Supplementary materials: Orienting the causal relationship between imprecisely measured traits using GWAS summary data

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Supplementary text 1

We assume the following model

$$\begin{aligned} x &= \alpha_g + \beta_g g + \epsilon_g \\ x_o &= \alpha_{mx} + \beta_{mx} x + \epsilon_{mx} \\ y &= \alpha_x + \beta_x x + \epsilon_x \\ y_o &= \alpha_{my} + \beta_{my} y + \epsilon_{my} \end{aligned}$$

where x is the exposure on the outcome y, g is an instrument that has a direct effect on x, x_o is the measured quantity of x, where measurement error is incurred from linear transformation in α_{mx} and β_{mx} and imprecision from ϵ_{mx}, and y_o is the measured quantity of y, where measurement error is incurred from linear transformation in α_{my} and β_{my} and imprecision from ϵ_{my}. Our objective is to estimate the expected magnitude of association between g and y after conditioning on x. Under the CIT, this is expected to be $cov(g, y_o - \hat{y}_o) = 0$ when x causes y, where $\hat{y}_o = \hat{a}_{x_o} + \hat{\beta}_{x_o} x_o$ is the predicted value of y_o using the measured value of x_o.

We can split $cov(g, y_o - \hat{y}_o)$ into two parts, $cov(g, y_o)$ and $cov(g, \hat{y}_o)$.

Part 1

$$\begin{aligned} cov(g, y_o) &= cov(g, \beta_{my} y) \\ &= cov(g, \beta_{my} \beta_x x) \\ &= cov(g, \beta_{my} \beta_x \beta_g g) \\ &= \beta_{my} \beta_x \beta_g var(g) \end{aligned}$$

Part 2

$$\begin{aligned} cov(g, \hat{y}_o) &= cov(g, \hat{\beta}_{x_o} x_o) \\ &= cov(g, \hat{\beta}_{x_o} \beta_{mx} x) \\ &= cov(g, \hat{\beta}_{x_o} \beta_{mx} \beta_g g) \\ &= \hat{\beta}_{x_o} \beta_{mx} \beta_g var(g) \end{aligned}$$

Simpifying further

$$
\begin{aligned}
\hat{\beta}_{x_o} &= \frac{cov(y_o, x_o)}{var(x_o)} \\
&= \frac{cov(\beta_{my} y, \beta_{mx} x)}{\beta_{mx}^2 var(x) + var(\epsilon_{mx})} \\
&= \frac{\beta_{mx}\beta_{my} cov(y, x)}{\beta_{mx}^2 var(x) + var(\epsilon_{mx})} \\
&= \frac{\beta_{mx}\beta_{my}\beta_x var(x)}{\beta_{mx}^2 var(x) + var(\epsilon_{mx})}
\end{aligned}
$$

which can be substituted back to give

$$
\begin{aligned}
cov(g, \hat{y}_o) &= \frac{\beta_{my}\beta_x\beta_g var(g) \beta_{mx}^2 var(x)}{\beta_{mx}^2 var(x) + var(\epsilon_{mx})} \\
&= \frac{\beta_{mx}^2 var(x)}{\beta_{mx}^2 var(x) + var(\epsilon_{mx})} \times \beta_{my}\beta_x\beta_g var(g)
\end{aligned}
$$

Finally

$$
cov(g, y_o - \hat{y}_o) = \beta_{my}\beta_x\beta_g var(g) - \frac{\beta_{mx}^2 var(x)}{\beta_{mx}^2 var(x) + var(\epsilon_m)} \times \beta_{my}\beta_x\beta_g var(g)
$$

thus $cov(g, y_o - \hat{y}_o) = 0$ if the measurement imprecision in x_o is $var(\epsilon_m) = 0$. However if there is any imprecision then the condition $cov(g, y_o - \hat{y}_o) = 0$ will not hold.

