**Assumed framework of data and genetic Associations**

Suppose that we have selected J independent genetic variants () to act as instruments in a two-sample Mendelian randomization study. Here, we have successfully extracted the summary results about the associations of each genetic variant () with the risk factor (or with each risk factor for the multivariable setting) and with the outcome including the beta coefficients (,) and their standard errors (, and). We assume throughout that the parametric assumptions of linearity with no effect heterogeneity hold for the causal exposure-outcome relationship, and for the instrumental variable-exposure and instrumental variable-outcome associations for all instruments.

Initially, we consider the causal effect of a risk factor X on an outcome Y using genetic variants () that are assumed to be uncorrelated (not in linkage disequilibrium) [1]. The association between genetic variant () and the outcome is denoted, and the association between genetic variant  and the risk factor is denoted[1]. The genetic association with the outcome can be decomposed into the sum of a direct (pleiotropic) effect and an indirect (causal) effect:



where is the effect of the genetic variant on the outcome that is not mediated via the risk factor of interest, and  is the causal effect of the risk factor on the outcome. A genetic variant is referred to as pleiotropic if it has associations with more than one risk factor on different causal pathways. Any such effect is included in, a genetic variant is pleiotropic if . A pleiotropic genetic variant violates the IV3 assumption, and is not a valid instrumental variable [1].

For a given genetic variant that meets the instrumental variable assumptions (), the causal effect of the risk factor on the outcome can be consistently estimated as a simple ratio of association estimates:

, their approximate variances 

**Inverse-variance weighted method**

When there are multiple genetic variants, the inverse-variance weighted (IVW) estimate is the weighted average of these causal estimates, using the inverse of their approximate variances as weights:



This estimate can be estimated using a weighted linear regression of the genetic associations with the outcome () on the genetic associations with the risk factor () using inverse variance weights () when the intercept is zero:

, weights=

Where is the residual term. If the residual standard error is set to one, this above weighted regression model, is equivalent to performing a fixed-effect meta-analysis [1]. If the pleiotropic effects of the genetic variants are all zero ( (), in other words, if all genetic variants are valid instrumental variables), then each of the  will be a consistent estimate of the causal effect, and the overall estimate  (a weighted mean of the ) will be a consistent estimate of the causal effect [1].

**Reference**

1. Burgess S, Thompson SG: **Interpreting findings from Mendelian randomization using the MR-Egger method**. *Eur J Epidemiol* 2017, **32**(5):377-389.