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Maternal cigarette smoking and cleft lip and palate: A systematic review and meta-analysis

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Abbreviations:

- CI – Confidence Interval
- CL±P – Cleft Lip ± Palate
- CP – Cleft Palate Only
- NOS – Newcastle Ottawa Scale
- CL/P – Cleft lip and/or cleft palate
- OR – Odds Ratio
- PAF – Proportional Attributable Fraction

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ABSTRACT

Objectives: A systematic review and meta-analysis to determine the association between active maternal smoking and cleft lip and palate etiology.

Data Sources: Medline, Embase, Web of Science and the Cochrane database from inception to November 2020.

Study selection: Observational studies of cigarette smoking habits in pregnant women. Outcomes included cleft lip and/or palate, cleft lip ± palate and cleft palate only.

Data analysis: Publication bias analyses were performed and the Newcastle Ottawa scales were used to assess study quality. Fixed or random effect models were used in the meta-analysis, dependent on risk of statistical heterogeneity.

Results: Forty-five studies were eligible for inclusion of which 11 were cohort and 34 were case-control studies. Sixteen studies were of sufficient standard for inclusion in the meta-analysis. The summary odds ratio for the association between smoking and cleft lip and/or palate was 1.42 (95%CI 1.27 to 1.59) with a population attributable fraction of 4% (95%CI 3% - 5%). There was limited evidence to show a dose-response effect of smoking.

Conclusions:

This review reports a moderate association between maternal smoking and orofacial cleft but the overall quality of the conventional observational studies included was poor. There is a need for high quality and novel research strategies to further define the role of smoking in the etiology of cleft lip and palate.

Keywords:

Cleft lip and palate, cleft palate, orofacial cleft, pregnancy, smoking

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INTRODUCTION

Cleft lip and/or palate (CL/P) is one of the most common craniofacial birth defects, occurring in approximately 1/700 births (Mossey et al., 2009). It affects children and their families because of appearance and functional difficulties with speech, eating, social interaction and child development. Seventy percent of children born with CL/P do not have an associated syndrome and the anomaly is believed to be caused by a complex pattern of inheritance with both genetic and environmental influences (Lebby et al., 2010). Defining the role of potentially modifiable environmental factors could reduce the incidence of this congenital abnormality (Raut et al., 2019). Maternal smoking is a modifiable environmental factor, which is considered a causal factor for CL/P in the 2014 US Surgeon General's Report (United States Department of Health and Human Services 2014).

Cigarette smoke is a complex aerosol comprising more than 4,000 different compounds that can cause harm (Martelli et al., 2015). Maternal smoking has attracted research interest because it is a common exposure and has been established as a risk factor for a spectrum of adverse offspring outcomes including preterm birth, low birth weight and birth anomalies (Krueger and Rohrich 2001; Hackshaw et al., 2011). It is biologically plausible that maternal smoking could cause CL/P, although the exact mechanism is unknown (Leite et al., 2002; Krapels et al., 2008). There may be a direct interaction of the smoking products with neonatal tissue, leading to induced hypoxia because of impaired angiogenesis and nicotine-mediated vasoconstriction, which has been shown to disrupt palatal fusion in animal models (Vieira and Dattilo, 2018). An alternative

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theory is that smoking affects DNA methylation in the fetus, which could impact upon gene expression responsible for lip and palate formation (Lebby et al., 2010).

Three previous meta-analyses have demonstrated weak to moderate links between maternal smoking and CL/P (Wyszynski et al., 1997; Julian Little et al., 2004; Xuan et al., 2016;). Whilst previous systematic reviews have been comprehensive, the included studies were not assessed for their quality and this might have compromised the validity of the findings (Crossan and Duane, 2018). Potential sources of bias in the primary studies include no adjustment for confounders, inappropriate control groups and recall bias. There is a need for an updated systematic review with rigorous methodology in this field. We conducted a systematic review and meta-analysis in order to determine the role of active maternal cigarette smoking in the etiology of CL/P.

METHODS

Identification of studies

A full protocol of this systematic review, carried out following PRISMA guidance(Moher et al., 2009), was adhered to (see supplementary Table 1) and is available from the PROSPERO systematic review register (registration number CRD42020222837; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020222837).

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Eligible studies were defined as full-text primary-data publications reporting on pregnant women from the general population who were assessed for pre-natal active cigarette smoking. Studies were required to document maternal smoking (either in the peri-conception period or any of the three trimesters) but the assessment of smoking status could have been performed prospectively or retrospectively. Studies of passive (or environmental) maternal smoking or paternal smoking were not included. The protocol included all epidemiological studies using an analytical design whereby an exposed group was compared to an unexposed group. Cohort, case-control, quasi-experimental, natural experiment, family based negative control and Mendelian Randomization study designs were eligible.

The outcome of interest was a live born child with CL/P or subtypes such as cleft lip only, cleft lip ± palate (CL±P), cleft palate only (CP) or submucous cleft. Where studies made a distinction between children born with an isolated cleft or a cleft co-occurring with other anomalies, or where results were provided for those with non-syndromic and syndromic orofacial clefts separately, effect estimates for isolated and non-syndromic clefts were extracted preferentially.

Studies were excluded if: full text was unavailable; they were conference proceedings only; they were descriptive studies such as case studies, case series, cross-sectional studies, expert opinion, letter, editorials or studies using secondary data such as reviews; they were animal studies; or there was insufficient data to estimate the effect size of the association between maternal

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smoking and CL/P (see Supplementary Table 2 for exclusion and exclusion criteria).

The databases searched included Medline, Embase, the Web of Science and the Cochrane Library from inception to 9th November 2020. The search was tailored individually to each database with input from a University Librarian (see Supplementary Figures 1-4 for search strategies) and there was no language restriction. The search focused on published literature and did not include grey literature. In addition, manual searches of reference lists of recent relevant systematic reviews and all studies included in the systematic review were performed.

Titles and abstracts were reviewed independently by two reviewers (MF/KD) according to the specified inclusion/exclusion criteria and differences resolved through discussion to reach a consensus. Where an abstract was not available or where a decision on inclusion/exclusion could not be reached by reviewing the abstract alone, full text screening was similarly performed independently by two reviewers for inclusion and any disagreements resolved through discussion. When multiple reports of a study were identified, the study with the greatest number of patients was selected. The Rayyan web application was used to facilitate the screening process (Ouzzani et al., 2016).

Data extraction

Data was extracted via Microsoft Forms into an excel spreadsheet. Data extracted included: title, authors, publication year, country of study population, study

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design, sample description, sample size, outcomes recorded, confounding factors measured and study outcomes including dose-response data. Adjusted measures of effect were extracted preferentially to reduce the impact of confounding factors. Data from each study was extracted by one reviewer (MF) and checked for accuracy by a second reviewer (KD)(Centre for Reviews and Dissemination, 2009).

Assessment of study quality

The Newcastle-Ottawa Scale (NOS)(Wells et al., 2000) was used to assess the quality of cohort and case-control studies included in this systematic review. The NOS for cohort studies consists of eight questions amongst three domains (selection, comparability and outcome). Similarly, the NOS for case-control studies consists of eight questions amongst three domains (selection, comparability and exposure). Stars are awarded for adequate methodology and were used to allocate a score of good, fair or poor to each study with pre-defined criteria (see Supplementary Table 3). Good and fair studies were deemed appropriate for meta-analysis, whereas studies categorized as poor were deemed to be of too low quality for inclusion. Maternal age and maternal alcohol consumption were identified as the most important confounding factors, followed by folic acid supplementation and obesity, based on previous findings (Bille et al., 2005; Badovinac et al., 2007; Molina-Solana et al., 2013; Izedonmwen et al., 2015). Studies were required to adjust for maternal age and alcohol consumption in order to achieve at least a 'fair' rating and be included in the meta-analysis.

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Funnel plots were used to visually assess the likelihood of small study publication bias if more than 10 studies were included and Egger's test was calculated to quantify funnel plot asymmetry (Sterne et al., 2011).

Data Synthesis

A descriptive summary and narrative analysis of the included studies was performed, alongside an indication of study quality, in accordance with published guidance (Popay et al., 2006). Heterogeneity of the included studies was analyzed by exploring the study characteristics and using the I^2 statistic where sufficiently similar studies were meta-analyzed.

The quantitative impact of maternal smoking as a cause of orofacial clefting was investigated using meta-analysis techniques where studies met the quality criteria for inclusion and shared sufficient methodological homogeneity. The minimum number of studies to conduct a meta-analysis was two. Pooled estimates for binary outcomes were calculated using the inverse variance method. The odds ration (OR) was the principle summary measure extracted from the primary studies and meta-analyzed. The fixed effects model was used where levels of statistical heterogeneity were low (I^2 <50%); otherwise the random effects model was used. The population attributable fraction (PAF) was calculated to assess the public health impact (Mansournia and Altman, 2018) using the pooled odds ratio and the prevalence of exposure among cases (Miettinen, 1974). The dose-response impact of maternal smoking was analyzed for studies in which the smoking dose categories used by the included studies were analogous. Subgroup meta-analysis of the smoking dose categories was

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performed using the random effects model. Meta-analysis was performed using the "meta" package (Harrer et al., 2021) via the R Project for Statistical Computing (http://www.R-project.org/).

RESULTS

Study Selection and Study Characteristics

A flowchart for the article review process is shown in Figure 1. A total of 1334 citation records were identified from searching the four databases. A manual search of relevant systematic reviews and included studies identified 15 additional studies. After exclusions (see Supplementary Table 4), 45 studies from 44 publications were included in the systematic review (one publication reported two case-control studies from distinctly separate populations (Shi et al., 2007); 11 cohort studies and 34 case control studies (see Table 1). In total, 28,405 mothers giving birth to a live born child with CL/P have had their smoking status during pregnancy analyzed amongst the 45 studies.

Reported outcomes

Twenty-two studies reported on CL/P outcome, with the funnel plot not indicating publication bias (see Supplementary Figure 5) and an Egger's test of 0.77 (95% Confidence Interval (CI): 0.32, 1.85, *P*=0.18). Nineteen studies

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reported on CL±P outcome with the funnel plot not indicating publication bias and an Egger's test of 0.09 (95% CI: -0.1, 1.17, *P*=0.88). Nineteen studies reported on CP outcome with the funnel plot not indicating publication bias and an Egger's test of -0.28 (95% CI: -1.77, 1.2, *P*=0.71). As only two studies reported with cleft lip alone as the outcome, a funnel plot was not performed for these. Nine studies reported smoking dose-response effects for CL/P outcome, a further 14 studies gave results by smoking dose for CL±P as the outcome and 13 studies for CP as the outcome.

Table 2 shows the study quality assessment for cohort and case-control studies based on the NOS. Only one study(Raut et al., 2019) of the 45 included studies had low scores in all eight NOS questions. Three studies were deemed to be good quality, 13 studies were deemed fair quality, and 29 deemed poor quality and the latter were excluded from the meta-analysis. A greater proportion of cohort studies (5/11) met the quality threshold for meta-analysis inclusion than case-control studies (11/34). The most common area lacking was the failure to adjust for confounding factors. The potential for exposure recall bias was present in all 34 of the case-control studies as by definition, information on exposure was collected retrospectively. Only four out of 11 cohort studies collected maternal smoking exposure data prospectively.

All of the 11 cohort studies were truly or somewhat representative of the general population and were able to demonstrate the outcome of interest was not present at the start of the study. Of the case control studies, 7 out of 34 did not meet the participant selection domain criteria due to failing to demonstrate

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independent validation of case definition (11 of 34), the potential for selection bias of cases (23 of 34) and/or selected controls from hospitalized populations (21/34).

Comparability criteria was not met in 6 out of 11 cohort studies and 20 out of 34 case-control studies due to not adjusting for at least maternal age and maternal alcohol consumption as confounders in the analysis. Folic acid supplementation and obesity were adjusted for in less than half of included studies (see Supplementary Table 5).

All of the 11 cohort studies used record linkage to verify OFC outcome. Exposure criteria was not met by 18 out of 34 case-control studies because of relying on self-assessment (8 of 34), using an interviewer who was not blinded to case/control status (23 of 34) and/or the non-response rate of cases/controls was not described (20 of 34).

Meta-analysis

Five studies reporting effect estimates for smoking and CL/P were included in the meta-analysis (see Figure 2). There was no strong evidence of between study heterogeneity (I^2=27%, P=0.24). The pooled OR using the fixed effects model was 1.42 (95% CI: 1.27, 1.59). Based on the proportion of maternal smoking amongst case mothers of 14% in these five studies, the PAF was 4% (95% CI: 3%, 5%).

Six studies reporting the effect for smoking and CL±P were included in the meta-analysis (see Figure 3). There was no evidence for statistical heterogeneity

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between the studies (I^2 = 0%, *P*=0.67). The pooled OR using the fixed effects model was 1.31 (95% CI: 1.19, 1.45). Five studies reporting measures of effect for smoking and CP were included in the meta-analysis (see Figure 4). The statistical heterogeneity between the studies was high (I^2 = 81%, *P*<0.01) due to an outlying case-control study performed in Hungary (Ács et al., 2020), reporting a stronger positive effect of smoking on CP than the other included studies. The pooled OR using the random effects model was 1.49 (95% CI: 1.01, 12.19). The exclusion of the outlying study in the CP meta-analysis resulted in no evidence for statistical heterogeneity (I^2 = 0%, *P*=0.49) and a fixed effect pooled OR of 1.25 (95% CI: 1.09, 1.44). It was not possible to calculate the PAF for maternal smoking and CL±P or CP due to missing data in included studies, precluding calculation of prevalence of exposure.

