

Drug target Mendelian Randomization: are we really instrumenting drug use?

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In a recent publication in *Diabetologia*, Zheng *et al.* attempt to examine whether metformin use could reduce risk of Alzheimer's disease (AD) using Mendelian Randomization (MR) (1). Drug target MR is a promising method for identifying drugs that we could repurpose for intervention in diseases other than those for which they were originally approved. MR has the potential to overcome some of the key limitations of observational pharmacoepidemiology, such as confounding, and it has previously been successfully applied to identify drugs for prioritisation in new clinical trials (e.g. interleukin-6 receptor antagonists for COVID-19 (2, 3)). It is also particularly promising for a disease like dementia, where clinical trials for prevention are challenging due to the long (up to 20 years) prodromal phase. Given that dementia is currently the only leading cause of death globally with no effective treatments, I share the enthusiasm for what this method can potentially offer in this field.

There are several caveats to drug target MR that mean causal effect estimates require careful interpretation. The authors of this study mention throughout 'genetically proxied metformin use'. However, metformin use *per se* is not being instrumented here. The authors instrument five (of potentially many) identified targets of metformin, and take what is essentially an average of those five targets. It's encouraging and reassuring that those five targets in particular all show neuroprotective effects. However, metformin's targets remain uncertain (4) and there may be other targets that, if included, could change the magnitude of this 'averaged' effect (possibly towards the null, or in a worst-case scenario, change the sign of the combined effect estimate to be reversed – i.e. harmful). Some of metformin's targets also may not be encoded by the genome, which could potentially prohibit the use of drug target MR entirely. Thus, it is not possible to accurately estimate the scale or magnitude of the effect of metformin use on AD risk using this method. The authors provide evidence of target-specific effects, not drug use effects, and this has implications for developing interventions (e.g. metformin use trials vs target-specific drug trials).

The averaging method used in this study does not account for the fact that each of the five targets may be differentially affected by metformin. For example, assuming metformin only has five targets, for a unit lowering of glucose or HbA1c induced by metformin, 40% of this lowering may be mediated by agonism or inhibition of target 1, 30% via target 2, 20% via target 3, and 5% each by targets 4 and 5. To accurately instrument metformin use, it would be necessary to weight the averaged effect by those proportions (provided these are known from pharmacological studies), rather than weighting the combined causal effect estimate by the precision of target-specific effects (which is dominated by the Complex I results).

Making sensible comparisons about the magnitudes of effect across different drugs is important for weighing up the potential clinical benefits (or harms), in conjunction with potential side effects, when considering the repurposing of an existing drug. The authors compare the magnitudes of effect from their own metformin MR findings to randomized controlled trials examining the effects of other existing antidiabetic medications on cognitive impairment, and state that the magnitude is similar. However, the magnitude of effects from trials measuring drug use are unlikely to be comparable with findings from MR studies of specific targets, unless all of the targets are known and

have valid instruments. It is also worth noting that almost all of the trials examining the effects of antidiabetic medication on cognitive impairment to date have been conducted in select clinical diabetic populations (5-7), rather general population samples, as with the metformin MR. The only trial that was conducted in a non-clinical sample – the TOMMORROW trial - was null (8). There is ongoing debate in the dementia literature about whether levels of circulating glucose are likely to affect AD risk in people who are not diabetic; interestingly, all MR results for fasting glucose and HbA1c on AD risk published to date are also null (9-14). It may be possible that metformin (or any other antidiabetic medication) exerts an off-target protective effect on cognitive impairment through mechanisms other than regulating glucose. This is where target-specific analyses may provide useful insights; but it is crucial that we acknowledge that these are not the estimated overall effects of using the drug.

There are several other caveats to be aware of when applying drug target MR to the field of AD. When analysing AD as the outcome, the authors use a GWAS that meta-analyses clinical AD cases along with AD-by-proxy cases (15). However, there is recent evidence to suggest that we should be cautious when using summary statistics from GWAS that have included by-proxy cases, as they have yielded some counterintuitive findings (16). By-proxy cases may be problematic for several reasons: participants defined as cases have not themselves been diagnosed with AD; the question does not specify Alzheimer's disease but asks about any form of dementia; and the question does not ask if family members were diagnosed by a doctor, so there is likely misclassification bias. An additional analysis using only the clinical cases as the outcome would add clarity. There is also the pervasive issue of survival bias, which like conventional MR, drug target MR is not immune to. In this case, it is possible that levels of the five metformin protein targets are associated with premature mortality, given their association with diabetes. Thus, the causal effect of these five protein targets observed in participants who lived long enough to receive a dementia diagnosis may be biased. That said, given that the magnitude of survival bias is dependent upon the magnitude of the effect of the exposure on mortality, the bias is likely to be lower for a drug target MR (where effects of target-specific proteins on mortality are relatively small) than a conventional MR of, for example, fasting glucose or HbA1c on AD risk (where associations with mortality are likely to be comparatively larger).

In conclusion, drug target MR is a promising method for identifying novel preventative therapeutics and treatments, particularly for diseases like dementia for which clinical trials are often unfeasible. Their findings, however, require careful interpretation and we must consider whether we are able to reliably instrument the effects of drug use *per se*. In cases like metformin where targets remain uncertain, it is important to base conclusions only on the targets being examined; not on the consequences of using the drug itself.

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