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SYSTEMATIC REVIEW

The association between caffeine and alcohol consumption and IVF/ICSI outcomes: A systematic review and dose–response meta-analysis

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Abstract

Introduction: The objective of this study was to evaluate the association between caffeine and alcohol consumption and in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) outcomes.

Material and methods: The protocol was registered in the PROSPERO database on May 23, 2021 (registration number: CRD42021256649), and updated on August 4, 2022. Two researchers performed a literature search in the PubMed, Embase, and MEDLINE databases for articles published before July 15, 2022 independently. Studies investigating the association between caffeine and alcohol consumption and IVF/ICSI outcomes were included, and studies reporting the consumption amount were analyzed using a one-stage robust error meta-regression-based method to explore potential dose–response relation. Funnel plot was used to assess publication bias if more than 10 studies were included.

Results: Twelve studies on caffeine consumption and 14 studies on alcohol consumption were included in the systematic review, of which seven and nine were eligible for the meta-analysis. These studies included 26 922 women and/or their spouses who underwent IVF/ICSI treatment. Women's and men's caffeine consumption was not significantly associated with the pregnancy rate (odds ratio [OR] 0.97, 95% confidence interval [CI] 0.85–1.12; OR 0.93, 95% CI 0.75–1.14; respectively) and the live birth rate (OR 0.98, 95% CI 0.89–1.08; OR 0.98, 95% CI 0.86–1.12; respectively) of IVF/ICSI. Maternal alcohol consumption was negatively associated with pregnancy after IVF/ICSI treatment (OR 0.83, 95% CI 0.69–1.01). Paternal alcohol consumption was negatively associated with partner's live birth after IVF/ICSI treatment (OR 0.88, 95% CI 0.79–0.99). Compared with abstainers, the chance of achieving a pregnancy after IVF/ICSI treatment decreased by 7% for women who consumed 84 g alcohol per week (OR 0.93, 95% CI 0.90–0.98), and the chance of partners achieving a live birth decreased by 9% for men who consumed 84 g alcohol per week (OR 0.91, 95% CI 0.88–0.94).

Abbreviations: ART, assisted reproductive technology; CI, confidence interval; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; OR, odds ratio; REMR, robust error meta-regression; ROS, reactive oxygen species.

Conclusions: There was no association between caffeine consumption and pregnancy or live birth rate of IVF/ICSI. Women's alcohol consumption was associated with decreased pregnancy rate after IVF/ICSI treatment when weekly consumption was greater than 84 g. Men's alcohol consumption was associated with decreased live birth rate after IVF/ICSI treatment when weekly consumption was greater than 84 g.

KEYWORDS
alcohol, assisted reproductive technology, caffeine, in vitro fertilization, intracytoplasmic sperm injection, meta-analysis

1 | INTRODUCTION

Assisted reproductive technology (ART) has been widely used around the world over the last decades. In 2012, a total of more than 1.9 million ART cycles were initiated and 1.1 million embryo transfers were performed based on both reported and estimated numbers.[1] Although the success rate of ART has been improving, many couples choose to discontinue fertility treatment before conceiving because of the considerable emotional and economic burden.[2] Modifiable factors such as lifestyle have an impact on reproductive health, and lifestyle modification could optimize couples' chances of conception after fertility treatment.[3] However, many women who undergo fertility treatment make potentially detrimental lifestyle choices that may decrease their chances of becoming pregnant, including the consumption of alcohol and caffeine.[4]

Caffeinated and alcoholic drinks are two of the most widely consumed beverages in the world. According to national surveys, 85% of the US population consumes caffeinated beverages on a daily basis and 50.8% of Americans aged 12 years or older had alcohol intake during the most recent month.[5,6] Previous studies have found that higher caffeine intake is associated with lower birthweight and a higher risk of pregnancy loss in natural pregnancy.[7] Similarly, alcohol is known for its detrimental effect on human health and has been associated with reduced fecundability in women.[8,9] However, the relation between these two substances and in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) outcomes remains uncertain, and studies have reported conflicting results. A previous study suggested that caffeine may exert a detrimental effect on IVF and gamete intra-Fallopian transfer (GIFT) outcome,[10] whereas some more recent studies suggested otherwise, that caffeine consumption did not show an association with or even improved IVF/ICSI outcomes.[11,12] A prospective study conducted in Sweden found that high alcohol consumption increased the risk of women's infertility examinations and decreased the number of first and second fetus.[13] In contrast, some studies did not find evidence of a significant relation between female alcohol consumption and ART outcomes.[14–16]

Considering the widespread consumption of caffeine and alcohol, it is essential to shed more light on the association between these two substances and IVF/ICSI outcomes. For this reason, we conducted a systematic review and dose–response meta-analysis to examine the associations between caffeine and alcohol consumption and IVF/ICSI outcomes.

Key message

Alcohol consumption is negatively associated with pregnancy rate of IVF/ICSI treatment when women drink more than 84 g per week, and is negatively associated with live birth rate of IVF/ICSI treatment when men drink more than 84 g per week.

2 | MATERIAL AND METHODS

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17] A review protocol is available from the PROSPERO database.[18] The protocol was registered on May 23, 2021 (registration number: CRD42021256649), and updated on August 4, 2022. Literature selection, and data extraction and analysis were performed by two authors (WR, YL) independently. Discrepancies were resolved by consensus or by consultation with a third reviewer.

