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Do Tobacco and Alcohol Use Reduce the Risk of Ectopic Pregnancy?

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1. Abstract

1.1. Background: Ectopic pregnancy (EP) is maternal death's most common cause in the first trimester.

1.2. Objective: To explore the effect of life factor intervention on ectopic pregnancy by Meta-analysis.

1.3. Methods: Our search of PubMed and SCIE databases included all case-control studies on the effects of smoking and alcohol consumption on PID, infertility and abortions in women with ectopic pregnancy. The effects of caffeinated drinks on infertility and time to conception were also studied. After screening the literature, evaluating the risk of the included data's bias, and extracting the data, the meta-analysis of the case-control studies was conducted using RevMan5.4.1 software.

1.4. Results: The meta-analysis consisted of 106 studies. 64 of these were meta-analyses of case-control studies, while 42 were meta-analyses of single-group studies. Among them, in a meta-analysis of case-control studies, it was found that infertility (OR=2.92 [2.44,3.49]), abortion (OR=1.37 [1.13,1.65]), pelvic inflammatory disease (OR=1.39 [1.23,1.57]), smoking (OR=1.45 [1.17,1.81]) and drinking alcohol (OR=2.13 [1.15,3.92]) may increase EP's risk. Smoking may also increase the risk of PID (OR=2.01 [1.62, 2.50]), abortion (OR=1.32[1.12,1.55]) and infertility (OR=0.97 [0.90, 1.05]), we speculate that smoking may directly affect the incidence of EP. It may also indirectly affect the incidence of EP by affecting the occurrence of PID, abortion and infertility. In addition, alcohol consumption may increase PID's risk (OR=1.57 [1.09,2.27]), abortion (OR=1.15 [1.11,1.19]) and infertility (OR=1.09 [0.67,1.76]), and we suspect that alcohol consumption may also affect the incidence of EP. Among them, the results of single group rate meta-analysis showed that smoking may also increase the risk of PID (OR=0.76 [0.22,2.65]), abortion (OR=0.42[1.12,1.48]). And drinking may also increase the risk of abortion (OR=2.89 [0.50,16.68]). Caffeine in high doses may increase the risk of infertility (OR=1.32 [0.88,1.98]) and may also prolong the time to conception (OR=1.32 [0.69,2.50]).

1.5. Conclusion: Smoking and drinking are likely to be the risk factors for EP. Caffeine may indirectly affect the occurrence of EP by affecting fertility.

2. Introduction

Life factors are inevitably related to many common diseases. The most common habits are smoking and drinking. Globally, lung cancer is the most common cancer. Researches have demonstrated that smoking and drinking can raise lung cancer's risk greatly, while drinking cessation and smoking can reduce lung cancer's risk greatly. Ectopic pregnancy's incidence is building up year by year worldwide. Ectopic pregnancy (EP), also recognized as extrauterine pregnancy or eccysis, is connected with an implantation of a underdeveloped blastocyst outside endometrial cavity of the uterus[1].In 2-3% of all pregnancies, it is a significant cause of occasional mortality and maternal morbidity [2].There were 90%

of ectopic pregnancies in the tubal region, and ovarian, abdominal, cervical, and broad ligament pregnancies were 10% of the cases [3]. In addition, cesarean scar pregnancy's incidence is also rising. An ectopic pregnancy can be caused by a variety of factors, including pelvic inflammatory disease, infertility, abdominal surgery, pelvic surgery, intrauterine devices, oral contraceptives, and history of ectopic pregnancy. In clinical practice, the occurrence of EP is often the result of the comprehensive influence of multiple factors. However, in daily life, as pregnant women, ectopic pregnancy's incidence can be reduced by life factors' intervention. Many studies have shown that there is a strong correlation between life factors such as smoking and drinking and a variety of diseases, but there are few studies on the correlation between life factors and EP. And the majority of EP risk factors are uterine diseases, such as PID, abortion and infertility. Mainly from the three lifestyle factors of smoking, drinking and caffeine, this study searched and analyzed the literature on lifestyle factors and EP in recent years, as well as the literature data of life factors and high-risk diseases causing EP. To explore whether there is a certain correlation between life factors and EP and whether the incidence of EP can be reduced by the intervention of adverse life factors. RevMan5.4.1 software to systematically evaluate the effects of smoking, drinking, caffeine, PID, infertility, and abortion on EP and caffeine on infertility.

3. Data and Methods

1.1. **Search strategy**

Pubmed and SCIE databases were searched for researches from March 2003 to March 2023 or all literature since the establishment of the database. Besides, the included studies' references were searched to supplement relevant literatures. The retrieval word "ectopic pregnancy (Mesh)", "risk factors", "smoking", "PID" and "infertility", "operation", "IUD", "drink", "inflammation", "age", "des", "Contraceptive pills", "spirit" and "movement". Take Pubmed as an example: (ectopic pregnancy[Mesh]) AND (risk factor) AND (abortion) AND ((2003/02/09[PDAT]: 2023/02/09[PDAT])); (ectopic pregnancy[Mesh]) AND ((risk factor) AND (smoking)) AND ((2003/02/09[PDAT]: 2023/02/09[PDAT])); (ectopic pregnancy[Mesh]) AND (risk factor) AND (alcohol)); (ectopic pregnancy[Mesh]) AND (risk factor) AND (IUD) AND ((2003/02/09[PDAT]: 2023/02/09[PDAT])); (ectopic pregnancy[Mesh]) AND (risk factor) AND (infertility) AND ((2003/02/09[PDAT]: 2023/02/09[PDAT])); (risk factor) AND (ectopic pregnancy[Mesh]) AND (inflammation); (risk factor) AND (ectopic pregnancy[Mesh]) AND (des); (ectopic pregnancy[Mesh]) AND (risk factor) AND (age) AND ((2003/02/09[PDAT]: 2023/02/09[PDAT])); (ectopic pregnancy[Mesh]) AND (risk factor) AND ((Pelvic surgery) OR (Fallopian tube surgery)) AND ((2003/02/09[PDAT]: 2023/02/09[PDAT])); (ectopic pregnancy[Mesh]) AND (risk factor) AND (Contraceptive pills); (diet) AND (ectopic pregnancy[Mesh]); (exercise) AND (ectopic pregnancy[Mesh]); (mental) AND (ectopic pregnancy[Mesh]); (pschcological) AND (ectopic pregnancy[Mesh]); (Drink alcohol) AND (Pelvic inflammation[Mesh]); (Smoking) AND (Pelvic inflammation[Mesh]); (drinking alchohol) AND (infertility[Mesh]) AND ((2013/03/26[PDAT]: 2023/03/26[PDAT])); (smoking)AND(infertility[Mesh])AND((2018/03/26[PDAT]:2023/03/26[PDAT])); (abortion[Mesh]) AND (Drink alcohol) AND ((2003/03/28[PDAT] : 2023/03/28[PDAT])); (abortion[Mesh]) AND (smoking) AND ((2013/03/28[PDAT]: 2023/03/28[PDAT])); (Pelvic inflammatory[Mesh]) AND (tea); (infertility[Mesh]) AND (tea); (abortion[Mesh]) AND (tea); (Pelvic inflammatory disease[Mesh]) AND (coffee); (abortion[Mesh]) AND (coffee); (infertility[Mesh]) AND (coffee). All search strategies conformed to database search specifications.

3.2. Inclusion and Exclusion Criteria

3.2.1. Inclusion Criteria

3.2.1.1. Study type: Case-control study.

3.2.1.2. Study Subjects: The experimental group comprised pregnant females with EP and the control group comprised pregnant females with IUP, the experimental group comprised infertile patients and the control group comprised normal pregnant females, the experimental group comprised patients with PID, the control group comprised patients with abortion and the control group comprised patients without abortion and the control group comprised patients that consumed caffeine and the control group comprised patients who did not drink caffeine.

3.2.1.3. Intervention: Various risk factors like smoking, alcohol consumption, PID, infertility, abortion and caffeine. Smoking was defined as current and past smoking as well as active and passive smoking. Drinking was defined as current drinking and past drinking, and alcohol included all beer, liquor and red wine containing alcohol.Low dose caffeine was defined as caffeine less than 200mg/ day, medium dose caffeine was defined as caffeine 200-500 mg/ day, and high dose caffeine was defined as caffeine more than 500mg/ day.

3.2.1.4. Outcome measures: Whether there are high risk factors.A number of factors may cause infertility, including primary and secondary causes. Abortion is defined as spontaneous abortion and artificial abortion (medical abortion and surgical abortion). PID is defined as all inflammatory diseases occurring in the pelvic cavity. Interventions were for different risk factors like PID, infertility, abortion,alcohol consumption, and smoking. Data on all risk factors that were related with EP were collected; each risk factor, nevertheless, was not analyzed in detail in the included studies' data. Difficulty in conception was defined as those who had not become pregnant for more than 12 months under normal pregnancy preparation.

3.2.2. Exclusion criteria: (1) Critical articles, animal studies, abstracts and letters; (2) studies of patients with a history affecting the outcome measures; (3) studies with unclear outcome indicators; (4) Conference papers. (5) Case-control study of smoking group and non-smoking group, drinking group and non-drinking group.