Individual study effect estimates and pooled analysis for all studies included in this systematic review reporting outcomes for CL/P, CL±P and CP can be found in Supplementary Figures 6-8.

Subgroup analysis

Five studies reporting measures of effect for the dose of smoking and CL/P were included in the subgroup meta-analysis (see Figure 5). All five studies measured three doses of smoking (low, medium and high) with comparable numbers of cigarettes smoked per day at each dose (1-10, 11-20 and >20 cigarettes per day). The pooled OR for the lowest dose of smoking was 1.20 (95% CI: 1.06, 1.36), for intermediate dose was 1.15 (95% CI: 0.97, 1.37) and highest dose was 1.45 (95% CI: 1.05, 2.00).

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Four studies were eligible for inclusion into the meta-analysis of the effect of smoking dose for both CL±P and CP respectively, but it was not possible to perform a meta-analysis because the reported smoking dose levels were not comparable.

DISCUSSION

Summary of evidence

There has been a large body of work to investigate the role of active maternal smoking in CL/P etiology, as shown by the 45 studies that met our inclusion criteria. This high volume of research should have provided a clear indication of the association between maternal smoking and CL/P, but the poor quality of studies overall has compromised the reliability of the reported findings. Only three studies out of the 45 included in this review were judged to be of good quality (Grewal et al., 2008; Raut et al., 2019; Sato et al., 2020;). The most common reason for poor quality within the studies was a failure to adjust for recognized confounding factors, placing the analyses at high risk of bias. Mother's age, alcohol intake and obesity are all strongly associated with smoking behavior and all have been hypothesized to be risk factors for orofacial clefts. Furthermore, alcohol intake during pregnancy is a known teratogen, making the adjustment of these confounding risk factors even more critical (Carreras-Torres et al., 2018; Taylor et al., 2018; Taylor et al., 2019).

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Our meta-analysis suggests that maternal smoking may have a moderate role in CL/P etiology with pooled OR of 1.42 (95% CI: 1.27, 1.59). The PAF estimates the proportion of the disease that would be reduced by eliminating exposure to a given risk factor, assuming the risk factor is causal. Smoking has previously been found to account for the largest risk when PAFs are calculated for a number of modifiable risk factors for CL/P (Raut et al., 2019). The pooled PAF of 4% (95% CI: 3%, 5%) in this review is similar to the previously reported range of 4-6% from three individual studies (Honein et al., 2007; Honein et al., 2014; Raut et al., 2019;). The indication here is that should maternal smoking be eliminated, 4% of CL/P would not occur. Evidence of a dose-response relationship can add support to a causal relationship. The analysis of dose effect in CL/P demonstrated the highest dose of smoking (>20 cigarettes per day) to have the strongest positive effect on risk of cleft, but the intermediate smoking dose (11-20 cigarettes per day) had a similar effect to the lowest dose (1-10 cigarettes per day). This may represent a threshold effect of more than 20 cigarettes needing to be smoked a day before a difference is noted in CL/P etiology. Alternatively, the greater effect in the highest smoking dose may reflect the propensity for risk taking behaviors associated with additional confounding by substance abuse (such as alcohol), which may not have been adequately adjusted for. The effect of the highest smoking dose on CL/P etiology should be interpreted with caution as the number of cases within the individual studies were less than for low and medium smoking doses, therefore the effect estimates were less precise.

Historically, CL/P has been subdivided in to CL±P and CP, reflecting different embryological origins from the primary palate and secondary palate respectively

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(Dixon et al., 2011). Studies included in this review reported individual outcomes for CL±P and CP and the respective pooled ORs demonstrated a moderately positive association with maternal smoking, similar to that of OFC. The pooled OR for CP (OR = 1.49) was greater than for CL±P (OR = 1.31) and this is an inverse of the relationship reported in two previous meta-analyses (Little et al., 2004; Xuan et al., 2016). The pooled OR for CP reported in this review should be interpreted with caution as it was influenced by the outlying result of a single study (Ács et al., 2020), with a heterogeneity between studies present. The only study with a good quality rating included in the CP meta-analysis (Raut et al., 2019), reported a more modest measure of effect, therefore the pooled OR following exclusion of the outlying study (OR = 1.25) may be a more accurate representation of the effect of smoking on CP etiology.

Strengths and Limitations

Strengths of this review include a comprehensive search strategy with concerted efforts made to include all languages and a wide variety of study designs. Thorough assessment of study quality facilitated the inclusion of studies into the meta-analysis only if they met pre-defined threshold criteria.

The main limitation of interpreting the results from the meta-analysis relate to the inherent flaws of the standard analytical cohort and case-control approaches and their associated potential for bias. Studies were included in the meta-analysis if they had adjusted for a minimum set of confounders (maternal age and maternal alcohol consumption), which means that there was scope for

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additional important confounding factors to be unaccounted for. Even when adjustment for all relevant confounding factors is performed, bias may be present due to inaccurate measurement of confounding factors, misclassifications of exposure and differential missing data (Lawlor et al., 2016). The small sample sizes of some studies included in the meta-analysis meant their effect estimates were imprecise. A dose-response relationship could not be tested in CL±P and CP outcomes due to differences in smoking dose categorization reported in the included studies. Restriction of the search to published studies could have introduced publication bias, despite the evidence for publication bias being weak. This review focused upon active cigarette smoking in females and whilst the association of both passive and paternal smoking on CL/P has been reported, there has been less scientific focus in these areas when compared to active maternal smoking (Savitz et al., 1991; Krapels et al. 2008; Figueiredo et al. 2015; Hao et al. 2015; Sabbagh et al. 2015).

Interpretation

Our understanding of the causal role of maternal smoking in CL/P is limited because of biases affecting traditional observational methods and the impracticalities of performing randomized controlled trials in this setting. If our reported moderate association is an accurate reflection of the role that maternal smoking plays then we would predict that the elimination of this risk factor would result in the reduction of 8,000 less cases per year worldwide as it is estimated that 200,000 children are born with CL/P per year (Mossey et al., 2009; The Central Intelligence Agency, 2021). This estimation is based on a 14% prevalence of maternal smoking in case mothers, originating from high income

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country publications, whereas the World Health Organisation estimates 17% of the global population use tobacco products, mostly from low and middle income countries (World Health Organisation, 2020).

The potential for maternal smoking to play a moderate role in CL/P etiology fits within our current understanding about the cause of CL/P being complex, multifactorial and involving both environmental and genetic factors (Dixon et al. 2011). Gene-environment interactions between smoking and CL/P have been the focus of a number of studies over the last two decades and these have improved our understanding of the pathogenesis of CL/P (Vieira, 2008; Krapels et al., 2008; Beaty et al., 2016; Garland et al., 2020). If smoking only accounts for 4% of the population attributable fraction, the environmental and genetic factors accounting for the remaining 96%, and the interplay between them, remains to be defined.

Recommendations / implications for practice/policy/ further research

This review seeks to address an important public health question regarding the role of maternal smoking in CL/P etiology. Tobacco use is still common worldwide in pregnancy and is the focus of campaigns by the World Health Organisation to reduce adverse health effects on woman and infants (World Health Organisation, 2013). The neonatal health risk associated with maternal smoking were highlighted to the public in 2014 by the U.S Surgeon General's Report, with smoking reported to increase the risk of CL/P by 30-50% (United States Department of Health and Human Services, 2014). Focus group research has highlighted the difficulties of changing smoking behaviors in pregnant

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women but suggests educational information with pictorial representation of babies risk may be an effective motivational method (Levis et al., 2014).

The methodologies used by the 45 eligible studies were all conventional observational design (cohort or case control designs). To strengthen our understanding of the causal role of maternal smoking in CL/P, this review highlights the need for high quality studies using a variety of methodological approaches with different directions of bias (Pearce et al., 2019). An instrumental variable model using genetic variants as proxies for smoking has been used in the past to assess the effect of maternal smoking on CL/P risk and reported a substantially stronger positive effect than traditional analytic studies, but the genetic variants used were not strongly associated with smoking and the sample size was small (Wehby et al., 2011). More powerful studies, using multiple novel epidemiological designs that can overcome some of the limitations of traditional methods are required and have been used as part of a triangulated approach to further the understanding of the causal role of cigarette smoking for other health outcomes (Gage et al., 2020).

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Figure Legends

Figure 1: A flow chart of the search strategy and study selection

Figure 2: Forest plot to display the measures of effect for studies reporting cleft lip and/or palate outcome. The overall effect has been calculated using a fixed effects method.

Figure 3: Forest plot to display the measures of effect for studies reporting cleft lip ± palate outcome. The overall effect has been calculated using a fixed effects method.

Figure 4: Forest plot to display the measures of effect for studies reporting cleft palate only outcome. The overall effect has been calculated using a random effects method.

Figure 5: A subgroup forest plot to display the dose-response effect of smoking on cleft lip and/or palate outcome. The overall effect for each of the three dose

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categories (1-10, 11-20 and >20) has been calculated using a random effects model

Supplementary Figure Legends

Supplementary Figure 1: Medline search strategy

Supplementary Figure 2: Embase search strategy

Supplementary Figure 3: Web of Science search strategy

Supplementary Figure 4: Cochrane search strategy

Supplementary Figure 2: Funnel plots to test publication bias for studies included in this review. The studies have been categorized depending the outcome reported: A) Cleft lip and/or palate; B) Cleft lip ± palate; C) Cleft Palate Only

Supplementary Figure 6: Forest plot to display the individual study measures of effect and pooled analysis for all studies included in this review reporting cleft lip and/or palate outcome.

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Supplementary Figure 7: Forest plot to display the individual study measures of effect and pooled analysis for all studies included in this review reporting cleft lip ± palate outcome.

Supplementary Figure 8: Forest plot to display the individual study measures of effect and pooled analysis for all studies included in this review reporting cleft palate only outcome.

Table 1: Characteristics of Included Studies

Author	Year	Country	Period	Sample details	Control details	No. of cases (proportion exposed)	No. of controls (proportion exposed)	Period of smoking	Effect of smoking dose	Outcome
Cohort Studies										
Shiono et al.	1986	USA	1974-1977	13 Northern California Kaiser Clinics	Births with no congenital deformity	56 (27%)	NS	T1	No	CL±P and CP
Malloy et al.	1989	USA	1980-1983	Missouri Centre for Health Statistics Multisource Birth Defects Registry	NS	451 (NS)	288067 (NS)	T1-3	No	CL/P
McDonald et al.	1992	USA	1982-1984	Survey in Montreal	Births matched to location and date	96 (39%)	89317 (33%)	T1	Yes	CL/P
Kallen	1997	Sweden	1983-1992	The Swedish Registry of Congenital Malformations and the Medical Birth Registry	Births with non-cleft congenital deformities	1634 (31%)	1002742 (27%)	T1	No	CL±P and CP
Woods et al.	2001	USA	1998-1999	The TriHealth Hospitals in Cincinnati	Births with and without non-cleft congenital birth defects	7 (14%)	18076 (11%)	T1-3	No	CL/P
DeRoo et al.	2003	USA	1987-1990	Washington State Birth Defects Registry (BDR)	Birth with non-cleft congenital deformities matched to location and date	608 (23%)	297530 (21%)	T1	No	CL±P and CP

Bille et al.	2007	Denmark	1997-2003	The Danish National Birth Cohort	Non-cleft births	192 (32%)	880 (25%)	T1	Yes	CL/P, CL±P and CP
Lebby et al.	2010	USA	2005	US Natality Database	Births without a congenital deformity	1654 (18%)	1654 (10%)	T1-3	No	CL/P
Gunnerbeck et al.	2014	Sweden	1999-2009	Swedish Medical Birth Register	Non-cleft births	1985 (10%)	1086213 (8%)	P	No	CL/P
Leite et al.	2014	Denmark	1997-2010	Danish Medical Birth Register	Non-cleft births	1564 (23%)	838265 (19%)	T1	No	CL±P and CP
Sato et al.	2020	Japan	2011-2014	Japan Environment and Children's Study	Non-cleft births	146 (16%)	94174 (13%)	T1	No	CL±P
Case-Control Studies										
Khoury et al. (	1989	USA	1968-1980	Atlanta Birth Defects Case-Control Study	Births matched to location and date	345 (41%)	2809 (NS)	P	Yes	CL±P and CP
Van Den Eeden et al.	1990	USA	1984-1986	Washington State Birth Records	Births without a congenital malformation matched to date	173 (NS)	4500 (23%)	T1-3	NS	CL±P and CP
Hwang et al.	1995	USA	1984-1992	Maryland Birth Defects Reporting and Information System (BDRIS)	Births with non-cleft congenital deformities	183 (37%)	284 (29%)	T1-3	No	CL±P and CP
Shaw et al.	1996	USA	1987-1989	California Birth Defects Monitoring Programme	Births matched to location and date	731 (32%)	734 (23%)	P	Yes	CLP and CPO
Lieff et al.	1999	USA	1976-1992	Slone Epidemiology Unit Birth Defects Study	Births with non-cleft congenital deformities	1072 (36%)	2295 (30%)	T1-3	Yes	CL, CL±P and CP

