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Bidirectional mendelian randomization analysis of fat/oil used in cooking and multiple types of abortions in women

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Abstract: Background: The relationship between 31 types of fat/oil used in cooking and various forms of abortion (habitual aborter, medical abortion, pregnancy with abortive outcome, spontaneous abortion, unspecified abortion, and other abortion) in women is unclear. This study aims to investigate this relationship using bidirectional Mendelian randomization (MR) analysis. Methods: Significant SNPs associated with types of fat/oil used in cooking ($P < 5e-8$) were extracted as instrumental variables (IVs) after clumping. Five MR methods, including inverse variance weighted (IVW), were employed to assess the relationship, with IVW, MR-Egger, and leave-one-out analyses used for sensitivity analysis. Associations with FDR-corrected $P < 0.05$ were considered statistically significant. For statistically significant associations, reverse MR was performed to assess potential reverse causality, extracting SNPs associated with abortion outcomes ($P < 5e-6$) as IVs. Results: After FDR correction, low-fat olive spread showed evidence of a potential association with spontaneous abortion (OR [95% CI] = 771.35 [16.50, 36068.62], $P = 7.00E-04$). Additionally, cholesterol-lowering olive spread showed evidence of a potential association with pregnancy with abortive outcome (OR [95% CI] = 4.01 [1.68, 9.58], $P = 1.70E-03$). Sensitivity analyses did not detect evidence of pleiotropy or heterogeneity. Reverse MR analyses did not support reverse causality. Conclusion: This bidirectional MR analysis suggests that selected cooking fat/oil choices, particularly low-fat olive spread and cholesterol-lowering olive spread, may be associated with spontaneous abortion and pregnancy with abortive outcome, respectively. Given the exploratory design and wide confidence intervals, especially for low-fat olive spread, these findings should be interpreted cautiously and considered hypothesis-generating until validated in larger independent studies.

Keywords: Mendelian randomization; dietary fats; cooking oils; spontaneous abortion; pregnancy with abortive outcome; sensitivity analysis; reverse causality

1. Introduction

Abortions, encompassing a wide spectrum of medical and spontaneous terminations of pregnancy, represent a significant public health concern globally [1]. The burden of abortions, both induced and spontaneous, has profound implications for women's health, with considerable social, psychological, and economic impacts[2].

Miscarriage is regarded as the most common and severe complication of early pregnancy. Some researchers reported the incidence of miscarriage among the clinical pregnancies is about 17-22% ,and 20–40% of all losses may occur before clinical detection[3][4].

Common complications of spontaneous abortion include blood loss, infection, symptomatic complaints such as bleeding and pain[5]. It also have adverse effects on women's subsequent pregnancy, such as neurological deficits, recurrent spontaneous

abortion, or perinatal death [6][7]. spontaneous abortion is mainly related to genetic factors and population factors. More than 50% of spontaneous abortions are related to chromosomal abnormality of the embryo[8].

in addition, acquired and environmental factors are also crucial, among which, there are many aspects that we could improve[9].

Annually, an estimated 56 million induced abortions occur worldwide, with varying rates and consequences across different regions and populations[10]. This global phenomenon is influenced by a myriad of factors including access to healthcare, socioeconomic status, legal frameworks, cultural beliefs, and individual health conditions. Induced abortions, often performed to the treatment for Embryonic Arrest, or to Terminate unintended pregnancies , are a critical aspect of reproductive health services.

Abortion is a sudden and stressful event. Women experiencing abortions, whether induced or spontaneous, they inevitably have to face the physiological, psychological and societal changes caused by the loss of the fetus, resulting in somatic symptoms and sleep disorders, and may further lead to moderate to high risk of psychological problems such as depression and anxiety[11]. Additionally, the economic burden is significant, with costs associated with medical care, loss of productivity, and long-term health consequences. The above factors will affect the quality of life of patients to varying degrees[12].

With the improvement of economic level, pregnant women's health care consciousness is constantly enhanced. More and more women are starting to think about whether they can avoid or reduce their exposure to factors harmful to embryonic development.

The types of fat and oil used in cooking may play a significant role in influencing reproductive health outcomes, including the risk of abortion[13]. Recent evidence suggests that dietary fats and oils might influence reproductive processes through mechanisms such as inflammation, hormone regulation, and cellular function[14] [15]. Fats and oils are essential nutrients that serve as major sources of energy and play pivotal roles in the absorption of fat-soluble vitamins, cellular membrane composition, and signaling pathways[16][17]. They can be broadly categorized into saturated fats, monounsaturated fats, polyunsaturated fats, and trans fats, each having distinct biochemical properties and physiological effects. The type of fat or oil consumed can influence systemic inflammation, oxidative stress, and lipid profiles, all of which are factors known to affect reproductive health[18]. For instance, olive oil, particularly rich in monounsaturated fats and antioxidants, has been associated with reduced inflammation and improved cardiovascular health, which could potentially translate into better reproductive outcomes. Conversely, high intake of trans fats and certain saturated fats has been linked to adverse health effects, including increased inflammation and oxidative stress, which might negatively impact reproductive health[19].

