Insights into risk factors of medical abortion: A Mendelian randomization study

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October 6, 2023

Abstract

Objective: To explore the potential factors that contribute to the occurrence of medical abortion(MA) through a Mendelian randomization(MR) study. **Design:** Univariate MR(UVMR) and multivariate MR(MVMR) analyses. **Setting:** Genetic variants from European populations. **Population or Sample:** Instrumental variants for MA were obtained from FinnGen with 36,232 cases and 149,622 controls. **Methods:** The inverse variance weighting method was adopted as the primary analysis. **Main outcome measures:** The associations of MA with household income(HI), education attainment(EA), cognitive performance(CP), risky behaviors: smoking behavior(SB), alcohol consumption(AC), and reproductive traits: age at first sexual intercourse(AFS), lifetime number of sexual partners(LNSP), age at first birth(AFB), age at last birth(ALB). **Results:** In the UVMR, increasing HI, EA, AFS and AFB appeared to reduce MA risk(HI, OR=0.569, P = 7.93E-08; EA, OR=0.875, P = 6.02E-21; AFS, OR=0.439, P = 5.17E-25; AFB, OR=0.815, P = 5.46E-12), whereas SB and LNSP appeared to add to MA risk((SB, OR=1.424, P =8.32E-11; LNSP, OR=2.777, P =2.14E-11). In the MVMR, EA, SB, LNSP and AFS seems to be the predominant risk factor for MA risk with the independent effect, while HI had no effect after controlling EA(HI in model 1, OR=0.890, P = 5.78E-01). AFB functioned as mediators in the causal chain of MA risk reduction by EA, with the mediated proportion of AFS and AFB being 57.8%. **Conclusions:** Our MR study demonstrated the causal potential of the associations of HI, EA, SB, LNSP, AFS and AFB with medical abortion.

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Keywords: medical abortion, risk, causality, Mendelian randomization.

Introduction

Abortion is a common healthcare intervention for unintended pregnancy. Changes in abortion knowledge and attitudes over time that are perceived as safer rather than more dangerous, easier as opposed to more difficult to access, acceptable as opposed to wrong, or self-identifying as pro-choice as opposed to pro-life[1]. It was estimated that there is a global average of 73.3 million abortions per year, which corresponded to 39 abortions for every 1,000 women aged 15-49 years[2]. However, abortion may be associated with a series of immediate complications(e.g. failed attempted abortion, hemorrhage, uterine perforation, cervical trauma, repeat aspiration, disseminated intravascular coagulation), late complications(e.g. pelvic inflammatory diseases, retained products of conception, continuing pregnancy) and poor reproductive outcomes (e.g. asherman syndrome, subfertility, ectopic pregnancy, miscarriage, preterm birth and low birth weight)[3].

It is particularly important to prevent abortions among minors and adults to the maximum extent possible, which requires extensive education, improvement of lifestyles and psychological conditions, and a focus on medical, legal and economic, key direction in health protection strategy not only of adolescents and the youth, but also of population as a whole[4]. Thus, reducing unintended pregnancy and abortion is an urgently need. Consequently, the risk factors for abortion need to be explored. Bearak J et al. estimated the relationship between income, region or legal status of abortion and rate of abortion or unintended pregnancy by a new statistical model[2].

Household income(HI), education attainment(EA), cognition performance(CP), risky behaviors: smoking behavior(SB), alcohol consumption(AC), and reproductive traits: age at first sexual intercourse(AFS), lifetime number of sexual partners(LNSP), age at first birth(AFB), age at last birth(ALB) may contribute to the occurrence of unintended pregnancies and may be responsible for forcing women to choose medical abortion(MA).

Mendelian randomization(MR), using genetic variants as instrumental variables (IV) from genome-wide association studies(GWAS), provides a more robust method for assessing a causal effect between a risk factor and an outcome than does much conventional observational epidemiology[5]. Furthermore, a two-sample MR design utilizing existing genetic data or DNA samples from large-scale genetic association studies increase the feasibility and cost-efficiency of MR studies[6]. MR studies are less susceptible to confounding factors and reverse causality based on the principle of genetic variants being randomly distributed at meiosis and fixed at conception.

Multivariable MR (MVMR) is a recent extension to MR, retaining the benefits of using genetic instruments for causal inference, such as avoiding bias due to confounding. This approach can be used to estimate the effect of multiple exposures on an outcome and/or the genetic variants associated with multiple, potentially related exposures on a single outcome[7].

MR studies have been successfully applied to various causal relationship analyses between individual behaviors, cognition, education, household income with various diseases[8-11]. Hence, we performed univariate MR(UVMR) and MVMR to explore the causal associations between income, education, cognition, risky

behaviors, reproductive traits and MA by using newly published summary genetic association statistics from large-scale genome-wide association studies.

Materials and methods

2.1 Study design

We performed UVMR and MVMR to comprehensively explore the effects of HI, EA, CP, and risky behaviors: SB, AC, and reproductive traits: AFS, LNSP, AFB, ALB on MA.