2.1 | Literature search and selection

We performed a literature search in the PubMed, Embase, and MEDLINE databases for articles published before July 15, 2022. The MeSH term and text words combinations used to identify studies were: ((caffeine) OR (coffee)) AND (reproductive techniques[MeSH Terms]); alcohol* AND (reproductive techniques[MeSH Terms]).

The study selection criteria for systematic review were as follows. (a) The study design was a case–control, cohort, or cross-sectional study. (b) The participants underwent IVF/ICSI treatment.

(c) Consumption of caffeine or alcohol was measured and reported. (d) Pregnancy and/or live birth rate were reported. Articles reported relative risks, odds ratios (ORs) or hazard ratios of the outcomes and their 95% confidence intervals (CI) were included in the meta-analysis, and articles reporting consumption amount were included in the dose–response analysis.

2.2 | Data extraction and quality assessment

Data were extracted using predesigned electronic extraction forms. Collected data included the authors, publication year, participant characteristics, treatment, exposure source and time frame, caffeine or alcohol consumption categories, IVF/ICSI outcomes, and effect sizes for all categories. A nine-score system of the quality assessment Newcastle–Ottawa Scale was applied to assess the quality of the included studies according to a pre-defined explanatory form for scoring.[19] Studies with a total score of more than 7 were considered as high-quality studies.

2.3 | Statistical analyses

A random-effects model was applied for the pooled analyses to calculate a weighted OR value, which was visualized by a forest plot. An OR less than 1 indicated decreased odds of pregnancy or live birth. The heterogeneity across studies was assessed using the I^2 statistic, and an I^2 value greater than 50% indicated significant heterogeneity, so subgroup analysis would be conducted. A sensitivity analysis was conducted by excluding one study at a time to assess the robustness of the data. Funnel plots and Egger's test were used to determine publication bias if 10 or more studies were pooled in the meta-analysis.

For studies that reported consumption amount, we performed a one-stage robust error meta-regression (REMR) based dose–response meta-analysis by including all consumption categories to examine the potential nonlinear relation between caffeine and alcohol consumption and IVF/ICSI outcomes.[20] For each category, the midpoint of upper and lower boundaries was assigned as the average consumption. If the highest category was open-ended, the average consumption was set to be its lower boundary plus 2 times the distance between the midpoint and upper limit of the closest category.[21] Studies reporting consumption in cups or standard drinks were recalculated into an approximate dose, assuming that one cup of coffee contains 100 mg of caffeine and one standard drink of alcoholic beverage contains 12 g of alcohol.[12,14] The model used restricted cubic splines with three random knots if no less than three studies were included. Otherwise, a linear model would be used to plot. Linear trends for every unit increase of intake were calculated using methods reported by Xu et al.[20]

All analyses were performed in STATA 16.0 (StataCorp) and REMR was conducted using the REMR module.[20]

3 | RESULTS

3.1 | Study characteristics

The search retrieved a total of 493 articles on caffeine and 1511 articles on alcohol consumption. After removing duplicates and screening by title, abstract and full text, 12 and 14 articles on caffeine and alcohol consumption were included in the systematic review. Of these included articles, seven and nine were pooled in the meta-analysis (Figure 1).[10,12,14–16,22–31] The main characteristics of the included studies are presented in Table 1. Detailed Newcastle–Ottawa Scale scores are presented in Table S1. All studies were published between 2002 and 2022 and included 26 922 women and/or their spouses who underwent IVF/ICSI treatment. Five studies were conducted in the USA,[10,25–27,29] four in Brazil,[23,24,30,31] three in Denmark,[12,14,16] two in Italy,[15,28] and one in Saudi Arabia.[22] Only six and five studies reported consumption amount to be included in the dose–response analysis.[10,12,14–16,22,25,27–30]

3.2 | Association between caffeine consumption and IVF/ICSI outcomes

We found null association between maternal or paternal caffeine consumption and IVF/ICSI outcomes based on seven studies (Figures 2 and 4A–C). Compared with women who did not consume caffeine, women who consumed caffeine on a daily basis were less likely to achieve pregnancy (OR 0.97, 95% CI 0.85–1.12) and live birth (OR 0.98, 95% CI 0.89–1.08) after IVF/ICSI treatment. Women whose spouses consumed caffeine on a daily basis were less likely to achieve pregnancy (OR 0.93, 95% CI 0.75–1.14) and live birth (OR 0.98, 95% CI 0.86–1.12). However, these results were not statistically significant.

3.3 | Association between alcohol consumption and IVF/ICSI outcomes

We found that maternal consumption of alcohol was negatively associated with pregnancy after IVF/ICSI treatment (OR 0.83, 95% CI 0.69–1.01), though this result was at the margin of statistical significance (Figure 3). However, the dose–response analysis showed a weak but significant inverse relation between alcohol consumption and pregnancy when women's weekly consumption was greater than 84 g (Figure 4D). Compared with abstainers, the chance of achieving a pregnancy after receiving IVF/ICSI treatment decreased by 7% for women who consumed 84 g alcohol per week (OR 0.93, 95% CI 0.90–0.98). Maternal alcohol consumption was negatively but not significantly associated with IVF/ICSI live birth (OR 0.95, 95% CI 0.88–1.02).

We also found that paternal alcohol consumption was negatively associated with partner's live birth after IVF/ICSI treatment (OR 0.88, 95% CI 0.79–0.99) (Figure 3). The dose–response analysis showed that the chance of partner's live birth decreased by 9% for men who consumed 84 g alcohol per week (OR 0.91, 95% CI 0.88–0.94) (Figure 4F).

