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Using causal analysis methods to understand the relationship between smoking and diabetes

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Lycett and colleagues report that quitting smoking is associated with poorer glycaemic control (as assessed by HbA1c) in diabetics immediately following smoking cessation 1. A key strength of this paper is the use of data from patients in the THIN database, which makes the findings highly relevant to general practice in the UK. However, we cannot infer from these results that stopping smoking *causes* increases in HbA1c levels because, despite adjustment for a range of clinical and demographic factors, the observational data presented may still be biased by residual confounding, both by indications for treatment and by other lifestyle factors. Furthermore, severity of diabetes may influence patients' success in stopping smoking, so reverse causality cannot be ruled out.

The causal nature of the link between smoking and diabetes is still not well understood. Whilst smoking is associated with a higher risk of developing diabetes 2, there is conflicting evidence regarding links between smoking and glycaemic control 3. Causal inference methods, such as instrumental variable analysis, could provide more robust evidence about the effects of smoking and smoking cessation on diabetes. Valid instruments should be associated with the exposure (smoking behaviour), but not with confounding factors that can bias observational associations. Furthermore, proposed instruments should not be affected by reverse causality 4. As instruments will generally only explain a small proportion of the variance in smoking behaviour, these analyses require much larger sample sizes than conventional analyses to be adequately powered.

Within clinical databases such as THIN, physicians' prescribing preferences for varenicline or nicotine replacement therapy (NRT) can be used as instrumental variables to investigate the effects of smoking cessation 5. Physicians' preferences influence the type of smoking cessation medication they issue to their patients. These preferences are not necessarily related to patient-level confounding factors. This could induce variation in quit rates between patients who attend physicians who tend to prescribe varenicline and patients who attend physicians who tend to prescribe NRT. The difference in HbA1c levels between these groups of patients could be used as a valid test of whether quitting smoking affects

Conflicts of Interest

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glycaemic control, because quit rates can be expected to be higher in the former group 6. An advantage of this approach is that results would be directly relevant to clinical prescribing decisions.

In Mendelian randomisation (MR) analysis genetic variants which are related smoking behaviour are used as instrumental variables 7. The strongest genetic variant for smoking behaviour identified to date, which is located in the *CHRNA5-A3-B4* gene cluster (nicotine receptor subunit genes) affects smoking heaviness within smokers and, to a lesser degree, smoking cessation 8. Using this variant, or potentially others identified in genome wide association studies of smoking behaviour, MR studies could investigate the effects of smoking on glycaemic control and diabetes, using data from collaborative consortia such as CARTA (Causal Analysis Research in Tobacco and Alcohol) (<http://www.bris.ac.uk/expsych/research/brain/targ/research/collaborations/carta/>) or large genetic studies such as UK Biobank (<http://www.ukbiobank.ac.uk/>).

MR analysis may also help us to better understand the mediating role of weight in the link between smoking and diabetes. Of note, MR analysis has provided robust evidence that smoking reduces weight 9. It follows that stopping smoking increases weight, which is well established 10, and this may have downstream effects on glycaemic measures. Lycett and colleagues suggest that the effects of quitting smoking on glycaemic control are not mediated by weight increases following cessation, because the associations they observe do not attenuate after adjustment for weight 1. The authors have made good use of available data by adjusting for weight change within individuals, but some caution is still justified as missing data are an issue and weight is not uniformly collected across participants. One advantage of MR is that it can reduce bias arising from measurement error. Extensions of MR methods, e.g., two step or network MR 7, may allow more accurate estimation of the degree to which a link between smoking and diabetes is mediated through weight change.

Establishing causality is unlikely to alter clinical messages regarding smoking cessation, as the benefits of quitting clearly outweigh any potential negative effects on health. However, better understanding of causal links between smoking and diabetes may help to improve clinical management of diabetes in both continuing smokers and successful quitters.

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