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Abstract

Cultural effects can influence the results of causal genetic analyses, such as Mendelian randomisation, but the potential influences of culture on genotype-phenotype associations are not currently well understood. Different genetic variants could be associated with different phenotypes in different populations, or culture could confound or influence the direction of the association between genotypes and phenotypes in different populations.

Title: Culture and causal inference: The impact of cultural differences on the generalisability of findings from Mendelian randomisation studies

Uchiyama and colleagues present a comprehensive overview of how cultural evolution can influence heritability estimates. We expand on this and discuss how cultural differences can influence causal analyses, such as Mendelian randomisation (MR). MR uses genetic variants associated with an exposure as proxies for that exposure when testing exposure-outcome associations (Smith & Ebrahim, 2003). Human genotypes are fixed at conception and, according to Mendel's laws, should be randomly and independently assorted within families. Therefore, in principle and under certain assumptions, MR allows researchers to draw causal conclusions by overcoming some limitations associated with observational epidemiology – in particular confounding, including reverse causation (Smith & Ebrahim, 2002). However, if the potential effects of culture on MR results are not adequately considered, MR assumptions and the generalisability of findings could be undermined.

MR studies of the relationship between educational attainment and BMI (as a marker of obesity) across high- and low-income countries illustrate this. MR studies using samples from high-income countries have found evidence for a causal effect of lower educational attainment and higher BMI (Sanderson, Davey Smith, Windmeijer, & Bowden, 2019).

However, there is observational evidence for the opposite association in low-income countries (Cohen, Rai, Rehkopf, & Abrams, 2013). No MR studies have been conducted in this setting, but it is warranted given the possibility that different causal pathways may operate. Cross-cultural variability could mean that different genetic variants are associated with different phenotypes in different populations, and/or that the causal pathways between genotypes and phenotypes operate through different mechanisms.

Are different genetic variants associated with different phenotypes in different populations?

MR assumes that the genetic instrument used is robustly associated with the exposure. Polygenic risk scores (PRS) derived from GWAS findings are generally used as genetic instruments. Approximately 80% of existing GWAS studies have used samples of European ancestry (Martin, et al., 2021) typically drawn from WEIRD (Westernised, Educated, Industrialised, Rich, Democratic) populations (Henrich, Heine, & Norenzayan, 2010). WEIRD populations differ from many other populations, so conclusions may not be generalisable. The predictive power of PRS is reduced in non-European populations (Scutari, Mackay, & Balding, 2016), which could reflect differences in allele frequency and population substructure, or differences in how phenotypes manifest in different populations (e.g., Abdellaoui & Verweij, 2021). This limits the generalisability of MR studies using European samples and the potential for using PRS derived from European populations as genetic instruments in studies sampling from other populations.

Is the pathway between the genotype and phenotype partially confounded?

MR also assumes that the association between the genetic instrument and outcome is independent of confounders. However, cultural effects can influence genetic features of populations and introduce confounding through population stratification. For example, educational attainment is influenced by both cultural (Bowles, Gintis, & Groves, 2009) and genetic (Morris, Davies, Hemani, & Davey Smith, 2020) factors and assortative mating may occur based on educational attainment (Morris, Davies, Hemani, & Davey Smith, 2020). This means that individuals with similar educational attainment phenotypes are more likely to produce offspring together. Because of the genetic influence on educational attainment, if assortative mating occurs based on this phenotype a pair of individuals who produce offspring are likely to be more genetically similar than a random pair of individuals. Assortative mating can influence the genetic features of a population, such as allele frequency (Yengo, et al., 2018) and population stratification (Sebro & Risch, 2012), which can confound the genotype-phenotype association. This is not limited to assortative mating – phenomena such as migration can also influence population genetics through culture (Rogers & Jorde, 1987). As culture influences behaviour, and behaviour influences populations' genetic features, it becomes increasingly difficult to make an estimate of a phenotype-genotype association that is not biased by cultural effects. One method often used to reduce this bias is to adjust analyses for the first 10-20 principal components of genetic architecture. However, even after accounting for 100 principal components, bias due to confounding may still be present (Abdellaoui, et al., 2019), although this bias is likely to be small (Morris, Davies, Hemani, & Davey Smith, 2020).

Is the causal pathway between the genotype and phenotype direct?

The final assumption of MR is that the genetic instrument influences the outcome solely via the exposure. If the genotype-phenotype association is mediated by another variable the interpretation of the causal pathway may be complex. For example, the effect of educational attainment and BMI may be opposite in high- vs low-income countries because the effect operates via access to resources, and the impact of access to resources may differ in each setting. Income and educational attainment increase in line with one another and as income increases, so does access to resources (Psacharopoulos & Patrinos, 2018). In high-income countries, a healthier diet composed of lean meat and fresh fruit and vegetables is generally more costly than an unhealthier diet consisting of processed meats, refined grains, and added sugars and fats. Conversely, in many low-income countries, foods with high levels of added sugars and fats are more costly, and the most affordable foods are the ones with the lowest nutrient density, such as corn (Headey & Alderman, 2019). In high-income countries people with lower educational attainment and income are generally priced out of the 'healthy' food market, which may result in higher BMI. In low-income countries lower educational attainment may lead to decreased likelihood of buying foods high in nutrient density, leading to lower BMI. If causal pathways between genotype and phenotype are indirect and differ between populations (as with educational attainment, access to resources and diet in higher- vs lower-income countries), interpretation of MR results may differ across these contexts and may not be generalisable.

Conclusion

MR represents an exciting opportunity to use genetic data to understand causal relationships between phenotypes. However, when interpreting results from MR studies researchers should carefully consider how cultural contexts can influence these results and their generalisability. We should also endeavour to extend the current evidence beyond samples of European ancestry to understand the full range of human genetic and cultural diversity, and how they interact.

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