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SYSTEMATIC REVIEW

Maternal alcohol consumption and the risk of miscarriage in the first and second trimesters: A systematic review and dose–response meta-analysis

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Abstract

Introduction: According to a precautionary principle, it is recommended that pregnant women and women trying to conceive abstain from alcohol consumption. In this dose–response meta-analysis, we aimed to examine the association between alcohol consumption and binge drinking and the risk of miscarriage in the first and second trimesters.

Material and methods: The literature search was conducted in MEDLINE, Embase and the Cochrane Library in May 2022, without any language, geographic or time limitations. Cohort or case–control studies reporting dose-specific effects adjusting for maternal age and using separate risk assessments for first- and second-trimester miscarriages were included. Study quality was assessed using the Newcastle–Ottawa Scale. This study is registered with PROSPERO, registration number CRD42020221070.

Results: A total of 2124 articles were identified. Five articles met the inclusion criteria. Adjusted data from 153 619 women were included in the first-trimester analysis and data from 458 154 women in the second-trimester analysis. In the first and second trimesters, the risk of miscarriage increased by 7% (odds ratio [OR] 1.07, 95% confidence interval [CI] 0.96–1.20) and 3% (OR 1.03, 95% CI 0.99–1.08) for each additional drink per week, respectively, but not to a statistically significant degree. One article regarding binge drinking and the risk of miscarriage was found, which revealed no association between the variables in either the first or second trimester (OR 0.84 [95% CI 0.62–1.14] and OR 1.04 [95% CI 0.78–1.38]).

Conclusions: This meta-analysis revealed no dose-dependent association between miscarriage risk and alcohol consumption, but further focused research is recommended. The research gap regarding miscarriage and binge drinking needs further investigation.

KEYWORDS
alcohol consumption, binge drinking, miscarriage, pregnancy, spontaneous abortion

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; OR, odds ratio.

1 | INTRODUCTION

An alcohol intake of one drink per day or more during pregnancy is associated with adverse outcomes for both the woman and the fetus, including miscarriage, intrauterine growth retardation, low birthweight, stillbirth and malformations.[1,2] A recent estimation revealed an estimated prevalence between 41.3% and 60.4% for alcohol use during pregnancy in Russia, Denmark, the UK, Belarus and Ireland.[3] These figures were extrapolated from prevalence estimates from the 1980s and 1990s, not accounting for potential decline over time. Therefore, it is likely that these estimates may overestimate the current situation,[4] but these figures still call for action. Binge drinking, usually defined as ≥4 or ≥5 drinks per occasion,[5] is a prevalent behavior,[6,7] and considering that more than 50% of pregnancies are unplanned,[8] there is a potential risk of early alcohol exposure, especially among women who are unaware of their pregnancy. Hence, alcohol exposure prior to awareness of pregnancy may be a public health concern. In most countries, alcohol abstinence is officially recommended for pregnant women and pregnancy planners.[7,9,10] However, the level at which alcohol consumption is considered harmful remains controversial.[1,11]

Miscarriage is a frequent complication during pregnancy; it is estimated to occur in 12%–22% of all clinically recognized pregnancies,[12,13] particularly in the first trimester.[14] There are multiple known causes of miscarriage in the first trimester,[15,16] including but not limited to increasing maternal age, obesity and reproductive history, ie previous (recurrent) pregnancy loss and assisted conception.[15–17] In the second trimester, other causes seem to dominate, such as infection, cervical weakness, antiphospholipid syndrome and placental insufficiency, but in approximately half of miscarriage cases, the cause is unknown.[18] Due to the different etiologies of miscarriage in the two trimesters, when investigating an association between alcohol consumption and the risk of miscarriage, it is essential to consider the time of the event.

A meta-analysis of alcohol-related adverse pregnancy outcomes such as low birthweight and preterm birth[19] showed a potential dose–response association and substantial heterogeneity in the results of studies that did and did not attempt to adjust for confounding. Of note, studies presenting unadjusted estimates showed stronger associations with alcohol-related outcomes than did studies presenting adjusted estimates. Binge drinking results in elevated blood alcohol levels and this peak in alcohol levels has been hypothesized to be particularly detrimental during pregnancy[5,20] and could be a risk factor for miscarriage. However, further investigation is needed to describe any causal mechanisms. We are not aware of any meta-analysis investigating the relation between binge drinking and the risk of miscarriage, which constitutes a significant knowledge gap.

Various biological mechanisms have been suggested to explain the potential adverse effects of alcohol on pregnancy outcomes, including miscarriage, asphyxia,[21] chromosomal defects[22] and effects on the production of the prostaglandins PGE_2 and $PGF_{2\alpha}$.[23]

Key message

No dose-dependent association between miscarriage risk and alcohol consumption was found but further focused research is recommended.

