Smoking, alcohol and coffee consumption and pregnancy loss: a Mendelian randomization investigation

Shuai Yuan, B.Med., M.Med.Sc.,[a] Jin Liu, M.D.,[b] and Susanna C. Larsson, Ph.D.[a,c]

[a] Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [b] Integrated Research Center for Fetal Medicine, Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, Maryland; [c] Unit of Medical Epidemiology, Department of Surgical Sciences, Uppsala University, Uppsala, Sweden

Objective: To determine the associations of smoking and alcohol and coffee consumption with pregnancy loss.
Design: Mendelian randomization study.
Setting: The UK Biobank study and FinnGen consortium.
Patients: A total of 60,565 cases with pregnancy loss and 130,687 noncases from UK Biobank and 3,312 cases with pregnancy loss and 64,578 noncases from FinnGen.
Intervention(s): None.
Mains Outcome Measure: Pregnancy loss.
Result(s): Genetic predisposition to smoking initiation was associated with an increased risk of pregnancy loss in both UK Biobank and FinnGen. The combined odds ratio (OR) was 1.31 (95% confidence interval [CI], 1.25–1.37) for one standard deviation increase in the prevalence of smoking initiation. There were no significant associations of genetically predicted consumption of alcohol (OR, 1.09; 95% CI, 0.93–1.27) or coffee (OR, 0.96; 95% CI, 0.87–1.06) with pregnancy loss.
Conclusion(s): This study on the basis of genetic data suggests the causal potential of the association of smoking but not moderate alcohol and coffee consumption with pregnancy loss. (Fertil Steril® 2021;116:1061-67. ©2021 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key words: Alcohol, causal inference, coffee, smoking, Mendelian randomization, pregnancy loss

Pregnancy loss is the death of a fetus at any time during pregnancy and happens to one-fifth of pregnant women (1). It can have a major impact on women's mental health (2) and may in addition be associated with an increased risk of other diseases, such as diabetes (3) and cardiovascular disease (4, 5), later in life. Cigarette smoking (6) as well as alcohol (7) and coffee consumption (8) have been identified as possible risk factors for pregnancy loss in observational studies. However, whether these associations are causal remains unclear because of inconsistent findings (9, 10) and potential biases, such as residual confounding, reverse causality, and misclassification (10, 11).

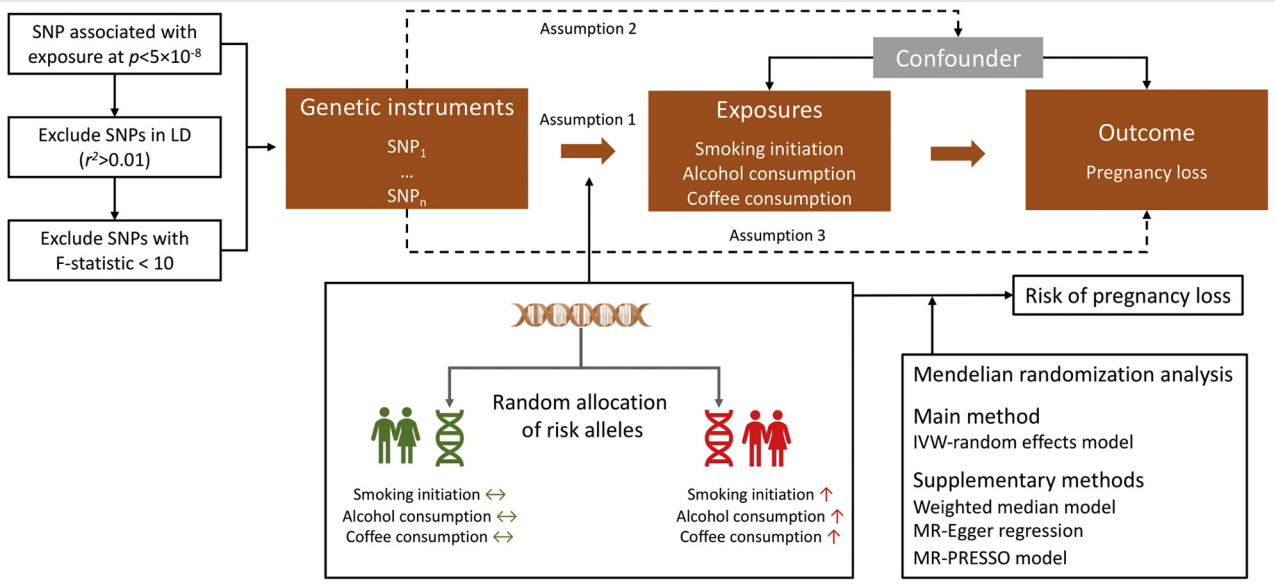
Utilizing genetic variants as instruments for an exposure (e.g., coffee consumption), Mendelian randomization (MR) design can overcome residual confounding and reverse causality, thereby strengthening the causal inference in an exposure–outcome association (Fig. 1) (12). Confounding is reduced because genetic variants are randomly assorted at conception, and therefore, one trait is generally unrelated to other traits. In addition, genetic variants cannot be modified by the onset and progression of the disease, and thus, MR analysis can additionally diminish reverse causation bias. Here, we used the MR design to determine whether smoking and moderate alcohol and coffee consumption are associated with an increased risk of pregnancy loss.

