Congenital anomalies in the offspring of occupationally exposed mothers: a systematic review and meta-analysis of studies using expert assessment for occupational exposures

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STUDY QUESTION: Is there an association between maternal occupational exposure to solvents, pesticides and metals as assessed by expert-based assessment and congenital anomalies in the offspring?

SUMMARY ANSWER: There is an association between maternal occupational exposure to solvents and congenital anomalies in the off-spring, including neural tube defects, congenital heart defects and orofacial clefts.

WHAT IS KNOWN ALREADY: One important environmental risk factor for development of congenital anomalies is maternal occupational exposure to chemicals in the workplace prior to and during pregnancy. A number of studies have assessed the association with often conflicting results, possibly due to different occupational exposure assessing methods.

STUDY DESIGN, SIZE, DURATION: For this systematic review with meta-analysis, the search terms included maternal occupation, exposure, congenital anomalies and offspring. Electronic databases MEDLINE and EMBASE were searched for English studies up to October 2017.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Two reviewers independently screened all citations identified by the search. Case-control studies and cohort studies were included if (I) they reported on the association between maternal occupational exposure to solvents, pesticides or metals and congenital anomalies, and (II) assessment of occupational exposure was performed by experts. Data on study characteristics, confounders and odds ratios (ORs) were extracted from the included studies for four subgroups of congenital anomalies. Methodological quality was assessed using the Newcastle-Ottawa Scale. In the meta-analysis, random effects models were used to pool estimates.

MAIN RESULTS AND THE ROLE OF CHANCE: In total, 2806 titles and abstracts and 176 full text papers were screened. Finally, 28 studies met the selection criteria, and 27 studies could be included in the meta-analysis. Our meta-analysis showed that maternal occupational exposure to solvents was associated with neural tube defects (OR: 1.51, 95%CI: 1.09–2.09) and congenital heart defects (OR: 1.31, 95%CI:1.06–1.63) in the offspring. Also maternal occupational exposure to glycol ethers, a subgroup of solvents, was associated with neural tube defects (OR: 1.93, 95%CI: 1.17–3.18) and orofacial clefts (OR: 1.95, 95%CI: 1.38–2.75) in the offspring. Only one study investigated the association between maternal occupational exposure to solvents and hypospadias and found an association (OR: 3.63, 95%CI: 1.94–7.17).

Results of the included studies were consistent. In our meta-analysis, we found no associations between occupational exposure to pesticides or metals and congenital anomalies in the offspring.

LIMITATIONS, REASONS FOR CAUTION: A limited number of studies was included, which made it impossible to calculate pooled estimates for all congenital anomalies, analyse individual chemicals or calculate exposure–response relations. Bias could have been introduced because not all included studies corrected for potentially confounding factors.

WIDER IMPLICATIONS OF THE FINDINGS: Employers and female employees should be aware of the possible teratogenic effects of solvent exposure at the workplace. Therefore, is it important that clinicians and occupational health specialist provide women with preconception advice on occupational solvent exposure, to reduce the congenital anomaly risk.

STUDY FUNDING/COMPETING INTEREST(S): NSp was paid by the Graduate School of Medical Sciences (MD/PhD program), UMCG, Groningen, the Netherlands. EUROCAT Northern Netherlands is funded by the Dutch Ministry of Health, Welfare and Sports. There are no competing interests.

REGISTRATION NUMBER: CRD42017053943.

Key words: congenital anomalies / maternal / occupational exposure / metals / offspring / pesticides / preconception / solvents

Introduction

Around 2–3% of pregnancies in Europe are affected by a major congenital anomaly (European Surveillance of Congenital Anomalies, 2017). The aetiology of most congenital anomalies is not fully understood, but genetic factors as well as environmental factors are involved. To decrease the prevalence of congenital anomalies, it is important to identify modifiable environmental factors and prevent maternal exposure to harmful factors. Examples of environmental factors known to increase the risk of having a child with a congenital anomaly include smoking during pregnancy (Nicoletti et al., 2014) and increased body mass index (BMI) (Stothard et al., 2009; Nicoletti et al., 2014). Air pollution is another factor that has been associated with development of congenital anomalies, in particular with congenital heart defects (Vrijheid et al., 2011).

One important environmental factor that has been associated with development of congenital anomalies is maternal exposure to chemicals in the workplace prior to and during pregnancy. Most studies that have investigated maternal occupational exposure have focused on exposure to solvents, pesticides and metals. Exposure to these chemical substances have been associated with various adverse reproductive outcomes. For instance, occupational exposure to solvents has been associated with reduced fertility and increased risks of spontaneous abortion and congenital anomalies (Burdorf et al., 2006; Figa-Talamanca, 2006). Pesticide and metal exposure in the workplace have been suggested to interfere with reproductive function and have been associated with prolonged time to pregnancy, spontaneous abortions, congenital anomalies, prematurity and reduced birth weight (Kumar, 2004; Burdorf et al., 2006; Figa-Talamanca, 2006; Snijder et al., 2012a).