2.2 Data Sources

2.2.1 EA and CP

The variable genetic information for EA represented by "years of education" were extracted from the BOLT-LMM (a mixed-model association method) summary association statistics released by Loh, P. R. et al.[12], which were available on the GWAS catalogue website (*https://www.ebi.ac.uk/gwas/*). The GWAS summary dataset for CP was extracted from Social Science Genetic Association Consortium (SSAGC) Data Portal (http://thessgac.com). We extracted single-nucleotide polymorphisms(SNPs) for CP from a meta-analysis combined a published study of general cognitive ability (n=35,298) conducted by the Cognitive Genomics Consortium with new GWAS of cognitive performance in the UKB (n =222,543)[13].

2.2.2 HI, LNSP, ALB

The variable genetic information for HI, LNSP, ALB in this study was extracted from the Integrative Epidemiology Unit (IEU) GWAS database (https://gwas.mrcieu.ac.uk/), which is a publicly available GWAS summary database[14]. HI status was represented by "average total household income before tax" of the GWAS summary dataset with 397,751 samples output from GWAS pipeline using Phesant derived variables from UKBiobank. The HI was collected using a 5-point scale corresponding to the average total household income before tax, 1 being less than 18,000 pounds, 2 being18,000–30,999 pounds, 3 being 31,000–51,999 pounds, 4 being 52,000–100,000 pounds, and 5 being greater than 100,000 pounds. Genetic instruments for lifetime number of sexual partners and age at last live birth were extracted from the GWAS summary datasets of 378,882 and 170,248 samples, respectively, which were output from GWAS pipeline using Phesant derived variables from UKBiobank.

2.2.3 SB and AC

The GWAS summary dataset for SB and AC was extracted from GWAS and the Sequencing Consortium of Alcohol and Nicotine use (GSCAN) (*https://genome.psych.umn.edu/index.php/GSCAN)*.SB represented by smoking initiation (n =1,232,091) is a binary phenotype, indicating whether an individual had ever smoked regularly; AC is a continuous phenotype measured with drinks per week (n=941,280)[15].

2.2.4 AFS and AFB

The variable genetic information for AFS and AFB were extracted from a GWAS study on the GWAS catalogue website (*https://www.ebi.ac.uk/gwas/*), conducted by Mills MC[16], in which 16,426,473 and 10,766,720 SNPs were identified, respectively.

2.2.5 GWAS summary statistics of MA from FinnGen

We used the medical abortion GWAS summary statistics from FinnGen (https://r9.finngen.fi/). This GWAS consisted of 36,232 cases and 149,622 controls, with about 20,159,347 single nucleotide polymorphisms (SNPs) were analyzed. In UKB, the GWAS was performed in 4,281 participants by Neale Lab (*http://www.nealelab.is/uk-biobank*).

2.3 Mendelian randomization design and instrumental variable (IV) selection

Figure 1 showed a brief description of the overall design of the study for UVMR and MVMR. The potential causal relationships between factors and abortion were deduced from UVMR and the main risk factors for

MA were identified through different models of MVMR. In MR, genetic variants are used as IVs to assess the causal effect of an exposure on an outcome. Genetic variants used as IV need to meet the following three pivotal assumptions: First, the SNPs are closely associated with exposure. Second, the SNPs are independent from any confounders of exposure-outcome causality. Third, the SNPs do not directly affect outcome, but only have an impact on outcomes via the exposure. We selected the significant genetic variants that match with the genome-wide statistical significance threshold ($P < 5 \times 10^{-8}$). Using PLINK clustering, the linkage disequilibrium between these SNPs for each exposure was estimated on the basis of the 1000 Genomes reference panel confined to the European population, and SNPs were thresholded at linkage disequilibrium $r^2 < 0.001$ at a 0-10,000 kb window to guarantee the independence of the selected genetic variants. Removing the SNPs for being palindromic with intermediate allele frequencies. For UVMR, we calculated the F-statistic for each exposure to assess the strength of each tool in the abortion GWAS, and SNPs with F statistics <10 were identified as weak instruments(Supplementary table 3-12). In addition, we calculated the conditional F-statistic for assessing instrument strength in two sample summary MVMR

Statistical analyses

2.4.1 UVMR and MVMR analyses

For UVMR, we used inverse variance weighted MR (IVW MR) along with the complementary methods: simple mode, MR–Egger, weighted mode and weighted median to assess the evidence of the causal effects of each factor on MA, in order to detect the sensitivity of the results to different patterns of violations of IV assumptions, as consistency of results across methods strengthens an inference of causality[17].

For our MVMR analyses, combining EA along with HI, and risky behaviors along with HI or EA, and reproductive factors (AFS, LNSP) along with HI or EA, we used the multivariable inverse-variance weighted (IVW) method as the primary method to estimate the causal associations since it possesses the highest statistical power. The multivariable MR-Egger method was adopted as a complementary method to strengthen the main results.

