

First-Trimester Influenza Infection Increases the Odds of Non-Chromosomal Birth Defects: A Systematic Review and Meta-Analysis

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Table S1. PRISMA 2020 checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|-------------------------------|--------|--|---------------------------------|
| TITLE | | | |
| Title | 1 | Identify the report as a systematic review. | 1-4 |
| ABSTRACT | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | 20-33 |
| INTRODUCTION | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 37-68 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 69-76 |
| METHODS | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 94-110 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 87-89 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 89-92, Supplementary Material |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 94-103, Supplementary Material |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 111-119 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 99-119 |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 99-119 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 143-148 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | 121-141 |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). | 121-141 |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|-------------------------------|--------|--|---|
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 121-141 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 121-141 |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 121-141 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | 121-141 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | 121-141 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 121-141 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | 149-152 |
| RESULTS | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | 154-173 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | 154-173 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | Table 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | 262-268, Supplementary Material Figure S4-S14 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | 176-261 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | 176-261 |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 176-261 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | 176-261 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | 176-261 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | 262-268, Supplementary Material Figure S4-S14 |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|--|--------|--|--|
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | 267-268, Supplementary Material Table S5 |
| DISCUSSION | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 269-330 |
| | 23b | Discuss any limitations of the evidence included in the review. | 331-343 |
| | 23c | Discuss any limitations of the review processes used. | 331-343 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | 344-351 |
| OTHER INFORMATION | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | 82-85 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 82-85 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | 85 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | 369 |
| Competing interests | 26 | Declare any competing interests of review authors. | 376 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | 357-358, 374-375 |

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: <http://www.prisma-statement.org/>

Table S2. MOOSE Checklist for Meta-analyses of Observational Studies

| Item No | Recommendation | Reported on Page No |
|---|--|---------------------------------------|
| Reporting of background should include | | |
| 1 | Problem definition | 1-2 |
| 2 | Hypothesis statement | 2 |
| 3 | Description of study outcome(s) | 2-3 |
| 4 | Type of exposure or intervention used | 2-3 |
| 5 | Type of study designs used | 2-3 |
| 6 | Study population | 2-3 |
| Reporting of search strategy should include | | |
| 7 | Qualifications of searchers (eg, librarians and investigators) | 3 |
| 8 | Search strategy, including time period included in the synthesis and key words | 3, Supplementary Material Appendix S1 |
| 9 | Effort to include all available studies, including contact with authors | 3 |
| 10 | Databases and registries searched | 2 |
| 11 | Search software used, name and version, including special features used (eg, explosion) | 2 |
| 12 | Use of hand searching (eg, reference lists of obtained articles) | 3 |
| 13 | List of citations located and those excluded, including justification | 3 |
| 14 | Method of addressing articles published in languages other than English | 3 |
| 15 | Method of handling abstracts and unpublished studies | 3 |
| 16 | Description of any contact with authors | 3 |
| Reporting of methods should include | | |
| 17 | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | 3 |
| 18 | Rationale for the selection and coding of data (eg, sound clinical principles or convenience) | 3 |
| 19 | Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability) | 3 |
| 20 | Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) | 3 |
| 21 | Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results | 3-4 |
| 22 | Assessment of heterogeneity | 3 |
| 23 | Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated | 3 |
| 24 | Provision of appropriate tables and graphics | 3 |
| Reporting of results should include | | |
| 25 | Graphic summarizing individual study estimates and overall estimate | 9-12 |
| 26 | Table giving descriptive information for each study included | 6 |
| 27 | | |
| 28 | Indication of statistical uncertainty of findings | 12, Supplementary |

Table S3. Table of included studies with outcomes

| Author, year | Congenital malformations |
|----------------------------|--|
| L. Ács et al. 2020[1] | Cleft palate |
| Ács et al. 2005[2] | Neural tube defects; Cleft lip/palate; Cleft palate; Esophageal atresia; Pyloric stenosis; Intestinal atresia/ stenosis; Rectal/anal stesia/stenosis; Renal a/dysgenesis; Obstructive urinary Cas; Hypospadiasis; Undescended testis; Exomphalos/gastroschisis; Congenital hydrocephaly, Ear CAs, Cardiovascular CAs, Clubfoot, Limb reduction defects, Poly/syndactilia, Diaphragmatic CAs, Other Isolated CAs, Multiple CAs |
| Aro et al. 1983[3] | limb reduction defects |
| Botto et al. 2001[4] | Congenital heart defects, Transposition of great arteries, Tetralogy of Fallot, Atrioventricular septal defect, Ebstein anomaly, Anomalous pulmonary venous return, All right obstructive defects, Tricuspid atresia, All left obstructive defects, Hypoplastic left heart, Aortic stenosis, Aortic coarctation, Ventricular septal defect, Atrial septal defect |
| Busby et al. 2005[5] | Anophtalmia, Micophtalmia |
| Czeizel et al. 2008 [6] | Neural-tube defects, Anencephalus+-spina bifida, Spina bifida aperta/cystica, Encephalocele, occipital, Microcephaly, primary, Congenital hydrocephalus, CAs of eye, Anophthalmia–microphthalmia, Primary congenital glaucoma, Congenital cataract, Ocular coloboma, CAs of ear, Auditory canal+ear Cas, An/microtia, Others, unspecified, Cardiovascular CAs, Transposition of great vessels, Ventricular septal defect, Atrial septal defect, type II, Hypoplastic left heart, Patent ductus arteriosus, CAs of aorta, CAs of pulmonary valve, Others or unspecified, Brachial cyst, cleft, fistula, preauricular sinus, CAs of respiratory system, Cleft palate, Robin sequence, Cleft lip+-cleft palate, Cleft lip, Cleft lip with palate, Esophageal atresia/stenosis with or without tracheoesophageal fistula, Cong hypertrophic pyloric stenosis, Atresia/stenosis of small intestine, Atresia/stenosis of rectum/anal canal, Other CAs of digestive system, Hirschprung's disease, Other CAs of intestine, Other CAs of digestive system, Undescended testis (diagnosed after 3rd postnatal month), Hypospadias (without coronal type), Other CAs of genital organs, Renal a/dysgenesis, Obstructive CAs of urinary tract, Cystic kidney (diseases), Obstructive CAs of renal pelvis and ureter (hydronephrosis, constriction of ureteropelvic junction and ureterovesical orifice) , Other CAs of urinary tract, Other CAs of kidney, Other CAs of bladder and urethra, Clubfoot, Poly/syndactyly, Polydactyly, Syndactyly (without minor), Limb deficiencies, Other CAs of limbs, |

| | |
|-------------------------|---|
| | CAs of diaphragm, CAs of abdominal wall (exomphalos and gastroschisis are not differentiated), Multiple CAs (major gene mutations and chromosomal aberrations are excluded) |
| Dymanus et al. 2019[7] | Cleft lip |
| Granroth 1978[8] | Anencephalia, Spina bifida, Congenital hydrocephaly, Microcephaly, Hydrancephaly, Polydactylia |
| Li et al. 2014[9] | All congenital heart defects, Septal defects, Conotruncal defects, Right-sided obstructive defects, Left-sided obstructive defects, Anomalous pulmonary venous return, Other isolated CAs |
| Lynberg et al. 1994[10] | Anencephalia, Spina bifida, Encephalocele |
| Ou et al. 2015[11] | Cardiovascular CAs, Ventricular septal defect, Atrial septal defect, Pulmonary stenosis, Dextro-transposition of great arteries, Tetralogy of Fallot |
| Park et al. 1993[12] | Anencephalia, Spina bifida |
| Saxen et al. 1975[13] | Cleft lip and palate |
| Saxen et al. 1975[14] | Cleft lip and palate |