Epidemiological studies have suggested that dietary patterns and specific nutrient intakes are associated with reproductive outcomes[20]. However, the specific impact of different types of cooking fats and oils on the risk of abortion remains underexplored. The biological plausibility for such associations stems from the roles of dietary fats in modulating systemic inflammation and hormonal balance, which are crucial for maintaining pregnancy[21]. For example, polyunsaturated fatty acids (PUFAs) are precursors to eicosanoids, which are potent mediators of inflammation and immune responses. An imbalance in the intake of omega-3 and omega-6 PUFAs

can lead to a pro-inflammatory state, potentially compromising reproductive health and increasing the risk of adverse pregnancy outcomes such as spontaneous abortion.

Moreover, certain fats and oils may influence the risk of abortion through their effects on metabolic health. Insulin resistance and dyslipidemia, conditions often exacerbated by unhealthy dietary fat consumption, have been associated with an increased risk of pregnancy complications. For instance, a diet high in trans fats and low in essential fatty acids can lead to metabolic disturbances, which might impair placental function and fetal development, thereby increasing the likelihood of abortion. On the other hand, diets rich in monounsaturated fats and omega-3 fatty acids have been shown to improve metabolic health and reduce the risk of pregnancy complications.

In addition to the direct biological effects of dietary fats and oils, there may be indirect influences on reproductive health through changes in body weight and adiposity. Obesity and excessive weight gain during pregnancy are well-known risk factors for adverse pregnancy outcomes, including abortion[22]. The type of fat consumed can significantly impact weight management, with diets high in unhealthy fats promoting weight gain and central adiposity, whereas diets rich in healthy fats, such as those found in olive oil and other sources of monounsaturated and polyunsaturated fats, are associated with better weight control and metabolic health.

Given the potential implications of dietary fat and oil consumption for reproductive health, it is important to investigate these associations using robust epidemiological methods. Mendelian randomization (MR) can help evaluate potential exposure-outcome relationships under specific assumptions by leveraging genetic variants as instrumental variables. Based on the information above, we hypothesized that dietary habits are linked to multiple types of abortion. To evaluate these potential associations, we conducted a two-sample bidirectional MR analysis. MR leverages two fundamental principles of genetics: (1) the law of segregation, which states that genetic variants are randomly inherited, with one allele coming from each parent, and (2) the law of independent assortment, which posits that alleles are passed to offspring independently of each other. Consequently, MR can reduce, although not eliminate, confounding from environmental factors and reverse causation. In this study, we explored the relationship between different types of cooking fats and oils and the risk of various forms of abortion in women using bidirectional MR analysis. By examining genetic variants associated with the consumption of specific fats and oils, we sought to identify dietary factors that may be related to abortion risk. Our findings may offer preliminary insights into the role of dietary fats in reproductive health and inform future validation studies.

2. Materials and methods

2.1. Data source

All GWAS summary data used in this study were derived from female participants to ensure the accuracy of the analysis. The GWAS data for 31 types of fat/oil used in cooking, including cooking fat unknown, olive oil, sunflower oil, vegetable oil, rapeseed oil, other oil, butter, spreadable butter, low fat butter, normal fat butter, unknown fat butter, lard, olive spread, low fat olive spread for, normal fat olive spread, cholesterol lowering olive spread, polyunsaturated margarine, very low fat polyunsaturated margarine, low fat polyunsaturated margarine, normal fat polyunsaturated margarine, cholesterol lowering polyunsaturated margarine, dairy spread, low fat dairy spread, normal fat dairy spread, soya margarine, low fat soya

margarine, unknown/other soft margarine, normal fat soft margarine, unknown soft margarine, hard margarine, other type fat, were obtained from the results of GWAS round 2 from Neale Lab. Detailed information, such as recruitment criteria of population and quality control of genetic data, can be found in the <http://www.nealelab.is/uk-biobank>. The imputed genotypes were from the HRC plus UK10K & 1000 Genomes reference panels as released by UK Biobank in March 2018. The UK Biobank is a large-scale biomedical database and research resource containing in-depth genetic and health information from half a million UK participants, designed to improve the prevention, diagnosis, and treatment of a wide range of serious and life-threatening illnesses. The details of the types of fat/oil used in cooking dataset can be found in **Supplementary Table 1**.

