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LKS Faculty of Medicine
School of Public Health
香港大學公共衞生學院

The causal role of adiponectin and triglycerides in ischemic heart diseases using a separate sample Mendelian randomization analysis from publicly available data (HMRF RFS #01150037)

Ryan Au Yeung

School of Public Health, LKS Faculty of Medicine,
The University of Hong Kong

BSc, MPH, PhD

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@Ryan_Au_Yeung

Introduction

- Identifying causes of disease remains one of the key components in epidemiologic research
  - The role of triglycerides and adiponectin in ischemic heart disease risk

- Discrepancies between observational studies and randomized controlled trials

VIEWPOINT

Viewpoint

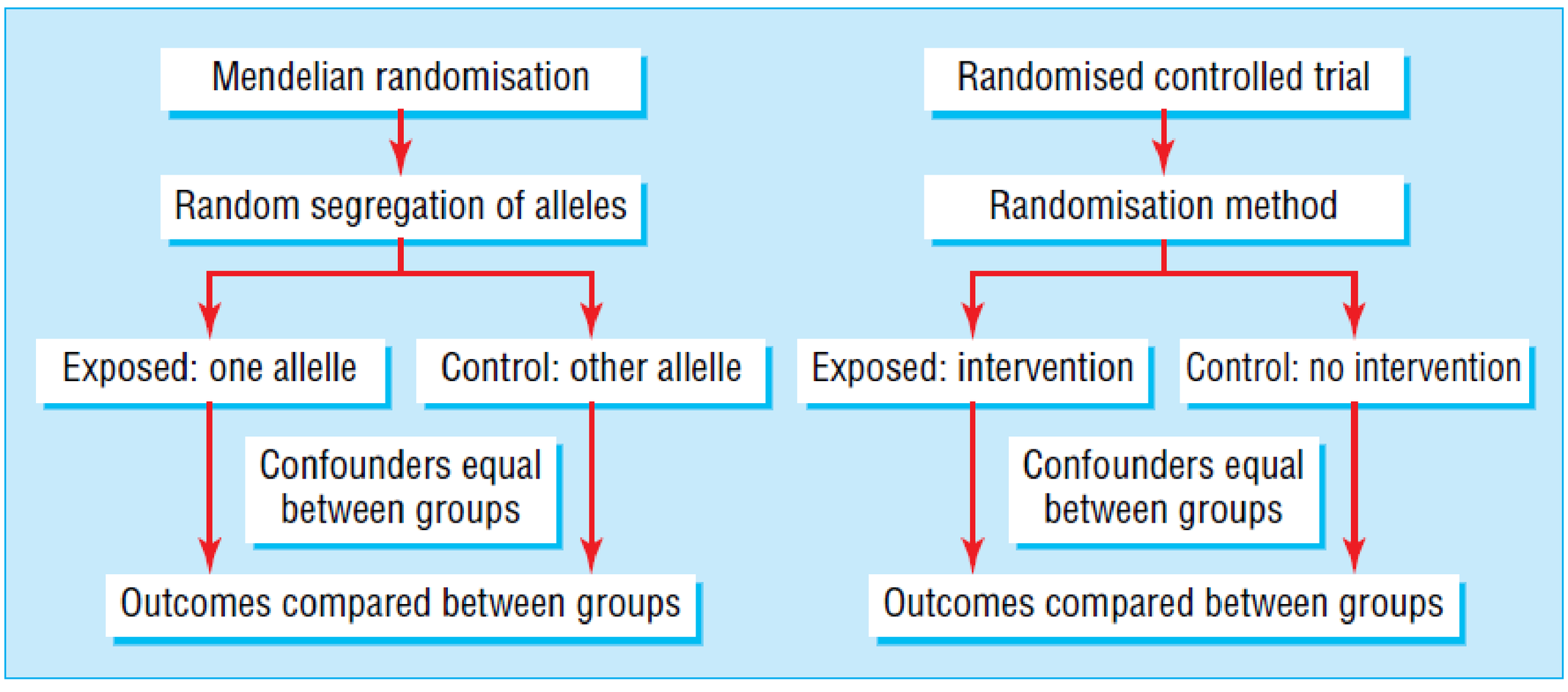
Those confounded vitamins: what can we learn from the differences between observational versus randomised trial evidence?