2.4.2 Heterogeneity and pleiotropy analyses

To evaluate heterogeneity, we used Cochran heterogeneity test. If there is heterogeneity, random-effects IVW models are applied; otherwise, the fixed-effect IVW model is applied. To evaluate pleiotropy, we used MR-Egger regression (assessing whether the MR-Egger intercept was different from zero). If causality was estimated in the same direction among the various MR methods, the conclusions will be considered as relatively robust causal inferences. Analyses were carried out using MendelianRandomization version 0.9.0, TwoSampleMR version 0.5.7 and MVMR version 0.4 in the R environment version 3.6.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

3.1 UVMR analyses of risk factors on medical abortion

We selected 45, 207, 136, 34, 85, 154, 60, 55 and 6 SNPs as genetic instruments meting genome-wide statistical significance for HI, EA, CP, AC, SB, AFS, LNSP, AFB and ALB after LD clumping, respectively. The mean F-statistics for risk factors ranged from 38.28 to 77.30 (see Supplementary table 1).

Primary IVW method showed that genetic variants associated with increased HI, EA, AFS, and AFB, were negatively causally related to the risk of medical abortion(HI, OR=0.569, 95% CI, 0.463–0.699, P =7.93E-08; EA, OR=0.875, 95% CI, 0.851–0.900, P=6.02E-21; AFS, OR=0.439, 95% CI, 0.376–0.513, P=5.17E-25; AFB, OR=0.815, 95% CI, 0.769-0.864, P=5.46E-12). Adversely, SB and LNSP were risk factors for medical abortion (SB, OR=1.424, 95% CI, 1.280-1.584, P =8.32E-11; LNSP, OR=2.777, 95% CI, 2.059-3.745, P=2.14E-11). We found no evidence for the causal effect of AC and ALB on the risk of MA(AC, OR=1.297, 95% CI, 0.980-1.716, P=6.92E-02; ALB, OR=0.659, 95% CI, 0.408-1.063, P=8.75E-02). The causal connection between CP and MA was in doubt, as the causal estimates were directionally inconsistent(see Figure 2).

3.2 MVMR analyses of risk factors on medical abortion

Household income

Using MVMR to assess each factor associated with MA by various model after controlling/adjusting EA(model 1), or EA plus LNSP(model 2), or EA, AC, LNSP(model 3), EA, SB, LNSP(model 4), we found increased HI not associated with risk of MA(HI in model 1, OR=0.896, 95%CI, 0.610-1.317, P=5.78E-01; HI in model 2, OR=0.815, 95%CI, 0.559-1.190, P= 2.90E-01; HI in model 3, OR=0.775, 95%CI, 0.531-1.132, P= 1.88E-01; HI in model 4, OR=0.830, 95%CI, 0.568-1.212, P= 3.34E-01) (see Figure 3).

Educational attainment

Impressively, EA not only presented a significant association with a decreased risk of MA in UVMR analysis, but was also causally associated with a decreased risk of abortion in MVMR analysis after adjusting for different factors(EA in model 1, OR=0.886, 95%CI, 0.840-0.934, P=8.44E-06; EA in model 2, OR=0.900, 95%CI, 0.854-0.948, P= 8.88E-05; EA in model 3, OR=0.905, 95%CI, 0.858-0.955, P=2.66E-04; EA in model 4, OR=0.917, 95%CI, 0.869-0.967, P=1.53E-03) (see Figure 3).

Risky behaviors(SB and AC)

Consistent with UVMR analysis, in the MVMR analysis, SB contributes to increased risk of MA, when controlling/adjusting EA, LNSP, HI (SB in model 4, OR=1.220, 95% CI, 1.020-1.458, P=1.53E-03). We found that AC was not associated with the risk of MA after adjusting EA, LNSP, HI (SB in model 3, OR=1.284, 95% CI, 0.941-1.790, P=1.41E-01) (see Figure 3).

Reproductive factors (AFS, LNSP and AFB)

In the MVMR analyses, we arrived at a result of causality between later age at first sexual intercourse and MA: reverse causality, by adjusting LNSP (AFS in model 5, OR=0.831, 95%CI, 0.785-0.880, P=1.64E-10). An increase in LNSP indicated greater likelihood of MA, after controlling/adjusting AFS(model 5), or EA, HI(model 2), or EA, AC, HI(model 3), or EA, SB, HI(model 4) (see Figure 3). Increasing years of schooling are accompanied by increases AFB (effect of EA on AFB, β= 0.377, 95% CI, 0.344 to 0.409, P = 1.56E-114), so EA may indirectly have an impact on the risk of MA through AFB (effect of AFB on MA, β= -0.205, 95% CI, -0.263 to -0.147, P = 5.46E-12) (Supplementary Table 1).By multiplying the estimate of the effect of EA on AFS, AFB with the estimate of the effect of AFB on MA, the mediation effect of AFB in the causal pathway from EA to MA was -0.08, accounting for 57.8% of the total effect (Supplementary Table 2).

