Supplementary Material

Environmental risk factors and congenital heart disease: an umbrella review of 165 systematic reviews and meta-analyses with more than 120 million participants

Table S1. Search strategy used in the umbrella review

Literature search strategy in PubMed
1: malformations OR deformations OR birth defect OR congenital abnormalities OR birth outcome OR obstetrical outcome 2: meta-analysis OR systematic review 3: 1 AND 2
Literature search strategy in EMBASE
1: malformations OR deformations OR birth defect OR congenital abnormalities OR birth outcome OR obstetrical outcome 2: 'meta analysis' OR 'systematic review' 3: 1 AND 2
Literature search strategy in Web of Science
1: Search TS= (malformations OR deformations OR birth defect OR congenital abnormalities OR birth outcome OR obstetrical outcome) 2: Search TS= (meta-analysis OR systematic review) 3: 1 AND 2
Literature search strategy in Cochrane library
1: "malformations" OR "deformations" OR "birth defect" OR "congenital abnormalities" OR "birth outcome" OR "obstetrical outcome" 2: "meta-analysis" OR "systematic review" 3: 1 AND 2

Table S2. Description of the 41 meta-analyses of environmental factors for CHD.

First author	Year	Journal	Study design included in meta-analysis	Exposure/Factor	Outcome	Type of effect metric
Nikfar et al.(23)	2012	DARU Journal of Pharmaceutical Sciences	Cohort	SSRI	CHD	OR
Rahimi et al.(24)	2006	Reproductive Toxicology	Cohort	SRI	CHD	OR
Painuly et al.(25)	2013	The Psychiatrist	Cohort/Case-control	Paroxetine	CHD	RR
Goldberg et al. (26)	2015	Journal of obstetrics and gynaecology Canada	Cohort/Case-control	Nitrofurantoin	CHD; HLHS	OR; RR
Bracken et al.(27)	1990	Obstetrics & Gynecology	Cohort	Oral contraceptive	CHD	RR
Grigoriadis et al.(28)	2019	Journal of Clinical Psychiatry	Cohort	Benzodiazepine	CHD	OR
Alsaad et al. (29)	2015	Reproductive Toxicology	Cohort	Fluconazole	CHD	OR
Tanoshima et al. (30)	2015	Clinical Pharmacology & Therapeutics	Cohort	Valproic acid	CHD	RR
Feng et al. (31)	2015	Scientific Reports	Cohort/Case-control/RCT	Folate	CHD	RR
De-Regil et al. (32)	2015	Cochrane Database of Systematic Reviews	RCT	Folate	CHD	RR
Riggin et al. (33)	2013	Journal of obstetrics and gynaecology Canada	Cohort	Fluoxetine	CHD	OR
Gao et al. (34)	2017	British Journal of Clinical Pharmacology	Cohort	Fluoxetine	Non-septal defects	RR
Wolf et al. (35)	2017	American Journal of Obstetrics & Gynecology	Cohort/Case-control	Multivitamin	CHD	RR
Zhang et al. (36)	2017	Scientific Reports	Cohort	SSRI	CHD	RR
Selmer et al. (37)	2016	Pharmacoepidemiology and	Cohort	SSRI	CHD	OR

		drug safety				
Gao et al. (38)	2018	BMC Medicine	Cohort	SSRI	CHD	RR
Heneghan et al. (39)	2018	F1000 Research	Cohort/Case-control	Oral hormone pregnancy tests	CHD	OR
Fan et al. (40)	2019	PLoS One	Cohort	Macrolides	CHD; ASD/VSD	OR
Fornaro et al.(51)	2020	American Journal of Psychiatry	Cohort	Lithium	CHD	OR
Munk-Olsen et al. (52)	2018	Lancet Psychiatry	Cohort	Lithium	CHD	OR
Chen et al.(41)	2014	International Journal of Environmental Research and Public Health	Cohort/Case-control	Air pollutants	ASD/VSD/COA/TOF	OR
Zhang et al. (42)	2020	European Journal of Preventive Cardiology	Cohort/Case-control	Maternal alcohol consumption	CHD; ASD/VSD/AVSD/TGA/ TOF/PVS	RR
Wen et al. (43)	2016	Italian Journal of Pediatrics	Cohort/Case-control	Maternal alcohol consumption	CHD	RR
Sun et al. (44)	2015	Congenit Heart Disease	Cohort/Case-control	Maternal alcohol consumption	CHD	RR
Yang et al. (45)	2015	PLoS One	Cohort/Case-control	Maternal alcohol consumption	CHD; VSD	OR
Zheng et al. (48)	2019	Birth	Case-control	Secondhand smoking	CHD	OR
Zhang et al. (49)	2017	The Journal of Maternal-Fetal & Neonatal Medicine	Cohort/Case-control	Smoking	CHD; Conotruncal heart defect; ASD/VSD/AVSD/TGA;	RR
Hackshaw et al. (50)	2011	Human Reproduction	Cohort/Case-control	Smoking	Septal defects; Cardiovascular/heart	OR

