Mendelian randomization study of maternal coffee consumption and its influence on birthweight, stillbirth and miscarriage

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Introduction

It has been estimated that around 70% of pregnant women consume caffeine with coffee being their main source. Caffeine is able to freely cross the blood-placental barrier and due to the inability of the fetus to metabolize the caffeine molecules, they are exposed to caffeine and its metabolites in proportion to maternal exposure. Increased maternal coffee consumption has been associated with increased number of spontaneous miscarriages, risk of stillbirth and low birthweight in observational studies. However, the causal relationship between coffee intake during pregnancy and these adverse outcomes remain unknown.

Mendelian Randomization (MR) is an epidemiological method that uses genetic variants associated with a modifiable exposure (coffee consumption) as instrumental variables to estimate the causal effect of the exposure on specific outcomes (low birthweight, spontaneous miscarriage, stillbirth)

Research objectives

Investigate if the observed relationship between maternal coffee consumption during pregnancy and the increased risk of stillbirth, spontaneous miscarriage and low birthweight is causal using Mendelian Randomization.

Methods

We performed a two-sample Inverse Variance Weighted (IVW) MR analyses using genome-wide association study (GWAS) summary data on coffee consumption (N=30,062) [1] as our exposure variable and its relationship with the following outcomes:

- Self-reported miscarriages (N=49,996) from a large meta-analysis [3]
- Stillbirths (N=78,867 from UK Biobank) [4]
- Birthweight (N=297,356 reporting own birthweight and N=173,259 reporting offspring's birthweight from the UKBB and the Early Growth Genetics Consortium) [2]

Three MR models were used: one including all 8 variants associated with coffee consumption, one removing variants associated with phenotypes that can effect the outcomes of interest (total of 6 variants) and another model excluding all potentially pleiotropic variants (total of 3 variants). Sensitivity analyses were also conducted using MR Egger regression, weighted median, simple and weighted mode estimations.

We also constructed a genetic risk score (GRS) of coffee consumption in UK Biobank women of European ancestry (up to N=194,196) and pregnant women in ALSPAC (Avon Longitudinal Study of Parents and Children) as follow-up (N=4,615).

Results

Both the two-sample MR and GRS analysis in UK Biobank showed no causal effect of maternal coffee consumption on the risk of sporadic miscarriages or stillbirths. However, both analyses showed some positive effect on birthweight when either all eight or six of the SNPs were included in the analysis.

Table 1. Inverse variance weighted summary of the Mendelian Randomization study of the causal effect of maternal coffee consumption on birthweight and number of miscarriages and stillbirths. Birthweight was analysed as Z-scores [2]. Miscarriages were defined as having had 1 or 2 spontaneous miscarriages [3] and stillbirth is the number of self-reported incidents.

		Beta	SE	P-value
Miscarriage	8 SNPs	-0.0484	0.0463	0.2960
	6 SNPs	-0.0486	0.0413	0.2397
	3 SNPs	-0.0464	0.0509	0.3615
Stillbirth	8 SNPs	0.0064	0.0087	0.4587
	6 SNPs	0.0047	0.0093	0.6125
	3 SNPs	0.0180	0.0162	0.2664
Birthweight	8 SNPs	0.0468	0.0333	0.1602
	6 SNPs	0.0498	0.0248	0.0443
	3 SNPs	0.0273	0.0291	0.3472

SNP: Single Nucleotide Polymorphism, SE: Standard Error

Limitations

We acknowledge that our study may be limited by the low number of instrumental variables. Some of the MR sensitivity analyses may not perform well when only three variants are included.

Conclusion

We did not find any evidence of a causal relationship between maternal coffee consumption and risk of stillbirths or spontaneous miscarriages. We did observe some potential evidence of a positive effect of maternal coffee consumption on offspring birthweight, however further studies are needed.

Selected references

[1] Cornelis, MC et al. 2015, 'Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption', Molecular psychiatry, vol. 20, no. 5, pp. 647–656. **[2]** Warrington, NM et al. 2019, 'Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors', Nature genetics, vol. 51, no. 5, pp. 804–814. **[3]** Laisk, T et al. 2020, 'The genetic architecture of sporadic and multiple consecutive miscarriage', Nature communications, vol. 11, no. 1, pp. 5980–5980. **[4]** Neale Lab (http://www.nealelab.is/uk-biobank)

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