Debbie A Lawlor, George Davey Smith, K Richard Bruckdorfer, Devi Kundu, Shah Ebrahim

Lancet 2004; **363:** 1724–27

Introduction

- Mendelian randomization studies – nature’s randomized trial



Comparison of design of mendelian randomisation studies and randomised controlled trials

Davey Smith and Ebrahim, 2005

Challenges concerning Mendelian randomization

- One-sample Mendelian randomization (Conventional)
  - Large sample sizes and instruments
    - Impossible to obtain large samples for small effect sizes
    - Genetic analysis can sometimes be very costly and subject to bio-specimen availability
- Two-sample Mendelian randomization
  - The use of publicly available data of genome wide association studies (GWAS) of different phenotypes (biomarkers, diseases etc)
    - Essentially no cost
    - Very large so as to reduce the likelihood of false negatives
    - Relatively new method and technically very advanced (Back in 2016)

Training programme

- Academic attachment to Professor Debbie Lawlor, University of Bristol

- Short course on Mendelian randomization

- Other research activities

Training programme

- Ways to identify genetic instruments
  - Genome wide association studies; ethnicities; adjustment models etc
- Ways to analyze the data using summary statistics and corresponding sensitivity analyses
  - Inverse variance weighting, weighted median method, MR-Egger etc
- Caveats in Mendelian randomization
  - Allele harmonization; issues concerning the above-mentioned analyses; interpretation of estimates and inference; applicability to RCTs

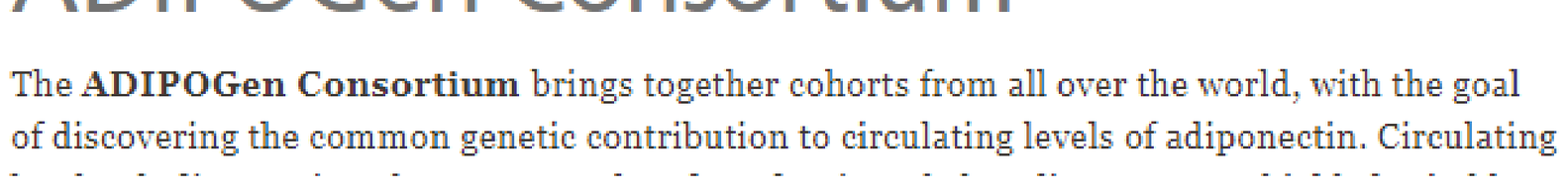
Application to the research questions – adiponectin and triglycerides

- Adiponectin and triglycerides are potential targets of intervention of ischemic heart disease (IHD) although the effect has not been thoroughly examined in randomized controlled trials

- Previous MR may have flaws (Jorgensen et al., 2013; Dastani et al., 2013) [At the time when I submitted the application]

- The aim of the project was to use MR with publicly available summary data to examine whether:
  - Higher adiponectin was associated with lower IHD risk
  - Higher triglycerides was associated with higher IHD risk

