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Dose-response relationship between alcohol consumption before and during pregnancy and the risks of low birth weight, preterm birth and small-size-for-gestational age (SGA) – A systematic review and meta-analyses

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Abstract

Background—The effects of moderate alcohol consumption during pregnancy on adverse pregnancy outcomes have been inconsistent.

Objective—To review systematically and perform meta-analyses on the effect of maternal alcohol exposure on the risk of low birth weight, preterm birth and small-size-for-gestational age (SGA).

Search Strategy—Using Medical Subject Headings, a literature search of MEDLINE, EMBASE, CINAHL, CABS, WHOlist, SIGLE, ETOH, and Web of Science between 1 January 1980 and 1 August 2009 was performed followed by manual searches.

Selection Criteria—Case control or cohort studies were assessed for quality (STROBE), 36 available studies were included.

Data collection and Analysis—Two reviewers independently extracted the information on low birth weight, preterm birth and SGA using a standardized protocol. Meta-analyses on dose-response relationship were performed using linear as well as first-order and second-order fractional polynomial regressions to estimate best fitting curves to the data.

Main Results—Compared to abstainers, the overall dose-response relationships for low birth weight and SGA had no effect up to 10 g/day (an average of about 1 drink/day) and preterm birth had no effect up to 18 g/day (an average of 1.5 drinks/day) of pure alcohol consumption; thereafter, the relationship had monotonically increasing risk for increasing maternal alcohol

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Contribution to authorship JP & JR conceived the study, conducted the underlying systematic reviews and supervised all aspects of its implementation and led the writing. JP and HI also contributed in the methodology and quantitative analysis of the study. JP, RA, SM and VWVJ were involved with data interpretation, critical revisions of the paper and provided approval for its publication.

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consumption. Moderate consumption during pre-pregnancy was associated with reduced risks for both outcomes.

Conclusions—Dose-response relationship indicates that heavy alcohol consumption during pregnancy increases the risks of all three outcomes while light to moderate alcohol consumption shows no effect. Preventive measures during antenatal consults should be initiated.

Keywords

alcohol; neonatal development; low birth weight; preterm birth; SGA; meta-analysis

INTRODUCTION

Many observational studies have been published on the topic of alcohol consumption in pregnant women and the effects on the development of their fetus and child. The association of heavy maternal alcohol consumption during pregnancy and various adverse birth outcomes has been well established [1;2]. Also, excessive alcohol consumption during pregnancy is associated with adverse postnatal behavioural development [3]. However, studies focused on the associations of low to moderate alcohol consumption during pregnancy with birth outcomes showed inconsistent results [4–9]. In general, low to moderate maternal alcohol consumption is considered as one alcoholic drink at most per day on average. Some studies did not find any associations, while others found adverse or even beneficial effects. A recent systematic review of Henderson et al [10] also observed no convincing evidence for adverse effects of low to moderate maternal alcohol consumption on pregnancy outcomes, such as miscarriage, stillbirth, fetal growth restriction, prematurity, birth weight, small-size-for-gestational age (SGA) at birth and birth defects including fetal alcohol syndrome. The authors were not able to perform a meta-analysis due to considerable high heterogeneity in the methods of the various studies used in their systematic review. They suggested that differences in results between studies might be due to differences in study design and in timing and methods of assessment of maternal alcohol consumption. Also, differences in adjustment for possible confounding factors between the studies may explain inconsistent results.

The aim of this systematic review and meta-analysis was to assess the dose-response association of maternal alcohol exposure before and during pregnancy with the risks of low birth weight, preterm birth and SGA.

METHODS

Search Strategy

We conducted a systematic literature search for potentially relevant original papers using the following electronic databases from January 1980 to first week of June 2009: MEDLINE, EMBASE, CINAHL, CABS, WHOlist, SIGLE, ETOH, and Web of Science. We used following keywords and medical subject headings to identify relevant articles in electronic databases: (‘alcohol*’ or ‘ethanol’ or ‘light drinking’ or ‘moderate drinking’) AND (‘birth weight’ or ‘low birth weight’ or ‘gestational age’ or ‘small for gestational age’ or ‘preterm*’ or ‘pregnancy outcome’ or ‘pregnancy complication’ or ‘prenatal*’) AND (‘case’ or ‘cohort’ or ‘ratio’ or ‘risk*’ or ‘prospective*’ or ‘follow*’). No language restrictions were applied. Eligible studies were original publications (we excluded letters, editorials, conference abstracts, reviews, and comments) of case-control and cohort studies reporting incidence, hazard ratios, relative risks or odds ratios of alcohol consumption in comparison to abstainers. In addition, bibliographies of key retrieved articles, relevant reviews and meta-analyses were hand searched.

The strategy resulted in 1345 hits; of which 90 appeared relevant upon initial inspection. The contents of these abstracts or full-text manuscripts identified during the literature search were reviewed independently by 2 reviewers to determine whether they met the criteria for inclusion. Articles were considered for inclusion in the systematic review if they reported data from an original study (i.e., no review articles). When there were discrepancies between investigators for inclusion or exclusion, a third reviewer (J.R.) conducted additional evaluation of the study and discrepancies were resolved in consultation. To be included in our meta-analysis, a published study had to meet the following criteria:

1. Reported data were from an original study (i.e., no review articles),
2. Cohort or case-control study in which medically confirmed low birth weight (defined as <2500 grams), preterm birth (<37 weeks gestation) and SGA (<10th percentile of gestational age adjusted birth weights) were the end points,
3. Reporting of relative risk or odds ratios or hazard ratios (or data to calculate these risks) of low birth weight, preterm birth and SGA associated with alcohol consumption.