Sensitivity analysis

In UVMR analyses, in the causality of MA in relation to EA, AFS, and AFB, heterogeneity was found in the results of the Cochran Q-test. However, the results analysed by IVW MR along with the complementary methods: simple mode, weighted mode and weighted median, apart from MR–Egger, showed that EA, AFS, AFB all had statistically significant causal relationship with MA, which suggested that these associations were robust and plausible. Uncertainty existed about the causal relationship between CP and MA, as the results of this analysis were not confirmed by all complementary methods. The MR Egger intercepts indicate directional pleiotropy. In the MVMR analyses, using the primary method IVW and the complementary method Egger, the consistency of the results of both can confirm the inference of causality. In addition, there was no significant evidence for a nonzero intercept of multivariable MR Egger regression, which also supports the reliability of the results for multivariable MR analyses.

4. Discussion

4.1 Main Findings

Our findings highlighted an important possible public health benefits for women that may accrue by moderating the positive and negative aspects of medical abortion: reducing the incidence of it. Firstly, both univariate and multivariate results confirmed a robust reverse causality between MA and EA, AFS, as well as a forward causality between MA and smoking, LNSP. Secondly, the inverse relationship between HI and MA was no longer observed in the MVMR analyses after EA or AFS and LNSP after accounting for EA, or

AFS and LNSP, which may be interpreted as a stronger effect of EA or AFS and LNSP on MA than that of HI on MA. Thirdly, AFS and AFB mediated EA to reduce the risk of abortion.

4.2 Strengths and limitations

Our work has several important strengths. The MR approach can largely reduce the risk of reverse causality bias and the effect of confounders by using genetic variation as instrumental variation to analyse the potential risks of medical abortion. In addition, complementary methods and MVMR methods were used for pleiotropy and sensitivity analysis, resulting in reliable conclusions that EA, SB, LNSP, AFB, AFS were associated with MA. The causal chains of EA-AFB-MA causality were elaborated through mediated MR. EA was elaborated to impact MA more than HI by MVMR. Finally, we limited the bias due to population stratification by using only genetic variants from European populations in all datasets.

There are several limitations to our study. Firstly, the strength of the test for multivariate MR was modest, leading to the possibility of false positives, which could be explained by the insufficient sample size. Secondly, there were significant heterogeneity in the analyses addressing the exposure factors: EA, AFS, and AFB, but the conclusions were plausible because of the consistency of the results from MVMR and mediated MR. Thirdly, there is a lack of published GWAS articles on outcome-medical abortion. A bidirectional study is essential if complete GWAS statistics for medical abortion become available in the future. Finally, abortion is a worldwide issue, but we only used summary data from European populations, resulting in data deficits, and this finding should be validated in other populations in further study.

4.3 Interpretation

4.3.1 Household income and medical abortion

As the costs of childbearing and parenting increase, households with low incomes struggle to support women to continue their pregnancies. By exploring mechanisms influencing the socioeconomic conditions leading to abortion, it was found that in Russia an increase of $1,000 in per capita gross regional product (GRP) led to a reduction in the abortion rate of 0.075[18]. Socioeconomic status is a closely associated with employment status, which is an important factor leading medical abortion demonstrated by Klutsey EE, et al[19].

Based on the data that economic conditions were procyclically associated with abortion rates from approximately 2004 to 2010, with abortion rates declining by approximately 5 per cent for every percentage point increase in the unemployment rate during that period, it can be argued that economic conditions may be an important factor influencing women's reproductive choices in the United States[20]. On the contrary, in Ghana, the risk of abortion is considerably higher among wealthy women[21, 22].

It should be noted, however, that the associations observed in these conventional epidemiological studies suffered from the limitations of modest sample sizes, reverse causality, and the inability to fully alleviate confounding effects. Using MR method, our study reliably concluded that HI was negatively associated with the risk of medical abortion.

4.3.2 Educational attainment, cognitive performance and medical abortion

Previous observational studies yielded inconsistent results on the association between educational attainment and medical abortion[19, 23, 24]. Women with primary and secondary education had higher odds of terminating their pregnancies compared to women with no education, but the odds of terminating their pregnancies were not higher among women with tertiary education[24], suggesting that there may not be a linear causal relationship between education and termination of pregnancies[19, 24].

However, education was observed to reduce the risk of medical abortion in present study in UVMR analysis using the IVW method, complementary methods and in MVMR analysis. The causal relationship between education and induced abortion may be influenced by the economic level of the region, as the frequency of abortion was high among less educated women in the developed region of Norway, however, the frequency of abortion was conversely high among university educated women in the less developed region of Pakistan[25]. We found that EA was still associated with decreased risk of MA, after moderating for HI. Educational

attainment is a proxy for intelligence, and cognitive ability is often measured through intelligence as well as educational attainment. Research published by Woodley Menie MA confirmed that there was no significant linear or quadratic relationship between the number of abortions and maternal cognitive ability (as measured by educational attainment or general intelligence)[26].

