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Methods for enabling and improving the power of Mendelian randomization studies of parental environmental exposures and offspring outcomes

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ABSTRACT:

There is growing interest in using Mendelian randomization (MR) to investigate the causal effect of parental influences on their offspring. However, a major obstacle is the paucity of large-scale cohorts around the world that have genotype information on mother-offspring pairs or parent-offspring trios. Another difficulty is that MR studies in this context often rely on simple regression models that may not be optimal in terms of statistical power. In this talk we summarize our efforts to devise techniques to facilitate MR analyses of summary results data in this context, and methods to improve the power of MR analyses when complete data on mother-offspring pairs/parent-offspring trios is available. We illustrate how genomic SEM can be used to combine estimates of maternal, paternal and offspring genetic effects that are derived from different data sources where the extent of relatedness and sample overlap is unknown, and subsequently use these in MR analyses. We also show how the genetic linear mixed model can be extended to include genetic relationship matrices indexing offspring, maternal, paternal similarity as well as the covariance between them in order to model error variance and provide more precise estimates of genetic effects for subsequent MR analyses. Finally, we illustrate these methods by using them to estimate the causal effect of parental phenotypes on first and second born offspring birthweight using summary results data from 39,432 mothers, 34,095 fathers and 10,066 offspring from the Norwegian HUNT cohort as well as 5,725 complete parent-offspring trios.

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