Published in final edited form as:

Curr Genet Med Rep. 2016 December ; 4(4): 207–212. doi:10.1007/s40142-016-0103-4.

Using Mendelian Randomization studies to Assess Causality and Identify New Therapeutic Targets in Cardiovascular Medicine

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Abstract

Integration of knowledge generated from genetic studies on intermediate biomarkers and CHD can provide a reliable approach to help assess causal pathways in coronary heart disease. Mendelian Randomization (MR) studies are a powerful tool to assess causal relevance of a range of pathways. These analyses use genetic variants as proxies for soluble biomarkers in association studies of disease risk. MR studies can provide unbiased estimates of causal effects and avoid distortions due to confounding factors arising later in life, because genetic variants are fixed at conception. MR studies have provided evidence pointing towards the likelihood of a causal relevance of a range of pathways in CHD, including LDL-C, triglycerides, lipoprotein (a), and interleukin-6 receptor. On the other hand, MR studies have refuted the causal relevance of a number of biomarkers, including C-reactive protein (CRP), fibrinogen, uric acid, LpPLA2 activity, and homocysteine. Carefully conducted MR studies should overcome the limitations that are inherent to other observational studies (e.g., residual confounding and reverse causality) to help assess causal relevance of a range of pathways in CHD.

Keywords

Mendelian Randomization; causal inference; risk factors; cardiovascular disease; coronary heart disease; novel therapies

Coronary heart disease (CHD) is the leading cause of death and disability globally (1). Despite several decades of research, the burden of CHD remains stubbornly high (1). There are only a handful of therapies (e.g., statins, anti-hypertensives) that are known to confer protection from CHD and a substantial residual risk for CHD remains among people who take such medicines (2;3). A large number of therapeutic programs focusing on CHD have had limited success. This has been suggested by unsustainably high rate of failures of new compounds in clinical trials of CHD, illustrated by failures of varespladib, dalcetrapib, and

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Compliance with Ethics Guidelines

Conflict of Interest

Each of the authors declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

niacin/laropiprant in the past few years (4–8). These observations highlight the need to pursue approaches that can rapidly identify causal pathways in CHD.

Large-scale array based genome-wide approaches have transformed our understanding on the genetic architecture of complex diseases. To-date >21,000 unique SNP-trait associations have been reported (9); these numbers are orders of magnitude greater than the discoveries made in the era prior to genome-wide array based studies. In CHD alone, >60 novel genetic loci have been discovered through GWAS (10–12). These discovery studies have securely identified many novel variants that were undetected after decades of research on candidate pathways or through linkage studies and have revealed biological pathways that were previously unsuspected as being relevant in CHD. With the exception of few (e.g., *PCSK9*, *APOC3*, *Lp[a]*), majority of these CHD loci do not overlap with intermediate pathways that have previously being shown in prior prospective epidemiological studies to be involved in the etiology of CHD (e.g., dysglycemic pathways, LpPLA2, Vitamin D and others). These observations have raised the possibility to consider residual confounding, chance or other biases that may have influenced prior observational studies. Importantly, many of these intermediate biomarkers have also been extensively interrogated through hypothesis free genetic studies (i.e., GWAS, exome-chip and sequencing studies) which have led to discovery of several dozen variants in association with each of these biomarkers (9). Integration of knowledge generated from genetic studies on intermediate biomarkers and CHD can provide a reliable approach to help assess causal pathways in CHD which could be subsequently prioritized for therapeutic development.