4.3.3 Risky behaviors and medical abortion

Women with planned pregnancies are reluctantly choosing abortion because of concerns that smoking and alcohol consumption may have a negative impact on the outcome of the pregnancy. Compared with never-smokers, active smokers in their reproductive years had a corresponding increase in the risk of spontaneous abortion, stillbirth and ectopic pregnancy by 16%, 44% and 43%, respectively[27]. A systematic review concluded that smoking interventions significantly increased birth weight[28]. Previous MR studies have found a positive correlation between smoking initiation and increased risk of pregnancy loss, but did not support any association between moderate alcohol and pregnancy loss[29, 30]. The present study found that smoking behavior motivated women to choose medical abortion.

Alcohol is known to have a significant negative impact on human health. Alcohol exposure is associated with an increased risk of congenital problems, including Fetal Alcohol Spectrum Disorder (FASD) and its most severe form, Fetal Alcohol Syndrome (FAS), which are long-lasting and lifelong with no treatment or cure available[31]. Many pregnant women choose abortion due to accidental exposure to alcohol before and during pregnancy, but our MR analyses did not provide valid evidence for this causal link.

4.3.4 Reproductive traits and medical abortion

Previous studies have provided robust genetic evidence of risk associations between sexual intercourse at an early age[32], having more sexual partners, and a higher risk of major depressive disorder[33]. Intriguingly, studies have found that increased genetic susceptibility to schizophrenia affects increased numbers of sexual partners, suggesting that schizophrenia susceptibility increases mating success in the wider population and may reflect potential reproductive success[34, 35]. Hence, reproductive traits factors may play a non-negligible role in induced abortion. We found that AFS, AFB, LNSP were causally associated with MA, and that LNSP were associated with MA independently of EA and HI, furthermore AFB mediated in education to reduce MA.

Conclusions

Our findings provided strong genetic evidence for a reverse causation of HI, EA, AFS, and AFB with MA, as well as a positive causation of SB and LNSP with MA. AFB played a mediating role in the causal link between EA and MA. These results may provide a strong guiding value for strengthening public health services and safeguarding women's reproductive health.

Author contribution

Fengping Shao was responsible for all elements of the study, including concepts, methods, software, data interpretation, graphical manipulation, writing-original draft preparation, etc.

Acknowledgments

This research was facilitated by the prior research of the Social Science Genetic Association Consortium (SSGAC), the Sequencing Consortium of Alcohol and Nicotine use (GSCAN), the NHGRI-EBI Catalog of human genome-wide association studies and the Medical Research Council Integrative Epidemiology Unit (MRCIEU, University of Bristol, UK). We acknowledge their contributing studies and the participants in those studies. We express our gratitude for all GWAS shared summary data used in this study. We also thanks to Ma Yuanlin, M.D. and Xu Zhang of Youhe AI and Medicine.

Funding statement

Publishing fees are funded by The First Affiliated Hospital of Sun Yat-sen University.

Ethics statement

The GWAS summary statistics data used in our study are publicly available, and thus ethical committee approval is not required.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability statement

All original data used in this study are publicly available GWAS summary data. The sources of these data and the analysed data are presented in the Materials and Methods and in the Supplementary Tables. Further inquiries can be directed to the corresponding author.

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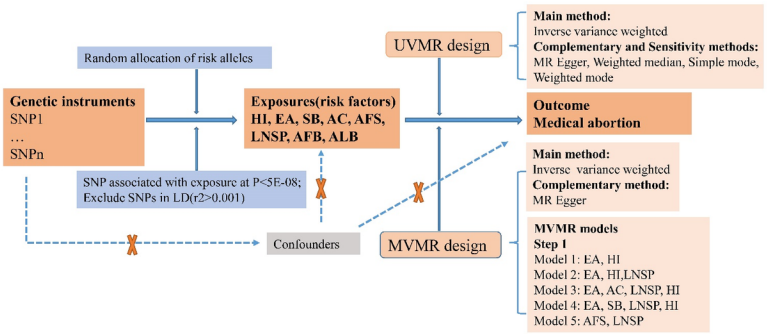


Figure 1. Schematic diagram of MR study design – potential risk factors for MA. Abbreviations: MA, medical abortion; HI, household income; EA, educational attainment; SB, smoking behaviors; AC, alcohol consumption; AFS, age at first sexual intercourse; LNSP, lifetime number of sexual partners; AFB, age at first birth; ALB, age at last birth.

Figure 2. UVMR results for associations between potential factors and MA. Abbreviations: MA, medical abortion; HI, household income; EA, educational attainment; SB, smoking behaviors; AC, alcohol consumption; AFS, age at first sexual intercourse; LNSP, lifetime number of sexual partners; AFB, age at first birth; ALB, age at last birth.