Supplementary text 2

Assuming that either $x \rightarrow y$ or $y \rightarrow x$, the causal direction can be inferred by evaluating which of $\rho_{g,x}$ and $\rho_{g,y}$ is larger in magnitude. The Steiger test is a hypothesis test that provides a p-value for observing the difference in these correlations under the null hypothesis that they are equal.

Assuming the causal direction is $x \rightarrow y$, two stage MR is formulated using the following regression models:

$$x = \alpha_1 + \beta_1 g + e_1$$

for the first stage and

$$y = \alpha_2 + \beta_2 \hat{x} + e_2$$

where $\hat{x} = \hat{\alpha}_1 + \hat{\beta}_1 g$. Writing in scale free terms, $\rho_{g,x}$ denotes the correlation between g and the exposure variable x, and it is expected that $\rho_{g,x} > \rho_{g,y}$ because $\rho_{g,y} = \rho_{g,x}\rho_{x,y}$, where $\rho_{x,y}$ is the causal association between x and y (which is likely to be less than 1).

In the presence of measurement error in x and y, however, the empirical inference of the causal direction will instead be based on evaluating $\rho_{g,x_o} > \rho_{g,y_o}$, which can be simplified:

$$\begin{aligned}
\rho_{g,x_O} &> \rho_{g,y_O} \\
\rho_{g,x}\rho_{x,x_O} &> \rho_{g,y}\rho_{y,y_O} \\
\rho_{g,x}\rho_{x,x_O} &> \rho_{g,x}\rho_{x,y}\rho_{y,y_O} \\
\rho_{x,x_O} &> \rho_{x,y}\rho_{y,y_O}
\end{aligned}$$

In order to assess how reliable the inference of the causal direction is in the presence of measurement imprecision, we can evaluate the range of potential values of measurement error in x and y over which the empirical difference in ρ_{g,x_o} and ρ_{g,y_o} would return the wrong causal direction.

For different values of ρ_{x,x_o}, $\rho_{g,x} = \frac{\rho_{g,x_o}}{\rho_{x,x_o}}$ and $\rho_{g,x_o} \leq \rho_{x,x_o} \leq 1$. For different values of ρ_{y,y_o}, $\rho_{g,y} = \frac{\rho_{g,y_o}}{\rho_{y,y_o}}$ and $\rho_{g,y_o} \leq \rho_{y,x_o} \leq 1$.

Call $z = \rho_{g,y} - \rho_{g,x}$ the true difference in the variance explained by the genetic variant in y and x. If $z < 0$ then we infer that $x \rightarrow y$. There will be some values of ρ_{x,x_o} and ρ_{y,y_o} that do not alter whether $z < 0$. To evaluate the reliability, R, of the inference of the causal direction with regards to measurement error, the objective is to compare the proportion of the parameter space that agrees with the inferred direction against the proportion which does not:

$$R = \frac{V_{z \geq 0}}{-V_{z<0}}$$

If $R = 1$ then the direction of causality is equally probable across the range of possible measurement error values. If $R > 1$ then R times as much of the parameter space favours the inferred direction of causality. V_z, the total volume of the function (Figure 4), can be obtained analytically by solving:

$$\begin{aligned}
V_z &= \int_{\rho_{g,x_o}}^{1} \int_{\rho_{g,y_o}}^{1} \frac{\rho_{g,y_o}}{\rho_{y,y_o}} - \frac{\rho_{g,x_o}}{\rho_{x,x_o}} \; d\rho_{y,y_o} d\rho_{x,x_o} \\
&= \rho_{g,x_o} log(\rho_{g,x_o}) - \rho_{g,y_o} log(\rho_{g,y_o}) + \rho_{g,x_o}\rho_{g,y_o}(log(\rho_{g,y_o}) - log(\rho_{g,x_o}))
\end{aligned}$$