Lorente et al.	2000	France / UK / Italy and Netherlands	1989-1992	European Registration of Congenital Anomalies	Consecutive births or births matched to location and date	133 (37%)	1134 (NS)	T1	Yes	CL±P and CP
Chung et al.	2000	USA	1996	US Natality Database	Births without a congenital malformation	2207 (21%)	4414 (15%)	T1-3	Yes	CL/P
Beaty et al.	2001	USA	1992-1998	The Maryland Birth Defects Reporting and Information System (BDRIS) and the Children's National Medical Centre in Washington DC	Births without a congenital deformity identified from clinical settings	135 (20%)	152 (14%)	P	No	CL±P and CP
Wyszynski and Wu	2002	USA	1997	US Natality Database	Births without congenital deformities	2029 (19%)	4050 (17%)	T1-3	Yes	CL/P
Little et al.	2004	UK	1997-2000	UK Cleft Teams	Non-cleft births	190 (42%)	248 (24%)	T1	Yes	CL±P and CP
Meyer et al.	2004	Sweden	1983-1997	Swedish Medical Birth Registry	Non-cleft births	1853 (30%)	128688 (24%)	T1	YEs	CL±P and CP
Krapels et al.	2006	Netherlands	1998-2003	Netherlands Cleft Teams	Births without a congenital malformation	350 (25%)	222 (23%)	P	Yes	CL±P and CP
Shi et al.(A)	2007	Denmark	1991 - 1994 (DBS)	Danish Case-Control study (DBS)	Non-cleft birth recruited from same hospital as case mother	270 (40%)	485 (32%)	P	Yes	CL±P and CP
Shi et al.(B)	2007	USA	1987-2001	Iowa Registry for Congenital and Inherited Disorders	Births without congenital deformities matched	379 (27%)	397 (20%)	P	Yes	CL/P, CL±P and CP

					by sex and date					
Grewal et al.	2008	USA	1999-2003	Hospital reports in California	Births without congenital deformity recruited from same hospital as case mother	701 (9%)	700 (18%)	P	Yes	CL±P and CP
Lie et al.	2008	Norway	1996-2001	Norway Cleft Teams	Non-cleft births	573 (42%)	763 (32%)	T1	Yes	CL±P and CP
Chevrier et al.	2008	France	1998-2001	7 French Hospitals	Births without congenital deformity recruited from same hospital as case mother	240 (28%)	236 (29%)	T1	Yes	CL±P and CP
Leite and Koifman	2009	Brazil	Not stated	Nossa Senhora de Loreto Municipal Hospital, Brazil	Births without congenital deformity recruited from same hospital as case mother	274 (19%)	548 (16%)	T1	Yes	CL/P
Mirilas et al.	2011	Greece	2004-2009	Single Greek Hospital	Non-cleft children presenting to the hospital surgical department	35 (17%)	35 (20%)	T1	No	CL/P
Zhang et al.	2011	China	2006-2009	University of Harbin Medical University, China	Births without congenital deformity recruited from same hospital as case mother	304 (5%)	453 (1%)	P +T1	Yes	CL, CL±P and CP
Ibarra-Lopez et al.	2013	Mexico	not stated	2 hospitals in Mexico	Non-cleft children presenting to the involved hospitals	88 (1%)	116 (7%)	T1	No	CL/P

Salihu et al.	2014	Kosovo	1996-2005	NS	NS	244 (NS)	488 (NS)	T1-3	No	CL/P
Bezerra et al.	2015	Brazil		2 hospitals in Brazil	Non-cleft children recruited from schools	140 (14%)	175 (13%)	T1		CL/P
Hao et al.	2015	China	2009-2014	3 hospital sites in China	Births without congenital deformity recruited from same hospital as case mother	499 (7%)	480 (6%)	T1-3	No	CL±P and CP
Martelli et al.	2015	Brazil	2009-2012	Single hospital in Brazil	Births without congenital deformity recruited from same hospital as case mother	843 (25%)	676 (14%)	T1	No	CL/P, CL±P and CP
Figueiredo et al.	2015	DRC, Vietnam, Philippines and Honduras	2009-2014	Operation Smile International Missions	Births without congenital deformity recruited from same hospital as case mother	430 (1%)	754 (<1%)	T1	No	CL/P
Ebadifar et al.	2016	Iran	2013-2015	Single center in Iran	Non-cleft children from Iran	105 (39%)	218 (2%)	T1	No	CL/P
Liu et al.	2016	China	2002-2014	Shanxi Province, China	NS	205 (<1%)	1223 (2%)	P	No	CL/P
Angulo-Castro et al.	2017	Mexico	2010-2015	Single hospital in Mexico	Non-cleft births recruited from same hospital as case mother	24 (46%)	24 (13%)	T1-3	No	CL/P
Xu et al.	2018	China	2013-2016	Single hospital in China	Children with frenulum	236 (21%)	209 (6%)	T1-3	No	CL/P

					abnormality recruited from same hospital					
Raut et al.	2019	USA	1997-2011	National Birth Defects Prevention Study	Births without congenital deformities	4003 (23%)	11395 (18%)	P	No	CL±P and CP
Acs et al.	2020	Hungary	1980-2009	Hungarian Congenital Abnormality Registry	Births without congenital deformities	751 (19%)	1196 (8%)	T1	No	CP
Regina et al.	2020	Brazil	2012-2014	Cleft unit at Brazilian Hospital	Births without congenital deformities	150 (9%)	300 (5%)	T1-3	No	CL/P
Ausländer et al.	2020	Vietnam, Philippines, Honduras, Nicaragua, Morocco, Congo and Madagascar	2012-2017	Operation Smile Internatinal Missions	Births without congenital deformities recruited from surrounding regions	2137 (<1%)	2014 (<1%)	T1-3	No	CL/P and CL±P

[1]

[1] Abbreviations: CL (Cleft Lip Only); CL/P (Cleft Lip and/or Cleft Palate); CL±P (Cleft Lip ±Palate); CP (Cleft Palate Only); NS (Not Stated); P (Peri-Conceptual); T1 (First Trimester); T1-3 (Anytime During Pregnancy).

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Table 2: Quality Assessment of Included Studies using the Newcastle Ottawa Scale.

Author	Year				Quality Score
Cohort Studies		**Selection**	**Comparability**	**Outcome**	
Shiono et al.	1986	★★★	★	★★★	Fair
Malloy et al.	1989	★★		★★	Poor
McDonald et al.	1992	★★★	★	★★	Fair
Kallen	1997	★★★★		★★★	Poor
Woods et al.	2001	★★★★		★★	Poor
DeRoo et al.	2003	★★		★★★	Poor
Bille et al.	2007	★★★★	★	★★★	Fair
Lebby et al.	2010	★★★	★	★★	Fair
Gunnerbeck et al.	2014	★★★★		★★★	Poor
Leite et al.	2014	★★★★		★★★	Poor
Sato et al.	2020	★★★	★★	★★★	Good
Case-Control Studies		**Selection**	**Comparability**	**Exposure**	
Khoury et al.	1989	★★★★	★	★	Poor
Van Den Eeden et al.	1990	★★★	★	★★	Fair
Hwang et al.	1995	★		★	Poor
Shaw et al.	1996	★★★★	★	★★★	Fair
Lieff et al.	1999	★★		★★	Poor
Lorente et al.	2000	★	★	★	Poor
Chung et al.	2000	★★★	★	★★	Fair
Beaty et al.	2001	★★	★	★	Poor
Wyszynski and Wu	2002	★★★	★	★★	Fair
Little et al.	2004	★★		★★	Poor
Meyer et al.	2004	★★★		★★★	Poor
Krapels et al.	2006	★★		★	Poor
Shi et al.(A)	2007	★		★★	Poor
Shi et al.(B)	2007	★★★★	★	★	Poor
Grewal et al.	2008	★★★★	★★	★★	Good
Lie et al.	2008	★★★★	★	★★	Fair
Chevrier et al.	2008	★★	★	★★	Fair
Leite and Koifman	2009	★★	★	★	Poor
Mirilas et al.	2011	★★		★	Poor
Zhang et al.	2011	★★	★	★	Poor
Ibarra-Lopez et al.	2013	★★		★	Poor
Salihu et al.	2014				Poor
Bezerra et al.	2015	★★★		★	Poor
Hao et al.	2015	★	★	★	Poor
Martelli et al.	2015	★★		★	Poor
Figueiredo et al.	2015	★★		★	Poor
Ebadifar et al.	2016	★★		★	Poor
Liu et al.	2016	★		★★	Poor
Angulo-Castro et al.	2017	★		★	Poor
Xu et al.	2018	★★	★	★★	Fair

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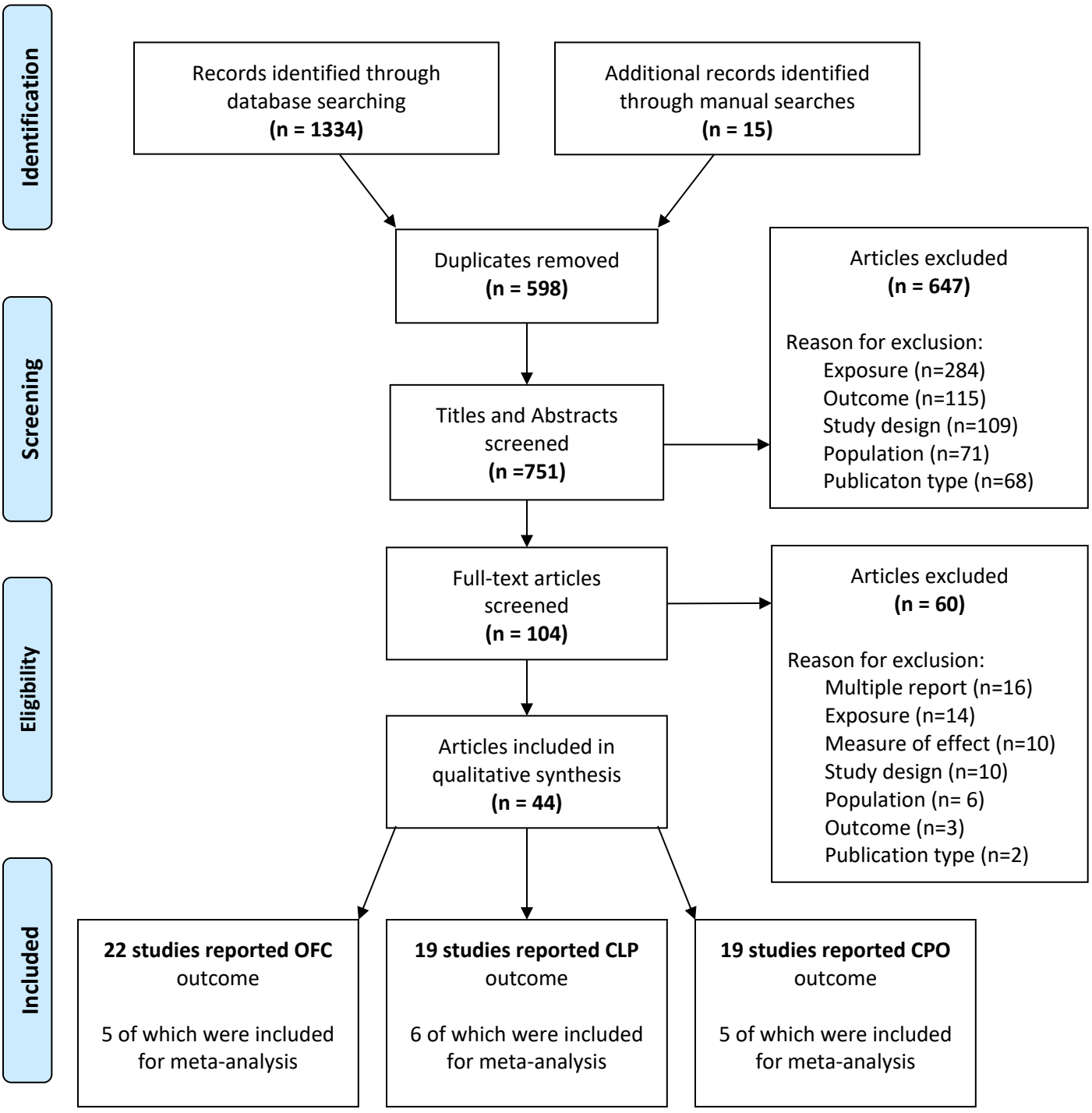
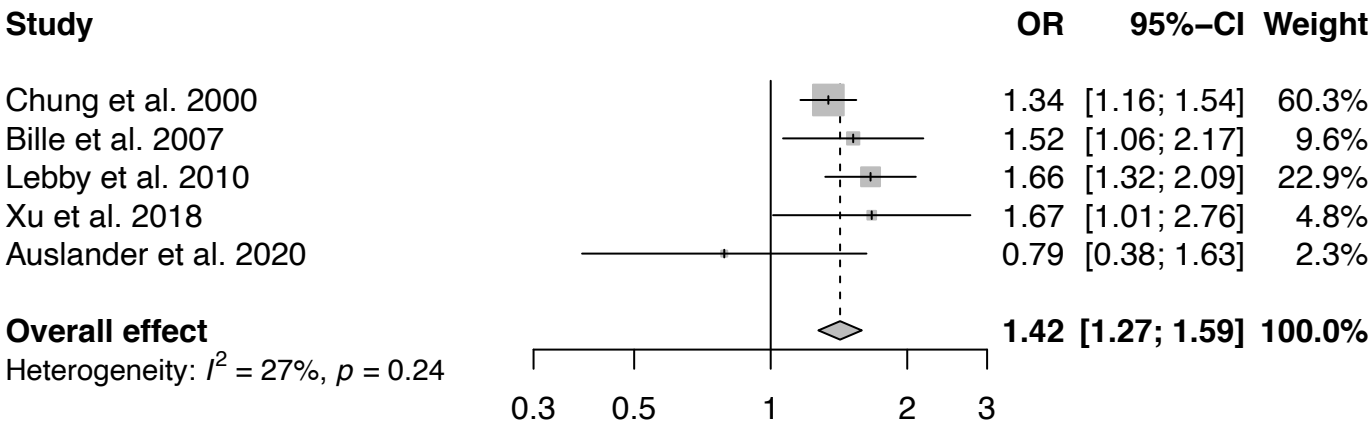
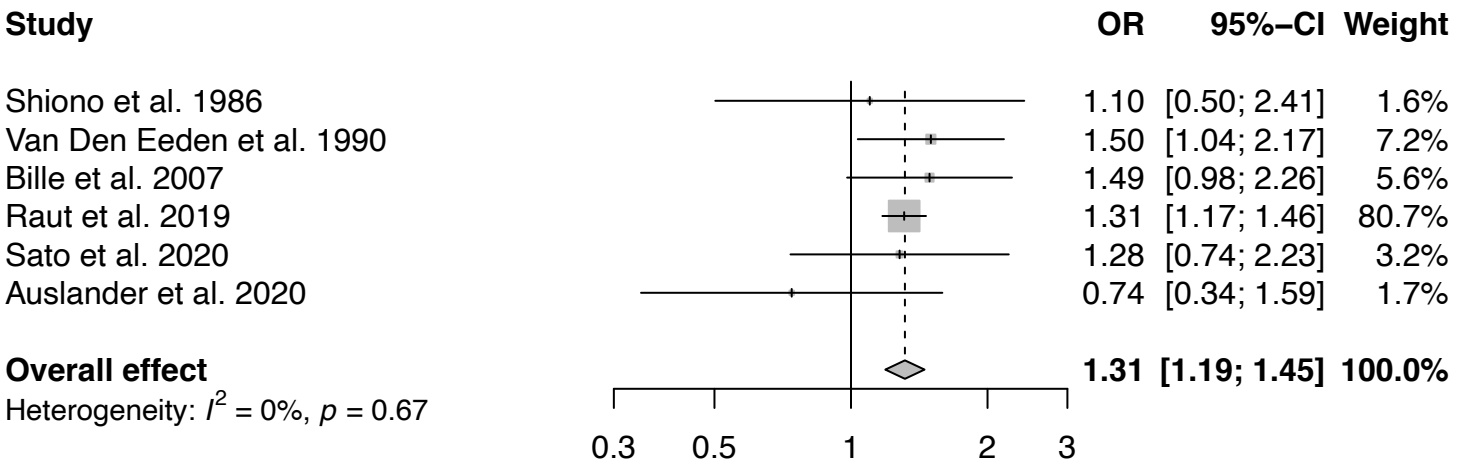
Raut et al.	2019	★★★★	★★	★★★	Good
Acs et al.	2020	★★★★	★	★★	Fair
Regina et al	2020	★★		★	Poor
Ausländer et al.	2020	★★	★★	★★	Fair

