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Maternal stressful life events during the periconceptional period and orofacial clefts: a systematic review and meta-analysis

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Abstract:

Objective: To assess whether women who experience stressful life events during the periconceptional period are at higher risk of giving birth to a baby with an orofacial cleft (OFC).

Design: Systematic review and meta-analysis of studies reporting the proportion of babies born with OFC to mothers exposed and unexposed to population-level or personal-level stressful life events during the periconceptional period. Six electronic databases were searched from inception to August 2020. Risk of bias was assessed using the Newcastle-Ottawa scale. Odds ratios (ORs) for the odds of OFC in babies of exposed mothers relative to unexposed controls were extracted and/or calculated. Random effects meta-analysis was undertaken, stratified by cleft subtype.

Results: Of 12 eligible studies, 8 examined experience of personal events and 4 examined population-level events. Studies demonstrated low-moderate risk of bias and there was indication of publication bias. There was some evidence that personal stressful life events were associated with greater odds of cleft lip and/or palate (six studies, OR 1.63, 95% confidence interval (CI) 1.16, 2.30, P=0.001) and cleft palate only (six studies, OR 1.45, 95% CI 1.02, 2.06, P=0.04). Population-level events were associated with higher odds of OFC in studies that did not specify subtype (three studies, OR 1.64, 95% CI 1.19, 2.25, P=0.002), but subtype stratified analyses were underpowered. Heterogeneity was high.

Conclusions: Limited evidence indicated a weak positive association between maternal stressful life events during the periconceptional period and risk of OFC in the offspring, but further studies with greater consistency in research design are needed.

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Introduction:

Orofacial clefts (OFCs) affect around one in 500-700 children worldwide (iWorld Health Organization, 2005), and can lead to feeding problems (Goswami et al., 2016), ear infection (Sharma and Nanda, 2009), poor dental health (Al-Dajani, 2009), and psychosocial issues (Sousa et al., 2009). As these anomalies arise during the first trimester of pregnancy (Centres for Disease Control and Prevention, 2017), various maternal exposures during the periconceptional period have been investigated as possible risk factors. Maternal stress has long been proposed as a potential cause of congenital abnormalities (Fraser and Warburton, 1964). Previous animal studies have suggested a corticosteroid-induced relationship between stress and OFC (Fraser and Fainstat, 1951; Greene and Kochhar, 1975), however similar studies in humans have yet to produce conclusive results (Skuladottir et al., 2014). Other human studies have also investigated stress by assessing women with diagnosed stress-related disorders (Ban et al., 2014), as well as women experiencing stressful life events (Carmichael et al., 2007). However, no clear consensus has yet been drawn.

We conducted a systematic review to assess the strength and quality of evidence surrounding maternal stress as a risk factor for OFC. This review focusses specifically on stressful life events occurring to pregnant mothers in the periconceptional period, which have been

associated with other offspring outcomes including low birth weight (Sable and Wilkinson, 2000), reduced head circumference and delayed neurobehavioural development (Su et al., 2015). Studies on stressful life events typically focus on either personal events, (e.g. bereavement, relationship difficulty, legal/financial problems, experience of violence/crime) (Carmichael et al., 2007; Ingstrup et al., 2013) or population-level events (e.g. war, natural disaster) (Hao et al., 2015; Jahanabin et al., 2013).

OFCs can be broadly subtyped into cleft lip and palate (CLP), cleft palate only (CPO), and cleft lip only (CLO). As there is evidence to suggest that these subtypes have distinctive aetiologies (Sharp et al., 2017), this review has undertaken subgroup analysis by cleft subtype, in order to further explore the associations of maternal stressful life events with possible differences in aetiology of different cleft subtypes. A better understanding of OFC risk factors will help inform strategies to predict these defects, therefore perhaps reducing their impact. Further, insights into prevention may be gained.

Materials and methods

This systematic review has been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses checklist. An unpublished review protocol was written according to the International Prospective Register of Systematic Reviews guidelines, which is available as a supplementary file.

Search Strategy

A search strategy was composed using the following key words: ("stress" OR "life event" OR "traumatic event" OR "life change" OR "stressful event" OR "life experience") AND ("cleft lip" OR "cleft palate" OR "cleft lip and palate" OR "orofacial cleft"). This was applied to 6 databases: PubMed, The Cochrane Library, Scopus, PsycINFO, Medline and EMBASE. The results were screened for duplicates and according to the eligibility criteria. The reference lists of included studies and relevant reviews were hand-searched for any relevant studies. The first search was run on 11th August 2017, and updated on 4th August 2020.

Eligibility Criteria

Studies investigating mothers of liveborn or still-born children with and without any form of physician-recorded non-syndromic OFC were included. The exposure of interest was broadly defined as any singular life event occurring during the periconceptional period defined by the study as ‘stressful’. Studies that focused on experience of a particular major population-level event (for example war or a natural disaster), as well as studies that recorded experience of “personal” stressful life events (for example bereavement or divorce), were also included. Studies that focused on chronic maternal stressors, stress-related mental health conditions, or undefined psychological stress not specifically attributed to life experiences were excluded. It is difficult to determine the duration of impact stressful life events have, and there is no consensus

on the span of periconceptional period. We therefore chose a broad duration of exposure (from 2 years preconception to the end of the first trimester), in order to maximise inclusion of relevant studies. The comparator group of interest were mothers who did not experience stressful life events during the periconceptional period. The outcome of interest was defined as any type of non-syndromic OFC, studied as either an individual subtype or combined. Studies with clear inclusion of syndromic OFC were excluded due to their presumed genetic elements. All publication types were considered, with the exception of reviews, book chapters, and editorials/commentaries. All types of observational studies were considered, including cohort, case-control and cross-sectional studies. No restrictions were placed on year of publication. Only publications in the English language were included.

Study selection and data collection

All references were imported into Endnote, which was used to remove duplicate articles. One study author (CT) screened the titles and abstracts of the records according to the inclusion criteria. The full texts of all potentially eligible records were independently assessed by two study authors (CT and GCS) to identify those meeting the eligibility criteria. Concordance was 90%, and disagreements were resolved by discussion. For publications which were unavailable online, or lacked sufficient data, an attempt to locate the publication offline or contact the author was made if the article had been published within the past five years.