3.3. Literature Screening and Data Extraction: One researcher independently searched and screened the literature, and decided whether to be included in the study according to the search results, which was reviewed by the second researcher to determine whether the data were qualified for inclusion. In the literature screening, the title, abstract and research methods should be read first. After keeping clearly unrelated literature out, the full text should be further read to decide whether to be included. Data extraction was independently completed by a researcher, who collected all the data of the literature by carefully reading the literature, and then sorted out the data needed for meta-analysis. The following details were involved in the meta-analysis: (1) names of authors; (2) year of publication; (3) the total number of subjects; (4) the number of subjects with risk factors.

3.4. Risk of bias assessment: Bias' risk was appraised using the Cochrane Collaboration's instrument for evaluating bias.This work was performed independently by one investigator, including (1) randomized sequence generation; (2) allocation concealment; (3) implementation of blinding; (4) blinded assessment results; (5) completeness of data; (6) selective reporting; (7) other biases. Bias risk was categorized as low, unclear, and high.

3.5. Statistical analysis: RevMan 5.4.1 software was utilized for meta-analysis, and the relative risk (OR) was used as the result index. The results were expressed with 95% confidence interval (95%CI), and $P < 0.05$ was considered statistically meaningful. The Q test was used to analyze the heterogeneity among the included studies and the I^2 index was used to quantify the heterogeneity. Fixed effect model was utilized while heterogeneity was low ($P > 0.05$, $I^2 < 40\%$). Otherwise, a random effects model was utilized. If the heterogeneity was still relatively large after the model transformation, the relevant literature would be removed one by one to reduce the heterogeneity.

3.6. Assessment of publication bias: Bias of publication was evaluated according to the outcome measures' symmetry applying funnel plots. Symmetrical funnel plots indicate any publication bias' absence, whereas asymmetrical funnel plots indicate publication bias.

3.7. Causes of heterogeneity: Due to the insufficient number of literatures and the lack of detailed baseline characteristics of some literatures, it is not possible to carry out a precise tracing of the source of heterogeneity. I speculate that it may be related to the differences in baseline characteristics such as age, BMI and geographic region of the included researchers.

4. Results

4.1. The results of the literature's preliminary screening were summarized.

A total of 1499 researches were concealed, of which 845 were about ectopic pregnancy. After excluding duplicate and unqualified articles, 106 studies were finally included. A total of 36 studies on the association between PID and EP, 34 studies on the association between infertility and EP, 36 studies on the association between abortion and EP, 27 studies on the association between smoking and EP, 3 studies on the association between drinking alcohol and EP, 9 studies on the association between smoking and PID, and 3 studies on the association between drinking alcohol and PID were included. There were 11 studies on the association between smoking and infertility, 4 studies on the association between drinking alcohol and infertility, 16 studies on the association between smoking and abortion, and 17 studies on the association between drinking alcohol and abortion. There were 5 studies of caffeine on infertility and prolonged time to conception. A total of 101studies were included. An overview of the details can be found in Figure 1.

4.2. Basic features included in the study.

There were 48 studies on EP's risk factors, and 53 studies smoking and drinking on EP's risk factors (such as PID, infertility and abortion). In a case-control study, the former case group was EP females, and the control group was IUP females; the latter case group was PID patients or infertility patients or abortion patients or patients who consume caffeine, and the control group was healthy normal childbearing women or patients who didn't consume caffeine. All subjects were women awaiting delivery.

4.3. Risk of bias assessment.

Of these 106 studies, six studies were not included because the heterogeneity due to various biases was too great, 34 studies were excluded because they were single-group studies with cases of ectopic pregnancy and no control group with intrauterine pregnancy, and other risk factors could make the results even more inaccurate. The other 61 articles had relatively low bias's risk. The risk percentages of individual biases in each study are depicted in Figure 2. Individual biases' overall risk is summarized in Figure 3.

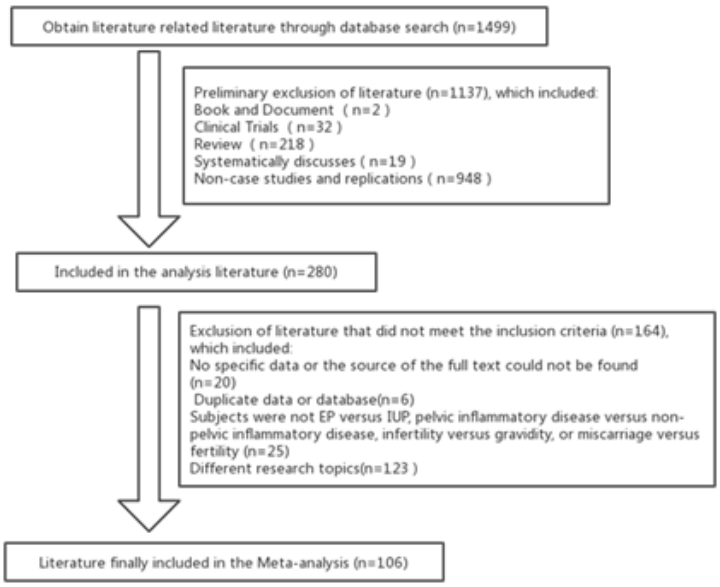

Figure 1: The results of preliminary literature screening

Figure 2: Single-item bias's risk in the included literature

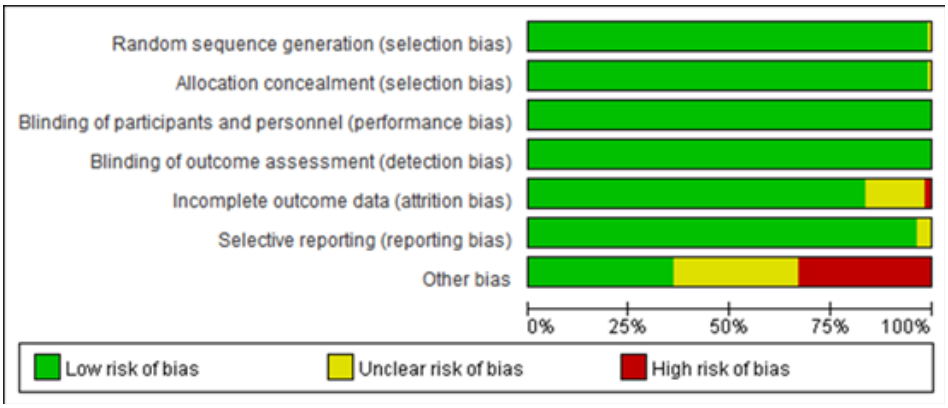

Figure 3: Individual biases' overall risk

4.4. Results of meta-analysis

4.4.1. Effect of PID on EP: A total of 11 case-control studies (4076 females in the experimental group, 100440 females in the control group) were included in the meta-analysis. The effect of PID on EP was explored by comparing the incidence of PID between the experimental and control group. For meta-analysis, a fixed effect model was utilized because the heterogeneity of the studies was low (I2 = 37%, P = 0.10,). The incidence of PID in the case group was higher than that in the control group (OR=1.39, P < 0.05,95%CI: 1.23-1.57). The data are summed up in Figures 4 and 5. The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies. One had bias' some unclear risk due to the inability to read the full text.

4.4.2. Effects of abortion on EP: A total of 11 case-control studies (1873 females in the experimental group, 25413 females in the control group) were included in the meta-analysis. The effect of miscarriage on EP was explored by comparing the miscarriage rate of the experimental and control group. Because the heterogeneity of the studies was significant, the random-effects model was applied for meta-analysis (P = 0.06, I^2= 43%). The abortion rate of the case group was higher than that of the control group (OR=1.37, 95%CI: 1.13-1.65, P < 0.05). The outcomes are summed up in Figures 6 and 7. The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

4.4.3. Effects of infertility on EP: A total of 15 case-control studies (9188 females in the experimental group, 22610 females in the control group) were included in the meta-analysis. The impact of infertility on EP was explored by comparing the infertility rates of the experimental and control group. For meta-analysis, a random-effect model was utilized because the heterogeneity of the studies was high (P = 0.02, I2 = 49%). The infertility rate of the case group was higher than that of the control group (OR=2.92, 95%CI: 2.44-3.49, P < 0.05). The outcomes are summed up in Figures 8 and 9. The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

4.4.4. Effects of smoking on EP: A total of 16 case-control studies (4628 females in the experimental group, 33639 females in the control group) were included in the meta-analysis. The effect of smoking on EP was explored by comparing the smoking prevalence of cases and controls. For meta-analysis, a random-effect model was utilized because the heterogeneity of the studies was high (P = 0.04, I^2= 42%). The smoking rate in the case group was higher than that in the control group (OR=1.45, 95%CI: 1.17-1.18, P < 0.05). The outcomes are summed up in Figures 10 and 11. The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