Thirty six studies met all of the inclusion criteria and were included in the meta-analysis. Twenty four had dose-response information with at least three or more drinking exposure groups and 12 studies had exclusive data on drinker versus no drinker. Four previous systematic reviews [10–13] and three meta-analyses [14–16] were identified and excluded. For details on study exclusion, please see Figure 1.

Data Extraction

All data were independently extracted by means of a standardized protocol. Study characteristics recorded were as follows: title of the study, lead author surname, publication year, source of publication, country of origin, study design (cohort or case-control), characteristics of the study population (e.g., size of the sample; method of sampling; age distribution, average age, and ethnicity), measures of outcome and exposure, duration of follow-up (for prospective cohort studies), confounding factors controlled for by matching or adjustment, and the risk estimates (relative risk or odds ratios or hazard ratios) of birth outcomes studied, compared to abstainers, associated with alcohol consumption and the corresponding confidence intervals. When a range of alcohol intake was given, the midpoint of the range was taken. In cases where open-end for the highest category was given (e.g. 40+ grams/day), three-quarters of the length of the immediate previous category range was added to the lower bound and was used as the measure. Where consumption was reported in drinks and not in grams, the gram pure alcohol equivalent (of 1 drink) explained in the article was used as a conversion factor if stated, and if not, conversion was based on geographical location: for Canada 13.6 grams, United States 12 grams, the UK 8 grams and for both New Zealand and Australia 10 grams of pure alcohol. For all other countries without any clear specifications 12 grams pure alcohol was used as an equivalent of 1 drink.

Information about the level of exposures in each study, the number of cases at each exposure level, the total population at risk at each exposure level, the adjusted estimates of relative risk (RR) compared to abstention for each exposure level, and the corresponding lower and upper 95% confidence intervals (CI) of the adjusted RR were obtained.

To ensure accuracy in data abstraction, five included and five excluded studies were randomly chosen to be abstracted independently by a co-author (H.I.) and the results were compared. Both authors agreed on 5/5 articles reviewed for inclusion/exclusion, and 611/654 data points abstracted over 10 articles. Where disagreements existed, both authors reviewed the materials together until a consensus was reached.

Drinkers versus non-drinkers meta-analysis

In the drinkers versus non-drinkers meta-analysis, the DerSimonian and Laird (1986) [17] random-effects method was used to combine the natural logarithm of the risk estimates across studies. Where a study provided a dose-response analysis only, the risk estimates for all drinking categories were pooled using the inverse variance weighted method to derive a single estimate. These statistical analyses were completed using the METAN command in STATA version 10.1, StataCorp, Texas, USA [18].

Meta-regression of dose-response relationship

Based on previously published research, the associations between maternal alcohol consumption with low birth weight, preterm birth and SGA could be either linear or nonlinear. In order to be flexible in fitting the best model, we conducted the meta-regression using linear as well as first-order and second-order fractional polynomial regression with powers –2, –1, –0.5, 0, 0.5, 1, 2, 3 to estimate a best fitting curve to the data. Best-fit curves were assessed using decreased deviance compared to the reference model. Comparisons of curves to determine the best fit were made using a Chi-square distribution [19]. The first order and second-order fractional polynomials take the general form shown in Equation 1 and 2, respectively:

$$\text{Log}\,(\text{RR}|x)=\beta_1 x^{P1} \quad \text{(Equation 1)}$$

$$\text{Log}\,(\text{RR}|x)=\beta_1 x^{P1}+\beta_2 x^{P2}, \quad \text{(Equation 2)}$$

where x is the alcohol exposure level in grams per day, P^1 and P^2 are the polynomial powers and β_1 and β_2 are the corresponding coefficients. No intercept term exists since all models have a starting point of Log RR = 0 (RR = 1 at zero consumption). All models were fitted in STATA version 10.1, StataCorp, Texas, USA, using the GLST function [18].

Heterogeneity & Publication bias

Statistical heterogeneity between studies was assessed using both the Cochrane Q test and the I^2 statistic [20]. Because all statistical tests for heterogeneity are weak, we also included the 95% CI for I^2 [21;22] that was calculated based on the method described by Higgins and Thompson (2002) [20]. Publication bias was assessed by visual inspection of Begg's funnel plot, the Begg-Mazumdar adjusted rank correlation test [23] and the Egger regression asymmetry test for funnel plot [24]. The RR estimates were prepooled using the inverse variance weighted method because funnel plot methodology assumes one overall RR per article. Statistically significant publication bias was defined as $p < 0.10$.

RESULTS

Characteristics of the included studies

We identified 36 observational studies that had met the inclusion criteria as outlined in Figure 1. Twenty four out of 36 studies had dose-response information (with at least three or more drinking exposure groups) and were the basis of meta-regression analysis. However, all 36 studies were used in a separate meta-analysis of maternal drinking vs. maternal non-drinking. For meta-regression analysis, out of 19 studies on low birth weight 15 were cohort studies [8;25–38] and 4 were case-control studies [39–42]. Collectively, the 19 studies provided 28 datasets for a total of 277,300 pregnant mothers with 20,582 cases of low birth weight. Similarly, on 14 studies on preterm birth condition, 12 cohort studies [8;25;26;28;29;31;33;34;43–46] and 2 case-control studies [39;47] had 26 datasets and a total of 280,443 pregnant mothers with 12,888 preterm birth cases. Likewise, 8 studies

provided 17 datasets for a total of 136,949 pregnant mothers with 8,679 cases of SGA. Six studies [25;29;30–31;37;46] were case-control and rest were cohort [40;42]. For drinker vs. non-drinker meta-analysis, in addition to above 24 studies, 12 more studies [9;48–58] were added. Only one [58] out of the above 12 studies was a case-control study.