Epidemiological studies that have investigated the association between maternal occupational exposure and congenital anomalies in the offspring have conflicting results. One explanation for these divergent results may be the type of exposure assessment used, e.g. job title as proxy for exposure, self-reported exposure or expert-based assessment. Job title as proxy for exposure can introduce non-differential misclassification (Snijder et al., 2012a). An example of using job title as

proxy for exposure are studies reporting on the association between a specific occupational group (e.g. agricultural workers) and congenital anomalies in the offspring in which it is hypothesised that the congenital anomalies could be associated with an occupational exposure that is expected to be present in this occupation (e.g. pesticide exposure in agricultural workers). Using self-reported occupational exposure can introduce misclassification of exposure compared to expert assessment (Fritschi et al., 1996). Both assessment methods may overestimate the effects of maternal occupational exposure and congenital anomalies in the offspring (Fritschi et al., 1996; Snijder et al., 2012a). In this systematic review, we have therefore only included papers that used expert assessment in order to have less heterogeneous human evidence. Experts have, by training, a better understanding of the mechanisms of exposure (Fritschi et al., 1996) and know which agents and which levels of exposure play a role in specific jobs (Nieuwenhuijsen, 2003). We considered both case-by-case expert assessment and Job-Exposure Matrices (JEMs) as expert-based assessments. Job-exposure matrices are occupational exposure assessment tools based on cross tabulations of jobs against occupational exposures where probability and intensity have been scored by exposure experts (occupational hygienists) (Pannett et al., 1985). Occupational hygienists assess occupational exposure on the individual level, whereas JEMs assign exposures at the job level.

The aim of this review is to summarise the current evidence about maternal occupational exposure to solvents, pesticides and metals and congenital anomalies in the offspring by conducting a systematic review and meta-analysis using expert assessment for occupational exposures.

Materials and Methods

This systematic review was conducted using the methods of the Cochrane Collaboration (Higgins and Green, 2011) and reporting according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (Liberati et al., 2009). The protocol of our systematic review is registered in PROSPERO, an International prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID = CRD42017053943).

Eligibility criteria, information sources, search strategy

A literature search of the electronic databases MEDLINE and EMBASE was conducted on 12 January 2017. Search strings included the indexing terms (MeSH terms, Emtrees and key terms): maternal occupation, exposure, congenital anomalies and offspring (Supplementary Table SI). A search update was conducted on 23 October 2017.

Study selection

Case-control and cohort studies with a non-exposed control group were included if they reported on the association between maternal occupational exposure to solvents, pesticides or metals and subtypes of congenital anomalies in their offspring. Occupational exposure had to be assigned by an occupational exposure expert, through a JEM or by using expert literature, for example National Institute for Occupational Safety and Health criteria documents. Studies using occupation as a proxy for occupational exposure without involvement of occupational expertise and studies using self-reported exposure were excluded.

Congenital anomalies had to be diagnosed or reported by a medical expert, identified by birth (defect) registries or identified using established guidelines (e.g. International Classification of Disease(ICD)-codes, EUROCAT guidelines). Studies in which only the parents reported on the congenital anomalies were excluded. Only full text studies published in English, German, French and Dutch were included. Case-reports and reviews were excluded.

Data extraction

All identified hits were screened on title and abstract for eligibility by two reviewers (NSp and JP) independently. Full texts of all potentially eligible articles were screened for final selection by the same reviewers. The reference lists of all included articles and relevant reviews were also screened to identify further eligible studies. Disagreements between the two reviewers' assessments were resolved in consensus meetings. In case of persistent disagreement, a final decision was made by a third reviewer (HdW).

Data on study design, study population, study period, exposure, exposure assessment, outcome, outcome assessment, confounders and crude or adjusted odds ratios (OR) was extracted from the included studies. When certain information/data was missing, we contacted the corresponding author. One reviewer (NSp) extracted all of the data and a second (JP) and third reviewer (JB, HdW, NSm, each one-third of the extracted data) checked all of the extracted data.

Methodological quality

The quality of the studies was assessed by two reviewers independently (NSp and JP) using the Newcastle-Ottawa Scale, adjusted to study specific requirements, which is designed for assessing the quality of non-randomised studies in meta-analyses (Wells et al.) (Supplementary Tables SII and SIII). 'Stars' could be awarded on different methodological quality items. A maximum of nine 'stars' could be allocated to each study. Although papers might have referred to methods papers, only index papers were used to assess methodological quality. Disagreements were discussed and resolved in consensus meetings between the first two reviewers (NSp and JP). To evaluate the inter-agreement of the methodological quality of the studies, we calculated the overall percentage agreement and Cohen's kappa a measure of congruence corrected for chance agreement (Higgins and Green, 2011).