The GWAS summary data for various types of abortions (habitual aborter, medical abortion, pregnancy with abortive outcome, spontaneous abortion, unspecified abortion, and other abortion) were obtained from FinnGen (<https://www.finnngen.fi/>). FinnGen is a large public-private partnership aiming to collect and analyze genome and health data from 500,000 Finnish biobank participants. FinnGen aims to provide novel medically and therapeutically relevant insights and construct a world-class resource that can be applied for future studies, detailed information, such as recruitment criteria of population and quality control of genetic data, can be found in the original paper[23]. The details of the various types of abortion dataset can be found in **Supplementary Table 2**.

These GWAS sample populations needed to be predominantly of European descent and largely independent of each other. The list of covariates varies between original GWASs, but always included sex and age. Details can be found in the original studies. The data analyzed in this secondary study is publicly available from existing, published GWASs and therefore the ethical approval and informed consent have been obtained by all original studies. This is a secondary analysis based on summary statistics from existing, published studies. The ethical approval and informed consent have been obtained by all original studies.

2.2. Genetic instrumental variables (IVs) selection

The selection of instrumental variables (IVs) is crucial for ensuring the accuracy and robustness of causal inferences in Mendelian randomization (MR) analysis. IVs must satisfy three key assumptions: (1) the genetic variants must be associated with the exposures; (2) the genetic variants must not be related to confounders; and (3) the genetic variants should influence the outcomes only through the exposures, without affecting other pathways. This study adhered to specific criteria for selecting instrumental variables (IVs). Firstly, each SNP had to demonstrate a significant association with the 31 types of fat/oil used in cooking, surpassing the genome-wide significance threshold of $P < 5E-8$. Secondly, linkage disequilibrium (LD) was assessed using European sample data from the 1000 Genomes Project reference panel, retaining only the most significant SNPs among those with an $R^2 < 0.001$ within a clumping window of 10,000 kb. Thirdly, SNPs with a minor allele frequency (MAF) of ≤ 0.01 were excluded to mitigate potential bias from genetic pleiotropy. The final set of SNPs meeting these criteria was employed as instrumental variables in the TSMR analysis.

2.3. Two-sample Mendelian randomization analysis

Our study utilized MR to investigate potential associations between 31 types of fat/oil used in cooking and various types of abortion in women. The analytical

approach required comprehensive datasets for both exposures and outcomes, including SNP rsids, effect sizes (beta coefficients), alleles (effect and other), standard errors (SEs), effect allele frequencies (EAFs), and P-values. To avoid ambiguities caused by palindromic SNPs (SNPs with the same alleles on both DNA strands), we excluded such SNPs from the analysis. Five analytical methods were employed: MR Egger, weighted median, inverse variance weighted (IVW), simple mode, and weighted mode. After applying false discovery rate (FDR) correction, associations with an FDR-corrected P-value < 0.05 were considered statistically significant. For these significant dietary habits, we conducted reverse MR to explore potential reverse associations between abortion outcomes and types of fat/oil used in cooking, using SNPs associated with abortion outcomes ($P < 5E-6$) as IVs and following the same methods as the primary analysis. The list of covariates varies between original GWASs, but always included sex and age. Details can be found in the original studies. MR analyses were performed using the “TwoSampleMR” package (version 0.5.10) in R (version 4.3.3).