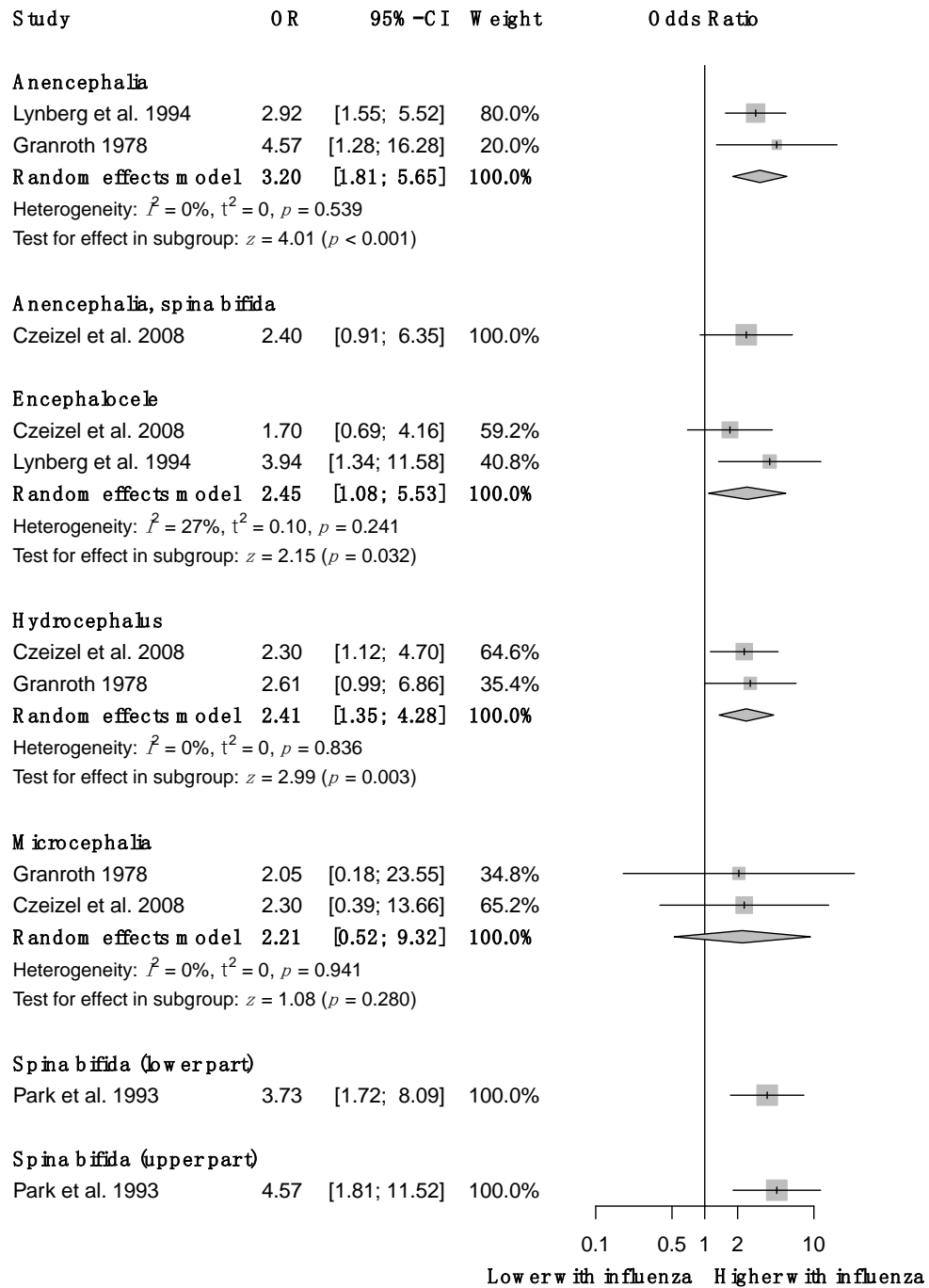


Figure S1. Forest plot representing that the odds for developing specific types of neural tube defects was increased after influenza in the first trimester.

Table S4. The odds ratios for developing specific types of congenital malformations after first trimester

| Author, year | Congenital malformations | Odd ratios |
|-------------------------|---|-------------------|
| Ács et al 2005 [2] | Esophageal atresia | 1.20 (0.20–6.30) |
| Ács et al 2005 [2] | Pyloric stenosis | 2.10 (0.20–7.00) |
| Ács et al 2005 [2] | Intestinal atresia/ stenosis | 3.00 (0.60–13.60) |
| Ács et al 2005 [2] | Rectal/anal stesia/stenosis | 0.70 (0.20–3.00) |
| Ács et al 2005 [2] | Renal a/dysgenesis | 1.50 (0.20–10.00) |
| Ács et al 2005 [2] | Obstructive urinary Cas | 1.20 (0.40–3.60) |
| Ács et al 2005 [2] | Hypospadias | 1.00 (0.70–1.40) |
| Ács et al 2005 [2] | Undescended testis | 0.70 (0.40–1.20) |
| Ács et al 2005 [2] | Exomohalos/gastrischisis | 1.70 (0.50–5.10) |
| Ács et al 2005 [2] | Clubfoot | 1.10 (0.70–1.70) |
| Ács et al 2005 [2] | Poly/syndactilia | 1.00 (0.60–1.60) |
| Ács et al 2005 [2] | Diaphragmatic Cas | 1.40 (0.40–4.50) |
| Ács et al 2005 [2] | Other isolated CAs | 1.30 (0.80–2.20) |
| Ács et al 2005 [2] | Multiple CAs | 1.50 (0.80–2.60) |
| Ács et al 2005 [2] | Total cases | 1.40 (1.30–1.60) |
| Czeizel et al. 2008 [6] | Primary congenital glaucoma | 2.00 (0.20–22.00) |
| Czeizel et al. 2008 [6] | Congenital cataract | 3.00 (0.60–14.90) |
| Czeizel et al. 2008 [6] | Ocular coloboma | |
| Czeizel et al. 2008 [6] | Brachial cyst, cleft, fistula, preauricular sinus | 0.90 (0.10–10.30) |
| Czeizel et al. 2008 [6] | CAs of respiratory system | |
| Czeizel et al. 2008 [6] | Cleft palate | 2.50 (1.40–4.30) |
| Czeizel et al. 2008 [6] | Robin sequence | 2.40 (0.20–39.7) |

| | | |
|-------------------------|---|-------------------|
| Czeizel et al. 2008 [6] | Cleft lip+-cleft palate | 2.90 (2.10–4.10) |
| Czeizel et al. 2008 [6] | Cleft lip | 2.40 (1.40–4.00) |
| Czeizel et al. 2008 [6] | Cleft lip with palate | 3.40 (2.20–5.30) |
| Czeizel et al. 2008 [6] | Esophageal atresia/stenosis with or without tracheoesophageal fistula | 1.70 (0.60–4.80) |
| Czeizel et al. 2008 [6] | Cong hypertrophic pyloric stenosis | 1.10 (0.40–3.00) |
| Czeizel et al. 2008 [6] | Atresia/stenosis of small intestine | 5.30 (1.40–20.20) |
| Czeizel et al. 2008 [6] | Atresia/stenosis of rectum/anal canal | 0.90 (0.30–2.40) |
| Czeizel et al. 2008 [6] | Other CAs of digestive system | 2.70 (1.10–6.60) |
| Czeizel et al. 2008 [6] | Hirschprung's disease | 3.00 (0.30–35.80) |
| Czeizel et al. 2008 [6] | Other Cas of intestine | 2.50 (0.90–7.30) |
| Czeizel et al. 2008 [6] | Other CAs of digestive system | 3.20 (0.30–36.60) |
| Czeizel et al. 2008 [6] | Undescended testis (diagnosed after 3rd postnatal month) | 0.50 (0.30–0.80) |
| Czeizel et al. 2008 [6] | Hypospadias (without coronal type) | 1.00 (0.80–1.40) |
| Czeizel et al. 2008 [6] | Other CAs of genital organs | 2.30 (0.40–12.50) |
| Czeizel et al. 2008 [6] | Renal a/dysgenesis | 1.00 (0.30–3.40) |
| Czeizel et al. 2008 [6] | Obstructive CAs of urinary tract | 1.30 (0.60–3.10) |
| Czeizel et al. 2008 [6] | Cystic kidney (diseases) | 1.60 (0.60–4.30) |
| Czeizel et al. 2008 [6] | Obstructive CAs of renal pelvis and ureter | 0.80 (0.10–4.30) |