Using a standardised, pre-piloted form in Microsoft Excel, two study authors (CT and GCS) independently extracted data from all eligible studies. Two study authors (CT and AC) then independently compared extracted data to ensure consistency and accuracy. Any disagreements were resolved by discussion between authors (CT, GCS and AC).

Risk of bias

The Newcastle-Ottawa Scale (NOS) (score range 0-9) was used to assess the risk of bias for all case-control and cohort studies (Wells et al., 2014). A modified NOS (score range 0-10), devised by Herzog et al. (2013) was used for cross-sectional studies. Studies were scored on the reliability of their case selection, comparability of cases and controls, and measurement of outcome or exposure. A higher NOS score indicated a lower risk of bias. The risk of bias was scored by one author (CT), with 50% of results independently confirmed by a second author (AAC).

Summary measures and synthesis of results

The studies fulfilling the eligibility criteria were assessed for common outcome measures. Most studies presented odds ratios (ORs) for the odds of OFC in exposed mothers relative to unexposed controls. Where these were not provided, ORs were calculated from reported

numbers or proportions. For studies that presented results as several unit change in stressful life index, these were converted into a 1-unit change in stressful life index. Where studies had considered exposures during the entire duration of pregnancy, only data from the first trimester was used.

Statistical methods and subgroup analysis

Studies were grouped according to cleft subtype: cleft lip and/or palate (CL/P), cleft palate only (CPO), cleft lip only (CLO), cleft lip and palate (CLP), and unspecified cleft subtype (any cleft). Most studies combined cleft subtypes as CL/P when reporting results. They were also subdivided by exposure type (personal and population-level event). Studies reporting ORs adjusted for potential confounders were meta-analysed separately to those reporting unadjusted ORs.

Meta-analysis was carried out using the statistical software R (version 4.0). A random effects model was used, as it was presumed that there would be between-study heterogeneity due to differences in population, definition of stressful life events and methodologies. ORs (and 95% CIs) from the meta-analysis were visually examined with forest plots. Statistical heterogeneity was assessed using the Cochran Chi^2 test (Q-test) and the I^2 statistic.

Results

Description of included studies

We identified 12 studies eligible for inclusion in the systematic review (table 1). Studies were mostly case-control (n=6) or cross-sectional (n=5), alongside one cohort study. Studies were mainly undertaken in the United States of America (USA) (n=4) and China (n=2), with the remainder from Canada, Chile, Denmark, Iran, Georgia, and Sweden (all n=1). A list of studies excluded after full-text screening, with reasons for exclusion, is available as supplemental data.

Nine studies focused on personal events as the exposure of interest (e.g. bereavement, change of employment, experience of crime), whilst the remaining focused on experience of population-level events (e.g. earthquake, hurricane). There was little concordance on the duration of the periconceptional period. Most studies (n=7) considered exposures until the end of the first trimester, with the preconception periods considered ranging from 15 months to 1 month. Most studies reported results for CL/P (n=7) or CPO (n=8) subtypes, with fewer reporting results for CLO (n=2), CLP (n=2), and any cleft subtype (n=4). The number of participants ranged from 102 – 1771663. In studies that reported their response rates, there was a high and similar response rate (range 60%, 100%) in both cases and controls. However, eight studies did not report a response rate.

[FIGURE 1]

Figure 1: Systematic search results for studies examining the effect of maternal stressful life events during the periconceptional period and OFC in the offspring.

Table 1: Characteristics of included studies, by year of study

[TABLE 1 HERE]

Risk of bias

The overall mean percentage score was 74.4%, indicating low-moderate risk of bias. The mean scores were 6.4/9 for case-control and 9/9 for cohort studies using the original NOS, and 7.2/10 for cross-sectional studies using the modified NOS. A breakdown of scores is available as supplementary data. Half of the studies assessed the exposure using interviews, allowing for the possibility of recall and selection bias, as engaged patients are more likely to participate (Delgado-Rodriguez & Llorca, 2004). Although nearly all the interviews were structured, none of the studies reported whether interviewer blinding took place, allowing for possibility of interviewer bias. Most studies were European/North American, with a third by Carmichael drawing data from the same US populations (but it is important to note that there was no overlap in study participants between the Carmichael studies). This may introduce some geographical bias to the results. A funnel plot and Egger test showed that the magnitude of study estimates were associated with the sample sizes of the studies (P=0.001), indicating the possibility of publication bias (Figure 2).

[FIGURE 2]

Figure 2: Funnel plot of all 12 included studies. (Circles indicate studies on personal exposures, triangles indicate studies on population-level exposures)

Cleft lip with or without cleft palate (CL/P)

Eight studies reported ORs for CL/P, unadjusted for any other factor (Figure 3). Overall, there was some evidence that stressful events during the periconceptional period were associated with greater odds of CL/P in the offspring (eight studies, OR 1.49, 95% CI 1.09, 2.03). However between-study heterogeneity was high (I^2 85.4%, 95% CI 76.8, 99.1, P=0.001). When stratified by exposure type, only personal stressful life events were associated with odds of CL/P (six studies, OR 1.63, 95% CI 1.16, 2.30), with no evidence that population-level events were associated with CL/P (two studies, OR 0.9, 95% CI 0.23, 3.54).

Four studies of personal life events reported ORs for CL/P after adjustment for various potential confounders listed in Table 1 (Figure 3). These adjusted results were in concordance with the unadjusted results, showing stressful life events were associated with a greater odds of CL/P (four studies, OR 1.33, 95% CI 1.01, 1.75). Between-study heterogeneity was high (total I^2 90.0, (95% CI 83.5, 99.9), but the direction of estimated effect was consistent.

[FIGURE 3]

Figure 3: Forest plots of CL/P incidence in exposed mothers relative to unexposed controls, stratified by exposure type

Cleft lip with cleft palate (CLP)

Two studies specifically reported results for CLP, unadjusted for any other factor. Overall, there was little evidence that stressful events during the periconceptional period were associated with greater odds of CLP in the offspring (two studies, OR 1.33, 95% CI 0.96, 1.84). Between-study heterogeneity was low (I^2 0%, 95% CI 0.0, 98.5, P=0.8).

