MATERNAL ALCOHOL CONSUMPTION DURING PREGNANCY AND THE RISK OF OROFACIAL CLEFTS IN INFANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: The teratogenic effects of maternal alcohol consumption during pregnancy include anomalies of craniofacial structures derived from the cranial neural crest cells. The presence of specific craniofacial anomalies contributes to the diagnosis of fetal alcohol spectrum disorders. Cleft lip and palate [orofacial clefts (OFCs)], also derived from the cranial neural crest cells, are common congenital anomalies but their relationship with prenatal alcohol consumption is unknown.

Methods: To evaluate the association between maternal consumption of alcohol during pregnancy and the occurrence of OFCs in infants, we conducted a systematic review and meta-analyses of published studies. We examined the associations between any alcohol consumption, binge level drinking, and heavy and moderate levels of consumption versus no or low levels of consumption.

Results: After screening 737 publications we identified 33 studies (23 case control and 10 cohort studies). There was considerable heterogeneity in individual study design, quality measures and study results. Findings from random effects meta-analyses suggest no relationship between prenatal alcohol consumption and the occurrence of OFCs [pooled odds ratios for any alcohol intake and binge level drinking respectively: cleft lip with or without cleft palate 1.00 (95% confidence interval [CI] 0.86, 1.16) from 18 349 participants in 13 studies, 1.04 (95% CI 0.87, 1.24) (8763 individuals, 4 studies); cleft palate only 1.05 (95% CI 0.92, 1.21) (21 459 individuals, 17 studies), 0.94 (95% CI 0.74, 1.21) (7730 participants, 4 studies)].

Conclusions: While we found no association between alcohol consumption during pregnancy and OFCs in infants, the influence of study design, particularly in relation to alcohol exposure measurement and OFC ascertainment cannot be ignored.

Keywords: alcohol, cleft lip, cleft palate, pregnancy, meta-analysis

Maternal consumption of alcohol during pregnancy can adversely affect the fetus, and a wide range of physical, behavioural and neurocognitive disabilities can result. The pattern and severity of these effects depend on the dose, timing, pattern and duration of the alcohol exposure. As well, the vulnerability to alcohol-induced damage varies across cell types and tissues as well as across stages of fetal development.[1] Animal studies have shown that gestational exposure to alcohol disrupts the cranial neural crest cells, the embryonic cells that contribute to the development of the face, including the lip and palate.[2] While many of the abnormal structures observed in, and defining fetal alcohol spectrum disorder (FASD) include craniofacial anomalies derived from these cells,[3] it is unclear whether maternal alcohol consumption during pregnancy is related to other facial congenital anomalies such as orofacial clefts (OFCs) which are also derived from these cells.

As the lip and palate have distinct developmental origins, OFCs are often classified and investigated as cleft lip with or without cleft palate (CL±P); or as cleft palate only (CPO), in which the lip is not affected.[4] The phenotypic variants of cleft lip [cleft lip only (CLO) and cleft lip with cleft palate (CL+P)] are usually considered to be the same defect and are thought to differ aetiologically from CPO. OFCs may be further classified as occurring without other congenital anomalies (isolated OFCs), or with other congenital anomalies and may or may not be part of recognised syndromes, or known chromosomal or gene abnormalities.[4]

OFCs are among the most common congenital malformations with a prevalence of around 14-20 per 10,000 births.[5] The causes of OFCs are largely unknown, but both genetic and environmental factors have been identified.[4] The association between prenatal alcohol exposure and OFCs has been investigated in many studies, but the relationship is unclear.

Therefore we conducted a systematic review of the studies that have investigated the association between maternal alcohol consumption during pregnancy and the risk of OFCs in infants.

Methods

Study identification and data extraction

We included published case control and cohort studies where maternal alcohol consumption during pregnancy and occurrence of OFCs in infants were reported. Review papers, ecological studies, case reports and case series, animal studies, and studies where alcohol consumption after delivery was reported, or where mothers' history of alcohol consumption was described but not their consumption during pregnancy, or where alcohol consumption was not reported by OFC status, or where OFCs were not reported, were excluded.

We identified potentially relevant publications by searching Medline (1950-July 2013), Premedline, and Embase (1980-July 2013) using exploded MeSH headings and text words. As OFCs are not always indexed specifically, we also conducted searches on congenital anomalies and malformations in general. To identify terms related to maternal alcohol consumption we combined the following search terms (subject headings and, or keywords) with OR: 'prenatal alcohol exposure', 'alcohol intake', 'alcohol consumption', 'alcohol drinking', 'fetal alcohol syndrome', 'fetal alcohol spectrum disorder', 'FASD' , 'FAS', 'alcohol'. Relevant outcomes were identified by searching subject headings and keywords for 'orofacial clefts', 'cleft lip', 'cleft palate', 'oral clefts', 'congenital anomalies', 'congenital abnormalities', 'congenital malformations', 'birth defects', 'alcohol related birth defects, 'ARBD' and combining these with OR. Both exposure and outcome searches were combined with AND, and the search was then limited to studies involving humans.

One author (JB) initially reviewed all titles and abstracts. Papers that could not be excluded based on the initial review were assessed independently by two authors (JB, CO'L) and any differences were resolved by consensus. We did not exclude papers based on language of publication and these were reviewed by speakers of those languages. We did not contact authors directly, and did not seek unpublished studies.

Study characteristics, quality and data from included studies were extracted by pairs of authors independently (CO'L, JB, CRG, NN) using prepared data extraction forms. Differences were resolved by discussion, and if necessary by conferring with a third author. Where results from an individual study were reported in multiple publications, we extracted the most relevant data, or data for the longer period. Data were extracted for CL±P and CPO separately, unless only data for OFCs as a group were reported.

We extracted data for any exposure to alcohol versus no alcohol intake (or low alcohol intake if that were the reference group, and if equivalent to around 1 drink or unit per week). Consumption levels were based on international guidelines.[6] Binge drinking was defined as drinking five or more drinks on one or more occasions. This equates with around 50-70+ grams of alcohol per occasion, depending on the definition of a standard drink. We did not regard heavy drinking as binge drinking unless it was defined or could be deduced from individual studies as equivalent to binge levels. To investigate whether the association between OFC occurrence varied by levels of alcohol consumption, we categorised alcohol consumption (in grams of alcohol consumed per week) into heavy and moderate levels. Heavy drinking during pregnancy was defined as around two or more drinks per day (approximately 90+ grams alcohol per week), with or without known binge drinking and

moderate consumption was characterised by drinking less than one drink/day and no more than two drinks per occasion (less than approximately 70-84 grams alcohol per week), and no known binge consumption.[7] Where exposure levels were reported as drinks, the number of drinks was converted to grams of alcohol per week using the drink size reported in the study, or if unavailable, the standard drink size for that country.[6] Published data in some papers differ from our extracted data due to combining of categories and applying consistent exposure levels. For example, exposure defined as 'moderate' in one paper may be defined as 'low' in another paper.

Timing of alcohol consumption was categorised as during the first trimester, or during pregnancy. If studies reported exposure during both the first trimester and over all of pregnancy, we extracted data for the first trimester as this period relates to the period of fetal facial development.

Study quality assessment

While there is no agreed 'gold standard' for assessing the quality of observational studies, we used the Newcastle-Ottawa Scale (NOS)[8] that examines quality of exposure and outcome assessment and adjustment for confounding. For each item of the NOS, we defined specific criteria relevant to studies reporting the association between alcohol in pregnancy and identification of OFCs.

Statistical analysis

Where only percentages of participants were reported and the denominator was known, we calculated numbers for study groups. For studies that reported odds ratios and confidence intervals, but not participant numbers, we imputed these.[9]

We conducted meta-analyses using the Mantel-Haenszel random effects method using numbers contributing to crude odds ratios because most studies reported these. If published, adjusted odds ratios are reported in the Figure footnotes. Where there was insufficient data to allow inclusion in meta-analyses, we reported results from studies separately in the relevant section. In studies with a cell count of zero, we applied a constant continuity correction of 0.5.[10] We assessed heterogeneity using the I^2 statistic. We compared the odds of infants having OFCs (CL±P, CPO, and OFCs as a group) between the reference group and mothers who consumed alcohol (any, and binge drinking) during the first trimester or during pregnancy. We also examined whether a dose-response relationship existed between maternal alcohol consumption and OFC occurrence.

We conducted sensitivity analyses to assess the robustness of results (see Supplementary Information 1). Funnel plots and a modified Egger's test [11] were conducted to assess publication bias. Meta-analyses were conducted using Revman and SAS version 9.3.

Results

Searches of the electronic databases identified 737 potential papers and 530 were excluded after initial review. From the remaining 207 papers and the 35 papers identified from reference lists and automated update searches we identified 23 case control studies and 10 cohort studies where maternal alcohol consumption during pregnancy and OFCs in infants were described (Figure 1).

Description of included studies

Supplementary Table 1 details characteristics of the case control studies.[12-35] Alcohol consumption in nearly 15,000 mothers of infants with OFCs was compared with nearly 27,000 mothers of infants without OFCs. Two case control studies did not contribute data to the meta-analyses; one because no women reported drinking alcohol[20] and in the second study the reference group could not be determined.[21] Another paper[32] reported the continuing results for their study[31] but not enough information to enable additional data to be extracted.

Details of the 10 included cohort studies[36-42] are reported in Supplementary Table 2. A total of 408 infants with OFCs were born to 293,534 women whose alcohol consumption was recorded. The birth prevalence of OFCs varied from 10.3 to 40.0 per 10,000 births.[37,41] No infants with OFCs were diagnosed in three cohort studies[40-42] and therefore did not contribute data to the meta-analyses.

Study quality

The 23 case control and 10 cohort studies scored between two and eight out of a possible nine on the NOS (Supplementary Figure 1). For exposure ascertainment, we pre-specified that studies where alcohol exposure was assessed before delivery, using a secure record, or a structured interview constituted agreement with this NOS attribute. However, it is important to recognise that while these characteristics may be met, many studies in the review did not provide enough detail to determine whether their exposure assessment was adequate for specifying quantity, frequency and timing of alcohol consumption.

Any alcohol consumption

Pooled data presented in Figures 2 and 3 show no difference in risk of CL±P [13 studies, I^2=68%, pooled OR 1.00 (0.86, 1.16)] or CPO [17 studies, I^2=24%; pooled OR 1.05 (0.92, 1.21)] between infants whose mothers drank alcohol in pregnancy and those who did not.