| | | |
|-------------------------|---|-------------------|
| | (hydronephrosis, constricture of ureteropelvic junction and ureterovesical orifice) | |
| Czeizel et al. 2008 [6] | Other CAs of urinary tract | 2.40 (0.90–6.40) |
| Czeizel et al. 2008 [6] | Other Cas of kidney | 2.10 (0.70–6.30) |
| Czeizel et al. 2008 [6] | Other Cas of bladder and urethra | 4.00 (0.40–44.10) |
| Czeizel et al. 2008 [6] | Clubfoot | 1.30 (0.90–1.80) |
| Czeizel et al. 2008 [6] | Poly/syndactyly | 1.10 (0.70–1.70) |
| Czeizel et al. 2008 [6] | Polydactyly | 1.00 (0.60–1.70) |
| Czeizel et al. 2008 [6] | Syndactyly (without minor) | 1.30 (0.70–2.60) |
| Czeizel et al. 2008 [6] | Limb deficiencies | 2.30 (1.30–4.10) |
| Czeizel et al. 2008 [6] | Other CAs of limbs | 0.30 (0.00–2.70) |
| Czeizel et al. 2008 [6] | CAs of diaphragm | 3.80 (1.40–10.20) |
| Czeizel et al. 2008 [6] | CAs of abdominal wall (exomphalos and gastroschisis are not differentiated) | 1.50 (0.60–3.80) |
| Czeizel et al. 2008 [6] | Multiple CAs (major gene mutations and chromosomal aberrations are excluded) | 2.20 (1.50–3.20) |

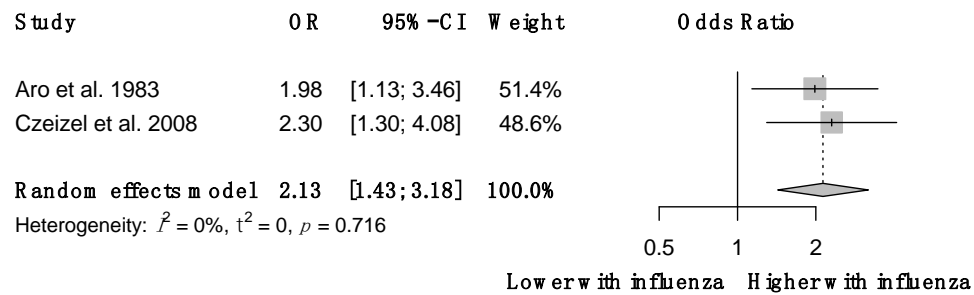


Figure S2. Forest plot representing that the adjusted odds for developing limb reduction defects was increased after influenza in the first trimester.

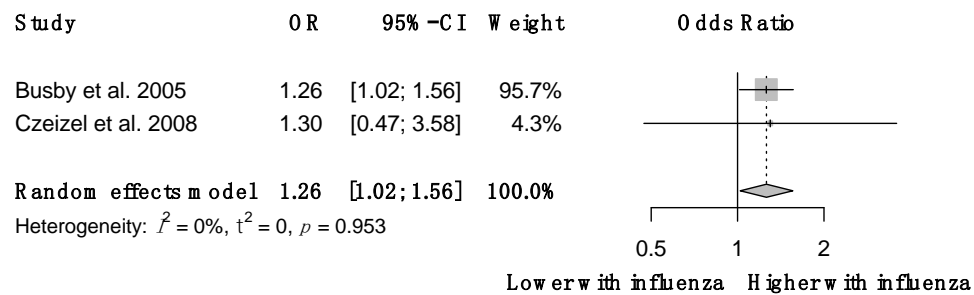


Figure S3. Forest plot representing that the adjusted odds for developing eye anomalies was increased after influenza in the first trimester.

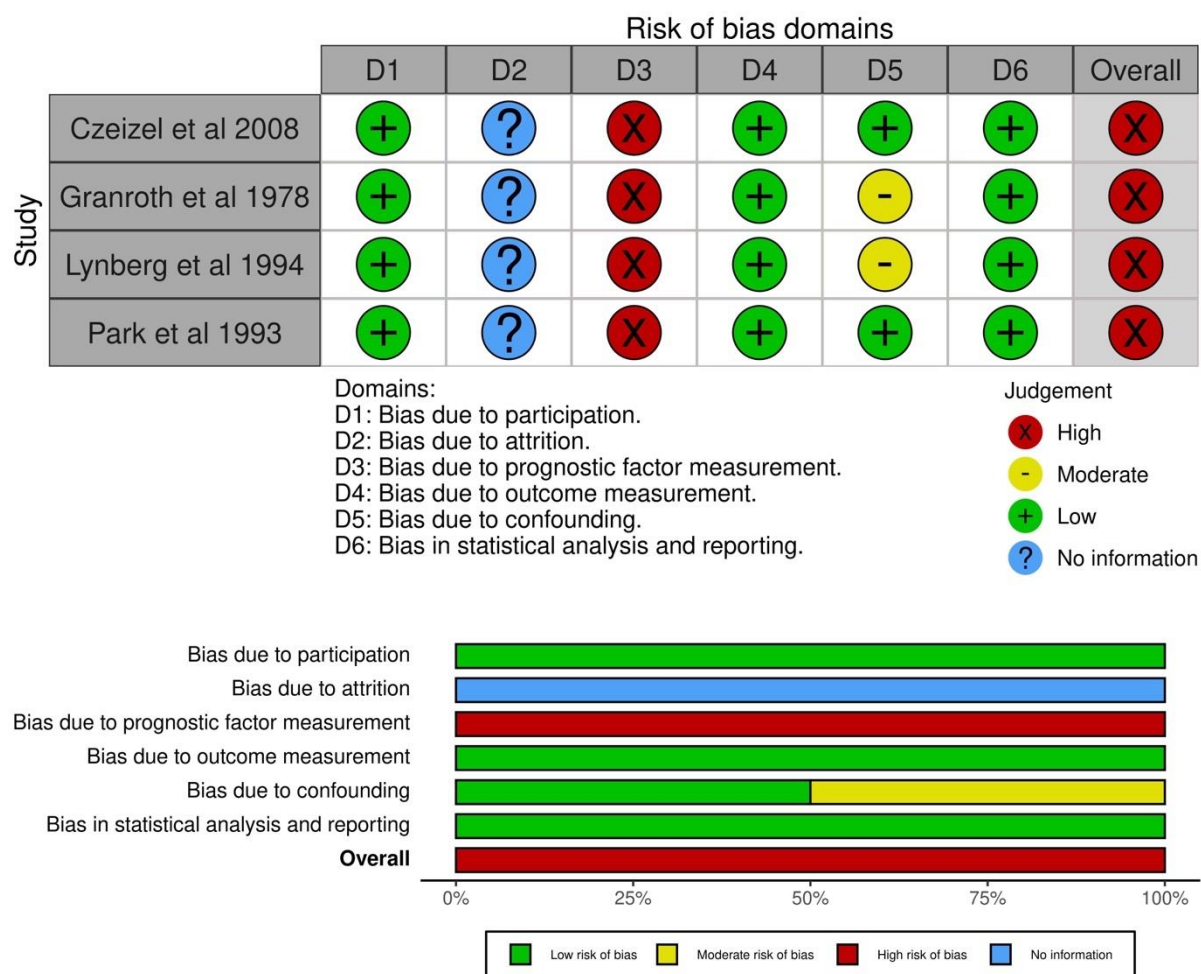


Figure S4. Risk of bias assessment at study and at domain level for all neural tube defects