The aim of this dose–response meta-analysis was to review systematically the literature and conduct an analysis based solely on adjusted data from original studies. Furthermore, in this systematic review and meta-analysis, we aimed to investigate a possible association between binge drinking and the risk of miscarriage.

2 | MATERIAL AND METHODS

This systematic review and dose–response meta-analysis was conducted according to the Preferred Reporting Item for Systematic reviews and Meta-Analysis (PRISMA) guidelines (Table S1). The protocol is available from the PROSPERO systematic review register (CRD42020221070). The study adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Table S2). No core outcome set was available for the outcomes of this review and the study was conducted without patient involvement.

2.1 | Data sources

With support from a medical librarian, the literature search was conducted in MEDLINE, Embase and the Cochrane Library. The final search was performed in May 2022. The full search terms for each search engine are described in detail in Appendix S1. The reference lists and citations of all obtained articles were read in full. If an article from a reference list or a cited article was not present in the search result, the article was added and read. Abstracts that were not published as full articles were not considered. There were no limitations regarding date of publication, geographic origin or language, but the search was limited to human studies. For studies with duplicate publications, the articles presenting adjusted data were chosen. Each study was included only once in the meta-analysis. The corresponding authors of studies with no clear trimester division or a poor description of the adjustments were contacted by email. We contacted three authors but, unfortunately, did not receive answers from any of them.

2.2 | Study selection

Titles, abstracts and relevant full text articles were evaluated by two independent reviewers (KRS and SGP) to assess the agreement between the inclusion and exclusion criteria. Any disagreements were resolved by a third party from the review team (USK). All articles

published in languages that the authors could not understand were translated into Danish/English by a competent translator.

2.3 | Eligibility criteria

Only original cohort or case–control studies investigating maternal alcohol consumption (in the preconception and/or early pregnancy periods or only in early pregnancy) and the risk of miscarriage were included. Alcohol intake in early pregnancy could be measured in the first trimester (for first- and second-trimester miscarriages) or second trimester (second-trimester miscarriage only). If a study measured alcohol exposure as a dichotomous exposure, the study was not considered further, as this precluded a dose–response meta-analysis. Studies with only unadjusted data were also excluded, as maternal age, at a minimum, should be accounted for. Furthermore, we only included studies with a clear distinction between first-trimester miscarriage, defined as a maximum gestational age of 11 + 6 weeks, and second-trimester miscarriage, defined as a gestational age ranging from 12 + 0 to 21 + 6 weeks or 27 + 6 weeks, depending on the time period for data collection; studies were only included if the definitions were clear and explicit. All studies fulfilling the inclusion criteria except the trimester classification were read in full to ensure that no relevant analyses were missed.

Studies on binge drinking were included if episodic drinking was defined as ≥4 drinks or ≥5 drinks on a single occasion during the preconception period or pregnancy.[5] For further descriptions of the inclusion and exclusion criteria, see Table S3.

2.4 | Outcome measures

The primary outcome measure was first-trimester miscarriage and the secondary outcome was second-trimester miscarriage.

2.5 | Data extraction

Data from the included studies were independently extracted by three reviewers. Any disagreements were resolved by discussion. The extracted information included the following study characteristics: author, year, country and study design, including the number of participants, exposure and reference group. Extracted information was related to pregnancy outcomes included trimester definitions, information on bias, adjustments and effect estimates with confidence intervals.

The Newcastle–Ottawa Scale[24] (scores ranging from 0–9, with 9 indicating the highest score) was used to assess the quality of the included studies as previously recommended by the Cochrane Non-Randomized Studies Methods Working Group. The scale is divided into three categories: the selection of the study group, the comparability between the groups and the ascertainment of the exposure for case–control studies and the outcome for cohort studies. Scoring was performed by two independent readers (KRS and SGP) and scores were subsequently compared. Disagreements were resolved by discussion with a third author (USK).

2.6 | Statistical analyses

A two-step meta-analysis was conducted using STATA 17 (StataCorp. LLC) with the package drmeta.[25] Log-linear dose–response effects were compared between articles. Standard errors and correlations were estimated by the command drmeta based on the Greenland and Longnecker method.[26] This method allowed for the comparison of the effect sizes reported as hazard ratios and risk ratios in the included studies. Inverse variance weighted random effects meta-analysis was employed using a Sidik–Jonkman two-step tau^2 estimator, which has been demonstrated to have reduced bias compared with other estimation methods.

A standard drink was defined as 12 g of pure alcohol;[27] for studies not using this definition, the estimates were recalculated to ensure that all estimates were comparable across studies. All estimates are presented for a one-drink increase per week.

Statistical heterogeneity between the studies was assessed by Cochran's Q-test. Furthermore, the I^2 index was used to evaluate the percent of total variation in the study estimates due to heterogeneity rather than chance. Due to the large amount of heterogeneity among the studies, a subgroup analysis was conducted using a linear effect regression model. A funnel plot of the linear effects was used to identify potential publication bias.