The eight studies that analysed OFCs as a group (all or isolated OFCs), showed a slightly higher risk, but there was considerable heterogeneity (I^2=63%) and the confidence interval still included unity [pooled OR 1.24 (0.98, 1.58)] (Supplementary Figure 2). Of these studies, the four measuring alcohol intake during the first trimester showed an association [pooled OR 1.52 (1.18, 1.97)]. Three studies examined the association between alcohol consumption and non-isolated OFCs. Shaw et al[33] included OFCs occurring with known syndromes and exposure to alcohol during the first trimester [OR 1.42 (0.87, 2.33)]; Czeizel et al[17] reported OFCs occurring with additional anomalies (but excluding those diagnosed with syndromes or chromosomal anomalies) and consumption during pregnancy [OR 0.80 (0.61, 1.04)]; and Saxen et al[31] analysed OFCs with an additional anomaly and drinking alcohol during pregnancy [OR 1.08 (0.65, 1.79)].

Sensitivity analyses did not alter the relationship between alcohol consumption and cleft types (Supplementary Information 1). Neither the funnel plots nor results from the modified Egger's test suggest publication bias for these meta-analyses (Supplementary Information 2).

Binge level drinking

Four studies contributed data to the association between binge drinking and CL±P and CPO; all measured binge drinking during the first trimester. No study reported an association; for CL±P the pooled OR was 1.04 (0.87, 1.24) and for CPO 0.94 (0.74, 1.21) (Figure 4). Heterogeneity between studies was negligible (I^2=0% for both analyses). Sensitivity analyses

did not alter the association (Supplementary Information 1). At a slightly lower level of consumption, Meyer compared maximum daily consumption of 3-4 drinks to less than 1 drink/day; the adjusted OR was 1.1 (0.8, 1.5) and 0.7 (0.4, 1.3) for isolated CL±P and CPO respectively.

The relationship between OFCs as a group and binge drinking could only be assessed from the Martinez-Frias study, where women who reported sporadic binges and, or women who drank ≥56 gms alcohol per day were compared with women who abstained [crude OR 2.66 (1.23, 5.74)].

Dose response relationship

Meta-analysis was not possible due to the differences between studies, particularly in alcohol consumption levels. Supplementary Table 3 shows no relationship between OFCs (including CL±P and CPO) and alcohol consumption at heavy or moderate levels with all ORs around unity. Four individual studies examined dose-response relationships for CL±P and CPO during the first trimester,[13,18,26,29,33] but no association and no change in the association at higher levels of consumption was found (Supplementary Table 4).

A comparison between very high (≥ 200 gms per week) and zero alcohol consumption could be differentiated in only three studies,[23,25,39] and each evaluated OFCs as a group. One reported no OFCs at this high level consumption[39]; the other two studies both reported elevated risk [Leite 2009 OR 1.95 (1.26, 3.02), Martinez-Frias 2004 OR 2.66 (1.23, 5.73)]; however quality scores for these studies were low.

Comment

Maternal alcohol in pregnancy is associated with craniofacial anomalies derived from the cranial neural crest cells from which the lip and palate also develop. It would seem reasonable that alcohol could also be associated with other structural anomalies derived from these cells, even if not currently recognised as part of FASD. This systematic review is the first to explore the impact of maternal alcohol consumption in pregnancy on the occurrence of OFCs in infants, but our findings suggest no association. However, the studies contributing to the review displayed considerable heterogeneity, limiting our ability to determine whether these results reflect a true relationship. Most of the included studies were limited by methodological issues in assessing and classifying alcohol exposure, in ascertaining and classifying OFCs, and in evaluating confounding variables. The difficulties investigating uncommon outcomes and in measuring alcohol exposure have undoubtedly led to pragmatic study designs. However these study characteristics limit the interpretation of the relationship between alcohol and OFCs.

Studies assessing the association between alcohol intake and health outcomes depend on the validity and reliability of self-reported alcohol intake. Self-reports are often retrospective and can be subject to recall or response bias due to the socially sensitive nature of the questions. Reliability of reported alcohol consumption during pregnancy varies, with concurrent or antenatal reports often being lower than retrospective or post-pregnancy reports.[43] In the majority of studies included in our review, alcohol consumption during the first trimester, or for all of pregnancy, was assessed after delivery, sometimes up to three years later. Increasing time between exposure and interview is more likely to be associated with decreases in the quality of data reported.[44]

Under-reporting of alcohol intake is also likely. Individuals tend to report their number of drinks in terms of the drink size they consume, and self-reported drinks often contain more alcohol than the presumed standard serving.[45] Alcohol consumption is also more likely to be under-reported on occasions of heavy drinking[46] and by women who consume at the highest levels.[43] Some studies reported an average intake, but averaging consumption can mask the assessment of low, moderate and binge drinking on infant outcomes.[7] The reference period for alcohol consumption (for example a 7-day recall) may also not accurately reflect an individual's typical consumption[47] with short term recall methods under-estimating the proportion of high risk drinkers.[48]

Risk may also not be evenly distributed within a defined exposure level. In any category of alcohol exposure, infants of women who drink at the heavier extreme of this category are at higher risk than those of women who drink at lower or more moderate levels, who are also included in the same exposure category. Likewise, infants of women with more efficient alcohol metabolism may be exposed to lower levels of alcohol, and for shorter periods than infants of other women despite similar levels of alcohol intake.[49]

Accurately determining the time of exposure in relation to pregnancy is critical. Facial development occurs very early in pregnancy, before the 10th week of gestation and it is during this period that many pregnancies may be exposed to alcohol, and at potentially high levels. A large proportion of pregnancies are unintended,[50] and the majority of women may not recognise their pregnancy until after the 4th week gestation.[51] In some populations around 80% of women of childbearing age consume alcohol[50,51] with a smaller proportion of women drinking at heavy or binge levels.[52] While most women reduce their intake once pregnancy is recognised, some women continue to consume at heavy or binge levels.[7,50-52] Women who

stop drinking after pregnancy awareness may be classified as unexposed, although their infants may have been exposed to alcohol during early pregnancy and before pregnancy was recognised.

OFC ascertainment and classification are influenced by timing of diagnosis, length of follow-up and sources of ascertainment. Infants with OFCs are under-ascertained if OFCs are identified in live births only, or in those who survive to be treated in surgical centres. Under-enumeration will also occur when the time allowed for diagnosis is limited; a recent population-based study found that 12% of children with CPO were diagnosed after one year of age.[53] Use of administrative databases (such as hospital discharge surveys and birth certificate data) for case identification also significantly under-estimates prevalence of OFCs (both CL±P and CPO).[54]

The association between alcohol and OFCs is potentially susceptible to confounding by other factors such as maternal age, parity, obstetric history, pregnancy planning, alcohol metabolism, diet, medications, smoking tobacco, and use of illicit substances.[55] While tobacco smoking during pregnancy increases the risk of CL±P by 34%, and CPO by 22%,[56] only nine studies reported their association between alcohol and OFCs adjusted for smoking and other covariates. As crude results from individual studies were available for meta-analyses, our pooled results may be confounded.

Despite the limitations of individual studies included in our review, we may not have identified all studies investigating the relationship between alcohol and OFCs. However, our findings of no association between prenatal alcohol exposure and OFCs and review of funnel plots suggest that publication bias may not be an important consideration in this review.

This is the first systematic review examining the association between prenatal alcohol exposure and occurrence of OFCs. Although a large number of studies contribute to the review, heterogeneity in study design, possibly due to pragmatic considerations, limits conclusive findings. Ideally future studies investigating prenatal alcohol exposure and outcomes relating to early fetal development should assess these outcomes in all pregnancies prospectively, and using multiple sources of ascertainment and longer follow-up allowing for later diagnoses. Alcohol exposure (dose, pattern and frequency of intake) and timing of exposure, should be documented when pregnancy is confirmed and confounding or modifying factors should also be evaluated.

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Supporting Information

Supplementary Figure 1. Quality assessment of included case control and cohort studies using the Newcastle-Ottawa Scale

Supplementary Figure 2. Forest plot - Odds ratios for association between alcohol consumption during pregnancy and OFCs

Supplementary Table 1. Characteristics of Case Control Studies Reporting Maternal Alcohol Consumption in Pregnancy and Occurrence of Orofacial Clefts

Supplementary Table 2. Characteristics of Cohort Studies Reporting Maternal Alcohol Consumption in Pregnancy and Occurrence of Orofacial Clefts

Supplementary Table 3. Association between OFC Types and Alcohol Consumption During Pregnancy at Heavy and Moderate Levels

Supplementary Table 4. Dose Response Relationship Between Maternal Alcohol Consumption in First Trimester and Infants With CL±P and CPO, Within Studies