Figure S5. Risk of bias assessment at study and at domain level for neural tube defects in the systematic review



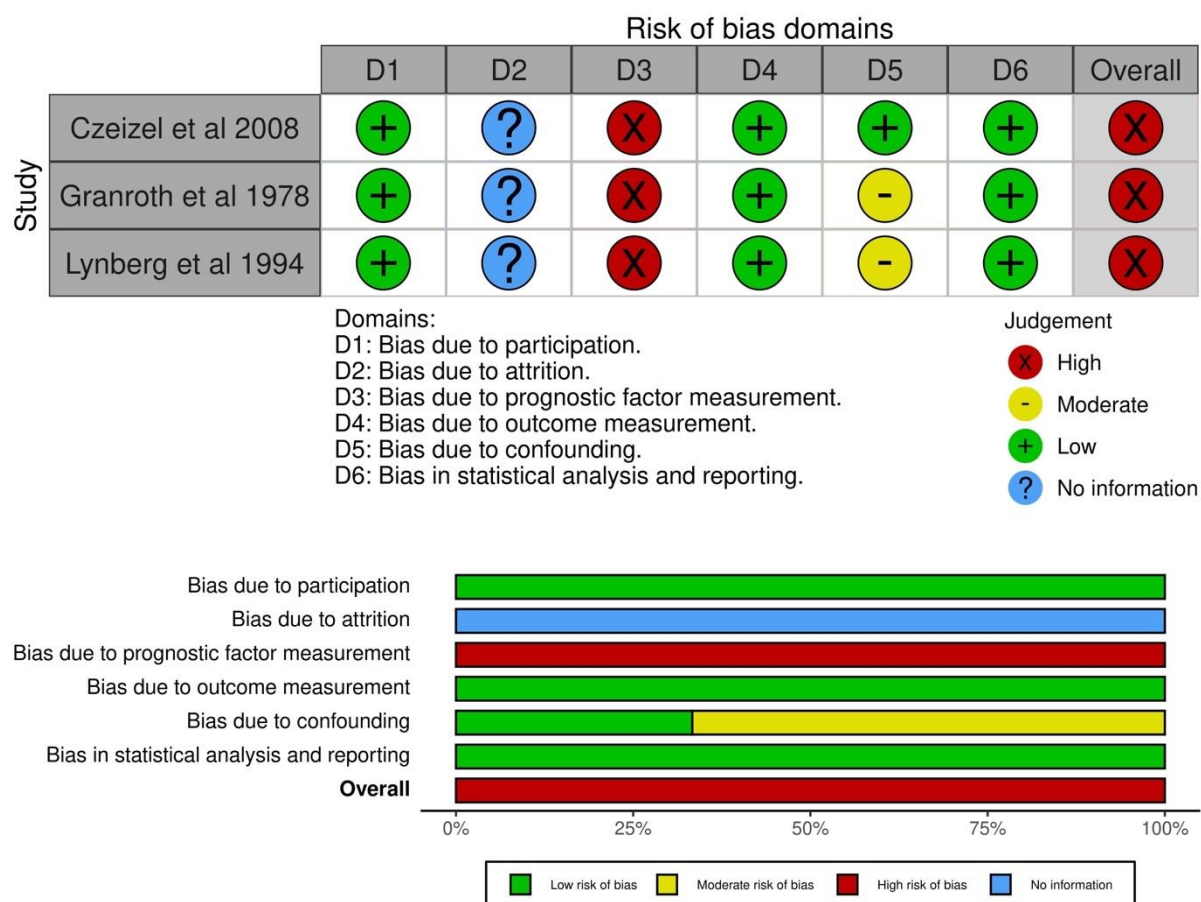


Figure S6. Risk of bias assessment at study and at domain level for spina bifida

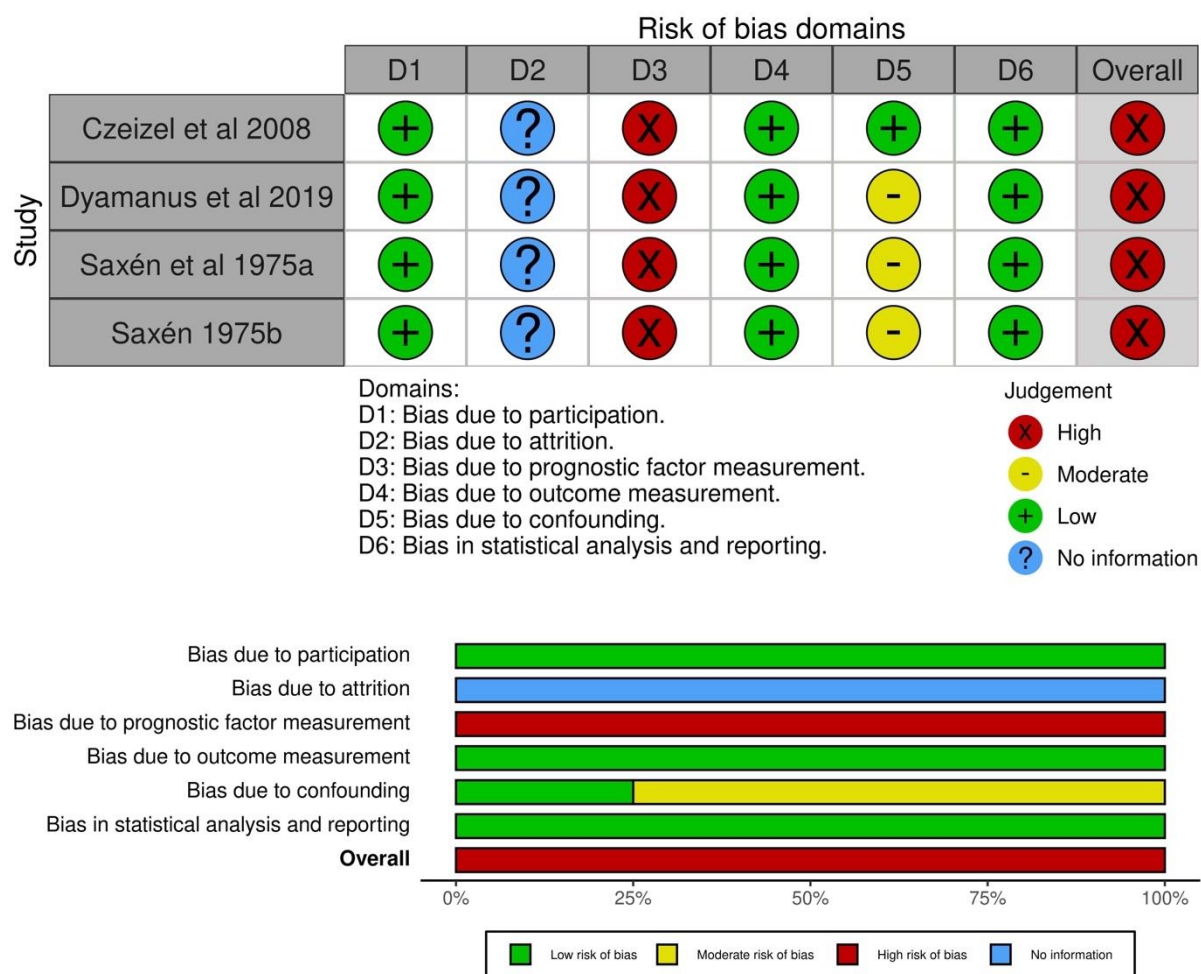


Figure S7. Risk of bias assessment at study and at domain level for cleft lip and palate

