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Review

Maternal alcohol consumption and oral clefts: a meta-analysis

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Abstract

Our aim was to evaluate the possible correlation between maternal alcohol consumption during the first trimester and the risk of having an offspring with non-syndromic oral cleft. We electronically searched all published papers from 1950 to 2019 about maternal alcohol consumption and oral clefts in PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Institute for Scientific Information (ISI) databases. Descriptive and quantitative data were extracted from eligible studies for systemic evaluation and meta-analysis. A total of 12 publications met our inclusion criteria, and nine of them presented sufficient data for quantitative analyses. The overall odds ratio of the nine reports was 1.00 (95% CI 0.87 to 1.15) for cleft lip with or without cleft palate (CL/P) and 1.02 (95% CI 0.92 to 1.14) for cleft palate only, indicating no significant difference between drinking and non-drinking mothers in the risk of having a child with a non-syndromic oral cleft. We found no confirmatory evidence for the presence of a dose-response relation between alcohol consumption and increase in the risk of oral cleft. Nevertheless, four of the studies enrolled found significantly increased risk of CL/P among mothers in the groups that consumed the most alcohol. All but one of the four studies suggested a positive correlation between binge drinking and the occurrence of non-syndromic oral cleft. Although we found no concrete correlation between mild alcohol consumption during pregnancy and the occurrence of non-syndromic oral cleft, precautions should still be taken to avoid binge drinking during the first trimester.

Keywords: Maternal exposure; binge drinking; alcohol; craniofacial anomalies; birth defect; cleft lip and palate

Introduction

Oral clefts are the most common craniofacial birth defects in humans, with an occurrence of about 1-2/1000 births.[1] According to the embryogenic aetiology, they can be categorised as cleft lip with or without cleft palate (CL/P), and cleft palate alone. Various models have been suggested to explain the origin of oral clefts, and the gene-environment interaction model is the most widely accepted.[2] Multiple maternal behavioural factors have been suggested that potentially correlate with the occurrence of an oral cleft, including smoking,[3] folate deficiency,[4] antiepileptic drugs,[5] and alcohol consumption during pregnancy.

In the United States, about 10% of pregnant women drink alcohol, and about 2% binge-drink or drink frequently.[6,7] More than half the women who did not use birth control reported alcohol use and 12.4% reported binge-drinking.[7] About 1-3/1000 live newborns had fetal alcohol syndrome (FAS), and about 9% to 18% of these have oral clefts.[8,9] Although maternal consumption of alcohol during pregnancy was suggested as a potential environmental risk factor for oral clefts as early as 1978,[10] subsequent studies have reported

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contrary results, which makes it difficult to form a consistent epidemiological opinion on the association between maternal alcohol intake and the occurrence of oral clefts.[8,11,12] During the same period, we know of few studies that focused on the development of oral clefts and maternal binge- drinking, which is usually defined as more than four drinks on any one occasion.[13]

It is therefore important to try to establish the relation between maternal alcohol consumption and oral clefts. We therefore systematically reviewed relevant publications and made a meta-analysis of eligible cohort and case-control studies, with the aim of clarifying whether maternal alcohol consumption during the first trimester is linked with an increased risk of oral clefts in their offspring.

Material and methods

Search strategy

Relevant publications were electronically retrieved from Ovid Medline® (January 1950-March 2019), the Institute for Scientific Information (ISI) (January 1980- March 2019), and the Cochrane Central Register of Controlled Trials (CENTRAL) with MeSH terms including "cleft palate", "cleft lip", "congenital abnormalities", "maternal exposure", "alcohol" and "pregnancy trimester, first", and key words including "cleft", "birth defect", "alcohol drinking" and "maternal". Reference lists of all identified studies were scanned by title, and the authors of six studies were contacted for potentially eligible unpublished results. There were no restrictions on language, publication status or date.

Cohort and case control studies about oral clefts were included during reviewing of abstracts. During the reviewing of the full texts, studies without detailed information about first-trimester maternal drinking and birth outcome were excluded. Studies that failed to differentiate between syndromic and non-syndromic oral clefts or between oral clefts and other malformations were also excluded. When it came to studies that shared overlapping data, only the one reporting the largest sample size was adopted.

Extraction of data

Data and descriptive information were extracted independently by two authors (XY and JL). The third author (YL) participated in the discussions when there were disagreements and uncertainties.