Mendelian randomization studies — a powerful tool to assess causal relevance of a range of pathways

Genetic studies that correlate genetic variants with intermediate soluble biomarkers, conventional risk factors, and clinical outcomes can be used to assess causal relevance of a range of biomarkers (13). This approach is known as “Mendelian Randomization” because it is based on Mendel’s second law which describes the independent assortment of alleles during gamete formation (13). These analyses use genetic variants as proxies for soluble biomarkers in association studies of disease risk (13–15). Under specific assumptions, MR studies can provide unbiased estimates of causal effects and avoid distortions due to confounding factors arising later in life, because genetic variants are fixed at conception. Hence, carefully conducted MR studies should overcome the limitations that are inherent to other observational studies (e.g., residual confounding and reverse causality). Mendelian Randomization analyses can therefore provide advantages similar to those in randomized trials (14), helping to judge the likelihood of cause-and-effect relationships between soluble biomarkers and the occurrence of disease. This information could be used to inform development and/or progression of pharmacological compounds that target these markers.

Making a causal inference through MR studies

Conventionally, MR studies involve multiple steps, including: (i) identifying genetic variant(s) through gene-biomarker association, (ii) checking the suitability of such genetic variant(s) for MR studies by conducting additional analyses (e.g., pleiotropy for other traits),

(iii) estimating gene-disease association to make inferences about causality, and (iv) comparing and contrasting genetically mediated effect estimates on disease risk with those obtained through observational studies (Figure-1)(15;16).

MR analyses could be done in a single study or a combination of studies. In some instances, it is not possible to conduct all the steps described above in a single dataset, hence MR studies have relied on effect estimates obtained through different datasets for each of the above steps. For instance, the effect of a genetic variant on a biomarker could be weak which would require a large sample size to appropriately estimate gene-disease association for making a causal inference. In such cases, MR studies have typically relied on effect estimates from large consortia that have conducted meta-analyses on disease outcomes by pooling data on several thousand participants enrolled from different studies. The CARDIoGRAMplusC4D consortium (12), for instance, currently comprises of genetic data on 60,801 CHD cases and 123,504 controls and provides an excellent resource for MR studies on CHD. With the growing number of hypothesis free genetic studies, large-scale consortia exist for many biomarkers and disease outcomes. This has greatly facilitated “Two-Sample” MR studies where evidence on the association of biomarker of interest and disease outcome could be derived from two non-overlapping data sources. An important assumption in such analyses is that the two data sources are derived from the same underlying population.

As noted above, the first step in MR studies is to find a single SNP or set of variants that relate to a biomarker of interest which could be used as a “genetic instrument” in MR studies. A genetic instrument can be constructed by using the summary-level statistics of a single variant or multiple variants associated with the biomarker of interest and the gene-disease estimate and the standard error can be subsequently obtained as described previously (17). To limit genetic confounding, genetic instrument should only associate with the biomarker of interest and not with a range of other traits (i.e., non-pleiotropic in nature). To assess for pleiotropy, the association of a genetic instrument could be assessed with a range of traits using data from several large-scale consortia. Below are some of the other key methods that could be used to implement MR studies.

The two-stage regression method—This technique has been implemented in other fields to perform a causal inference (16). When individuals’ genotypes are available, such a method could be used to assess the causal effect of a biomarker and a disease outcome. In the first stage, the biomarker level is regressed on genetic marker(s) and the fitted values are obtained; in the second stage, the disease outcome is then regressed on the fitted value of the biomarker and the coefficient of the biomarker obtained can be used to draw an inference on the causal effect. A statistically significant coefficient usually indicates a causal effect.

The ratio method—This method constructs the point estimate of a causal effect by forming a ratio of the effects of a genetic marker on the outcome (β_O , $\ln(OR)$ for a binary outcome) and the biomarker (β_B): $R = \beta_O/\beta_B$. The genetic marker could be a single SNP or a genetic risk score built on multiple SNPs. The standard error of such an estimate is usually constructed by using the delta method (16;18). The 95% confidence interval of the ratio

estimate can then be calculated and an interval with zero excluded indicates the causal nature of the effect.