Received December 1, 2020; revised May 20, 2021; accepted May 24, 2021; published online June 27, 2021.
S.Y. has nothing to disclose. J.L. has nothing to disclose. S.C.L. has nothing to disclose.
Data Availability: Data used in the present study are available in the OSF data respiratory (https://osf.io/zph5n/).
Reprint requests: Susanna C. Larsson, Ph.D., Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Box 210, Stockholm 171 77, Sweden (E-mail: susanna.larsson@ki.se).

Fertility and Sterility® Vol. 116, No. 4, October 2021 0015-0282

https://doi.org/10.1016/j.fertnstert.2021.05.103

FIGURE 1



Overview and assumptions of the Mendelian randomization study design. **Assumption 1** indicates that the genetic variants proposed as instrumental variables should be robustly associated with the exposure. **Assumption 2** indicates that used genetic variants should not be associated with potential confounders of the exposure–outcome relationship. **Assumption 3** indicates that the selected genetic variants should affect the risk of the outcome merely through the risk factor, not via alternative pathways. IVW = inverse-variance weighted; LD = linkage disequilibrium; SNP = single-nucleotide polymorphism.

Yuan. Smoking and pregnancy loss. Fertil Steril 2021.

MATERIALS AND METHODS

Genetic Instrument Selection

A total of 378, 99 and 14 single-nucleotide polymorphisms (SNPs) associated with smoking initiation and alcohol and coffee consumption, respectively, were identified at the genome-wide significance threshold ($P<5\times10^{-8}$) in meta-analyses of genome-wide association studies on tobacco and alcohol use (up to 1.2 million individuals) (13) and coffee consumption (375,833 individuals) (14). Linkage disequilibrium among these SNPs for each exposure was estimated on the basis of the 1000 Genomes reference panel confined to the European population using the PLINK clumping method. We excluded SNPs with linkage disequilibrium ($r^2 > 0.01$ and clump window < 10,000 kb) and retained the SNP with the lowest *P* value, leaving 314, 84, and 12 SNPs as instrumental variables for smoking initiation and alcohol and coffee consumption, respectively. These instruments have been previously used in other MR studies (15–17). Detailed information on instrument selection and corresponding genome-wide association meta-analyses is present in Table 1.

Data Source for Pregnancy Loss

Summary-level data for pregnancy loss were derived from the UK Biobank study (18) and FinnGen consortium (19). In UK Biobank, pregnancy loss was defined as the history of having stillbirth spontaneous miscarriage or termination. We used the second wave of Neale Lab's genome-wide association analyses in UK Biobank, which recruited 191,252 women (60,565 cases and 130,687 controls) after the exclusion of individuals of non-European ancestry, closely related individuals (or at least one of a related pair of individuals), individuals with sex chromosome aneuploidies and missing information on pregnancy loss, and individuals who had withdrawn consent from the UK Biobank study. For FinnGen, we used the data from the R3 release where pregnancy loss was defined as spontaneous abortion on the basis of International Classification of Diseases 8th to 10th codes. After the removal of individuals with ambiguous gender, high genotype missingness (>5%), excess heterozygosity (±4 standard deviation), and non-Finnish ancestry, 3,312 cases and 64,578 controls were included in the genome-wide association analysis. The present MR study on the basis of summary-level data was approved by the Swedish Ethical Review Authority.