$V_{z \geq 0}$, the proportion of the volume that lies above the $z = 0$ plane, can also be obtained analytically. The region of this volume is bound by the values of ρ_{x,x_o} and ρ_{y,y_o} where $0 = \rho_{g,y} - \rho_{g,x}$, which can be expanded to $\rho_{y,y_o} = \rho_{g,y_o}\rho_{x,x_o}/\rho_{g,x_o}$. Hence,

$$
\begin{aligned}
V_{z\geq 0} &= \int_{\rho_{g,x_o}}^{1} \int_{\rho_{g,y_o}}^{\frac{\rho_{g,y_o}\rho_{x,x_o}}{\rho_{g,x_o}}} \frac{\rho_{g,y_o}}{\rho_{y,y_o}} - \frac{\rho_{g,x_o}}{\rho_{x,x_o}} \; d\rho_{y,y_o} d\rho_{x,x_o} \\
&= 2\rho_{g,x_o}\rho_{g,y_o} - 2\rho_{g,y_o} - \rho_{g,y_o} log(\rho_{g,x_o}) - \rho_{g,x_o}\rho_{g,y_o} log(\rho_{g,x_o})
\end{aligned}
$$

Thus $V_{z<0} = V_z - V_{z\geq 0}$.

Supplementary text 3

We have assumed no unmeasured confounding in these simulations. Unmeasured confounding will however have potentially large influences on mediation-based methods for inferring causal directions, and can also adversely influence the estimate of the causal direction for the Steiger test.

Unmeasured confounding in mediation

Including an unmeasured confounder, u, after ignoring intercept terms the exposure x and outcome y variables can be modelled as

$$\begin{aligned} y &= \beta_x x + \beta_{uy} u + \epsilon_x \\ x &= \beta_g g + \beta_{ux} u + \epsilon_g \end{aligned}$$

The observational estimate of the causal effect of x on y, $\hat{\beta}_x$ is obtained from

$$\begin{aligned} \hat{\beta}_x &= cov(x, y)/var(x) \\ &= \frac{\beta_g^2 \beta_x var(g) + \beta_{ux}^2 \beta_x var(u) + \beta_x var(\epsilon_g)}{\beta_g^2 var(g) + \beta_{ux}^2 var(u) + var(\epsilon_g)} \end{aligned}$$

From this it is clear that β_x and $\hat{\beta}_x$ will differ when both β_{uy} and β_{ux} are non-zero. Relating to mediation, where we attempt to test if g associates with y after adjusting y for x, such that

$$\hat{y}^* = \hat{\beta}_x x$$

and

$$\begin{aligned} cov(g, y - \hat{y}^*) &= cov(g, \beta_x x + \beta_{uy} u + \epsilon_x - \hat{\beta}_x x) \\ &= cov(g, (\beta_x - \hat{\beta}_x)(\beta_g g + \beta_u x u + \epsilon_x)) \\ &= (\beta_x - \hat{\beta}_x) var(g) \end{aligned}$$

should any amount of unmeasured confounding exist, therefore, there will remain an association between g and $y|x$, which will introduce errors in inferring causal directions.