		Update			defects	
Zhu et al. (20)	2018	Congenital Heart Disease	Cohort/Case-control	BMI	CHD	RR
Cai et al. (21)	2014	American Journal of Obstetrics & Gynecology	Case-control	BMI	CHD; Hypoplastic left heart syndrome; Outflow tract defects; Conotruncal defects; ASD/TOF/VSD/AVSD/COA/TGA	OR
Stothard et al. (22)	2009	JAMA-The Journal of the American Medical Association	Case-control	BMI	CHD; All septal anomalies; TOF/TGA	OR
Nieuwenhuijsen et al. (53)	2009	Environmental Health Perspectives	Cross-sectional	Chlorination by-products	VSD	OR
Browne et al. (54)	2006	Epidemiology	Cohort/Case-control	Coffee	CHD	OR
Gijtenbeek et al.(55)	2019	Journal of Clinical Medicine	N/A	Monochorionic twins	CHD	RR
Shi et al. (56)	2014	Journal of Perinatology	Case-control	Maternal fever	CHD; ASD/VSD; Right/Left obstructive defects; Conotruncal defects	OR
Spinder et al. (57)	2019	Human Reproduction	Cohort/Case-control	Occupational exposure to solvents/pesticides/metals	CHD	OR
Giorgione et al. (58)	2018	Ultrasound in Obstetrics & Gynecology	Cohort	ART/IVF	CHD; Major/Minor CHD	OR
Feng et al. (59)	2015	Pediatric Cardiology	Case-control	Reproductive history	CHD	OR
Feng et al. (60)	2014	PLoS One	Cohort/Case-control	Parity	CHD	RR
Peng et al. (46)	2019	Clinical Investigation	Case-control	Paternal factors	CHD	OR

Oldereid et al. (47)	2018	Human Reproduction Update	Cohort/Case-control	Paternal factors	CHD	OR

*ART, assisted reproductive technology; ASD, atrial septal defect; AVSD, atrioventricular septal defect; BMI, body mass index; CHD, congenital heart disease; COA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; IVF, in-vitro fertilization; PVS, pulmonary valve stenosis; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Table S3. References of studies excluded in the umbrella review.

Not meta-analysis (N = 23)

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Study specific data missing (N = 44)

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evidence from a case-control study and meta-analysis. Bmc Cardiovasc Disor. 2019;19(2771).
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Publications not in English (N = 5)