Statistical Analysis

We used the random effects inverse-variance weighted approach (20) as the primary statistical analysis method. Estimates of associations of smoking and alcohol and coffee consumption with the risk of pregnancy loss from UK Biobank and FinnGen were combined using the fixed-effects meta-analysis. The weighted median method, MR-Egger regression and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) model were used as supplementary analyses. Assuming over a half of weights from valid instruments, the weighted median method provides consistent estimates of associations (21). The MR-Egger regression offers estimates after the adjustment for pleiotropy

TABLE 1

Information on genetic instruments and outcome data sources.

Exposures	Unit	Participants included in analysis	Adjustments	Identified SNPs	Used instruments	PubMed ID or web link
Smoking initiation	SD in prevalence of smoking initiation	1,232,091 European-descent individuals	Age, sex, and the first 10 genetic principal components	378	314	30643251
Alcohol drinking	SD increase in log-transformed alcoholic drinks/week	941,280 European-descent individuals	Age, sex, and the first 10 genetic principal components	99	84	30643251
Coffee consumption	50% change	375,833 European-descent individuals	Age, sex, body mass index, total energy, proportion of typical food intake, and 20 genetic principal components	14	12	31046077
Pregnancy loss (stillbirth, spontaneous miscarriage or termination)	-	60,565 cases and 130,687 controls of European ancestry	Age, sex, and up to 20 genetic principal components	-	-	UK Biobank (http://www.nealelab.is/uk-biobank)
Spontaneous abortion	-	3,312 cases and 64,578 controls of European ancestry	Age, sex, 10 genetic principal components, and genotyping batch	-	-	FinnGen consortium (https://www.finngen.fi/fi)

Note: PubMed ID = PubMed identifier; SD = standard deviation; SNPs = single-nucleotide polymorphisms.

Yuan. Smoking and pregnancy loss. Fertil Steril 2021.

but compromises statistical power (22). The *P* value for the MR-Egger intercept was used to indicate directional pleiotropy. The MR-PRESSO approach aims at detecting possible outliers and generating estimates after removal of outliers, and its embedded distortion test can distinguish the differences between estimates before and after outliers removing (23). We used the Cochran Q value to represent the heterogeneity among used instruments for one exposure. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of pregnancy loss for exposures were scaled to the unit listed in Table 1. All analyses were performed using the TwoSampleMR (24) and MR-PRESSO (23) packages in R Software 3.6.0.

RESULTS

Genetic predisposition to smoking initiation was associated with an increased risk of pregnancy loss in both the UK Biobank study and FinnGen consortium (Fig. 2). The combined OR of pregnancy loss was 1.31 (95% CI, 1.25–1.37) for one standard deviation increase in the prevalence of smoking initiation. The association was consistent in supplementary analyses albeit nonsignificant in the MR-Egger regression analysis (Table 2). The *P* value for the intercept in MR-Egger was below 0.05 on the basis of UK Biobank, indicating a possible pleiotropic effect. However, no outlier was identified in the MR-PRESSO model.

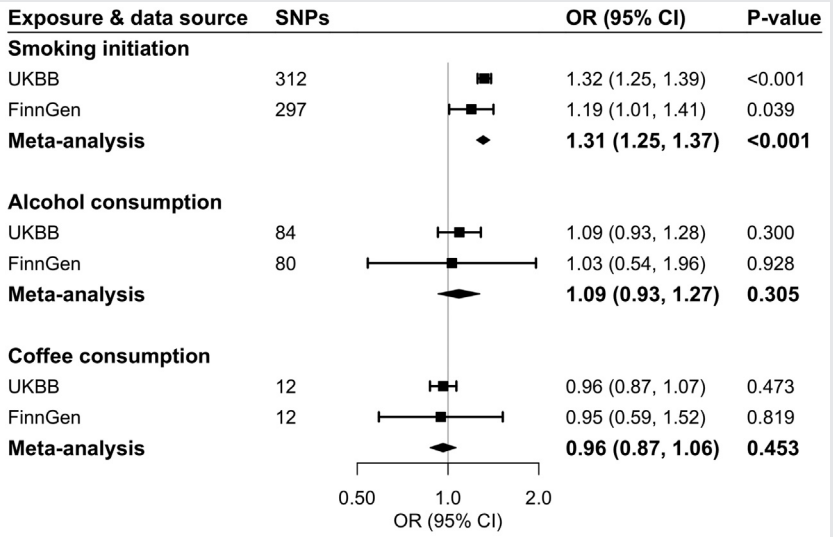
Genetically predicted moderate alcohol and coffee consumption showed no association with pregnancy loss (Fig. 2). The combined ORs of pregnancy loss were 1.09 (95% CI, 0.93, 1.27) for alcohol consumption and 0.96 (95% CI, 0.87–1.06) for coffee consumption. These null associations were stable in supplementary analyses, and no possible pleiotropy was detected (Table 2). Several outliers were detected in the analysis of alcohol consumption, whereas the *P* values for the distortion tests were >.05, which implies no significant difference between estimates before and after removal of outliers.

