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Maternal Exposure to Alcohol and Low Birthweight: A Systematic Review and Meta-Analysis

Exposição maternal ao álcool e baixo peso ao nascer: revisão sistemática e metanálise

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Abstract

Objective To investigate the relationship between maternal exposure to alcohol and low birthweight (LBW).

Methods The literature search was performed in January 2017 using the following electronic databases: Medline, Embase, LILACS, SciELO, Web of Science, Scopus, CINHAL, Proquest, and PsychInfo. The search strategy used the following terms: *alcohol drinking*, *binge drinking*, *alcohol-related disorders*, *alcoholism*, *alcohol addiction/use/abuse/consumption*, *light/moderate/social/low drinking*, *low birthweight*, *case-control studies*, *retrospective studies*, and *cohort studies*. No restrictions regarding language or publication date were considered. The literature search yielded 2,383 articles, and after screening and eligibility assessment, 39 articles were included in the systematic review, and 38 studies were included in the meta-analysis.

Results Maternal alcohol consumption was associated with LBW among retrospective cohort studies (relative risk [RR] = 1.37; 95%CI [confidence interval]:1.10–1.77; $I^2 = 98.4\%$; $p < 0.01$). Prospective cohort studies (RR = 1.11; 95%CI: 0.98–1.25; $I^2 = 81.5\%$; $p < 0.01$), and case-control studies (odds ration [OR] = 1.16; 95%CI: 0.68–1.97; $I^2 = 61.2\%$; $p = 0.05$) showed no association between alcohol and LBW. No publication bias was identified, and the meta-regression showed that the sample size influenced the high heterogeneity among retrospective cohort studies. The subgroup analysis showed differences in association between groups when compared by sample size, type of adjustment, or crude measures and publication year.

Conclusions We have not found an association between alcohol consumption during gestation and LBW in the analysis in all of the subgroups. In addition, we have found a high heterogeneity between the primary studies, which is related to methodological differences in the conduction of these studies.

Keywords
- pregnant women
- low birthweight
- alcoholic beverages
- systematic review
- meta-analysis

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Resumo

Objetivo Investigar a associação entre a exposição maternal ao álcool e o baixo peso ao nascer.

Método A busca na literatura ocorreu em janeiro de 2017 nas seguintes bases de dados eletrônicas: Medline, Embase, LILACS, SciELO, Web of Science, Scopus, CINHAL, Proquest, e PsychInfo. A estratégia de busca utilizou os seguintes termos: *alcohol drinking*, *binge drinking*, *alcohol-related disorders*, *alcoholism*, *alcohol addiction/use/abuse/consumption*, *light/moderate/social/low drinking*, *low birthweight*, *case-control studies*, *retrospective studies*, e *cohort studies*. Não houve restrição de idioma e ano de publicação. A busca na literatura identificou 2.383 artigos, e depois de analisados conforme os critério de elegibilidade, foram incluídos na revisão sistemática 39 estudos, e 38 estudos foram incluídos na metanálise.

Resultados A amostra foi composta por 497.023 gestantes. O consumo materno de álcool foi associado ao baixo peso ao nascer entre os estudos de coorte retrospectiva (risco relativo [RR] = 1,37; IC [intervalo de confiança] 95%: 1,10–1,77; $I^2 = 98,4\%$; $p < 0,01$). Os estudos de coorte prospectiva (RR = 1,11; IC95%: 0,98–1,25; $I^2 = 81,5\%$; $p < 0,01$) e caso-controle (razão de chances [OR, na sigla em inglês] = 1,16; IC95%: 0,68–1,97; $I^2 = 61,2\%$; $p = 0,05$) não apresentaram associação entre o consumo e o desfecho. Não foi identificado viés de publicação, e a metarregressão mostrou que o tamanho da amostra influenciou a heterogeneidade entre os estudos de coorte prospectiva. Na análise por subgrupo, houve diferenças entre os grupos por tamanho de amostra, por tipo de ajuste e por ano de publicação.

Conclusão Não encontramos associação entre o consumo e o baixo peso ao nascer em todas as análises por subgrupo. Além disso, encontramos alta heterogeneidade entre os estudos primários, e isto se deve possivelmente às diferenças metodológicas na condução destes estudos.

Palavras-chave

- gestante
- baixo peso ao nascer
- consumo de álcool
- revisão sistemática
- metanálise

Introduction

Alcohol consumption is becoming an increasingly common habit among women. The amount and type of consumption differ depending on social, economic, and cultural aspects. The prevalence of alcohol intake by pregnant women varies from 4.5 to 31% in countries such as the United States of America, India, and Canada.[1,2]

The negative effects of alcohol consumption on a fetus are mainly related to the pattern of drinking and genetic factors. The type of drink, the amount of alcohol consumed per occasion, its continuous or sporadic use, the gestational period of the woman, and both maternal and fetal abilities to metabolize alcohol influence the occurrence of adverse effects on fetal growth and development.[3,4]

Maternal alcohol exposure has been associated with infertility, spontaneous miscarriage, prematurity, and physical, neurological, and psychological alterations.[5] The intake of one shot of an alcoholic drink per day during the pregestational period might decrease birthweight (BW) by 91 g on average. If this same amount is ingested over the last 3 months of pregnancy, then the BW might be decreased by 160 g.[6]

Birthweight is a widely used indicator to evaluate social, economic and environmental conditions to which pregnant women are exposed. Low birthweight (LBW) is defined by the World Health Organization (WHO) as newborns weighting < 2,500 g, regardless of the gestational age.[7]

Low birthweight contributes to between 60% and 80% of neonate deaths worldwide. The global prevalence of LBW is of 15.5%, and 96.5% of the cases occur in developing countries. Infants who were born with LBW have a higher risk of developing infectious diseases in their 1st year of life. Moreover, they are more likely to develop metabolic and cognitive disorders during childhood and adolescence.[8]

Low birthweight is directly related to preterm birth, to intrauterine growth restriction, or to a combination of both. In turn, these events depend on maternal characteristics, such as age, race, educational level, economic conditions, genetic aspects, obstetric history, nutrition, and lifestyle.[9,10]

A systematic review by Patra et al[3] found a risk association between maternal alcohol consumption and LBW. Henderson et al,[10,11] in two systematic reviews without meta-analysis, regarding moderate consumption and binge drinking, showed no consistent evidence for a risk association regarding LBW, on both consumption types.