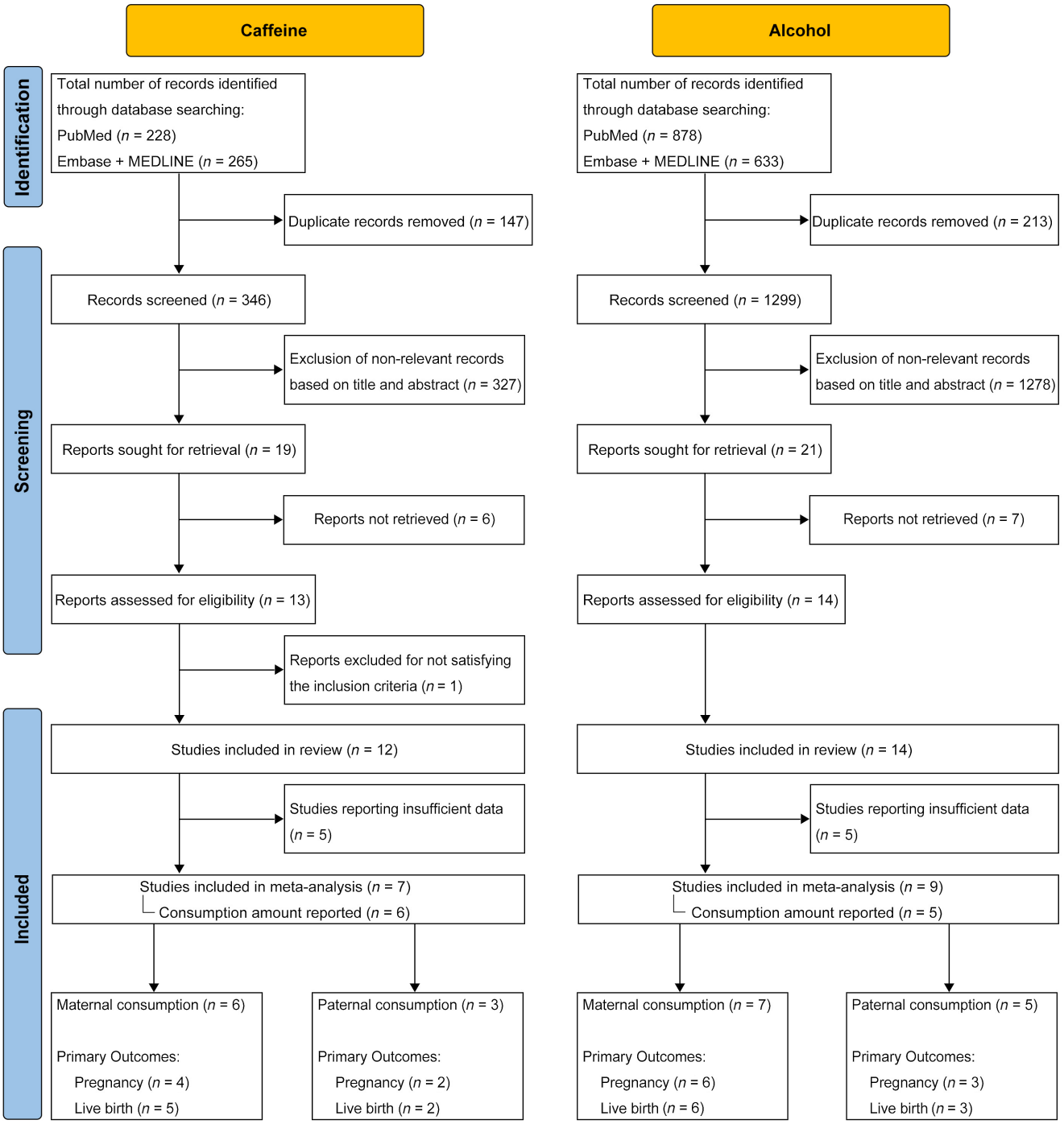

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart.

Paternal alcohol consumption was negatively but not significantly associated with IVF/ICSI pregnancy (OR 0.96, 95% CI 0.85–1.08).

3.4 | Sensitivity analysis and risk of bias in included studies

One of the I^2 values was greater than 50%, indicating high heterogeneity across studies in this synthesis (Figure 3). The heterogeneity mainly came from the study by Setti et al.,[31] but excluding this study did not significantly change the result. The results remained materially unchanged when excluding one observation at a time (Figure S1). We could not conduct funnel plots to assess publication bias because the number of studies included in each synthesis was less than 10.

4 | DISCUSSION

We found that caffeine consumption does not appear to have an effect on IVF/ICSI outcomes. As for women's alcohol consumption,

TABLE 1 Characteristics and main results of the studies included in the meta-analysis ($N = 15$)