Data synthesis

Meta-analyses were performed for the following categories of congenital anomalies: (I) neural tube defects, (II) congenital heart defects, (III) orofacial clefts and (IV) hypospadias, because these categories of major congenital anomalies are the most prevalent. Subgroup analyses were performed on cleft lip, with or without cleft palate, and cleft palate. Separate analyses were performed for the most prevalent subgroups of maternal occupational exposure to (a) solvents, (b), pesticides and (c) metals. A subgroup analysis was performed for maternal occupational exposure to glycol ethers, because this is a large subcategory of solvents.

The OR was used to calculate a pooled estimate. To reduce potential confounding effects, adjusted ORs were used for the meta-analyses where possible. When crude or adjusted ORs were not given, the available raw data was used in a 2×2 table to calculate the OR. When occupational exposure was categorised, categories were dichotomised so that the lowest category (no exposure) was tested against all other categories combined (e.g. low and high). Papers reporting zero exposed cases/controls were excluded from the meta-analysis because an OR could not be calculated. When multiple papers were based on the same study population, we selected a paper based on the following criteria: (I) results reported an estimate useful for the meta-analysis and (II) largest sample size.

A random effects method was used to pool effect estimates. Heterogeneity was examined by the I^2 index. If the I^2 index was higher than 50% (Higgins and Green, 2011), the results of the studies in the pooled analyses were considered to be heterogeneous, and no pooled estimate was calculated (Higgins and Green, 2011; Kuiper et al., 2015). Sources of heterogeneity were explored by conducting subgroup analyses for differences in study design (cohort versus case-control studies), study population (case ascertainment by hospital versus registry), exposure time window (first trimester versus three months before conception through the first trimester), exposure assessment (industrial hygienist versus JEM), and methodological quality (per item) as assigned by the Newcastle-Ottawa Scale.

Publication bias was assessed by constructing funnel plots for the relation between various occupational exposures and congenital anomalies. Asymmetry of the funnel plots was assessed by Egger's test. If the P-value was <0.10, publication bias is likely (Egger et al., 1997; Higgins and Green, 2011). All statistical analyses were performed with Comprehensive Meta-Analyses (version 3).

Results

Study selection

In total, 2806 titles and abstracts were screened and 176 full texts were read (Figure 1). Screening the references of the included studies and other relevant reviews identified one additional eligible article. An updated search performed in October 2017 included one additional article. In total, 28 studies were included in the systematic review and 27 were included in the meta-analysis. One study was excluded from the meta-analysis because the results were based on the same study population as another included study.
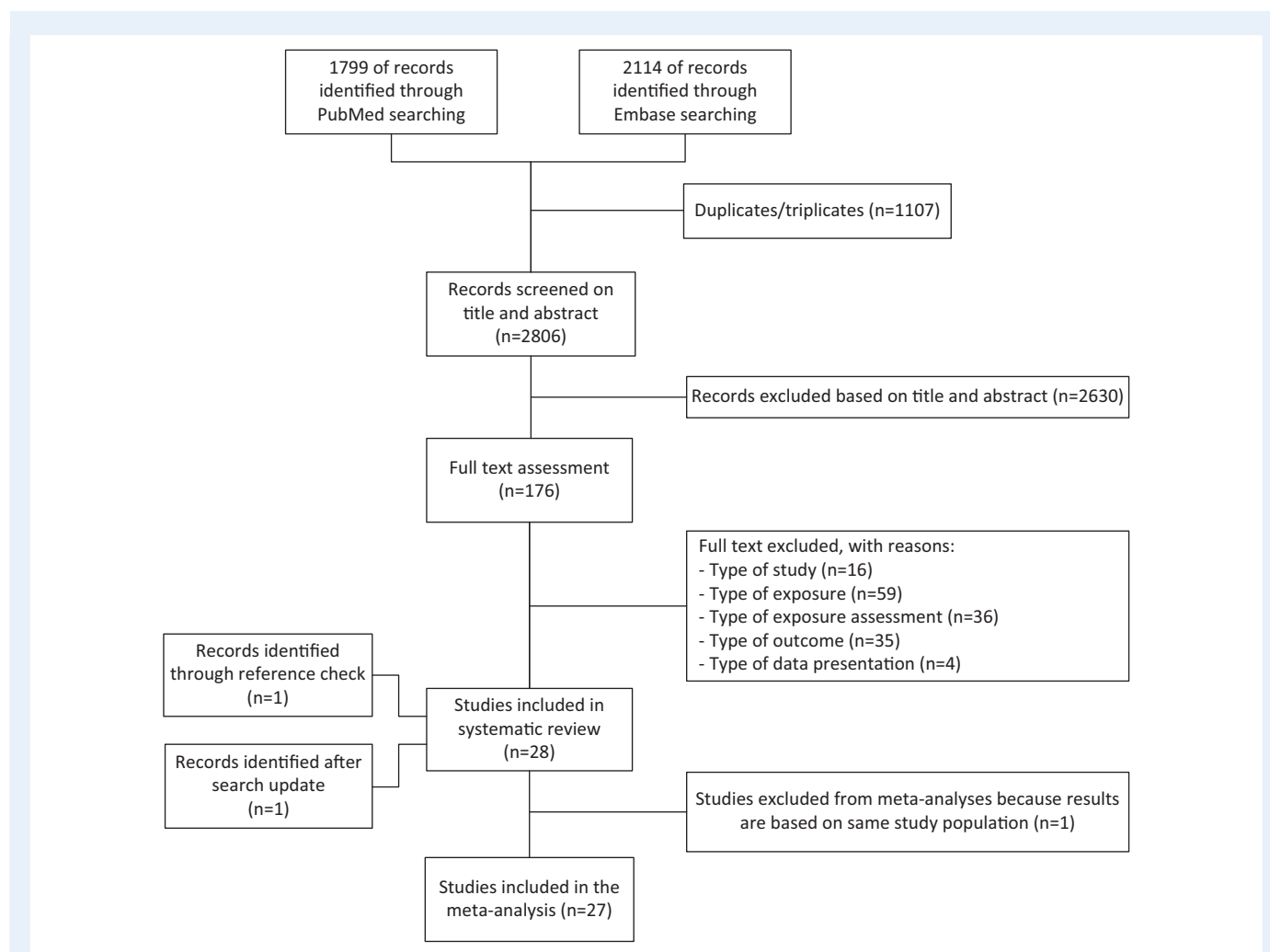
Figure 1 Flowchart of study selection.