Meta-analysis

We made meta-analyses separately for CL/P and cleft palate in Stata software (version 10.0 StataCorp). Syndromic cases were omitted, and multiple cases were distinguished from isolated ones wherever possible. Heterogeneity was evaluated with the Q test and a random effect model was used if the probability was less than 0.1.

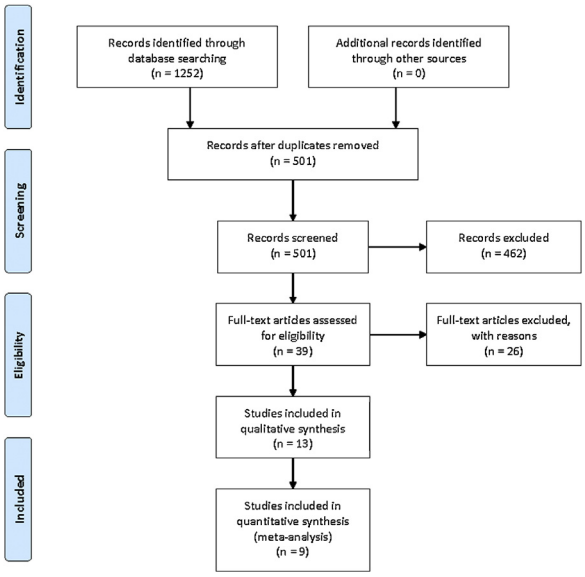

Fig. 1. PRISMA flowchart showing how the papers were retrieved.

Publication bias was assessed using Begg's funnel plot and Begg's and Egger's formal tests. Quality was appraised using the Newcastle-Ottawa scale to indicate the risk of bias.

Dose-response analysis

We used the Cochran-Armitage trend test on SAS software (version 9.0, SAS Institute) to explore the presence of dose-dependent relations where graded quantitative drinking information was available. In addition, we summarised OR for the highest alcohol consumption category in each study and discussed accessible results for maternal binge-drinking.

Results

Retrieval of papers

A total of 1252 records were identified by our searching strategy (526 from Medline and 726 from the ISI). Meticulous screening of abstracts and full-text assessment enrolled one cohort study[14] and 12 case-control studies[8,11,12,15–23] for the final analyses (Fig. 1). Detailed characteristics of the reports included are presented in Table 1.

Common confounders discussed in most of the studies included cigarette smoking, vitamin supplementation, folic acid intake, and socioeconomic status. The paper by Werler et al[15] was not included in the meta-analyses for low level drinking mothers (<1drink/drinking day) and non-drinking mothers combined as its control group, but was included in the following dose-response analysis. Missing and unknown cases were excluded. Information about sample size extracted from the other 12 studies is shown in Table 2. Quality

Table 1
Design characteristics of enrolled studies concerning alcohol consumption and oral clefts.

First author and reference	Region	Time span	Case/exposed types	Control/unexposed types	Drinking timing	Confounder analysis	Outcome type	Study design
Deroo[8]	Norway	1996–2001	CL ± P|CP|NS	Normal	M1–M3	Yes	Dichotomous Continuous	Case control
Romitti[20]	USA (Multicentre)	1997–2002	CL|CLP|CP|ALL	Normal	B1–M3	Yes	Continuous	Case control
Bille[14]	Denmark	1997–2003	CL ± P|CP|ALL	Non-drinking	M1–M3	Yes	Dichotomous Continuous	Cohort
Chevrier[19]	France Multicentre	1998–2001	CL ± P|CP|NONSYN	Normal	B1–M3	Yes	Dichotomous Period	Case control
Meyer[18]	USA Multicentre	1983–1998	CL|CLP|CP|P-R SYN	Normal & malformed	M1–M4	Yes	Dichotomous Continuous	Case control
Beaty[11]	USA Maryland	1992–1998	CL|CLP|CP|NONSYN	Normal	M1–M3	No	Dichotomous	Case control
Lorente[17]	France, UK, Italy, Netherlands	1989–1992	CL ± P|CP|NONSYN	Normal & malformed	M1–M3	Yes	Continuous	Case control
Romitti[16]	USA Iowa	1987–1994	CL ± P|CP|NONSYN	Normal	B3–M9	Yes	Continuous	Case control
Shaw[12]	USA California	1987–1989	CL ± P|CP|ALL	Normal	B1–M3	Yes	Continuous	Case control
Werler[15]	USA Multicentre	1983–1987	CL ± P|CP|ALL	Malformed	M1–M4	Yes	Continuous	Case control
Butali[21]	Europe	1989–2009	CL ± P|CP|ALL	Normal	M1-M9	Yes	Dichotomous	Case control
Yang[22]	USA California	1997–2006	CL ± P|CP|ALL	Normal	B1-M2	Yes	Dichotomous	Case control
Hao[23]	China Heilongjiang	2009–2014	CL ± P|CP|ALL	Normal	M1-M3	Yes	Dichotomous	Case control