3 | RESULTS

The systematic literature search resulted in 2124 articles, of which five met the inclusion criteria for this study (Figure 1). A description of the studies included in this meta-analysis is presented in Table 1. Information on the excluded studies is provided in Table S4.

The primary meta-analysis regarding the association between alcohol consumption and the risk of miscarriage in the first trimester included four studies. Two studies were from Denmark (Nilsson et al.[17] and Kesmodel et al.[30]), one was from the USA (Gaskins et al.[28]) and one was from Italy (Parazzini et al.[31]). One of the studies was a case–control study[31] and the remaining three were cohort studies.[17,30,32] Lifestyle information was derived from interviews[17,31] or questionnaires[28,30] quantifying alcohol consumption per week. Of the four studies, two revealed an association between alcohol consumption and the risk of miscarriage, whereas the other two studies showed no association.

In the meta-analysis of miscarriage in the first trimester, data from 153 619 women were analyzed. We estimated a 7% increased risk of miscarriage for each additional drink consumed per week in the first trimester (odds ratio [OR] 1.07, 95% confidence interval [CI] 0.96–1.20), although the CI indicates the findings to be compatible with no increased risk overlapped 1 (Figure 2). Due to

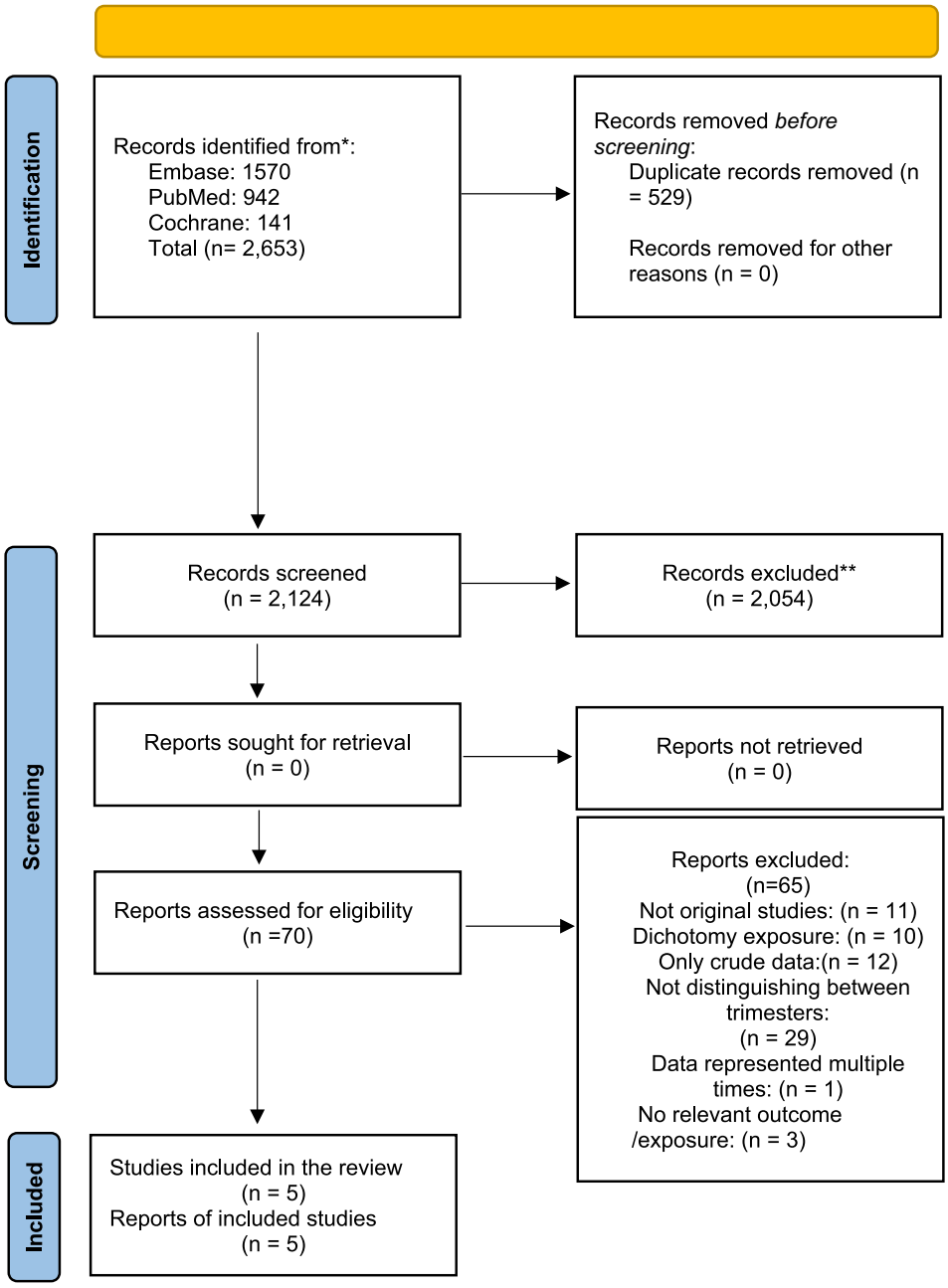

FIGURE 1 PRISMA 2020 flow diagram.

