A Cautionary Note on Using Mendelian Randomization to Examine the Developmental Origins of Health and Disease (DOHaD) Hypothesis

Shannon D'Urso[1], Geng Wang[1], Liang-Dar Hwang[1], Gunn-Helen Moen[1,2,3,4], Nicole M Warrington[1,3], David M Evans*[1,5]

[1]The University of Queensland Diamantina Institute, The University of Queensland, Brisbane, Australia

[2]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo

[3]K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Norway

[4]Population Health Science, Bristol Medical School, University of Bristol, UK.

[5]Medical Research Council Integrative Epidemiology Unit at the University of Bristol, Bristol, UK

Corresponding author: David M Evans

Email: d.evans1@uq.edu.au

Telephone: +61 7 3443 7347

Address: University of Queensland Diamantina Institute

Level 7, 37 Kent St

Translational Research Institute

Woolloongabba, QLD 4102

Australia

Abstract

Recent studies have used Mendelian randomisation (MR) to investigate the observational association between low birthweight and increased risk of cardiometabolic diseases, and inform on the validity of the Developmental Origins of Health and Disease (DOHaD) hypothesis. We used simulations to assess the validity of these previous MR studies, and to determine whether a better formulated model can be used in this context. Genetic and phenotypic data were simulated under a model of no direct causal effect of offspring birthweight on cardiometabolic outcomes and no effect of maternal genotype on offspring cardiometabolic risk through intrauterine mechanisms, and the observational relationship is driven entirely by horizontal genetic pleiotropy in the offspring (i.e. no DOHaD mechanism). We investigated the performance of four commonly used MR analysis methods (weighted allele score MR, inverse variance weighted MR, weighted median MR and MR-Egger) and a new approach which tests the association between maternal genotypes related to offspring birthweight and offspring cardiometabolic risk (after conditioning on offspring genotype at the same loci). We caution against using traditional MR analyses, which do not take into account the relationship between maternal and offspring genotypes, to assess the validity of DOHaD as results are biased in favour of a causal relationship. In contrast, we recommend the aforementioned conditional analysis as a valid test of DOHaD.

Key Words

Mendelian randomisation, causal inference, cardiometabolic, conditional analysis

Introduction

There is a robust and well-documented relationship between birthweight (BW) and higher risk of cardiometabolic diseases like type 2 diabetes (T2D) and hypertension in later life [1–3]. The Developmental Origins of Health And Disease (DOHaD) hypothesis, which posits that adverse intrauterine environments result in fetal growth restriction and increased future risk of cardiometabolic disease through developmental compensations, may explain this observed relationship [1]. Evidence in favour of this theory has primarily come from experimental studies on animals [4], which may not generalize to humans, and observational epidemiological studies [5], which are susceptible to confounding, bias and reverse causality [6]. However, because randomized controlled trials (RCTs) cannot be performed easily in this context, definitive proof of the hypothesis in humans has been lacking. Regardless, DOHaD has become one of the most preeminent theories in life course epidemiology over the last thirty years.

Mendelian randomization (MR) is an epidemiological method that uses genetic variants robustly associated with a modifiable environmental exposure to estimate the causal relationship between the exposure and a medically relevant outcome of interest [7]. Mendel's Law of Segregation ensures that genetic variants segregate randomly and independently of environmental factors, whilst Mendel's Law of Independent Assortment suggests that the genetic variants should also segregate independently of other traits provided certain conditions are met [7]. This means that genetic variants are less susceptible to reverse causality and confounding than the "traditional" variables used in observational studies. In other words, genetic variants can be used to classify a study sample into subgroups, which differ systematically with respect to the exposure of interest, but not with respect to confounding factors (i.e. similar to a randomized controlled trial). If groups defined by their genotypes also show differences in the outcome of interest, then, provided core assumptions are met, this provides evidence of a causal relationship.