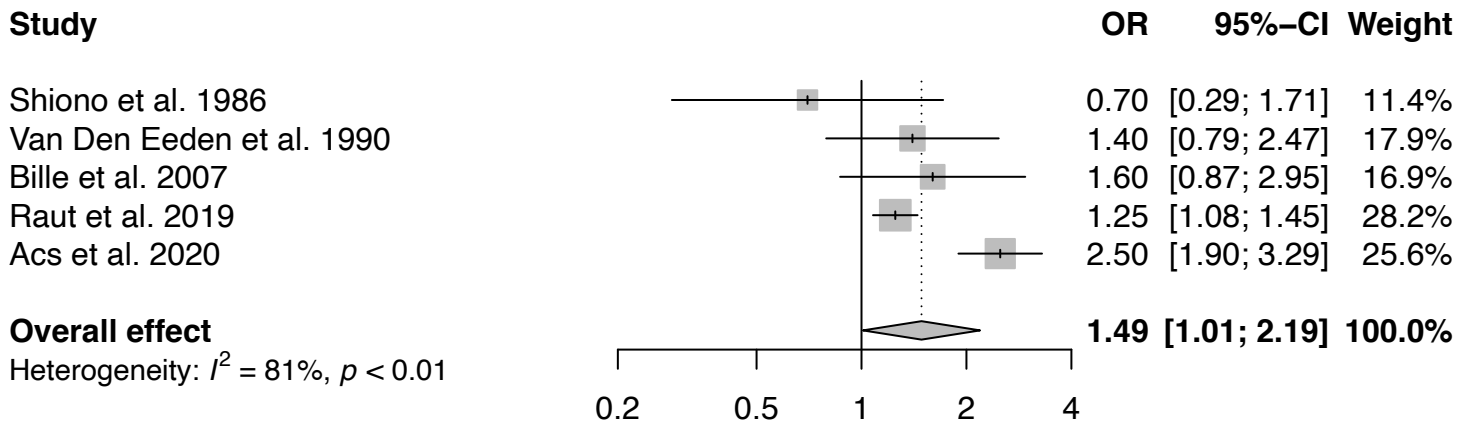
[1]

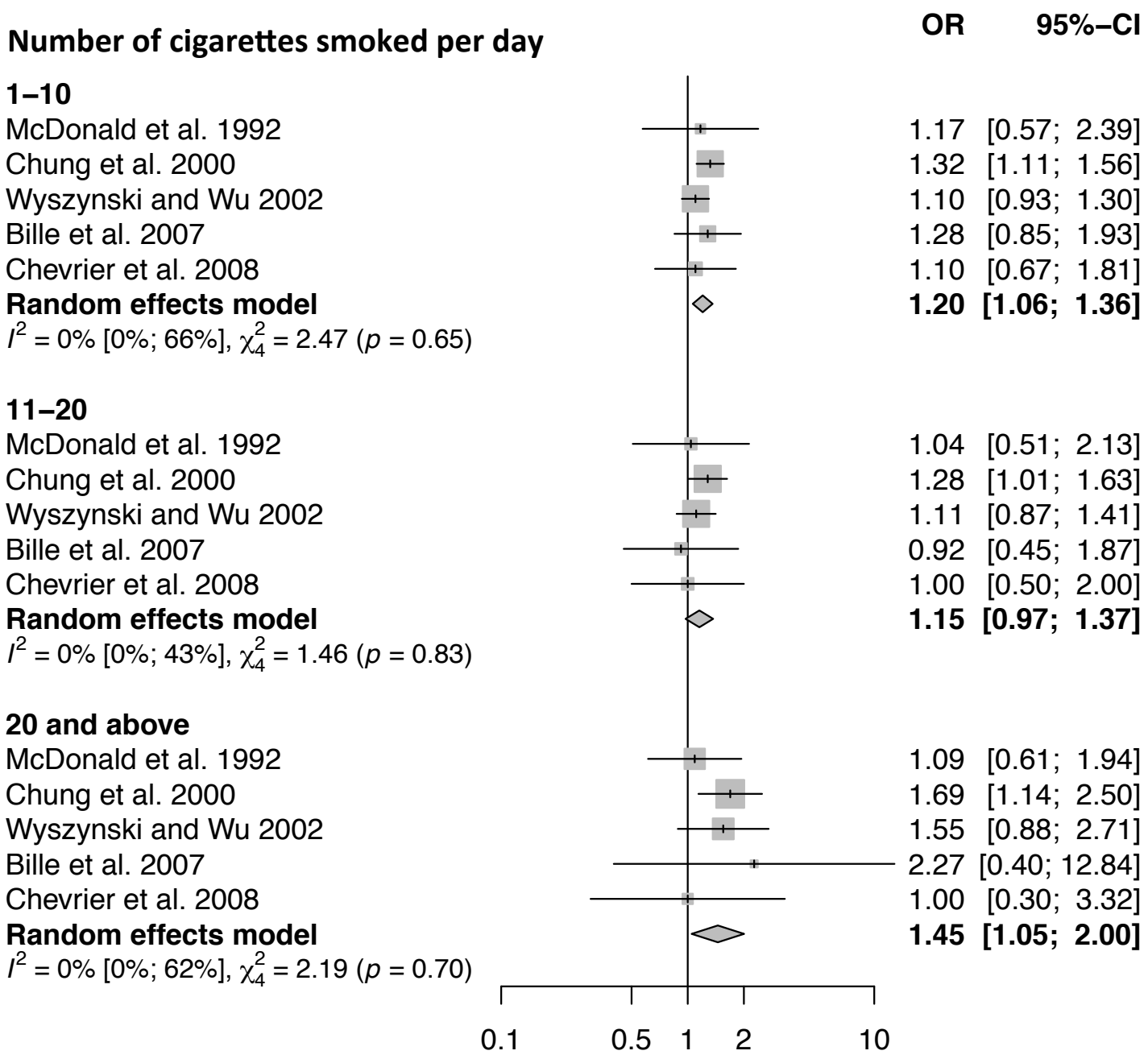
[1] Good quality: 3 or 4 stars (★) in selection domain AND 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 1334)
Additional records identified through manual searches (n = 15)
Duplicates removed (n = 598)
Titles and Abstracts screened (n =751)
Articles excluded (n = 647)
Reason for exclusion:
Exposure (n=284)
Outcome (n=115)
Study design (n=109)
Population (n=71)
Publicaton type (n=68)
Full-text articles screened (n = 104)
Articles excluded (n = 60)
Reason for exclusion:
Multiple report (n=16)
Exposure (n=14)
Measure of effect (n=10)
Study design (n=10)
Population (n= 6)
Outcome (n=3)
Publication type (n=2)
Articles included in qualitative synthesis (n = 44)
22 studies reported OFC outcome
5 of which were included for meta-analysis
19 studies reported CLP outcome
6 of which were included for meta-analysis
19 studies reported CPO outcome
5 of which were included for meta-analysis


Study
OR
95%−CI
Weight
Chung et al. 2000
1.34 [1.16; 1.54] 60.3%
Bille et al. 2007
1.52 [1.06; 2.17] 9.6%
Lebby et al. 2010
1.66 [1.32; 2.09] 22.9%
Xu et al. 2018
1.67 [1.01; 2.76] 4.8%
Auslander et al. 2020
0.79 [0.38; 1.63] 2.3%
Overall effect
1.42 [1.27; 1.59] 100.0%
Heterogeneity: I^2 = 27%, p = 0.24
0.3
0.5
1
2
3


Study
OR
95%–CI
Weight
Shiono et al. 1986
1.10 [0.50; 2.41] 1.6%
Van Den Eeden et al. 1990
1.50 [1.04; 2.17] 7.2%
Bille et al. 2007
1.49 [0.98; 2.26] 5.6%
Raut et al. 2019
1.31 [1.17; 1.46] 80.7%
Sato et al. 2020
1.28 [0.74; 2.23] 3.2%
Auslander et al. 2020
0.74 [0.34; 1.59] 1.7%
Overall effect
1.31 [1.19; 1.45] 100.0%
Heterogeneity: I^2 = 0%, p = 0.67
0.3
0.5
1
2
3


Study
OR
95%–CI
Weight
Shiono et al. 1986
0.70 [0.29; 1.71] 11.4%
Van Den Eeden et al. 1990
1.40 [0.79; 2.47] 17.9%
Bille et al. 2007
1.60 [0.87; 2.95] 16.9%
Raut et al. 2019
1.25 [1.08; 1.45] 28.2%
Acs et al. 2020
2.50 [1.90; 3.29] 25.6%
Overall effect
1.49 [1.01; 2.19] 100.0%
Heterogeneity: I^2 = 81%, p < 0.01
0.2
0.5
1
2
4


Number of cigarettes smoked per day
OR
95%–CI
1–10
McDonald et al. 1992 1.17 [0.57; 2.39]
Chung et al. 2000 1.32 [1.11; 1.56]
Wyszynski and Wu 2002 1.10 [0.93; 1.30]
Bille et al. 2007 1.28 [0.85; 1.93]
Chevrier et al. 2008 1.10 [0.67; 1.81]
Random effects model 1.20 [1.06; 1.36]
I^2 = 0% [0%; 66%], χ^2_4 = 2.47 (p = 0.65)
11–20
McDonald et al. 1992 1.04 [0.51; 2.13]
Chung et al. 2000 1.28 [1.01; 1.63]
Wyszynski and Wu 2002 1.11 [0.87; 1.41]
Bille et al. 2007 0.92 [0.45; 1.87]
Chevrier et al. 2008 1.00 [0.50; 2.00]
Random effects model 1.15 [0.97; 1.37]
I^2 = 0% [0%; 43%], χ^2_4 = 1.46 (p = 0.83)
20 and above
McDonald et al. 1992 1.09 [0.61; 1.94]
Chung et al. 2000 1.69 [1.14; 2.50]
Wyszynski and Wu 2002 1.55 [0.88; 2.71]
Bille et al. 2007 2.27 [0.40; 12.84]
Chevrier et al. 2008 1.00 [0.30; 3.32]
Random effects model 1.45 [1.05; 2.00]
I^2 = 0% [0%; 62%], χ^2_4 = 2.19 (p = 0.70)
0.1
0.5
1
2
10