Study characteristics

Table I shows the characteristics of the included studies, consisting of 26 case-control studies and two cohort studies. The included studies were conducted between 1980 and 2014. Most studies used birth registries or birth defect registries to identify children with congenital anomalies (n = 16). Other studies were conducted in hospitals, rehabilitations centers, paediatric services and obstetric clinics. The critical time window of exposure was most often defined as three to one month before conception through the first trimester of pregnancy. Most studies used occupational hygienists to assess occupational exposure (n = 15), whereas eleven studies used a JEM and two studies used expert-based literature. In most studies, congenital anomalies were reported to registries by health care professionals, often by a clinical geneticist. When a study was performed in a hospital, diagnoses were confirmed by (paediatric) specialists. Most studies excluded cases diagnosed with chromosomal abnormalities or monogenic syndromes (Supplementary Table SIV).

Risk of bias of included studies

The results of the methodological quality assessment of the included studies are presented in Supplementary Table SV. Study quality varied

from poor (four stars) to high (nine stars). All case-control studies met the quality criteria for same method of exposure ascertainment for cases and controls. Most of the case-control studies included met quality criteria for adequate case definition, selection of controls, and definition of controls. Seven case-control studies did not meet quality criteria on representativeness of the cases. Six case-control studies scored medium risk of bias on comparability of cases and controls based on the design or analysis, and eight studies scored a high risk of bias on this item. Six case-control studies did not meet criteria on ascertainment of exposure. Most case-control studies (n = 17) did not report non-response rate, making it not possible to judge the likelihood of bias on this item (attrition bias).

The two cohort studies included in this systematic review met quality criteria on selection of the non-exposed part of the cohort, adequate ascertainment of exposure, demonstration that the outcome of interest was not present at start of study, comparability of cohort on the basis of design or analysis and ascertainment of exposure, and the follow-up was long enough for outcomes to occur. Garlantézec et al. did not meet the criteria on representativeness of the exposed cohort (Garlantézec et al., 2009). Morales-Suarez-Varela et al. did not meet the criteria on adequacy of follow-up (Morales-Suarez-Varela et al., 2011).

Table 1 Study Characteristics of 28 Included Studies in the Systematic Review.

Study	Country	Study design	Study period	Source of case	Source of control	Exposure	Exposure time window	Method of occupational exposure assessment	Type of congenital anomalies	Identification method of congenital anomalies	Adjusted, matched or crude data	Adjustment for covariates	Risk of bias (NOS score)
Blatter et al. (1996)	The Netherlands	Case-control	1980–1992	Seven hospitals and two rehabilitation centers	Most from general population recruited from birth registries, some from seven hospital and two rehabilitation centers, all without congenital anomaly	Organic solvents Pesticides Mercury	Two weeks before conception until six weeks after conception	Expert assessed occupation, occupational task and rated exposure level. Occupational information was provided by mothers during a specific personal interview	Spina bifida aperta	Medical records were searched to identify spina bifida aperta cases	Stratified Adjusted[a]	Size of municipality and geographical location Vitamin A, anti-epileptics, ovulation stimulating agents, oral contraceptives, alcohol, smoking, positive family history of NTDs, consanguinity, diabetes, diagnosis of homocysteinaemia, parity, foetal loss	8
Brender et al. (2002)	USA	Case-control	1995–2000	Mexican Americans in the Texas NTD Project	Hospital or midwife-attended birthing center during the same time period as the case women	Solvents (including glycol ethers)* Pesticides Lead*	Three months before through three months after conception	Occupational codes were linked to specific exposures based on different literature sources. Occupational information was provided by mothers during an interview	NTD	Active surveillance of NTD births through multiple sources, including hospitals, birth centers, genetic clinics	Matched Adjusted	Year of index birth and site of delivery Mother's age, education and BMI	8
Brender et al. (2006)	USA	Case-control	1995–2000	Mexican Americans in the Texas NTD Project	Hospital or midwife-attended birthing center during the same time period as the case women	Heavy metals (arsenic, cadmium, lead, mercury)	Three months before through three months after conception	Occupational codes were linked to specific exposures based on different literature sources. Occupational information was provided by mothers during an interview	NTD	Active surveillance of NTD birth through multiple sources, including hospitals, birth centers, genetic clinics	Crude		6
Carbone et al. (2007)	Italy	Case-control	1998–2002	Paediatric service in highly agricultural district	Controls born in the same year in same municipality selected from public paediatric records	Pesticides	Before or during pregnancy	Directly asked by researchers/experts during interviews	Hypospadias	Recorded in the paediatric service records and confirmed by surgical consultants	Adjusted[b]	Birth weight, parity, mother's age, mother's education, time to pregnancy, condom use, mother's gynaecological diseases, father's urogenital diseases, use of anti-abortion drugs, mother's alcohol use during pregnancy, same exposure variable of the other parent	8