Previous systematic reviews and primary studies indicate that there is no consensus regarding a risk association between alcohol consumption during pregnancy and LBW. The most recent systematic review published by Patra et al[3] included studies performed until 2009, and did not include studies conducted in South and Central America and in Asia. Furthermore, these authors did not investigate the high heterogeneity found among the included studies. Therefore,

we aimed to update the systematic reviews regarding the association between maternal exposure to alcohol and LBW.

Methods

The present research is registered at the International Prospective Register of Systematic Reviews (PROSPERO) under the Center for Reviews and Dissemination (CRD) number 42015023706.

Eligibility Criteria

We have included case-control, cohort studies (retrospective and prospective), and systematic reviews that evaluated the relationship of maternal exposure to alcohol and LBW (defined as $< 2{,}500$ g); 1 study defined LBW as $< 2{,}000$ g, and 1 study evaluated only consumption for very LBW (1,500 g).

Information Sources, Search Strategy, and Study Selection

The literature search for potential eligible studies was performed in January 2017 using the following electronic databases: Medline, Embase, LILACS, SciELO, Web of Science, Scopus, CINHAL, Proquest, and PsychInfo. No restrictions regarding language or publication date were considered.

The search strategy primarily applied for Medline (via PubMed) was *alcohol drinking* (Mesh) OR *alcohol drinking* (TIAB) OR *binge drinking* (TIAB) OR *alcohol-related disorders* (Mesh) OR *alcohol-related disorders* (TIAB) OR *alcoholism* (TIAB) OR *alcohol addiction* (TIAB) OR *alcohol use* (TIAB) OR *light drinking* (TIAB) OR *moderate drinking* (TIAB) OR *social drinking* (TIAB) OR *low drinking* (TIAB) OR *alcohol abuse* (TIAB) OR *alcohol consumption* (TIAB) AND *infant, low birthweight* (Mesh) OR *low birthweight* (TIAB) OR *birthweight* (TIAB) AND *case-control studies* (Mesh) OR *case-control studies* (TIAB) OR *retrospective studies* (Mesh) OR *retrospective studies* (TIAB) OR *case-control study* (TIAB) OR *case-comparison studies* (TIAB) OR *cohort studies* (Mesh) OR *cohort studies* (TIAB) OR *case* (TIAB) OR *cohort* (TIAB) OR *ratio* (TIAB) OR *risk* (TIAB) OR *prospective* (TIAB) OR *follow* (TIAB). The search strategy was slightly modified based on the specific criteria of each database (Complementary Material - ►**Table S1**). In addition, reference lists from the included articles and gray literature were searched manually.

The retrieved studies were assessed and classified according to the eligibility criteria. After duplicate removal, two authors (Pereira P. P. S. and Mata F. A. F.) screened the titles and abstracts, and assessed the full texts articles according to the eligibility criteria. Disagreements were settled by consensus.

Data Extraction

A standardized data extraction form was used to gather the following information: title, last name of the first author, country and city, data collection date, publication date, sample characteristics (size, sampling method, and age), exposure and outcome measures, follow-up period of cohort studies, controlled confounder variables, and estimated risk with respective confidence intervals (CIs). Data was extracted from systematic reviews in cases in which the primary studies did not give enough information to calculate association measures. Data were independently extracted by the two investigators (Pereira P. P. S. and Mata F. A. F.).

Quality Assessment

The Newcastle-Ottawa Scale was used for the methodological quality assessment, which is recommended by the Cochrane Collaboration for cohort and case-control studies.[12] This scale evaluates eight items on three perspectives: (1) group selection, (2) group comparability, and (3) determination of any exposure or outcome to case-control or cohort studies. Each question receives one point (marked as *), except for the comparability item, which may receive one or two points. A total score varying between one and three indicates a low-quality study, between four and six an average-quality study, and from seven to nine points a high-quality study.

Data Synthesis

The outcome of interest was LBW (with maternal exposure to alcohol during pregnancy). We considered as risk measures the relative risk (RR) for prospective cohorts and retrospective cohorts with a 95%CI and odds ratio (OR) for case-control. A random effect meta-analysis was performed using the inverse variance method when I-squared (I^2) $> 40\%$, and when $I^2 < 40\%$, the meta-analysis used a fixed-effect model.[13]

The statistical heterogeneity between studies was assessed using both the Cochrane Q test and I^2 statistic. Higgins and Thompson [13] I^2 statistic was used to evaluate the magnitude of the inconsistency, where $I^2 > 50\%$ was classified as high heterogeneity, between 25 and 50% as average, and $< 25\%$ as low.[14] A Galbraith[15] plot was adopted to show the studies that resulted in heterogeneity. As clinical and methodological differences may be sources of heterogeneity, the data were analyzed by meta-regression, subgroup, and sensitivity analyses to explore these differences.

The meta-regression aimed to investigate the influences of the methodological quality score, of the number of confounders, of the publication year, of the year of data collection, and of the sample size on the summarized measure of effect. The subgroup analysis was performed by sample size ($< 1{,}000$ versus $> 1{,}000$), by the type of measure (crude versus adjusted), by the quality of the study (low, average, and high), by the year of publication (1980–1989, 1990–1999, 2000–2009, 2010- 2016), and by geographic region (Americas, Europe, Africa, Asia, and Oceania).

Publication bias was evaluated by Begg funnel plot and by Egger regression ($p < 0.05$).[16] All of the statistical analyses were conducted using Stata 13.0 (StataCorp, College Station, TX, USA).

Results

Study Selection

We have identified 2,376 studies from databases, and 7 from manual search on reference lists (total of 2,383). From these, 472 duplicates were excluded, and 76 studies were selected for eligibility assessment, resulting in 39 studies included in the present review (►**Fig. 1**).