Author and year	Country	Design	Study groups included in the analysis	Exposure	Adjustment variables	Main results	NOS score
Klonoff-Cohen et al., 2002	USA	Prospective cohort	$N = 192$ American women undergoing their first non-donor IVF or GIFT cycle	Caffeine	Women's smoking, alcohol use, age, race, years of schooling, parity, type of infertility, type of procedure, and number of attempts	Women with a usual caffeine intake of >2–50 and 50 mg/day had an increased risk of not achieving a live birth. OR 3.1 (95% CI 1.1–9.7) and OR 3.9 (95% CI 1.3–11.6), respectively	8
Al-Saleh et al., 2010	Saudi Arabia	Prospective cohort	$N = 474$ Saudi Arabian women undergoing their first IVF cycle	Caffeine	Age, BMI, family income, smoking status, use of herbal treatment, cause of infertility, and health status	No association was found between the success rate of pregnancy and coffee intake of 5–10 and >10 cups/day. OR 0.864 (95% CI 0.410–1.820) and OR 0.773 (95% CI 0.219–2.736), respectively	9
Choi et al., 2011	USA	Prospective cohort	$N = 2474$ American couples undergoing IVF treatment at three IVF clinics in Boston and contributing to 4716 cycles	Caffeine	Female age, BMI, clinic site, study enrollment period, female tobacco use, female alcohol use, and primary infertility diagnosis	No association was found between live birth and female caffeine intake of 0–800, 800–1400, and >1400 mg/week. OR 1.00 (95% CI 0.83–1.21), OR 0.89 (95% CI 0.71–1.12), and OR 1.07 (95% CI 0.85–1.34), respectively. No significant association was found between male caffeine intake and live birth. $p_{trend} = 0.27$	9
Braga et al., 2012	Brazil	Prospective cohort	$N = 250$ male patients undergoing ICSI cycles	Caffeine, Alcohol	Maternal and paternal age, the number of retrieved oocytes, number of transferred embryos and endometrium thickness and FSH dose, maternal smoking, and female BMI	The chance of pregnancy was not influenced by the male consumption of alcohol and coffee. OR 1.02 (95% CI 0.69–1.50) and OR 0.83 (95% CI 0.54–1.26), respectively	9
Ricci et al., 2018	Italy	Prospective cohort	$N = 339$ Italian couples undergoing IVF/ICSI treatment	Caffeine	Women's age class and college degree, smoking habits, calorie and alcohol intake for both men and women, previous ART cycles, and partner's caffeine intake	No association was found between live birth and female caffeine intake. aRR for second tertile 1.07 (95% CI 0.76–1.50), aRR for third tertile 1.00 (95% CI 0.70–1.43). No association was found between clinical pregnancy and female caffeine intake. aRR for second tertile 1.09 (95% CI 0.79–1.50), aRR for third tertile 0.99 (95% CI 0.71–1.40). No association was found between male caffeine intake and clinical pregnancy or live birth	8

(Continues)

TABLE 1 (Continued)

Author and year	Country	Design	Study groups included in the analysis	Exposure	Adjustment variables	Main results	NOS score
Setti et al., 2018	Brazil	Retrospective cross-sectional	*N* = 488 Brazilian women undergoing ICSI cycles	Caffeine	Maternal age, number of retrieved oocytes, maternal weight, smoking habit, and physical activity	No association was found between clinical pregnancy and live birth and the consumption of unsweetened coffee, coffee with sugar, or coffee with artificial sweetener	7
Lyngsø et al., 2019	Denmark	Prospective cohort	*N* = 1708 Danish women undergoing fertility treatment contributing with 437 IUI cycles, 1421 IVF/ICSI cycles (first initiated treatment cycle)	Caffeine	Female age, BMI, cigarette smoking, weekly alcohol consumption, chronic diseases, education	Women consuming 1–5 cups vs none had higher probability of achieving a pregnancy or a live birth when receiving IUI (first initiated treatment cycle). OR for clinical pregnancy 1.92 (95% CI 1.05–3.51), OR for live birth 2.13 (95% CI 1.13–4.02). No associations were found between women's daily coffee consumption and achieving a pregnancy or a live birth from IVF/ICSI (1–5 cups vs none, first initiated treatment cycle). OR for clinical pregnancy 1.04 (95% CI 0.84–1.29), OR for live birth 1.04 (95% CI 0.83–1.31)	9
Klonoff-Cohen et al., 2003	USA	Prospective cohort	*N* = 217 women undergoing fresh non-donor IVF or GIFT cycle	Alcohol	Smoking, woman's age, race, total years of schooling, parity, indications, type of procedure, and number of attempts	Women who consumed 12 g more of alcohol per day during the month before the attempt had an increase in risk of not achieving pregnancy. RR 2.86 (95% CI 0.99–8.24). No significant association between female alcohol consumption and live birth was found. Men who consumed 12 g more of alcohol per day increased the risk of not achieving a live birth by 2.28 (95% CI 1.08–4.80) to 8.32 (95% CI 1.82–37.97) times, depending on the time period	8

TABLE 1 (Continued)

Author and year	Country	Design	Study groups included in the analysis	Exposure	Adjustment variables	Main results	NOS score
Rossi et al., 2011	USA	Prospective cohort	*N* = 2545 couples undergoing IVF contributing 4729 cycles	Alcohol	Cycle number and women's age, BMI, and cigarette use in the women's drinking exposure models; and cycle number, women's age, men's age, BMI, and cigarette use in the men's drinking exposure models	Women drinking at least four drinks per week had 16% less odds of a live birth rate compared with those who drank fewer than four drinks per week. OR 0.84 (95% CI 0.71–0.99). The effect of male drinking overall was not statistically significantly associated with live birth. OR 0.90 (95% CI 0.79–1.03). For couples in which both partners drank at least four drinks per week, the odds of live birth were 21% lower compared with couples in which both drank fewer than four drinks per week. OR 0.79 (95% CI 0.66–0.96)	9
Dodge et al., 2017	USA	Retrospective cohort	*N* = 2134 women undergoing their first fresh-embryo, non-donor IVF contributing to 5028 cycles	Alcohol	Age	In the first cycle, compared with non-drinkers, daily drinkers had a twofold increased risk of spontaneous abortion (aRR 2.2; 95% CI 1.1–4.5), while their risk of live birth was 30% lower (aRR 0.7; 95% CI 0.4–1.3). By the end of six cycles, social drinkers and daily drinkers did not differ from non-drinkers in the cumulative incidence of live birth ($p \geq 0.28$)	7
Vittrup et al., 2017	Denmark	Prospective cohort	*N* = 12 981 Danish women undergoing IVF/ICSI contributing to 29 834 cycles	Alcohol	Female age, female smoking, female BMI, male age, male smoking, and male BMI	No statistically significant associations between alcohol consumption and live birth were observed. aOR_{trend} were 1.00 (95% CI 0.99–1.01) and 0.99 (95% CI 0.97–1.01) for every 1-unit increase in female and male weekly alcohol consumption respectively	9