Methods



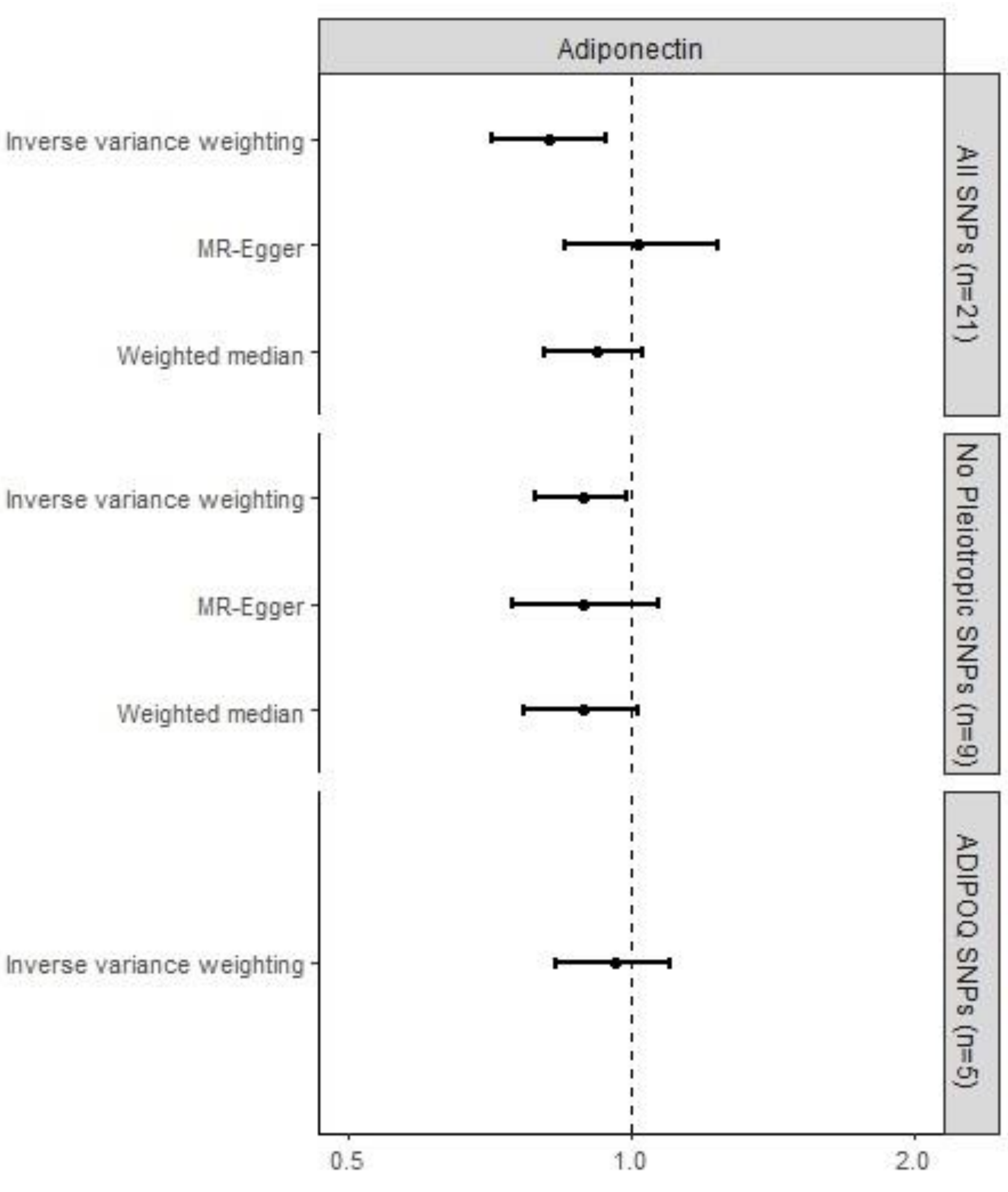
- Exposure data (p value $<5x10^{-8}$; and not in linkage disequilibrium ($r^2<0.05$))
  - ADIPOGen Consortium (n=39,883) for adiponectin (log transformed) -> 21 SNPs
  - GLGC (n=188,577) for triglycerides (standard deviation) -> 102 SNPs

- Outcome data
  - CARDIoGRAMplusC4D 1000 Genomes based GWAS (60,801 cases and 123,504 controls) for ischemic heart diseases