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Table I *Continued*

Study	Country	Study design	Study period	Source of case	Source of control	Exposure	Exposure time window	Method of occupational exposure assessment	Type of congenital anomalies	Identification method of congenital anomalies	Adjusted, matched or crude data	Adjustment for covariates	Risk of bias (NOS score)
Chevrier et al. (2006)	France	Case-control	1998–2001	Seven hospitals	Same hospitals as cases, but hospitalised for treatment of other disorder (infection, minor surgery)	Organic solvents	First trimester	Expert chemist assessed exposure using mothers work and job tasks provided by mothers during an interview in the hospital with a standardised questionnaire	Non-syndromic oral clefts	During initial hospitalisation for surgery in the maxillofacial surgery department	Matched Adjusted[b]	Sex, age, mother's geographic origin and residence Study center, child's sex, mother's geographic origin	9
Cordier et al. (1992)	France	Case-referent	1984–1987	15 maternity hospitals	First infant born without anomaly after case child in same maternity hospital	Solvents	During pregnancy	Occupational histories of mothers, provided by mothers during an interview, were reviewed by an industrial hygienist	CHD Oral clefts	Cases were identified in hospital according to specific 'British Paediatric Association Classification of Diseases' codes	Matched Adjusted	Hospital of birth Residential area, age, and socioeconomic status of the mother	8
Cordier et al. (1997)	France, Italy, United Kingdom, the Netherlands	Case-control	1989–1992	Six EUROCAT registries	First infant born without anomaly after case child in same maternity hospital	Glycol ethers	First trimester	An expert chemist assessed exposure guided by a detailed description of women's occupational tasks provided by mothers during an interview	NTD CHD Oral clefts	Active case-finding by physicians, midwives, with help of hospital or registry staff following EUROCAT guidelines	Matched Adjusted	Place of birth, date of birth, mother's residence. Maternal age, socioeconomic status, area of residence, country of origin, and center	8
Cordier et al. (2001)	Slovakia	Case-control	1995–1996	26 maternity hospitals and obstetrical clinics	First infant born without anomaly after case child in same maternity hospital or clinic	Glycol ethers	First trimester	Chemist specialising in glycol ethers evaluated exposure using job description provided by mothers during an interview by their physicians using a study questionnaire	NTD CHD Oral clefts	No description	Adjusted[c]	Maternal age at birth, socioeconomic status and residence	4
Desrosiers et al. (2012)	USA	Case-control	1997–2002	National Birth Defects Prevention Study	Non-malformed live birth selected from birth certificates or hospital records from the same base population as the cases	Organic solvents	One month before through end of third month of pregnancy	Occupational epidemiologists and industrial hygienists rated maternal jobs provided by mothers during a telephone interview	NTD Oral clefts	Surveillance by birth defect registries, clinical geneticists performed review of medical records to confirm eligibility	Adjusted[b]	Maternal age, race/ ethnicity, education, pre-pregnancy BMI, folic acid and smoking	9