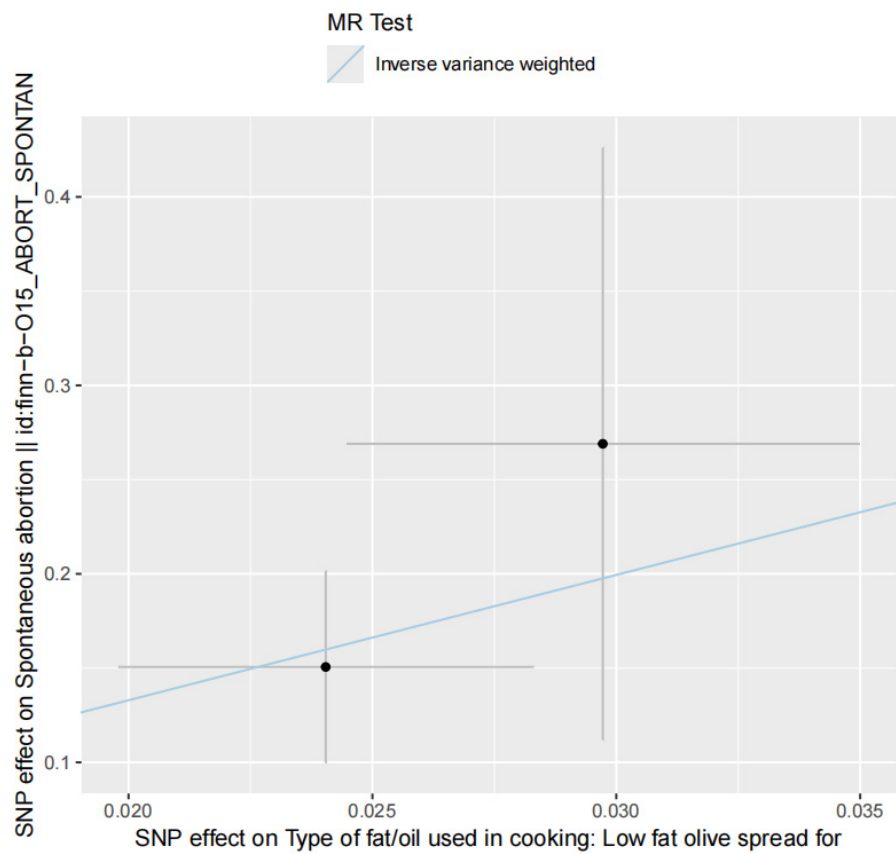
2.4. Sensitivity analysis

Heterogeneity in this study refers to the variability in causal estimates across the different genetic variants used as instrumental variables (IVs), which can indicate potential inconsistencies in causal effects. We assessed heterogeneity using the MR Egger and Inverse Variance Weighted (IVW) methods, considering types of fat/oil used in cooking with a $Q_pval < 0.05$ as indicative of heterogeneity. Pleiotropy, where a genetic variant influences multiple phenotypic traits and may confound causal estimates, was evaluated using the MR Egger method. Types of fat/oil used in cooking with a p-value < 0.05 were considered to suggest pleiotropy. To evaluate the robustness and potential impact of individual variants, we employed the leave-one-out method, which involves iteratively removing one genetic variant at a time to assess its influence on the overall causal estimate. Visual representations of the MR analysis results were provided through scatter plots, forest plots, and leave-one-out plots.

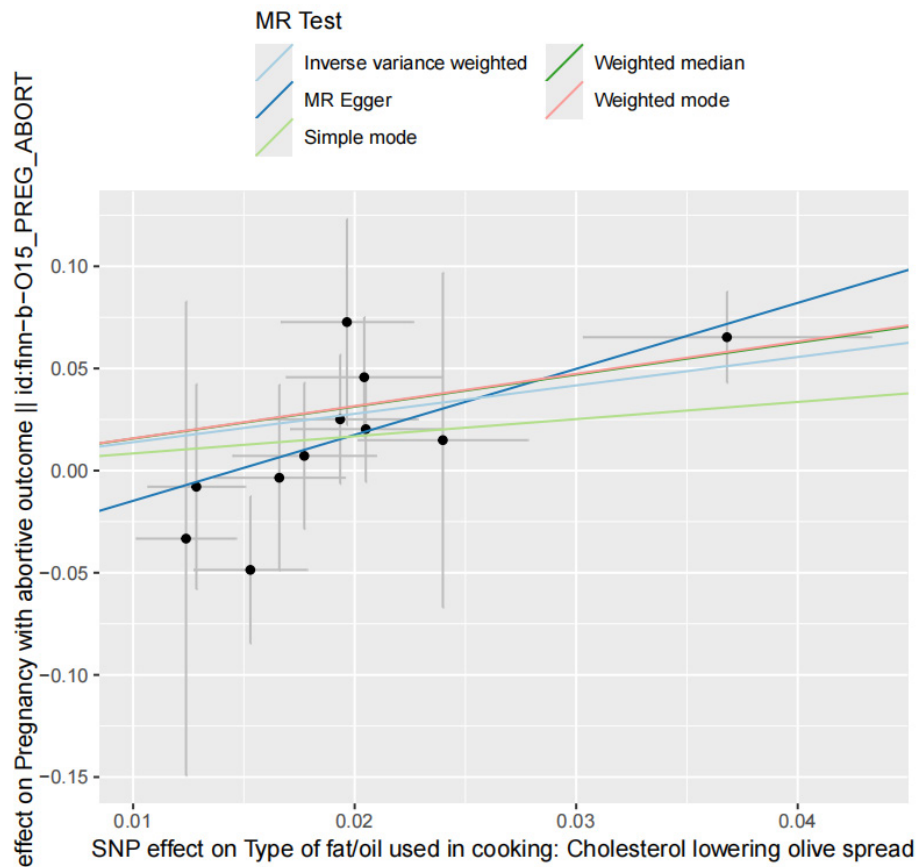
3. Results

According to our IV selection strategy described previously, this study extracted a total of 148 SNPs as instrumental variables (IVs) for 20 types of fat/oil used in cooking, with the number of IVs per exposure ranging from 1 to 24. Subsequently, these SNPs and their proxies were extracted from datasets for the six types of abortion. The details of all IVs in the exposure and outcome datasets, including SNP rsids, effect sizes (beta coefficients), alleles (effect and other), standard errors (SEs), effect allele frequencies (EAFs), P-values, total outcome sample sizes, and the corresponding numbers of cases and controls for each abortion outcome, can be found in **Supplementary Table 3**.