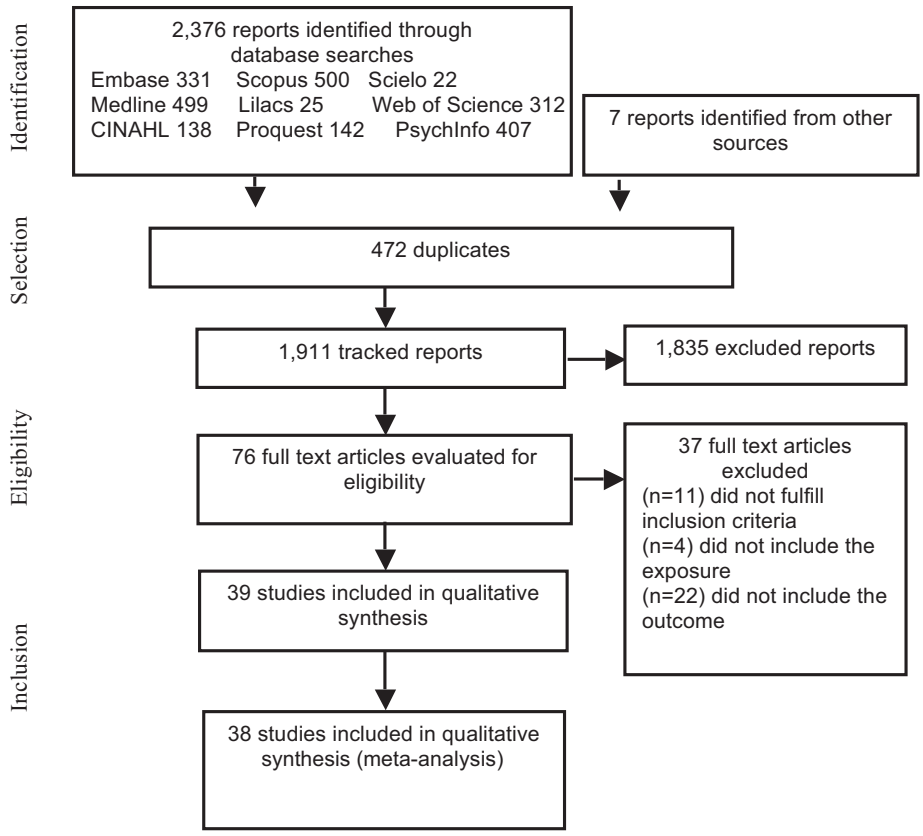

Fig. 1 Flowchart of article eligibility and final inclusion in the present systematic review.

Study Characteristics

A total of 39 studies were included in the present review, comprising 497,023 women. A total of 21 studies were conducted in the Americas, 12 in Europe, 3 in Asia, 2 in Oceania, and 1 in Africa (►**Table 1**).

A total of 8 studies were published in the 1980's, and the oldest was published in the United States of America.[17] A total of 12 studies were published between 1990 and 1999, and the other ones were published between 2000 and 2016. We have included 15 retrospective studies, 20 prospective cohort studies, and 4 case-control.

The studies included 19 provided only the crude association measure and 20 studies showed adjusted measures. The most considered confounding variables were: age, income, education, marital status, body mass index (BMI), gestational morbidities, and number of prenatal appointments.

A total of 19 studies reported the drinking pattern during pregnancy, including the number of alcoholic drinks per day,[27,37,39,42,54] and per week.[20,22,26,33,38,39,44,46,55] The studies included also reported the amount of alcohol (g) consumed monthly,[25,27] and the number of drinking occasions in the previous year.[22] Three studies reported some type of classification for consumption (light, moderate, and heavy; abuse or dependence),[23,31,32] and one study showed results by type of beverage.[22] A total of 5 studies showed results by gestational age,[19,21,30,33,34] and only 1 reported measures by birthweight ($<$ 1,500 g and $<$ 2,500 g).[31]

The majority of the studies had high quality, 13 had average quality,[17,23,25,27,31,36,38–43] and 1 had low methodological quality.[44]

Association Between Maternal Exposure to Alcohol and Low Birthweight

From the studies included in the qualitative synthesis, 38 were included in the meta-analysis. A study was excluded from the meta-analysis because it did not present the CI of the summary measure and it was not possible to calculate the measure.[40] The meta-analysis for retrospective cohort studies showed that maternal exposure to alcohol was associated with LBW (RR = 1.37; 95%CI:1.10–1.71; $I^2 = 98.4\%$; $p < 0.01$; ►**Fig. 2**). This association was not observed for prospective cohort studies (RR = 1.11; 95%CI: 0.98–1.25; $I^2 = 81.5\%$; $p < 0.01$; ►**Fig. 3**), or case-control studies (OR = 1.16; 95%CI: 0.68–1.97; $I^2 = 61.2\%$; $p = 0.05$; ►**Fig. 4**).

Publication Bias

The Egger test and the visual inspection of the funnel plot indicated no publication bias among the studies included in the meta-analysis (retrospective cohort studies: $p = 0.23$; prospective cohort studies: $p = 0.31$; and case-control studies: $p = 0.14$).

Sensitivity Analysis

For retrospective cohort studies, the value of heterogeneity was 98.4%. The Galbraith plot showed that six studies[25,36,45–48] were the main sources of heterogeneity (Complementary