heterogeneity among the studies (Cochran's Q = 92.81, $p < 0.001$; $I^2 = 95.7\%$), a subanalysis restricted to the two Danish cohort studies was conducted. This analysis showed a 16% increased risk for miscarriage for each additional drink in the first trimester (OR 1.16, 95% CI 0.49–2.73); however, the CI was wide due to the reduced sample size.

A leave-one-out sensitivity analysis was also performed (Appendix S2). The leave-one-out sensitivity analysis did not meaningfully alter the estimates and 95% CI by leaving out any of the studies.

Two Danish studies (Nilsson et al. and Kesmodel et al.)[17,30] and two studies from the USA (Gaskins et al. and Harlap et al.)[28,32] were included in the assessment of miscarriage in the second trimester.

In the meta-analysis of the assessment of miscarriage in the second trimester, data from 458 154 women were analyzed. In the second trimester, we observed a 3% increased risk for each additional drink consumed per week (OR 1.03, 95% CI 0.99–1.08), with the CI indicating compatibility with no increased risk (Figure 3).

The methodological quality was generally higher in the cohort studies (NOS scores of 6–7) than in the case–control study (NOS score of 5) (Table 1).

Only one article regarding binge drinking and the risk of miscarriage was found; therefore, no meta-analysis was performed. The study results showed no association between binge drinking and the risk of miscarriage in the first trimester (OR 0.84, 95% CI 0.62–1.14) or the second trimester (OR 1.04, 95% CI 0.78–1.38).[20]

TABLE 1 Description of the studies included in the meta-analysis.

Author/year/ref/ country/NOS score	Study design and sample size	Exposure	Reference	Outcome	Collection of exposure and birth outcome data	Effect estimate and confidence interval	Model adjustment
Gaskins et al. 2016[28] USA NOS score of 6	Prospective cohort study of 116480 female nurses aged 24–44 years at baseline (1989) The final sample consisted of 27580 pregnancies for 17929 women.	Average prepregnancy alcohol consumption	Pregnant women with no alcohol use	**Spontaneous abortions and stillbirths** 1: GA <8 weeks 2: GA of 8–11 weeks 3: GA of 8–11 weeks 4: GA of 12–19 weeks 5: GA >20 weeks	**Exposure:** Self-report questionnaire. **Birth outcomes:** Self-report questionnaire.	**g/day** aRR 95% CI **1st trimester (<8 weeks)** 0: 1.00 0.1–1.9: 1.02 (0.90–1.16) 2–4.9: 0.95 (0.82–1.10) 5–9.9: 0.98 (0.83–1.16) >10: 1.09 (0.92–1.30) **1st trimester (8–11 weeks)** 0: 1.00 0.1–1.9: 1.08 (0.96–1.22) 2–4.9: 1.06 (0.93–1.21) 5–9.9: 1.00 (0.86–1.17) >10: 1.02 (0.86–1.22) **2nd trimester** 0: 1.00 0.1–1.9: 1.07 (0.91–1.25) 2–4.9: 1.07 (0.89–1.28) 5–9.9: 1.06 (0.86–1.30) >10: 0.81 (0.62–1.05)	**Maternal age** **Energy intake** **Prepregnancy BMI** (kg/m^2) 18.5 18.5–24.9 25–29.9 >30 missing **Smoking status** Never Former Current Missing **Physical activity** (MET-h/wk) 3, 3–8.9 9–17.9 18–26.9 27–41.9 >42 Missing **Year of pregnancy** **History of infertility** No Yes Missing **Marital status** Married Not married **Race** White Other **Multivitamin use** Yes No Missing **Caffeine intake** (quintiles)

(Continues)

TABLE 1 (Continued)