One study reported CLP after adjustment for various potential confounders listed in Table 1. In concordance with the unadjusted results, very little evidence of association between stressful life events and CLP was shown (one study, OR 1.31, 95% CI 0.92, 1.86) (Ingstrup et al. 2013).

Cleft lip only (CLO)

Two studies reported ORs for CLO, unadjusted for any other factor. Overall, there was some evidence of stressful life events being associated with higher odds of CLO (OR 2.93), but the confidence interval was wide and crossed the null (CI 0.47, 18.44), so we can have little confidence in this association. Between-study heterogeneity was high (I^2 91.7%, 95% CI 58.2, 99.9, P=0.10).

One study reported ORs for CLO after adjustment for various potential confounders listed in Table 1. In concordance with the unadjusted results, no evidence for an association between stressful life events and CLO in the offspring was shown (one study, OR 1.19, 95% CI 0.47, 18.44) (Ingstrup et al., 2013).

Cleft palate only (CPO)

Seven studies reported ORs for CPO, unadjusted for any other factor (Figure 4). Overall, there was some evidence that stressful life events during the periconceptional period were associated with greater odds of CPO in the offspring (seven studies, OR 1.42, 95% CI 1.02, 1.98). Between-study heterogeneity was high (I^2 71.4%, 95% CI 17.2, 93.9, P=0.002). When stratified by exposure type, only personal stressful life events were associated with odds of CPO (six studies, OR 1.45, 95% CI 1.02, 2.06), with very little evidence that population-level events were associated with CL/P (one study, OR 0.92, 95% CI 0.22, 3.94).

Three studies on personal life events reported ORs for CPO after adjustment for various potential confounders listed in Table 1 (Figure 4). These adjusted results were not in concordance with the unadjusted results, showing no evidence of an association between stressful life events and CPO in the offspring (three studies, OR 1.07, 95% CI 0.89, 1.28). Between-study heterogeneity was moderate (I^2 50.4%, 95% CI 0.0, 99.2, P=0.1).

[FIGURE 4]

Figure 4: Forest plot of CPO incidence in exposed mothers relative to unexposed controls, stratified by exposure type

Unspecified cleft subtype

Four studies reported ORs for unspecified cleft subtype, unadjusted for any other factor (Figure 5). Overall, there was some evidence that stressful life events were associated with greater odds of any cleft subtype in the offspring (four studies, OR 1.40, 95% CI 1.17, 1.67). Between-study heterogeneity was low (I^2 0%, 95% CI 0.0, 87.8, P=0.6).

One study on personal life events reported ORs for any cleft subtype after adjustment for various potential confounders listed in Table 1 (Figure 5). In concordance with the unadjusted results, some evidence for an association between stressful life events and a greater odds of any cleft subtype in the offspring was shown (one study, OR 1.28, 95% CI 1.04, 1.59) (Ingstrup et al., 2013).

[FIGURE 5]

Figure 5: Forest plot of any cleft incidence in exposed mothers relative to unexposed controls, stratified by exposure type

Discussion

Key findings

Overall, our systematic review found weak positive associations between maternal stressful life events during the periconceptional period and odds of OFC in offspring. The association was stronger in studies of personal events than studies of population-level events. When stratified by OFC subtype, there was evidence of an association with CL/P and CPO unadjusted for potential confounders, as well as for unspecified OFC subtype. After adjustment for potential confounders, there was evidence of association only with CL/P, as well as unspecified OFC subtype. This discordance might be explained by a differential influence of maternal stressful life events on developing different OFC subtypes, or might be due to differences in statistical power to detect any association. Most of the included studies had a low-to-moderate risk of bias, however substantial asymmetry in the funnel plot indicated possible publication bias.

Comparison with existing studies

At the time of writing, there are two extant systematic reviews (Molina-Solana et al., 2013, Jafari et al. 2017) investigating the association between OFC and stressful life events. Both reviews found an association between stressful life events and OFC, which is in concordance with our findings. Both reviews included in the review by Molina-Solana et al. (2013) were also included in this present review. Jafari et al. (2017) included one study investigating maternal stress, however this was excluded from the present review as it was not published in the English language. Due to the low number of included studies in both reviews, they were considered insufficient to determine the presence or absence of association between stressful life events and OFC.

Strengths and limitations

This is the largest systematic review of its kind to date, providing a comprehensive analysis of the existing literature. This is also the first systematic review of its kind to collate the evidence for different cleft subtypes, which is important as there is evidence to suggest that these subtypes are aetiologically distinct. Assessment of both risk of bias of included studies and publication bias was also undertaken. The large sample sizes of included studies and broad selection of populations included contribute towards the generalisability of our findings.

There are also several limitations to the methodology of this review. Firstly, although no restrictions were placed on publication date, we excluded articles that were lacking sufficient data if they were published more than five years ago. Exclusion of grey literature may also have introduced publication bias to the findings, as small studies with negative findings were less likely to be included. Furthermore, studies which could not be accessed online or were not published in the English language were excluded. The resources required to access or translate these studies was thought to outweigh their possible impact. It is unclear whether, had they met the eligibility criteria, these studies would have changed the conclusions of our review. Secondly, studies were assessed to have low-moderate risk of bias using the NOS. However, it should be noted that half of the included studies did not adjust for confounding factors. The NOS may be insufficiently rigorous in assessing comparability, as it allocates only two additional points for adjusting for confounding factors. Therefore, findings should be interpreted with caution.

Moreover, there were also several limitations to the available evidence. Firstly, although our broad eligibility criteria enabled us to meta-analyse 12 studies, this meant including studies that employed a wide range of methodologies to study several different types of stressful life event defined in different ways. Therefore, heterogeneity between studies was generally high. However, results were generally concordant between analyses stratified by either population- or personal-level stressful life events. Further investigation of heterogeneity, such as subgroup analysis or meta-regression, was not considered appropriate due to the small number of available studies for each OFC subtype. Secondly, we also found generally concordant results

with different subtypes of OFC, although ability to assess OFC subtype-specific associations was limited by how results have been generated and reported in previous studies, with most studies combining CLO and CLP into CL/P. Finally, findings of possible publication bias should be interpreted with caution due to the low number of included studies.