Recently, several studies have attempted to use the technique of Mendelian randomization (MR) to investigate the relationship between BW and cardiometabolic disease and in some cases explicitly inform on the validity of DOHaD [8–10]. For example, Zanetti et al. used two sample MR to examine the relationship between BW and a variety of cardiometabolic outcomes in the UK Biobank. The authors found evidence for an inverse correlation between BW associated single nucleotide polymorphisms (SNPs) and low-density lipoprotein cholesterol, 2-hour glucose, coronary artery disease, and T2D and a positive correlation between BW associated SNPs and body mass index. The authors interpreted their findings as providing evidence that lower BW was causally related with increased susceptibility to coronary artery disease and T2D.

Whilst MR has a number of potential advantages over traditional observational epidemiological studies, we believe that previous studies that have used MR in an attempt to investigate the DOHaD hypothesis [8–10] contain several flaws that render them unsuitable for valid inference in this context. First, previous MR studies have used genetic variants in the fetal genome that are associated with their own BW as instrumental variables. We believe this framework is problematic because the DOHaD hypothesis postulates that an adverse intrauterine environment leads to intrauterine growth restriction, which in turn results in low BW and increased risk of future cardiometabolic disease [11]. This is different from postulating that BW itself has a direct causal effect on cardiometabolic disease (Fig. 1). We would therefore argue that the underlying model used in previous MR studies is inappropriate because SNPs in the fetal genome are likely to be associated with BW through many different processes, and therefore do not necessarily proxy the intrauterine environment.

Second, due to the transmission of alleles from mother to offspring, offspring and maternal genotypes are correlated ($r \approx 0.5$). Consequently, any association between offspring genotype and offspring outcomes, when no adjustment has been made for maternal genotype, could actually reflect an effect of maternal genotype on offspring outcome, complicating interpretation of the analysis [12]. Finally, many of the genetic variants robustly associated with BW are known to exert pleiotropic effects on

cardiometabolic phenotypes [12,13]. This means that the SNPs used in the analyses may violate the no horizontal pleiotropy assumption underlying MR [14]. Additionally, variants most strongly related to BW are also likely to have the strongest pleiotropic associations with cardiometabolic phenotypes, meaning that the INSIDE assumption [15] may also be violated in these instances, and so MR Egger regression will also yield biased estimates of the causal effect.

Our aim was to use simulation and two contrived examples to show that MR using BW associated SNPs in the offspring genome to examine the DOHaD hypothesis can provide spurious evidence of a causal effect of BW on future cardiometabolic risk, when no such relationship exists (Fig. 1). We also examined if testing whether maternal genetic variants associated with decreased offspring BW were also associated with *increased* offspring cardiometabolic risk (after conditioning on offspring genotypes at the same loci) was a valid method for testing the validity of DOHaD [16].

Methods

Simulations

We simulated data where the correlation between offspring BW and future cardiometabolic traits was generated by a combination of genetic pleiotropy (i.e. the genetic variants in the offspring had direct effects on offspring outcome not through BW) and maternal and offspring genetic effects on BW; we did not include a direct causal path between maternal genotypes and offspring outcomes or a direct causal effect of BW on cardiometabolic risk (Fig. 2). We simulate two models, both which represent plausible explanations for the empirical negative genetic correlation between BW and cardiometabolic phenotypes and have support from large scale genetic studies [13,16–18].

Scenario 1 represents a possible model for blood pressure related SNPs; we have previously shown evidence that SNPs that increase maternal systolic blood pressure causally lower offspring BW through intrauterine mechanisms, and those alleles are then transmitted from mother to offspring increasing offspring blood pressure in later life offspring [13,17].

Scenario 2 is similar to the model espoused under the Fetal Insulin Hypothesis in which T2D associated variants in mothers lead to increased maternal glucose levels during pregnancy (promoting increased fetal growth), but may also decrease insulin sensitivity (and fetal growth) when transmitted to offspring, and subsequently increase risk of offspring T2D in later life [19].