Author/year/ref/ country/NOS score	Study design and sample size	Exposure	Reference	Outcome	Collection of exposure and birth outcome data	Effect estimate and confidence interval	Model adjustment
Harlap et al. 1980[29] USA NOS score of 7	Prospective cohort study. Women who were attending their first antenatal visit in 1974–1977 at one of 13 clinics in Northern California were invited to participate. 32 019 women were included in the study.	Average alcohol consumption during early pregnancy	Pregnant women with no alcohol use	**Spontaneous abortions** 1: GA of 5–14 weeks 2: GA of 15–27 weeks	**Exposure:** Self-report questionnaire. **Birth outcomes:** Surveillance of patient hospital admissions, medical record numbers, names, and dates of admissions.	**Drinks per day** aRR 95% CI **2nd trimester** 0: 1.00 0.5: 1.03 (0.57–1.86) 1–2: 1.98 (1.04–3.77) >3: 3.53 (1.77–7.01)	**Maternal age (years)** <20 20–24 25–29 30–36 >35 **Gestational age at entry of the study**
Kesmodel et al. 2002[30] Denmark NOS score of 6	Prospective cohort study of women from Århus, Denmark (1989–1996) 18 226 women completed the questionnaire	Average alcohol consumption during pregnancy	Pregnant women consuming less than 1 drink per week.	**Spontaneous abortion in the first or second trimester** 1: GA of 7–11 weeks 2: GA of 12–27 weeks	**Exposure:** Self-report questionnaire. **Birth outcomes:** From register data (Danish National Patient Registry) and questionnaires.	**Drinks per week** aHR 95% CI **First trimester** <1: 1.00 1–2: 1.3 (0.8–2.0) 3–4: 0.8- (0.4–1.7) >5: 3.7 (2.0–6.8) **2nd trimester** <1: 1:00 1–2: 1.2 (0.9–1.7) 3–4:1.1 (0.7–1.9) >5: 0.6 (0.2–1.9)	**Maternal age (years)** 24 25–29 30–34 >34 **Smoking** (Cigarettes/day) 0 1–10 >11 cigarettes **Caffeine** (mg/day) <200 200–399 >400 **BMI** <18.5 18.5–24 25–29 ≥30 **Marital status** Married/Cohabiting Single **Occupational status** Employed Not employed Student **Education (years)** <10 10 ≥10 **Parity** 0 1 ≥2

TABLE 1 (Continued)

Author/year/ref/ country/NOS score	Study design and sample size	Exposure	Reference	Outcome	Collection of exposure and birth outcome data	Effect estimate and confidence interval	Model adjustment
Nilsson et al. 2014[17] Denmark NOS score of 7	Prospective cohort study based on the DNBC (1996–2002) 88 373 women completed interviews.	Average alcohol consumption the first 16 weeks of pregnancy	Pregnant women with no alcohol use	**Miscarriage** 1: GA of 6–12 weeks 2: GA of 13–16 weeks 3: GA of 17–22 weeks 4: GA >22 weeks	**Exposure**: Telephone interview at a GA of 12 weeks (mean GA of 10.6 weeks) **Birth outcomes**: From register data (Danish National Patient Registry) and self-reported information.	**Drinks per week** aHR 95% CI **First trimester** 0: 1.00 ½ −1½.: 1.05 (0.93–1.18) 2–3½: 1.56 (1.34–1.81) 4+: 2.81 (2.25–3.50) **2nd trimester** 0: 1:00 ½ −1½: 1.13 (1.00–1.26) 2–3½: 1.34 (1.13–1.58) 4+: 1.64 (1.23–2.19)	**Maternal age (years)** <24 25–29 30–34 35–39 +40 **Amount of exercise during pregnancy (minutes/week)** 0 1–60 61–120 121–180 181–300 ≥300 **Smoking**: 0 1–10 >11 cigarettes **Coffee consumption during pregnancy** (cups per day) 0 ½-7½ 8+ **Parity** Nulliparous Parous **Highest household occupational status** Higher grade Lower grade Skilled workers Unskilled Students Economically inactive for >1 year **Prepregnancy weight status** Underweight Normal weight Overweight Obese **Work schedule during pregnancy** Not working Daytime Fixed evening Fixed night Rotating shift (− nights) Rotating shift (+nights) **Previously diagnosed genital diseases** No diagnosis of genital disease Ever had cervical conization Dysplasia in the cervix Other genital diseases

(Continues)

TABLE 1 (Continued)

Author/year/ref/ country/NOS score	Study design and sample size	Exposure	Reference	Outcome	Collection of exposure and birth outcome data	Effect estimate and confidence interval	Model adjustment
Parazzini et al. 1994[31] Italy NOS score of 5	Case–control study. Women admitted for miscarriage confirmed by uterine curettage and pathological examination. Controls: women who gave birth to healthy infants at term. (1990–1993) 462 cases and 814 controls.	Average alcohol consumption during the preconception and early pregnancy periods	Non-drinkers	**Spontaneous abortions**	**Exposure:** Interviews by trained interviewers. **Outcomes:** Admission for miscarriage/ giving birth at term.	**Drinks/week** aRR (95% CI) **First trimester** 0 or occasional: 1 1–7: 1.3 (0.9–1.7) >7: 0.9 (0.7–1.3)	**Maternal age (years)** <25 26–30 31–35 >35 **Education (years)** <12 ≥12 **Previous live births** 0 ≥1 **Previous miscarriages** 0 ≥1 **Smoking in the first trimester** Yes/No **Coffee drinking in the first trimester** Yes/No

Abbreviations: aHR, adjusted hazard ratio; aRR, adjusted risk ratio; DNBC, Danish National Birth Cohort; NOS, Newcastle–Ottawa Scale.