Study	Country	Design	Period	Source (cases)	Controls	Exposure	Exposure timing	Exposure assessment	Outcome	Outcome assessment	Analysis	Confounders	Quality
Garlantézec et al. (2009)	France	Prospective cohort	2002–2005	Recruitment by gynaecologists, obstetricians or ultrasono-graphers at visits for prenatal care	Recruitment by gynaecologists, obstetricians or ultrasonographers at visits for prenatal care	Solvents	Occupation before 19 weeks of gestational age	JEM based on occupation code and industrial activity code based on information provided by a questionnaire before 19 weeks of gestation	CHD Oral clefts	Validation of anomaly by a paediatrician based on clinical examination of live born infants, pathology and karyotype examinations on non-live births	Adjusted	Alcohol consumption Maternal age, tobacco and alcohol consumption, education level	8
Gilboa et al. (2012)	The USA	Case-control	1997–2002	National Birth Defects Prevention Study	Non-malformed live birth selected from birth certificates or hospital records	Organic solvents	One month before through end of first trimester	Industrial hygienists rated maternal jobs based on job description provided by mother from an interview[d]	Isolated CHD	Surveillance by birth defect registries, clinical geneticists performed review of medical records to confirm eligibility	Adjusted	Maternal age, race/ethnicity, education, smoking, periconceptional folic acid intake	8
Giordano et al. (2010)	Italy	Case-control	2005–2007	Two Roman hospitals	Healthy male infants attending the Outpatient Vaccination Service	Pesticides* Heavy metals	Three months before through three months after conception	JEM using job title provided during an interview	Hypospadias	Recruited if required surgical treatment (first, second and third degree hypospadias)	Adjusted	BMI at conception, education father	8
Jackson et al. (2004)	The USA	Case-control	1981–1989	Hospitals	Infant born without cardiovascular malformations in same hospital	Lead	Three months before conception through first trimester	Industrial hygienists and occupational epidemiologists reviewed all jobs, a JEM and self-reported exposure was used and reviewed by staff having expertise. Mother was classified as exposed if classified exposed by any of the methods	Total anomalous pulmonary venous return (TAPVR) (CHD)	Confirmed by echocardiography, cardiac catheterisation, surgery, and/or autopsy. Updated at one year of age	Stratified	Stratified by month, year, and hospital of birth	5
Kalfa et al. (2015)	France	Case-control	2009–2014	Multi-institutional/hospitals	Hospitalised boys without congenital malformation	Organic solvents Pesticides	During all three trimesters of pregnancy	JEM using occupational information from a questionnaire filled in by surgeon or endocrinologist	Isolated hypospadias	Clinical diagnosis made via direct clinical examination by a paediatric urologist and/or paediatric endocrinologist	Matched	Ethnic origin	4
Lorente et al. (2000)	France, Italy, UK, the Netherlands	Case-referent	1989–1992	Six EUROCAT registrations	First infant born without anomaly on same date or in same town or next born infant	Glycol ethers* Lead	First trimester	Industrial hygienist based on job description provided by mother during an interview	Oral clefts	Cases were identified by the registries	Adjusted[e]	Center, mothers socioeconomic status, urbanisation, country of origin, maternal age	8

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Table I *Continued*

Study	Country	Study design	Study period	Source of case	Source of control	Exposure	Exposure time window	Method of occupational exposure assessment	Type of congenital anomalies	Identification method of congenital anomalies	Adjusted, matched or crude data	Adjustment for covariates	Risk of bias (NOS score)
Makelarski et al. (2014)	The USA	Case-control	1997–2002	National Birth Defects Prevention Study	Non-malformed live births selected from birth certificates or hospital records	Pesticides	One month before through two months after conception	Industrial hygienist using coded job information provided by mothers during a telephone interview	NTD	Surveillance by birth defect registries, clinical geneticists performed review of medical records to confirm eligibility	Adjusted	Maternal BMI (continuous), maternal education, study site	5
Morales-Suarez-Varela et al. (2011)	Denmark	Prospective cohort	1997–2002	Danish National Birth Cohort	All other male births from the Danish National Birth Cohort	Pesticides Heavy metals	Three months before pregnancy and during pregnancy	JEM using job title provided by women in a telephone interview at 16 weeks of gestation	Hypospadias	National Hospital Discharge Registry which included information about congenital anomalies based on the ICD10	Adjusted[b]	Parental age and smoking, earlier spontaneous abortion, parity, birth weight, gestational age, oral contraceptive use, treatment of infertility, time to conceive, maternal alcohol consumption, binge drinking, pre-pregnancy BMI, vegetarian diet, gynaecological disease	8
Nassar et al. (2010)	Australia	Case-control	1980–2000	Western Australian Birth Defects Registry	Random sample from Western Australian Maternal and Child Health Research Database	Pesticides Heavy metals	At least 20 weeks or more gestation	Exposure assigned by researchers according to a JEM using occupation available from the Western Australian Maternal and Child Health Research Database	Hypospadias	Statutory and voluntary sources of notification coded with the ICD9	Matched Adjusted	Birth year Maternal age, parity, race, location, marital status, socioeconomic status, plurality, small for gestational age, year of birth	9
Pettigrew et al. (2016)*	The USA	Case-control	1997–2002	National Birth Defects Prevention Study	Non-malformed live birth selected from birth certificates or hospital records	Pesticides	One month before through one month after conception	Industrial hygienist using coded job information provided by mothers during a telephone interview	Spina bifida	Surveillance by birth defect registries, clinical geneticists performed review of medical records to confirm eligibility	Adjusted	Maternal race/ethnicity, maternal education level, study site	5
Pierik et al. (2004)	The Netherlands	Nested Case-control	1999–2001	Child health care centers Rotterdam	Boys without cryptorchidism or hypospadias if their age was compatible with the observed age range of cases from child health care centers Rotterdam	Pesticides	The year before delivery	JEM based on job title provided by parents in an interview	Hypospadias	Child health care center physician trained by paediatric urologist and paediatric endocrinologist	Crude		6