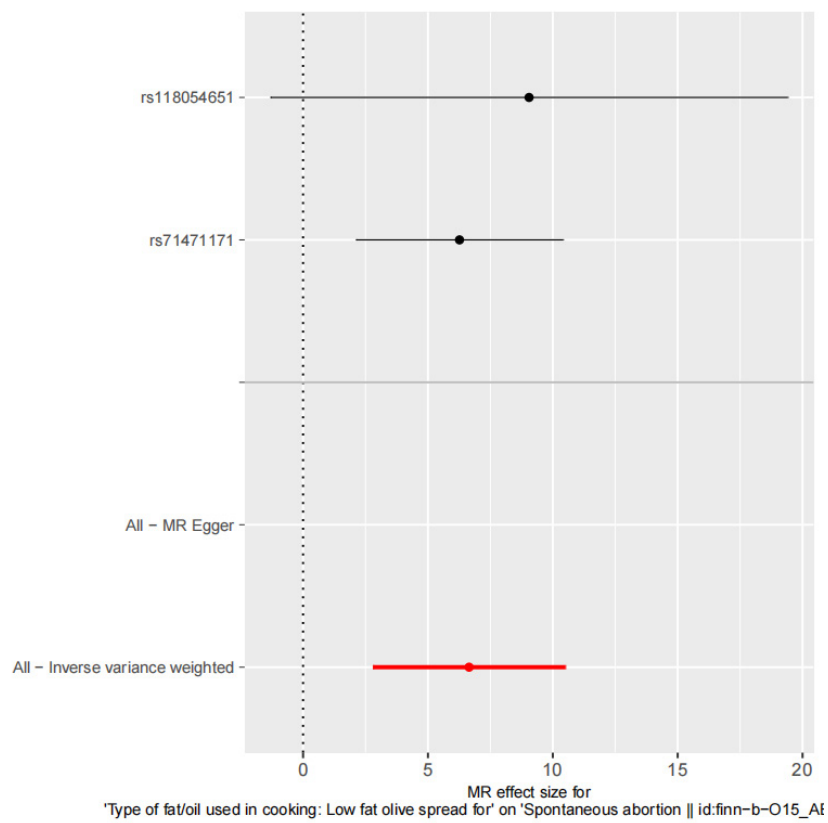
The MR analysis identified five nominal positive associations before FDR correction. After FDR correction, as shown in **Figure 1**, low-fat olive spread showed evidence of a potential association with spontaneous abortion (OR [95% CI] = 771.35 [16.50, 36068.62], $P = 7.00E-04$). Additionally, cholesterol-lowering olive spread showed evidence of a potential association with pregnancy with abortive outcome (OR [95% CI] = 4.01 [1.68, 9.58], $P = 1.70E-03$). All MR results, including those from the five MR methods, can be found in **Supplementary Table 4**. In the sensitivity analyses, no evidence of heterogeneity or directional pleiotropy was detected for these results (**Supplementary Tables 5 and 6**). As shown in **Figure 2**, the leave-one-out analysis indicated that the results were not driven by any single SNP.