Unmeasured confounding in the MR Steiger test

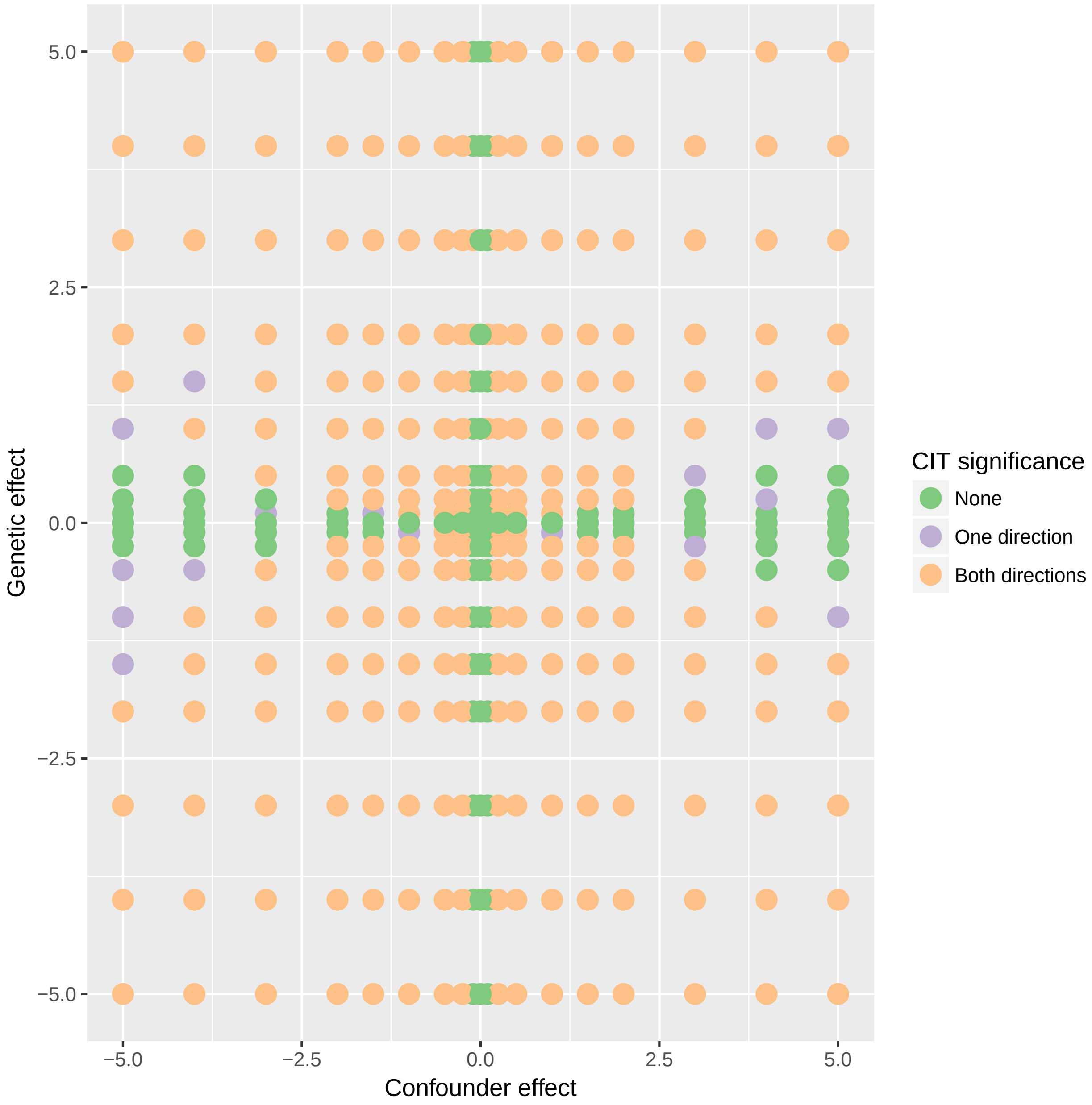
Similarly, we can investigate the extent to which unmeasured confounding will lead to the wrong causal direction between x and y using the MR Steiger test, evaluating the liability for the inequality $cor(g, x)^2 > cor(g, y)^2$ being incorrect. After some algebra

$$cor(g, x)^2 = \frac{\beta_g^2}{\beta_g^2 var(g) + \beta_{ux}^2 var(u) + var(\epsilon_x)}$$