Table 1 Studies and participant's characteristics

First author, publication year	Country	Study period	Sample size	Association measure OR/RR (95%CI) reported on the article	Type of measure	Methodological quality of the study	Comments
Retrospective cohort							
1. Oster et al (2016)[36]	Canada	2000–2009	28,286	Birthweight 1,500–2,500 g: 1.45 (1.26–1.67); ≤ 1,500 g: 1.34 (1.05–1.72)	Adjusted	7	Sample composed only by native people.
2. Irner et al (2014)[43]	Denmark	1993–1995	164	2.20 (0.76–5.42)	Crude	5	Measure generated through contingency table. Pregnant women who are using substances. Includes multiple pregnancies.
3. Silva et al (2011)[46]	Brazil	2007–2008	957	4.20 (1.25–14.12)	Adjusted	8	Consumption defined by CAGE scale (positive if > 2 points)
4. Gorn et al (2007)[23]	Mexico	Not reported	134	Any consumption during pregnancy: 1.90 (0.54–7.00) > 2 times/week: 0.42 (0.13–1.30) Dependence: 1.33.73 (1.1– 12.0)	Crude	5	Women who required help for problems related with alcohol consumption on treatment practices.
5. Okah et al (2005)[51]	USA	1990–2002	78,397	0.96 (0.58–1.58)	Adjusted	7	All infants who were born at term gestation and on their mothers over a 13-year period.
6. Bada et al (2005)[25]	USA	1993–1995	8,637	1 d/w: 1.57 (1.12–2.22); 1–3 d/m: 1.17 (0.83–1.65); < 1 d/m: 0.99 (0.79–1.24)	Crude	6	Included women that could have used cocaine, marijuana and opioids.
7. Dičkutė et al (2002)[45]	Lithuania	1995–1998	151,700	10.3 (8.34–12.73)	Crude	7	National database.
8. Maruoka et al (1998)[52]	Japan	1987–1995	23,132	0.90 (0.74–1.09)	Crude	7	Measure generated through contingency table. Consumption was assumed as more than one drink per month during pregnancy.
9. Faden et al (1997)[47]	USA	1988	15,737	1.02 (1.01–1.04)	Crude	8	Measure from the systematic review by Patra et al[3] (n = 10,083)
10. Windham et al (1995)[24]	USA	1986–1987	1,201	0.1-2 d/w: 0.99 (0.58–1.7); 3–5 d/w: 2.5 (1.1–6.0); ≥6 d/w: 2.8 (0.77–10.4); > 3 ≥ d/w: 2.6 (1.2-5.8)	Adjusted	7	Telephone interviews on 8th and 9th postpartum months. Consumption on 1st month before pregnancy and 20 first weeks of pregnancy.
11. Lazzaroni et al (1993)[18]	Italy	1989–1990	2,145	1–10 g/d: 0.75 (0.22–1.33); 11–20 g/d: 1.38 (0.62–3.75); > 20 g/d: 2.27 (0.86–6.02)	Adjusted	9	Low birhweight < 2,000 g.
12. Primatesta et al (1993)[53]	Italy and UK	1986–1990	2,512	0.71 (0.50–1.00)	Crude	7	Measure generated through contingency table. In Italy, only a few selected women, mainly of lower social classes.

(*Continued*)

Table 1 (*Continued*)

First author, publication year	Country	Study period	Sample size	Association measure OR/RR (95%CI) reported on the article	Type of measure	Methodological quality of the study	Comments
13. McDonald et al (1992)[48]	Canada	1982–1984	40,445	0.86 (0.79–0.94)	Adjusted	9	Measure from the systematic review by Patra et al.[3].
14. Virji (1991)[31]	USA	1980	5,400	1.13 (0.96–1.34); Light: 1.03 (0.84–1.26); Moderate: 1.23 (0.96–1.58); Heavy: 2.66 (1.32–5.38)	Crude	5	Measure generated through contingency table. Data related to white, married mothers giving birth to singletons.
15. Marbury et al (1983)[35]	USA	1982	12,440	0.89 (0.76–1.04)	Crude	6	Measure from the systematic review by Patra et al.[3] Article only reported the consumption measure >14 g/w: 1.1 (0.4–3.4)
Prospective cohort							
16. Witt et al (2016)[34]	USA	2001	9,350	Alcohol use before pregnancy: 1.07 (0.88–1.29); Use on the last trimester: 0.88 (0.54–1.42)	Adjusted	8	Only among very low birthweight (< 1,500 g).
17. Bird et al (2016)[30]	New Zealand	2009–2010	6,822	Alcohol use before pregnancy: < 1 d/w: 0.82 (0.56–1.19); 1 d/w: 0.88 (0.49–1.51); ≥2 d/w: 0.78 (0.56–1.08); Alcohol use in 1st trimester <1 d/w :0.85 (0.52–1.31); 1 d/w: 0.95 (0.40–1.92); 2 d/w: 0.70 (0.43–1.08). Alcohol use in rest of pregnancy < 1 d/w: 0.70 (0.42–1.11); 1 d/w: 1.05 (0.36–2.38); ≥2 d/w: 0.54 (0.16–1.30)	Crude	7	Interview on the last month of pregnancy.
18. Sbrana et al (2016)[49]	Brazil	2010–2011	1,370	1.62 (1.03–2.54)	Adjusted	9	–
19. Lundsberg et al (2015)[33]	USA	1996–2000	4,496	Alcohol use before pregnancy: (n = 4,116) < 0.10 g/d: 0.96 (0.61–1.5); 0.10–0.25 g/d: 0.57 (0.24–1.36); > 0.25 g/d: 0.52 (0.24–1.12); 1st trimester (n = 4,105): 0.78 (0.47–1.31) Use on baseline interview (n = 4,115): 0.66 (0.46–0.96); 7th month (n = 3,726): 0.67 (0.33–1.39); 3rd trimester (n = 3,672): 0.56 (0.34–0.94)	Adjusted	9	Interview performed until 1st month after birth.

Table 1 (*Continued*)