Supplementary Information 1. Sensitivity Analyses

Supplementary Information 2. Funnel Plots and Tests For Funnel Plot Asymmetry

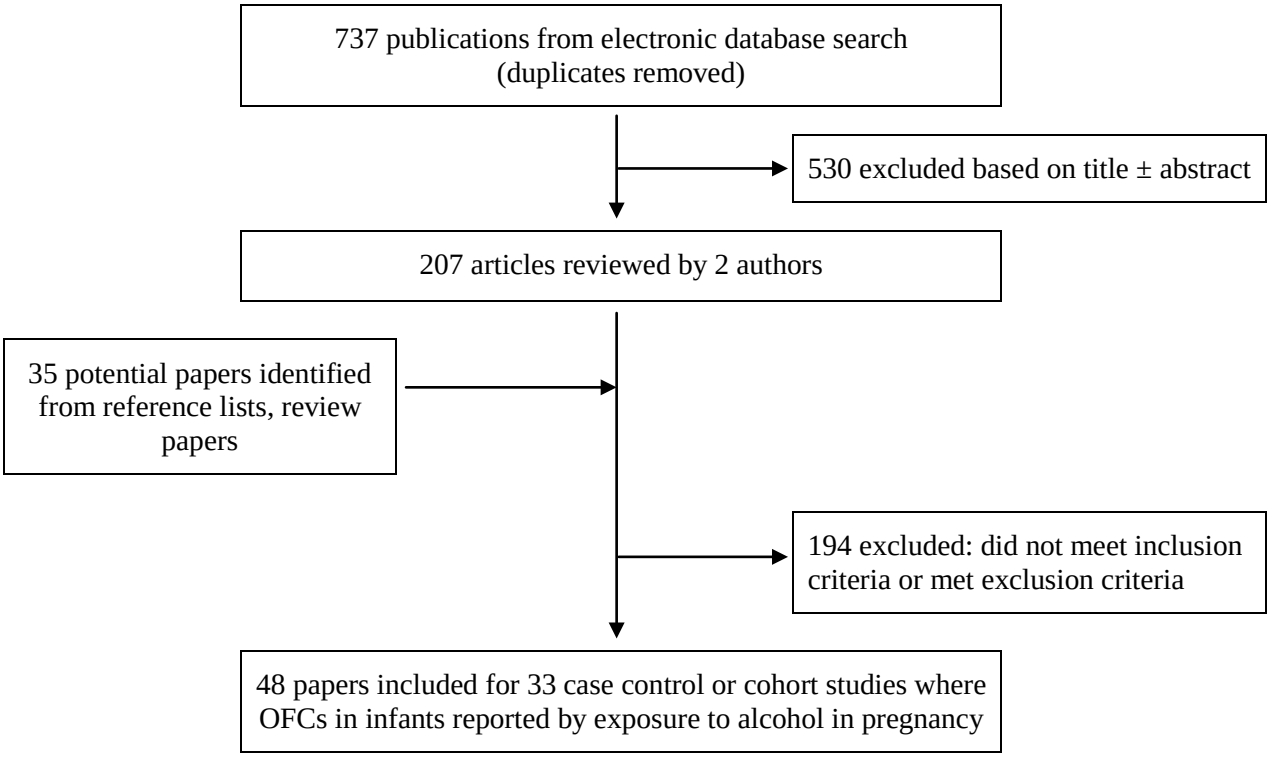

Figure 1. Process for identifying studies assessing the association between maternal alcohol consumption during pregnancy and the risk of orofacial clefts in infants.

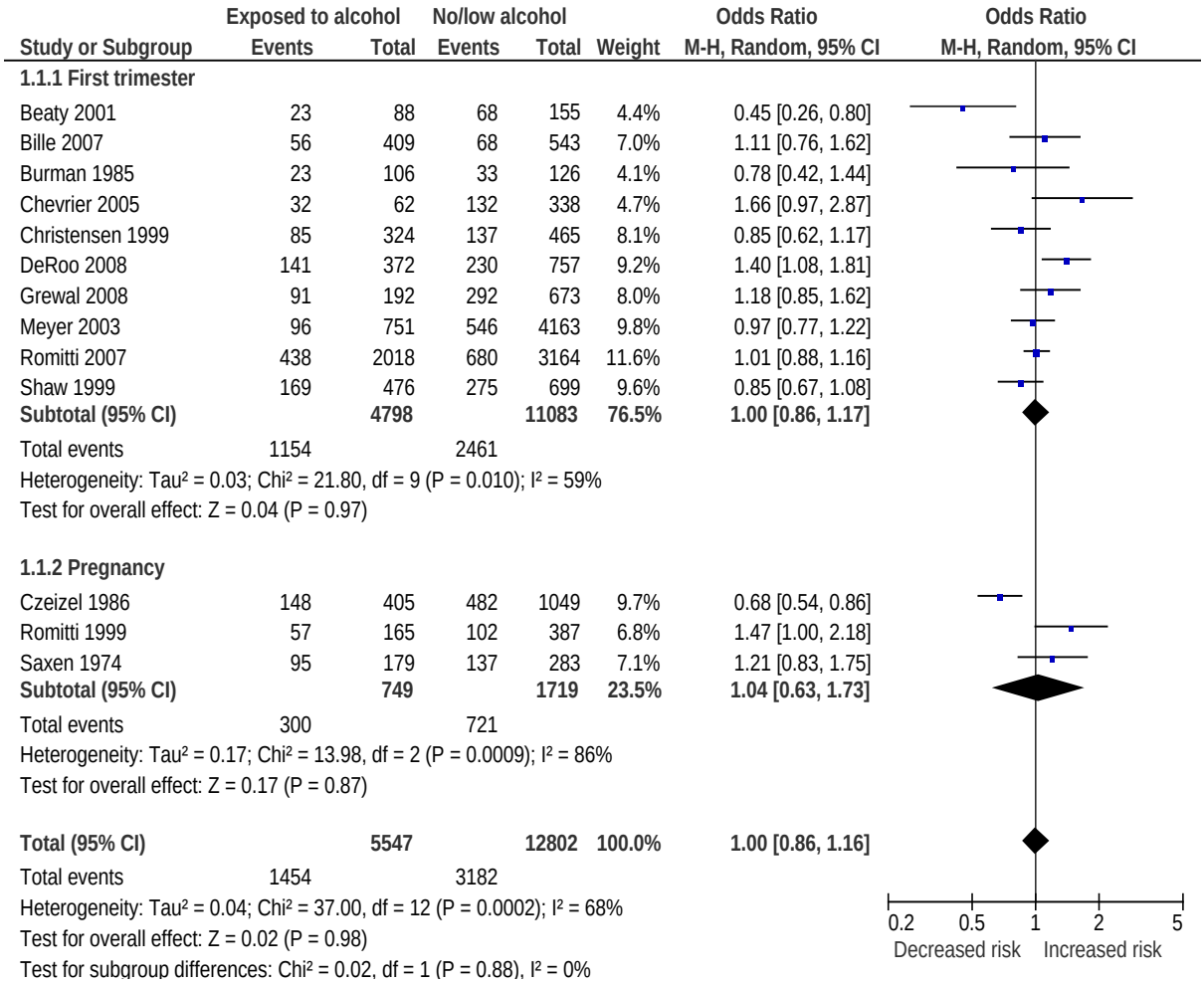

Figure 2. Odds ratios for cleft lip, with or without cleft palate (CL±P) in infants, by maternal consumption of alcohol during pregnancy (any alcohol versus none or low levels of consumption), by period of exposure.

Abbreviations: aOR, adjusted OR; M-H, Mantel-Haenszel
Beaty 2001: Isolated CL±P; imputed cell numbers to meet crude OR 0.44 (0.25, 0.79); aOR 0.40 (0.21, 0.76)
Bille 2007: All CL±P; imputed cell numbers to meet aOR 1.11 (0.75, 1.64)
Burman 1985: All CL±P
Chevrier 2005: Excluded known syndromes; reference exposure: < 1 drink/week
Christensen 1999: Isolated CL±P
DeRoo 2008: All CL±P
Grewal 2008: All CL±P; reference exposure: no alcohol+no smoking during two months before pregnancy to 2nd month of pregnancy v exposure during 1st month postconception
Meyer 2003: Isolated CL±P; reference exposure: < 1 drink/week; exposure during first 4 months pregnancy
Romitti 2007: Excluded syndromic and chromosomal anomaly diagnoses; exposure during one month before pregnancy to 3rd month pregnancy
Shaw 1999: Excluded known syndromes; exposure during one month before pregnancy to 3rd month pregnancy
Czeizel 1986, Romitti 1999, Saxen 1974: Isolated CL±P

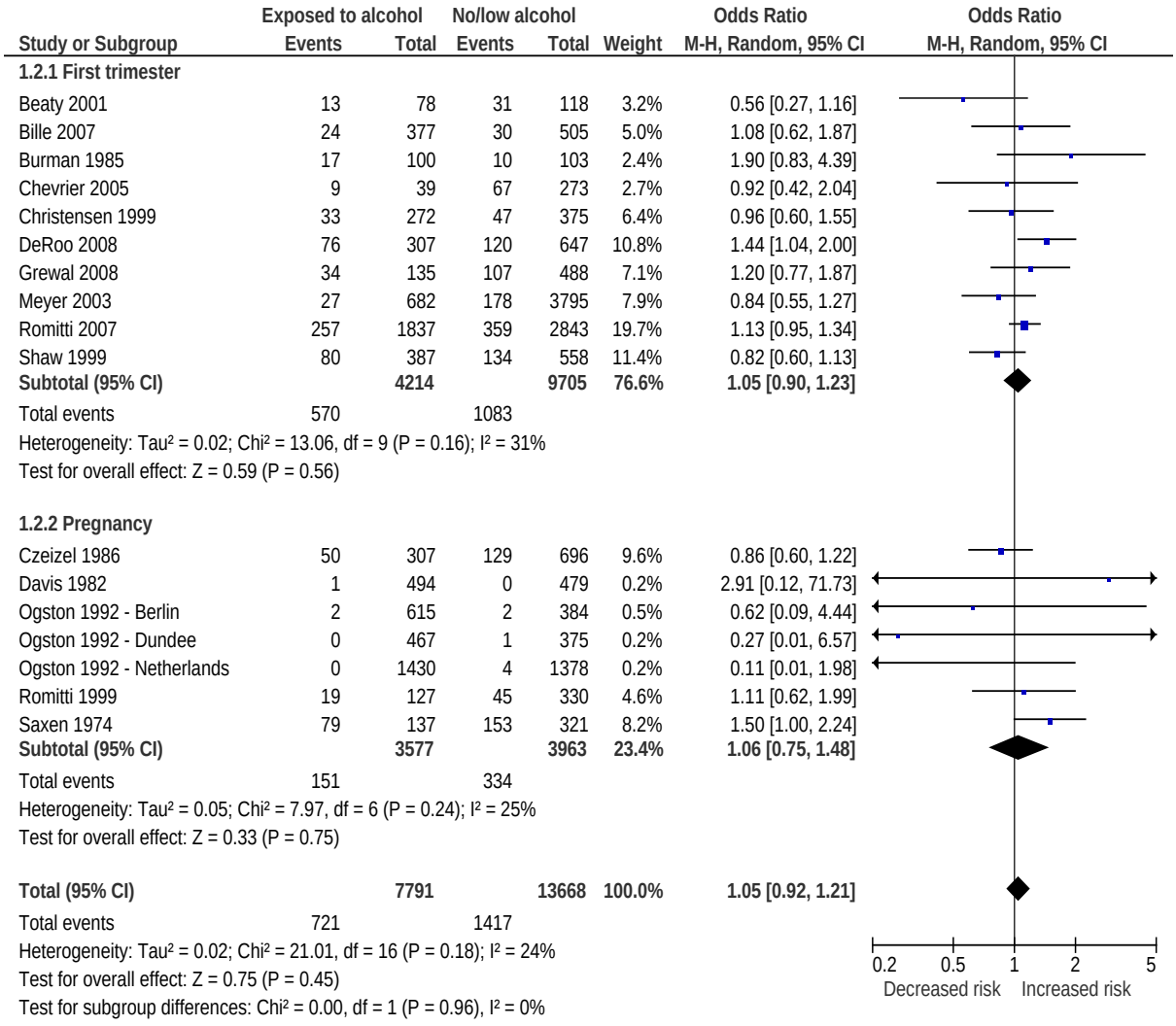

Figure 3. Odds ratios for cleft palate only (CPO) in infants, by maternal consumption of alcohol during pregnancy (any alcohol versus none or low levels of consumption), by period of exposure.