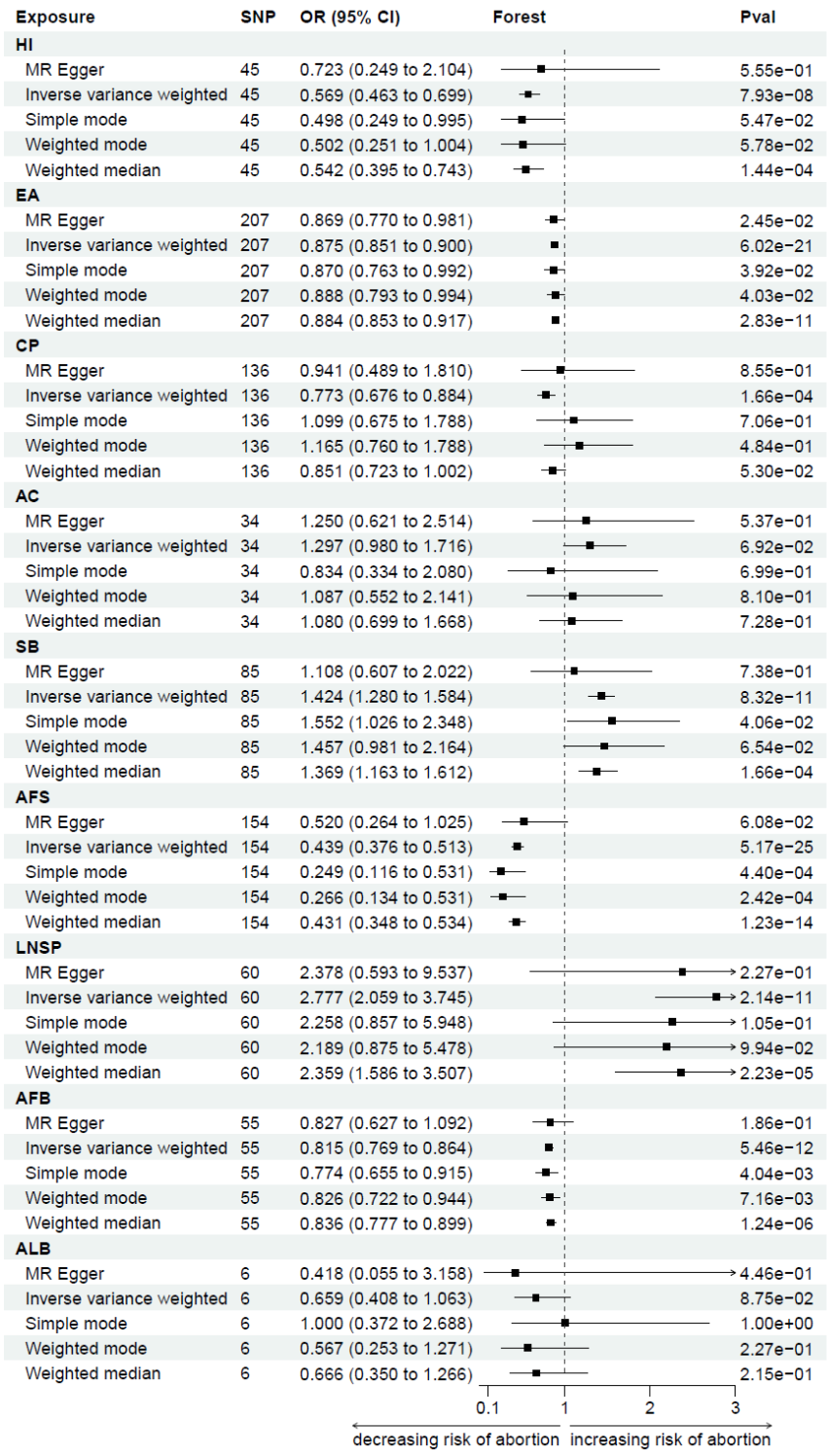
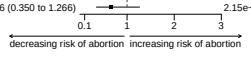


Figure 3. Results of various MVMR models with education as the primary risk factor, controlling for other factors. Abbreviations: MA, medical abortion; HI, household income; EA, educational attainment; SB, smoking behaviors; AC, alcohol consumption; AFS, age at first sexual intercourse; LNSP, lifetime number

of sexual partners; AFB, age at first birth; ALB, age at last birth.