Following Fig. 2, we simulated maternal and offspring genotypes, the offspring's BW (*X*) and cardiometabolic outcomes (Y), for each family *i*, using the following equations:

$$X_i = \sum_{j=1}^{n} \beta_{m_j} G_{m_{ij}} + \sum_{j=1}^{n} \beta_{O_j} G_{O_{ij}} + \varepsilon_{1i} \quad [1]$$

$$Y_i = \sum_{j=1}^{n} \gamma_j G_{O_{ij}} + \varepsilon_{2i} \quad [2]$$

where $G_{O_{ij}}$ and $G_{m_{ij}}$ refer to the offspring and maternal genotype dosage (0, 1 ,2) respectively for family *i* at locus *j*. The offspring and maternal effects of SNP_j on BW are quantified by β_{O_j} and, β_{m_j} respectively, γ_j reflects the pleiotropic effect of the offspring SNP_j on the cardiometabolic outcome *Y*, and ε_1 and ε_2 are residual terms affecting the exposure and outcome respectively (with covariance ρ). Consistent with the absence of DOHaD mechanisms, we assume that there are no effects of maternal genotypes on the offspring outcome *Y* (either directly or mediated by offspring BW), and no causal effect of offspring BW on offspring outcome *Y*. Allele frequencies were drawn from a uniform distribution between 0.1 and 0.9, and for each replicate we sampled maternal (G_m) and paternal dosages at each locus (0, 1 or 2) assuming Hardy-Weinberg Equilibrium. We simulated transmission of genotypes to offspring assuming autosomal Mendelian inheritance.

For each scenario, we performed 10,000 replicates using 50,000 mother-offspring pairs, 20 SNPs, and a moderate covariance between the residuals (ρ = -0.3). In *Scenario 1*, all β_{O_j} were set to zero (i.e. no effect of offspring SNPs on offspring BW), whilst negative β_{M_j} were drawn from a uniform distribution (between -0.05 and -0.01). The pleiotropic effect γ_j was induced to have a negative correlation with β_{M_j} by multiplying β_{M_j} by -1.1 and adding independently drawn error terms (drawn from a uniform

distribution between -0.03 and 0.03). In *Scenario 2*, values for β_{O_j} were drawn from a uniform distribution (between -0.05 and -0.01). Values for β_{M_j} were drawn from a uniform distribution between 0.01 and 0.05, while values for γ_j were calculated by multiplying β_{M_j} by 1.1 and adding error terms (drawn from a uniform distribution between -0.03 and 0.03). These procedures induced positive or negative effects of the genotypes on the exposures and outcomes according to Fig. 2.

Mendelian Randomisation and Conditional Analyses

We investigated the performance of several types of MR analysis on the simulated data including MR using an allele score of offspring BW associated SNPs weighted by the (offspring) effect size on BW (WAS-MR) [20], inverse variance weighted MR (IVW-MR) [21], weighted median MR (WM-MR) [22], and MR-Egger regression [15]. These methods all use BW associated SNPs in the offspring to perform MR analysis, similar to what has been done by previous authors investigating DOHaD [8–10]. We compare these methods to the procedure which we recommend which involves regressing offspring cardiometabolic outcome on an allelic score of maternal SNPs that are associated with offspring BW, whilst conditioning on offspring genotypes at the same loci [16]. We note that whilst our procedure uses MR principles to increase its robustness to confounding and reverse causality, it does not yield estimates of a causal effect. This is because we do not believe that BW causally influences future cardiometabolic phenotypes, but rather is only an imperfect marker of intrauterine growth restriction, and so estimating causal effect sizes in this context is inappropriate.

First, we regressed the simulated offspring cardiometabolic outcome on an unweighted maternal genetic score (i.e. a simple count of the number of BW increasing alleles in each individual) whilst conditioning on an unweighted offspring genetic score of the same SNPs. Second we regressed offspring outcome on a weighted maternal genetic score of BW associated SNPs, controlling for each of the 20 SNPs (as separate terms) in the offspring.

The R code used for performing the simulations used the TwoSampleMR package for many of the analyses [23] and is available on request from the authors.

Results

The average causal effect estimates and type 1 error rate ($\alpha = 0.05$) over 10,000 replicates are presented in Table 1.