(Continues)

TABLE 1 (Continued)

Author and year	Country	Design	Study groups included in the analysis	Exposure	Adjustment variables	Main results	NOS score
Borges et al., 2018	Brazil	Prospective cohort	*N* = 233 male patients undergoing their first ICSI cycle	Alcohol	Male and female ages, number of retrieved and injected oocytes	There were no significant influences of paternal alcohol consumption on ICSI pregnancy rate (OR 3.00, 95% CI 0.19–7.58). When patients were subdivided into occasional and frequent alcohol consumers, no significant differences were observed. Alcohol consumption negatively influenced fertilization rate (β −3.617, slope 20.1380, $p = 0.041$) and blastocyst formation on day 5 (β −34.801, slope 30.0446, $P = 0.042$)	7
Lyngsø et al., 2019	Denmark	Prospective cohort	*N* = 1708 women undergoing IUI or IVF/ICSI cycles	Alcohol	Female age, BMI, cigarette smoking, daily coffee consumption, chronic diseases, education, and cycle number	Low-to-moderate average weekly alcohol intake was not statistically significantly associated with the chance of achieving a clinical pregnancy or a live birth following IUI or IVF/ICSI treatment cycles	9
Ricci et al., 2020	Italy	Prospective cohort	*N* = 427 Italian women undergoing an IVF/ICSI cycle and embryo transfer	Alcohol	Age class, college degree, BMI class, occupational physical activity, previous ART cycles, and calories intake	No significant association was found between female alcohol consumption and clinical pregnancy or live birth. In women in the third tertile of alcohol intake, aRR was 0.90 (95% CI 0.62–1.30) and 0.89 (95% CI 0.57–1.37) for clinical pregnancy and live birth, respectively	9
Setti et al., 2022	Brazil	Retrospective cohort	*N* = 752 couples undergoing their first ICSI cycle.	Alcohol	Maternal age, BMI, and the number of retrieved oocytes	Clinical pregnancy and live birth rates were significantly negatively associated with alcoholic beverages intake. OR 0.1 (95% CI 0.05–0.2) and OR 0.5 (95% CI 0.3–0.7), respectively. The intake of alcoholic beverages showed inverse dose-dependent relationships with clinical pregnancy ($p = 0.012$ to $p < 0.001$) and live birth rates ($p = 0.008$ to $p < 0.001$)	8

Abbreviations: aOR, adjusted odds ratio; aRR, adjusted relative risk; ART, assisted reproductive technology; BMI, body mass index; CI, confidence interval; FSH, follicle-stimulating hormone; GIFT, gamete intra-Fallopian transfer; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; NOS, Newcastle–Ottawa score; OR, odds ration; RR, relative risk.