Implications for research and clinical care

Currently, formal screening for life event stress is not routinely carried out at antenatal appointments in the United Kingdom National Health Service (National Health Service, 2016). As experience of stressful life events is largely non-modifiable, interventions regarding avoidance of stressful life events in the periconceptional period may not be useful. Instead, a better understanding of their association with OFC may be used for improved management of these anomalies.

Although this systematic review finds a weak association between stressful life events and OFC, the limitations discussed should highlight the need for caution when interpreting these results. When considered alongside the various sources of bias affecting the included studies, as well as the relatively small and heterogenous dataset, there is insufficient evidence to justify any changes to the current management of pregnant women to reduce OFC prevalence. There is a need for further research in this area before changes to clinical practice can be advised.

In conclusion, this systematic review finds a weakly positive association between stressful life events during the periconceptional period and risk of OFC in the offspring, however further evidence with greater consistency in research design is needed.

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Table 1: Characteristics of included studies, by year of studies

First author	Country	Purpose	Design	Number of participants	Sampling method	Recruitment/response rate	Exposure	Timing of exposure	Comparison group	OFC subtype	Adjusting factors	Funding	NOS score
Studies investigating personal events													
Fraser, 1964	Canada	Assess association between stressful life events and birth defects	Case-control	527*	Convenience, single centre	(interview)	Any stressful life event	First trimester	No reported experience of stressful life events	CL/P, CPO	None reported	Not reported	4
Blomberg, 1980	Sweden	Assess association between denied abortion and OFC	Cross-sectional	2554	Multicentre; parish offices	Not reported	Denied abortion	First trimester	No experience of seeking abortion	CPO	None reported	Not reported	5
Carmichael, 2000	USA	Assess association between stressful life events and birth defects	Case-control	850*	Multicenter; hospitals and genetic counselling centres	97% cases, 97% controls (interview)	Any of 3 stressful life events (Bereavement, relationship breakdown, job loss)	1 month preconception to end of first trimester	No experience of 3 specific stressful life events	CL/P, CPO	Ethnicity, education, smoking, binge drinking vitamin supplement intake, folate consumption, obesity, age, corticosteroid intake, presence of uncommon allele for TGF-a	University grant	8
Carmichael, 2007	USA	Assess association between maternal stressful life events and birth defects	Case-control	920*	Multicenter; all hospitals and genetic counselling centres in 3	80% cases, 77% controls (interview)	Any of 18 stressful life events (Job loss, illness/injury, legal/financial	2 months preconception to 2 months post conception	No experience of 18 specific stressful life events	CL/P, CPO	Maternal ethnicity, education, BMI, age, smoking, alcohol, folic acid intake, vitamin	NIH & university grant, CDC cooperative agreement	7

					counties		problems, drinking/drug problems, immigration problems, violence/crime, bereavement, relationship difficulty, serious disagreements)				supplement intake, chronic environmental stress: neighbourhood crime, food insecurity		
Ingstrup, 2013	Denmark	Assess association between antenatal bereavement and OFC	Cohort	1771663	Registry (national)	99.9% cases, 100% controls	Maternal bereavement	12 months preconception to end of first trimester	No experience of bereavement	Any cleft, CL/P, CPO, CLP CLO	Parental age, education, income, parity, cohabitation, place of residence, smoking, birth year	Research grant	9
Carmichael, 2014	USA	Assess association between stressful life events and social support and birth defects	Case-control	3387*	Registry (8 states)	63% cases, 60% controls (interview)	Any of 7 stressful life events (relationship difficulty, legal/financial problems, violence/crime, illness/injury, relative's death)	3 months preconception to end of first trimester	No experience of 7 specific stressful life events	CL/P, CPO	Maternal ethnicity, age, BMI, smoking, alcohol, folic acid intake, mineral supplement intake, social support	NIH & university grant, CDC cooperative agreement	7
Hao, 2015	China	Assess association between various intrauterine exposures and OFC	Case-control	617	Multicenter; 3 hospitals	(interview)	Any of 5 stressful life events (relationship difficulty, legal/financial problems,	1 month preconception to end of first trimester	No experience of 5 specific stressful life events	CL/P, CPO	Maternal Age, sex of offspring, parental education, annual household income, parity, gravidity,	Government grant	6

							violence/crime, illness/injury, relative's death)				maternal BMI, history of negative reproduction		
Chincharadze, 2017	Georgia	Assess association between various intrauterine exposures and OFC	Case-control	102	Multicentre, maternity houses	Not reported	History of stressful situation	1 month preconception to end of first trimester	No experience of stressful situation	CL/P	None reported	Not reported	6
Studies investigating population-level events													
Montenegro, 1995	Chile	Observe monthly OFC incidence in year of earthquake – then simulating in mice	Cross-sectional	9842	Multicentre; 3 public hospitals	Not reported	Santiago earthquake	Conception to end of pregnancy	No experience of Santiago earthquake	Any cleft	None reported	Not reported	7
Tan, 2009	China	Compare birth defect incidence before and after earthquake	Cross-sectional	13003*	Multicenter; all hospitals in 2 counties	Not reported	Wenchuan earthquake	15 months preconception to end of pregnancy	No experience of Wenchuan earthquake	CL/P	None reported	Government grant	8
Goenjian, 2011	USA	Compare OFC incidence before and after hurricane	Cross-sectional	47412	Registry (regional)	Not reported	Hurricane Katrina	Conception to end of pregnancy	No experience of Hurricane Katrina	Any cleft	None reported	Not reported	8
Jahanabin, 2013	Iran	Compare OFC incidence during and after war	Cross-sectional	101435	Multicenter; 6 hospitals	'Most cases' from 1 location in exposed group missing data	Iran-Iraq war		No experience of Iran-Iraq war	Any cleft, CL/P, CPO, CLP, CLO	None reported	University grant	8