4.4.5. Effects of alcohol consumption on EP: Two case-control studies (418 females in the experimental group, 18157 females in the control group) were included in the meta-analysis. The effect of alcohol consumption on EP was explored by comparing the drinking rates of the experimental and control group. For meta-analysis, a random-effect model was utilized because the heterogeneity of the studies was high (P = 0.13, I^2= 56%). Due to the insufficient number of literatures and the lack of detailed baseline characteristics of some literatures, it is not possible to carry out a precise tracing of the source of heterogeneity. I speculate that it may be related to the differences in baseline characteristics such as age, BMI and geographic region of the included researchers. Although heterogeneity was high, data from both studies showed that the experimental group had a higher drinking rate than the control group (OR=1.84, 95%CI: 1.35-2.50, P < 0.05). The outcomes are summed up in Figures 12 and 13. The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

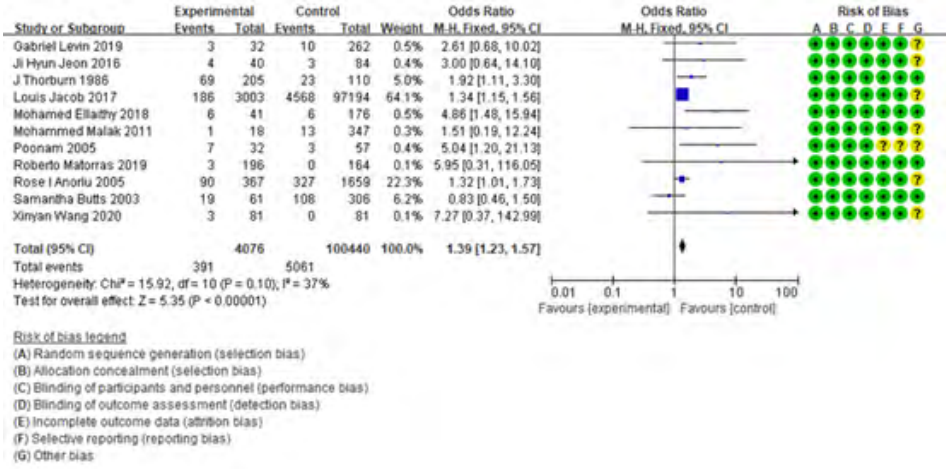

Figure 4: Results of the effect of PID on EP analysis.

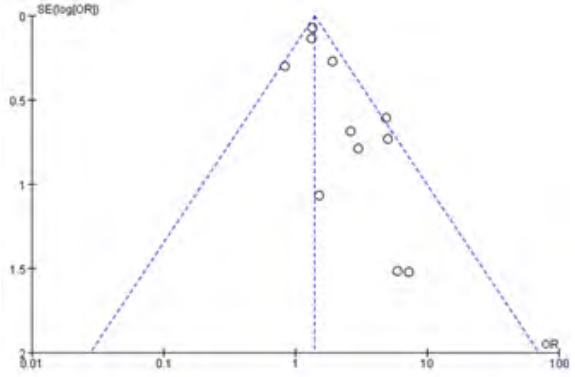

Figure 5: Results of funnel plot.

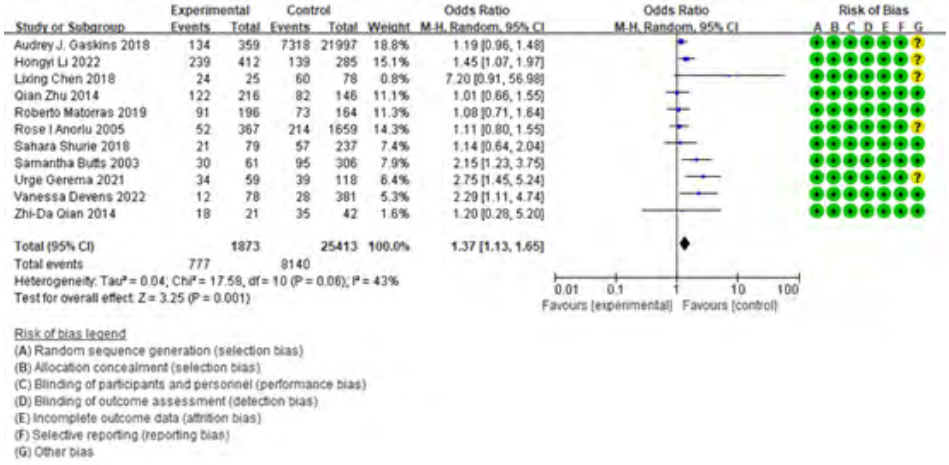

Figure 6: Results of the effect of abortion on EP analysis.

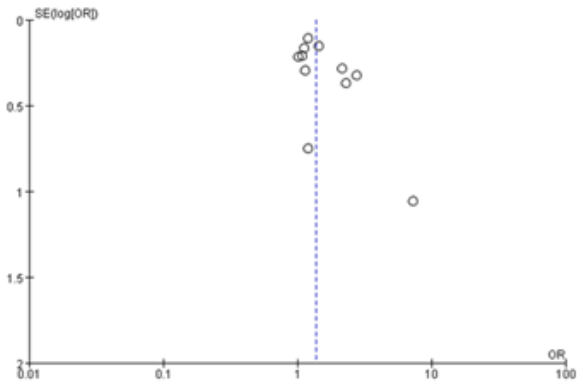

Figure 7: Results of funnel plot.

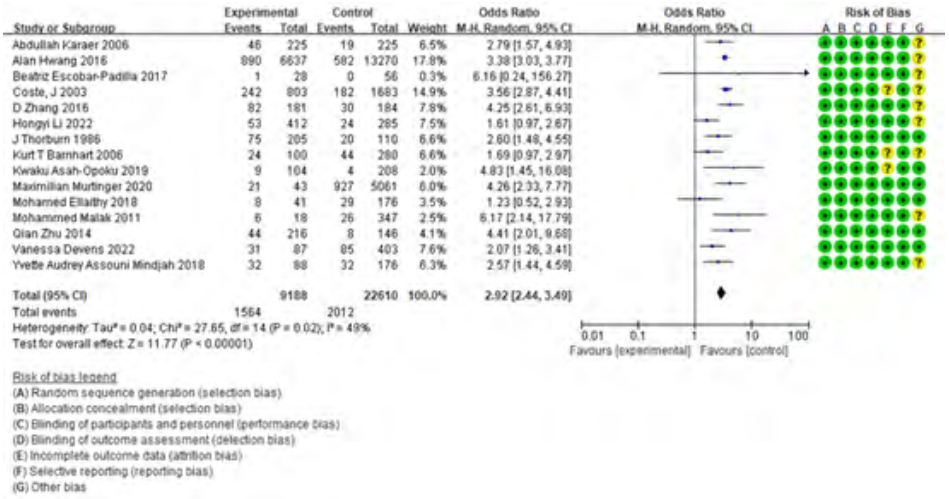

Figure 8: Results of the effect of infertility on EP analysis.

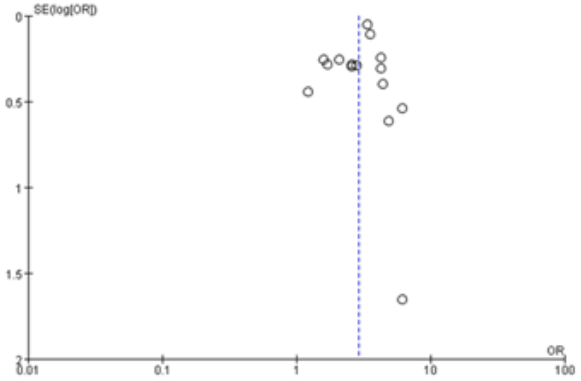

Figure 9: Results of funnel plot.

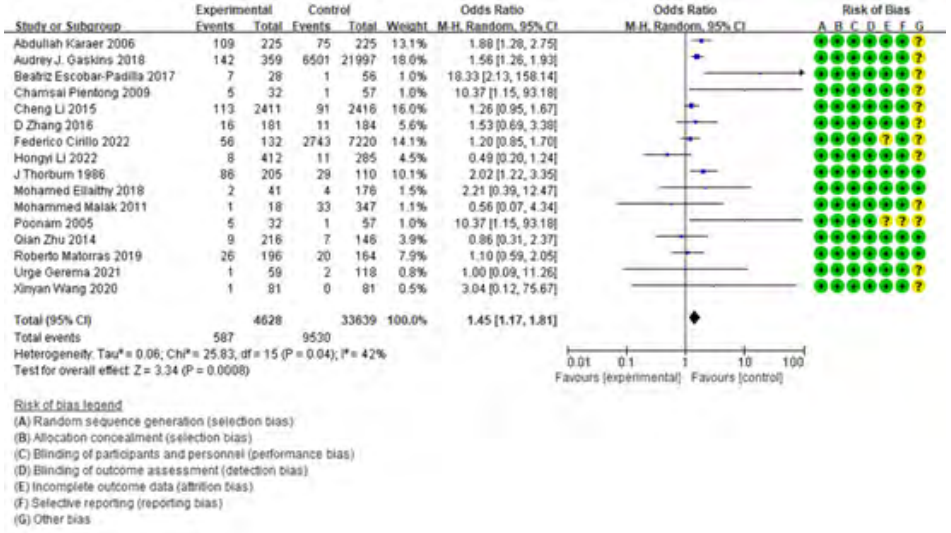

Figure 10: Results of the effect of smoking on EP analysis.