Multivariate MR method—The two-stage regression method, the ratio method and the conventional two sample MR method all require that the genetic variants used are non-pleiotropic. However, finding such non-pleiotropic variants may not always be easy, e.g. it has been challenging to find genetic variants exclusively associated with triglycerides (TG) but not low density lipoprotein cholesterol (LDL-C) or high density lipoprotein cholesterol (HDL-C). To address such a problem, *Do et al.* (19) developed a multivariate MR method which is able to take into account the effect of pleiotropy of a genetic instrument for other traits when estimating the effects of genetically mediated changes in a biomarker of interest on the disease outcome (19). Moreover, *Burgess et al.* (20) also developed a multivariate MR tool based on Bayesian methods which gives the posterior distribution of the causal parameter. However, the application pipeline developed by *Burgess et al.* is implemented through a WinBug machine, the parameter-tuning of which is not straightforward. Egger Regression is another multivariate MR method which is also able to take into account pleiotropy of genetic instruments which is mediated through unmeasured or unknown traits (21).

Some examples of MR studies conducted to assess causality in CHD

Plasma LDL-C in CHD—Numerous prospective studies have shown that levels of LDL-C are log-linearly associated with the risk of CHD independent of other vascular risk factors (22). Also, randomized controlled trials have shown that treatment with cholesterol-lowering statins reduce the risk of CHD (23); hence proving that LDL-C is causally related to CHD. MR studies on CHD therefore use LDL-C as a positive example to illustrate the validity of this approach. For instance, *Voight et al.* (24) have shown that genetic variants that have been found exclusively associated with increased LDL-C levels have been shown to increase CHD risk, consistent with prior epidemiological studies. They further demonstrated that for a 1 standard deviation (SD) increase in LDL-C, the CHD odds ratio (OR) from observational epidemiology was 1.54 (95% CI 1.45–1.63) which was concordant with the OR of 2.13 (95% CI 1.69–2.69, P -value = 2×10^{-10}) conferred by a genetic score exclusively associated with a 1 SD increase in LDL-C levels; hence illustrating through a MR study design that plasma LDL-C is causally associated with CHD (24).

Plasma HDL-C in CHD—Levels of HDL-C are inversely associated with the risk of CHD, as demonstrated by prospective epidemiological studies (22). This association is statistically independent of other CVD risk factors, including LDL-C levels (22). Direct anti-atherogenic effects of HDL-C or its major protein apoA-I have been demonstrated in preclinical studies, including increased atherosclerosis in mice with genetic defects in HDL biosynthesis and regression of lesions in atherosclerotic animal models subsequent to administration of HDL-C or apoA-I (25–28). These observations have led to the attractiveness of HDL-C as a therapeutic target for the prevention and treatment of CVD. Despite such evidence from observational and animal based studies, various randomized controlled trials have led to the conclusion that pharmacological lowering of HDL-C does not translate into CHD risk reduction (4–6).

To help answer this paradox, *Voight et al* (24) investigated the association of a missense (Asn396Ser) variant in *LIPG* gene which was specifically associated with HDL-C levels (P -value = 8×10^{-13}) but not with lipid traits. They used this variant as a Mendelian Randomization instrument to assess the causal relevance of HDL-C in CHD. Under the assumption of a causal association between HDL-C and CHD risk, carriers of the *LIPG* 396Ser allele (2.6% frequency) that had higher HDL cholesterol levels (0.14 mmol/L higher compared to non-carriers) should have had a 13% CHD risk reduction (OR: 0.87). In contrast, using genetic data from 116,320 participants from 20 studies (20,913 CHD cases), *Voight et al.* (24) did not observe any association of this variant with CHD risk. *Voight et al* (24) further used a genetic risk score comprising of 14 SNPs that were specifically associated with HDL-C (P -values $< 5 \times 10^{-8}$) levels but not with LDL-C or TG (P -values > 0.01) and found that a 1-SD increase in HDL-C due to this genetic score was not associated with MI risk (OR 0.93, 95% CI: 0.68–1.26). These MR analyses used both a single variant and a genetic risk score and concluded that HDL-C is not causally relevant in CHD (24), which was consistent with the evidence obtained through clinical trials (4–6).