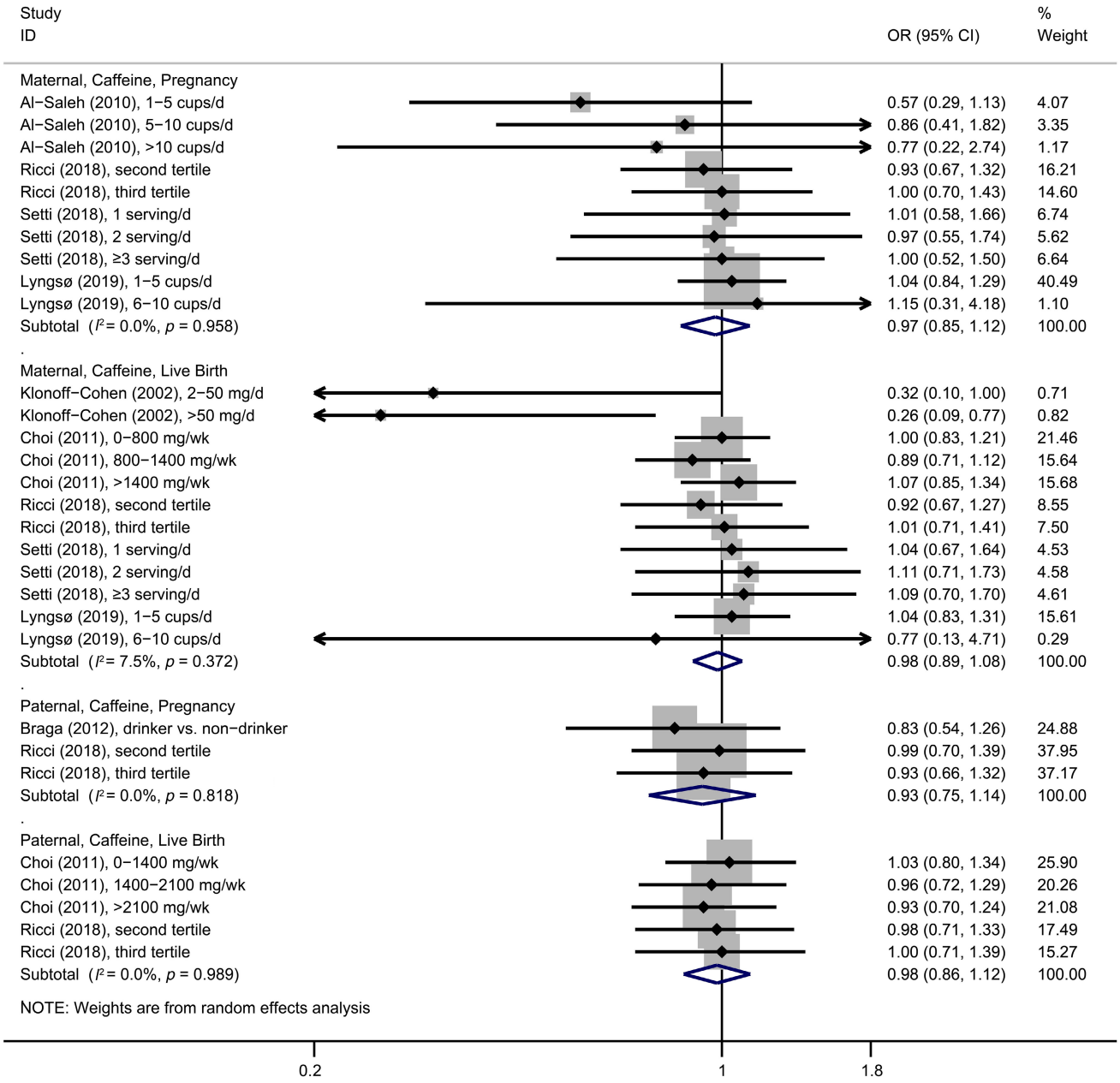

FIGURE 2 Forest plot of the association between caffeine consumption and in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) outcomes. CI, confidence interval; OR, odds ratio.

the associations were weak and mostly not significant, although a significantly decreased chance of pregnancy but not live birth was found for women drinking 84 g or more per week. For men, alcohol consumption was associated with decreased live birth rate after IVF/ICSI treatment when weekly consumption was greater than 84 g, but no association was found between men's alcohol consumption and partners' pregnancy rate.

Despite the long-held belief that caffeine is potentially unhealthy and may be harmful to the reproductive system, our analysis suggested that there was no association between caffeine consumption and IVF/ICSI pregnancy or live birth rate. These results were consistent with the majority of studies, which suggested that caffeine consumption might be unrelated to natural fertility.[32,33] However, a previous meta-analysis based on 27 studies showed an increased risk of spontaneous abortion in the general population, although significant heterogeneity and publication bias were found.[32] With regards to couples undergoing IVF/ICSI treatment, three included studies investigated the effect of caffeine consumption on miscarriage rate.[10,24,30] Only one study found significant associations between female's caffeine consumption, but the sample size was small (N = 62), and the CIs were very wide.[10] The relation between caffeine intake and spontaneous abortion after IVF/ICSI treatment still remains unclear because of the lack of research. To reduce the risk of pregnancy loss and low-birthweight neonates, it is still advised