CL ± P = Cleft lip with or without cleft palate; CL = Cleft lip; CLP = Cleft lip and palate; CP = Cleft palate; SYN = Syndromic type; NONSYN = Non-syndromic type. NS = Not stated; ALL = Including both syndromic and non-syndromic types; P.R.SYN = Pierce-Robinson syndrome.
Normal: Mothers of absolutely normal children; Malformed: Mothers of children with congenital malformation that is not an oral cleft.
B = Month before pregnancy; M = Month during pregnancy.

Table 2
Information about sample size extracted from enrolled studies.

First author and reference	Consumption	Control	Cleft lip and palate	Cleft palate
Deroo[8]	Yes	236	147	76
	No	527	230	120
Romitti[20]	Yes	1610	448	186
	No	2484	680	263
Bille[14]	Yes	353	54	23
	No	475	80	35
Chevrier[19]	Yes	30	32	9
	No	206	132	67
Meyer[18]	Yes	655	96	27
	No	3617	546	178
Beaty[11]	Yes	67	23	13
	No	85	68	31
Lorente[17]	Yes	189	16	14
	No	941	93	37
Romitti[16]	Yes	108	57	19
	No	285	102	45
Shaw[12]	Yes	307	80	80
	No	424	134	134
Werler[15]	Yes	254	66	27
	No	1162	333	188
Butali[21]	Yes	308	248	50
	No	574	394	102
Yang[22]	Yes	131	41	21
	No	654	236	96
Hao[23]	Yes	72	43	26
	No	408	319	111
Overall	–	16162	4698	1978

appraisal of these reports using the Newcastle-Ottawa scale is shown in Table 3.

Maternal alcohol consumption and occurrence of CL/P

For maternal drinking and CL/P, a formal test of heterogeneity was significant ($\chi 2 = 25.01$, df = 8, p = 0.002) and a random effects model was adopted. An overall OR of 1.00 (95% CI 0.87 to 1.15) was yielded ranging from 0.43[11] to 1.66 (Fig. 2).[19] Heterogeneity came solely from two studies.[8,11] With data from the two studies excluded, the pooled OR stayed as 1.00 with p = 0.144. The Begg funnel plot was roughly symmetrical with a p value of 0.667, which indicated no remarkable proof of publication bias (p = 0.677, Fig. 3). Neither Begg's nor Egger's test gave any significant results.

Maternal alcohol consumption and occurrence of cleft palate

For maternal drinking and cleft palate, the result of the test of heterogeneity (chi squared 13.98, df = 8, p = 0.082) also suggested using a random effects model, in which an overall

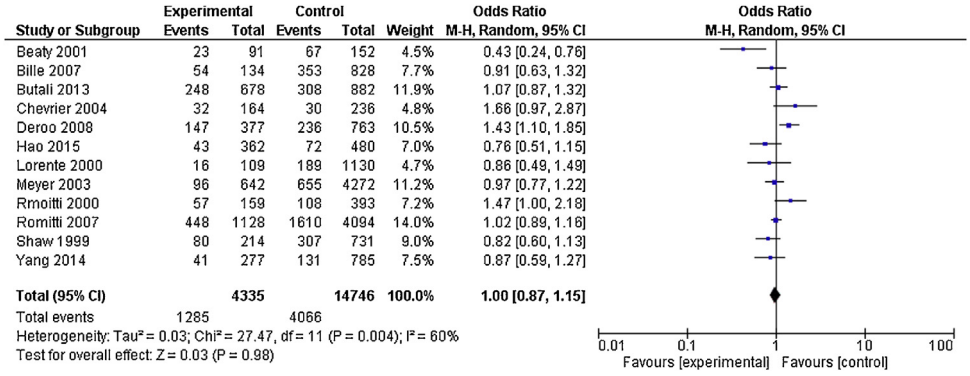

Fig. 2. Results of random-effects meta-analysis of the odds ratio for cleft lip and palate.