First author, publication year	Country	Study period	Sample size	Association measure OR/RR (95%CI) reported on the article	Type of measure	Methodological quality of the study	Comments
20. Strutz et al (2014)[54]	USA	1994–2008	3,014	0.49 (0.14–1.69)	Adjusted	8	Self-reported birth weight.
21. Miyake et al (2014)[19]	Japan	2007–2008	1,565	< 10 g/d: 0.98 (0.46–1.85); ≥ 10 g/d: 1.31 (0.52–2.84)	Adjusted	8	–
22. Nykjaer et al (2014)[29]	UK	2003–2006	1,303	Before pregnancy ≤ 2 d/w: 0.4 (0.1–2.7); > 2 d/w: 1.1 (0.2–6.1); 1st trimester ≤ 2 d/w: 4.6 (1.4–14.7); > 2 d/w:: 3.5 (1.1–11.2) 2nd trimester ≤ 2 d/w: 0.8 (0.3–1.8); > 2 d/w: 0.9 (0.43–2.1); 3rd trimester ≤ 2 d/w: 1.0 (0.3–3.2); > 2 d/w:1.0 (0.3–2.9)	Adjusted	9	Consumption was evaluated between 4 weeks before pregnancy until the 12th week of gestation; between weeks 13th to 28th; and between the 29th to 40th weeks of gestation.
23. Jaddoe et al (2007)[20]	Netherlands	2002–2006	7,141	< 1 d/w: 1.31 (0.87–2.44); 1- 6 d/w: 1.38 (0.66–2.90); > 1 d/d: 4.81 (1.10–21.08)	Adjusted	9	Information about maternal alcohol consumption was obtained by postal questionnaires in early, middle, and late pregnancy.
24. Li et al (2005)[55]	Taiwan	1998–1999	1,128	1.16 (0.39–3.42)	Adjusted	8	–
25. Ruijter et al (1999)[42]	USA	1996–1997	225	5.15 (1.07–24.80)	Adjusted	5	Only African-Americans
26. Lundsberg et al (1997)[21]	USA	1988–1991	2,714	1st month ≤ 0.10 g/d: 0.79 (0.48–1.28); 0.10–0.25 g/d: 0.88 (0.48–1.59); 0.25–1.00 g/d: 1.24 (0.66–2.33); ≥ 1.00 g/d: 0.93 (0.23–3.72); 7th month ≤ 0.10 g/d: 3.20 (1.87–5.46); 0.10–0.25 g/d: 1.36 (0.48–3.88)	Adjusted	7	–
27. Passaro et al (1996)[41]	UK	1991–1992	10,539	0.74 (0.64–0.85)	Crude	6	Measure from the systematic review by Patra et al.[3]. Limiting analysis to exclude users of marijuana, crack, and cocaine, and excluding women with a history of alcoholism.
28. Olsen et al (1991)[26]	Denmark	1984–1987	11,698	1 g/w: 1.0 (0.7–1.3); 30 g/w: 1.0 (0.7–1.5); 60 g/w: 0.9 (0.5–1.5); 90 g/w: 0.9 (0.5–2.5); >120 g/w: 2.7 (1.5–4.8)	Adjusted	9	Information collected on 36th gestational week.

(*Continued*)

Table 1 (*Continued*)

First author, publication year	Country	Study period	Sample size	Association measure OR/RR (95%CI) reported on the article	Type of measure	Methodological quality of the study	Comments
29. Day et al (1989)[40]	USA	Not reported	650	1.46	Crude	5	Did not report 95%CI
30. Brooke et al (1989)[28]	UK	Not reported	1,513	1–19 g/w: 1.037 (1.02–.05); 20–49 g/w: 1.032 (1.02–1. 05); 50–99 g/w: 1.02 (0.99 to 1.05); > 100 g/w: 1.00 (0.96–1.04)	Crude	7	Only White women. Interviews performed on the 28th and 36th gestational weeks.
31. Little et al (1986)[39]	UK	1979–1980	144	8.70 (2.18–34.72)	Crude	5	Measure of systematic review by Patra et al.[3] Sample of white women, aged 19–35 years, athletes, low middle class, non-smoker, non-alcoholic, good health and with the first prenatal visit until the 16th gestational week.
32. Lumley et al (1985)[50]	Australia	1981–1982	10,319	1.04 (0.88–1.23)	Crude	7	Measure from the systematic review by Patra et al.[3] All Tasmanian births.
33. Mills et al (1984)[37]	USA	1974–1977	31,503	1.20 (1.09–1.32)	Crude	6	
34. Grisso et al (1984)[38]	UK	1972–1973	1,256	0.95 (0.56–1.63)	Crude	5	Measure from the systematic review by Patra et al.[3] Survey mailed to participants. Group from a previous randomized trial regarding smoking.
35. Sokol et al (1980)[17]	USA	Not reported	12,127	1.89 (1.47–2.43)	Crude	5	Only white women, including Latin American.
Case-control							
36. Márquez et al (2011)[44]	Cuba	2007–2008	84	20.76 (1.08–400.49)	Crude	3	
37. Jackson et al (2007)[32]	South Africa	2002–2003	400	Some use during pregnancy: 1.38 (0.37–5.13); current drinking: 2.15 (1.37–3.39); CAGE score > 2: 1.28 (0.59–2.79)	Adjusted	7	
38. Mariscal et al (2006)[22]	Spain	1998–2002	2,003	Alcohol consumption 1–5.9 g/d: 0.64 (0.46–0.88); 6–11.9 g/d: 0.92 (0.52–1.62); > 12 g/d: 1.56 (0.91–2.69); Type of beverage: Beer only: 0.59 (0.35–1.00); Wine only: 0.88 (0.64–1.22); Spirits only: 0.89 (0.34–2.35); Other patterns: 0.84 (0.46–1.53); On weekdays during pregnancy: 1–11.9 g/d: 0.96 (0.44–2.06) > 12 g/d: 2.67 (1.39–5.12)	Adjusted	7	

Table 1 (*Continued*)

First author, publication year	Country	Study period	Sample size	Association measure OR/RR (95%CI) reported on the article	Type of measure	Methodological quality of the study	Comments
39. Borges et al (1993)[27]	Mexico	1988	1,372	Alcohol during pregnancy: 1.32 (0.85–2.06) Alcohol frequency last year: > once a month 1.17 (0.79–1.72); once a month 0.66 (0.32–1.37); 2–3 t/m: 0.79 (0.33–1.94); 1–2 t/w: 1.72 (0.81–3.67); ≥ 3 to 4 t/w: (0.17–3.34) Grams of alcohol 0.01–1,800 g/y: 1.04 (0.73–1.50); 1,800.01–3,600 g/y: 0.61 (0.18–2.08); ≥ 3600.01 g/y: 1.28 (0.61–2.65) Drunkenness frequency last year: Never: 0.90 (0.63–1.31); 1 to 7 t/y: 1 0.97 (1.09–3.56); once a month and more often: 2.45 (0.46–12.88); Alcohol drinking pattern: Infrequent: 1.17 (0.77–1.77); Less frequent, low maximum: 0.55 (0.27–1.14); Less frequent, high maximum: 1.30 (0.68–2.49); Frequent, low maximum: 1.13 (0.42–3.03); Frequent, high maximum: 1.20 (0.40–3.65); Frequent, heavy drinker: 4.21 (0.90–19.74); Alcohol dependency: 16.29 (1.65–160.9)	Adjusted	5	Household survey. Self-reports of alcohol consumption in the last 12 months.