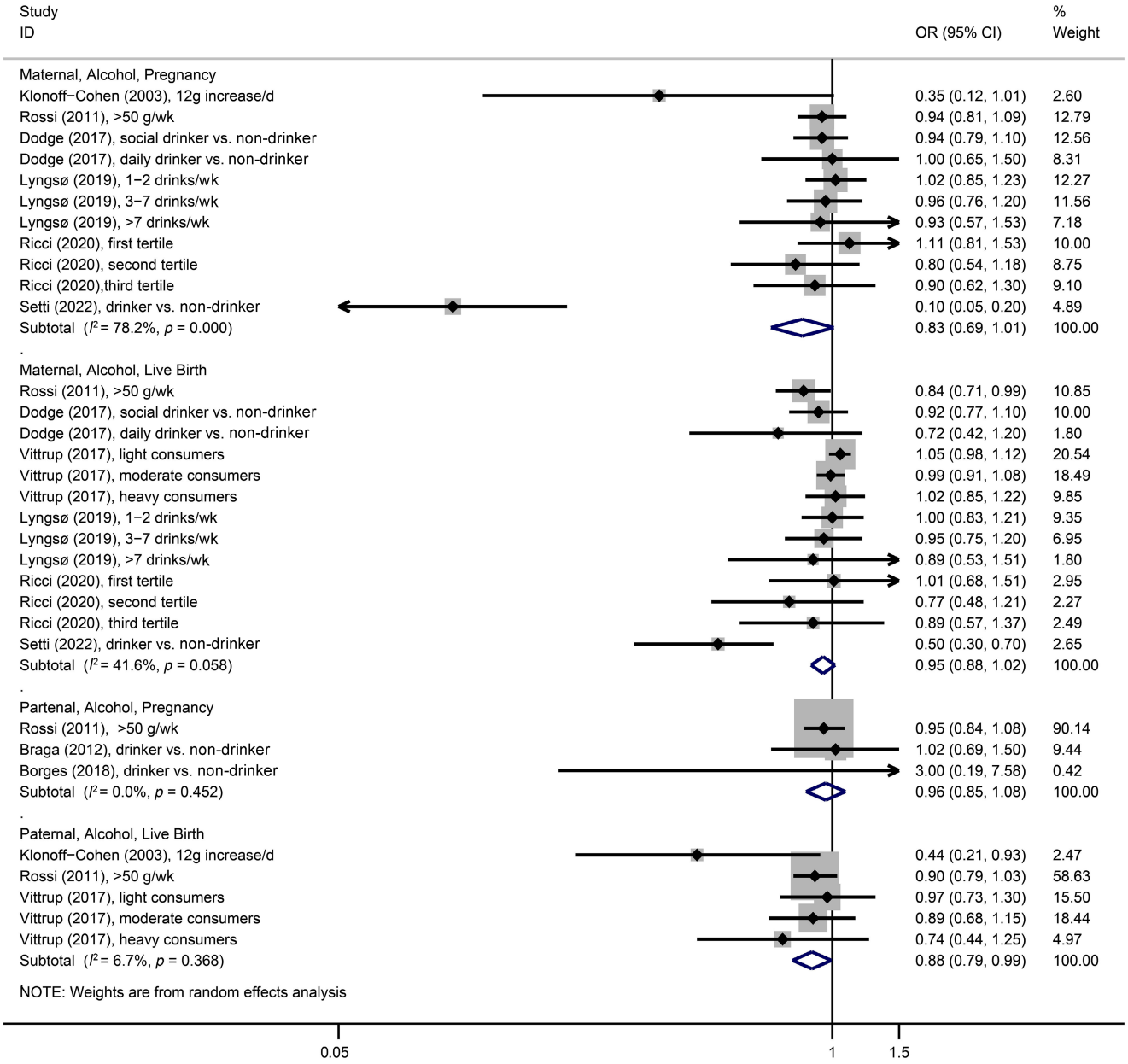

FIGURE 3 Forest plot of the association between alcohol consumption and in vitro fertilization/intracytoplasmic sperm (IVF/ICSI) outcomes. OR, odds ratio.

that women about to undergo fertility treatment should reduce their daily caffeine intake to 200 mg (two cups) as recommended by the European Food Safety Authority.[34]

Our analysis also found that women's alcohol intake was associated with decreasing IVF/ICSI pregnancy rate when weekly consumption was greater than 84 g, which was comparable to a previous review.[35] Of these pooled studies, two found that couples in which both partners consumed alcohol had a reduced probability of live birth after IVF/ICSI compared with couples in which one partner or both partners reported abstinence,[16,29] indicating that the detrimental effect will be more pronounced if both partners are drinkers. Yet, studies in the general population showed conflicting results and failed to reveal the adverse effect of moderate drinking on fertility.[35,36]

The main characteristics and results of studies not eligible for meta-analysis are presented in Table S2.[4,37–41] The majority of these studies are consistent with our meta-analysis. However, Karmon et al. found that there was an inverse relation between caffeine consumption and clinical pregnancy and live birth, whereas a positive association was found between the male's alcohol consumption and IVF/ICSI live birth rate.[39] The included studies also demonstrated that alcohol consumption was associated with poorer fertilization rate[23,24] and blastocyst formation rate,[23] as well as an increased spontaneous abortion rate.[26]

One of the included studies found that women who abstained from drinking or reduced the consumption of alcohol had a higher rate of becoming pregnant after IVF/ICSI treatment compared with