Regarding publication bias, the visual inspection of the funnel plot was noninformative due to the small number of studies included. For the same reason, and because there were no high-scoring studies, no subanalyses based on NOS score were performed

4 | DISCUSSION

In this systematic review, we found a limited number of studies assessing the specific association between alcohol intake and the risk of miscarriage in the first and second trimesters separately with adjustment for maternal age. The meta-analysis revealed that alcohol consumption during early pregnancy is not associated with the risk of miscarriage in the first or second trimester. The subgroup analysis including the more homogeneous studies yielded larger but more uncertain estimates regarding the putative effect of alcohol consumption. We only identified one study on binge drinking and the risk of miscarriage; this did not show an association between binge drinking and the risk of miscarriage in either the first or second trimester.

There is a large body of literature on alcohol consumption and its effects on pregnancy, including the risk of miscarriage. The inclusion criteria for this meta-analysis were defined before the literature search was conducted. The main reasons for the exclusion of 65 articles that did not meet the inclusion criteria were their lack of differentiation between trimesters and/or their lack of adjustment for confounding.

Previous meta-analyses on other alcohol-related adverse pregnancy outcomes[19] showed substantial heterogeneity in the results of studies adjusting vs not adjusting for confounding. The criteria to only include adjusted estimates reduced the number of available studies. However, we believe that this trade-off was necessary, as confounding factors such as maternal age, smoking and body mass index (BMI) have been shown to be crucial with regard to adverse pregnancy outcomes.[29] To our knowledge, this is the first meta-analysis regarding alcohol consumption and the risk of miscarriage with exclusively adjusted data.

Other inclusion criteria that substantially reduced the number of studies in this meta-analysis were our strict definitions and the division of trimesters. Because of changes in the gestational cut-off between stillbirth and miscarriage in clinical practice over time, we used different thresholds according to the cohorts included in this review. Furthermore, older studies generally did not distinguish between the trimesters.

We observed a homogeneous distribution of estimates between maternal alcohol consumption and the risk of miscarriage in the second trimester (within the range of 0.99–1.08), indicating that an association between maternal alcohol consumption and the risk of miscarriage in the second trimester is unlikely. However, the estimates of the association between maternal alcohol consumption and the risk of miscarriage in the first trimester were more heterogeneous. This heterogeneity of the estimates could partly be explained by the differences in the studied populations

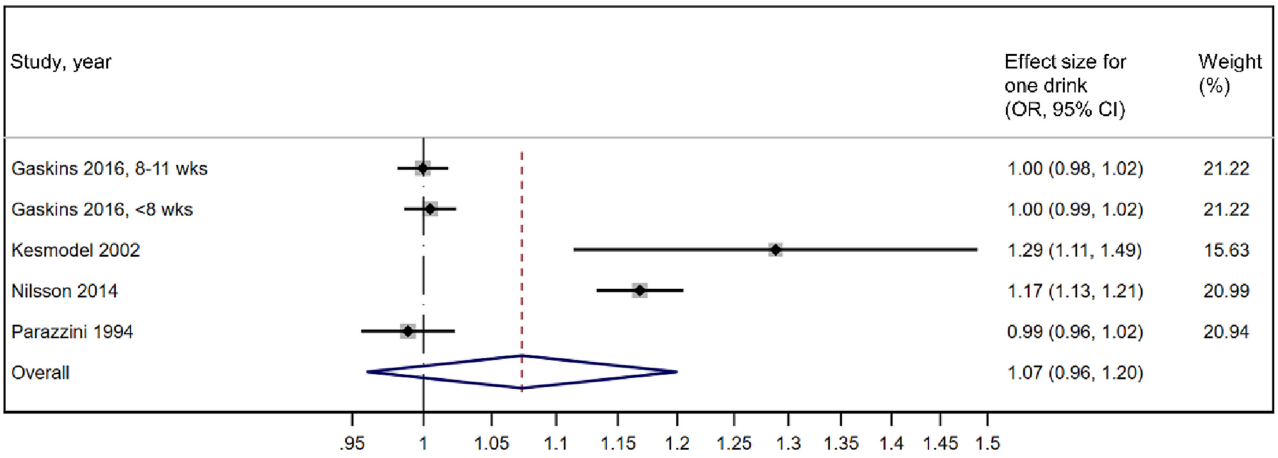

FIGURE 2 Forest plot showing the meta-analyzed association between maternal alcohol consumption and the risk of first-trimester miscarriage ($n = 153\,619$). Random effects inverse-variance weighted meta-analysis was performed using a Sidik–Jonkman two-step tau^2 estimator. The forest plot shows the estimated association between maternal alcohol consumption (effect size for one drink) and the risk of first-trimester miscarriage. Heterogeneity: Cochran's Q = 92.81, $p < 0.001$, $I^2 = 95.7\%$.