Discussion

All "standard" MR methods which didn't take into account the relationship between maternal and offspring genotypes produced inflated type 1 error rates ($\alpha = 0.05$ under the null) and biased spurious estimates of the causal effect of BW on the outcome under Scenario 1 and Scenario 2 (Table 1). Therefore investigators naively using these methods would likely come to the incorrect conclusion that BW has a causal effect on risk of cardiometabolic disease. In contrast, conditional association analyses using either an unweighted or weighted maternal allelic score corrected for offspring genotypes yielded no evidence of association with the outcomes and produced correct type 1 error rates (Table 1; Mean $\hat{\beta} = 0$; type 1 error rate = 0.05 all scenarios).

The results of our simulations clearly show that traditional MR analyses, even those that are more robust to violations of core instrumental variable assumptions like MR-Egger regression [15] and weighted median approaches [22], that do not take into account the relationship between maternal and offspring genotypes, can produce spurious evidence in favour of a causal relationship between BW and cardiometabolic disease in later life, when in fact no such relationship exists. We therefore recommend a strategy of testing for association between maternal genotypes related to BW (or indeed maternal SNPs related to any adverse environmental factor that is likely to result in intrauterine growth restriction) and offspring cardiometabolic phenotypes conditional on offspring genotypes at the same loci [16]. We have demonstrated that when these scores are conditioned on offspring genotype, the

results maintain correct type 1 error in the absence of maternal genetic effects on the offspring cardiometabolic phenotype. Ideally, evidence for association should also be examined using conditional analysis of father offspring pairs as a negative control. If a similar, non-zero association is also observed using paternal SNPs (conditional on offspring genotype at the same loci), then this strongly implies that the association between parental genotype and offspring phenotype may be mediated through the post-natal environment, rather than the intrauterine environment.

In our analyses, we have used a simple multivariable regression analysis to test our hypotheses. This is because using instrumental variables analysis to estimate the causal effect of intrauterine growth restriction would not be appropriate in this situation, since we have not directly measured the exposure of interest, merely BW- an imperfect proxy of intrauterine growth restriction [24]. That being said, it may still be possible to estimate the causal effect of intrauterine growth restriction on later life phenotypes using e.g. latent variable methods (making certain assumptions). Indeed, creating statistical genetics models to do this is a current focus of our research group.

Finally, we note that our procedure requires estimates of the association between maternal SNPs, conditional on offspring genotypes at the same loci, and offspring phenotype. Whilst conditional estimates can be obtained using genotyped mother-offspring pairs, there is a paucity of cohorts around the world with such information available, particularly where the offspring are old enough to have developed cardiometabolic conditions implicated by DOHaD. Therefore, such conditional analyses may be under powered [25,26]. This shortfall in numbers may be partially addressed by calculating conditional estimates of maternal and offspring genetic effects using separate GWAS of unrelated mothers and offspring via e.g. structural equation modelling [12,16] or similar statistical procedures [27,28]. However, the power to accurately estimate conditional effect estimates is far less compared to if mothers and children from the same families are used [26]. We are currently developing methods that impute "virtual" parental genotypes from genetic studies of relative pairs that can be used to derive conditional maternal genetic effect estimates and further increase power of these sorts of analyses [25]. We are

hopeful that new statistical methods such as these, large-scale genetic studies with information on families [29,30], and collaborations such as the within families genetics consortium [31], can be combined productively to enable appropriate testing of hypotheses such as DOHaD using MR in the near future.