Abbreviations: CI, confidence interval; d/d, drinks per day; d/m, drinks per month; d/w, drinks per week; g/day, grams of absolute alcohol per day; g/week, grams of absolute alcohol per week; g/y, grams per year; OR, odds ratio; RR, relative risk; t/m, times a month; t/w, times a week; t/y, times a year.

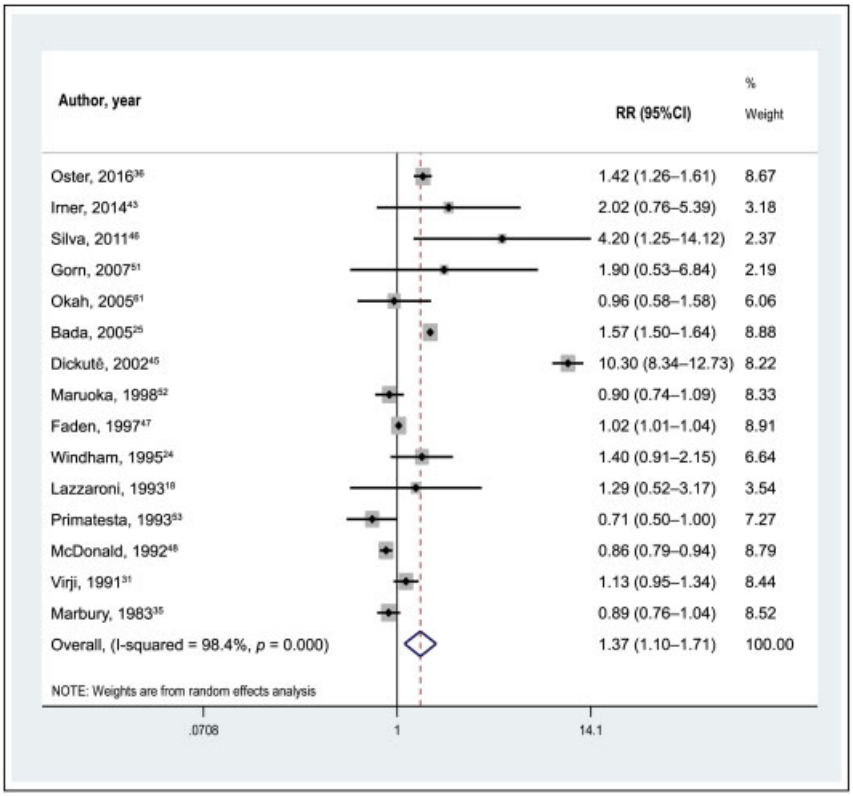

Fig. 2 Effect of prenatal alcohol exposure on low birthweight (< 2,500 g) for retrospective cohort studies. Abbreviations: CI, confidence interval; RR, relative risk.

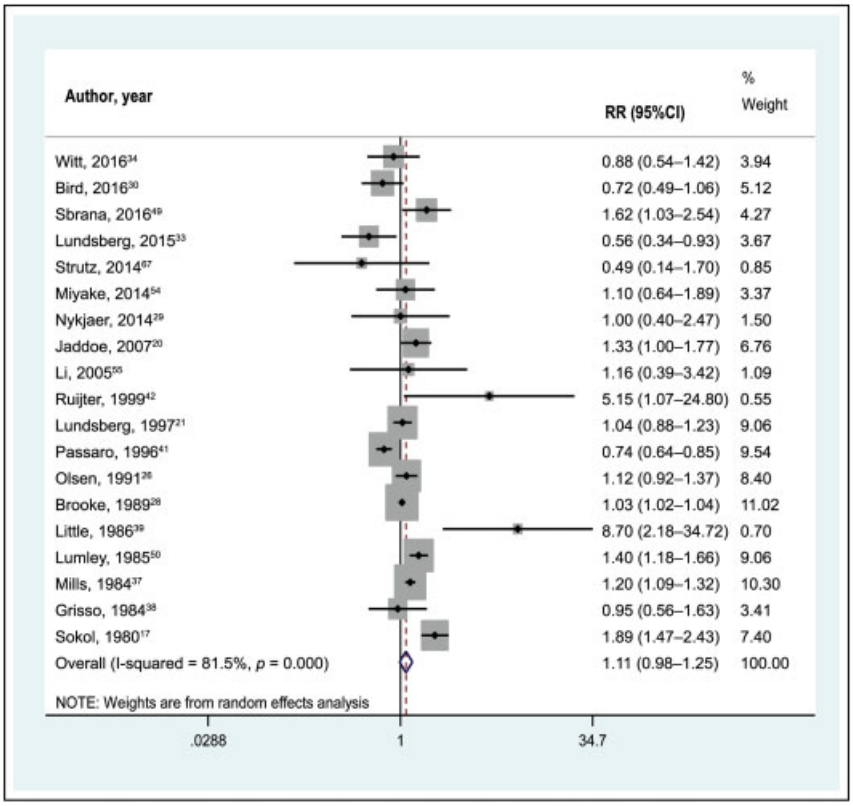

Fig. 3 Effect of prenatal alcohol exposure on low birthweight (< 2,500 g) for prospective cohort studies. Abbreviations: CI, confidence interval; RR, relative risk.

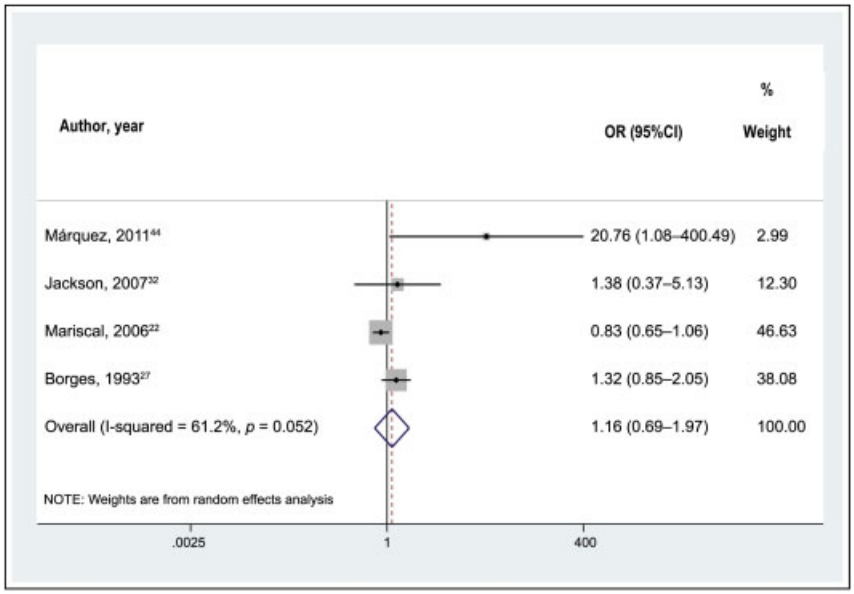

Fig. 4 Effect of prenatal alcohol exposure on low birthweight (< 2,500 g) for case-control studies.