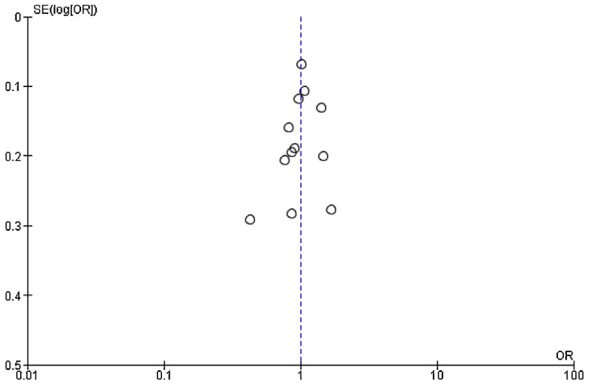

Fig. 3. Funnel plot (with pseudo 95% CI) detecting possible publication bias for the association between cleft lip and palate and maternal drinking.

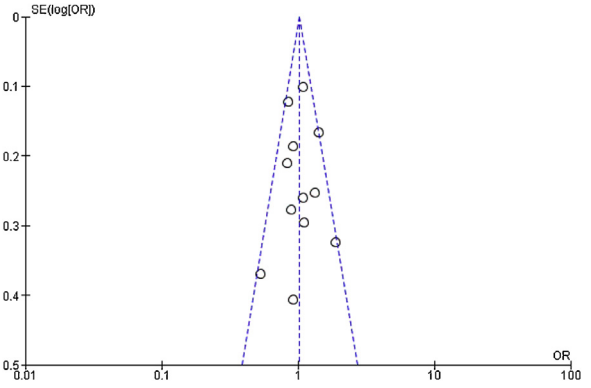

Fig. 5. Funnel plot (with pseudo 95% CI) for detecting possible publication bias for the association between cleft palate and maternal drinking.

OR of 1.02 (95% CI 0.92 to 1.14) was reached ranging from 0.53[11] to 1.88 (Fig. 4).[17] Heterogeneity here came from three studies.[8,12,17] Excluding data from Deroo et al[8] the overall OR was 0.97 with p = 0.188. Excluding data from Lorente et al[17] the overall OR was 0.99 with p = 0.162. Excluding data from Shaw and Lammer,[12] the overall OR was 1.07 with p = 0.121. When all three were excluded, the pooled OR was 0.99 with p = 0.447. No significant indication of publication bias was found in Begg's funnel plot (p = 0.835, Fig. 5) or Begg's or Egger's test.

Dose-response analysis

Seven studies provided sufficiently quantifiable data for dose-response analysis (Table 4). As each study had its own drinking grading standards, which differed from each other, the comparability was relatively weak. No confirmatory evidence of a positive dose-response relation was found concerning CL/P. Three studies showed a weak dose-response relation, and two showed a reduced association with amount of alcohol intake but an increased association in the high level of consumption. Our dose-response analysis for cleft palate

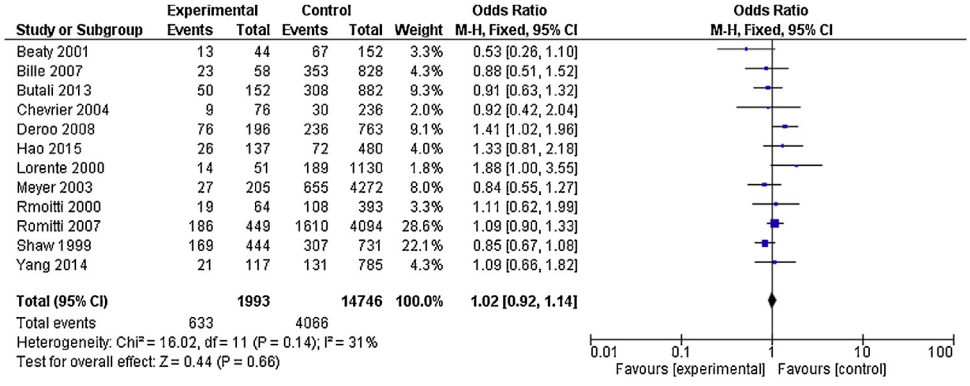

Fig. 4. Results of random-effects meta-analysis of the odds ratio for cleft palate.

Table 3
Quality appraisal of included studies using the Newcastle-Ottawa scale.