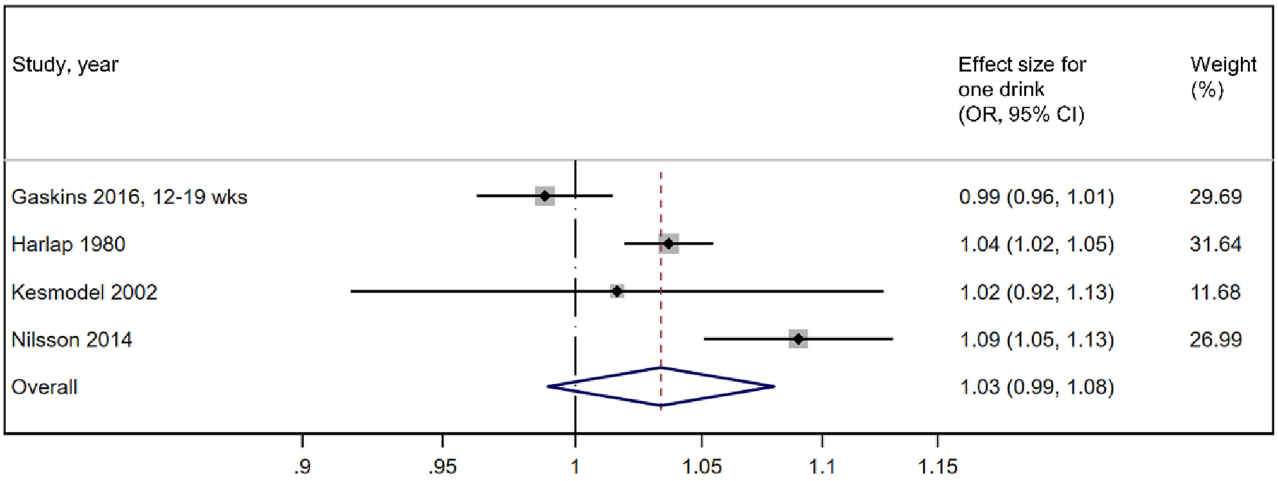

FIGURE 3 Forest plot showing the meta-analyzed association between maternal alcohol consumption and the risk of second-trimester miscarriage ($n = 458\,154$). Random effects inverse-variance weighted meta-analysis was performed using a Sidik–Jonkman two-step tau^2 estimator. The forest plot shows the estimated association between maternal alcohol consumption (effect size for one drink) and the risk of second-trimester miscarriage. Heterogeneity: Cochran's Q = 19.39, $p < 0.001$, $I^2 = 84.5\%$.

or in the adjustments for potential confounders. However, heterogeneity could also have originated from the possibility that many of the miscarriages occurring before potential study inclusion were missed, and if alcohol has differential effects at different gestational weeks in early pregnancy, this may partly explain such heterogeneity. A recent prospective cohort study including pregnancy planners and women in early pregnancy showed an 8% increased risk of miscarriage (adjusted HR 1.08, 95% CI 1.04–1.12) for each additional week of alcohol exposure, which aligns with our study results.[33]

The etiology of miscarriage is a combination of various factors and pathways. It is known that up to 60% or more of miscarriages in the first trimester are caused by chromosomal aberrations.[34,35] In animal studies in which eggs were briefly exposed to ethanol, chromosome aberrations were induced in some eggs.[36] This could partly explain an association between alcohol consumption and the risk of miscarriage in the first trimester, as alcohol may lead to chromosomal aberration and thereby miscarriage.

Chromosomal abnormity disorders are estimated to account for 15% of second-trimester miscarriages[37]; however, a range of other reasons for miscarriage are known to exist.[18] Placental abnormalities are known to be related to adverse pregnancy outcomes, and alcohol exposure has been shown to affect the placenta in different ways.[38] Dose-dependent vasoconstriction is caused by ethanol, leading to lower blood perfusion of the fetus, and increased nitric oxygen levels, which could lead to acidosis.

Furthermore, an association between alcohol exposure and placental abruption has been described.[39] A study suggested that the risk of stillbirth increased with increasing maternal alcohol intake, mainly due to fetoplacental dysfunction.[40] Although these studies were limited to the later part of pregnancy, these pathophysiological mechanisms could also be relevant during the second trimester.