DISCUSSION

The present MR study found a positive association between smoking initiation and an increased risk of pregnancy loss but did not support any association of moderate alcohol and coffee consumption with pregnancy loss. To our knowledge, this is the first study exploring the potential causal associations of modifiable risk factors with pregnancy loss on the basis of genetic data.

Our finding on smoking in relation to pregnancy loss is in line with most but not all previous studies. A systematic review including 98 studies found that any active smoking behavior was associated with an increased risk of miscarriage and the risk became greater when smoking exposure was defined in pregnancy (6). Such association was observed in a subsequent large-scale cross-sectional study compromising 80,762 women (25). Compared with never smokers, women who were active smokers during their reproductive years had 16% higher risk of spontaneous abortion, 44% higher risk of stillbirths, and 43% higher risk of ectopic pregnancies (25). Smoking less than 10 cigarettes showed no relation to

FIGURE 2



Associations of genetic predisposition to smoking initiation and moderate alcohol and coffee consumption with pregnancy loss in two independent populations. The estimates in each population were derived from the inverse-variance weighted model with random effects. CI = confidence interval; OR = odds ratio; SNPs = single-nucleotide polymorphisms; UKBB = UK Biobank.

Yuan. Smoking and pregnancy loss. Fertil Steril 2021.

early miscarriage in a case–control study with 620 women with early miscarriage and 1,240 normal pregnant women, but only 3.1%–3.4% of women had smoking behavior (26). The reason of no clear pattern of the association between smoking in a light dose and early miscarriage may be that the number of cases in smoking was too small to detect a weak association. The present study was on the basis of genetic data from 259,142 women strengthened the evidence that smoking is a causal risk factor for pregnancy loss. Except for maternal smoking, studies suggested that paternal smoking increases the risk of pregnancy loss among never-smoking women (27). Therefore, it should be recommended

TABLE 2

Associations of genetic predisposition to smoking initiation and moderate alcohol and coffee consumption with pregnancy loss in supplementary MR analyses.

		Effect estimate on PL			Test of pleiotropy	
Exposure	**MR method**	**OR**	**95% CI**	***P***	**Test**	
UKBB						
Smoking initiation (312 SNPs)	Weighted median	1.24	1.16–1.32	1.34×10^{-9}	Cochran Q value	418
	MR-Egger	1.02	0.83–1.26	.844	MR-Egger intercept (*p*)	0.016
	MR-PRESSO	NA	NA	NA	Distortion test (*p*)	NA
Alcohol consumption (84 SNPs)	Weighted median	1.04	0.81–1.34	.756	Cochran Q value	127
	MR-Egger	0.86	0.63–1.18	.350	MR-Egger intercept (*p*)	0.090
	MR-PRESSO[a]	1.03	0.89–1.2	.658	Distortion test (*p*)	0.214
Coffee consumption (12 SNPs)	Weighted median	0.94	0.82–1.07	.342	Cochran Q value	11
	MR-Egger	0.94	0.77–1.15	.561	MR-Egger intercept (*p*)	0.781
	MR-PRESSO	NA	NA	NA	Distortion test (*p*)	0.503
FinnGen						
Smoking (297 SNPs)	Weighted median	1.24	0.96–1.61	.095	Cochran Q value	295
	MR-Egger	1.71	0.84–3.48	.141	MR-Egger intercept (*p*)	0.312
	MR-PRESSO	NA	NA	NA	Distortion test (*p*)	0.531
Alcohol consumption (80 SNPs)	Weighted median	0.90	0.4–2.03	.799	Cochran Q value	109
	MR-Egger	1.00	0.2–4.96	.997	MR-Egger intercept (*p*)	0.972
	MR-PRESSO[a]	1.13	0.61–2.08	.701	Distortion test (*p*)	0.860
Coffee consumption (12 SNPs)	Weighted median	1.07	0.34–3.4	.911	Cochran Q value	17
	MR-Egger	1.35	0.54–3.38	.540	MR-Egger intercept (*p*)	0.399
	MR-PRESSO	NA	NA	NA	Distortion test (*p*)	0.159