Material –►**Fig. S1**). The meta-analysis performed without including the aforementioned studies showed no association (RR = 0.99; 95%CI: 0.86–1.15; $I^2 = 44.0\%$). Eight prospective cohort studies were the main sources of heterogeneity[28,33,38,39,41,42,49,50] (Complementary Material ►**Fig. S2**). The I^2 value of heterogeneity decreased from 81.5% to 62.4% after excluding those 10 studies and the meta-analysis performed showed association (RR = 1.14; 95%CI: 0.98–1.33). One case-control study reported a discrepant OR and a sample size < 100 participants,[44] and the summarized OR excluding this study was 1.02 (95%CI: 0.60–1.74; $I^2 = 43.6\%$; $p = 0.17$).

Subgroup Analysis

Among the retrospective cohort studies, those that reported a crude association measure or those published between 2010 and 2016, regardless of their sample size, maintained the association between alcohol consumption and LBW (►**Table 2**).

In prospective cohorts, two studies with sample sizes < 1,000 showed a strong association between exposure and outcome (RR = 6.92; 95%CI: 2.54–19.55). We have also observed an association between exposure and outcome in the studies published in the period between 1980 and 1989.

One case-control study recently published, reporting crude association measure, and with low methodological quality, showed a significant association between maternal exposure to alcohol during pregnancy and LBW.[44]

Heterogeneity Tests

High heterogeneity was observed between the studies. The results of the meta-regression indicated that part of the heterogeneity between retrospective cohort studies can be explained by sample size ($p < 0.01$). The higher the sample size, the stronger the association between maternal alcohol consumption and LBW (Complementary Material – ►**Fig. S3**). However, among prospective cohorts, sample size did not explain the high heterogeneity. Meta-regressions were not performed due to the small number of case-control studies ($n = 4$).

Publication year, data collection year, number of confounder variables, and methodological quality did not explain the heterogeneity among cohort studies.

Discussion

In the present systematic review, maternal alcohol consumption was identified as a risk factor for LBW according to retrospective cohort studies. However, an association was observed for cohort and case-control studies when subgroup analysis was performed for sample size, crude or adjusted measure, methodological quality, and publication year.

We have found three systematic reviews on the subject. Henderson et al[10] performed two systematic reviews on this subject. The first one, about binge drinking (considered more than 5 doses in 2 hours) included 14 original studies.[10] They concluded that the available evidence about the negative effects of binge drinking were not consistent. Their second review referred to moderate alcohol use. They included 19 cohort studies majorly performed in the United States of America. Only one study indicated moderate alcohol consumption as a risk factor for LBW, and seven studies described moderate use as a protective factor.[11]

A systematic review by Patra et al[3] performed between 1980 and 2009 included 28 studies sampled from countries in the Americas, Europe, Africa, and Oceania. These authors showed a RR of 1.12 (95%CI: 1.04–1.20; $I^2 = 80\%$) toward the relationship between alcohol consumption during pregnancy and LBW. They also evaluated the dose–response effect among the 19 included studies. They found that a daily consumption of 10 g of alcohol (around one and a half shots of an alcoholic beverage) did not show an effect on BW. However, alcoholic drink intake above this measure showed a linear relationship between alcohol use and BW decrease.

Table 2 Subgroup analysis for the effect of prenatal alcohol exposure on low birthweight, by study design

Variable	Groups	Number of studies/ participants	RR (95%)	I^2 (%)	Number of studies/ participants	RR (95%)	I^2 (%)	Number of studies/ participants	OR (95%)	I^2 (%)
		Retrospective cohort $n = 15$			Prospective cohort $n = 19$			Case-control $n = 4$		
Sample size	< 1,000	3 /1,255	2.46 (1.28–4.74)	<1	2 /369	6.92 (2.45–19.55)	<1	2 /484	3.82 (0.29–50.01)	68.8
	≥ 1,000	12 / 370,032	1.31 (1.04–1.63)	98.7	17 / 120,858	1.08 (0.97–1.21)	81.0	2 / 3,375	1.01 (0.64–1.58)	62.8
Type of measure	Crude	9/ 219,856	1.45 (1.08–1.96)	99.0	8/ 33,780	1.13 (0.95–1.35)	91,1	1/ 84	20.75 (1.08–400.49)	–
	Adjusted	6/ 151,437	1.24 (0.88–1.72)	90.1	11 / 84,447	1.08 (0.91–1.29)	44.2	3/ 3,775	1.02 (0.70–1.47)	43.6
Methodologic quality	High	10/ 330,793	1.36 (0.96–1.92)	98.4	13/ 62,433	1.08 (0.95–1.21)	61.5	2/ 2,403	0.84 (0.66–1.08)	<1
	Average	5/ 26,775	1.26 (0.90–1.77)	93.1	6/ 55,794	1.38 (0.93–2.03)	92.1	1/ 1,372	1.32 (0.85–2.05)	–
	Low	–	–	–	–	–	–	1/ 84	20.75 (1.08–400.49)	–
Year of publication	2010–2016	3 / 29,407	1.80 (1.05–3.10)	42.8	7 / 27,920	0.89 (0.65–1.21)	52.6	1 / 84	20.75 (1.08–400.49)	–
	2000–2009	4 / 238,868	2,38 (0,62–8,17)	99.0	2 / 8,269	1.32 (1.00–1.74)	<1	2 / 2,403	0.84 (0.66–1.08)	<1
	1990–1999	7/ 90,572	0.97 (0.87–1.09)	74.9	4/ 27,176	1.00 (0.75–1.33)	84.5	1/ 1,372	1.32 (0.85–2.05)	–
	1980–1989	1 / 12,440	0.89 (0.76–1.04)	–	6 / 56,862	1.32 (1.08–1.60)	90.7	–	–	–
Region	America	10 / 191,643	1.17 (0.97–1.43)	97.8	8 / 64,799	1.17 (0.92–1.48)	78.2	2 / 1,456	3.49 (0.26–46.13)	69.3
	Europa	4 / 156,521	2.11 (0.38–11.65)	98.3	7 / 33,594	1.05 (0.86–1.28	82.2	1 / 2,003	0.83 (0.65–1.06)	–
	Asia	1 / 23,132	0.90 (0.74–1.09)	–	2 / 2,693	1.11 (0.68–1.80)	89.6	–	–	–
	Oceania	–	–	–	2/ 17,141	1.03 (0.54–1.97)	<1	–	–	–
	Africa	–	–	–	–	–	–	1 / 400	1.38 (0.37–5.13)	–