Adjustment for confounders varied between studies. All but seven studies on low birth weight and 9 out of 14 studies on preterm birth and all studies on SGA adjusted for confounders (such as smoking, socio economic status, body mass index, etc). Ascertainment on these birth outcomes was determined through written self-report, interview after birth, outcomes from clinical/medical record, paediatrician examination and hospital delivery record. Supplementary Tables S1 and S2 summarize the characteristics of included studies.

Overall, marked heterogeneity was found for all birth outcomes (low birth weight (Q=122.5, p=0.006; I^2 = 80%, 95% CI (73%, 85%), p<0.001); preterm birth (Q=98.03, p<0.072; I^2 = 89%, 95% CI (84%, 92%), p<0.001); SGA (Q=131.20, p<0.001; I^2 = 92%, 95% CI (88%, 95%), p<0.001). Random effects models were used for all subsequent analyses. No significant publication bias was detected.

Drinkers versus non-drinkers meta-analysis

The summary of 28 studies related to low birth weight indicated an overall pooled RR of 1.12 (95% CI: 1.04, 1.20) among mothers drinking before or during pregnancy. When this analysis was restricted to studies with confounders, the adjusted RR was slightly affected and not significant (1.06 (95% CI: 0.99, 1.13)) (Figure 2). Similarly, the pooled OR of preterm birth between 21 studies was 1.03 (95% CI: 0.91, 1.16). This effect estimate attenuated (0.93 (95% CI: 0.86, 1.01)) when the analysis was restricted to studies which adjusted for confounders (Figure 3). The pooled OR of SGA among 11 studies was 1.11 (95% CI: 0.95, 1.30) (Figure 4). The effect estimate on studies that adjusted for confounders resulted in almost no effect (0.99 (95% CI: 0.89, 1.10)).

Dose-response meta-analyses

A total of 44 first-degree fractional polynomial models were examined (8 first-order models and 36 second-order fractional polynomials) for both low birth weight and preterm birth. Overall among pregnant mothers for low birth weight, the best second-degree model with powers 0.5 and 1 (and function $\beta_1 x^5 + \beta 2x$) fitted significantly better than the linear and first-degree models (p<0.001). For preterm birth and SGA, the best fitting model was the second-degree fractional polynomials with powers 0.5 and 0.5 (and function $\beta_1 x^5 + \beta_2 x^5 \ln x$) (p<0.001).

Figures 5 to 7 show an overall dose-response relationship between alcohol consumption and risk of low birth weight, preterm birth and SGA, respectively. Compared to abstainers, the risk of low birth weight with alcohol consumption was not apparent until more than 10 g/day or an average of about 1 drink per day (based on US conversions) but linearly associated thereafter up to 120 g/day to a maximum of 7.48 (95% CI: 4.46, 12.55), indicating a steeper slope after 10 g/day. The risk becomes twofold only after 52 g/day (equivalent to an average of 4–5 drinks a day) (**also see** Supplementary Table S3). Relative to non-drinking mothers, alcohol consumption of less than 19 g/day, or an average of about 1.5 drinks per day, was not associated with the risk of preterm birth. However, at an average of 3 drinks (36 g/day), risk of having preterm birth is 23% more likely than in non-drinking mothers (RR of 1.23 (95% CI: 1.05, 1.44)) (**see** Supplementary Table S4). Similarly, compared to abstained mothers, maternal drinking up to 10 g/day was not associated with the risk of SGA. With an average of 3 or more drinks a day, risk of having SGA looks more apparent (**see** Supplementary Table S5).

In a sensitivity analysis, we looked into the type of studies i.e., case-control vs. cohort. As a result, we repeated the analyses separately for case-control and cohort studies. We observed that study type did affect the risk relation with increasing volume of alcohol exposure with preterm birth. But for other two pregnancy outcomes, it didn't affect much. Although there were a similar risk patterns up to an average of 1 drink per day, however, a linearly increasing dose-response relationships existed, thereafter, among case-control studies [15] and a model very similar to the main analysis, in the cohort studies (**see** Supplementary Tables S3, S4, & S5).

The second sensitivity analysis compared risks of both pregnancy outcomes on pre- (i.e., until pregnancy is known) and during pregnancy. Consumption during pre-pregnancy was associated without a risk of low birth weight, preterm birth and SGA up to 30 g/day (an average of 2.5 drinks/day), 50 g/day (an average of about 4 drinks/day) and 18 g/day (an average of 1.5 drinks/day), respectively. On the other hand, compared to main analysis, risk estimates changed a little among studies during pregnancy or consumption during different trimesters of the pregnancy period (**see** Supplementary Tables S3, S4 & S5).

The final sensitivity analysis, performed using studies which adjusted for confounders (at least smoking as one of the confounders), resulted in models remarkably similar to those in the main analysis (**see** Supplementary Tables S3, S4 & S5).

DISCUSSION

This systematic review and meta-analysis indicates a non-linear association between maternal alcohol consumption and the risks of low birth weight, preterm birth and SGA. The risk of low birth weight and SGA with alcohol consumption increased linearly in mothers who consumed an average of 1 drink or more per day. Similarly, mothers who consumed more than 3 alcoholic drinks, the risk of having a preterm born child was increased by 23%.

Methodological considerations

In total, 36 observational studies were identified in this meta-analysis. We analyzed a large dataset with, depending on the outcome measure, 277,300 or 280,443 pregnant mothers with 20,582 children with low birth weight, 12,888 preterm birth and 8,679 SGA cases.