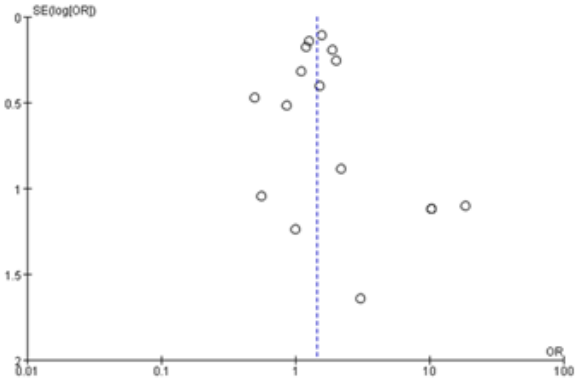

Figure 11: Results of funnel plot.

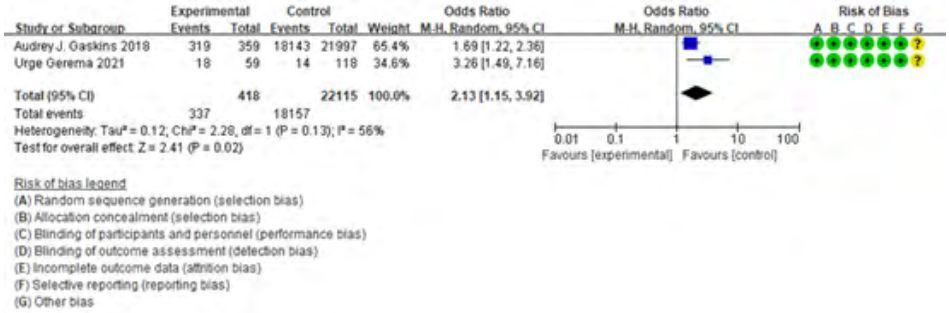

Figure 12: Results of the effect of alcohol consumption on EP analysis.

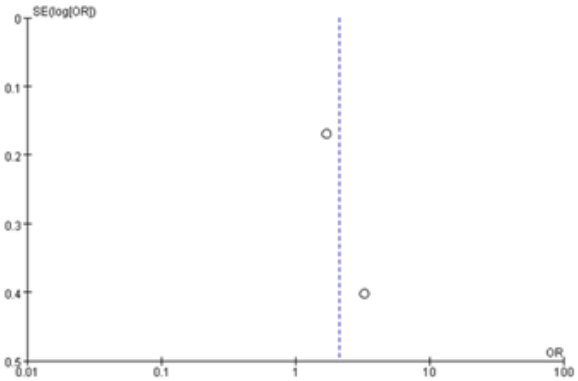

Figure 13: Results of funnel plot.

4.4.6. Effects of smoking on PID: A total of 4 case-control studies (471females in the experimental group 3402 females in the control group) were included in the meta-analysis. The effect of smoking on PID was explored by comparing the smoking rate of the experimental and control group. For meta-analysis, a fixed effect model was utilized because the heterogeneity of the studies was low (P = 0.23, I^2= 30%). The smoking rate in the case group was higher than that in the control group (OR=2.01, 95%CI: 1.62-2.50, P < 0.05). The outcomes are summed up in Figures 14 and 15.

A total of 3 studies had no control group but only case group (651 cases), and meta-analysis of single group rate was performed. For meta-analysis, a random-effect model was utilized because the heterogeneity of the studies was high (P＜0.05, I^2= 98%). The results suggest that the smoking rate may be higher in patients with PID (OR=0.76, 95%CI: 0.22-2.65, P < 0.05). The outcomes are summed up in Figures 16 and 17.

The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

4.4.7. Effects of cigarette smoking on abortion: A total of 4 case-control studies (14149 females in the experimental group 41160 females in the control group) were included in the meta-analysis. The effect of smoking on miscarriage was explored by comparing the smoking prevalence between the case and control groups. For meta-analysis, a random-effect model was utilized because the heterogeneity of the studies was high (P = 0.04, I^2= 49%). The smoking rate in the experimental group was higher than that in the control group (OR=1.32, 95%CI: 1.12-1.55, P < 0.05). The outcomes are summed up in Figures 18 and 19.

3 studies had no control group, only case group (10283 cases), and meta-analysis of single group rate was performed. For meta-analysis, a random-effect model was utilized because the het-

erogeneity of the studies was high(P＜0.05, I^2=100%).The outcomes demonstrated that abortion patients' smoking rate was very high(OR=0.42 95%CI: 0.12-1.48, P =0.18). The outcomes are summed up in Figures 20 and 21.

The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

4.4.8. Effects of cigarette smoking on infertility: A total of 6 case-control studies (1284 females in the experimental group 7173 females in the control group) were included in the meta-analysis. The effect of smoking on infertility was explored by comparing the smoking prevalence of cases and controls.For meta-analysis, a fixed effect model was utilized because the heterogeneity of the studies was low(P = 0.35, I^2= 10%). The smoking rate of the experimental group may be lower than that of the control group, but the difference was statistically meaningful (OR=0.97, 95%CI: 0.90-1.05, P < 0.05). The outcomes are summed up in Figures 22 and 23.

The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies. One of these articles had bias's high risk with incomplete data.

4.4.9. Effects of alcohol consumption on PID: A total of 3 case-control studies (223females in the experimental group 2540 females in the control group) were included in the meta-analysis. The effect of alcohol consumption on PID was explored by comparing the drinking rates of the experimental and control group. For meta-analysis, a fixed effect model was utilized because the heterogeneity of the studies was low (P=0.80, I^2=0%). The drinking rate of the case group was higher than that of the control group (OR=1.57, 95%CI: 1.09-2.27, P < 0.05). The outcomes are summed up in Figures 24 and 25.

The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

4.4.10. Effects of alcohol consumption on abortion: A total of 6 case-control studies (1284 females in the experimental group 7173 females in the control group) were included in the meta-analysis. The effect of alcohol consumption on miscarriage was explored by comparing the rates of alcohol consumption between the case and control groups. For meta-analysis, a fixed effect model was utilized because the heterogeneity of the studies was low (P = 0.22, I^2= 23%). The drinking rate of case group was higher than that of control group (OR=1.15, 95%CI: 1.11-1.19, P < 0.05). The outcomes are summed up in Figures 26 and 27.

Three studies had no control group but only case group (1767 cases), and meta-analysis of single group rate was performed. For meta-analysis, a random-effect model was utilized because the heterogeneity of the studies was high (P＜0.05, I^2= 100%). The outcomes demonstrated that the prevalence of smoking in infertile females is extremely high (OR=2.89, 95%CI :0.50-16.68, P =0.24). The outcomes are summed up in Figures 28 and 29.

The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

4.4.11. Effects of alcohol consumption on infertility: Two case-control studies (2338 females in the experimental group, 558 females in the control group) were included in the Meta-analysis. The effect of alcohol consumption on infertility was explored by comparing the rates of alcohol consumption between the experimental and control group. For meta-analysis, a random-effect model was utilized because the heterogeneity of the studies was high(P=0.84, I^2=0%). The smoking rate of the experimental group was higher than that of the control group, but the difference was statistically meaningful (OR=1.09, 95%CI: 0.67-1.76, P > 0.05). The outcomes are summed up in Figures 30 and 31.

The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

4.4.12. Effects of caffeine on infertility: Three case-control studies (12402 females in the experimental group, 12867 females in the control group) were included in the subgroup Meta-analysis. The effect of caffeine on infertility was explored by comparing the rates of infertility between the experimental and control group. For meta-analysis, a random-effect model was utilized because the heterogeneity of the studies was high (P=0.66, I^2=0%; P＜0.05, I^2=88%; P＜0.05, I^2=83%). In the low-dose caffeine group, the abortion rate of the case group was not higher than that of the control group, but the difference was statistically meaningful (OR=0.95, 95%CI: 0.82-1.10, P > 0.05). In the medium-dose caffeine group, the abortion rate of the case group was higher than that of the control group, but the difference was statistically meaningful (OR=1.18, 95%CI: 0.74-1.89, P > 0.05). In the high-dose caffeine group, the abortion rate of the case group was higher than that of the control group, but the difference was statistically meaningful (OR=1.32, 95%CI: 0.88-1.98, P>0.05). Overall, caffeine still increases the risk of infertility. (OR=1.14, 95%CI: 0.92-1.41) The outcomes are summed up in Figures 32 and 33.

The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

4.4.13. Effects of caffeine on Time to conception: Two case-control studies (3547 females in the experimental group, 2038 females in the control group) were included in the subgroup Meta-analysis. The effect of caffeine on time to conception was explored by comparing time to conception between the case group and the control group. For meta-analysis, a random-effect model was utilized because the heterogeneity of the studies was high(P=0.09,

I^2=66%;P=0.05, I^2=75%;P＜0.05, I^2=64%). In the low-dose caffeine group, the abortion rate of the case group was not higher than that of the control group, but the difference was statistically meaningful (OR=0.70, 95%CI: 0.37-1.35, P > 0.05). In the medium-dose caffeine group, the abortion rate of the case group was higher than that of the control group, but the difference was statistically meaningful (OR=1.23, 95%CI: 0.51-2.95, P > 0.05). In the high-dose caffeine group, the abortion rate of the case group was higher than that of the control group, but the difference was statistically meaningful (OR=1.32, 95%CI: 0.69-2.50, P>0.05). Overall, caffeine may Prolonging conception time.(OR=0.98, 95%CI: 0.64-1.50) The outcomes are summed up in Figures 34 and 35.