Abbreviations: aOR, adjusted OR; M-H, Mantel-Haenszel
Beaty 2001: Isolated CPO; imputed cell numbers to meet crude OR; aOR 0.53 (0.23, 1.20)
Bille 2007: All CPO; imputed cell numbers to meet aOR 1.10 (0.62, 1.95)
Burman 1985: All CPO
Chevrier 2005: Excluded known syndromes; referent exposure: < 1 drink/week
Christensen 1999: Isolated CPO
DeRoo 2008: All CPO
Grewal 2008: All CPO; referent exposure: no alcohol+no smoking during two months before pregnancy to 2nd month of pregnancy v exposure during 1st month postconception
Meyer 2003: Isolated CPO; referent exposure: < 1 drink/week; exposure during first 4 months pregnancy
Romitti 2007: Excluded syndromic and chromosomal anomaly diagnoses; exposure during one month before pregnancy to 3rd month pregnancy
Shaw 1999: Excluded known syndromes; exposure during one month before pregnancy to 3rd month pregnancy
Czeizel 1986: Isolated CPO
Davis 1982: All CPO
Ogston 1992, Berlin, Dundee, Netherlands: All CPO; alcohol exposure in previous week
Romitti 1999, Saxen 1974: Isolated CPO

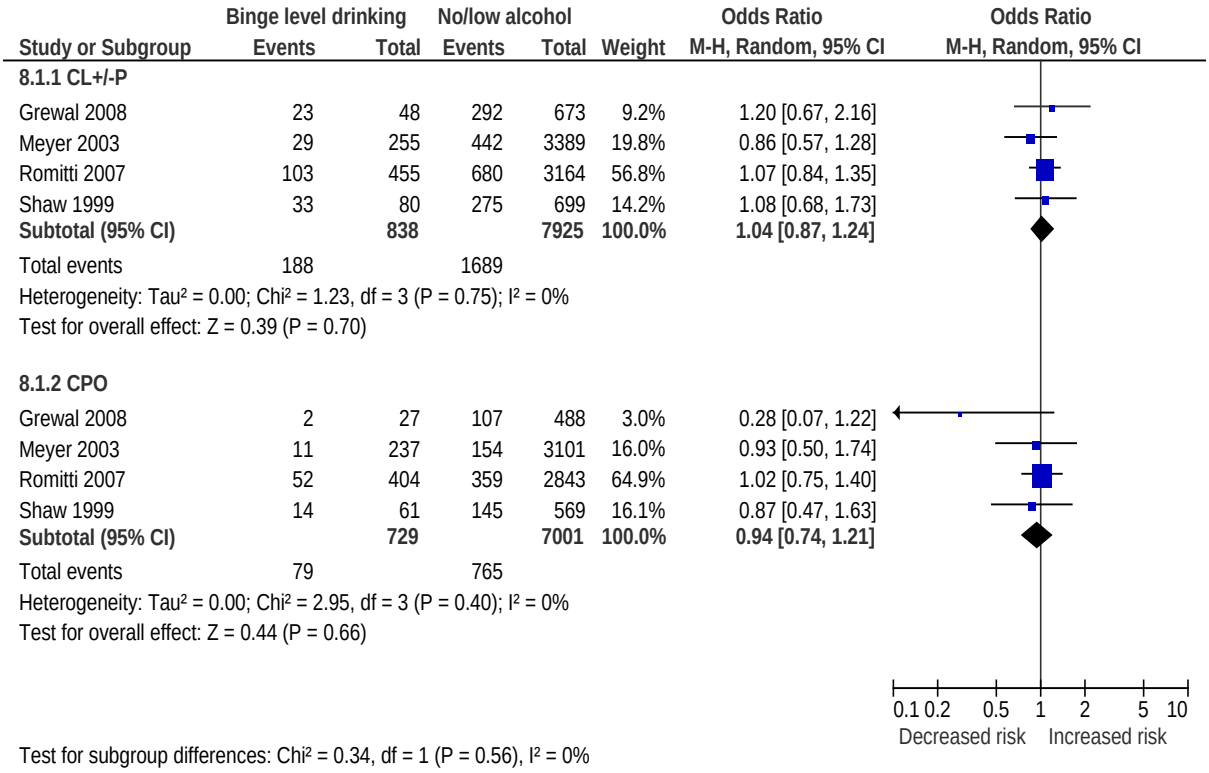

Figure 4. Odds ratios for cleft lip, with or without cleft palate (CL±P) and cleft palate only (CPO) in infants, by maternal consumption of alcohol (binge level drinking versus none or low levels of consumption), during the first trimester of pregnancy, by cleft type.

Abbreviation: M-H, Mantel-Haenszel
Grewal 2008: All clefts; 5+ drinks on any occasion during 1st month postconception v no alcohol+no smoking during two months before pregnancy to 2nd month of pregnancy
Meyer 2003: Isolated clefts; maximum daily consumption of 5+ drinks v <1 drink/week during first 4 months pregnancy
Romitti 2007: Excluded syndromic and chromosomal anomaly diagnoses; 5+ drinks on an occasion, more than once a month v 0 alcohol, during one month before pregnancy to 3rd month pregnancy
Shaw 1999: Excluded known syndromes; 5+ drinks on any occasion v 0 alcohol during one month before pregnancy to 3rd month pregnancy

Supplementary Figure 1. Quality assessment of included case control and cohort studies using the Newcastle-Ottawa Scale.

Case control studies First author year (Reference No.)	Case definition	Representativeness of cases*	Control selection	Control definition	Results reported adjusted for smoking	Results reported adjusted for other factors	Ascertainment exposure	Exposure measurement same both groups	Exposure response rate similar both groups
Beaty 2001[1]	●			●		●		●	
Bille 2007[2]			●	●		●	●	●	●
Burman 1985[3]	●	●	●					●	●
Chevrier 2005[4]	●		●	●		●		●	●
Christensen 1999[5]	●		●	●				●	●
Czeizel 1986[6]	●			●				●	
DeRoo 2008[7]	●		●		●	●		●	●
Grewal 2008[8]		●	●	●				●	●
Kalaskar 2013 [9]				●				●	●
Laumon 1996[10]	●			●				●	
Lebby 2010[11]			●	●				●	
Leite 2009[12]	●			●	●	●		●	
Lorente 2000[13]	●			●	●	●		●	●
Martinez-Frias 2004[14]	●			●				●	
Meyer 2003[15]					●	●		●	
Natsume 2000[16]								●	●
Romitti 1999[17]	●			●				●	●
Romitti 2007[18]	●	●		●	●	●		●	●
Rouget 2005[19]	●		●	●				●	●
Saxen 1974[20,21]	●		●	●				●	●
Shaw 1999[22]	●	●	●	●	●	●		●	●
Spilson 2001[23]			●	●				●	●
Wyszynski 2002[24]			●	●	●	●		●	●

Cohort studies First author year (Reference No.)	Representativeness exposed cohort	Selection non-exposed cohort	Ascertainment exposure	OFC not present at start of study	Results reported adjusted for smoking	Results reported adjusted for other factors	OFC ascertainment assessment	'Length of follow up' appropriate**	Loss to follow up <25%
Baumann 2006[25]	●	●	●	●	●	●			●
Davis 1982[26]	●	●	●	●			●		●
McDonald, 1992[27]	●	●	●		●	●		●	●
Mills 1987[28]	●	●	●	●				●	●
O'Connor 1986[29]			●				●		

Ogston, 1992, Berlin[30]		●	●	●					
Ogston, 1992, Dundee [30]	●	●	●	●					
Ogston, 1992, Netherlands[30]		●	●	●					
Ogston 1992, Vizcaya[30]		●	●	●					
Rosett 1983[31]	●	●	●	●			●		

● indicates study met criterion

* Cases were considered representative if live births, stillbirths and pregnancy losses were included.

** Cohort 'length of follow-up' was considered appropriate if live births, stillbirths and pregnancy losses were all examined for the occurrence of OFCs.

Studies

1 Beaty TH, Wang H, Hetmanski JB, Fan YT, Zeiger JS, Liang KY, et al. A case-control study of nonsyndromic oral clefts in Maryland *Annals of Epidemiology* 2001;11:434-442.

2 Bille C, Olsen J, Vach W, Knudsen VK, Olsen SF, Rasmussen K, et al. Oral clefts and life style factors - a case-cohort study based on prospective Danish data *European Journal of Epidemiology* 2007;22:173-181.

3 Burman NT. A case: control study of oro-facial clefts in Western Australia *Australian Dental Journal* 1985;30:423-429.

4 Chevrier C, Perret C, Bahuau M, Nelva A, Herman C, Francannet C, et al. Interaction between the ADH1C polymorphism and maternal alcohol intake in the risk of nonsyndromic oral clefts: an evaluation of the contribution of child and maternal genotypes *Birth Defects Research* 2005;73:114-122.

5 Christensen K, Olsen J, Norgaard-Pedersen B, Basso O, Stovring H, Milhollin-Johnson L, et al. Oral clefts, transforming growth factor alpha gene variants, and maternal smoking: a population-based case-control study in Denmark, 1991-1994 *American Journal of Epidemiology* 1999;149:248-255.

6 Czeizel A, Nagy E. A recent aetiological study on facial clefting in Hungary *Acta Paediatrica Hungarica* 1986;27:145-166.