Most studies in this meta-analysis adjusted their multiple regression analyses for possible confounders, i.e. smoking, socio-economic status, body mass index, and ethnicity. After adjusting for these confounding factors there presumably is still residual confounding, due to inaccuracy in measuring these confounders or by not adjusting for other important, possible unmeasured, confounders. These unmeasured confounders may be mainly lifestyle- and socioeconomic-related factors. The potential for residual confounding is also reflected by the larger effect estimates for the unadjusted estimated than the adjusted models. The majority of studies in this meta-analysis had data at low to moderate alcohol consumption levels compared to heavy consumption levels, making the dose-response curves of maternal alcohol consumption and low birth weight, preterm birth and SGA (Figures 5 to 7) more stable at the low to moderate levels and more variable at the higher consumption levels. Also, we observed marked heterogeneity of the identified studies on all outcomes. This could be due to methodological or actual differences between the studies. To address this heterogeneity, we used random effects models for the pooled effect estimates analyses. The use of these random effects models explain why we are able to perform this meta-analysis compared to the systematic review of Henderson et al. [10]. Also, due to a different inclusion period we were able to add four large studies [25, 31, 40, 41] performed worldwide on this topic, and finally, we performed a dose-response meta-regression as well as a drinker vs. non-drinker meta-analysis. Another important limitation of meta-analyses is

the presence of publication bias. Such bias occurs when a research that appears in the published literature is systematically not representative of the population of completed studies [59]. We did not, however, observe any publication bias in our analyses.

Different definitions of birth outcomes did not occur. All identified studies used the common criteria for defining low birth weight (<2500 grams), preterm birth (<37 weeks of gestation) and SGA (below the 10th percentile). Low birth weight analyses in the included studies were adjusted for gestational age at birth. Additionally, different collection methods, of alcohol consumption levels and timing of consumption, used in the included studies may have influenced our results as well. Some studies used averaged alcohol consumption habits due to repeated assessment, while others only collected this information once during pregnancy, or even postnatally. This latter method may have introduced recall bias. Women with adverse pregnancy outcomes may underreport their alcohol consumption than had really occurred [60]. while women with good pregnancy outcomes may not underreport. The high levels of alcohol consumption reported retrospectively could be more similar in magnitude to the levels reported for the postpartum period, hence influence their retrospective recall [61]. For example, when interviewed retrospectively about alcohol consumption on a typical week, many mothers do not either recognize or likely forget the exact consumption and end up reporting their postpartum intake. This can cause overestimation of the effect estimates. Besides, misclassification error of the alcohol exposure may have occurred due to the use of self-reporting questionnaires or postpartum interviews [62;63]. If underreporting was present in all categories of alcohol consumption, the effect estimates would have been underestimated. However, if mothers with heavy alcohol consumption selectively underreported their average number of drinks, the differences between no alcohol consumption and the lower categories of alcohol consumption would have been overestimated. This misclassification could be averted by using more objective measures of alcohol consumption levels. Unfortunately, the use of current biomarkers to assess alcohol consumption levels, including carbohydrate-deficient transferrin and gamma-glutamyltransferase, seem to be inappropriate for the assessment of light to moderate alcohol consumption levels [64]. But for heavy maternal drinking (average 1.5 ounces of absolute alcohol ingested daily), fatty acid ethyl esters (FAEEs) extracted from meconium are found to be a reliable biomarker [65;66]. Using meconium, a Canadian research group [67] showed that they could objectively detect babies exposed to excessive maternal drinking of alcohol in pregnancy. Finally, a potential limitation in the studies is the use of the average number of alcoholic drinks per day or per week without taking into account the patterns of alcohol consumption. The explanation of our findings may lie in patterns of drinking (see O'Leary and colleagues [31], for an exception). Several previous studies reported harmful effects of more concentrated drinking patterns or binge drinking on fetal and postnatal development [68;69]. One recent study [70] suggests ignoring the pattern and frequency may in some circumstances completely mask the association (e.g., language delay, behavioural problems at early age). To deal with this, their study has proposed a new method of classification that reflects real-life drinking patterns.

Maternal alcohol consumption and low birth weight, preterm birth and SGA

This analysis adds weight to previous findings that light to moderate alcohol consumption during pregnancy does not increase the risks of low birth weight, preterm birth and SGA. The results are similar to findings in a recently published systematic review on low to moderate prenatal alcohol exposure and pregnancy outcomes of [10]. Henderson et al. suggested that small amounts of alcohol appeared to have a small protective effect on birth weight, and found either no effect or a reduction in risk of prematurity with the consumption of up to 72 g of alcohol per week. These results should be interpreted with caution, since no information on drinking patterns was taken into account. Consumption of small amount of

alcohol concentrated within a few days may be harmful. The authors provided a possible explanation for this finding with the 'healthy-drinkers effect', in which women with poorer obstetric history or prognosis are more prone to abstain from alcohol consumption during pregnancy.

This meta-analysis also shows that for alcohol consumption levels a cut-off value of the average number of alcoholic drinks may exist at which alcohol consumption may lead to adverse effects on birth outcomes. According to our study this cut-off lies between 1 to 1.5 averaged alcoholic drinks per day, which means approximately 10 to 18 g of alcohol per day. Previous studies also suggested effects of maternal alcohol consumption on postnatal growth and development. It was shown that the rate of postnatal growth is reduced in children who were prenatally exposed to alcohol [68;69]. Postnatal weight, length and head circumference were negatively affected at least through 14 or 21 years of age due to alcohol exposure during pregnancy [71–74]. However, a more recent longitudinal study showed that moderate maternal alcohol consumption during pregnancy was not associated with either weight or head circumference at the age of five years [75]. Also, inconsistent results were found on behavioural development and cognitive processing in children prenatally exposed to alcohol [76;77]. A study of Faden et al. [78] showed a higher activity level, a greater difficulty in following instructions and have eating problems among offspring exposed to alcohol during pregnancy. Furthermore, binge drinking during pregnancy was shown to be associated with increased odds for the appearance of psychiatric disorders [3]. Although, previous studies did not show consistent associations either of binge drinking during pregnancy with several outcomes, except for neurodevelopmental outcomes [2]. Whether light to moderate alcohol consumption is related to postnatal growth and development still needs to be examined. The effects of alcohol consumption are dependent on the absorption and metabolism in the mother and the fetus. This may be partially genetically determined. Therefore, the effects of alcohol consumption in specific groups of women should still be studied.

