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TITLE: Modifiable risk factors and miscarriage: a Mendelian Randomization analysis

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ABSTRACT:

Miscarriage, the loss of an embryo or fetus before 20 weeks of gestation, is estimated to end between 10-25% of clinically confirmed pregnancies. While approximately 50% of these miscarriages have been shown to be due to chromosomal abnormalities, observational studies have suggested various modifiable lifestyle factors may also increase miscarriage risk. Consequently, health guidelines typically suggest that prospective parents eliminate, limit or modify these factors, particularly the consumption of coffee and alcohol, smoking, and adiposity, before and during pregnancy. However, definitive causal relationships between these risk factors and miscarriage have not yet been demonstrated.

Here, we present a genome-wide association and Mendelian randomization analysis including >200,000 women in the UK Biobank and two QIMR Berghofer samples to investigate potential causal associations between miscarriage and the four most-often cited miscarriage risk factors – the consumption of coffee and alcohol, smoking and increased body mass index. Using the most significant genetic variants from recent

genome-wide association studies for these factors as instrumental variables we find evidence for a causal relationship between smoking initiation and spontaneous miscarriage (Inverse variance weighted Odds Ratio = 1.17, 95% CI = 1.10-1.24,  $P = 2.7 \times 10^{-07}$ ), but not for any other risk factor tested and either spontaneous or recurrent miscarriage. We suggest the significant observational associations for coffee and alcohol consumption and increased body mass index require further exploration, so as not to add to the distress or feelings of guilt and personal responsibility that are often associated with pregnancy loss.

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