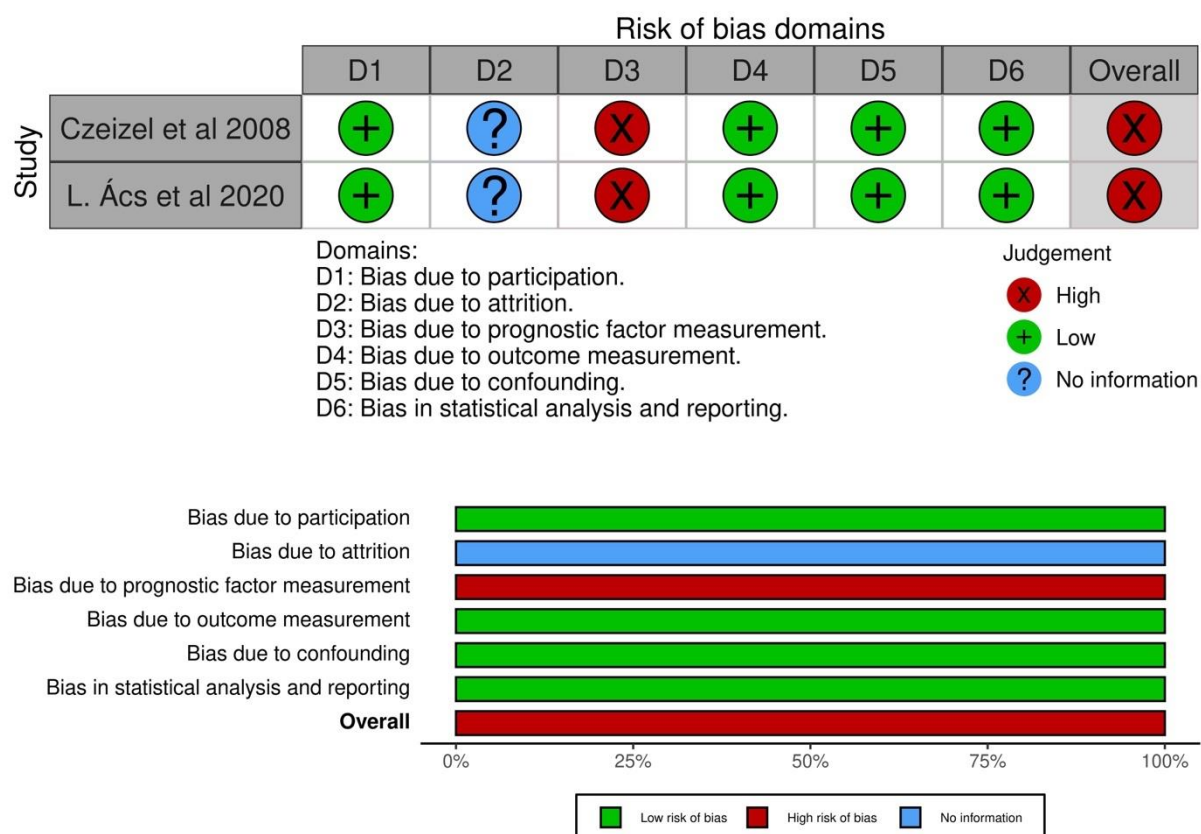


Figure S8. Risk of bias assessment at study and at domain level for cleft lip, palate

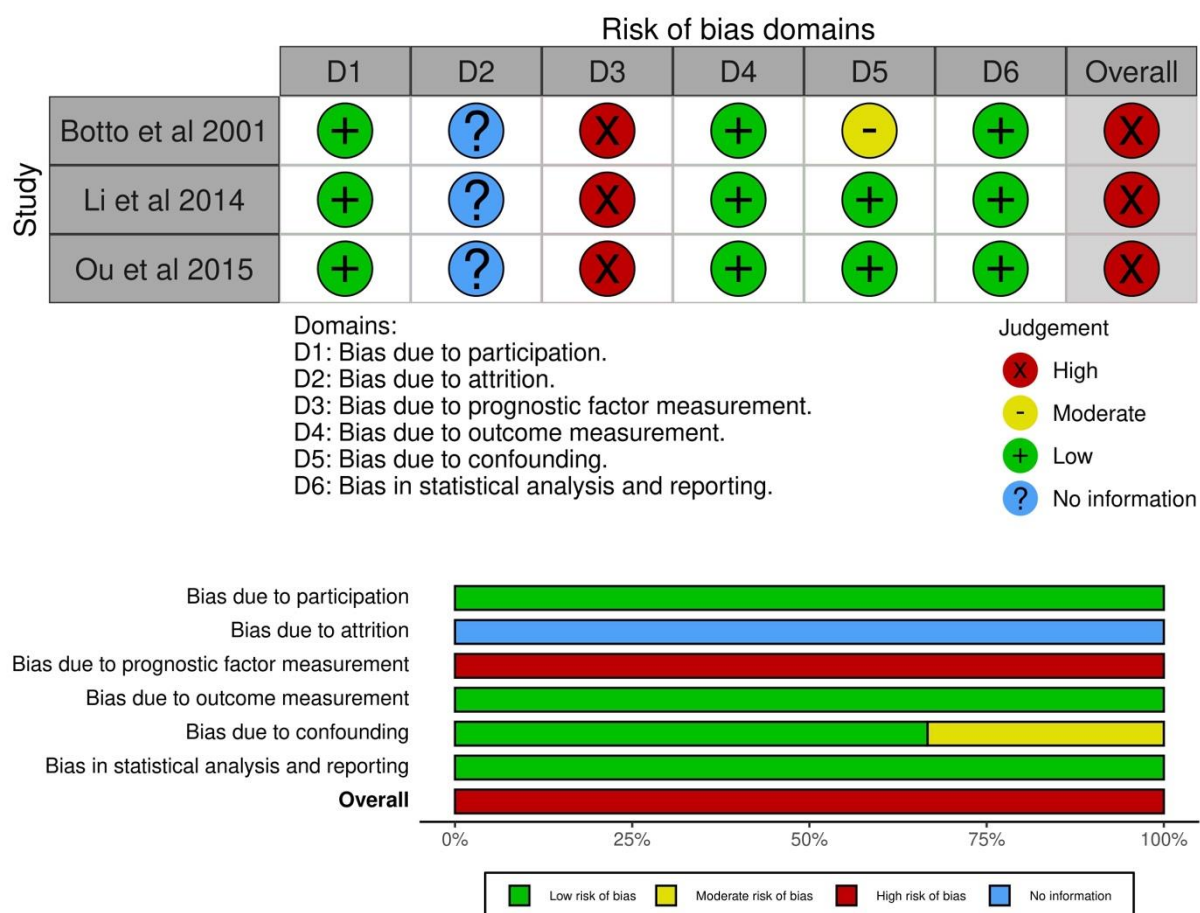


Figure S9. Risk of bias assessment at study and at domain level for congenital heart disease in the systematic review (adjusted)