Supplementary Table 1: PRISMA 2009 Checklist for the systematic review and meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Suppl. Table 2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. Figures 1-4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8

Supplementary Table 1: PRISMA 2009 Checklist for the systematic review and meta-analysis

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures 2-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figures and Suppl. Figures 6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 5
DISCUSSION			

Supplementary Table 1: PRISMA 2009 Checklist for the systematic review and meta-analysis

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title Page

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Supplementary Table 2: Criteria for including or excluding papers

Include	Exclude
1. Publication: Full-text papers published in a peer-reviewed journal. All languages included	**1. Publication:** Title, abstract or conference proceedings only or published in a non-peer reviewed journal (book, newspaper, or website)
2. Study: Primary data using analytical study designs (comparing exposed versus unexposed groups). These may include cohort, case-control, RCT, quasi experimental, Mendelian Randomization studies, natural experiment and family based negative control designs	**2. Study:** Descriptive studies (i.e. no comparison between exposed and unexposed groups). Approaches to exclude will be case studies, case series, cross-sectional studies, expert opinion, letters and editorials). Secondary data from reviews
3. Population: Pregnant women or women who have given birth to live born children in the general population	**3. Population:** Women who are not or have not been pregnant, partners/fathers and animal studies.
4. Exposure: Active cigarette smoking in women during pregnancy measured either by self-reporting or by proxy measurements	**4. Exposure:** Cigarette smoking before or after pregnancy but not explicitly during pregnancy. Intervention in study is not active cigarette smoking (i.e. cigar smoking, recreational drug smoking, vaping, passive/secondary smoking)
5. Outcome: children born with an orofacial cleft. This includes cleft lip, cleft palate, cleft lip and palate and submucous cleft palate.	**5. Outcome:** Other offspring outcomes such as craniofacial abnormalities or developmental abnormalities
6. Measures of effect: A calculation made to define the association between exposure and outcome	**6. Measures of effect:** No calculation made to define the association between exposure and outcome

Supplementary Table 3: The Assignment of Stars for Study Quality using the Newcastle Ottawa Scale

Case Design	Domain	Criteria	Acceptable (Star Awarded)	Unacceptable (Star not awarded)
Cohort	Selection	Representativeness of the exposed cohort	Cohort represents or somewhat represents pregnant women in the general population	Selected group of pregnant women or no description of the derivation of the cohort
		Selection of the non-exposed cohort	Pregnant women drawn from the same community as the exposed cohort	Pregnant women drawn from a different source or no description
		Ascertainment of exposure	Structured interview or secure record (such as birth certificate)	Written self-report (i.e., survey) or no description
		Outcome of interest was not present at start of study	Demonstrated	Not demonstrated
	Comparability	Comparability of cohorts on the basis of the design or analysis	Study controls for maternal age and maternal alcohol consumption (for 1 star) and additionally for maternal folic acid supplementation and body mass index (for 2 stars)	Major confounding factors not controlled for
	Outcome	Assessment of outcome	Orofacial cleft confirmed via record linkage or independent blind assessment	Orofacial cleft outcome confirmed by self-report or not stated
		Was follow-up long enough for outcomes to occur	An adequate follow-up period was allocated after the birth of the baby to make a diagnosis of orofacial cleft	The cohort did not allow for follow-up on birth outcomes
		Adequacy of follow up of cohorts	The follow up was >90% or a reasonable description for those lost to follow-up	The follow-up was <90% and no description for those lost to follow-up or not stated
Case-Control	Selection	Is the case definition adequate?	Diagnosis of cleft independently validated	Diagnosis of orofacial cleft made by record linkage alone or no description
		Representativeness of the cases	All eligible cases of orofacial cleft over a defined period of time, in a defined catchment area or all cases from a treatment provider or a random sample taken	Case group selected is not consecutive or has potential for biased selection or not stated
		Selection of Controls	Controls in the study selected from the same population as the cases	Controls derived from a hospitalised population or no description
		Definition of Controls	Controls verified to have no history of orofacial cleft	No description

Comparability	Comparability of cases and controls on the basis of the design or analysis	Study controls for maternal age and maternal alcohol consumption (for 1 star) and additionally for maternal folic acid supplementation and body mass index (for 2 stars)	Major confounding factors not controlled for
Exposure	Ascertainment of exposure	Structured interview where blind to case/control status	Interview not blinded to case/control status or self-completed survey or no record
	Ascertainment of exposure for cases and controls	Same method used for cases and controls	Different method used for cases and controls
	Non-Response rate	Similar rate for cases and controls	Non-response rate appreciably different between cases and controls or not stated

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Supplementary Table 4: Articles Excluded at the Full Text Screening Stage and Reasons for Exclusion

Author	Year	Publication Title	Reason for exclusion	Explanation
Saxen	1974	Cleft lip and palate in Finland: Parental histories, course of pregnancy and selected environmental factors	Study design	No comparison group
Evans et al.	1979	Maternal smoking habits and congenital malformations: A population study	Association	No measure of effect calculated between exposure and outcome
Ericson et al.	1979	Cigarette smoking as an etiologic factor in cleft lip and palate	Association	No measure of effect calculated between exposure and outcome
Christianson et al.	1980	The relationship between maternal smoking and the incidence of congenital anomalies	Outcome	Cleft not specified as an outcome studied
Hemminki et al	1983	Smoking and the occurrence of congenital malformations and spontaneous abortions: Multivariate analysis	Association	Incomplete measure of effect calculation
Niebyl et al.	1985	Lack of maternal metabolic, endocrine, and environmental influences in the etiology of cleft lip with or without cleft palate	Association	No measure of effect calculated between exposure and outcome
Khoury et al.	1987	Maternal cigarette smoking and oral clefts: A population-based study	Multiple report of study	Crossover with Hwang et al., 1995
Werler et al.	1990	Maternal cigarette smoking during pregnancy in relation to oral clefts	Multiple report of study	Crossover with Lieff et al 1999
Loffredo et al.	1994	Oral clefts - a case-control study	Exposure	No calculation for smoking as an exposure of interest
Munger et al.	1996	Maternal alcohol use and risk of orofacial cleft birth defects	Exposure	No calculation for smoking as an exposure of interest
Beaty et al	1997	Testing for Interaction between Maternal Smoking and TGFA Genotype among Oral Cleft Cases Born in Maryland 1992–1996	Multiple report of study	Crossover with Beaty et al., 2001
Lieff et al.	1999	Selection bias and the use of controls with malformations in case- control studies of birth defects	Multiple report of study	Crossover with Lieff et al, 1999
Romitti et	1999	Candidate genes for non-syndromic cleft	Multiple report	Crossover with

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al.		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	of study	Shi et al 2007
Christensen et al.	1999	Oral clefts, transforming growth factor alpha gene variants, and maternal smoking: A population-based case-control study in Denmark, 1991- 1994	Multiple report of study	Crossover with Shi et al 2007
Kallen	2000	Multiple malformations and maternal smoking	Outcome	Cleft not an outcome
Van Rooij et al.	2001	Smoking, genetic polymorphisms in biotransformation enzymes, and non-syndromic oral clefting: A gene-environment interaction	Multiple report of study	Crossover with Krapels et al., 2006
Yoon et al.	2001	The National Birth Defects Prevention Study	Association	No association calculated between exposure and outcome
Kallen	2002	Maternal smoking and congenital malformations	Association	Incomplete measure of effect calculation
Van Rooij et al.	2002	Orofacial clefts and spina bifida: N-acetyltransferase phenotype, maternal smoking, and medication use	Multiple report of study	Crossover with Van Rooij et al., 2001 which has a greater number of patients
Werler et al.	2003	Findings on potential teratogens from a case-control study in Western Australia	Outcome	Cleft not specified as an outcome studied
Lammer et al	2004	Maternal smoking and the risk of orofacial clefts: Susceptibility with NAT1 and NAT2 polymorphisms	Multiple report of study	Crossover with Shaw et al., 1996, which had the primary data
Bille et al.	2005	Changing lifestyles and oral clefts occurrence in Denmark	association	No association calculated between exposure and outcome
Rouget et al.	2005	Periconceptional folates and the prevention of orofacial clefts: Role of dietary intakes in France	Multiple report of study	Crossover with Chevrier et al., 2008
Lammer et al.	2005	Maternal smoking, genetic variation of glutathione S-transferases, and risk for orofacial clefts	Multiple report of study	Crossover with Shaw et al., 1996, which had the primary data
Shaw et al.	2005	Endothelial nitric oxide synthase (NOS3) genetic variants, maternal smoking, vitamin use, and risk of human orofacial clefts	Multiple report of study	Crossover with Shaw et al., 1996, which had the primary data

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Wilcox et al.	2007	Folic acid supplements and risk of facial clefts: National population based case-control study	Exposure	No calculation for smoking as an exposure of interest
Honein et al.	2007	Maternal smoking and environmental tobacco smoke exposure and the risk of orofacial clefts	Multiple report of study	Crossover with MacLehose et al., 2009 which is an updated dataset
Mossey et al.	2007	Prevention of orofacial clefts: Does pregnancy planning have a role?	Exposure	No calculation for smoking as an exposure of interest
Ramirez et al.	2007	Maternal smoking during early pregnancy, GSTP1 and EPHX1 variants, and risk of isolated orofacial clefts	Exposure	In this gene-association study, smoking was only analysed within genetic subgroups
Gebreab et al.	2008	Visualization and interpretation of birth defects data using linked micromap plots	Study design	Descriptive study
Shaw et al.	2009	Mid-Pregnancy Cotinine and Risks of Orofacial Clefts and Neural Tube Defects	Exposure	No calculation for active smoking estimation
MacLehose et al.	2009	Bayesian methods for correcting misclassification: An example from birth defects epidemiology	Multiple report of study	Crossover with Raut et al., 2019
Marshall et al.	2010	Oral cleft defects and maternal exposure to ambient air pollutants in New Jersey	Exposure	Active smoking was not the exposure
Munger et al.	2011	Oral clefts and maternal biomarkers of folate-dependent one-carbon metabolism in Utah	Exposure	No calculation for smoking as an exposure of interest
Zhang et al.	2011	Cigarette smoke exposure before pregnancy and the associated risk of having a child with orofacial clefts in china: A case-control study	Publication type	Abstract only
Bahado-Singh et al.	2011	Male gender significantly increases risk of oxidative stress related congenital anomalies in the non-diabetic population	Exposure	Maternal smoking not assessed as an independent exposure
Wehby et al.	2011	Genes as instruments for studying risk behavior effects: An application to maternal smoking and orofacial clefts	Multiple report of study	Primary data from Lie et al., 2008
Zandi et al.	2011	An epidemiologic study of orofacial clefts in Hamedan City, Iran: A 15-year study	Exposure	No smokers in the control group
Reiter et al.	2012	Genetic and environmental risk factors for submucous cleft palate	Study design	Secondary data used for the

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				control group
Taghavi et al.	2012	Orofacial clefts and risk factors in Tehran, Iran: A case control stud	Exposure	Population described as ex-smokers rather than current smokers
Buyu et al.	2012	Orofacial clefts at Bugando Medical Centre: Associated factors and postsurgical complications	Association	No association calculated between exposure and outcome
Jurek et al.	2013	Adjusting for outcome misclassification: The importance of accounting for case-control sampling and other forms of outcome-related selection	Study design	Secondary data used
Jurek et al.	2013	Adjusting for multiple-misclassified variables in a study using birth certificates	Study design	Secondary data used
Campos et al.	2016	Environmental factors related to the occurrence of oral clefts in a Brazilian subpopulation	Study design	Descriptive study
Kummet et al.	2016	Passive Smoke Exposure as a Risk Factor for Oral Clefts-A Large International Population-Based Study	Study design	Secondary data used
Sabbagh et al.	2016	Environmental risk factors in the aetiology of non-syndromic orofacial clefts in the western region of Saudi Arabia	Population	Paternal smoking
Wehby et al.	2017	Interaction between smoking and body mass index and risk of oral clefts	Study design	Secondary data used
Lili et al.	2017	Association between non-syndromic cleft lip with or without cleft palate and environmental factors in Ningxia	Population	Paternal smoking
Gao et al.	2017	Do smoking bans improve infant health? Evidence from U.S. Births: 1995-2009	Association	No association calculated between exposure and outcome
Silva et al.	2018	Risk factors and comorbidities in Brazilian patients with orofacial clefts	Study design	Descriptive study
Crossan et al.	2018	Is there an association between maternal smoking and oral clefts?	Publication type	Review
Bui et al.	2018	Association Between Cleft Lip and/or Cleft Palate and Family History of Cancer: A Case-Control Study	Population	No defined maternal smoking group
Bui et al.	2018	Maternal Tobacco Exposure and Development of Orofacial Clefts in the Child	Population	Paternal smoking
Acs et al.	2019	First data from the new, unified database of the Hungarian case-control surveillance of congenital abnormalities	Association	No association calculated between

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				exposure and outcome
Dastgiri et al.	2019	Estimation of the preventable proportion of congenital anomalies by selected risk factors in mothers: A case study in Iran	Population	No definition of maternal smoking group
Yu et al.	2019	Birth anomalies in monozygotic and dizygotic twins: Results from the California twin registry	Exposure	Smoking was a cofactor and not an independently studied exposure
Chowchuen et al.	2020	Birth Prevalence and Risk Factors Associated With CL/P in Thailand	Exposure	No association calculation for active smoking
Hong et al.	2020	Environmental Risk Factors for Non-syndromic Cleft Lip and/or Cleft Palate in Xinjiang Province, China: A Multi-ethnic Study	Population	Paternal smoking
Kruse et al.	2020	Impact of Maternal Smoking on Non-syndromic Clefts: Sex-Specific Associations With Side and Laterality	Study design	Descriptive study
Heinke et al.	2020	Quantification of selection bias in studies of risk factors for birth defects among livebirths	Multiple report of study	Crossover with Raut et al., 2019