Reference	Country	Design	Years	Data source	Control definition	Exposure	Exposure period	Exposure assessment	Outcome	Outcome ascertainment	Effect	Adjustment variables	Score
Rocheleau et al. (2011)	The USA	Case-control	1997–2002	National Birth Defects Prevention Study	Non-malformed live birth selected from birth certificates or hospital records	Pesticides	One month before conception through end of first trimester	Exposures were assigned by an expert, assisted by a JEM, from a job history completed by mothers during a telephone interview	Hypospadias (second and third degree), categorised as isolated or multiple	Surveillance by birth defect registries, clinical geneticists performed review of medical records to confirm eligibility	Adjusted	All other pesticides, parity, maternal race and age, infant gestational age, study center	6
Rocheleau et al. (2015)	The USA	Case-control	1997–2002	National Birth Defects Prevention Study	Non-malformed live birth selected from birth certificates or hospital records	Pesticides	One month before conception through end of first trimester	Exposure was assigned by an expert-guided task-exposure matrix and job history details reported by mothers during a telephone interview	CHD	Surveillance by birth defect registries, clinical geneticists performed review of medical records to confirm eligibility	Adjusted[b]	Maternal education, study site, income, pre-pregnancy BMI, alcohol consumption, language of interview, paternal education	8
Shaw et al. (1999)	The USA	Case-control	1987–1988[f]	California Birth Defects Monitoring Program	Randomly selected from infants born alive in same geographic area and time period without major congenital anomaly diagnosed before first birthday	Pesticides	One month before conception through end of first trimester	Industrial hygienist assigned exposure using narrative job information provided by mothers during a telephone interview	NTD Conotruncal heart defects Oral clefts (isolated)	Surveillance by birth defect registry. Determed by medical geneticist using detailed information	Adjusted[b]	Maternal periconceptional vitamin use, cigarette smoking, education level and race/ethnicity	6
Snijder et al. (2012)	The Netherlands	Case-control	2003–2010	HAVEN study	Healthy children with similar age to case children ascertained in regular health checks by child physicians in the same region	Pesticides Heavy metals	Four weeks prior to conception until eight weeks after conception	JEM using job title and description of work tasks provided by mothers in a questionnaire	CHD	Anomalies were identified with echocardiography and/or cardiac catheterisation and/or surgery	Adjusted	Maternal age, educational level, ethnicity, parity, CHD in family, periconceptional alcohol use, periconceptional medication use, periconceptional folic acid use, urban density	8
Spinder et al. (2017)	The Netherlands	Case-control	1997–2013	EUROCAT Northern Netherlands	Malformed babies/foetuses registered in EUROCAT with a non-chromosomal/non-monogenic disorder, without an oral cleft	Solvents Pesticides Heavy metals	Three months before conception through the first trimester	JEM using job title provided by mothers in a questionnaire	Isolated oral clefts	Surveillance by a birth defect registry. Classification of congenital anomalies is performed according to EUROCAT guidelines	Adjusted	Child sex and previous births	6

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Table I *Continued*

Study	Country	Study design	Study period	Source of case	Source of control	Exposure	Exposure time window	Method of occupational exposure assessment	Type of congenital anomalies	Identification method of congenital anomalies	Adjusted, matched or crude data	Adjustment for covariates	Risk of bias (NOS score)
Tikkanen et al. (1988)	Finland	Case-control	1980–1981	Finnish Register of Congenital Malformations	Next born infant in same Maternity care District	Organic solvents Pesticides	First trimester	Industrial hygienist explored and grouped exposure information provided by mothers during an interview	CHD	Experienced pathologist checked diagnosis based on autopsy findings of stillbirths. Paediatric cardiologist identified through catheterisation, echocardiography, cardiac surgery or clinical follow-up	Matched	Next born and same district	4
Vrijheid et al. (2003)	The UK	Case-control	1980–1989/ 1992–1996	National Congenital Anomaly System	All cases with a congenital anomaly registered in the National Congenital Anomaly System	Pesticides Heavy metals	Job early in pregnancy	JEM based on job classified by industrial hygienists. Jobs were reported on standardised reporting forms collected from doctors and midwives	Hypospadias	Notification from doctors and midwives using standardised reporting forms	Adjusted	Year of birth, region, maternal age, social class of mother, social class of father	7
Wang et al. (2015)	China	Case-control	2012–2013	Two university medical centers	Healthy infants with similar age to case children from same medical centers	Pesticides Heavy metals	Four weeks prior to conception until end first trimester	JEM using job description provided by parents in a face to face interview	CHD (isolated)	Diagnosis confirmed by cardiac catheterisation/ paediatric cardiologists	Adjusted	Maternal age at birth, maternal education level, gravity, parity, artificial abortion, folic acid use, medication use, drinking capacity, area of residence periconceptionally	7