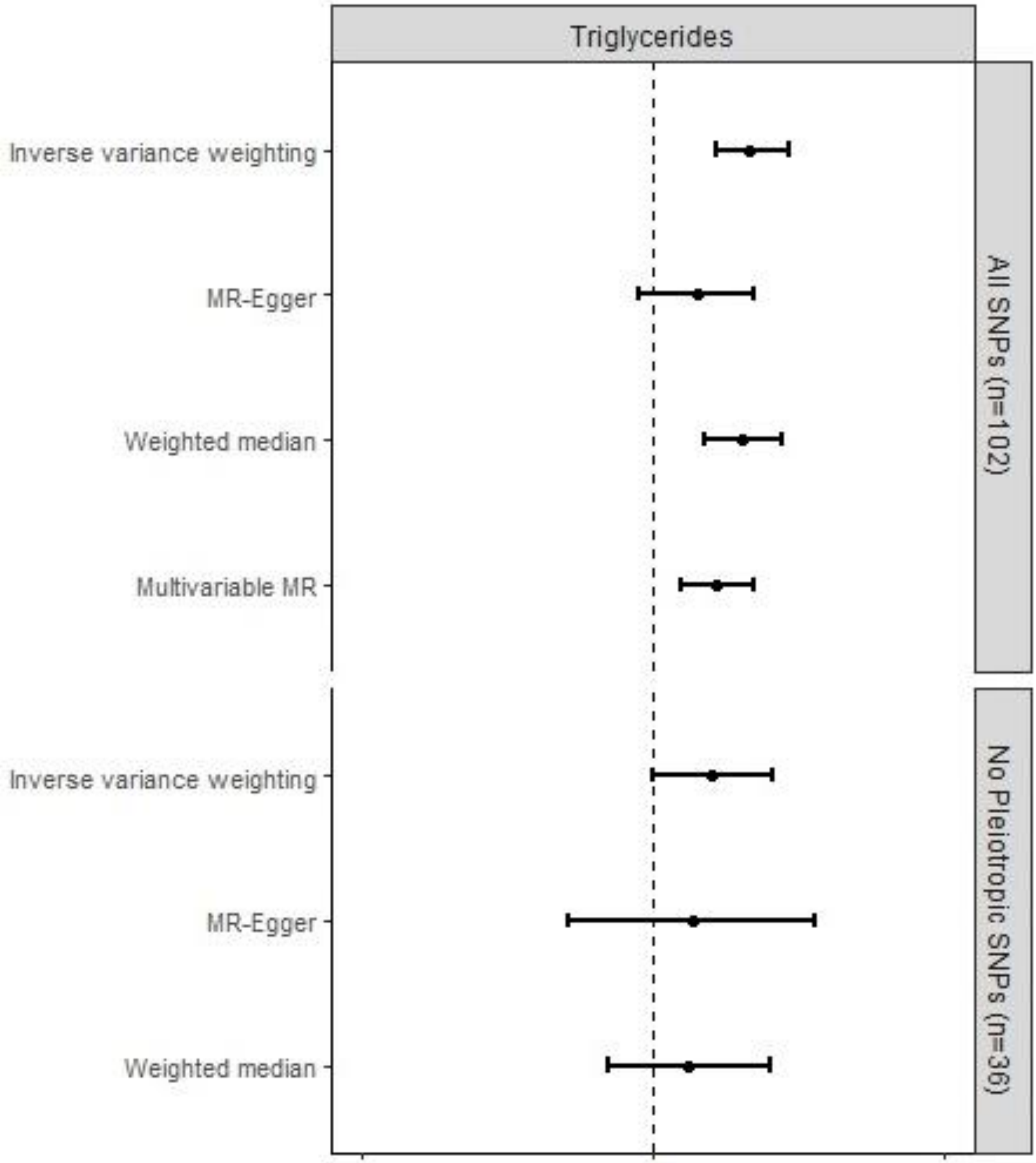
- Main analyses
  - Inverse variance weighting with multiplicative random effects

- Sensitivity analyses
  - Weighted median method, MR-Egger, exclusion of pleiotropic instruments, multivariable Mendelian randomization analysis etc

Main findings for adiponectin



Main findings for triglycerides



Discussion

Research Article

Statistics in Medicine

Received 22 May 2016, Accepted 10 December Published online 23 January 2017 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.7221