*where studies have investigated birth defects other than cleft, the non-cleft cases have been excluded

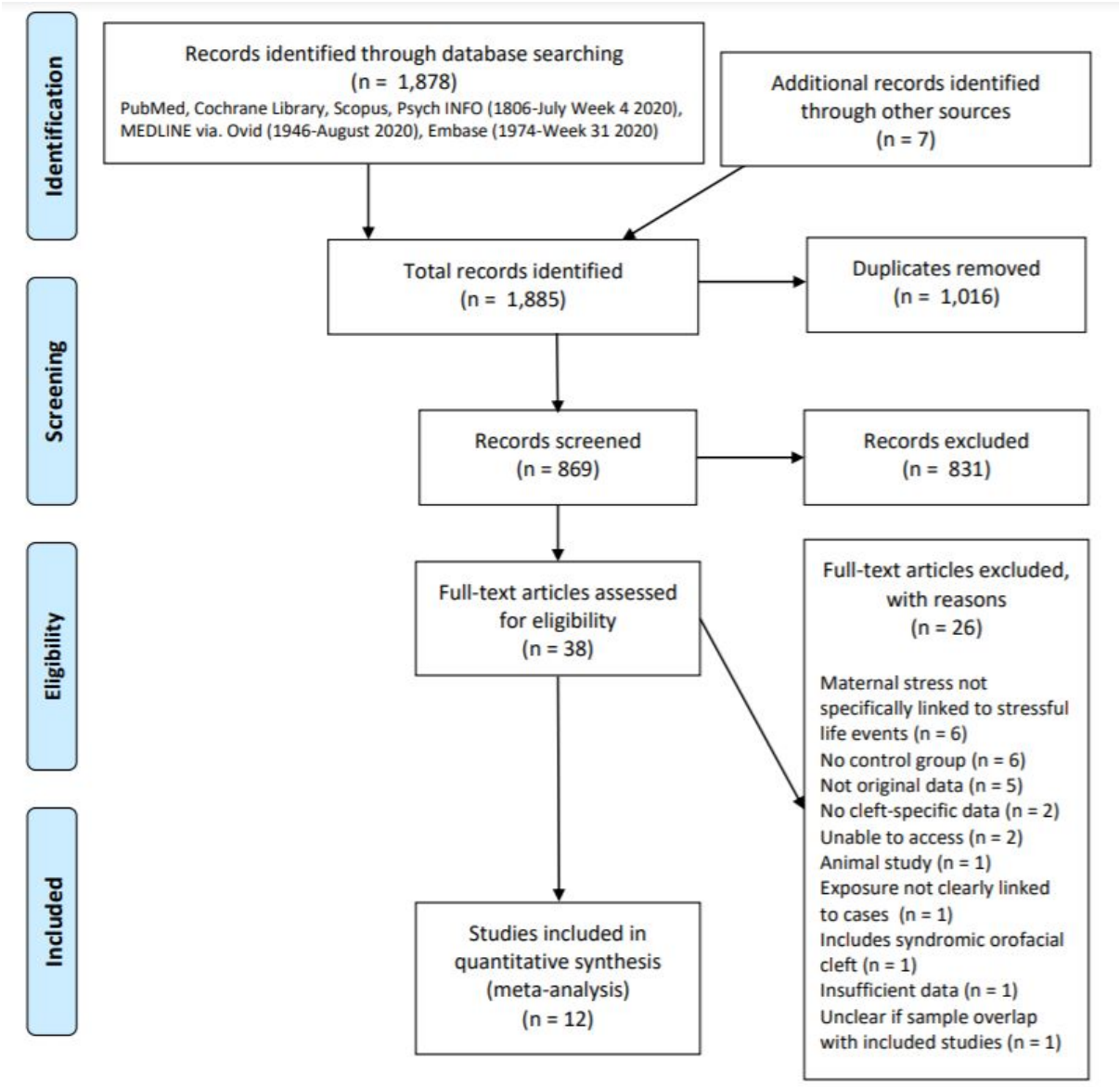

Figure 1: Systematic search results for studies examining the effect of maternal stressful life events during the periconceptional period and OFC in the offspring.

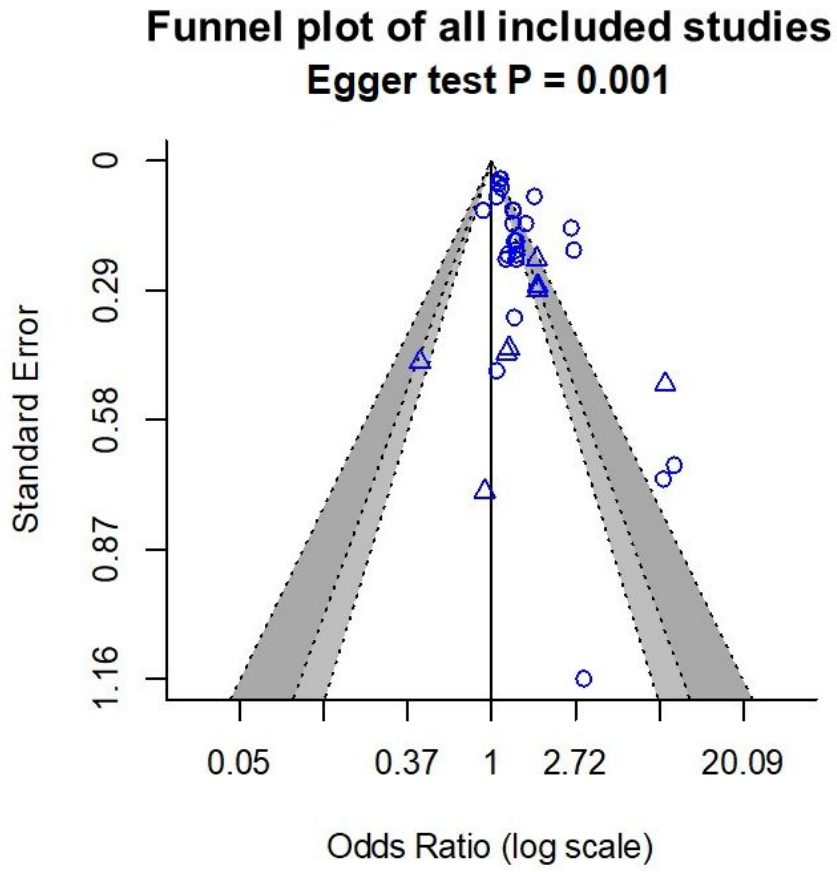

Figure 2: Funnel plot of all 12 included studies. (Circles indicate studies on personal exposures, triangles indicate studies on population-level exposures)