The risk of the included studies' bias was relatively low, which may have a certain impact on the results because There were retrospective studies among the included studies.

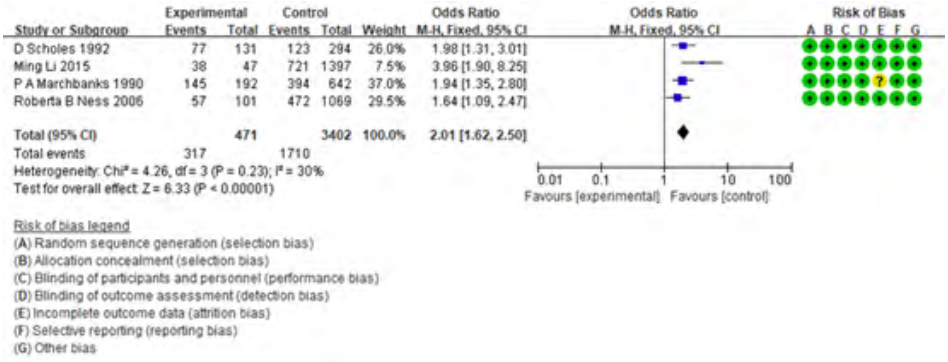

Figure 14: Results of the effect of smoking on PID analysis.

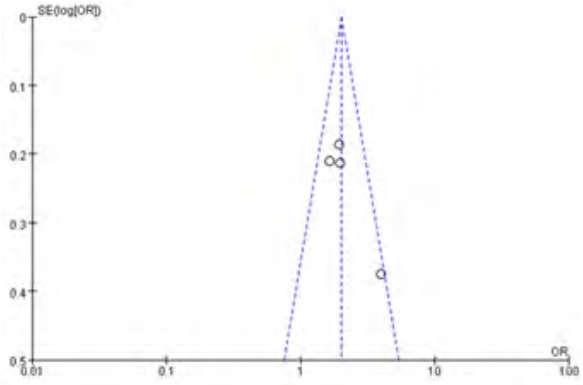

Figure 15: Results of funnel plot.

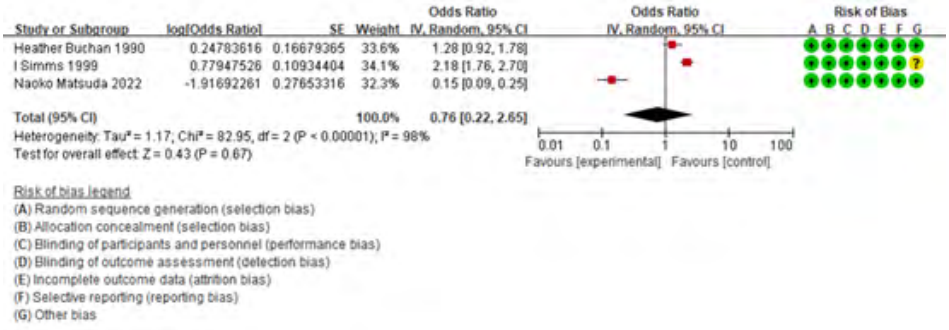

Figure 16: Results of the effect of smoking on PID analysis.

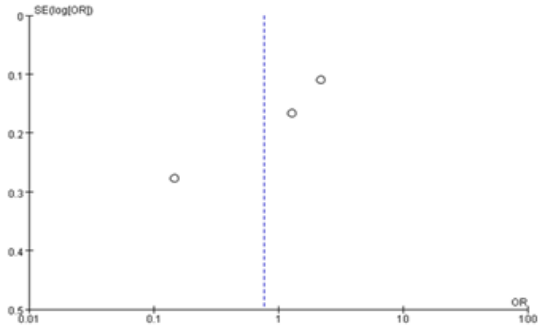

Figure 17: Results of funnel plot.

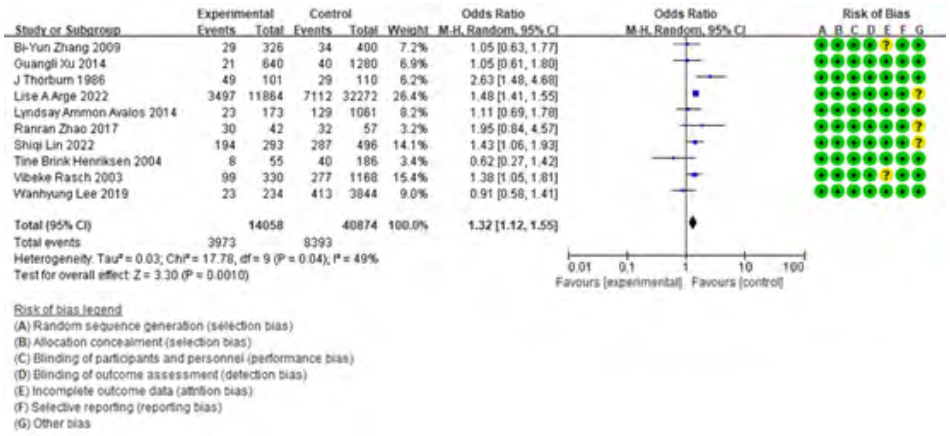

Figure 18: Results of the effect of smoking on abortion analysis.

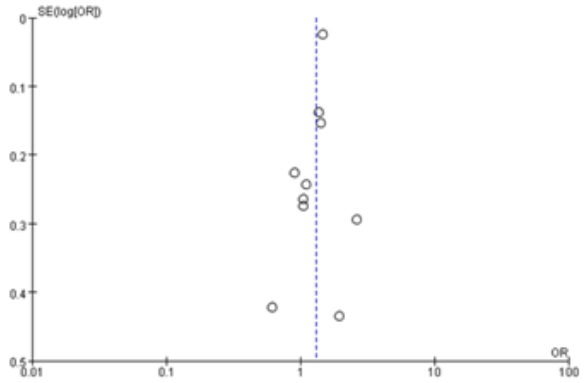

Figure 19: Results of funnel plot.

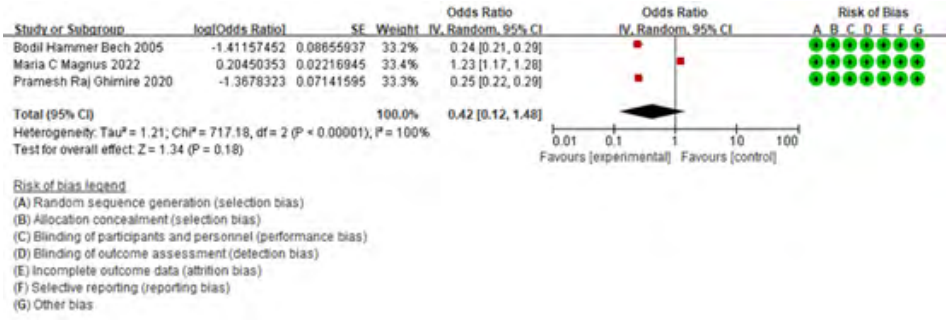

Figure 20: Results of the effect of smoking on abortion analysis.

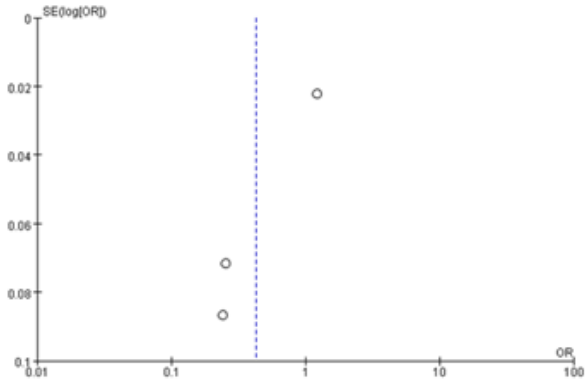

Figure 21: Results of funnel plot.

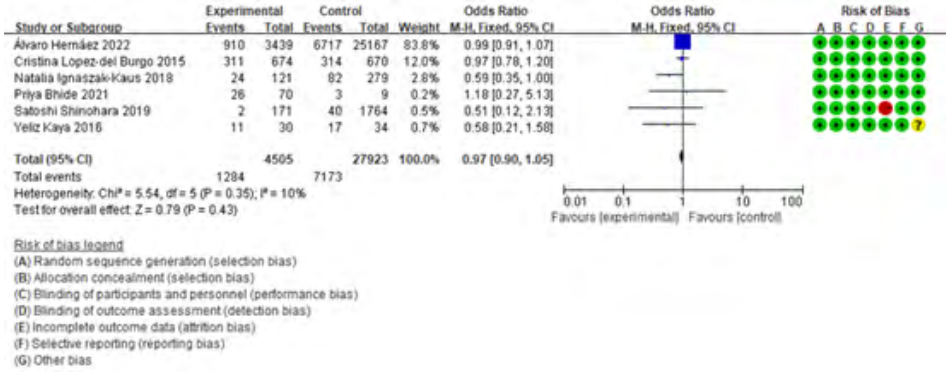

Figure 22: Results of the effect of smoking on Infertility analysis.