68. Li SS, Zhang R, Lan X, Qu PF, Dang SN, Chen FY, Yan H. Prenatal exposure to ambient air pollution and congenital heart disease: a Meta-analysis. Zhonghua Liu Xing Bing Xue Za Zhi. 2017;38(8): 1121-1126.
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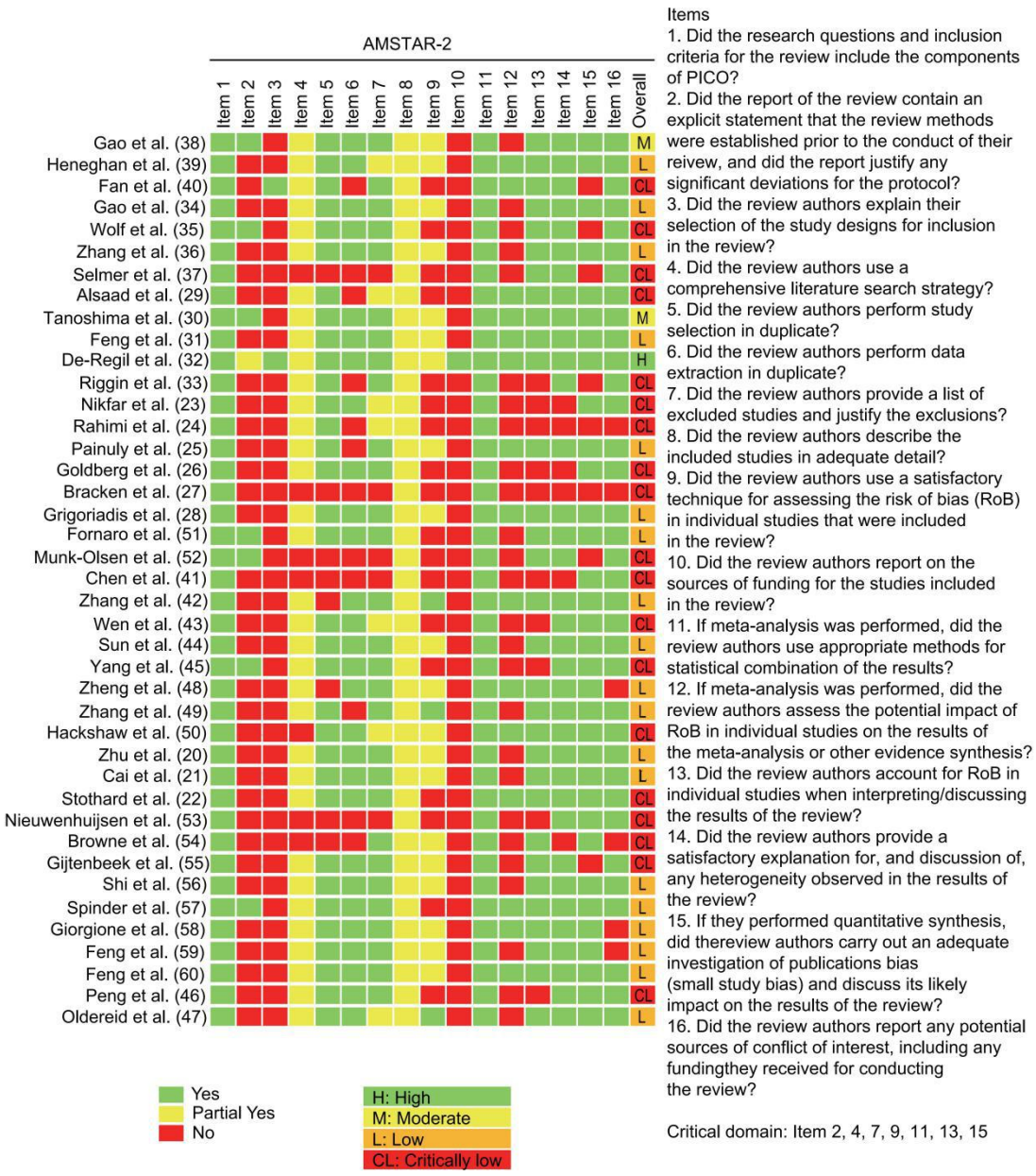
Meeting abstract (N = 1)

73. Tzani A, Economopoulos KP. Maternal tobacco use during pregnancy and risk of congenital heart defects in offspring: A systematic review. Tob Induc Dis. 2014;12.

Supplementary Figure 1. The detailed results of methodological quality assessment.



Moose Checklist

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	3
3	Description of study outcome(s)	3
4	Type of exposure or intervention used	3
5	Type of study designs used	3
6	Study population	3
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	3-4
8	Search strategy, including time period included in the synthesis and key words	3-4 Supplementary Table S1
9	Effort to include all available studies, including contact with authors	3-4
10	Databases and registries searched	3-4
11	Search software used, name and version, including special features used (eg, explosion)	3-4
12	Use of hand searching (eg, reference lists of obtained articles)	3-4
13	List of citations located and those excluded, including justification	Supplementary Table S3
14	Method of addressing articles published in languages other than English	3-4
15	Method of handling abstracts and unpublished studies	3-4
16	Description of any contact with authors	None
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	3-4
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	None
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	None
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	4-5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	4-5
22	Assessment of heterogeneity	4-5
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	4-5

	cumulative meta-analysis) in sufficient detail to be replicated	
24	Provision of appropriate tables and graphics	None
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	5-6
26	Table giving descriptive information for each study included	Supplementary Table S2
27	Results of sensitivity testing (eg, subgroup analysis)	6-7
28	Indication of statistical uncertainty of findings	None
Item No	**Recommendation**	**Reported on Page No**
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	8-9
30	Justification for exclusion (eg, exclusion of non-English language citations)	9
31	Assessment of quality of included studies	8-9
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	8-10
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	11
34	Guidelines for future research	8-11
35	Disclosure of funding source	12

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008. Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United Sates. August 2012.

PRISMA Checklist

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.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
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.	PROSPERO CRD42020193381
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.	3-4
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	3-4

		searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3-4 Table S1
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).	3-4
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.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
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.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4-5
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.	4-5
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).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5

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.	3-6 Figure 1 Table S3
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.	5-6 Table S2
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).	5-6
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.	5-6 Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5-6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	5-6
DISCUSSION			
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).	7-9
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).	10-11

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
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.	12

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