7 DeRoo LA, Wilcox AJ, Drevon CA, Lie RT. First-trimester maternal alcohol consumption and the risk of infant oral clefts in Norway: a population-based case-control study *American Journal of Epidemiology* 2008;168:638-646.

8 Grewal J, Carmichael SL, Ma C, Lammer EJ, Shaw GM. Maternal periconceptional smoking and alcohol consumption and risk for select congenital anomalies *Birth Defects Research* 2008;82:519-526.

9 Kalaskar R, Kalaskar A, Naqvi FS, Tawani GS, Walke DR. Prevalence and evaluation of environmental risk factors associated with cleft lip and palate in a central Indian population *Pediatric Dentistry* 2013;35:279-283.

10 Laumon B, Martin JL, Collet P, Bertucat I, Verney MP, Robert E. Exposure to organic solvents during pregnancy and oral clefts: a case-control study. *Reproductive Toxicology* 1996;10:15-19.

11 Lebby KD, Tan F, Brown CP. Maternal factors and disparities associated with oral clefts *Ethnicity & Disease* 2010;20:S1-146-149.

12 Leite ICG, Koifman S. Oral clefts, consanguinity, parental tobacco and alcohol use: a case-control study in Rio de Janeiro, Brazil *Pesquisa Odontologica Brasileira = Brazilian Oral Research* 2009;23:31-37.

13 Lorente C, Cordier S, Goujard J, Ayme S, Bianchi F, Calzolari E, et al. Tobacco and alcohol use during pregnancy and risk of oral clefts. Occupational Exposure and Congenital Malformation Working Group *American Journal of Public Health* 2000;90:415-419.

14 Martinez-Frias ML, Bermejo E, Rodriguez-Pinilla E, Frias JL. Risk for congenital anomalies associated with different sporadic and daily doses of alcohol consumption during pregnancy: a case-control study *Birth Defects Research* 2004;70:194-200.

15 Meyer KA, Werler MM, Hayes C, Mitchell AA. Low maternal alcohol consumption during pregnancy and oral clefts in offspring: the Slone Birth Defects Study *Birth Defects Research* 2003;67:509-514.

16 Natsume N, Kawai T, Ogi N, Yoshida W. Maternal risk factors in cleft lip and palate: case control study *British Journal of Oral & Maxillofacial Surgery* 2000;38:23-25.

17 Romitti PA, Lidral AC, Munger RG, Daack-Hirsch S, Burns TL, Murray JC. Candidate genes for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype-environment interactions from a population-based case-control study of orofacial clefts *Teratology* 1999;59:39-50.

18 Romitti PA, Sun L, Honein MA, Reefhuis J, Correa A, Rasmussen SA. Maternal periconceptional alcohol consumption and risk of orofacial clefts *American Journal of Epidemiology* 2007;166:775-785.

19 Rouget F, Monfort C, Bahuau M, Nelva A, Herman C, Francannet C, et al. Periconceptional folates and the prevention of orofacial clefts: role of dietary intakes in France *Revue d Epidemiologie et de Sante Publique* 2005;53:351-360.
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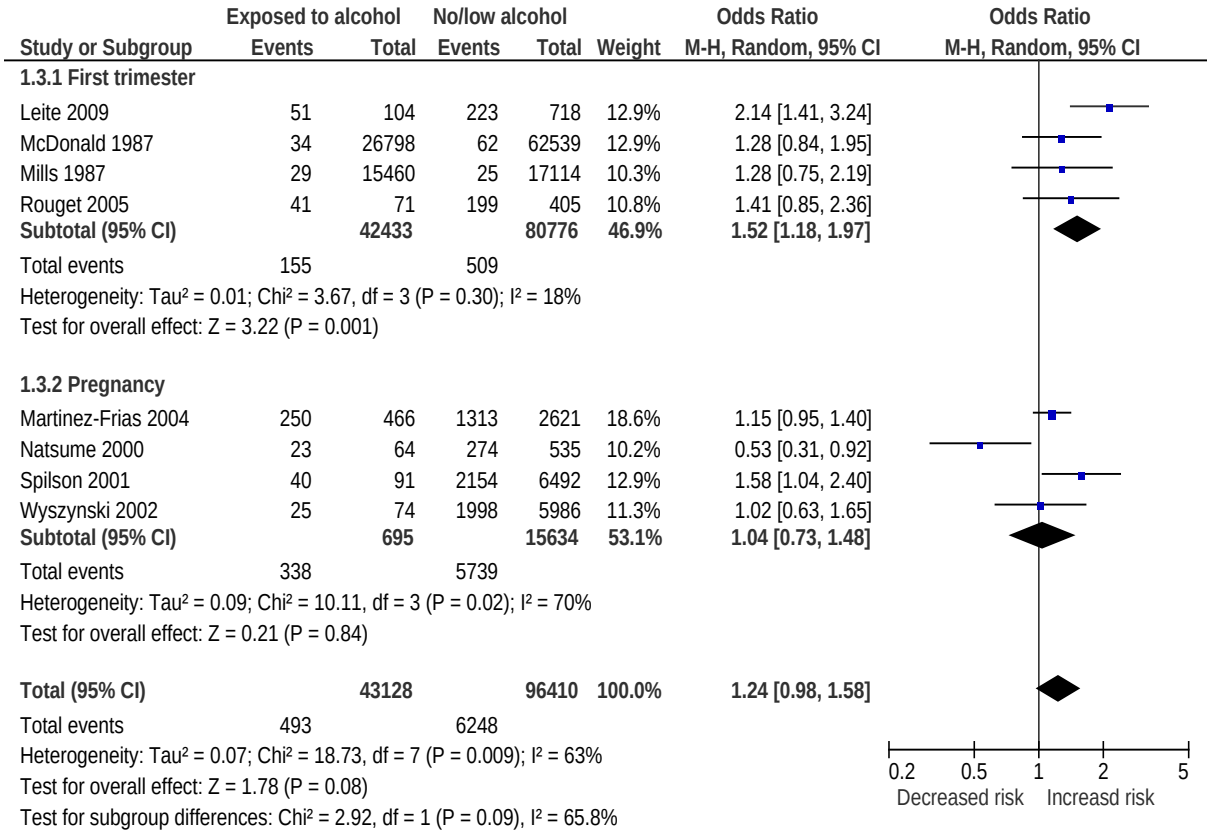
Supplementary Figure 2. Odds ratios for orofacial clefts (OFCs) in infants, by maternal consumption of alcohol during pregnancy (any alcohol versus none or low levels of consumption), by period of exposure.



Abbreviations: aOR, adjusted OR; M-H, Mantel-Haenszel
Leite 2009: Isolated OFCs
McDonald 1987: All OFCs
Mills 1987: All OFCs
Rouget 2005: Excluded chromosomal anomaly & genetic syndrome diagnoses
Martinez-Frias 2004: All OFCs
Natsume 2000: Referent exposure: < 1 unit/week
Spilson 2001: Isolated OFCs
Wyszynski 2002: Isolated OFCs, aOR 0.8 (0.5, 1.4)

Supplementary Table 1. Characteristics of Case Control Studies Reporting Maternal Alcohol Consumption in Pregnancy and Occurrence of Orofacial Clefts

Author, Publication Year (Reference No.)	Description of Cases	Description of Controls	Alcohol Exposure Ascertainment	
			Method	Timing of exposure Ref grp exposure
Beaty 2001[1] 1992-1996 USA (Maryland)	135 Caucasian children with isolated non-syndromic OFCs identified at treatment centres.	152 Caucasian mothers of healthy, 'unaffected' infants from 1 hospital, or a paediatric clinic	Postnatal: interview at 1st treatment visit, then phone interview	T1 Zero
Bille 2007[2] 1996-2002 Denmark	220 children with code for OFC or for reconstructive surgery in National Patient Registry, or maternal report in post-pregnancy interview	880 randomly selected from participants at baseline (first interview).	Prenatal: T2-questionnaire & then phone interview	T1 Zero
Burman 1985[3] 1982-84 Australia (Western Australia)	83 infants registered on the WA Congenital Malformations Register (all pregnancy outcomes)	Midwives notification forms. 176/180 participated	Postnatal: maternal mail questionnaire	T1 Zero
Chevrier 2005[4] 1998-2001 France	263 of 300 children with OFC treated in hospital pediatric department of facial surgery participated	Hospital based: no CAs, no cancer, no genetic disease. Frequency matched on sex, date of birth, ethnicity, region. 261 identified, 236 included	Postnatal: interview in hospital at ~ 5 mths age for CL±P; 8 mths age for CPO; assume soon after birth for controls	T1 < 1 drink / week
Christensen 1999[5] 1991-94 Denmark	Live born infants w OFC identified in hospital, & alive at time planned for interview; no associated major CAs. 302/316 mothers interviewed	Preceding live births with no major CA, alive at time of interview; ± associated minor CAs. 567/604 interviewed	Postnatal: from birth record and interview ~ 2wks after birth (cases), 5 days after birth (controls)	T1 Zero
Czeizel 1986[6] 1970-76 Hungary	1201 individuals with OFCs on Hungarian Congenital Malformations Registry. Excluded: PRS, syndromes, chromosomal anomalies	Hospital based: matched on place and week of birth, sex, pregnancy outcome. 905/1954 responded, 824 evaluated	Postnatal : mail questionnaire (unknown timing after delivery)	Pregnancy Zero
DeRoo 2008[7] 1996-2001 Norway	676 infants born with OFCs and referred to surgical centres. 573 participated	Randomly selected from Medical Birth Registry of Norway. 1022 selected, 763 participated	Postnatal: mail questionnaire after delivery, median 14 wks (cases), 15 wks (controls)	T1 Zero
Grewal 2008[8] 1999-2003 cases 1999-2004 controls	701 infants w OFC identified from live births, stillbirths and elective termination of pregnancy from hospital & medical records. Excluded: chromosomal anomalies; single gene disorders	Hospital based: Random selection of live births, no CAs. 700/907 mothers of control infants interviewed	Postnatal: phone interview, cases-median 10 mths after EDD, controls 8 mths after EDD	First month pregnancy No alcohol and no smoking in B2-P2
Kalaskar 2013[9] 2009-2011 India (Nagpur)	Children with OFCs referred to one hospital 91 infants with OFCs (88 non-syndromic)	Hospital based: 88 infants with no CAs selected from 1000 infants	Postnatal: questionnaire, assume soon after birth	No mothers reported alcohol consumption