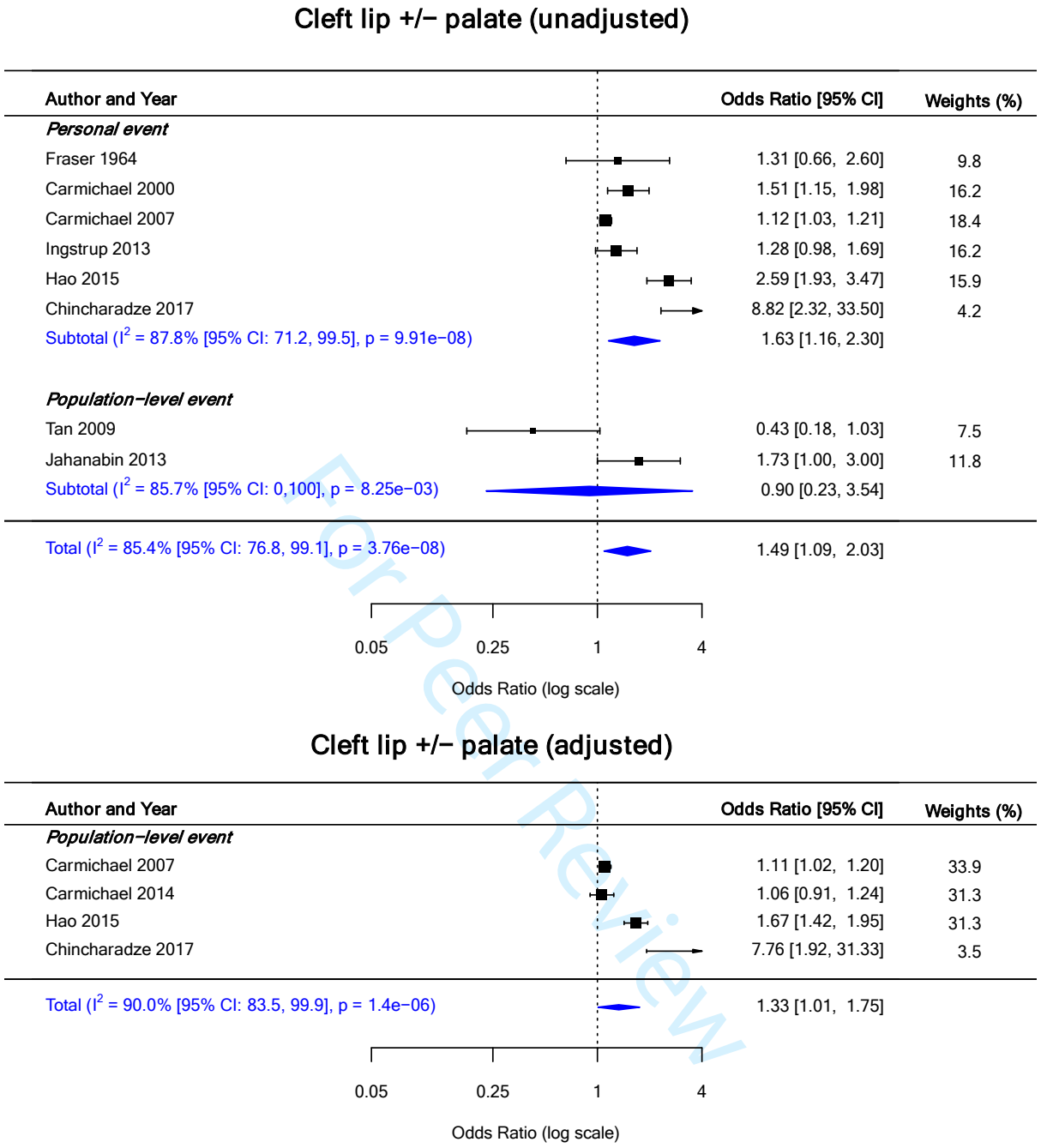

Figure 3: Forest plots of CL/P incidence in exposed mothers relative to unexposed controls, stratified by exposure type