First author and reference	Adequate definition of case	Representativeness of cases	Selection of controls	Definition of controls	Comparability	Ascertainment of exposure	Same method of two groups	Non-response rate
Deroo[8]	Yes	Yes	Yes	No	Yes	No	Yes	No
Romitti[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bille[14]	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Chevrier[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Meyer[18]	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Beaty[11]	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Lorente[17]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Romitti[16]	Yes	Yes	Yes	Yes	Yes	Uncertain	Yes	No
Shaw[12]	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Werler[15]	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Butali[21]	Yes	Yes	Yes	Yes	Uncertain	No	Yes	Yes
Yang[22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Hao[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

also failed to suggest any strong affirmation of such a relation. Only two studies gave weak positive results, and another two studies showed a reduced association between low and medium amounts of drinking but an increased association with large amounts drunk.

Binge-drinking

OR for the highest drinking level of eight studies are summarised in Table 5. Four of the studies showed an increased risk for giving birth to children with CL/P with high alcohol intake, while the others showed no such increase. None of these studies provided evidence for the presence of an increased risk of cleft palate with their individually-defined highest drinking level. All but one of the four studies taking binge-level drinking into discussion reported increased risk for both CL/P and cleft palate.

Discussion

The effect of moderate maternal alcohol consumption on the outcome of pregnancy has long been discussed.[24–26] Results of our meta-analyses may lend some support to the opinion that the side-effects of low-level maternal drinking have been exaggerated.[27] Ignoring various exposure levels of drinking mothers, only two of the enrolled studies gave a significant OR for CL/P and one for cleft palate. As moderate drinking is unlikely to be more dangerous than heavy drinking, the potential risk for moderate drinking may be weakened if cases of heavy-drinking mothers were excluded. One study[18] used mothers with both no consumption and low consumption as controls, and no significant discrepancy was observed, which further attenuates the association between low maternal alcohol consumption and increased risk for orofacial clefts.

While a linear dose-response relation is regarded as proof of causation,[28] our dose response analysis failed to provide such proof. However, the results of our Cochran-Armitage analysis must be taken with great caution. The definition of low, medium, and high consumption was weak.

It has previously been suggested that there is a positive relation between maternal binge-drinking and many birth defects.[28–29] In addition, oral clefts are commonly found in FAS.[30] Although only half of the studies listed in Table 5 showed an increased risk for CL/P, and only one for cleft palate, underestimation of the potential danger of binge-drinking during pregnancy could not be justified. Considering that the risk of spontaneous abortion might increase among mothers who were frequent binge-drinkers, and none of the studies investigated aborted cases, paradoxical results may arise.[31] The representativeness of the results concerning cleft palate could be undermined by an inadequate sample size, which may serve as an explanation for all the null results of an increased risk of cleft palate with high alcohol consumption. The risk of heavy drinking during the first trimester of pregnancy should therefore not be underestimated.

Table 4
Risks of having a child with oral cleft by different maternal alcohol consumption level.

First author and reference	Type of cleft	Low consumption[a]	Medium consumption[a]	High consumption[a]	Chi squared for trend	p value
Deroo[8]	CL/P	1.35	1.15	2.39	1.0609	0.1515
	CP	1.38	1.30	2.19	0.2416	0.3116
Romitti[20]	CL/P	1.04	0.83	1.14	0.0620	0.4013
	CP	0.86	0.66	0.81	0.4356	0.2546
Bille[14]	CL/P	1.07	1.46	–	–	–
	CP	1.20	1.68	–	–	–
Meyer[b 18]	CL/P	1.0	1.1	0.9	0.1378	0.3553
	CP	1.0	0.8	1.0	0.1559	0.3465
Lorente[17]	CL/P	1.30	0.87	-	1.0428	0.1536
	CP	2.76	1.74	-	2.5753	0.0543
Romitti[b 16]	CL/P	1.3	2.8	-	2.6814	0.0508
	CP	1.1	1.7	-	0.5173	0.2360
Werler[b 15]	CL/P	0.8	1.2	3.0	0.0017	0.4832
	CP	0.7	0.3	0.9	4.4091	0.0179

[a] Consumption level by reference: Deroo: low:1-4 drinks/1-2 days, medium:1-4 drinks/≥3 days, high:≥5 drinks/≥1 day; Romitti(2007): low:1-4 drinks/month, medium:5-30 drinks/month, high:>30drinks/month; Bille: low:1-2 units/week, medium:≥3 units/week; Meyer; low:<1 drinks/week, medium:1-2.9 drinks/week, high:>3 drinks/week; Lorente: low:<70 g/week, medium:≥70 g/week; Romitti(2000): low:1-3 drinks/month, medium:≥4 drinks/month; Werler: low:<3 drinks/drinking day, medium:3-4 drinks/drinking day, high:≥5 drinks/drinking day.
[b] OR directly from references.