Laumon 1996[10] 1985-89 France (Rhône-Alpes)	200 live born infants with OFC (no other major CA) ascertained through outpatient departments. Excluded twins	400 newborns from same hospital, no CA	Postnatal: interview; soon after birth	Timing in pregnancy & exposure in ref grp unknown
Lebby 2010[11] 2005 USA	1654 singleton births with isol, non-syndromic OFC + maternal race noted on US Natality Database	Random sample of 1654 from Natality Database, with no CA	Natality Database - assume alcohol consumption recorded prenatally	Pregnancy Zero
Leite 2009[12] 2005 Brazil (Rio de Janeiro)	274 infants aged 0-24 mths at paediatric referral hospital with OFC (no other CA or syndrome)	Hospital based: 548 patients, no CA. Matched on sex, age ± 2 mths, region of parents' residence	Postnatal: questionnaire (unknown time after delivery)	T1 Zero
Lorente 2000[13] 1989-92 6 Congenital Malformation Registries France; UK, Italy, Netherlands	Any infants or fetus with a major CA diagnosed prenatally and up to 6 days after birth + on the Congenital Anomaly Registers. Excluded: chromosomal anomalies, monogenic syndromes. 63% of cases with CAs participated (161 w OFC)	Infants with no CA at birth, France and Italy – hospital based controls , UK, Netherlands – population based controls. 183 controls matched to OFC cases + 951 controls matched to cases with other CAs, combined 1134	Postnatal: interview ~5-7 days after delivery	T1 < 1 drink/day
Martinez-Frias 2004 [14] 1977-2001 Spain Spanish Collaborative Study of Congenital Malformations	Live born infants with major or minor CAs diagnosed in first 3 days (N=30,836). Excluded infants with known syndromes, chromosomal abnormalities, or exposed prenatally to known teratogens other than alcohol.	Next infant born same hospital, no CA, matched for sex. 'Similar number' of controls to cases selected	Postnatal: interview soon after delivery	Pregnancy Zero
Meyer 2003[15] 1983-98 USA (Boston, Philadelphia, Iowa) & Canada (Toronto) Slone Epidemiology Unit Birth Defects Study	Infants with CAs derived from cranial neural crest, identified from hospital & speciality clinic records. Excluded chromosomal abnormalities, Mendelian disorders, those with additional CAs. 912 with OFC	Mothers of infants with CAs not derived from cranial neural crest cells and not reported to be due to alcohol use, identified from hospital & speciality clinics records. 4272 controls.	Postnatal: interview at home within 6 mths of delivery	First 16 weeks pregnancy < 1 drink
Natsume 2000[16] Unknown period Japan (Nagoya)	306 children born with OFC, treated at oral surgery department.	306 infants without CAs, born in same district and same time period.	Postnatal: interview	Pregnancy < 1 unit/week
Romitti 1999[17] 1987-94 USA (Iowa)	Infants diagnosed with OFC in first year of life (all pregnancy outcomes), 366/556 participated	Pseudo-random selection of live births without CAs, from all Iowa births. Matched by birth timing and sex. 763 identified, 407 consented	Postnatal: phone interview or mailed questionnaire. Interviewed ave 2.5-3 yrs after birth	Pregnancy Zero
Romitti 2007[18] 1997 or 1998-2002 USA	Children with OFC diagnosed up to 1 year of age. Excluded: single gene disorders, chromosomal abnormalities, OFC related to other CAs. 2329	Live born infants without major congenital anomaly with EDD similar to cases randomly selected from hospital delivery logs or birth	Postnatal: phone interview 6 weeks-2 years after birth. Median time between EDD and interview: cases	B1-P3 Zero

National Birth Defects Prevention Study	cases identified, 1749 had full interview	certificate files. 6004 eligible controls	9.3 mths, controls 7.3 mths	
Rouget 2005[19] 1998-99 France	Infants referred in the month after birth, for surgical repair of OFC. 300 children with non-syndromic OFC, 240 participated	Hospital based: matched by sex, ethnicity, residence, age. Excluded if admission for CAs, genetic disorders, cancer. ~10% refusal, 236 included	Postnatal: interview in hospital (after surgery for cases)	T1 Zero
Saxen 1974[20] 1967-71 Finland	599 children w OFC diagnosed within first year life & reported to Finnish Registry of Congenital Malformations	Preceding birth in same maternity welfare district 590/599 participated (98.5%)	Postnatal: interview, soon after birth	Pregnancy Zero
Saxen 1975[21] 1972-73 Continuation of Saxen 1974 study	As above 194 OFCs	As above Unknown how many	As above	
Shaw 1999[22] 1987-89 USA, California Birth Defects Monitoring Program	Infants diagnosed up to 1 year of age, with OFC (all pregnancy outcomes). Excluded bifid uvula, submucous cleft palate, notches of alveolar ridge, vermillion border upper lip, chromosomal anomalies. 972 identified, 891 eligible	Random selection of live born infants from same area and time period, no major CAs. 972 controls	Postnatal: maternal telephone interviews; ~3.5 yrs after delivery	T1 (B1-P3) Zero
Spilson 2001[23] 1996 USA	Infants with isol OFC (no other CAs) + maternal diabetes status noted on US Natality Database. 2207 infants with isol OFC, 2194 with maternal diabetes data	4414 randomly selected from US Natality Database, no CA.	Natality Database - assume alcohol consumption recorded prenatally	Pregnancy Zero
Wyszynski 2002[24] 1997 USA	Infants with isol OFC (no other CAs) + smoking data noted on US Natality Database. 2644 infants with isol OFC, 2029 with smoking data	4050 randomly selected from US Natality Database, no CA + smoking data available, matched on race, sex, county & month of birth	Natality Database - assume alcohol consumption recorded prenatally	Pregnancy Zero

Abbreviations: ~, approximately; B1-P3, 1 month preconception to 3 months pregnancy; B2-P2, two months before conception to 2 months pregnancy; CA, congenital anomaly; CL±P, cleft lip with or without cleft palate; CPO, cleft palate only; EDD, estimated date of delivery; gms, grams; isol, isolated; LB, live born; LMP, last menstrual period; mths, months; mult, multiple; non-isol, non-isolated; OFC, orofacial cleft; P1, first month of pregnancy; ref grp, reference group; T1, first trimester; T2, second trimester; wks, weeks.

Studies

1 Beaty TH, Wang H, Hetmanski JB, Fan YT, Zeiger JS, Liang KY, et al. A case-control study of nonsyndromic oral clefts in Maryland *Annals of Epidemiology* 2001;11:434-442.

2 Bille C, Olsen J, Vach W, Knudsen VK, Olsen SF, Rasmussen K, et al. Oral clefts and life style factors - a case-cohort study based on prospective Danish data *European Journal of Epidemiology* 2007;22:173-181.

3 Burman NT. A case: control study of oro-facial clefts in Western Australia *Australian Dental Journal* 1985;30:423-429.

4 Chevrier C, Perret C, Bahuau M, Nelva A, Herman C, Francannet C, et al. Interaction between the ADH1C polymorphism and maternal alcohol intake in the risk of nonsyndromic oral clefts: an evaluation of the contribution of child and maternal genotypes *Birth Defects Research* 2005;73:114-122.

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8 Grewal J, Carmichael SL, Ma C, Lammer EJ, Shaw GM. Maternal periconceptional smoking and alcohol consumption and risk for select congenital anomalies *Birth Defects Research* 2008;82:519-526.
9 Kalaskar R, Kalaskar A, Naqvi FS, Tawani GS, Walke DR. Prevalence and evaluation of environmental risk factors associated with cleft lip and palate in a central Indian population *Pediatric Dentistry* 2013;35:279-283.
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12 Leite ICG, Koifman S. Oral clefts, consanguinity, parental tobacco and alcohol use: a case-control study in Rio de Janeiro, Brazil *Pesquisa Odontologica Brasileira = Brazilian Oral Research* 2009;23:31-37.
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21 Saxen I. Epidemiology of cleft lip and palate. An attempt to rule out chance correlations *British Journal of Preventive & Social Medicine* 1975;29:103-110.
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Supplementary Table 2. Characteristics of Cohort Studies Reporting Maternal Alcohol Consumption in Pregnancy and Occurrence of Orofacial Clefts

Author Publication Year (Reference No.) Study Years Location	Description of Cohort	Alcohol Exposure Ascertainment		OFC Ascertainment
		Method	Timing of Exposure Ref Grp Exposure	
Baumann 2006[1] 1991-97 Germany (Schleswig-Holstein)	Perinatal database, singleton pregnancies n=170,258	Prenatal: recorded at admission for birth	Pregnancy ≤900 ml beer or 400ml wine/day, no binge drinking	Code on perinatal database 248 infants w OFC
Davis 1982[2] 1980 UK (Warwickshire)	Sequential enrolment of pregnant white women attending booking clinic, 1 hospital. 1120 invited, 973 (86.9%) pregnancies examined	Prenatal: self-administered questionnaire at booking	Assume pregnancy (not stated) Zero	Neonatal examination in hospital 0 CL±P, 1 CPO
McDonald 1992[3] 1982-84 Canada (Montreal)	56,067 pregnant women in 11 maternity units, included current and previous pregnancies. 104,649 pregnancies included.	Postnatal: interview after delivery	T1 Zero	Current pregnancy: reviewed paediatric records. Previous pregnancies: maternal report, then review medical records. 96 w OFC
Mills 1987[4] 1974-77 USA (Kaiser-Permanente facilities)	36,504 pregnant women, 34,660 pregnancies examined. Excluded: children born previously in study, multiple births. 32,870 included	Prenatal: self-administered questionnaire at first visit	T1 Zero	CAs abstracted from hospital records. 54 w OFC
O'Connor 1986[5] Unknown period USA (Los Angeles)	Random selection of women aged 30-41 years who underwent amniocentesis, and later delivered at 1 hospital. 25 women and children participated.	Postnatal: self-report questionnaire (Jessor's AA score) when infants 1 year old	Pregnancy	Paediatric examination at 1 year of age 0 OFC identified
Ogston 1992[6] 1978-79 Netherlands	Pregnant women attending Midwives Clinics. 3447 women included, 3378 live born singletons	Prenatal: interview ~18 weeks gestation.	Alcohol in the 7 days before the interview. Zero	OFCs from hospital birth record 0 CL±P, 4 CPO
Ogston 1992[6] 1988-89 Spain (Vizcaya)	944 pregnant women attending health centres, likely to deliver at reference hospital. 944 interviewed, included 880 live born singletons	Prenatal: interview at ~12-16 weeks gestation.	As above	As above 0 OFC identified
Ogston 1992[6] 1985-1986 Scotland (Dundee)	All primiparous pregnant women in antenatal care Dundee district (n=952). 901 interviewed, 864 live born singletons	Prenatal: interview at first antenatal visit regardless of gestation.	As above	As above 0 CL±P, 1 CPO