Figures

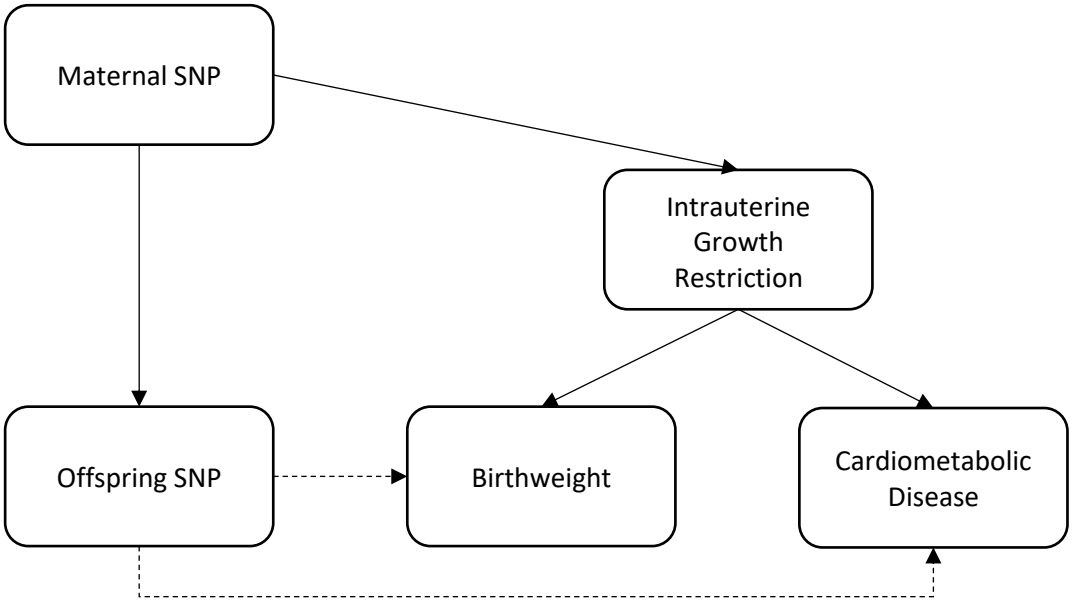

Fig. 1. Diagrammatic representation of how MR can be used to investigate the Developmental Origins of Health and Disease (DOHaD) Hypothesis. Maternal genotype at a given single nucleotide polymorphism (SNP) loci can be used to proxy environmental exposures that lead to intrauterine growth restriction. By conditioning on offspring genotypes at the same locus, the two potential paths (dotted lines) are blocked. According to the DOHaD hypothesis, intrauterine growth restriction subsequently results in decreased birthweight and increased risk of cardiometabolic disease in later life. Notably there is no causal effect of birthweight on the risk of cardiometabolic disease outcomes.