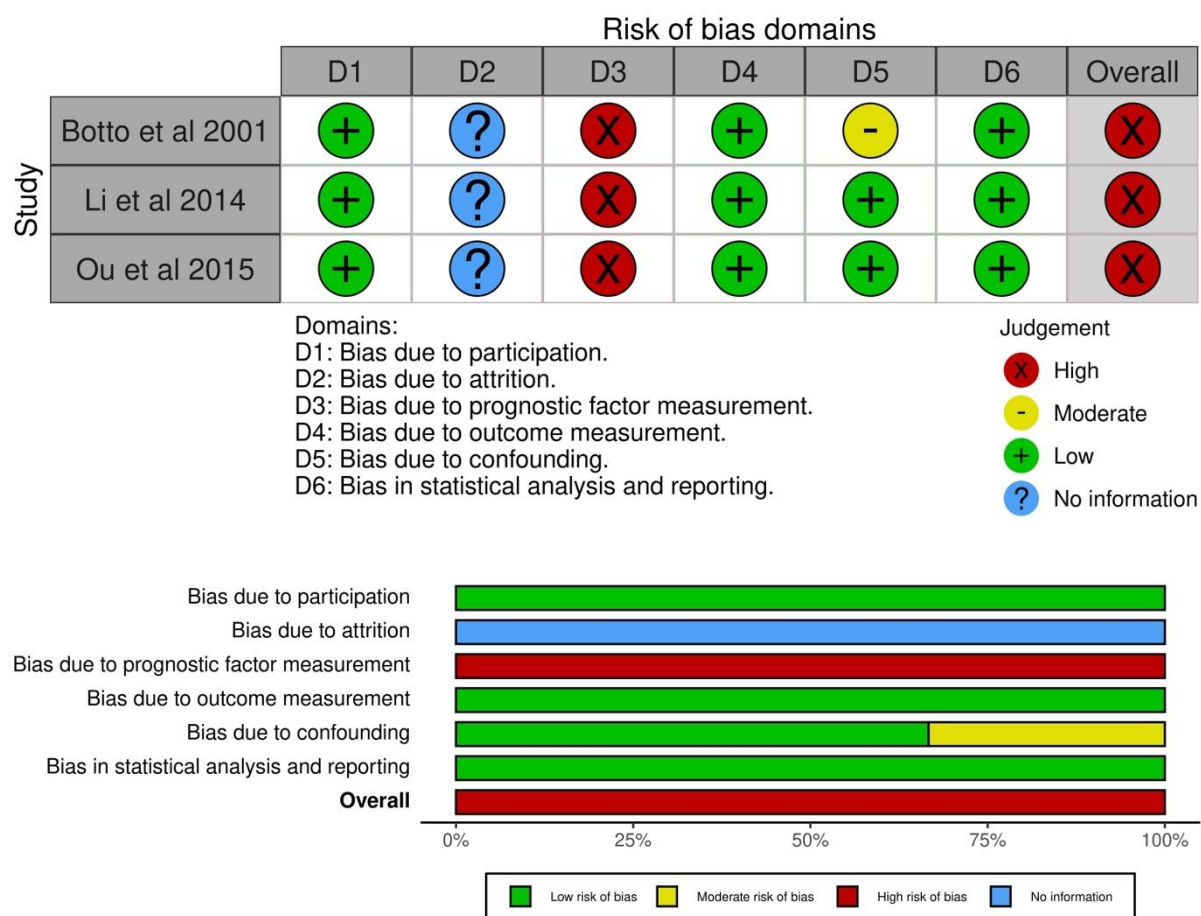


Figure S10. Risk of bias assessment at study and at domain level for congenital heart disease (adjusted)

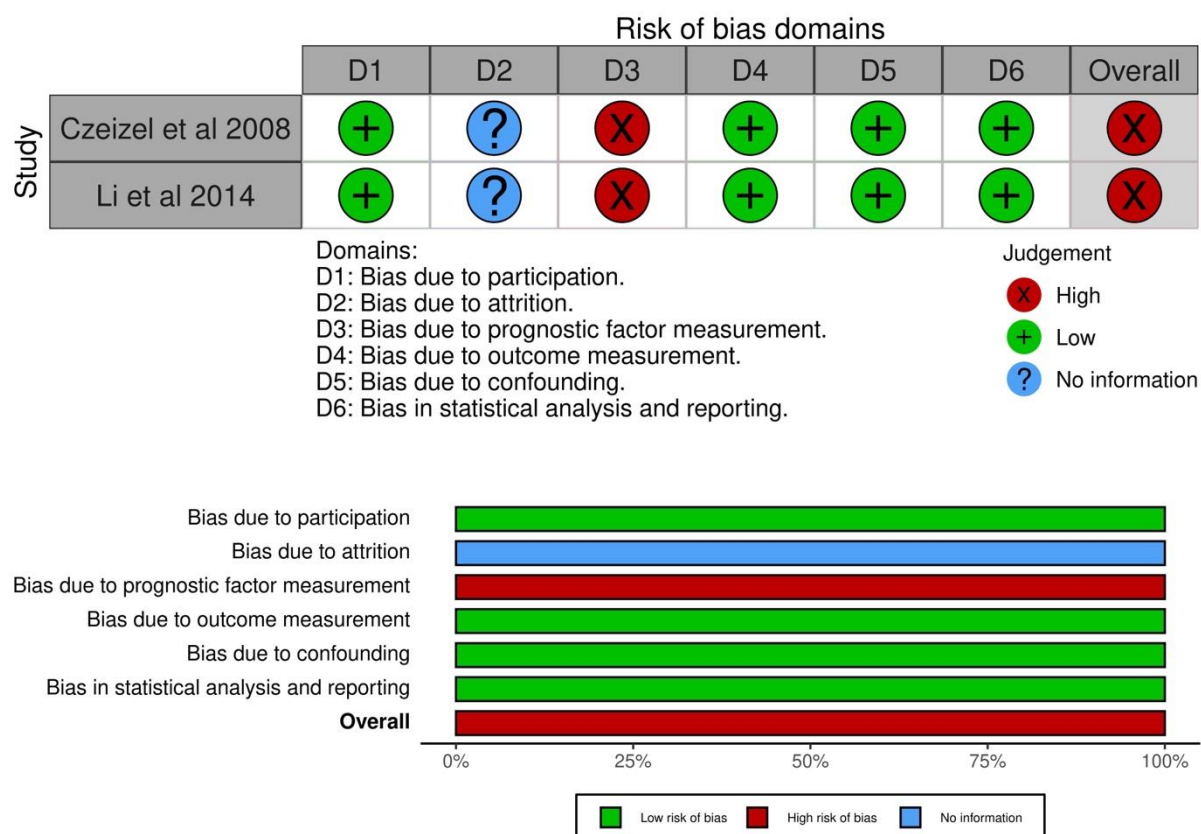


Figure S11. Risk of bias assessment at study and at domain level for congenital heart disease in the systematic review (unadjusted)