Conclusion and future research

The results of this meta-analysis indicate that heavy alcohol consumption during pregnancy increases the risk of low birth weight and preterm birth while light alcohol consumption may not affect these neonatal outcomes. Preventive measures needed could be initiated. Promotion of a healthy lifestyle could be optimized in antenatal care. In this way current awareness of risks of certain lifestyle factors may increase and may subsequently decrease the adverse effects. Most important, emphasizing the harmful effects of heavy alcohol consumption, in even the preconceptional period, should be acknowledged. Future research should be focused on the associations of low to moderate alcohol consumption with postnatal growth and development before new public health strategies can be developed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI confidence interval

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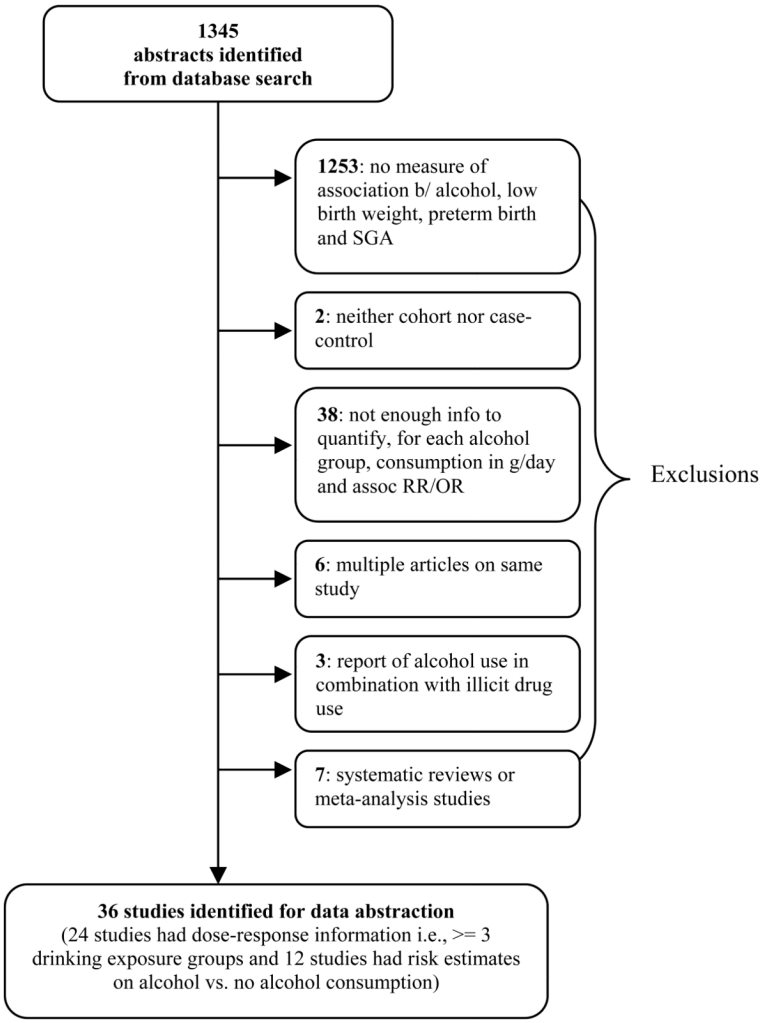

Figure 1.
Results of systematic review of the relationship between maternal alcohol consumption and low birth weight, preterm birth and small-size-for-gestational age (SGA)