Note: CI = confidence interval; NA = not available; OR = odds ratio; PL =pregnancy loss; SNPs = single-nucleotide polymorphisms; UKBB = UK Biobank

[a] The MR-PRESSO analysis detected 2 and 1 outliers in the analysis of alcohol consumption in UKBB and FinnGen, respectively.

Yuan. Smoking and pregnancy loss. Fertil Steril 2021.

reducing the prevalence of smoking initiation and promoting smoking cessation in both parents preparing pregnancy.

Evidence on moderate alcohol consumption in relation to pregnancy loss is conflicting. A meta-analysis of 46 studies detected no clear effects of prenatal low to moderate alcohol consumption on miscarriage, stillbirth, and intrauterine growth restriction (9). Nevertheless, a succeeding meta-analysis with 231,808 pregnant women revealed that miscarriage risk increased by approximately 6% for each additional drink/week at the basis of 5 or fewer drinkers/week. The current MR study showed no association of lifelong habitual alcohol consumption with pregnancy loss, but the possibility that a weak association may have been overlooked cannot be excluded. In addition, moderate alcohol consumption was revealed to increase the risk of other pregnancy and childhood outcomes, such as small-for-gestational-age and preterm births (28), although the conclusion remained undetermined (29).

Most studies have acknowledged a higher risk of pregnancy loss in women with high or heavy coffee consumption in pregnancy compared with that in abstainers (30). The effect of low to moderate coffee consumption may be different. According to the World Health Organization's recommendation, total caffeine consumption below 300 mg/day (equaling to three 6-ounce cups of coffee) generates few negative impacts on pregnancy and childhood outcomes (31). A recent meta-analysis encompassing 130,456 participants and 3,429 cases revealed that low and moderate caffeine consumption (50–350 mg/day) were not associated with any form of pregnancy loss (30). In a large hospital-based study with 18,478 singleton pregnancies, an increased risk of stillbirth was only observed in individuals with 8 cups/day of coffee consumption (32). The finding of the present study was in line with previous studies and found that lifelong moderate coffee consumption was not associated with pregnancy loss.

The present study has several strengths and limitations. The major strength was the MR designs, which diminished residual confounding and reverse causality and, thereby, improved the causal inference in associations of smoking and alcohol and coffee consumption with pregnancy loss. In addition, this study was on the basis of a large number of cases with pregnancy loss in two independent study samples. All analyses were confined within populations of European ancestry and genome-association tests adjusted for population structures. Thus, our findings were not likely distorted by population stratification bias. However, this restriction to European populations limits the generalizability of our findings to other populations. The quality control criteria in the genome-wide association analyses for pregnancy loss differed in FinnGen and UK Biobank, and the difference may introduce heterogeneity between causal estimates of associations, although we observed this heterogeneity to be minimal. Another limitation is that the interaction effects across these exposures on pregnancy loss could not be assessed in a two-sample MR design (33).

Pleiotropy challenges causal inference in any MR study. Two types of pleiotropic effects, including horizontal and vertical pleiotropies, have been noted (34). Vertical pleiotropy means that the genetic instruments for an exposure (e.g., smoking initiation) influence the risk of the outcome (e.g., pregnancy loss) partly or completely via a mediator. Horizontal pleiotropy indicates that the genetic instruments are associated with the outcome via a factor that is genetically correlated with the exposure (not as a mediator). The existence of horizontal pleiotropy but not vertical pleiotropy biases the MR causal inference (34). In the present study, the MR-Egger model suggested possible horizontal pleiotropy in the analysis of smoking initiation in UK Biobank. Nevertheless, no outlier was observed in the MR-PRESSO analysis, and no corresponding pleiotropy was revealed in the FinnGen consortium, which indicated that our results are likely valid. On the other hand, the variants associated with smoking behaviors may be linked to a variety of systems related to nicotinic, dopaminergic, and glutamatergic neurotransmission. The study could not rule out the possibility that pregnancy loss may be linked to other factors or behaviors that result from differences in neurotransmission, including the use of other drugs, prior pregnancy terminations, or other risk-taking behaviors.