Abbreviations: CI, confidence interval; OR, odds ratio; RR, relative risk.

The authors of the systematic review with meta-analysis already published[3] did not investigate the causes for high heterogeneity among the primary studies included (80%). We sought to investigate the causes for heterogeneity in our systematic review, which may be due to methodological differences among the studies and sample specificities. The results of the meta-regression indicated that part of the heterogeneity between retrospective cohort studies can be explained by the sample size. Also in the subgroup analysis, prospective cohorts with sample size $< 1{,}000$ showed a strong association with LBW. We do not know whether it is the larger or the smaller studies that give the better answer. We believe particularly with measures of diet where the smaller studies can potentially use more in depth measures. In the sensitive analysis, six retrospective studies were the main sources of heterogeneity. Of these six studies, three used information from databases, one study limited the sample to race,[36] and one study limited the age of the subjects (until 28 years old).[47] In addition, one study used CAGE screening questionnaire for alcohol use for excessive drinking and alcoholism.[19] Eight prospective studies were the main sources of heterogeneity, five were of average methodological quality, four limited the sample to race,[17,28,39,42] and one study quantified the consumption of alcohol by means of laboratory tests.[38] The Galbraith plot showed that these studies are responsible for the high heterogeneity in the meta-analysis, and that they used very specific samples: limiting the sample by race, by specific ways to measure alcohol consumption (CAGE and laboratory examination), and by having average methodological quality.

In view of the results of the present systematic review, it is important to consider information bias and residual confounding. Self-reported alcohol consumption may underestimate the association between exposure and outcome. Only one study dosed the alcohol consumption by means of a laboratory examination.[38] The moment and the method of questioning consumption may introduce information bias. For example, an interview taken after the birth of a child, when adverse effects or the nonoccurrence of these effects are already apparent, may influence the response of the woman about her exposure to substances. As women with healthy newborns may not feel embarrassed when reporting alcohol consumption during pregnancy, women with adverse outcomes during pregnancy or after the birth of their children may not report the actual consumption because they may feel guilty or misjudged.[3,41,56]

Residual confounding may also have contributed to the lack of association between alcohol and LBW. Even after adjustment, nutritional and socioeconomic aspects may not have been well measured due to inaccuracies of their measurements.[3] Pregnant women who drank during pregnancy may have been healthier in terms of nutrition, lifestyle, and health state, and they might have consumed alcohol at moderate quantities and might not have smoked.[57,58] A study showed that women who consumed alcoholic beverages moderately also consumed less animal meat, egg, dairy fat, and consumed more fruits, vegetables, and carbohydrates.[59]

In the present review, we have evaluated the alcohol exposure dichotomously. A total of 19 studies showed the drinking patterns of pregnant women. However, these measures were not summarized due to differences among consumption categorization across studies. Low, moderate, or heavy alcohol consumption may influence a higher or lower decrease on BW. Heavy drinking is well-established in the literature as a risk factor for low BW[3,10,22,37] A low to moderate consumption or occasional drinking may not have a statistically significant association or even be identified as a protective factor.[11,18,21,24,31,47,60,61]

The physiological explanation for moderate drinking as a protective factor is related to the effects on the maternal cardiovascular system. Alcohol activates endogenous plasminogen, which increases fibrinolytic activity, inhibiting placental aggregation. It also influences the hemostatic mechanism of blood vessels by promoting relaxation, leading to higher growth levels of the vascular endothelium. These vascular alterations contribute to better placental development and increases in fetal oxidation and nutrition, which reflect on the growth pattern.[62–64]

It is important to highlight that although the majority of studies indicate that moderate drinking is not considered a risk factor for low birthweight, many studies note the association between drinking and other outcomes related to the growth and development of the child. Some cognitive and behavioral changes during infancy and adolescence, such as difficulty to follow instructions, aggressive behavior, risk of eating disorders, hyperactivity, and other mental disorders, were found to be associated with low maternal exposure to alcohol.[60,65–68]

Among the strengths of the present study, we have investigated the causes for the high heterogeneity found in the meta-analysis, so we believe that our systematic review may contribute to the discussion of the main causes for heteronomy between primary studies on alcohol consumption and outcomes on newborns. Besides that, we have aimed to reach the recommendations for conducting a good systematic review, including: sensitive literature search, no publication language or date restrictions, inclusion of a gray literature search, and study selection, data extraction, and methodological assessment performed independently by at least two authors. The present systematic review followed the Moose Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies.[69]

Conclusion

We did not find an association between alcohol consumption during gestation and LBW in the analysis in all subgroups. In addition, we have found high heterogeneity between the primary studies, and this is related to methodological differences in the conduction of these studies. As relevant directions for future studies, we suggest that primary studies investigate the association between maternal exposure to alcohol and the adverse effects on fetal health, considering the many levels of consumption and different populations. Methodological variations between the studies and the different assortment of alcohol consumption tools may

introduce a misclassification and impair a comparison between the studies. We recommend that future studies on this subject use validated data collection tools and standardized methods for describing alcohol consumption among pregnant women.

Conflicts of interests

The authors have no conflicts of interests to declare.

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