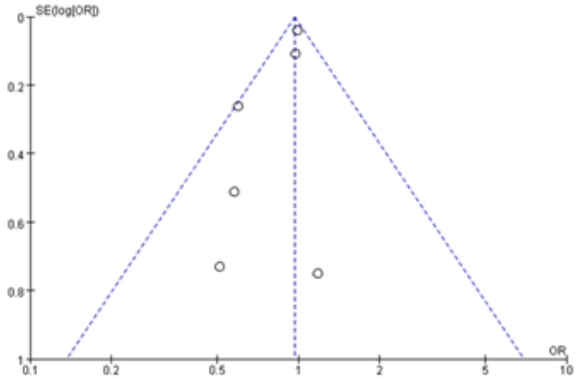

Figure 23: Results of funnel plot.

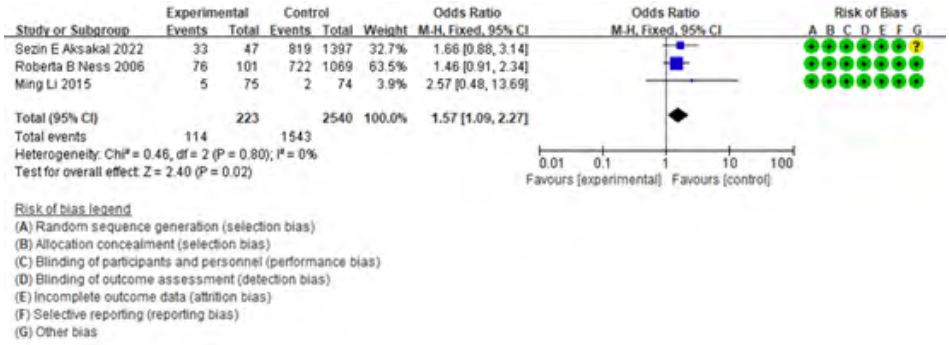

Figure 24: Results of the effect of alcohol consumption on PID analysis.

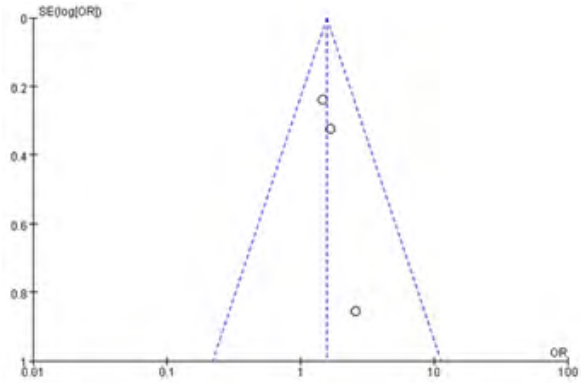

Figure 25: Results of funnel plot.

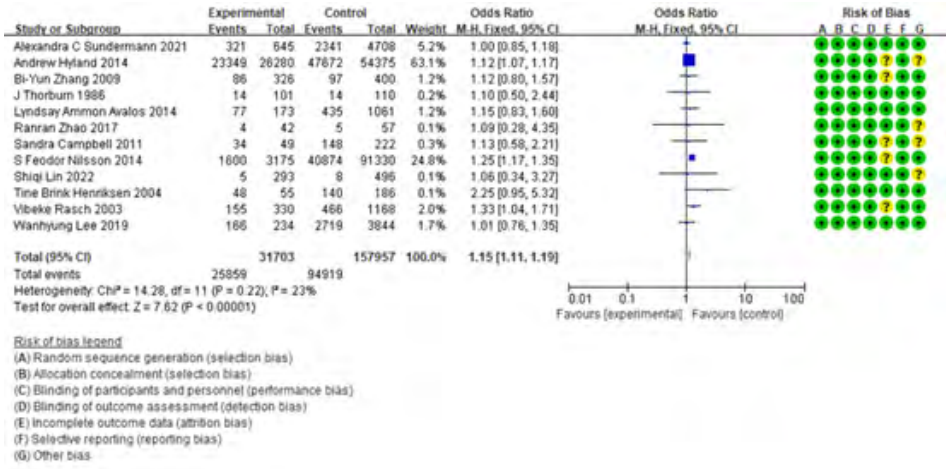

Figure 26: Results of the effect of alcohol consumption on abortion analysis.

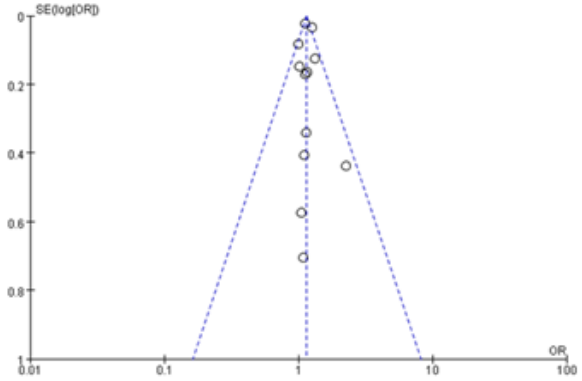

Figure 27: Results of funnel plot.

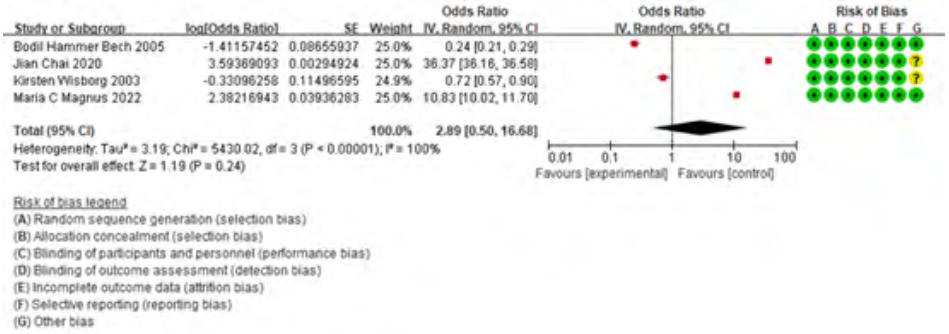

Figure 28: Results of the effect of alcohol consumption on abortion analysis.

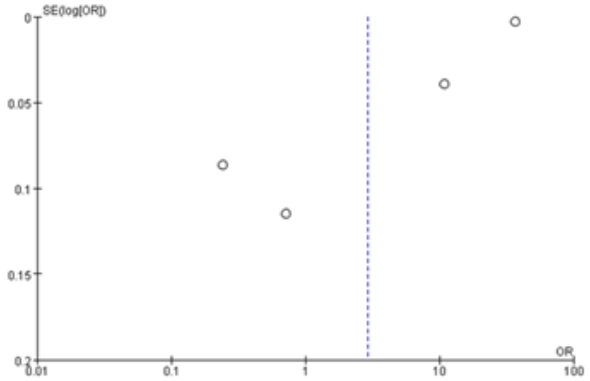

Figure 29: Results of funnel plot.

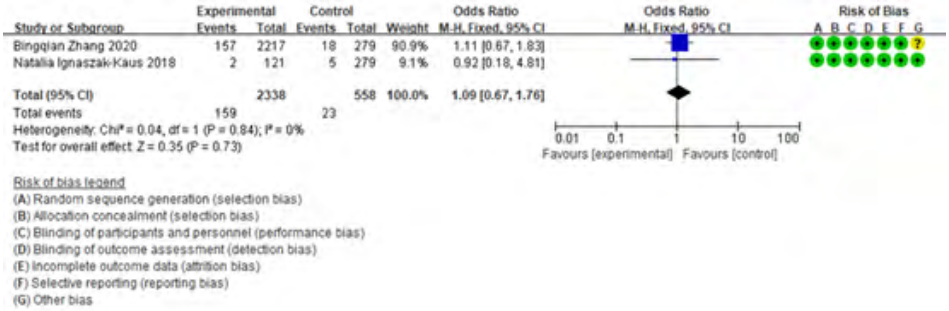

Figure 30: Results of the effect of alcohol consumption on infertility analysis.

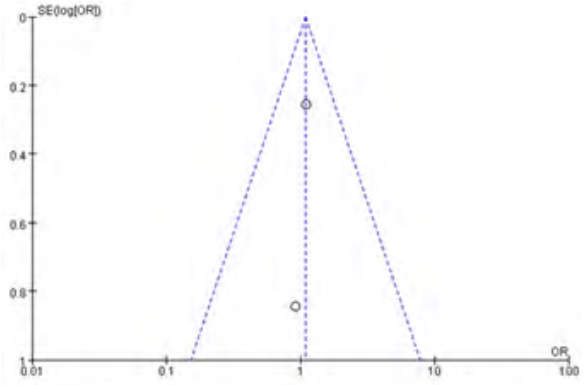

Figure 31: Results of funnel plot.