Despite the aforementioned strengths, our study has some limitations. Reverse causation has been suggested as a possible explanation for the association between lifestyle factors and the risk of miscarriage, primarily in association with caffeine intake.[41] The mechanism is that when nausea disappears, caffeine and alcohol intake may increase, and in the case of a missed abortion, the disappearance of nausea may lead to increased exposure. Nausea occurs in up to 80% of all pregnant women and could be a proxy for reverse causation.[42] However, in our systematic review, we did not find any studies adjusting for nausea. A statistical limitation in this study was the considerable heterogeneity, especially in the first trimester, which was expected due to geographic differences, varying study designs, data collection methods, adjustments and the statistical methods employed. Age was the only confounder adjusted for in all five studies, but four studies accounted for smoking and caffeine intake and three accounted for BMI and parity. Such differences may well explain some of the differences in the results among the studies. It is particularly noteworthy that the study revealing the most prominent positive associations was the one accounting for only age and GA at study entry, possibly leaving more room for confounding compared with the remaining studies.[32] Furthermore, the ascertainment of exposure differed among studies. However, for all the studies, as anticipated, the majority of pregnant women did not consume alcohol during the first trimester. Even so, a small group did consume low amounts of alcohol, and a minority consumed ≥4 drinks a week. For the two Danish studies, less than 5% of the women who experienced miscarriage had a continued high alcohol consumption of ≥4 drinks a week, whereas ~10% of the women from Italy and the USA did so. Unfortunately, none of the studies investigated whether drinking patterns were related to binge drinking.

We developed a random effects model accounting for the between-study variation. Furthermore, we explored the observed heterogeneity and conducted subgroup analysis on a homogeneous subset of studies. No studies were excluded due to heterogeneity. Another limitation in this meta-analysis relates to the small number of studies included. This is clearly a result of our strict inclusion criteria, but these criteria were decided a priori based on limitations in earlier studies, which revealed the importance of taking confounding into account and distinguishing between trimesters.

The results of our meta-analysis indicate no statistically significant associations between alcohol consumption and the risk of miscarriage. However, it is still plausible that there is an association in the very early part of the first trimester, and as miscarriage is a frequent complication in very early pregnancy, even a small change in risk may be of clinical relevance.

A recent meta-analysis that did not focus on differences between trimesters showed that exposure to alcohol during pregnancy was associated with an increased risk of miscarriage, with results very similar to ours; for women consuming <5 alcoholic drinks per week, each additional drink per week was associated with a 6% increase in miscarriage risk (OR 1.06, 95% CI 1.01–1.10).[43]

The meta-analysis of Lyngsø et al.[44] investigating the association between caffeine consumption and fecundity and the risk of miscarriage, showed a higher risk of miscarriage with the consumption of coffee, with a relative risk of 1.37 (95% CI 1.19–1.57) for 300 mg caffeine/day and 2.32 (95% CI 1.62–3.31) for 600 mg caffeine/day, equivalent to 3 and 6 cups of coffee/day, respectively. Studies adjusting for nausea mainly revealed higher risk estimates, suggesting that the role of reverse causation in relation to lifestyle factors is, at best, unclear.

Four of the five studies included in our meta-analysis adjusted for coffee/caffeine intake. The results of our meta-analysis reveal the difficulty of addressing associations between alcohol and adverse outcomes during pregnancy,[43,45] eg adjusting for potential confounders such as age and nausea and distinguishing between trimesters. Even though we included only confounder-adjusted studies, unmeasured confounding may still explain some or all of the association described, as seen in comparable areas.[46] Another crucial challenge regarding studies on miscarriage is to include women early enough, ensuring that all miscarriages, including the earliest ones, are detected. Most miscarriages occur early in pregnancy[14] and are not always reported to a clinician. This could lead to an underestimation of the number of miscarriages that could be associated with alcohol consumption. In one of the included studies, the rate of miscarriage was lower than expected, possibly due to early miscarriages being missed.[17] Alcohol consumption during early pregnancy may increase the risk for miscarriage. Although the critical timing of drinking remains unknown, every additional drink per week seems to increase the risk. This finding complements present guidelines,[9,10] where total abstinence is recommended during pregnancy. From a public health point of view, a recommendation of abstinence is still warranted. However, from a clinical perspective, when counseling women who have consumed a few occasional drinks during early pregnancy, our findings show that solid evidence remains limited, and the best available estimate is compatible with no increased risk, which can be used to calm women if they worry. It is the role of the healthcare personnel to support these women with low alcohol consumption, to encourage them to stop drinking but support them if they had a drink, eg before pregnancy recognition. Changing national or international guidelines on alcohol drinking in general during pregnancy would not be appropriate.

5 | CONCLUSION

There is a gap in the evidence regarding binge drinking and the risk of miscarriage; due to the occurrence of binge drinking among women of fertile age, this is a point of interest for future research. Future studies should include pregnancy planners or women in the very early stage of pregnancy to minimize the underestimation of

early miscarriage. Furthermore, collecting information about alcohol consumption and the most important confounders, including age, smoking status and nausea, will continuously be challenging but important factors in future studies.

AUTHOR CONTRIBUTIONS

KRS, KS-L, SGP and USK contributed to the conception and design of the study and the acquisition of data, and the interpretation of the results. NHB performed the statistical analysis. KRS drafted the paper, and all authors revised it critically for important intellectual content, approving the final version to be published. All authors agree to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

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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