Ogston 1992[6] 1987-88 Germany (Berlin)	Women who attended antenatal care and delivered at 1 hospital (n=1071). 1027 women interviewed, included 1002 live born singletons	Prenatal: interview at ~12-16 weeks gestation.	As above	As above 0 CL±P, 4 CPO
Rosett 1983[7] 1977-79 USA (Boston)	Women registering for prenatal care and delivered Feb 1977-Oct 1979 at 1 hospital. 937 women interviewed.	Prenatal: Interview at registration for prenatal care.	Pregnancy Rare (zero, or <1 drink/month, never ≥5 drinks on any occasion)	Paediatrician examination soon after birth 0 OFC identified

Abbreviations: CA, congenital anomaly; CL±P, cleft lip with or without cleft palate ; CPO, cleft palate only; gms, grams; OFC, orofacial cleft; Ref grp, reference group; T1, first trimester; T2, second trimester; T3, third trimester.

Studies

1 Baumann P, Schild C, Hume RF, Sokol RJ. Alcohol abuse-a persistent preventable risk for congenital anomalies *International Journal of Gynaecology & Obstetrics* 2006;95:66-72.
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3 McDonald AD, Armstrong BG, Sloan M. Cigarette, alcohol, and coffee consumption and congenital defects *American Journal of Public Health* 1992;82:91-93.
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Supplementary Table 3. Association between OFC Types and Alcohol Consumption During Pregnancy at Heavy and Moderate Levels

Outcome ***Consumption level*** **First author, year (Reference No.)**	**Alcohol Consumption (grams/week) v Exposure in Reference Group**	**Timing**	**OR**	**95%CI**
CL±P				
Heavy				
Romitti 2007[1]	max ave 90+ v 0	T1 (B1-P3)	1.14	0.78, 1.66
Borderline heavy				
Romitti 2007[1]	max ave 48-90 v 0	T1 (B1-P3)	0.83	0.60, 1.14
Moderate				
Romitti 1999[2] (isol)	3.5-10.5 v 0	P	1.33	0.87, 2.01
Bille 2007[3]	12-24 v 0	T1	1.05 [a]	0.70, 1.59
DeRoo 2008[4]	0.8-5.1 v 0	T1	1.35	1.00, 1.81
Shaw 1999[5] (isol)	< 14 v 0	T1 (B1-P3)	1.1 [a b]	0.61, 2.1
			0.76 [a c]	0.52, 1.1
Romitti 2007[1]	max ave 3-45 v 0	T1 (B1-P3)	1.04	0.90, 1.20
Meyer 2003[6] (isol)	14-41 v < 14	T1 (B1-P4)	1.1 [a]	0.8, 1.4
CPO				
Heavy				
Romitti 2007[1]	max ave 90+ v 0	T1 (B1-P3)	1.1 [a]	0.6, 2.2
Borderline heavy				
Romitti 2007[1]	max ave 48-90 v 0	T1 (B1-P3)	0.97	0.66, 1.44
Moderate				
Romitti 1999[2] (isol)	3.5-10.5 v 0	P	1.04	0.56, 1.93
Ogston 1992 – Berlin[7] [d]	< 60 v 0	P	0.70	0.10, 5.02
Bille 2007[3]	12-24 v 0	T1	1.06 [a]	0.59, 1.92
DeRoo 2008[4]	0.8-5.1 v 0	T1	1.45	1.01, 2.10
Shaw 1999[5] (isol)	< 14 v 0	T1 (B1-P3)	0.87 [a]	0.56, 1.3
Romitti 2007[1]	max ave 3-45 v 0	T1 (B1-P3)	1.15	0.96, 1.39
Meyer 2003[6] (isol)	14-41 v < 14	T1 (B1-P4)	0.8 [a]	0.4, 1.4
OFC				
Heavy				
Martinez-Frias 2004[8]	≥ 112 v 0	P	1.35	1.05, 1.73
McDonald, 1992[9]	≥ 95.2 v 0	T1	1.06 [a]	0.3, 4.2
Mills 1987[10]	ave ≥ 95.2 v 0	T1	0.71	0.10, 5.28
Leite 2009[11] (isol)	> 672 v 0	T1	1.95	1.26, 3.02
Natsume 2000[12]	98.75-118.5 v < 19.75	P	0.64	0.11, 3.83
Borderline heavy				
Mills 1987[10]	ave < 95.2 v 0	T1	1.32	0.77, 2.27
Moderate				
Martinez-Frias 2004[8]	Approx < 90 v 0 (10-	P	0.93	0.68, 1.25

	20 gms sporadically)			
McDonald 1992[9]	13.6-81.6 v 0	T1	1.36	0.89, 2.08
Natsume 2000[12]	19.75-79.0 v < 19.75	P	0.53	0.30, 0.92

Alcohol consumption levels: Heavy = approx. > 2 drinks/day or > 90 gms alcohol/week, with or without binge; Borderline heavy = approx. 90 gms alcohol /week; Moderate = less than approx. 1 drink/day and no more than 2 drinks/occasion ie less than approx. 70-84 gms alcohol/week; no binge

[a] = adjusted odds ratio, reported in study.

[b] = no multivitamin supplements taken

[c] = multivitamins supplements taken

[d] Ogston 1992: alcohol consumption was measured for one week during pregnancy; '0' levels may not indicate abstention throughout pregnancy

Abbreviations: ave, average; isol, isolated; max ave, maximum average; ref, reference group; OR, crude odds ratio; P, pregnancy; T1, first trimester (B1-P3,month before conception up to third month pregnancy; B1-P4, month before conception up to fourth month pregnancy)
All clefts are included (isolated and multiple) unless otherwise noted.

Studies

1 Romitti PA, Sun L, Honein MA, Reefhuis J, Correa A, Rasmussen SA. Maternal periconceptional alcohol consumption and risk of orofacial clefts *American Journal of Epidemiology* 2007;166:775-785.

2 Romitti PA, Lidral AC, Munger RG, Daack-Hirsch S, Burns TL, Murray JC. Candidate genes for nonsyndromic cleft lip and palate and maternal cigarette smoking and alcohol consumption: evaluation of genotype-environment interactions from a population-based case-control study of orofacial clefts *Teratology* 1999;59:39-50.

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6 Meyer KA, Werler MM, Hayes C, Mitchell AA. Low maternal alcohol consumption during pregnancy and oral clefts in offspring: the Slone Birth Defects Study *Birth Defects Research* 2003;67:509-514.

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Supplementary Table 4: Dose Response Relationship Between Maternal Alcohol Consumption in First Trimester and Infants With CL±P and CPO, Within Studies

Author Year	Exposure (grams/week) v Exposure in Referent Group	CL±P OR	CL±P 95% CI	CPO OR	CPO 95% CI	Covariates adjusted for
Bille 2007[1]	12-24 v 0	1.05 [a]	0.70, 1.59	1.06 [a]	0.59, 1.92	Parental age, social class
	≥36 v 0	1.48 [a]	0.68, 3.19	1.36 [a]	0.45, 4.15	
DeRoo 2008[2]	0.8-2.5 v 0	1.2 [a]	0.9, 1.8	1.4 [a]	0.9, 2.2	Child's year of birth, maternal age group, prenatal
	3.4-5.1 v 0	1.4 [a]	0.8, 2.4	2.0 [a]	1.1, 3.7	smoking, education, household income, family
	≥5.9 v 0	1.2 [a]	0.8, 1.9	1.5 [a]	0.9, 2.7	history of OFC
Romitti 2007[3]	max ave 3-12 v 0	1.11	0.94, 1.32	1.3 [a]	1.0, 1.9	Family history, maternal race/ethnicity, pre-
	max ave 15-45 v 0	0.93	0.75, 1.15	1.1 [a]	0.8, 1.7	pregnancy BMI, smoking, centre, duration alcohol
	max ave 48-90 v 0	0.83	0.60, 1.17	1.1 [a]	0.6, 1.8	exposure
	max ave ≥90 v 0	1.14	0.78, 1.66	1.1 [a]	0.6, 2.2	
Shaw 1999[4] (isolated clefts)	<14 v 0	0.76 [a b]	0.52, 1.1	0.87 [a]	0.56, 1.3	Maternal race and ethnicity, maternal education,
		1.1 [a c]	0.61, 2.1			smoking (and for CPO -use of multivitamin
	≥14 v 0	0.56 [a b]	0.27, 1.2	0.63 [a]	0.28, 1.4	supplements)
		2.4 [a c]	0.86, 6.4			
Meyer 2003[5] (isolated clefts)	14-41 v < 14	1.1 [a]	0.8, 1.4	0.8 [a]	0.4, 1.4	Geographic centre, interview year, maternal age
	42+ v < 14	0.9 [a]	0.7, 1.4	1.0 [a]	0.6, 1.9	group, race, education, smoking during pregnancy

[a] adjusted
[b] with multivitamin supplements
[c] no multivitamin supplements

Abbreviations: CL±P, cleft lip with or without cleft palate; CPO, cleft palate only; max ave, maximum average; OFC, orofacial cleft

Studies

1 Bille C, Olsen J, Vach W, Knudsen VK, Olsen SF, Rasmussen K, et al. Oral clefts and life style factors - a case-cohort study based on prospective Danish data *European Journal of Epidemiology* 2007;22:173-181

2 DeRoo LA, Wilcox AJ, Drevon CA, Lie RT. First-trimester maternal alcohol consumption and the risk of infant oral clefts in Norway: a population-based case-control study *American Journal of Epidemiology* 2008;168:638-646.

3 Romitti PA, Sun L, Honein MA, Reefhuis J, Correa A, Rasmussen SA. Maternal periconceptional alcohol consumption and risk of orofacial clefts *American Journal of Epidemiology* 2007;166:775-785.