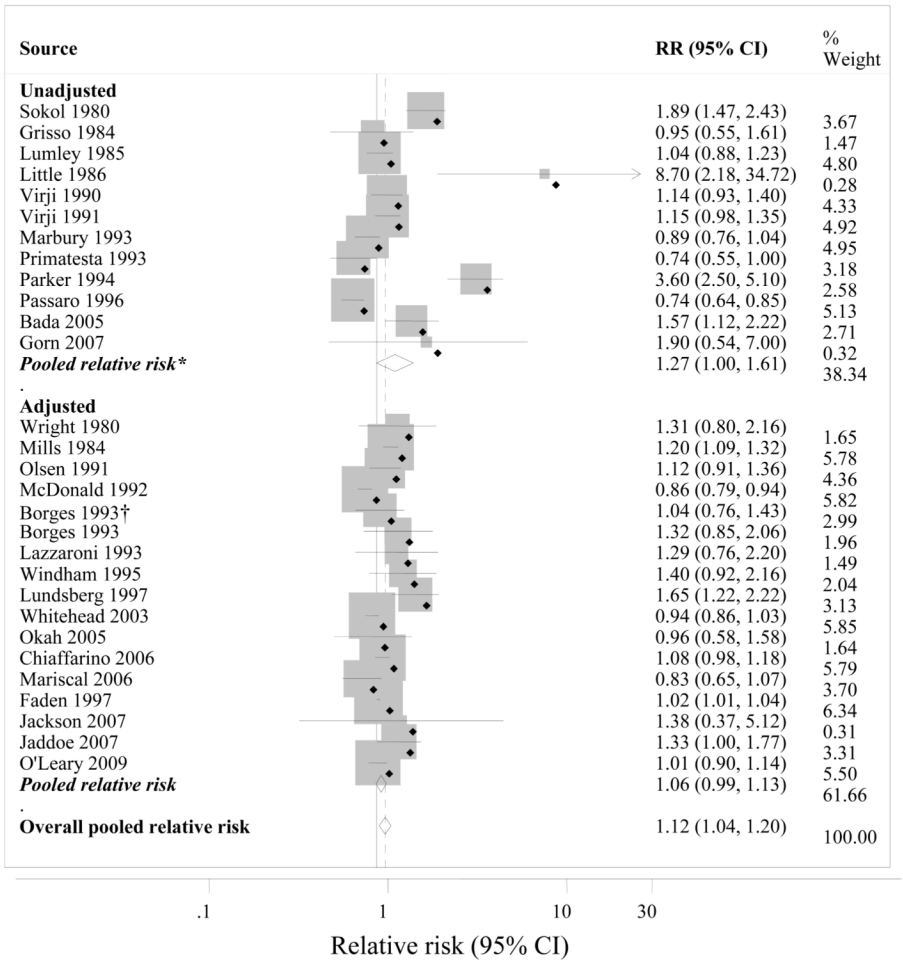

Figure 2. Relative risks for low birth weight comparing alcohol consumption versus no alcohol consumption (28 studies)

*The unadjusted pooled relative risk does not include unadjusted estimates from adjusted studies

Unadjusted I^2 = 89%, 95% CI (84% – 93%), p<0.001

Adjusted I^2 = 62%, 95% CI (41% – 75%), p<0.001

Overall I^2 = 80%, 95% CI (73% – 85%), p<0.001

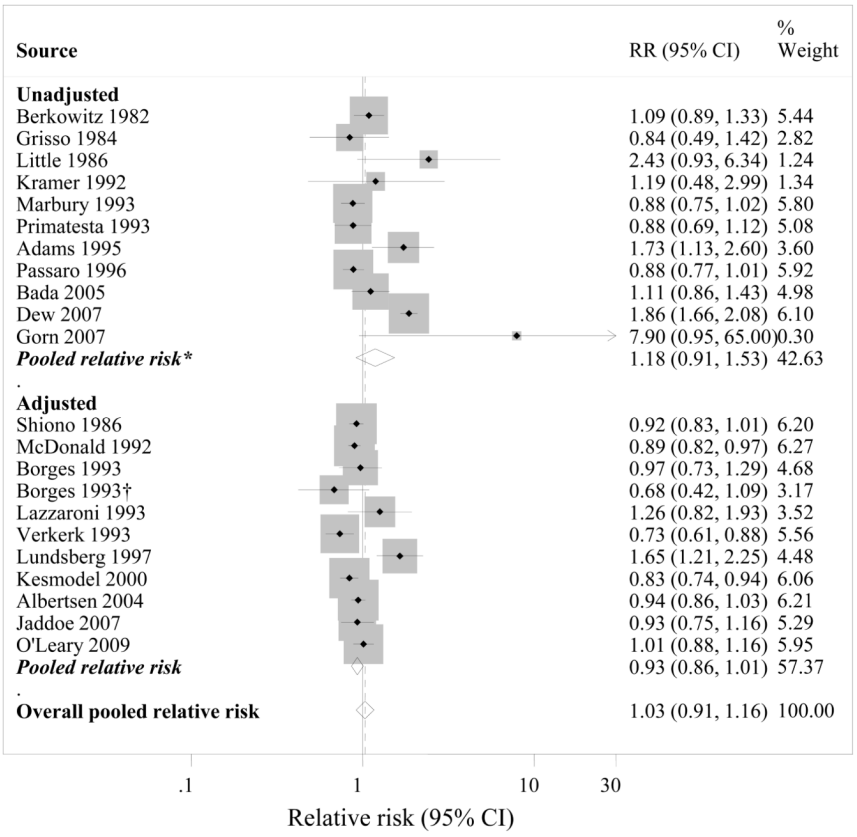

Figure 3. Relative risks for preterm birth comparing alcohol consumption versus no alcohol consumption (21 studies)

*The unadjusted pooled relative risk does not include unadjusted estimates from adjusted studies