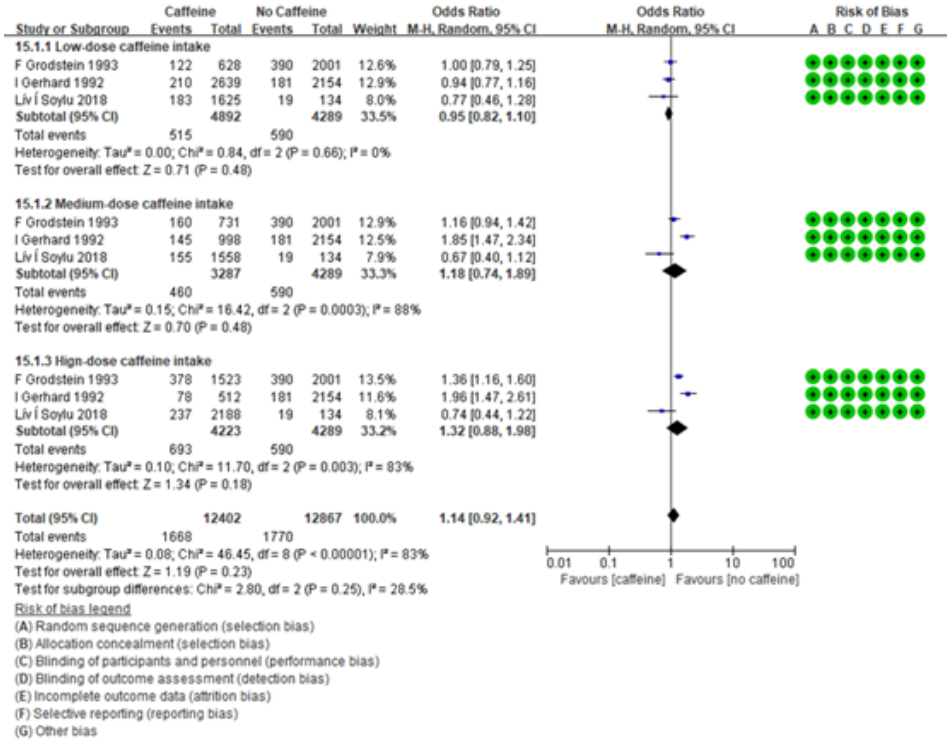

Figure 32: Results of the effect of caffeine on infertility analysis.

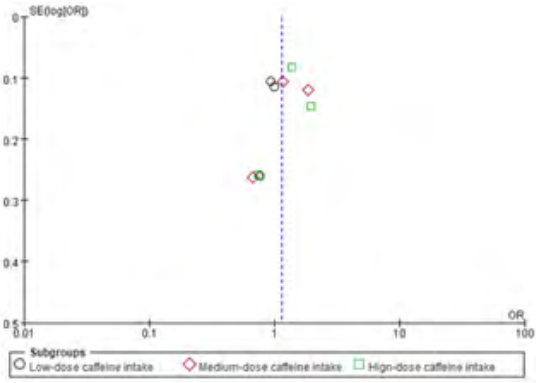

Figure 33: Results of funnel plot.

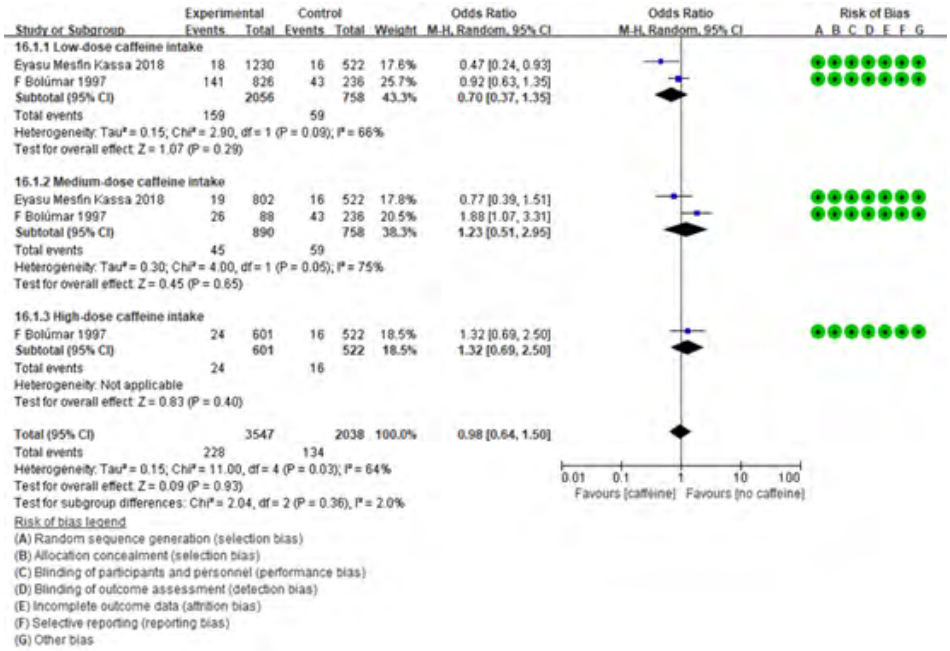

Figure 34: Results of the effect of caffeine on TTP analysis.

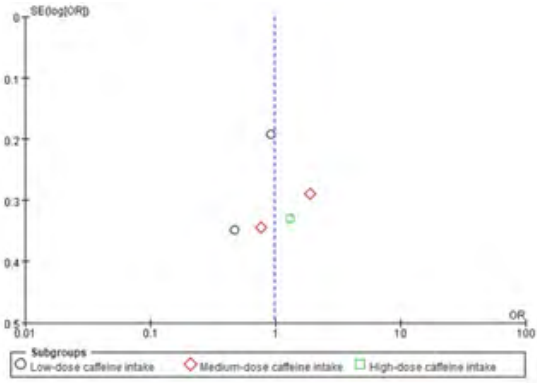

Figure 35: Results of funnel plot.

5. Discussion

It's well known that unhealthy living habits have harmful effects on the occurrence of many diseases. The most common unhealthy living habits are smoking and drinking. A lot of studies have demonstrated that there is a causal correlation between smoking and ectopic pregnancy, and 35% of EP risk is caused by tobacco, and this proportion rises with the rise of the number of smokers [73]. However, the specific mechanism of smoking remains to be studied, which may be the toxic effect of tobacco on fallopian tubes (direct and indirect) and abnormal trapping of oocytes by fallopian tubes [73]. Whether alcohol use and ectopic pregnancy are causal has been less studied, but I suspect that they are also causal and may be through toxic effects (both direct and indirect) on the fallopian tubes. The risk factors of EP are as follows: PID, infertility, abortion, history of ectopic pregnancy, oral contraceptives [74].

Since there are few studies on the association between alcohol consumption, smoking and EP, direct studies on the association between alcohol consumption, smoking and EP may be affected by insufficient sample size and other factors, making the results not rigorous enough. We therefore need other indirect methods to reduce bias' risk and make the results more rigorous. We found that there may be causal associations between drinking and smoking and PID, infertility and abortion. We explored the association between drinking and smoking and EP' risk factors by "bypass", and indirectly deduced the association and mechanism of smoking and drinking with EP.

Smoking and drinking may directly affect EP'occurrence. Only three of the case-control meta-analyses on smoking and EP found that there is a causal association between EP and smoking. This discrepancy may be related to recall bias and selection bias of retrospective studies, but the final meta-analysis results showed that smoking patients had a 45% increased relative risk of EP (OR=1.45, P＜0.05,95%CI: 1.17-1.81). In conclusion, it is highly likely that EP is causally related to smoking. There were only two case-control studies on alcohol consumption and EP. Although the heterogeneity of the meta-analysis was great, the data were still statistically significant. A relative increase of 84% in EP risk was noticed (OR=1.84, 95%CI: 1.35-2.50, P＜0.05), both studies suggested a causal association between alcohol consumption and EP, but the sample size was not sufficient due to too few studies. We look forward to more studies on alcohol consumption and EP in the future. At the same time, we can indirectly prove the association between the two by means of "bridging".

There are direct data suggesting a causal association between PID and EP. In the meta-analysis of included case-control studies of EP, we found that most of them showed that patients with pelvic inflammatory disease were at risk for EP, and only one study suggested that PID was not associated with EP. A relative increase of 39% in EP risk was noticed (OR=1.39, 95%CI: 1.23-1.57, P＜0.05). Infection with Chlamydia trachomatis or Neisseria gonorrhoeae is connected with a fourfold raised risk of extrauterine pregnancy compared with women without salpingitis. Chlamydial infection produces a specific protein, PROKR2, which has chemotactic properties that make it more likely to implant in damaged fallopian tubes [75]. Tubal damage, tubal obstruction, and pelvic adhesions may therefore be caused by PID [75], and EP's risk may be increased by PID's episodes significantly.

Data directly suggest a causal association between miscarriage and EP. All the included case-control studies on EP demonstrated that miscarriage patients had a 37% increased EP's relative risk (OR=1.37, P＜0.05, 95%CI: 1.13-1.65). Abortion may be caused by maternal own genital abnormalities affecting embryo implantation development, which may also cause ectopic pregnancy. In addition, during the process of abortion, there may be no residual tissue, which may cause uterine cavity infection, or even spread to the abdominal cavity and pelvic cavity, causing uterine cavity damage and fallopian tube damage, increasing EP's risk. Therefore, there is a direct link between miscarriage and EP.