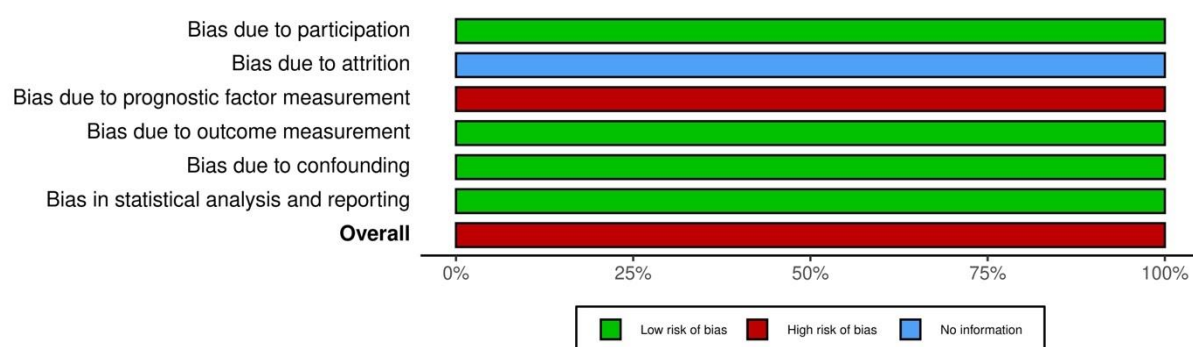
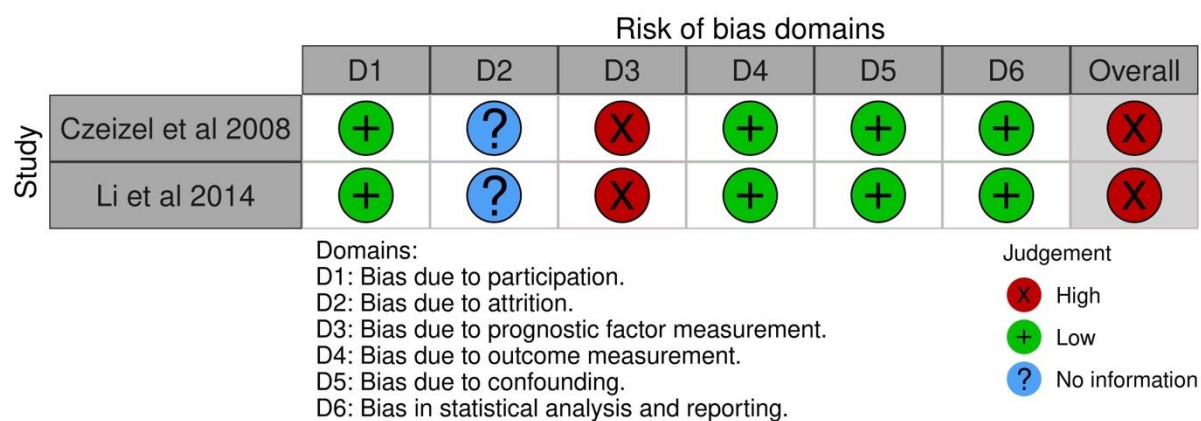


Figure S12. Risk of bias assessment at study and at domain level for congenital heart disease (unadjusted)

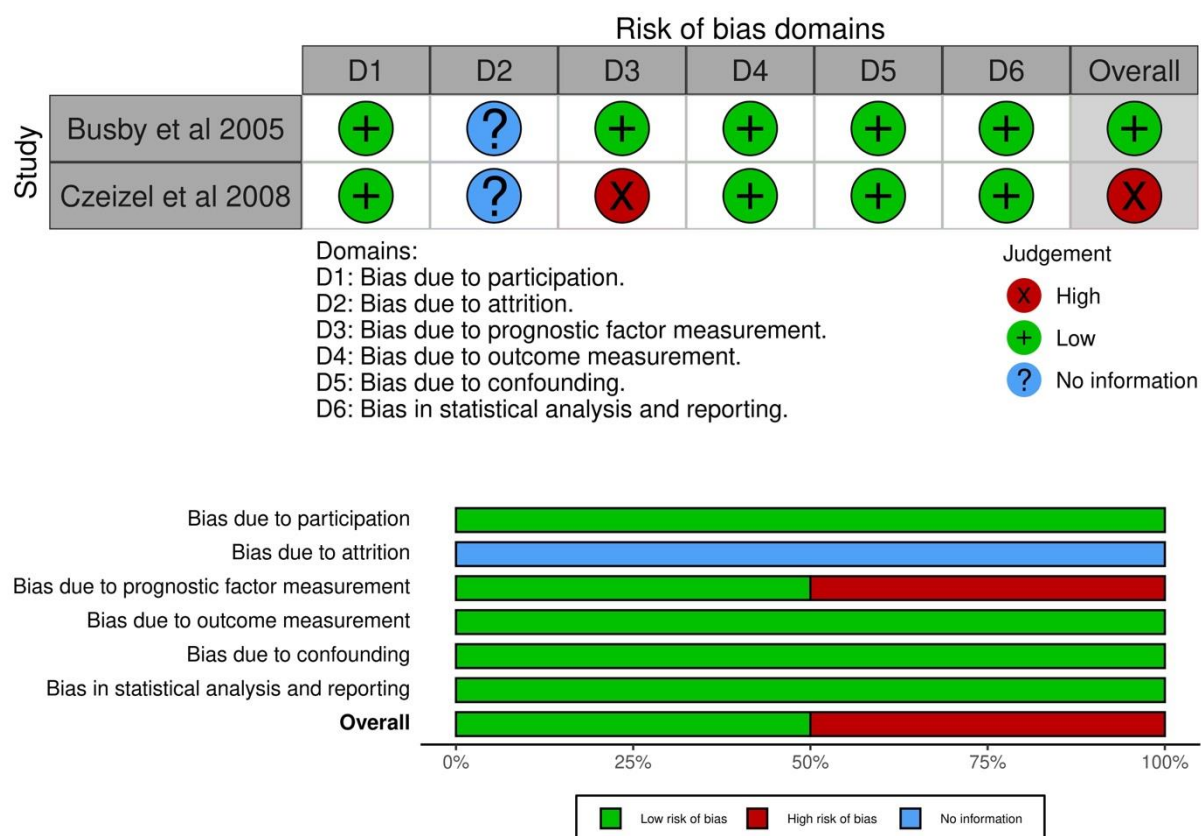


Figure S13. Risk of bias assessment at study and at domain level for eye anomalies