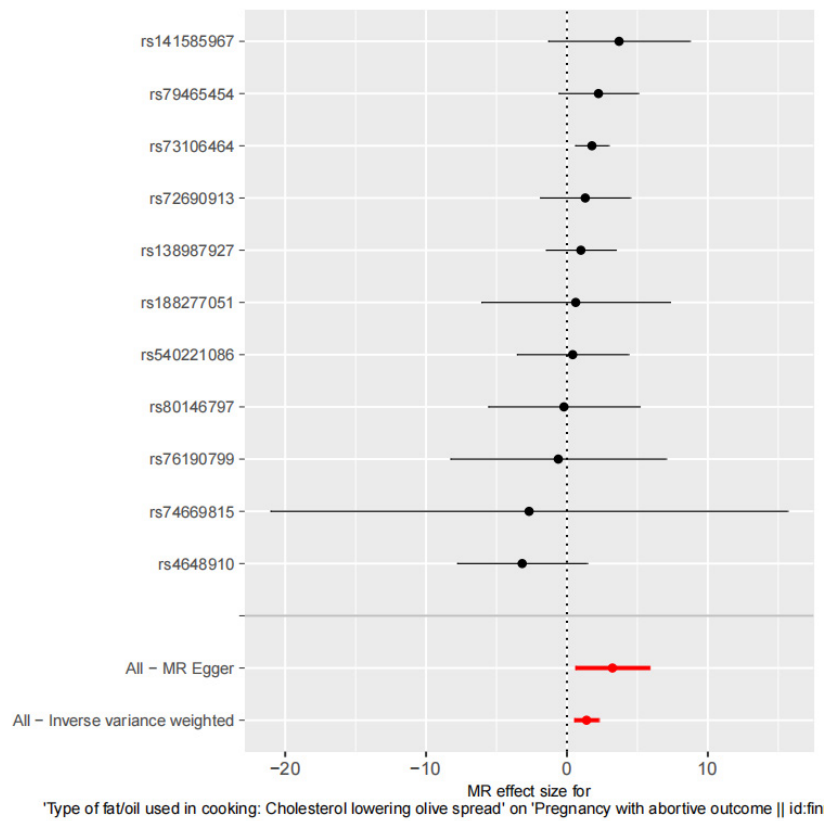
(a)



(c)

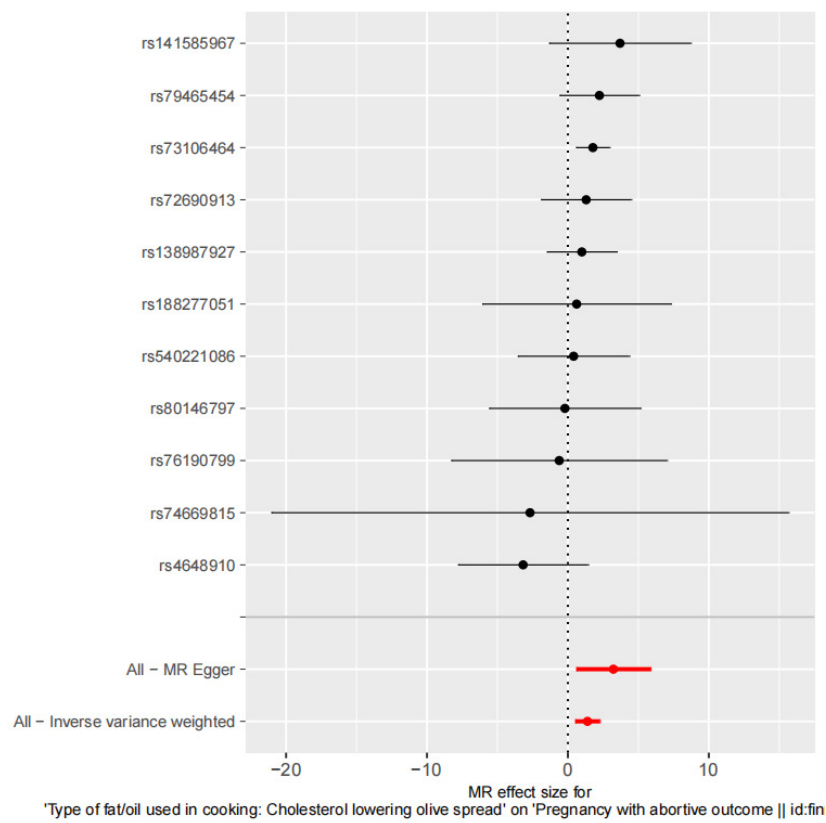


(b)

