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

## S3 Text. The influence of unmeasured confounding on the inference of causal directions

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

$$y = \beta_x x + \beta_{uy} u + \epsilon_x$$
$$x = \beta_a g + \beta_{ux} u + \epsilon_a$$

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

$$\beta_x = cov(x, y)/var(x)$$
  
= 
$$\frac{\beta_g^2 \beta_x var(g) + \beta_{ux}^2 \beta_x var(u) + \beta_x var(\epsilon_g)}{\beta_g^2 var(g) + \beta_{ux}^2 var(u) + var(\epsilon_g)}$$

From this it is clear that  $\beta_x$  and  $\hat{\beta}_x$  will differ when both  $\beta_{uy}$  and  $\beta_{ux}$  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

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

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

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

S2 fig 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  $\beta_{gx}$ . We note that in most cases for the parameter values explored, where the observational absolute  $\hat{R}_{xy}^2$  is less than 0.2, unmeasured confounding will not incur the wrong causal direction in the MR Steiger test.