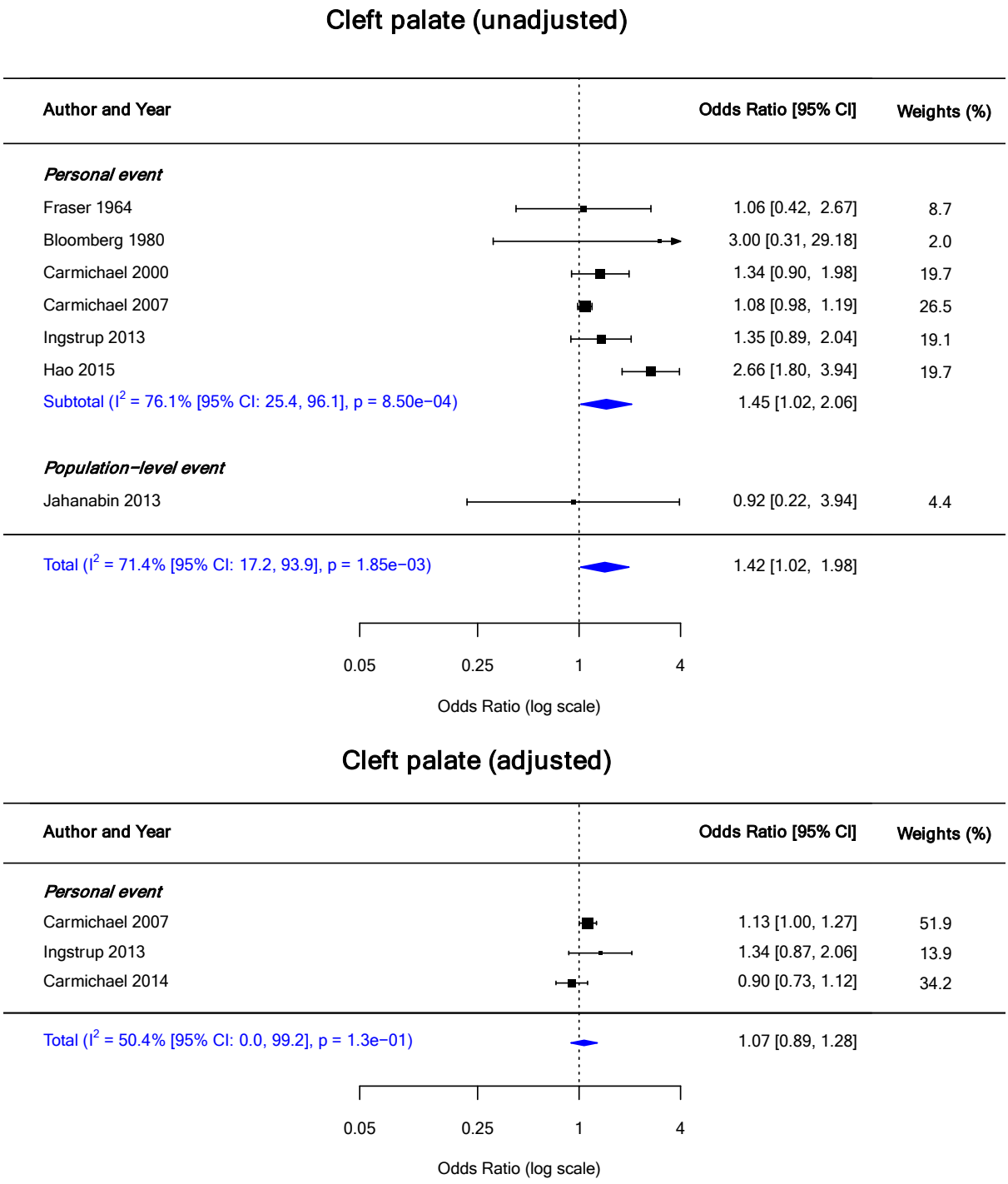

Figure 4: Forest plot of CPO incidence in exposed mothers relative to unexposed controls, stratified by exposure type

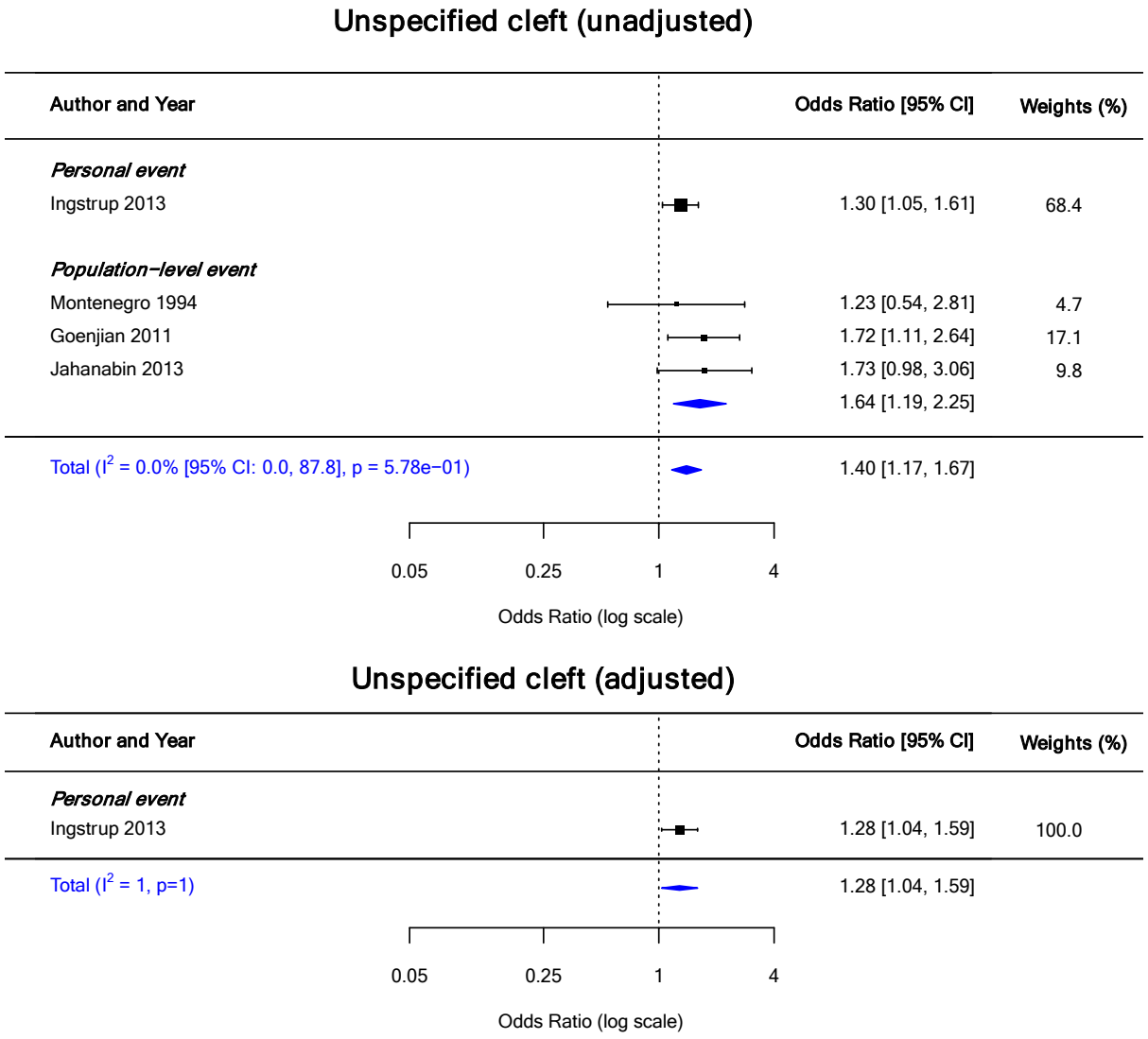

Figure 5: Forest plot of any cleft incidence in exposed mothers relative to unexposed controls, stratified by exposure type