Exposure	SNP	OR (95% CI) Ivww	Pval_ivw	OR (95% CI) Egger	Pval_egger
Model 1					
EA	198	0.886 (0.840 to 0.934)	8.44e−06	0.877 (0.783 to 0.983)	0.024
HI	23	0.896 (0.610 to 1.317)	5.78e−01	0.890 (0.599 to 1.320)	0.561
(intercept)				1.001	0.855
Model 2					
EA	188	0.900 (0.854 to 0.948)	8.58e−05	0.890 (0.816 to 0.972)	0.010
LNSP	31	2.569 (1.863 to 3.542)	8.56e−09	2.588 (1.868 to 3.586)	0.000
HI	22	0.815 (0.559 to 1.190)	2.90e−01	0.813 (0.557 to 1.189)	0.286
(intercept)				1.001	0.774
Model 3					
EA	175	0.905 (0.858 to 0.955)	2.66e−04	0.914 (0.839 to 0.996)	0.040
AC	22	1.284 (0.921 to 1.790)	1.41e−01	1.271 (0.905 to 1.786)	0.167
LNSP	29	2.449 (1.748 to 3.430)	1.90e−07	2.433 (1.732 to 3.421)	0.000
HI	23	0.775 (0.531 to 1.132)	1.88e−01	0.775 (0.530 to 1.132)	0.187
(intercept)				1.001 (NA to NA)	0.778
Model 4					
EA	171	0.917 (0.869 to 0.967)	1.53e−03	0.945 (0.875 to 1.020)	0.150
SB	47	1.220 (1.020 to 1.458)	2.92e−02	1.210 (1.012 to 1.448)	0.036
LNSP	28	1.915 (1.315 to 2.789)	7.04e−04	1.863 (1.275 to 2.724)	0.001
HI	22	0.830 (0.568 to 1.212)	3.34e−01	0.839 (0.574 to 1.228)	0.367
(intercept)				0.998	0.283
Model 5					
AFS	46	0.831 (0.785 to 0.880)	1.64e−10	0.837 (0.759 to 0.923)	0.000
LNSP	45	2.389 (1.732 to 3.295)	1.12e−07	2.385 (1.725 to 3.297)	0.000
(intercept)			NA	1.000	0.869

Exposure	SNP	OR (95% CI)	Pval
HI			
MR Egger	45	0.723 (0.249 to 2.104)	5.55e−01
Inverse variance weighted	45	0.569 (0.463 to 0.699)	7.93e−08
Simple mode	45	0.498 (0.249 to 0.995)	5.47e−02
Weighted mode	45	0.502 (0.251 to 1.004)	5.78e−02
Weighted median	45	0.542 (0.395 to 0.743)	1.44e−04
EA			
MR Egger	207	0.869 (0.770 to 0.981)	2.45e−02
Inverse variance weighted	207	0.875 (0.851 to 0.900)	6.02e−21
Simple mode	207	0.870 (0.763 to 0.992)	3.92e−02
Weighted mode	207	0.888 (0.793 to 0.994)	4.03e−02
Weighted median	207	0.884 (0.853 to 0.917)	2.83e−11
CP			
MR Egger	136	0.941 (0.489 to 1.810)	8.55e−01
Inverse variance weighted	136	0.773 (0.676 to 0.884)	1.66e−04
Simple mode	136	1.099 (0.675 to 1.788)	7.06e−01
Weighted mode	136	1.165 (0.760 to 1.788)	4.84e−01
Weighted median	136	0.851 (0.723 to 1.002)	5.30e−02
AC			
MR Egger	34	1.250 (0.621 to 2.514)	5.37e−01
Inverse variance weighted	34	1.297 (0.980 to 1.716)	6.92e−02
Simple mode	34	0.834 (0.334 to 2.080)	6.99e−01
Weighted mode	34	1.087 (0.552 to 2.141)	8.10e−01
Weighted median	34	1.080 (0.699 to 1.668)	7.28e−01
SB			
MR Egger	85	1.108 (0.607 to 2.022)	7.38e−01
Inverse variance weighted	85	1.424 (1.280 to 1.584)	8.32e−11
Simple mode	85	1.552 (1.026 to 2.348)	4.06e−02
Weighted mode	85	1.457 (0.981 to 2.164)	6.54e−02
Weighted median	85	1.369 (1.163 to 1.612)	1.66e−04
AFS			
MR Egger	154	0.520 (0.264 to 1.025)	6.08e−02
Inverse variance weighted	154	0.439 (0.376 to 0.513)	5.17e−25
Simple mode	154	0.249 (0.116 to 0.531)	4.40e−04
Weighted mode	154	0.266 (0.134 to 0.531)	2.42e−04
Weighted median	154	0.431 (0.348 to 0.534)	1.23e−14
LNSP			
MR Egger	60	2.378 (0.593 to 9.537)	2.27e−01
Inverse variance weighted	60	2.777 (2.059 to 3.745)	2.14e−11
Simple mode	60	2.258 (0.857 to 5.948)	1.05e−01
Weighted mode	60	2.189 (0.875 to 5.478)	9.94e−02
Weighted median	60	2.359 (1.586 to 3.507)	2.23e−05
AFB			
MR Egger	55	0.827 (0.627 to 1.092)	1.86e−01
Inverse variance weighted	55	0.815 (0.769 to 0.864)	5.46e−12
Simple mode	55	0.774 (0.655 to 0.915)	4.04e−03
Weighted mode	55	0.826 (0.722 to 0.944)	7.16e−03
Weighted median	55	0.836 (0.777 to 0.899)	1.24e−06
ALB			
MR Egger	6	0.418 (0.055 to 3.158)	4.46e−01
Inverse variance weighted	6	0.659 (0.408 to 1.063)	8.75e−02
Simple mode	6	1.000 (0.372 to 2.688)	1.00e+00
Weighted mode	6	0.567 (0.253 to 1.271)	2.27e−01
Weighted median	6	0.666 (0.350 to 1.266)	2.15e−01