Data directly indicate a direct causal association between infertility and EP. In the meta-analysis, EP was found to be 2.92 times more common in infertile patients than IUP. The outcomes of the Meta-analysis showed that EP's incidence in infertile females was 2.92 times higher than that of IUP (OR=2.92, 95%CI: 2.44-3.49, P＜0.05). Ovulatory disorders, infertility, and tubal disease are the most common causes of infertility [75]. Fallopian tube detriment can be triggered by fallopian tube disease, and even pelvic adhesion and PID, which may increase EP's risk significantly. Thus, infertility significantly increases EP's risk.

The results of Meta-analysis of case-control studies on PID demonstrated that PID's incidence in smokers was 2.01 times higher than that in non-smokers (OR=2.01, P＜0.05, 95%CI: 1.62-2.50). Results of a meta-analysis of the single-group rate for PID cases are shown that smokers were 0.76 times more likely to be PID patients than non-smokers (OR=0.76, P＜0.05, 95%CI: 0.22-2.65). Although the results of the single-group rate meta-analysis showed a modest association between smoking and PID, this may be due to the insufficient sample size and the greater interference of PID by other risk factors. We look forward to more research on smoking and PID in the future. But this can prove that smoking significantly increases the risk of developing PID. Meta-analysis of case-control studies on abortion demonstrated that smoking raised abortion's relative risk by 32%(OR=1.32, P＜0.05, 95%CI: 1.12-1.55); The meta-analysis of the single group of induced abortion rates demonstrated that although the risk of induced abortion in smokers was 0.42 times that of non-smokers, that of non-smokers is timed by the 95%CI that is showed that the risk of induced abortion in smokers was 0.12 to 1.48 to. Although the results of the single-group rate meta-analysis showed a modest association between smoking and miscarriage, this may be due to the insufficient sample size and the greater interference of miscarriage by other risk factors. We look forward to more research on smoking and abortion in the future. Case-control's meta-analysis studies on infertility that is showed that smoking did not raise the relative risk of infertility (OR=0.97, 95%CI: 0.90-1.05, P＜0.05), but the 95%CI demonstrated that smoking may increase infertility's risk, and most of the studies thought that smoking did not increase infertility's incidence to, and most of the studies thought that smoking did not increase the incidence of infertility, only one study thought that smoking may increase the incidence of infertility, which may be due to insufficient sample size, and could not show that there was a association between smoking and infertility. We look forward to more research on smoking and infertility in the future. It has been suggested that smoking is associated with dose-dependent dysfunction of tubal motility, impaired immunity and even delayed ovulation. Abnormal fallopian tube activity may slow the

rate at which embryos move within the fallopian tube. Immunodeficiency may be a predisposing factor for PID and fallopian tube injury. Smokers were 3.5 times more likely to develop PID than nonsmokers [1]. Therefore, we can conclude that smoking increases EP's risk, partly indirectly by affecting the occurrence of PID and abortion.

Case-control's meta-analysis studies on PID found that patients who consumed alcohol had a 57% increased risk of PID (OR=1.57, 95%CI: 1.09-2.27, P＜0.05), which proves that alcohol consumption significantly increases the relative risk of PID. There was a 2.89 times higher rate of drinking among abortion patients than non-drinkers, according to a meta-analysis of the single group miscarriage rate. (OR=2.89, 95%CI: 0.50-16.68, P=0.24); This suggests that alcohol consumption significantly increases the risk of miscarriage, despite confounding by other factors. There was a 1.15 times higher rate of drinking among abortion patients than non-drinkers, according to a meta-analysis of case-control studies miscarriage rate. (OR=1.15, 95%CI: 1.11-1.19, P＜0.05), indicating that alcohol consumption can also increase the risk of abortion. according to a meta-analysis of case-control studies infertility rate, infertility's relative risk was increased by alcohol consumption by 9%. (OR=1.09, 95%CI: 0.67-1.76, P=0.73). Because there were too few studies that were included, the data were statistically insignificant, and the two studies' results were different, but the results of the two studies told us that there may be a association between infertility and alcohol consumption were combined by the meta-analysis, and we look forward to more research on drinking alcohol and infertility in the future. In the case of heavy drinking, miscarriage and ectopic pregnancy are more likely to occur [76]. Since there is not enough research on alcohol consumption and gynecological diseases to understand the mechanism of alcohol consumption on gynecological diseases, nevertheless, the overall actual data indicate that alcohol consumption is associated with an increased risk of PID, abortion, and infertility. we know that drinking alcohol may also raise the risk of EP, and PID, abortion and infertility are high risk factors for EP. We hypothesized that, it is possible that drinking alcohol's effect on EP is caused by promoting the occurrence of infertility, miscarriage and PID.

Subgroup meta-analysis of case-control studies on caffeine demonstrated that low-dose caffeine was not linked to infertility (OR=0.95, 95%CI: 0.82-1.10, P＞0.05); Caffeine's medium doses raised infertility's risk by 18% (OR=1.18, 95%CI: 0.74-1.89, P＞0.05); Caffeine's high doses raised infertility's risk by 32% (OR=1.32, 95%CI: 0.88-1.98, P＞0.05), suggesting that medium and high doses significantly raise the risk of infertility. However, the research data on this aspect are not enough, and the heterogeneity among the only data is great, so we look forward to more research. The second subgroup meta-analysis showed that low-dose caffeine was not linked to the duration of pregnancy (OR=0.70, 95%CI: 0.37-1.35, P＞0.05); Moderate caffeine dose increased the risk of prolonged time to conception by 23% (OR=1.23, 95%CI: 0.51-2.95, P＞0.05); High doses of caffeine increased the risk of prolonged time to conception by 32%(OR=1.32, 95%CI: 0.69-2.50,P＞0.05), suggesting that medium and high doses may prolong the time to conception. The research mechanism of the effect of medium and high doses of caffeine on fertility is not as clear as that of catechins in tea, but it may be achieved by the effect on human endocrine function. The specific research mechanism is expected to be shared by more scholars in the future. Although there is no study on the direct association between caffeine and ectopic pregnancy, it may also indirectly affect the occurrence of ectopic pregnancy by affecting pregnancy. We look forward to more research on caffeine and ectopic pregnancy.

This research also has got a quantity of limitations, several limitations also exist in this study, such as the paucity of studies on smoking's effects on miscarriage and infertility. In addition, the influence of other lifestyle factors on ectopic pregnancy deserves further exploration. In some single-group rate meta-analyses investigating EP, the resulting data may not be rigorous enough due to the large number of risk factors for EP, PID, infertility, and miscarriage. As most of the included literatures were retrospective analysis, the rigor and accuracy of the data still need to be further investigated. Due to inadequate data, the association between EP and caffeine has not been collected, and the argument is not strong enough to investigate fertility and caffeine.

In the above studies, we found that smoking increased the relative risk of EP by 45% (OR=1.45, 95%CI: 1.17-1.18, P < 0.05), and statistics showed that non-smoking reduced the relative risk of EP by 41.6%. Drinking alcohol raised the relative risk of EP by 84%(OR=1.84, 95%CI: 1.35-2.50, P < 0.05), and according to statistics, not drinking alcohol reduced the relative risk of EP by 7.6%. Medium-dose caffeine raised the risk of infertility by 18% (OR=1.18, 95%CI: 0.74-1.89, P ＞0.05), and raised the risk of prolonged conception time by 23% (OR=1.23, 95%CI: 0.51-2.95, P＞0.05). Caffeine's high doses raised infertility's risk by 32% (OR=1.32, 95%CI: 0.88-1.98, P＞0.05), and raised the risk of prolonged conception time by 32% (OR=1.32, 95%CI: 0.69-2.50,P＞ 0.05)

Therefore, females should pay attention to smoking and drinking in preparation for pregnancy or during pregnancy, and also avoid the harm of second-hand smoke, so as to reduce the risk of ectopic pregnancy.Although tea, coffee and cola are not associated with infertility, high-dose caffeine intake can increase the risk of infertility, which may affect the occurrence of ectopic pregnancy. Therefore, caffeine intake should be paid attention to during pregnancy. There are more life habits that may affect the occurrence of ectopic pregnancy, which are worthy of further exploration by more scholars. In the future, we hope to see more studies on interventions to reduce ectopic pregnancy rates.

6. Conclusion

Smoking and drinking can significantly raise the incidence of EP, while non-smoking and non-drinking can reduce the incidence of EP. Pregnant women can therefore decrease ectopic pregnancy's incidence by quitting smoking and alcohol. Caffeine's low doses have a protective effect on fertility, but caffeine intake's high doses can increase infertility's risk and prolong the time to pregnancy, which may affect the occurrence of EP. Therefore, it is necessary to limit the intake of caffeine-containing beverages, such as cola, coffee, and tea.

7. Acknowledgements

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8. Disclosure Statement

Concerning this publication, no conflict of interest exists between the authors.

9. Funding Sources

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10. Data Availability Statement

Access to confidential data is available to researchers who meet the criteria. The paper and its supporting information files contain all relevant data.

It has never been submitted to another journal for publication and is not currently being considered for publication.

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