A framework for the investigation of pleiotropy in two-sample summary data Mendelian randomization

Jack Bowden,[a*†] Fabiola Del Greco M,[b] Cosetta Minelli,[c] George Davey Smith,[a] Nuala Sheehan[d] and John Thompson[d]

- Adiponectin
  - Likely a reflection of confounding such as by adiposity (Borges et al., 2017)
  - Consistent with a more recent Mendelian randomization study (Borges et al., 2016)
- Triglycerides
  - Inflammation as a potential mechanism (Nordestgaard and Varbo, 2014)
  - Discrepant findings compared to RCTs need further investigation (Jakob et al., 2016)
- Assumption of Mendelian randomization; generalizability

Obesity-induced hypoadiponectinaemia: the opposite influences of central and peripheral fat compartments

MC Borges,[1]* IO Oliveira,[1,2] DF Freitas,[1] BL Horta,[1] KK Ong,[3] DP Gigante[1] and AJD Barros[1]

International Journal of Epidemiology, 2017, 2044–2055
doi: 10.1093/ije/dyx022
Advance Access Publication Date: 27 March 2017
Original article

Reflections

- Substantially impacted my career in research, especially in the era of big data

- Foster potential collaborations between The University of Hong Kong and University of Bristol

- As an educator, I have also disseminated my knowledge to my colleagues within SPH, and MPH students

The Impact of Glycated Hemoglobin (HbA_{1c}) on Cardiovascular Disease Risk: A Mendelian Randomization Study Using UK Biobank

American Diabetes Association. Diabetes Care

Shiu Lun Au Yeung[1]⇑, Shan Luo[1] and C. Mary Schooling[1,2]

Association of genetically predicted testosterone with thromboembolism, heart failure, and myocardial infarction: mendelian randomisation study in UK Biobank

BMJ 2019 ; 364 doi: https://doi.org/10.1136/bmj.l476 (Published 06 March 2019)
Cite this as: *BMJ* 2019;364:l476

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Shan Luo, PhD candidate [1], *Shiu Lun Au Yeung, assistant professor* [1], *Jie V Zhao, research assistan* Circulation: Genomic and Precision Medicine
Stephen Burgess, statistician [2 3], *C Mary Schooling*, *professor* [1 4]

ORIGINAL ARTICLE

Association of Genetic Instrumental Variables for Lung Function on Coronary Artery Disease Risk

A 2-Sample Mendelian Randomization Study

See Editorial by Nowak

Shiu Lun Au Yeung, MPH, PhD
Maria-Carolina Borges, MSc, PhD
Debbie A. Lawlor, MSc, MBChB, PhD, MPH, MRCGP, MFPHM

BACKGROUND: Lung function, assessed by forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), is inversely associated with coronary artery disease (CAD), but these associations could be because of confounding or reversed causality. We conducted a 2-sample Mendelian randomization study, using publicly available data from

Contents lists available at ScienceDirect
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Adiponectin and coronary artery disease risk: A bi-directional Mendelian randomization study

Shiu Lun Au Yeung [a,*], C. Mary Schooling [a,b]

Acknowledgement

- Data on ischemic heart disease have been contributed by CARDIoGRAMplusC4D investigators and have been downloaded from www.CARDIOGRAMPLUSC4D.ORG. Data on adiponectin have been contributed by ADIPOGen consortium and downloaded from https://www.mcgill.ca/genepi/adipogen-consortium. Data on lipids have been contributed by GLGC and downloaded from http://csg.sph.umich.edu/willer/public/lipids2013/. Au Yeung SL was supported by the Health and Medical Research Fund Research Fellowship Scheme [#01150037], Food and Health Bureau, HKSAR, People's Republic of China. The funder had no role in the design, analyses, interpretation of results or writing of the paper. We thank CARDIoGRAMplusC4D, ADIPOGen Consortium, and GLGC for making the summary statistics publicly available.

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