Supplemental data:

Document 1: Unpublished review protocol
Table 1: List of studies excluded after full text screening, with reason for exclusion
Table 2: Breakdown of Newcastle-Ottawa scores of included studies

Document 1: Unpublished review protocol

Review title: Maternal stressful life events during the periconceptional period and orofacial clefts: a systematic review and meta-analysis

Anticipated start date: 11/08/2017
Anticipated completion date: 31/08/2017
Named contact: Christina Tran
Named contact email: christinat.bristol@gmail.com
Named contact address: University of Bristol, Beacon House, Queens Road, Bristol, BS8 1QU
Organisational affiliation of the review: University of Bristol Dental School, INSPIRE, The Cleft Collective, MRC Integrative Epidemiology Unit
Review team members and their organisational affiliations:
Funding sources/sponsors:
Conflicts of interest: None
Review question: Are women who experience stressful life events around the time of conception at higher risk of giving birth to a baby with an orofacial cleft?
Searches: PubMed, The Cochrane Library, Scopus, PsycINFO, Medline, EMBASE
Search strategy: : ("stress" OR "life event" OR "traumatic event" OR "life change" OR "stressful event" OR "life experience") AND ("cleft lip" OR "cleft palate" OR "cleft lip and palate" OR "orofacial cleft")
Condition or domain being studied: Any type of orofacial cleft, including cleft lip and palate, cleft lip only, cleft palate only
Participants/population: Women who have given birth to a child with or without orofacial cleft
Interventions/exposures: Any stressful life event, population-level (eg. Natural disasters, war) or personal level (eg. Bereavement, job loss, relationship difficulty, etc.) occurring during the periconceptional period (any time period defined as peri-conceptional accepted)
Comparators: Women who did not experience any stressful life event in the periconceptional period
Types of study to be included: Case-control, cross-sectional, cohort
Main outcomes: Incidence of orofacial cleft in offspring
Measures of effect: Odds ratios for odds of cleft in exposed mothers relative to unexposed controls.
Data extraction: Standardised, pre-piloted form in Microsoft Excel. To extract: First author, country purpose, design, number of participants, sampling method, recruitment/response rate, exposure, timing of exposure, comparison group, cleft subtype, adjusting factors, funding, NOS score,

Risk of bias assessment: Newcastle-Ottawa scale for case-control and cohort studies, modified Newcastle-Ottawa scale (Herzog et al., 2013) for cross-sectional studies.
Strategy for data synthesis: Meta-analysis with R. Random effects model. Odds ratios and 95% confidence intervals visually examined with forest plots. Heterogeneity assessed using Cochran Chi^2 test and the I^2 statistic.
Analysis of subgroups or subsets: Each cleft subtype to be analysed separately: cleft lip with/without palate, cleft palate only, cleft lip only, cleft lip and palate, unspecified cleft subtype. Studies on personal-level and population-level exposures to be analysed separately. Unadjusted results analysed separately to results adjusted for confounding factors.

Table 1: List of studies excluded after full text screening, with reason for exclusion

Study reference	**Reason for exclusion**
Fathallah, 2007	No control group
Graeme et al., 2010	
Hozyasz et al., 2009	
Jagomagi et al., 2010	
Strean and Peer, 1956	
Wallace et al., 2019	
Altoe et al., 2020	Maternal stress not specifically linked to stressful life events
Carmichael et al., 2007	
Larsen et al., 2014	
Saxen et al., 1975	
Saxen, 1974	
Burdof et al., 2006	Not original data
Hozyasz et al., 2005	

Molina-Solana et al., 2013	
Saxen, 1975	
Shkoukani et al., 2013	
Carter and Kostaras, 2005	No cleft-specific data
Hansen et al., 2000	
Schaller at al., 1981	Unable to access
Shu et al., 2010	
McDonald et al., 1961	Insufficient data
Phyu et al., 2020	Includes syndromic orofacial cleft
Fraser et al., 1966	Animal study
Xia et al., 2015	Exposure not clearly linked to cases
Xu et al., 2017	Maternal stress not specifically linked to stressful life events

Table 2: Breakdown of Newcastle-Ottawa scores of included studies

Case control studies:										
	Selection				Comparability			Exposure		
	Adequate case selection	Representativeness of cases	Selection of controls	Definition of controls	Study controls of most important factor	Study controls for any additional factor	Ascertainment of Exposure	Similar ascertainment for cases and controls	Non-response rate	Total score (/9)
Fraser, 1964	0	0	1	1	0	0	1	1	0	4
Carmichael, 2000	1	1	1	1	1	1	0	1	1	8
Carmichael, 2007	1	1	0	1	1	1	0	1	1	7
Carmichael, 2013	1	0	1	1	1	1	0	1	0	6
Carmichael, 2014	1	1	1	1	1	1	0	1	1	8
Hao, 2015	1	1	0	1	1	1	0	1	0	6
Chinchara dze, 2017	1	1	0	1	1	1	0	1	0	6
Cohort studies:										
	Selection				Comparability		Outcome			
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest not	Study controls for most important factor	Study controlled for any additional factor	Assessment of outcome	Adequate follow-up period	Adequacy of follow-up	Total score (/9)

				present at start of study						
Ingstrup, 2013	1	1	1	1	1	1	1	1	1	9
Cross-sectional studies:										
	Representativeness of sample	Sample size	Non-respondents	Ascertainment of exposure	Study controls for most important factor	Study controls for any additional factor	Assessment of outcome	Statistical test		Total score (/10)
Blomberg, 1980	0	1	0	2	0	0	2	0		5
Montenegro, 1995	1	1	1	2	0	0	2	0		7
Tan, 2009	1	1	1	2	0	0	2	1		8
Goenjian, 2011	1	1	1	2	0	0	2	1		8
Jahanabin, 2013	1	1	1	2	0	0	2	1		8