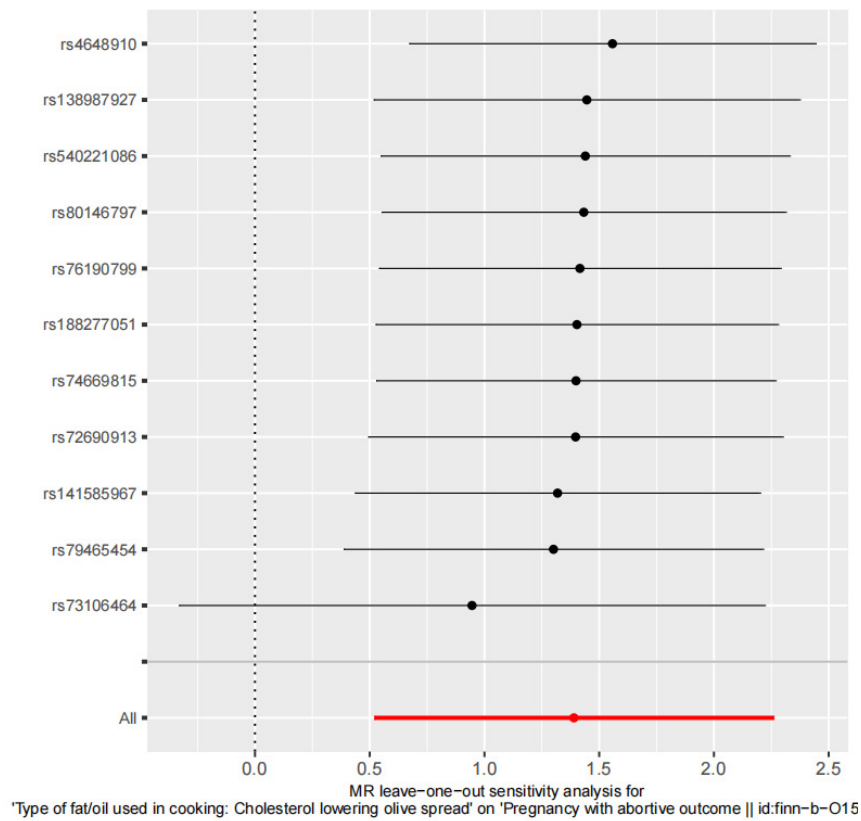


(d)

Figure 1. The scatter plots and the forest plots for the MR result of low-fat olive spread with spontaneous abortion (a and c), and cholesterol-lowering olive spread with pregnancy with abortive outcome (b and d).



(a)



(b)

Figure 2. The leave-one-out plots for the MR result of low-fat olive spread with spontaneous abortion (a), and cholesterol-lowering olive spread with pregnancy with abortive outcome (b).

For reverse MR, a total of 15 IVs were extracted for spontaneous abortion in the analysis of low-fat olive spread, and 19 IVs were extracted for pregnancy with abortive outcome in the analysis of cholesterol-lowering olive spread. The IVW estimates did not support reverse associations: spontaneous abortion to low-fat olive spread (beta = 0.030, OR [95% CI] = 1.03 [0.93, 1.14], P = 0.572) and pregnancy with abortive outcome to cholesterol-lowering olive spread (beta = -0.103, OR [95% CI] = 0.90 [0.79, 1.03], P = 0.120). Results from the other MR methods were also not statistically significant (**Supplementary Table 7**).

4. Discussion

In this study, we conducted a bidirectional Mendelian randomization analysis to investigate potential associations between 31 types of fat/oil used in cooking and multiple types of abortion in women. Using significant single nucleotide polymorphisms associated with types of fat/oil used in cooking as instrumental variables, we observed evidence suggesting that low-fat olive spread may be associated with spontaneous abortion (OR [95% CI] = 771.35 [16.50, 36068.62], P = 7.00E-04), and that cholesterol-lowering olive spread may be associated with pregnancy with abortive outcome (OR [95% CI] = 4.01 [1.68, 9.58], P = 1.70E-03). Sensitivity analyses, including IVW heterogeneity tests, MR-Egger intercept tests, and leave-one-out analyses, did not detect evidence of heterogeneity, directional pleiotropy, or single-SNP dominance. Furthermore, reverse MR analysis did not support reverse causality. These results highlight the need for further research to validate these associations and understand the underlying biological mechanisms.

The observed association between low-fat olive spread and spontaneous abortion may have several possible explanations, but it should be viewed as preliminary. Low-fat olive spreads may contain additives and stabilizers used to mimic the texture and flavor of full-fat spreads, and these components could theoretically influence inflammatory or hormonal pathways relevant to pregnancy maintenance[23]. The process of reducing fat content may also alter the availability of essential fatty acids and fat-soluble vitamins, which are important for fetal development and placental function[24]. In addition, genetic liability to using low-fat olive spread may capture broader dietary or lifestyle patterns rather than the biological effect of a single cooking fat/oil product. Therefore, the observed association could reflect product composition, dietary pattern, residual pleiotropy, or chance, and should not be interpreted as direct evidence that low-fat olive spread itself causes spontaneous abortion.

It is important to note that the association between low-fat olive spread and spontaneous abortion showed an unusually large effect size (OR = 771.35, 95% CI: 16.50-36068.62) and was based on only two genetic instrumental variables. Such a magnitude of effect is highly uncommon in dietary exposure studies and may reflect limited instrument strength, residual pleiotropy, sparse outcome information, or a chance finding. Therefore, this result should be interpreted with extreme caution; it should not be construed as a clinically predictive risk marker, but rather as preliminary hypothesis-generating evidence that requires independent validation in larger, well-powered studies.

