases should be identified, such as via triangulation of evidence.

Applicability to the Research Project: The training was directly applicable to my research project, particularly on 2 sample Mendelian randomization (formerly known as separate sample Mendelian randomization). These included substantial improvements in the choice of genetic instruments, and the sensitivity analyses needed to conduct such study.

(ii) Research Project
Introduction and Project Objectives: Adiponectin and triglycerides are related to ischemic heart disease (IHD) although results are not always consistent across different study designs. Verifying their role in IHD may help identify new targets of interventions to improve population health. The project objectives were to verify the causal role of adiponectin and triglycerides in IHD using Mendelian randomization.

Methods: We extracted strong, independent genetic instruments (p value <5x10-8), i.e. single nucleotide polymorphisms (SNPs), from ADIPOGen Consortium for adiponectin (n=39,883); and Global Lipids Genetics Consortium (GLGC) for triglycerides (n=188,577), which were then applied to CARDIoGRAMplusC4D 1000 Genomes-based genome wide association studies (GWAS) (IHD cases: 60,801; controls: 123,504). We obtained the causal estimate of adiponectin, triglycerides on IHD risk using inverse variance weighting (IVW). Sensitivity analyses included MR-Egger, weighed median, and exclusion of pleiotropic instruments.

Results: Using 21 SNPs for adiponectin, adiponectin was inversely associated with IHD in IVW (Odds ratio (OR) 0.82 per log transformed adiponectin unit increase, 95% confidence interval (CI) 0.71 to 0.94). However, the results were not robust to sensitivity analyses. On the contrary, using 102 SNPs for triglycerides, triglycerides was positively associated with IHD in IVW (OR: 1.26 per SD increase, 95% CI 1.16 to 1.38), with directionally consistent estimates from sensitivity analyses.

Conclusions: Triglycerides likely causes IHD although the relation of adiponectin and IHD is likely non-causal, reflecting confounding in previous studies. This study implies medications which raise adiponectin unlikely decrease IHD risk. Efforts should be redirected to other more promising targets of intervention, such as triglycerides, with rigorous evaluation from properly designed randomized controlled trials.

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