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Supplementary Table 5: Confounding Factors Adjusted For in All Included Studies

Author	Year	Maternal age	Alcohol	Folic Acid	Obesity
Shiono et al.	1986	◆	◆		
Khoury et al.	1989	◆	◆		
Malloy et al.	1989	◆			
Van Den Eeden et al.	1990	◆	◆		
McDonald et al.	1992	◆	◆		
Hwang et al.	1995	◆			
Shaw et al.	1996	◆	◆	◆	
Kallen	1997	◆			
Lieff et al.	1999	◆			
Lorente et al.	2000	◆	◆		
Chung et al.	2000	◆	◆		
Beaty et al.	2001	◆	◆	◆	
Woods et al.	2001	◆			
Wyszynski and Wu	2002	◆	◆		
DeRoo et al.	2003	◆			
Little et al.	2004		◆	◆	
Meyer et al.	2004	◆			
Krapels et al.	2006		◆	◆	
Shi et al. A	2007		◆	◆	
Shi et al. B	2007	◆	◆		
Bille et al.	2007	◆	◆	◆	
Grewal et al.	2008	◆	◆	◆	◆
Lie et al.	2008	◆	◆	◆	
Chevrier et al.	2008	◆	◆	◆	
Leite and Koifman	2009	◆	◆		
Lebby et al.	2010	◆	◆		
Mirilas et al.	2011				
Zhang et al.	2011	◆	◆	◆	
Wehby et al.	2011		◆	◆	◆
Ibarra-Lopez et al.	2013			◆	
Gunnerbeck et al.	2014	◆			
Leite et al.	2014	◆			◆
Salihu et al.	2014	◆			
Bezerra et al.	2015		◆		
Hao et al.	2015	◆	◆		◆
Martelli et al.	2015				
Figueiredo	2015		◆		
Ebadifar et al.	2016	◆			
Liu et al.	2016				
Angulo-Castro et al.	2017		◆	◆	
Xu et al.	2018	◆	◆	◆	
Raut et al.	2019	◆	◆	◆	◆
Sato et al.	2020	◆	◆	◆	◆

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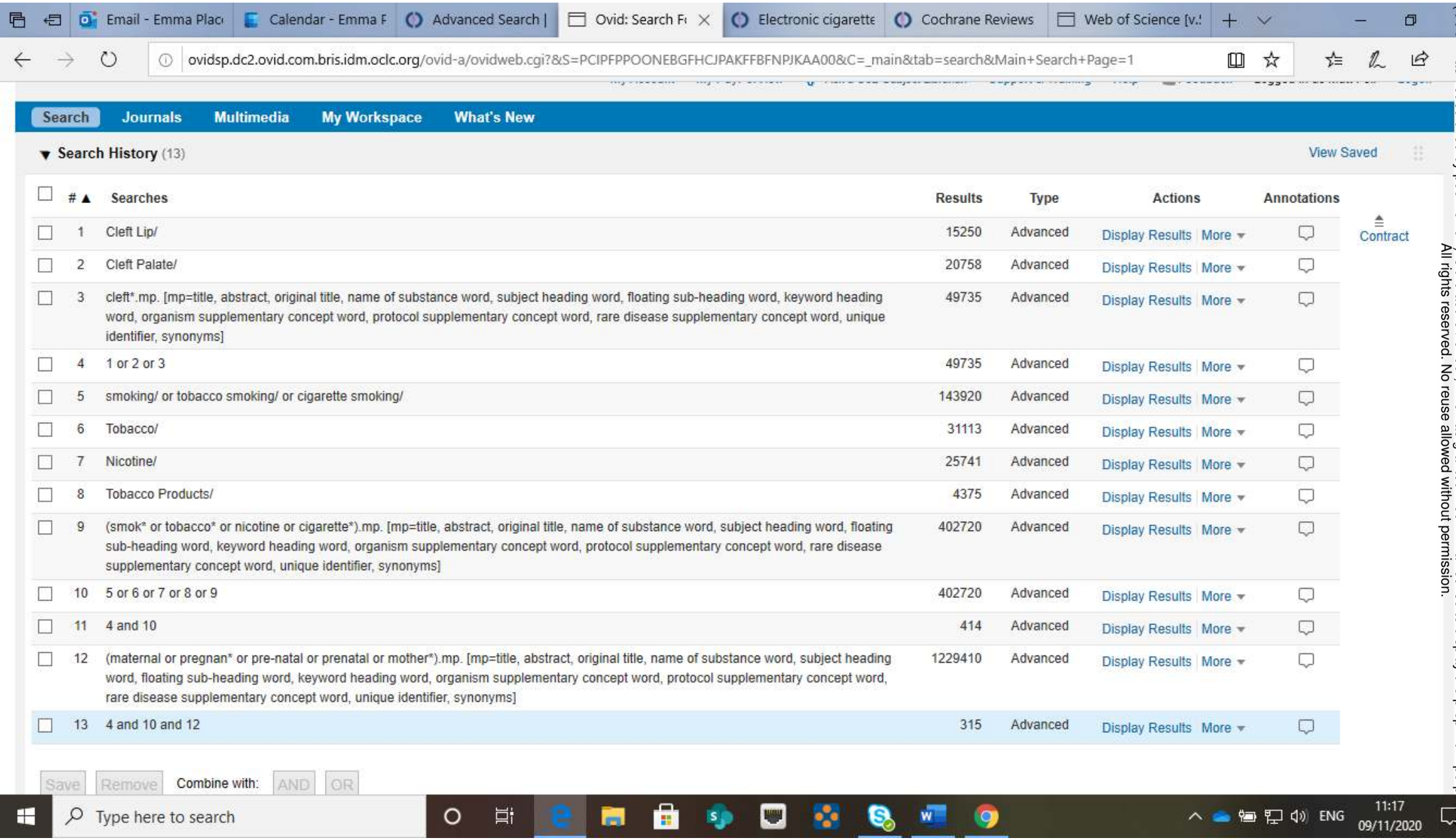
Acs et al.	2020	◆	◆		
Regina et al	2020		◆	◆	◆
Ausländer et al.	2020	◆	◆	◆	◆



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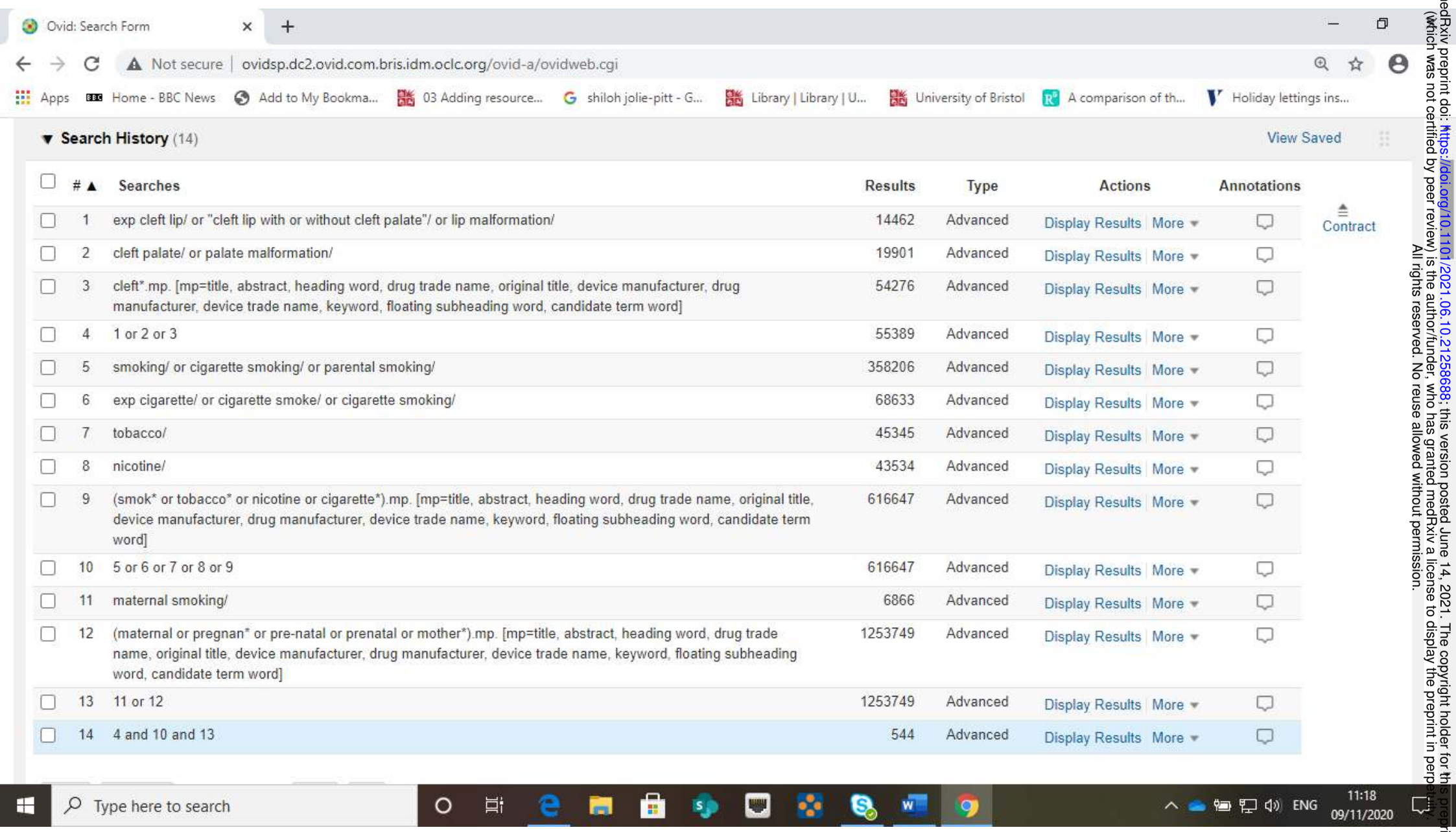

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☐	1	exp cleft lip/ or "cleft lip with or without cleft palate"/ or lip malformation/	14462	Advanced	Display Results | More	
☐	2	cleft palate/ or palate malformation/	19901	Advanced	Display Results | More	
☐	3	cleft*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	54276	Advanced	Display Results | More	
☐	4	1 or 2 or 3	55389	Advanced	Display Results | More	
☐	5	smoking/ or cigarette smoking/ or parental smoking/	358206	Advanced	Display Results | More	
☐	6	exp cigarette/ or cigarette smoke/ or cigarette smoking/	68633	Advanced	Display Results | More	
☐	7	tobacco/	45345	Advanced	Display Results | More	
☐	8	nicotine/	43534	Advanced	Display Results | More	
☐	9	(smok* or tobacco* or nicotine or cigarette*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	616647	Advanced	Display Results | More	
☐	10	5 or 6 or 7 or 8 or 9	616647	Advanced	Display Results | More	
☐	11	maternal smoking/	6866	Advanced	Display Results | More	
☐	12	(maternal or pregnan* or pre-natal or prenatal or mother*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1253749	Advanced	Display Results | More	
☐	13	11 or 12	1253749	Advanced	Display Results | More	
☐	14	4 and 10 and 13	544	Advanced	Display Results | More	