The observed association between cholesterol-lowering olive spread and pregnancy with abortive outcome (OR [95% CI] = 4.01 [1.68, 9.58], P = 1.70E-03) raises the possibility that dietary modifications aimed at reducing cholesterol may be relevant to reproductive health. Cholesterol-lowering spreads often contain plant

sterols or stanols, which reduce serum cholesterol levels by inhibiting intestinal cholesterol absorption[25]. Although this mechanism is beneficial for cardiovascular health, cholesterol is also a precursor for steroid hormones, including progesterone and estrogen, which are important for maintaining pregnancy[12]. Therefore, altered cholesterol availability or related dietary patterns could plausibly influence reproductive outcomes. However, the present MR findings cannot establish the exact biological pathway, and the potential roles of product formulation, additives, emulsifiers, and broader dietary patterns require further investigation[26][27].

Beyond biological plausibility, these findings may have psychosocial relevance for the readership of *Psycho-Oncologie*. Abortion, whether spontaneous or induced, can be accompanied by anxiety, depressive symptoms, grief, sleep disturbance, and broader quality-of-life impairment[6][11]. If modifiable dietary factors are confirmed to contribute to abortion-related outcomes, evidence-based nutritional counseling could become one component of interdisciplinary care for women at risk of or recovering from abortion. Such counseling should be framed carefully, avoiding blame or deterministic claims, while potentially helping to reduce pregnancy-related anxiety, improve self-efficacy, and support perinatal psychological care.

Several limitations must be acknowledged. Firstly, the use of summary-level data from genome-wide association studies limits our ability to explore individual-level information, such as lifestyle factors, detailed dietary intake, pregnancy history, and clinical characteristics, which could potentially confound the observed associations. While bidirectional MR helps mitigate confounding and reverse causality, residual bias from unmeasured variables cannot be entirely ruled out. Secondly, the genetic instruments used in this study may not capture the full spectrum of genetic variation influencing dietary habits and abortion outcomes. The exclusion of SNPs with minor allele frequencies of ≤ 0.01 might also have led to the omission of potentially relevant genetic variants. Furthermore, although we applied stringent criteria for SNP selection and conducted sensitivity analyses, the possibility of horizontal pleiotropy remains a concern. MR-Egger and other sensitivity analyses did not indicate clear evidence of pleiotropy, but these methods have limited power when the number of instruments is small. Thirdly, the generalizability of our findings is constrained by the study populations. The GWAS data for dietary habits were derived from the UK Biobank, predominantly representing individuals of European descent, while the abortion data were obtained from FinnGen, which also has primarily European ancestry. This homogeneity limits the applicability of our results to other ethnic and demographic groups. Future studies should include more diverse populations to validate and extend our findings. Another limitation is that the available GWAS data capture dietary habits and abortion outcomes at the population level rather than through repeated longitudinal dietary assessments and detailed reproductive histories. Therefore, prospective cohort studies and independent MR analyses with larger datasets are needed to evaluate whether these associations are reproducible and clinically meaningful. Lastly, the scope of dietary habits examined in this study was broad but not exhaustive. We focused on 31 types of fat/oil used in cooking, yet other potentially influential dietary factors, such as overall dietary patterns, micronutrient intake, and specific food components, were not investigated. Future research should consider a more comprehensive assessment of diet, including interactions between different dietary components and their cumulative effects on reproductive health. In summary, while our study provides novel insights into the potential role of specific cooking fats/oils, particularly low-fat olive spread and cholesterol-lowering olive

spread, in abortion-related outcomes, these findings should be interpreted with caution due to the aforementioned limitations. Further research, particularly longitudinal studies and independent MR analyses in diverse populations, is essential to validate our results and uncover the underlying biological mechanisms. Understanding these mechanisms could inform future dietary recommendations and interventions aimed at improving reproductive and psychosocial health outcomes.

Supplementary materials: Supplementary Tables S1-S7 are provided in the supplementary file. Figure legends and figures are provided separately.

Author contributions: Conceptualization, HL and ML; methodology, HL, ML and XZ; software, HL and RW; validation, ZS, XZ and RW; formal analysis, HL and XZ; investigation, HL and XZ; resources, HL and ZS; data curation, RW and ZS; writing—original draft preparation, HL, and XZ; writing—review and editing, ZS; visualization, RW; supervision, ML; project administration, ZS and XZ; funding acquisition, HL. All authors have read and agreed to the published version of the manuscript.

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Ethical approval: This is a secondary analysis based on summary statistics from existing, published GWASs; ethical approval and informed consent were obtained by the original studies.

Informed consent statement: Informed consent was obtained by the original studies included in the publicly available GWAS summary data.

Data availability statement: The GWAS summary data used in this study were obtained from the Neale Lab UK Biobank GWAS and FinnGen; dataset details are provided in Supplementary Tables S1 and S2.

Conflict of interest: The authors declare that they have no conflict of interest.

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