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(intercept)					0.998		0.283
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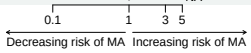
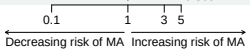
LNSP	45	2.389 (1.732 to 3.295)		1.12e−07	2.385 (1.725 to 3.297)		0.000
(intercept)				NA	1.000		0.869





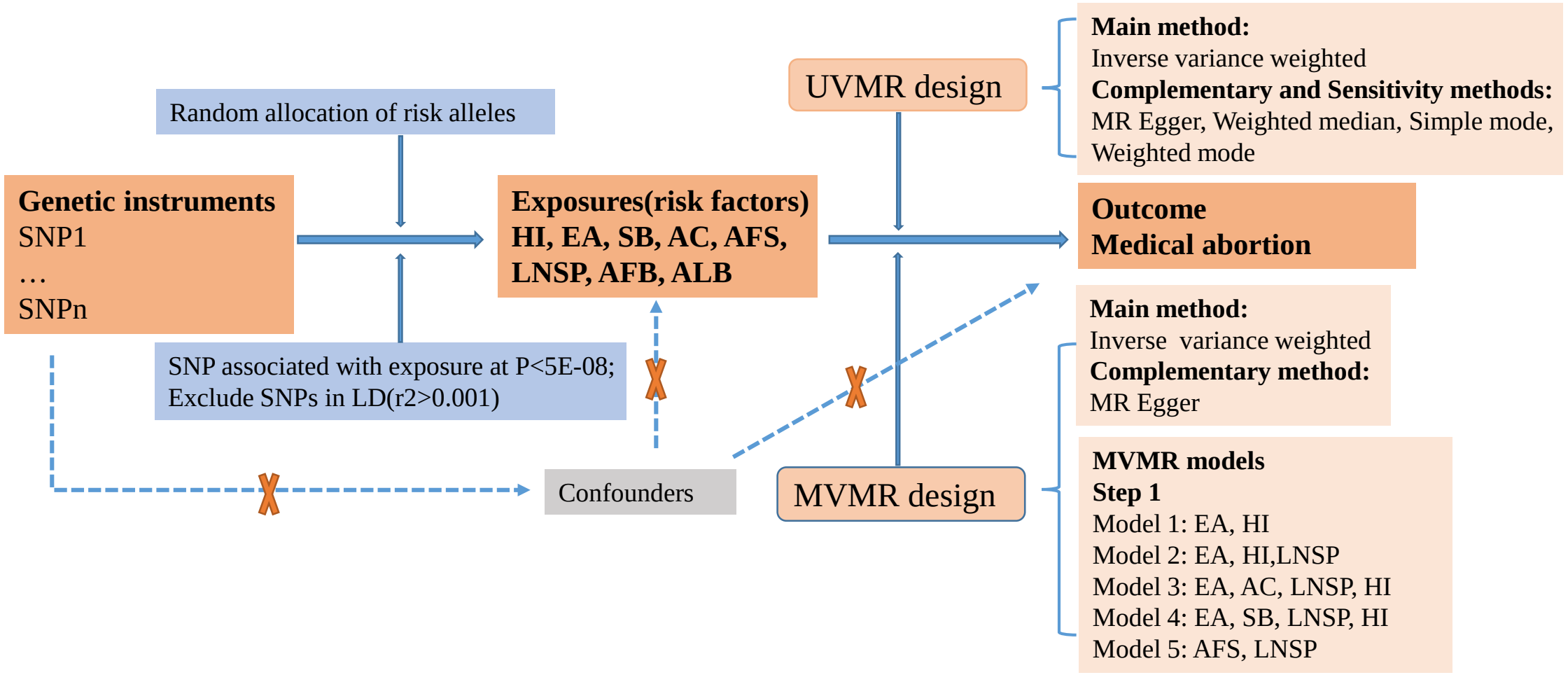

Random allocation of risk alleles
Genetic instruments
SNP1
…
SNPn
Exposures(risk factors)
HI, EA, SB, AC, AFS,
LNSP, AFB, ALB
UVMR design
Main method:
Inverse variance weighted
Complementary and Sensitivity methods:
MR Egger, Weighted median, Simple mode,
Weighted mode
Outcome
Medical abortion
SNP associated with exposure at P<5E-08;
Exclude SNPs in LD(r2>0.001)
Confounders
MVMR design
Main method:
Inverse variance weighted
Complementary method:
MR Egger
MVMR models
Step 1
Model 1: EA, HI
Model 2: EA, HI,LNSP
Model 3: EA, AC, LNSP, HI
Model 4: EA, SB, LNSP, HI
Model 5: AFS, LNSP

Figure 1 The basic assumptions of Mendelian randomization and the main design of this study. Abbreviations: HI, household income; LNSP, lifetime number of sexual partners; AFS, age at first sexual intercourse; AFB, age at first birth; ALB, age at last birth; EA, educational attainment; CP, cognitive performance; UVMR, univariable Mendelian randomization; MVMR, multivariable Mendelian randomization