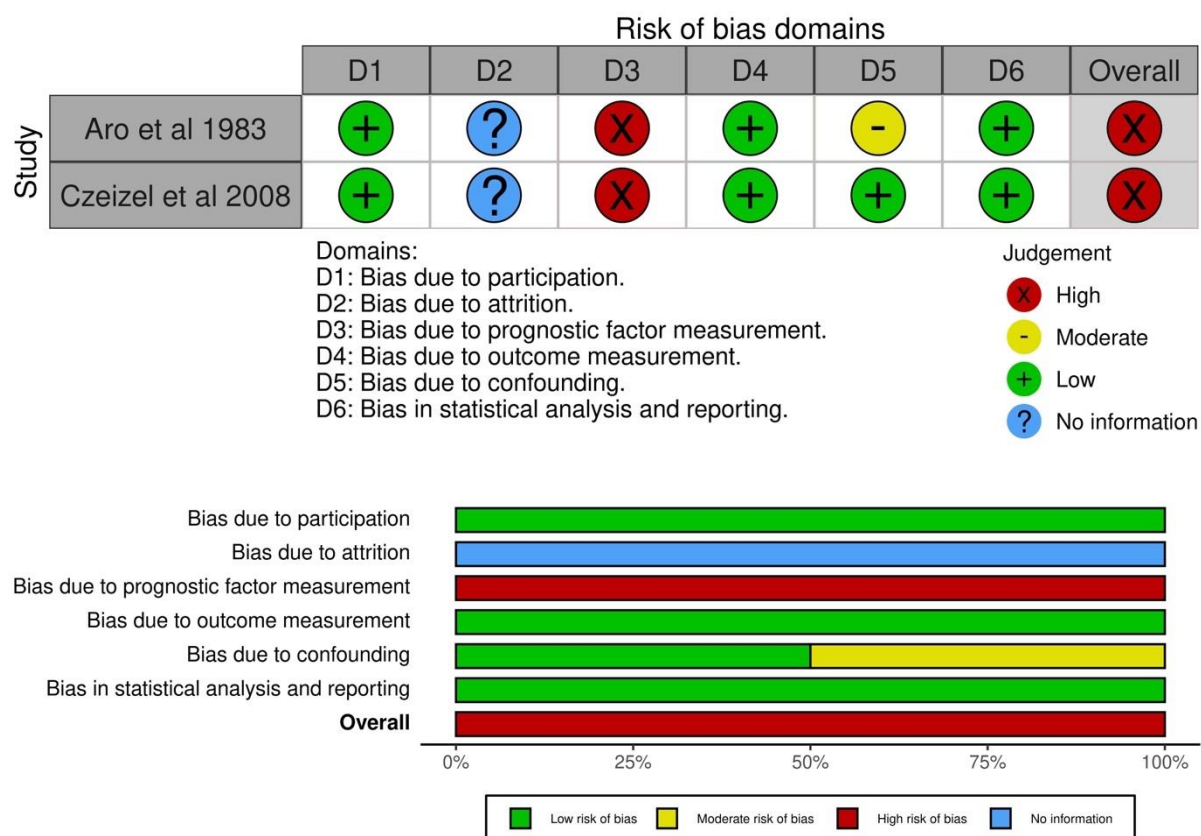


Figure S14. Risk of bias assessment at study and at domain level for limb reduction

PubMed:

(influenza OR flu) AND ((pregnant OR pregnancy) OR ((congenital OR birth) AND (anomaly OR anomalies OR abnormality OR abnormalities OR disorder OR disorders OR malformation OR malformations OR defect OR defects)))

Central:

(influenza OR flu) AND ((pregnant OR pregnancy) OR ((congenital OR birth) AND (anomaly OR anomalies OR abnormality OR abnormalities OR disorder OR disorders OR malformation OR malformations OR defect OR defects)))

Embase:

(influenza OR flu) AND ((pregnant OR pregnancy) OR ((congenital OR birth) AND (anomaly OR anomalies OR abnormality OR abnormalities OR disorder OR disorders OR malformation OR malformations OR defect OR defects)))

Figure S15. Search key of the systematic search

Table S5. Quality of evidence

| Certainty assessment | | | | | | | Summary of findings | | | | |
|--|--------------|---------------|--------------|-------------|--------------------|-------------------------------|-----------------------------------|--------------------------------|--------------------------|--|--|
| Participants (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With Risk of CA without Influenza | With Risk of CA with influenza | | Risk with Risk of CA without Influenza | Risk difference with Risk of CA with influenza |
| Neural tube defects | | | | | | | | | | | |
| 0 cases 0 controls (4 observational studies) | very serious | not serious | not serious | not serious | strong association | ⊕○○○ Very low | 0 cases 0 controls | | OR 2.48 (1.95 to 3.14) | Low | |
| | | | | | | | | | | 0 per 1 000 | 0 fewer per 1 000 (from 0 fewer to 0 fewer) |
| Spina bifida | | | | | | | | | | | |
| 0 cases 0 controls (3 observational studies) | very serious | not serious | not serious | not serious | strong association | ⊕○○○ Very low | 0 cases 0 controls | | OR 2.22 (1.58 to 3.12) | Low | |
| | | | | | | | | | | 0 per 1 000 | 0 fewer per 1 000 (from 0 fewer to 0 fewer) |
| Cleft lip and palate | | | | | | | | | | | |
| | | not serious | not serious | not serious | | | 0 cases 0 controls | | | Low | |

| Certainty assessment | | | | | | | Summary of findings | | | |
|---|--------------|--|--|--|--------------------|------------------|---------------------|----------------------------------|-------------|---|
| 0 cases 0 controls (4 observational studies) | very serious | | | | strong association | ⊕○○○ Very low | | OR 2.48 (1.87 to 3.28) | 0 per 1 000 | 0 fewer per 1 000 (from 0 fewer to 0 fewer) |

Cleft lip

| | | | | | | | | | | |
|---|--------------|-------------|-------------|-------------|--------------------|------------------|--------------------|----------------------------------|-------------|---|
| 0 cases 0 controls (1 observational study) | very serious | not serious | not serious | not serious | strong association | ⊕○○○ Very low | 0 cases 0 controls | OR 2.40 (1.42 to 4.06) | Low | |
| | | | | | | | | | 0 per 1 000 | 0 fewer per 1 000 (from 0 fewer to 0 fewer) |

Cleft palate

| | | | | | | | | | | |
|---|--------------|-------------|-------------|-------------|--------------------|------------------|--------------------|----------------------------------|-------------|---|
| 0 cases 0 controls (1 observational study) | very serious | not serious | not serious | not serious | strong association | ⊕○○○ Very low | 0 cases 0 controls | OR 2.95 (1.75 to 4.95) | Low | |
| | | | | | | | | | 0 per 1 000 | 0 fewer per 1 000 (from 0 fewer to 0 fewer) |

Congenital heart defects (adjusted)

| | | | | | | | | | | |
|---|--------------|-------------|-------------|-------------|------|------------------|--------------------|----------------------------------|-------------|---|
| 0 cases 0 controls (3 observational studies) | very serious | not serious | not serious | not serious | none | ⊕○○○ Very low | 0 cases 0 controls | OR 1.63 (0.33 to 8.17) | Low | |
| | | | | | | | | | 0 per 1 000 | 0 fewer per 1 000 (from 0 fewer to 0 fewer) |

Congenital heart defects (unadjusted)

| | | | | | | | | | | |
|--|--|-------------|-------------|-------------|------|--|--------------------|--|------------|--|
| | | not serious | not serious | not serious | none | | 0 cases 0 controls | | Low | |
|--|--|-------------|-------------|-------------|------|--|--------------------|--|------------|--|

| Certainty assessment | | | | | | Summary of findings | | | | |
|---|--------------|--|--|--|--|---------------------|--|----------------------------------|-------------|---|
| 0 cases 0 controls (2 observational studies) | very serious | | | | | ⊕○○○ Very low | | OR 1.80 (1.49 to 2.18) | 0 per 1 000 | 0 fewer per 1 000 (from 0 fewer to 0 fewer) |

Eye anomalies

| | | | | | | | | | | |
|---|---------|-------------|-------------|-------------|------|------------------|--------------------|----------------------------------|-------------|---|
| 0 cases 0 controls (2 observational studies) | serious | not serious | not serious | not serious | none | ⊕○○○ Very low | 0 cases 0 controls | OR 1.26 (1.02 to 1.56) | Low | |
| | | | | | | | | | 0 per 1 000 | 0 fewer per 1 000 (from 0 fewer to 0 fewer) |

Limb reduction defects

| | | | | | | | | | | |
|---|--------------|-------------|-------------|-------------|--------------------|------------------|--------------------|----------------------------------|-------------|---|
| 0 cases 0 controls (2 observational studies) | very serious | not serious | not serious | not serious | strong association | ⊕○○○ Very low | 0 cases 0 controls | OR 2.13 (1.43 to 3.18) | Low | |
| | | | | | | | | | 0 per 1 000 | 0 fewer per 1 000 (from 0 fewer to 0 fewer) |

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