Unadjusted I^2 = 91%, 95% CI (86% – 94%); p <0.001

Adjusted I^2 = 64%, 95% CI (31% – 81%), p <0.001

Overall I^2 = 89%, 95% CI (84% – 92%), p <0.001

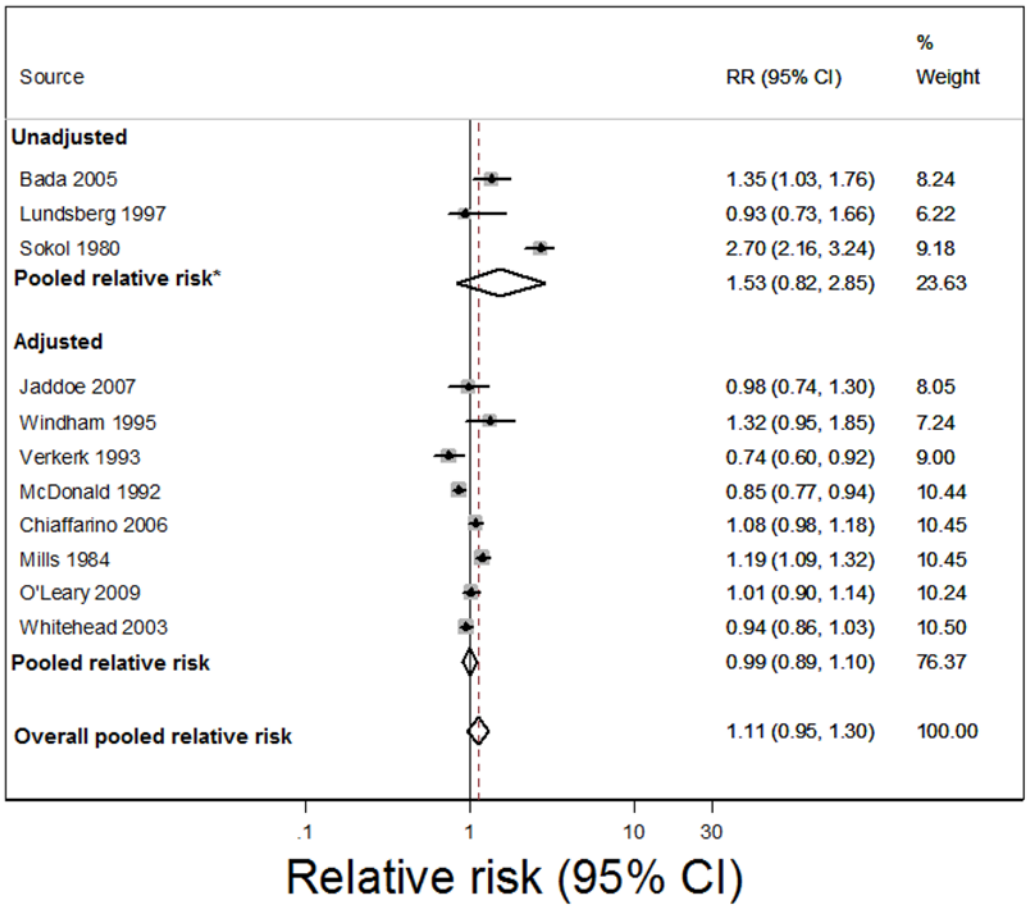

Figure 4. Relative risks for SGA comparing alcohol consumption versus no alcohol consumption (11 studies)

*The unadjusted pooled relative risk does not include unadjusted estimates from adjusted studies

Unadjusted I^2 = 93%, 95% CI (83% – 97%); p <0.0001

Adjusted I^2 = 82%, 95% CI (65% – 91%), p <0.0001

Overall I^2 = 92%, 95% CI (88% – 95%), p <0.0001

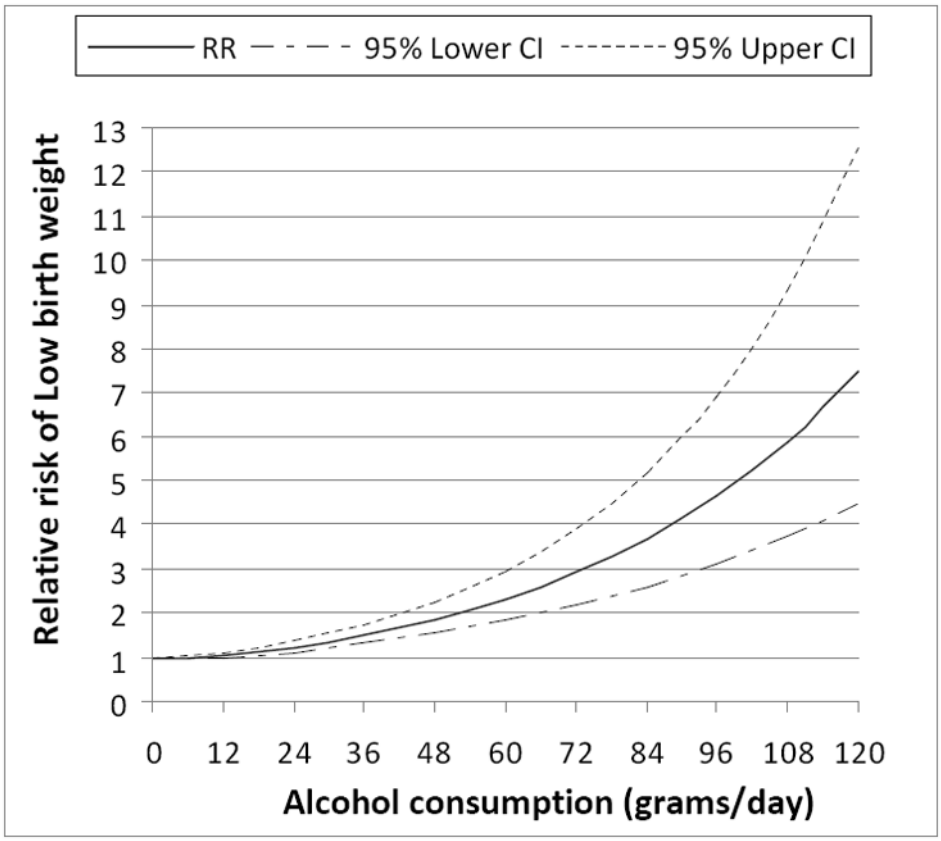

Figure 5. Meta-analysis 19 studies* showing the dose-response relationship between maternal alcohol consumption and low birth weight