Triglycerides—Higher levels of plasma triglycerides (TG) have been shown to be associated with higher risk of CHD in various prospective epidemiological studies (24). It was however not known whether such an association was independent of other lipids. Because of the high degree of correlation observed between plasma TG and other lipids, epidemiological studies were limited as they could not adjust the effects of other lipids in analyses involving plasma TG and incident CHD risk.

Conventional MR methods were not able to dissect the effect of genetically mediated changes in plasma TG on CHD as variants associated with TG were also found associated with either HDL-C or LDL-C. To tease out the effects of genetically mediated changes in TG on CHD, *Do et al.* (19) developed a multivariate MR framework incorporating the effects of SNPs on CAD (β_{CAD}), TG (β_{TG}), HDL-C (β_{HDL-C}) and LDL-C (β_{LDL-C}) by using a multivariate linear regression model. In this multivariate MR framework, residuals were first calculated by regressing β_{CAD} on β_{HDL-C} and β_{LDL-C} , residuals were regressed on β_{TG} and the causal effect of TG on CHD was assessed. By using 185 SNPs moderately or strongly associated with TG, the multivariate MR framework showed that plasma TG is likely causally involved in CHD (19). These findings have prompted initiation of therapeutic programs focusing on lowering plasma TG to lower CHD risk.

Plasma Lipoprotein(a)—Various prospective epidemiological studies have shown that elevated plasma lipoprotein(a) (Lp[a]) are associated with increased CHD risk (29). Genetic studies found two variants, rs10455872 and rs3798220, associated with Lp(a) levels at GWAS levels of significance (30). These two variants explained 36% of variation in the Lp(a) levels. Alleles at these variants were further used as proxies for plasma Lp(a) in MR studies to assess causality. Alleles at these two variants that were associated with increased Lp(a) levels were subsequently found to increase CHD risk (30). A genotype score involving both *LPA* SNPs that increased Lp(a) levels was found to increase the risk of CHD (OR: 2.57 [95% CI, 1.80 to 3.67]). After adjustment for the Lp(a) level, the association between the

LPA genotype score and the risk of coronary disease was abolished (30). These findings have increased the likelihood that Lp(a) pathway is causally relevant in CHD.

Other biomarkers evaluated through MR studies—MR studies have been successfully implemented to assess the causal relevance of a number of other biomarkers. Using evidence from human genetic studies, MR studies have refuted the causal relevance of a number of biomarkers, including C-reactive protein (CRP) (31;32), fibrinogen (33;34), uric acid (35), LpPLA2 activity (36), and homocysteine (37). On the other hand, MR studies have provided evidence pointing towards the likelihood of a causal relevance of other pathways in CHD, including interleukin-6 receptor (38).

Conclusions

Mendelian randomization studies have emerged as a powerful tool to provide one piece of evidence on causal hypotheses for range of pathways and biomarkers for clinical disease outcomes. These analyses use genetic variants as *instruments* for soluble biomarkers in association studies of disease risk. Under specific assumptions, MR studies can provide unbiased estimates of causal effects and avoid distortions due to confounding factors arising later in life, because genetic variants are fixed at conception. Hence, carefully conducted MR studies should overcome the limitations that are inherent to other observational studies (*e.g.*, residual confounding and reverse causality) to help assess causal relevance of a range of pathways in CHD.

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Figure-1.
Schema of a Mendelian Randomization study

Table 1

Current evidence on the causal associations of biomarkers with CHD from MR studies

Biomarker	MR evidence supports a causal association with CHD?	Reference
LDL-C	Yes	(24)
HDL-C	No	(24)
TG	Yes	(19)
Lp(a)	Yes	(30)
CRP	No	(31;32)
Interleukin-6 receptor	Yes	(39)
Fibrinogen	No	(33;34)
Uric acid	No	(35)
Homocysteine	No	(37)
LpPLA2 activity	No	(36)