CONCLUSION

In conclusion, this MR study suggests that smoking is a risk factor for pregnancy loss and recommends that women preparing for pregnancy should avoid smoking. The safety of moderate alcohol and coffee consumption on pregnancy outcomes merits more study.

Acknowledgments: Summary-level genetic data for pregnancy loss were obtained from the UK Biobank study (Neale Lab) and FinnGen consortium. The investigators thank all investigators for sharing these data. The study is funded by the Swedish Research Council for Health, Working Life and Welfare (Forte; grant no. 2018-00123) and the Swedish Research Council (Vetenskapsrådet; grant no. 2019-00977). The sponsors or funders play no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

DIALOG: You can discuss this article with its authors and other readers at https://www.fertstertdialog.com/posts/31946

REFERENCES

1. Rossen LM, Ahrens KA, Branum AM. Trends in risk of pregnancy loss among US women, 1990-2011. Paediatr Perinat Epidemiol 2018;32:19–29.
2. Farren J, Mitchell-Jones N, Verbakel JY, Timmerman D, Jalmbrant M, Bourne T. The psychological impact of early pregnancy loss. Hum Reprod Update 2018;24:731–49.
3. Peters SAE, Yang L, Guo Y, Chen Y, Bian Z, Sun H, et al. Pregnancy, pregnancy loss and the risk of diabetes in Chinese women: findings from the China Kadoorie biobank. Eur J Epidemiol 2020;35:295–303.
4. Ranthe MF, Andersen EA, Wohlfahrt J, Bundgaard H, Melbye M, Boyd HA. Pregnancy loss and later risk of atherosclerotic disease. Circulation 2013;127:1775–82.
5. Maino A, Siegerink B, Algra A, Martinelli I, Peyvandi F, Rosendaal FR. Pregnancy loss and risk of ischaemic stroke and myocardial infarction. Br J Haematol 2016;174:302–9.