4 Shaw GM, Lammer EJ. Maternal periconceptional alcohol consumption and risk for orofacial clefts *Journal of Pediatrics* 1999;134:298-303.

5 Meyer KA, Werler MM, Hayes C, Mitchell AA. Low maternal alcohol consumption during pregnancy and oral clefts in offspring: the Slone Birth Defects Study *Birth Defects Research* 2003;67:509-514.

Supplementary Information 1. Sensitivity Analyses

We conducted sensitivity analyses to consider the effects of study quality by restricting the analyses to studies with higher quality (NOS ≥5 and ≥6); to studies where alcohol exposure was assessed before delivery; and studies where OFCs could be identified in all pregnancies (live births, stillbirths and terminations of pregnancy or miscarriage). We also compared our results to an analysis including only studies with zero alcohol intake as the reference group, and to studies whose main aim was to assess the relationship between alcohol during pregnancy or risk factors, and OFCs. To consider whether the constant continuity correction produced a biased result, we re-conducted analyses requiring continuity corrections, adding 0.5 to the reciprocal of the opposite exposure group to account for uneven group sizes.[1]

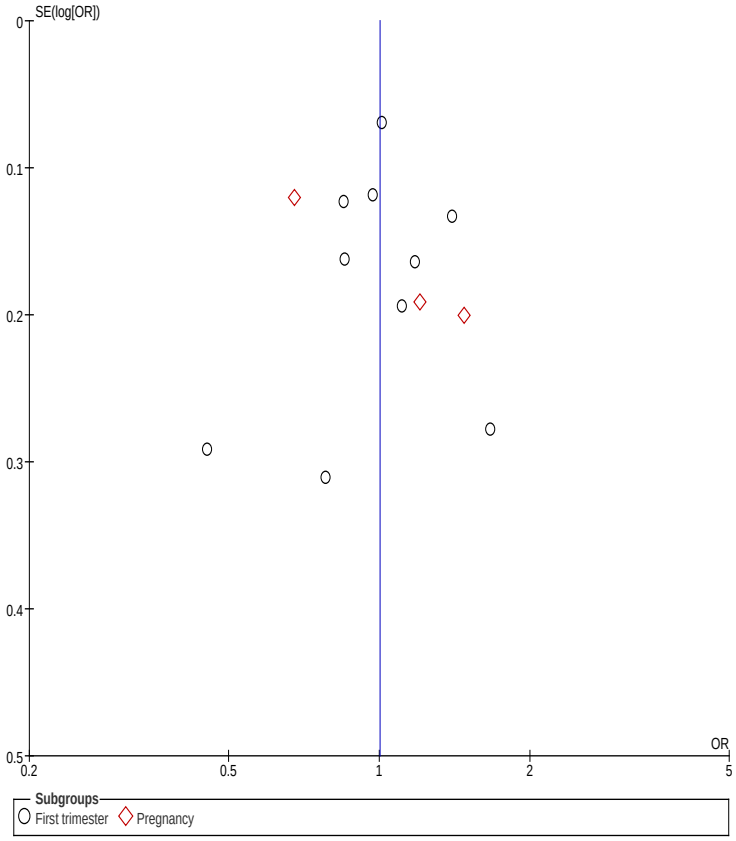
1 Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Statistics in Medicine* 2004;23:1351-1375.

Results of Sensitivity Analyses: Pooled Odds Ratios by Study Characteristics, Quality Measures and Analytical Methods

	CL±P				CPO				OFC			
Consumption Level Study Characteristics	No. Studies	I^2 %	Pooled OR	95% CI	No. Studies	I^2 %	Pooled OR	95% CI	No. Studies	I^2 %	Pooled OR	95% CI
Any alcohol v none												
All studies	13	68	1.00	0.86, 1.16	17	24	1.05	0.92, 1.21	8	63	1.24	0.98, 1.58
NOS ≥5	9	44	1.07	0.93, 1.22	10	14	1.15	1.00, 1.31	4	0	1.24	0.97, 1.57
NOS ≥6	5 (T1)	63	1.11	0.91, 1.35	6	24	1.10	0.92, 1.31	3	0	1.19	0.91, 1.57
Alcohol intake during pregnancy assessed before delivery	1 (T1)		1.11	0.76, 1.62	5	0	0.96	0.57, 1.60	3	0	1.30	0.99, 1.71
OFCs in all pregnancy outcomes included	5	44	1.03	0.87, 1.22	5	21	1.08	0.90, 1.29	0			
Study aim: association between prenatal alcohol intake or risk factors and OFCs	11	69	0.99	0.84, 1.16	11	41	1.07	0.92, 1.25	3	88	1.07	0.48, 2.36
Comparison group: zero alcohol only	11	70	0.98	0.83, 1.15	12	31	1.09	0.94, 1.26	7	32	1.35	1.12, 1.62
Continuity correction (0.5 to reciprocal of opposite exposure group)	n				17	10	1.07	0.95, 1.20	n			
Binge drinking v no alcohol												
All	4 (T1)	0	1.04	0.87, 1.24	4 (T1)	0	0.94	0.74, 1.21				
NOS ≥5	3 (T1)	0	1.09	0.89, 1.32	3 (T1)	32	0.88	0.58, 1.35				
NOS ≥6	2 (T1)	0	1.07	0.87, 1.32	2 (T1)	0	0.99	0.75, 1.31				
Alcohol intake during pregnancy assessed before delivery	0				0							
OFCs in all pregnancy outcomes included	3 (T1)	0	1.09	0.89, 1.32	3 (T1)	32	0.88	0.58, 1.35				

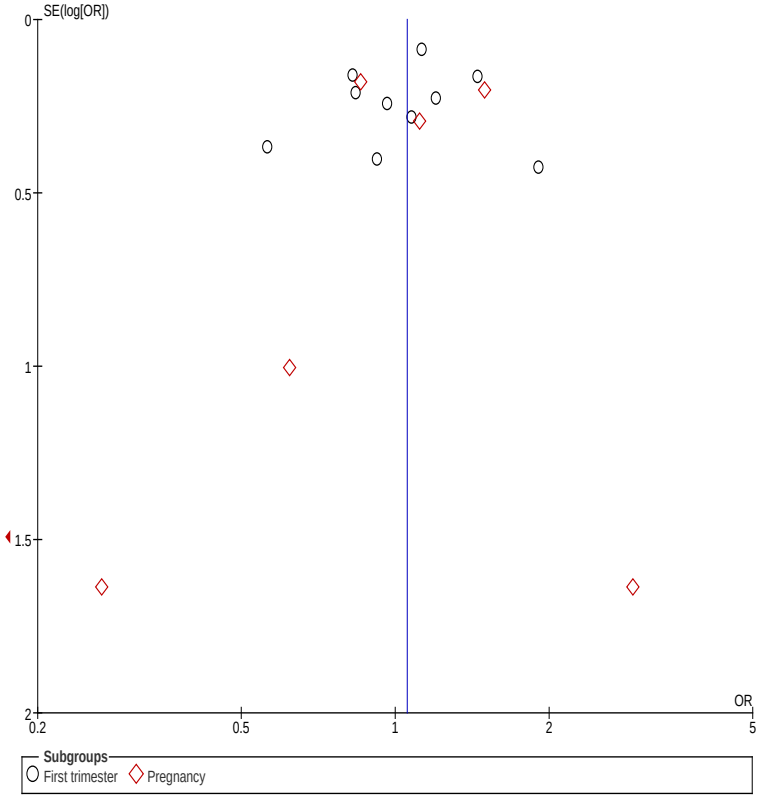
Abbreviations: CL±P, cleft lip with or without cleft palate; CPO, cleft palate only; n, not needed; NOS, Newcastle-Ottawa Scale score; OFC, orofacial cleft; T1, first trimester

Supplementary Information 2. Funnel Plots and Tests For Funnel Plot Asymmetry



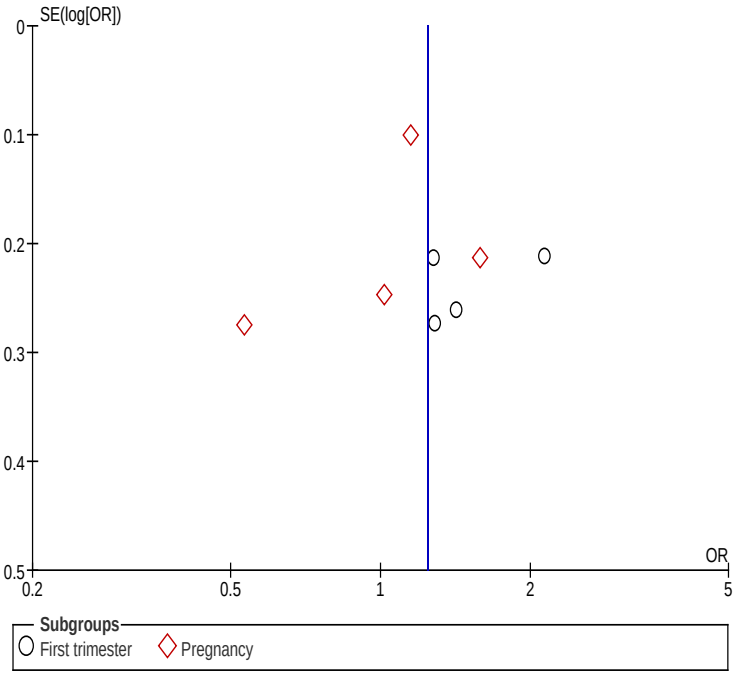
Any alcohol v no or low alcohol consumption, CL±P

modified Egger's test[1] for funnel plot asymmetry: P = 0.81



Any alcohol v no or low alcohol consumption, CPO

modified Egger's test[1] for funnel plot asymmetry: P = 0.32



Any alcohol v no or low alcohol consumption, OFC

No test for funnel plot asymmetry as too few studies included.

Binge level drinking – Assessment of publication bias

There are too few included studies in the analysis of the effects of binge drinking (4 studies each for CL±P and CPO) to assess whether publication bias is an important factor (using funnel plots or statistical tests.

Reference:

1 Harbord RM, Egger M, Sterne JAC. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints *Statistics in Medicine* 2006;25:3443-3457.