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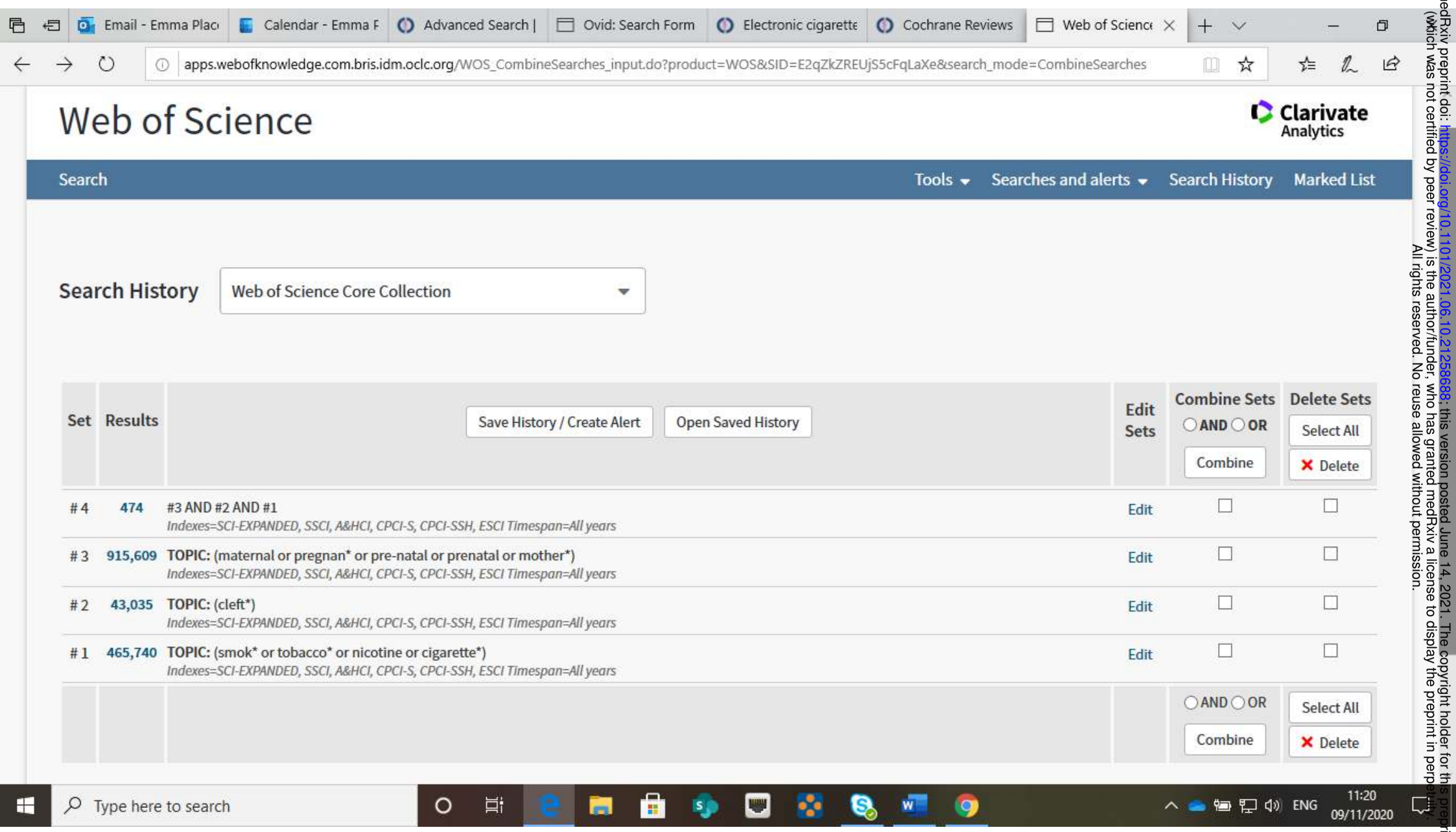

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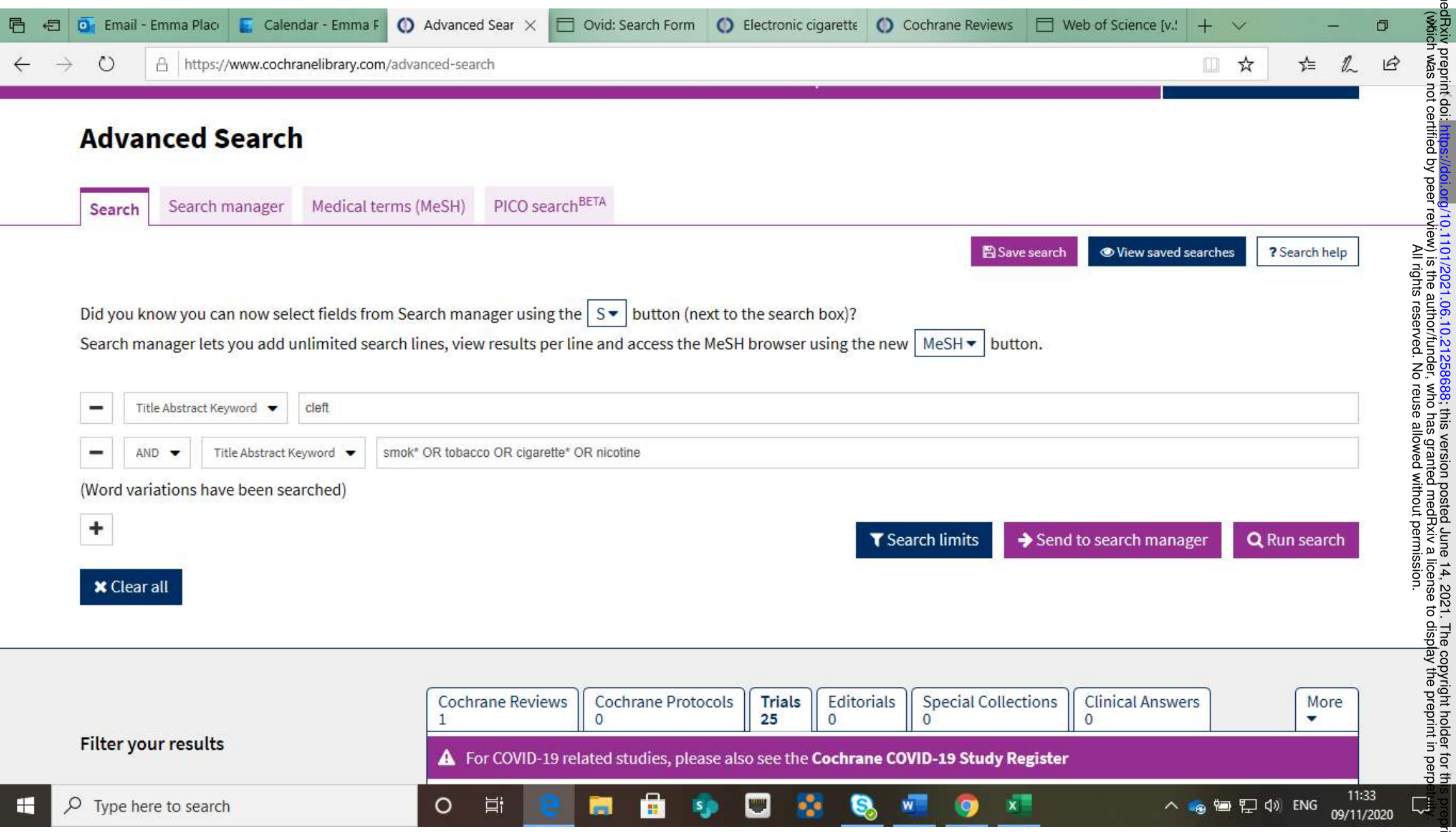

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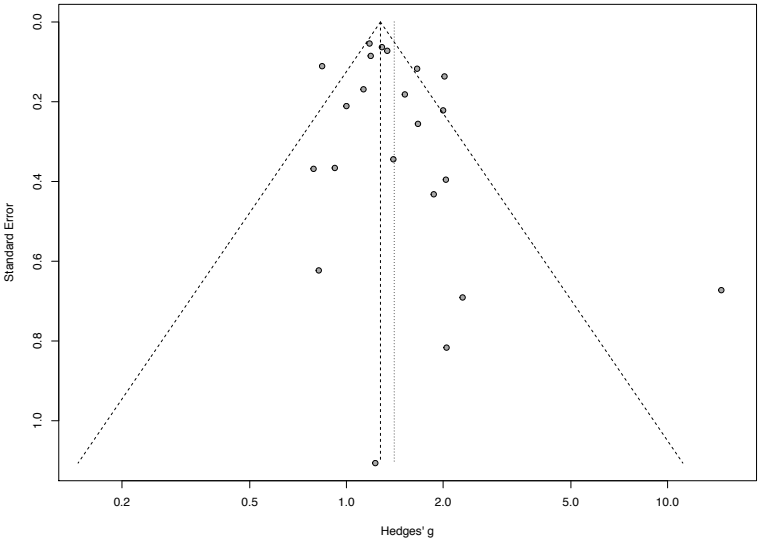
A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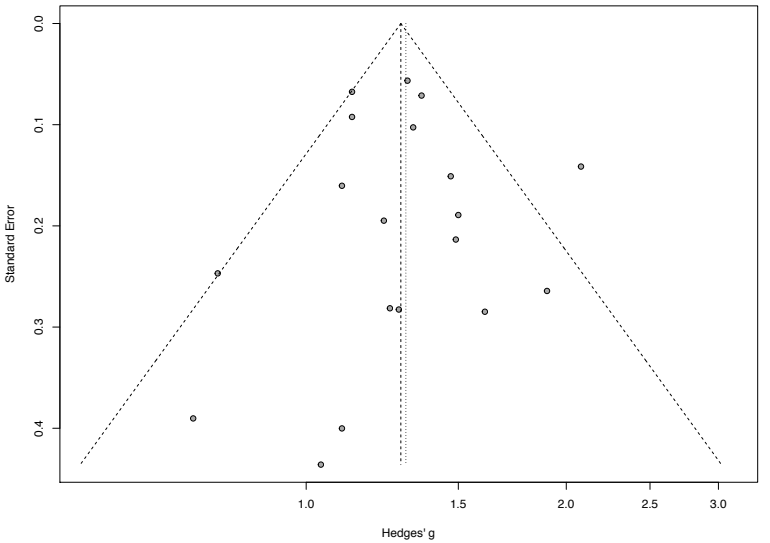
B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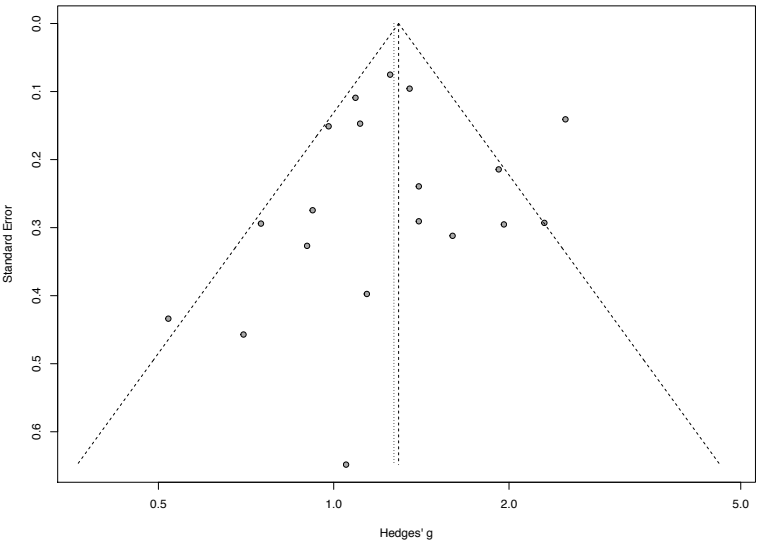
2.0
2.5
3.0
Hedges' g