6. Pineles BL, Park E, Samet JM. Systematic review and meta-analysis of miscarriage and maternal exposure to tobacco smoke during pregnancy. Am J Epidemiol 2014;179:807–23.
7. Sundermann AC, Zhao S, Young CL, Lam L, Jones SH, Velez Edwards DR, et al. Alcohol use in pregnancy and miscarriage: a systematic review and meta-analysis. Alcohol Clin Exp Res 2019;43:1606–16.
8. Lyngsø J, Ramlau-Hansen CH, Bay B, Ingerslev HJ, Hulman A, Kesmodel US. Association between coffee or caffeine consumption and fecundity and fertility: a systematic review and dose-response meta-analysis. Clin Epidemiol 2017;9:699–719.
9. Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome. BJOG 2007;114:243–52.
10. Signorello LB, McLaughlin JK. Maternal caffeine consumption and spontaneous abortion: a review of the epidemiologic evidence. Epidemiology 2004;15:229–39.
11. Bailey BA, Sokol RJ. Prenatal alcohol exposure and miscarriage, stillbirth, preterm delivery, and sudden infant death syndrome. Alcohol Res Health 2011;34:86–91.
12. Stephen Burgess SGT. Mendelian randomization: methods for using genetic variants in causal estimation. Londong, UK: Chapman and Hall/CRC; 2015.
13. Liu M, Jiang Y, Wedow R, Li Y, Brazel DM, Chen F, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. Nat Genet 2019;51:237–44.
14. Zhong VW, Kuang A, Danning RD, Kraft P, van Dam RM, Chasman DI, et al. A genome-wide association study of bitter and sweet beverage consumption. Hum Mol Genet 2019;28:2449–57.
15. Yuan S, Gill D, Giovannucci EL, Larsson SC. Obesity, type 2 diabetes, lifestyle factors, and risk of gallstone disease: a Mendelian randomization investigation. Clin Gastroenterol Hepatol 2021;S1542-3565(21)00001-X.
16. Larsson SC, Mason AM, Bäck M, Klarin D, Damrauer SM, Michaëlsson K, et al. Genetic predisposition to smoking in relation to 14 cardiovascular diseases. Eur Heart J 2020;41:3304–10.
17. Yuan S, Larsson SC. An atlas on risk factors for type 2 diabetes: a wide-angled Mendelian randomisation study. Diabetologia 2020;63:2359–71.
18. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med 2015;12:e1001779.
19. FinnGen documentation of R3 release, 2020. Available at: https://finngen.gitbook.io/documentation/v/r3/. Accessed May 24, 2021.
20. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from Mendelian randomization analyses with multiple genetic variants. Epidemiology 2017;28:30–42.
21. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol 2016;40:304–14.
22. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol 2015;44:512–25.
23. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 2018;50:693–8.
24. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, et al. The MR-Base platform supports systematic causal inference across the human phenome. Elife 2018;7.
25. Hyland A, Piazza KM, Hovey KM, Ockene JK, Andrews CA, Rivard C, et al. Associations of lifetime active and passive smoking with spontaneous abortion, stillbirth and tubal ectopic pregnancy: a cross-sectional analysis of historical data from the Women's Health Initiative. Tob Control 2015;24:328–35.
26. Xu G, Wu Y, Yang L, Yuan L, Guo H, Zhang F, et al. Risk factors for early miscarriage among Chinese: a hospital-based case-control study. Fertil Steril 2014;101:1663–70.
27. Wang L, Yang Y, Liu F, Yang A, Xu Q, Wang Q, et al. Paternal smoking and spontaneous abortion: a population-based retrospective cohort study among non-smoking women aged 20-49 years in rural China. J Epidemiol Community Health 2018;72:783–9.
28. Mamluk L, Edwards HB, Savović J, Leach V, Jones T, Moore THM, et al. Low alcohol consumption and pregnancy and childhood outcomes: time to change guidelines indicating apparently 'safe' levels of alcohol during pregnancy? A systematic review and meta-analyses. BMJ Open 2017;7:e015410.
29. Patra J, Bakker R, Irving H, Jaddoe VW, Malini S, Rehm J. Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birthweight, preterm birth and small for gestational age (SGA)-a systematic review and meta-analyses. BJOG 2011;118:1411–21.
30. Chen LW, Wu Y, Neelakantan N, Chong MF, Pan A, van Dam RM. Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose-response meta-analysis of prospective studies. Public Health Nutr 2016;19:1233–44.
31. Tunçalp Ö, Pena-Rosas JP, Lawrie T, Bucagu M, Oladapo OT, Portela A, et al. WHO recommendations on antenatal care for a positive pregnancy experience-going beyond survival. BJOG 2017;124:860–2.
32. Wisborg K, Kesmodel U, Bech BH, Hedegaard M, Henriksen TB. Maternal consumption of coffee during pregnancy and stillbirth and infant death in first year of life: prospective study. BMJ 2003;326:420.
33. Morales-Suárez-Varela M, Nohr EA, Olsen J, Bech BH. Potential combined effects of maternal smoking and coffee intake on foetal death within the Danish National Birth Cohort. Eur J Public Health 2018;28:315–20.
34. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 2018;362:k601.

Consumo de tabaco, alcohol y café y perdida gestacional: Una investigación mendeliana aleatorizada.

Objetivo: Determinar las asociaciones del consumo de tabaco, alcohol y café con la pérdida gestacional.

Diseño: Estudio aleatorización mendeliano.

Lugar de realización: Biobanco UK y consorcio FinnGen.

Paciente (s): Un total de 60,565 casos con perdida gestacional y 130,687 casos control del UK Biobank y 3,312 casos con perdida gestacional y 64,578 casos control de FinnGen.

Intervención (es): ninguna.

Variable principal (es): Perdida gestacional.

Resultados: La predisposición genética a iniciarse en el tabaquismo se asoció con un riesgo aumentado de perdida gestacional en UK Biobank y FinnGen. El Odds ratio (OR) combinado fue 1,31 (95% intervalo de confianza [CI], 1.25-1.37) para un aumento de una desviación estándar en la prevalencia del inicio del tabaquismo. No existían asociaciones significativas para la predicción genética del consumo de alcohol (OR, 1.09;95%CI, 0.93-1.27) o café (OR, 0.96; 95% CI, 0.87-1.06) con la perdida de embarazo.

Conclusiones: Este estudio en base a datos genéticos sugiere el potencial causal de la asociación del tabaquismo con la pérdida del embarazo, pero no con el consumo moderado de alcohol o café.