Table 5
Adjusted OR (95% CI) for highest alcohol consumption.

First author and reference	Highest consumption	Cleft lip and palate	Cleft palate
Deroo[8]	≥5 drinks/≥3 days	3.2 (1.0 to 10.2)	3.0 (0.7 to 13.0)
Romitti[20]	≥30 drinks/month	*see footnote	1.1 (0.6 to 2.2)
Bille[14]	≥3 units/week	1.20 (0.68 to 3.19)	1.68 (0.45 to 4.15)
Meyer[18]	≥3 drinks/drinking day	1.0 (0.6 to 1.7)	0.9 (0.4 to 2.1)
Lorente[17]	≥70 g/week	1.07 (0.39 to 2.99)	2.22 (0.67 to 7.34)
Romitti[16]	≥4 drinks/month	2.8 (1.2 to 6.6)	1.7 (0.5 to 6.4)
Shaw[12]	≥5 drinks ≥ once a week	3.4 (1.1 to 9.7)	1.0 (0.23 to 8.5)
Werler[15]	≥5 drinks/drinking day	3.0 (1.1 to 8.5)	0.9 (0.1 to 7.2)

* 1.0(0.5 to 2.1) for cleft lip only, 0.8 (0.5 to 1.6) for cleft lip with cleft palate.

Another confounder in the studies is the definition of heavy drinking. Unlike cigarette smoking or use of drugs, precise alcohol consumption is difficult to evaluate, as alcohol concentration varies widely among beverages (such as wine, beer and distilled spirits) and a drink, which is usually used as a scale for consumption, is rather vaguely defined.[32] A description of a heavy drinking pattern should include both the frequency and intensity of the drinking, and occasional and frequent binge-drinking must also be defined and differentiated.[33] In addition, timing of the alcohol consumption and gestational age should be taken into account, as embryogenesis of the palate and lip is largely finished by the end of the first trimester.[1] We found no increased risk of orofacial clefts among mothers who binged occasionally before pregnancy but gave up drinking during the first trimester.[8]

Although our analyses were restricted to published studies, no significant evidence for publication bias was found using Begg's and Egger's tests, even though the detecting power of these tests is limited.[34] Considering the uncertainty of how maternal alcohol intake affects the occurrence of orofacial clefts, studies with negative results are equally likely to be published as those with positive results.

The limitations of case control studies should always be considered. Even though they are economically and temporally convenient, they do not measure risk directly. It is also important to be aware of recall bias, as mothers of affected cases may be more likely to admit to alcohol consumption than mothers of controls, so as to justify the occurrence of orofacial clefts. Furthermore, selection bias may exist if the likelihood is increased participation from mothers exposed to alcohol during pregnancy of affected cases compared with mothers of controls. When we considered the sensitivity of case control studies in populations where maternal exposure rate to alcohol is low, not all studies were able to include numbers large enough to detect risk. All of these limitations may give rise to conflicting study results.

Confounding control is another important issue. In most studies, sociodemographic factors that might be related to lifestyle were adjusted. Adjustment was made for cigarette smoking in four studies,[8,12,17,18] where adjusted and unadjusted OR were similar. Alcohol has been called a folic acid

antagonist, and vitamin supplementation has been associated with a reduced risk of orofacial clefts.[35–37] However, those studies that we included in our analyses that considered the effect of folic acid intake were conflicting about its modifying effect on the association between drinking and clefts.[12,18]

Conclusions

In summary, the overall standardised OR reflect no significant association between moderate maternal alcohol consumption and clefts. However, enough awareness should be given to the potential risk of binge-drinking. Meta-analysis on heavy drinking and the occurrence of orofacial clefts would be necessary when adequate reports are available.

Ethics statement/confirmation of patients' permission

No ethics approval or patients' permission required.

Conflict of interest

We have no conflicts of interest.

Data availability statement

There are no restrictions on the availability of materials or information in this study.

Acknowledgements

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjoms.2019.08.013.

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