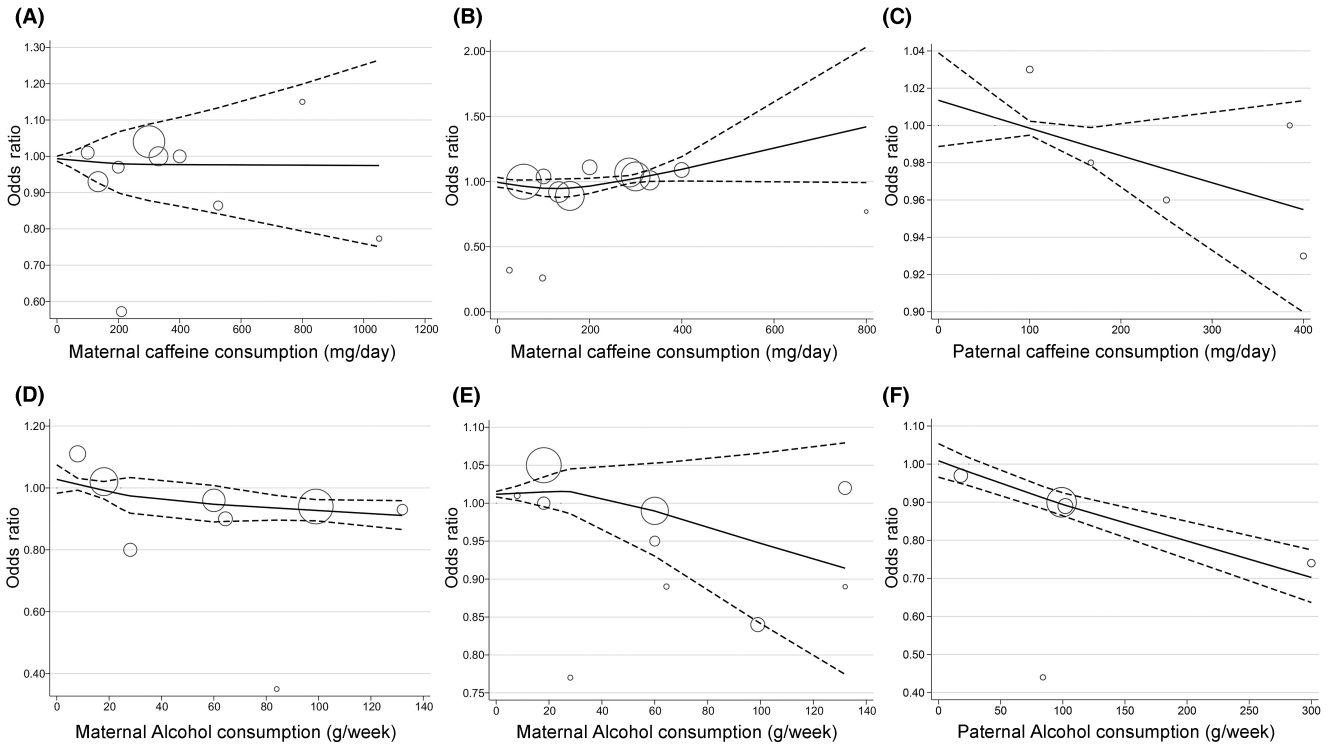

FIGURE 4 Dose–response association between caffeine and alcohol consumption and in vitro fertilization/intracytoplasmic (IVF/ICSI) outcomes. (A) Maternal caffeine consumption and pregnancy; (B) maternal caffeine consumption and live birth; (C) paternal caffeine consumption and live birth; (D) maternal alcohol consumption and pregnancy; (E) maternal alcohol consumption and live birth; (F) paternal alcohol consumption and live birth. OR, odds ratio.

those who maintained their drinking habits.[4] This emphasized the effect of exposure time and lifestyle change before and during the fertility treatment. However, in most pooled studies, the exposure data were self-reported and collected from the baseline questionnaire. Couples undergoing fertility treatment were reported to be prone to change their lifestyle, such as reducing caffeine and alcohol intake, and these changes could eliminate or attenuate the effect on IVF/ICSI outcomes.[4] Moreover, few studies focus on the impact of exposure time, as alcohol is an addictive substance that can cause various chronic diseases.[10,27] Hence, further studies should also consider these factors and examine the couple's follow-up consumption of caffeine and alcohol.

Caffeine, the most widely consumed methylxanthine, can act as a non-selective adenosine antagonist within the human body and therefore increase the intracellular concentration of cAMP and induce an increase in catecholamine excretion in the mother and fetus, which may lead to uteroplacental vasoconstriction and hypoxia.[32,42–44] In addition, it was reported that caffeine may alter circulating levels of luteal estrogens and sex hormone-binding globulin, suggesting that caffeine may exert a potential detrimental effect on the reproductive system by affecting the hypothalamic–pituitary–gonadal axis.[45] However, the results were inconsistent and detailed mechanisms or pathways are still poorly understood.

Compared with caffeine, the toxicity of alcohol has been well established and the safest level of drinking was reported to be zero.[46,47] Nevertheless, 25% of women and 39% of men globally were current drinkers in 2016, which corresponded to 2.4 billion people.[47] In the process of alcohol metabolism, reactive oxygen species (ROS) may form.[48] Excessive production of ROS will give rise to oxidative stress, which was thought to afflict the reproductive system and contribute to endometriosis, polycystic ovary syndrome, unexplained infertility, spontaneous abortion, and recurrent pregnancy loss.[49,50] Modifiable lifestyle factors such as smoking and habitual alcohol drinking may contribute to the endogenous production and exogenous exposure of ROS, which may partially explain why alcohol intake is associated with impaired IVF/ICSI outcomes.

Due to individual differences in caffeine and alcohol metabolism, the actual exposure may differ from the self-reported data. Only one study assessed the levels of caffeine in serum and follicular fluid, which found that serum caffeine levels were weakly but significantly correlated with the number of coffee cups.[22] More research focusing on caffeine levels in body fluids is needed to establish a greater degree of precision on this matter.

Our analysis provides a comprehensive and intuitive description of the association between caffeine and alcohol and IVF/ICSI outcomes by using a dose–response method. The included studies are of high quality, and our results remained materially unchanged with the sensitivity analysis. However, limitations should also be noted. The most important limitation lies in the relatively small number of included studies and the lack of randomized control trials. The effect of a higher amount of caffeine consumption (more

than six cups/day) remained uncertain because of the small sample size ($N = 23$ and $N = 16$).[12,22] As a result, the threshold effect shown in Figure 4B, that higher amount of caffeine consumption seemed to be positively associated with the chance of live birth, was unreliable.

Although most of the included studies adjusted for important potential confounders such as maternal age, body mass index, and smoking habits, the presence of residual or unmeasured confounding cannot be excluded because of the observational nature. Baseline laboratory test results such as follicle-stimulating hormone and anti-Müllerian hormone were related with IVF/ICSI outcomes,[51] but these included studies were not adjusted for them. Furthermore, the sources of exposure were various and different sources can contain other bioactive compounds in addition to caffeine and alcohol, such as sugar and artificial sweetener.[30,40] Further research is therefore needed to better understand the potential association between caffeine and alcohol consumption and IVF/ICSI outcomes.

5 | CONCLUSION

There was no association between caffeine consumption and pregnancy or live birth rate after IVF/ICSI treatment. However, women's alcohol consumption was associated with decreased pregnancy rate after IVF/ICSI treatment when weekly consumption was greater than 84 g. Men's alcohol consumption was associated with decreased live birth rate after IVF/ICSI treatment when weekly consumption was greater than 84 g.

AUTHOR CONTRIBUTIONS

YL and WR conceived and designed this study. WR and YL conducted database search, data extraction and analysis. WR wrote the manuscript. NL and QY revised the manuscript.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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