** For the information supporting this figure, please see the details in* Supplementary Table S3

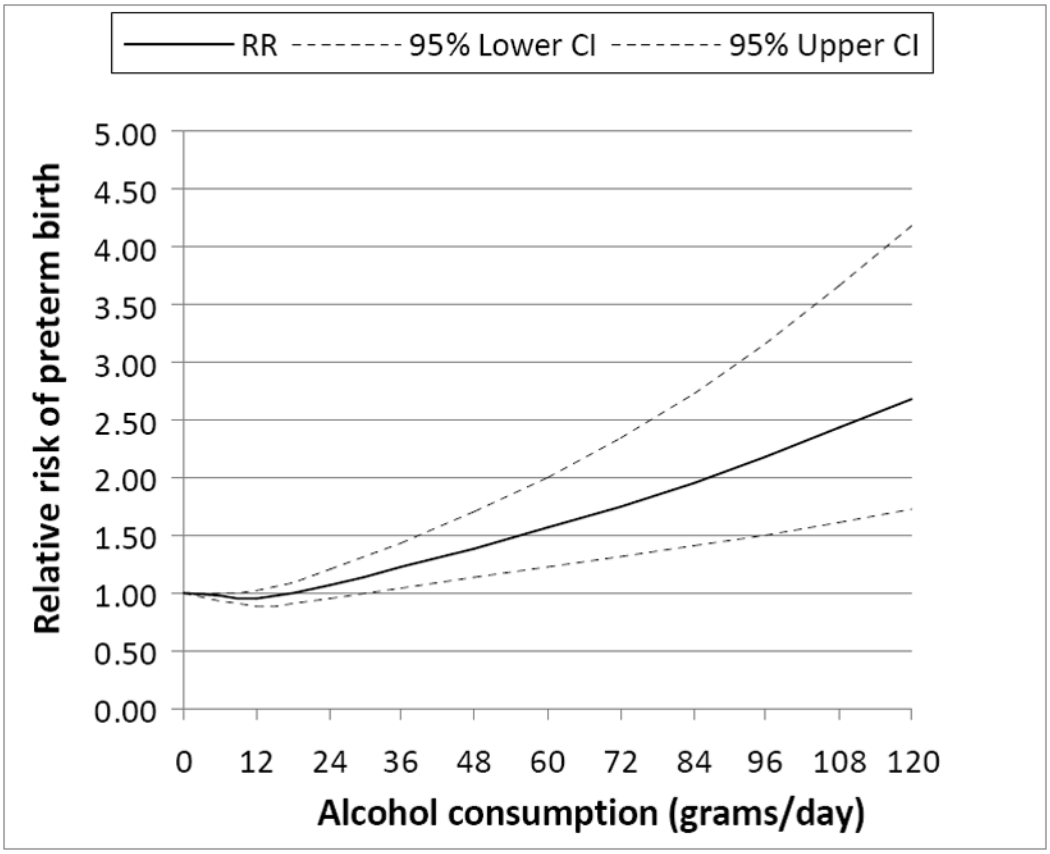

Figure 6. Meta-analysis of 14 studies* showing the dose-response relationship between maternal alcohol consumption and preterm birth

** For the information supporting this figure, please see the details in* Supplementary Table S4

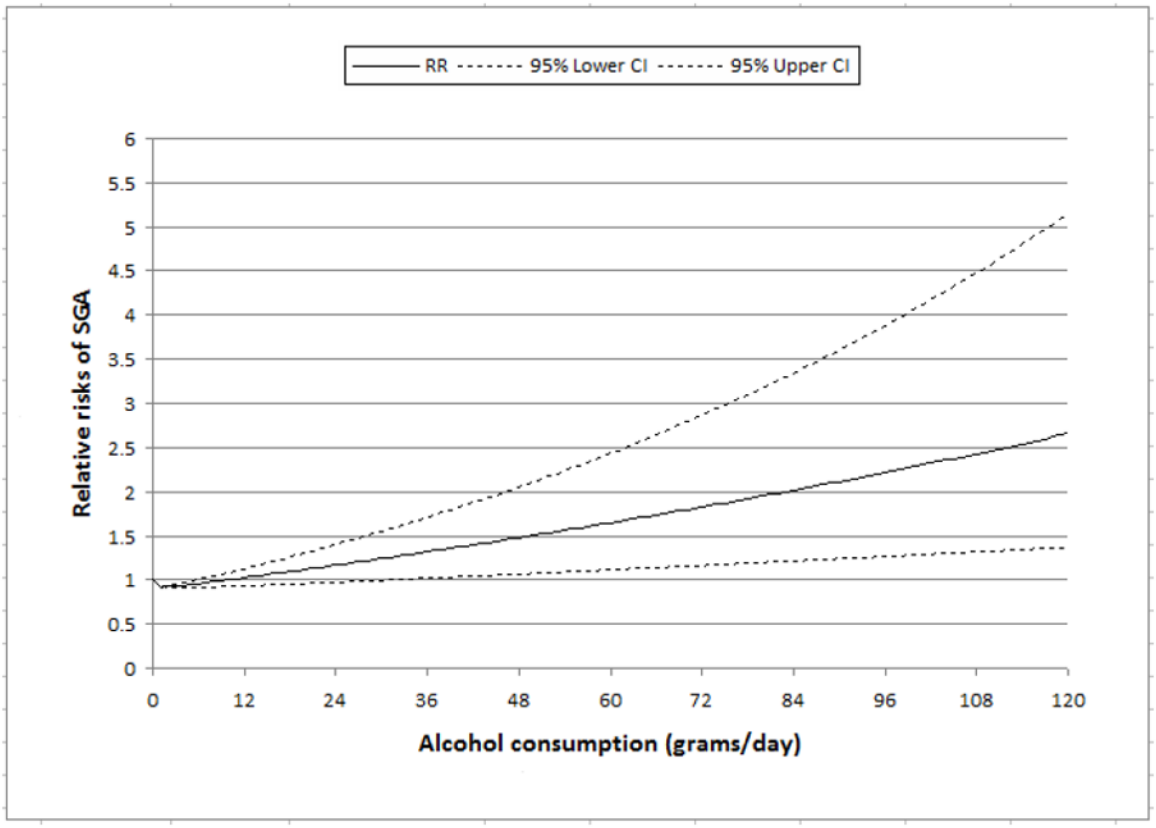

Figure 7. Meta-analysis of 8 studies* showing the dose-response relationship between maternal alcohol consumption and SGA

** For the information supporting this figure, please see the details in* Supplementary Table S5