C


Standard Error
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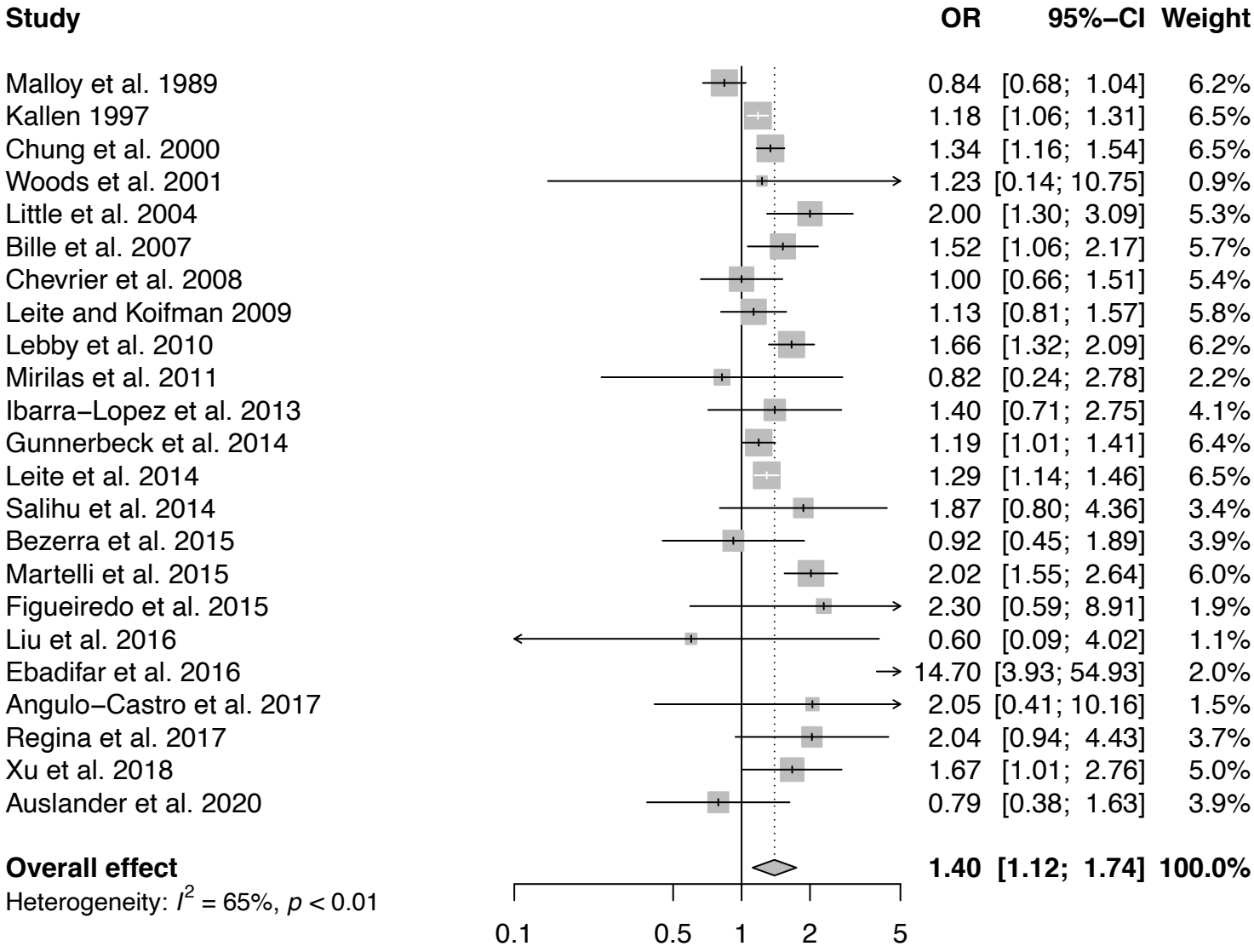
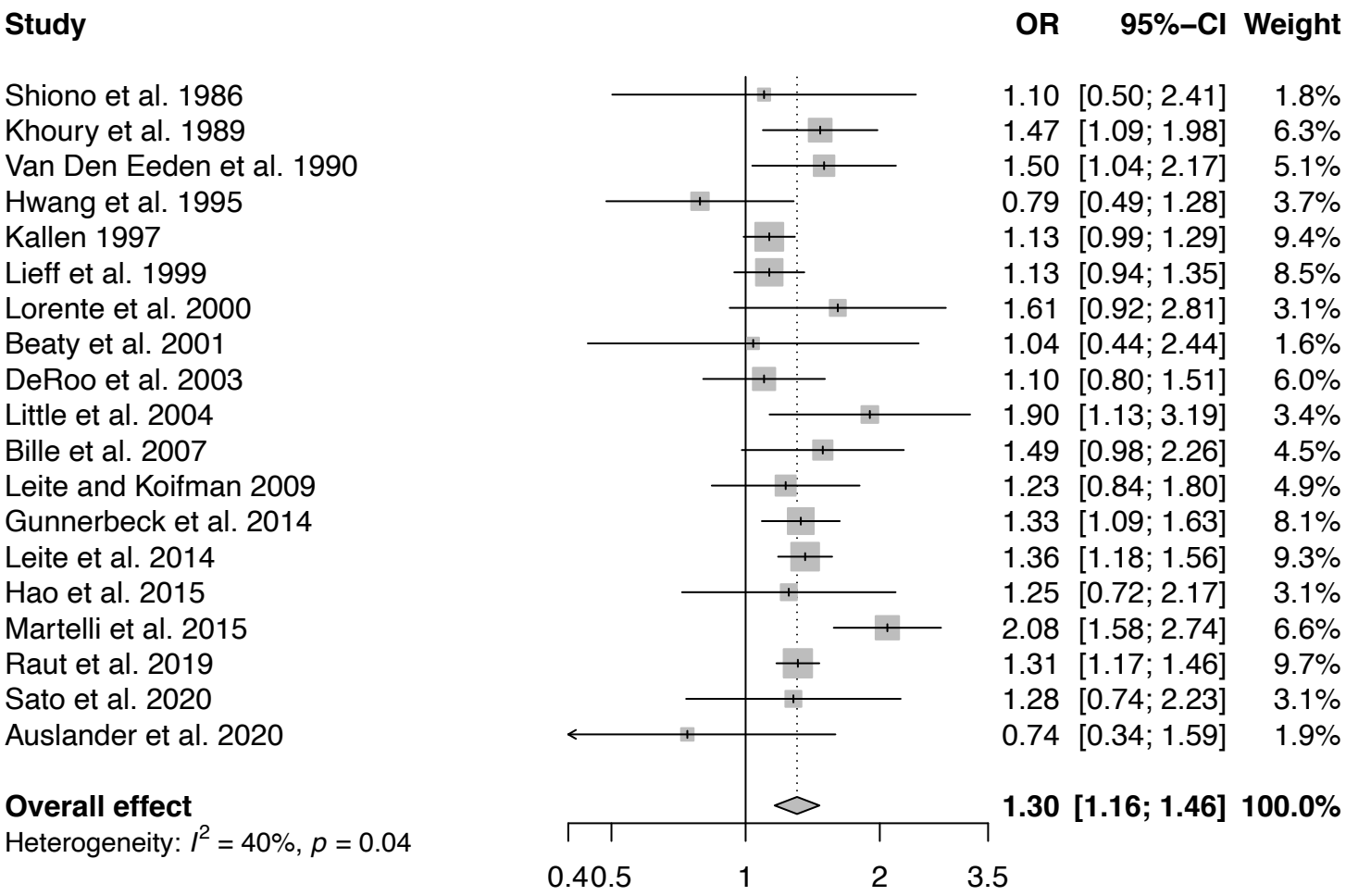
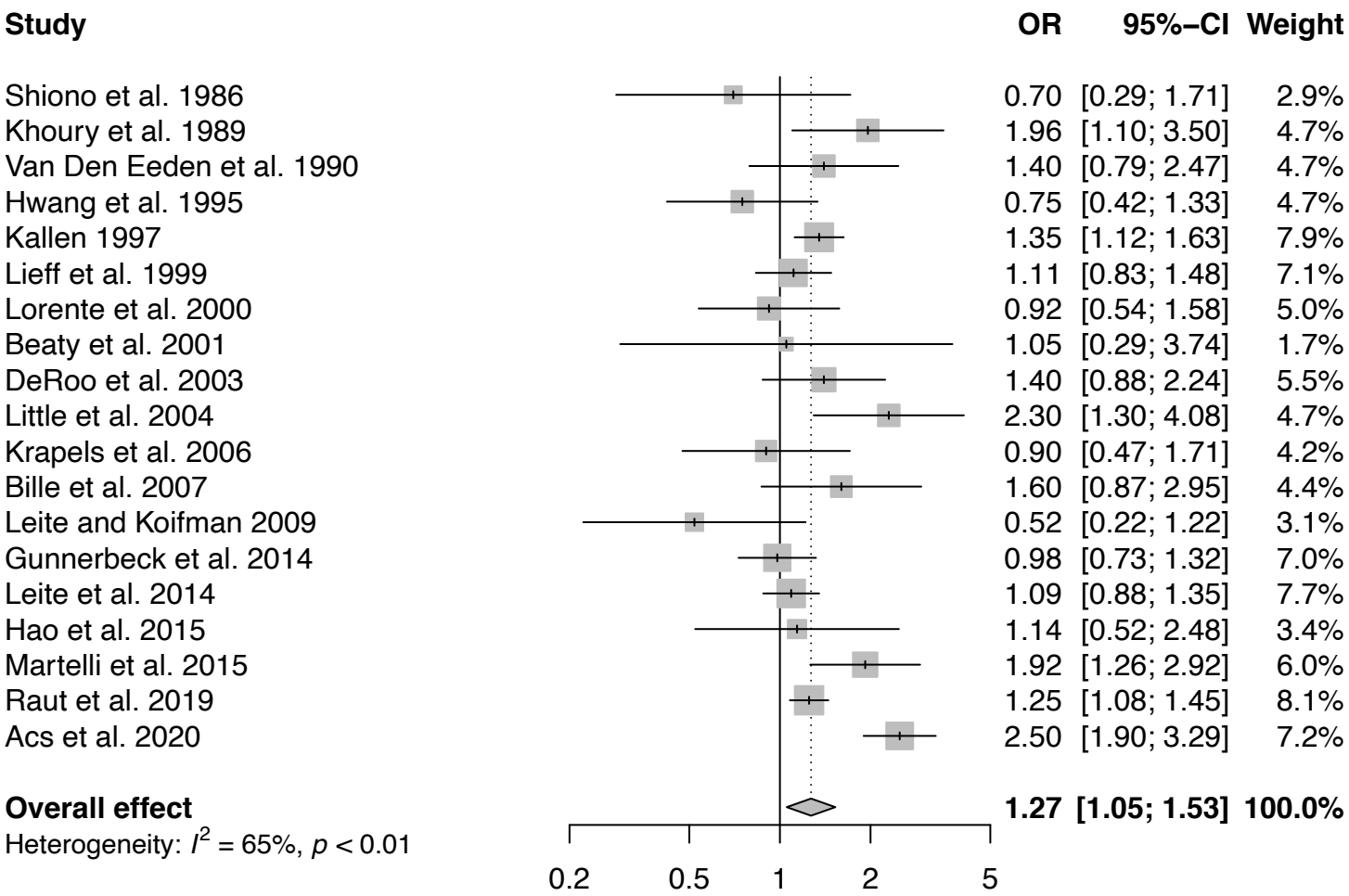

Study
OR
95%–CI
Weight
Malloy et al. 1989 0.84 [0.68; 1.04] 6.2%
Kallen 1997 1.18 [1.06; 1.31] 6.5%
Chung et al. 2000 1.34 [1.16; 1.54] 6.5%
Woods et al. 2001 1.23 [0.14; 10.75] 0.9%
Little et al. 2004 2.00 [1.30; 3.09] 5.3%
Bille et al. 2007 1.52 [1.06; 2.17] 5.7%
Chevrier et al. 2008 1.00 [0.66; 1.51] 5.4%
Leite and Koifman 2009 1.13 [0.81; 1.57] 5.8%
Lebby et al. 2010 1.66 [1.32; 2.09] 6.2%
Mirilas et al. 2011 0.82 [0.24; 2.78] 2.2%
Ibarra–Lopez et al. 2013 1.40 [0.71; 2.75] 4.1%
Gunnerbeck et al. 2014 1.19 [1.01; 1.41] 6.4%
Leite et al. 2014 1.29 [1.14; 1.46] 6.5%
Salihu et al. 2014 1.87 [0.80; 4.36] 3.4%
Bezerra et al. 2015 0.92 [0.45; 1.89] 3.9%
Martelli et al. 2015 2.02 [1.55; 2.64] 6.0%
Figueiredo et al. 2015 2.30 [0.59; 8.91] 1.9%
Liu et al. 2016 0.60 [0.09; 4.02] 1.1%
Ebadifar et al. 2016 14.70 [3.93; 54.93] 2.0%
Angulo–Castro et al. 2017 2.05 [0.41; 10.16] 1.5%
Regina et al. 2017 2.04 [0.94; 4.43] 3.7%
Xu et al. 2018 1.67 [1.01; 2.76] 5.0%
Auslander et al. 2020 0.79 [0.38; 1.63] 3.9%
Overall effect 1.40 [1.12; 1.74] 100.0%
Heterogeneity: I^2 = 65%, p < 0.01
0.1
0.5
1
2
5


Study
OR
95%–CI
Weight
Shiono et al. 1986 1.10 [0.50; 2.41] 1.8%
Khoury et al. 1989 1.47 [1.09; 1.98] 6.3%
Van Den Eeden et al. 1990 1.50 [1.04; 2.17] 5.1%
Hwang et al. 1995 0.79 [0.49; 1.28] 3.7%
Kallen 1997 1.13 [0.99; 1.29] 9.4%
Lieff et al. 1999 1.13 [0.94; 1.35] 8.5%
Lorente et al. 2000 1.61 [0.92; 2.81] 3.1%
Beaty et al. 2001 1.04 [0.44; 2.44] 1.6%
DeRoo et al. 2003 1.10 [0.80; 1.51] 6.0%
Little et al. 2004 1.90 [1.13; 3.19] 3.4%
Bille et al. 2007 1.49 [0.98; 2.26] 4.5%
Leite and Koifman 2009 1.23 [0.84; 1.80] 4.9%
Gunnerbeck et al. 2014 1.33 [1.09; 1.63] 8.1%
Leite et al. 2014 1.36 [1.18; 1.56] 9.3%
Hao et al. 2015 1.25 [0.72; 2.17] 3.1%
Martelli et al. 2015 2.08 [1.58; 2.74] 6.6%
Raut et al. 2019 1.31 [1.17; 1.46] 9.7%
Sato et al. 2020 1.28 [0.74; 2.23] 3.1%
Auslander et al. 2020 0.74 [0.34; 1.59] 1.9%
Overall effect 1.30 [1.16; 1.46] 100.0%
Heterogeneity: I^2 = 40%, p = 0.04
0.4 0.5 1 2 3.5


Study
OR
95%–CI
Weight
Shiono et al. 1986 0.70 [0.29; 1.71] 2.9%
Khoury et al. 1989 1.96 [1.10; 3.50] 4.7%
Van Den Eeden et al. 1990 1.40 [0.79; 2.47] 4.7%
Hwang et al. 1995 0.75 [0.42; 1.33] 4.7%
Kallen 1997 1.35 [1.12; 1.63] 7.9%
Lieff et al. 1999 1.11 [0.83; 1.48] 7.1%
Lorente et al. 2000 0.92 [0.54; 1.58] 5.0%
Beaty et al. 2001 1.05 [0.29; 3.74] 1.7%
DeRoo et al. 2003 1.40 [0.88; 2.24] 5.5%
Little et al. 2004 2.30 [1.30; 4.08] 4.7%
Krapels et al. 2006 0.90 [0.47; 1.71] 4.2%
Bille et al. 2007 1.60 [0.87; 2.95] 4.4%
Leite and Koifman 2009 0.52 [0.22; 1.22] 3.1%
Gunnerbeck et al. 2014 0.98 [0.73; 1.32] 7.0%
Leite et al. 2014 1.09 [0.88; 1.35] 7.7%
Hao et al. 2015 1.14 [0.52; 2.48] 3.4%
Martelli et al. 2015 1.92 [1.26; 2.92] 6.0%
Raut et al. 2019 1.25 [1.08; 1.45] 8.1%
Acs et al. 2020 2.50 [1.90; 3.29] 7.2%
Overall effect 1.27 [1.05; 1.53] 100.0%
Heterogeneity: I^2 = 65%, p < 0.01
0.2
0.5
1
2
5