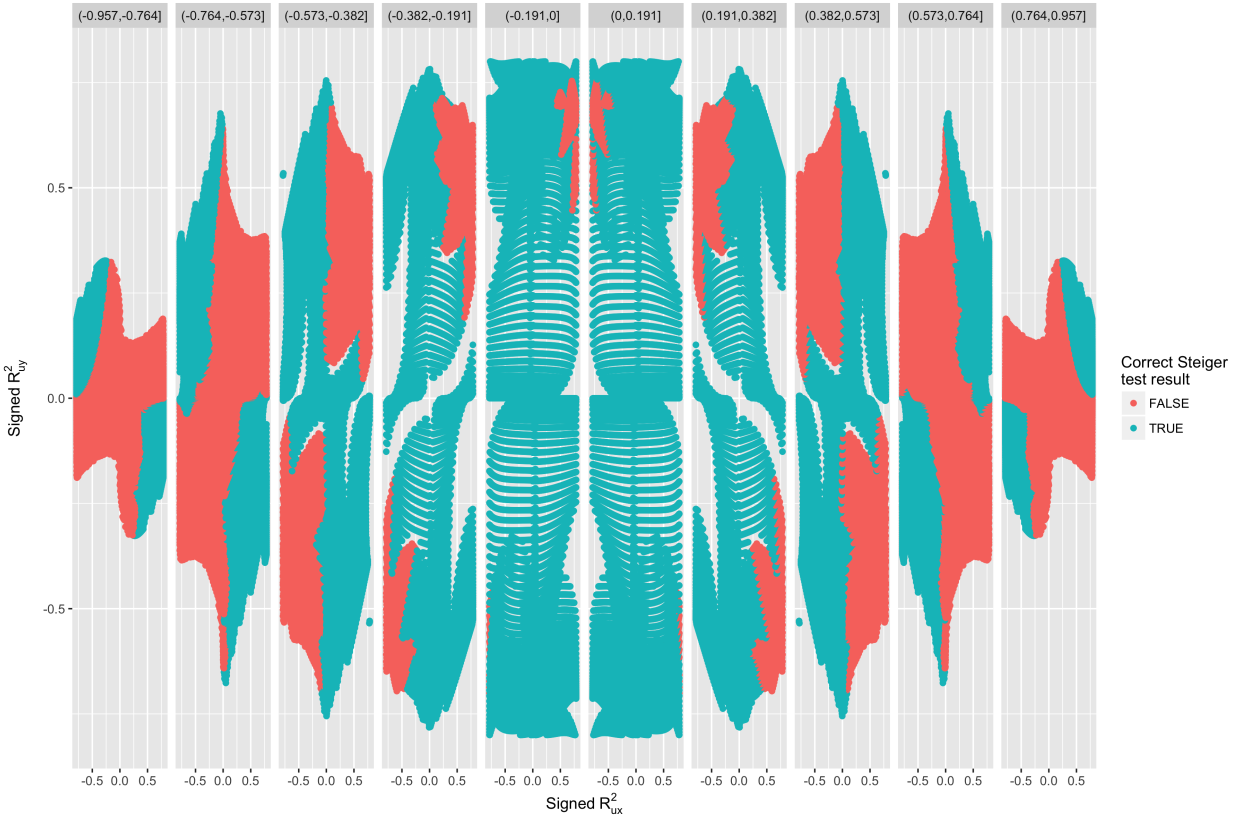
and

$$cor(g, y)^2 = \frac{\beta_x^2 \beta_g^2 var(g)^2}{\hat{\beta}_x^2 \beta_g^2 var(g) + \hat{\beta}_x^2 \beta_{ux}^2 var(u) + \beta_{uy}^2 var(u) + var(\epsilon_y)}$$

Supplementary figure 2 shows the relationship between the magnitude of the correlations between x, y and the confounder u for a range of $\beta_{xy} = (-2, 2)$, $\beta_{gx} = 0.1$ and a range of confounder effects. The pattern of results were similar for different values of β_{gx}. We note that in most cases for the parameter values explored, where the observational absolute $\hat{R}^2_{xy}$ is less than 0.2, unmeasured confounding will not incur the wrong causal direction in the MR Steiger test.



Supplementary figure 1: Illustrative simulations ($n = 5000$) showing the results from CIT analysis under a model of confounding. Here, the phenotypes x and y are not causally related, but there is a genetic effect and a confounder both influencing each phenotype. Each point represents a single simulation. Where power is high (when the absolute values of the x and y axes are large) the CIT returns a significant result ($p < 0.01$) when testing the causal effect of x on y, and when testing the causal effect of y on x.



Supplementary figure 2: Graph representing the unmeasured confounding parameters that will lead to the MR Steiger test returning the wrong causal direction. Columns of boxes represent different signed values of the observational variance explained between x and y (R^2_{xy}).