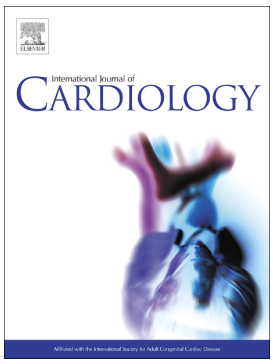

Mendelian randomization: A powerful method to determine causality of biomarkers in diseases

Vinicius Tragante, Folkert W. Asselbergs

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Mendelian randomization: a powerful method to determine causality of biomarkers in diseases

Vinicius Tragante[1], Folkert W. Asselbergs[1,2,3,4]

[1] Department of Cardiology, Division Heart & Lungs, University Medical Center Utrecht, Utrecht University, the Netherlands;
[2] Durrer Center for Cardiovascular Research, Netherlands Heart Institute, Utrecht, the Netherlands;
[3] Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom;
[4] Farr Institute of Health Informatics Research and Institute of Health Informatics, University College London, London, United Kingdom

Correspondence address
Vinicius Tragante do O
Heidelberglaan 100
Postbox STR 3.135
3584CX Utrecht
The Netherlands

Assessing the influence of a marker or exposure on a given outcome is a challenging task, since a multitude of factors can influence levels of given marker, and therefore confound correlation-causation inferences. Notable exceptions are genetic markers, since those are innate and not bound to change through an individual's lifetime. Furthermore, inheritance of each trait is independent of every other according to Mendel's law of inheritance [1]. That's the principle behind Mendelian randomization (MR), a method proposed in the 80's by Katan [2] to understand if alterations in plasma cholesterol levels in cancer patients were the cause or consequence of the disease (later shown through MR that there is no causal relation of cholesterol in cancer development) [3]. More recently the method has become ever more popular due to the continuously increasing availability of cohorts with genetic information, well-determined levels of biomarkers and deep-phenotyped outcome data. A simple PubMed query for the term "Mendelian randomization" shows a continuous increase from one publication in 2003 to 252 papers in 2017, demonstrating that the method has become a common practice in the field of genetic epidemiology.

Yeoung and Schooling [ref from this issue] report in this issue of *International Journal of Cardiology* a bi-directional MR to study the correlation between adiponectin levels and coronary artery disease (CAD). Taking advantage of the fact that many genetic markers have been significantly and independently associated with adiponectin levels and CAD, it is possible to group signals of one trait and test against the other with the possibility of giving a more definitive answer about the causality between adiponectin and CAD in both directions (a graphical demonstration of the method is in Figure 1). Using only significant and independent SNPs as genetic instrument, the researchers found