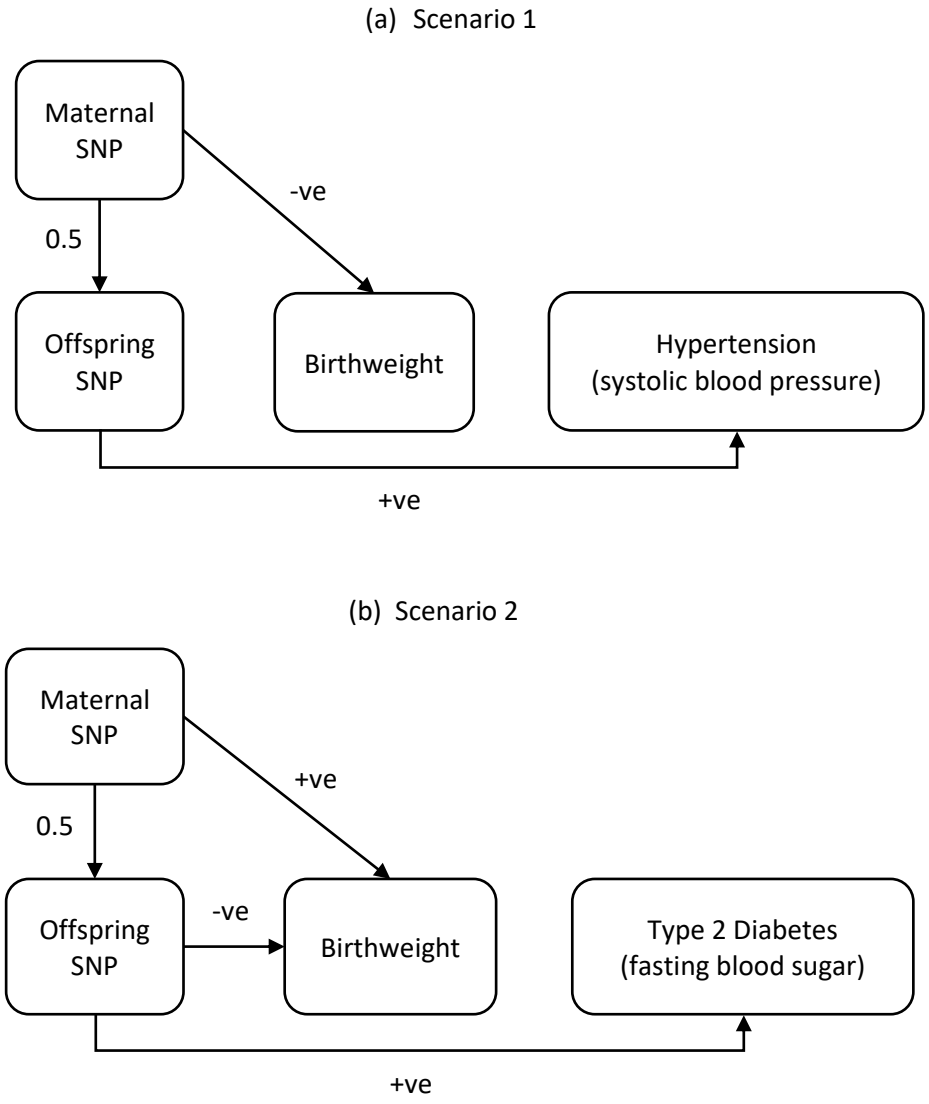

Fig. 2. Diagrams illustrating the two models underlying the relationship between birthweight and cardiometabolic phenotypes that were simulated in this manuscript. In Scenario 1, maternal single nucleotide polymorphisms (SNPs) negatively (-ve) affect offspring BW via intrauterine mechanisms. When alleles at these loci are transmitted from mothers to their children, they also exert positive (+ve) pleiotropic effects on hypertension as evaluated by systolic blood pressure in later life. In Scenario 2 the SNPs used as instrumental variables are associated with increased offspring BW when present in the mother and also exert direct effects on lowering offspring BW through the fetal genome. These genotypes are associated with later life Type 2 Diabetes (measured by fasting blood sugar levels). In both scenarios, the correlation between birthweight and cardiometabolic phenotypes is due solely to genetic pleiotropy (i.e. not Developmental Origins of Health and Disease mechanisms).

Tables

Table 1. Results of simulation study. The average effect estimate (causal estimate in the case of the four Mendelian Randomisation (MR) methods, and regression coefficient in the case of the two conditional analyses), 95% confidence intervals (CI), and type 1 error rates (α = 0.05). The four MR methods used were: weighted allele score MR (WAS-MR), inverse variance weighted MR (IVW-MR), weighted median MR (WM-MR), and MR-Egger regression. The conditional analyses estimated the effect of the maternal genetic scores (conditioned on offspring genotype) on cardiometabolic outcomes.

Scenario 1	**Mean Effect Estimate (95% CI)**	**Type 1 error rate (α = 0.05)**
WAS-MR	-1.90 (-2.08, -1.72)	1
IVW-MR	-1.90(-2.47, -1.34)	1
WM-MR	-1.13 (-1.68, -0.59)	0.95
MR-Egger	-1.39 (-2.56, -0.22)	0.59
Unweighted Conditional Analysis	0.00 (-0.00, 0.00)*	0.05
Weighted Conditional Analysis	0.00 (-0.11, 0.11)*	0.05
Scenario 2	**Mean Effect Estimate (95% CI)**	**Type 1 error rate (α = 0.05)**
WAS-MR	-1.01 (-1.17, -0.86)	1
IVW-MR	-1.02 (-1.75, -0.28)	0.80
WM-MR	-0.54 (-0.89, -0.20)	0.75
MR-Egger	-0.69 (-2.00, 0.61)	0.14
Unweighted Conditional Analysis	0.00 (-0.00, 0.00)*	0.05
Weighted Conditional Analysis	0.00 (-0.11, 0.11)*	0.05

*The confidence intervals are larger for weighted than unweighted analyses because the weighted analyses involve multiplying each increaser allele by a small beta coefficient i.e. the apparently increased interval sizes are an artefact of scale

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Conflicts of Interest

None.

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