NOS = Newcastle-Ottawa Scale, NTD = Neural Tube Defect, USA = United States of America, BMI = body mass index, CHD = Congenital Heart Defect, EUROCAT = European Registry Of Congenital Anomalies and Twins, JEM = Job Exposure Matrix, ICD = International Classification of Diseases. UK = United Kingdom, * = not included in the meta-analysis.[a] = crude odds ratios are shown because adjusted did not change results,[b] = raw data was used to calculate crude odds ratios for meta-analyses because subgroups of exposures were merged,[c] = raw data for NTD was used because odds ratios was not given, cleft palate without cleft lip were only adjusted for maternal age at birth and residence,[d] = exposure was assisted with a literature-based approach as well, for this study data of the expert consensus-based approach was used,[e] = raw data was used to calculate odds ratios for meta-analyses because subgroups of congenital anomalies were merged,[f] = study period 1987–1989 for oral clefts.

Table II Overview of associations between maternal exposure and several congenital anomalies.

Congenital anomaly	Maternal occupational exposure	Studies	Exposed/total cases	Exposed/total controls	Pooled OR	95% CI	Heterogeneity (%)
Neural tube defects							
	Solvents	4	124/888	419/4145	**1.51**	**1.09–2.09**	35
	Glycol ethers	2	29/110	142/882	**1.93**	**1.17–3.18**	0
	Pesticides	4[*]	183/1097	918/3734	0.93	0.76–1.15	0
	Metals	2	12/458	18/539	NA	NA	82
Congenital heart defects							
	Solvents	6	185/2526	848/6744	**1.31**	**1.06–1.63**	0
	Glycol ethers	2	61/291	142/882	1.63	0.94–2.84	18
	Pesticides	5[*]	1088/4742	970/4477	0.81	0.54–1.21	38
	Metals	3	27/1185	48/1595	1.83	0.65–5.20	49.8
Orofacial clefts							
	Solvents	7[*]	354/1854	2111/11 120	NA	NA	65
	Glycol ethers	3[*]	91/256	183/1037	**1.95**	**1.38–2.75**	0
	Pesticides	2	39/644	131/4773	NA	NA	57
	Metals	2	15/487	89/5107	1.62	0.91–2.86	0
Cleft lip with or without cleft palate							
	Solvents	5	198/866	1532/8371	**1.35**	**1.10–1.66**	8
	Glycol ethers	3	61/167	183/1037	**1.95**	**1.38–2.75**	0
	Pesticides	2	30/449	131/4773	1.30	0.84–2.01	0
	Metals	2	9/327	89/5107	1.45	0.70–3.01	0
Cleft palate							
	Solvents	5	142/966	1532/8371	1.25	0.94–1.65	26
	Glycol ethers	3[*]	30/89	183/1037	**1.85**	**1.10–3.09**	0
	Pesticides	2	9/195	131/4773	NA	NA	70
	Metals	2	6/160	89/5107	2.06	0.63–6.75	26
Hypospadias							
	Solvents	1	7/300	5/302	**3.63[a]**	**1.94–7.17**	
	Pesticides	7	227/5748	1190/82 120	0.97	0.75–1.24	24
	Metals	4	89/4870	1303/79 939	NA	NA	67

Bold values represent statistically significant values. * = Egger's test indicated that publication bias was likely, NA = not applicable: pooled estimate could not be calculated because of heterogeneity (>50%). [a] = no pooled OR, because only one study is included.

Agreement on methodological quality between the two reviewers was moderate (overall agreement 83% (238/288); Cohen's Kappa statistic: 0.45). Most disagreements were caused by criteria on comparability and ascertainment of exposure.

Synthesis of results

Table II shows an overview of the results of our meta-analyses. Results of individual studies are presented in Supplementary Table SIV. Forest plots of significant findings of the main analyses are shown in the main figures. All other forest plots and all funnel plots are shown in Supplementary figures.

Neural tube defects

Five papers examined the association between occupational exposure to solvents and neural tube defects (Blatter et al., 1996; Cordier et al., 1997, 2001; Brender, et al., 2002; Desrosiers et al., 2012). One study was excluded from the meta-analysis because the OR could not be calculated (Brender et al., 2002). Two studies included in the meta-analysis reported a positive association between solvent exposure and neural tube defect (Cordier et al., 1997; Desrosiers et al., 2012). The pooled estimate of the forest plot in Figure 2 showed that maternal occupational exposure to solvents was associated with a higher risk of neural tube defects in the offspring (OR: 1.51, 95%CI: 1.09–2.09). Egger's test indicated that publication bias was unlikely (Supplementary Figure S1). A subgroup analysis was performed on the three studies that reported on glycol ethers as exposure (Cordier et al., 1997, 2001; Brender et al., 2002). One study was excluded from the meta-analysis because the OR could not be calculated (Brender et al., 2002). The pooled estimate showed a statistically significant higher risk of neural tube defects in the offspring (OR: 1.93, 95%CI: 1.17–3.18, Supplementary Figure S2). The likelihood of
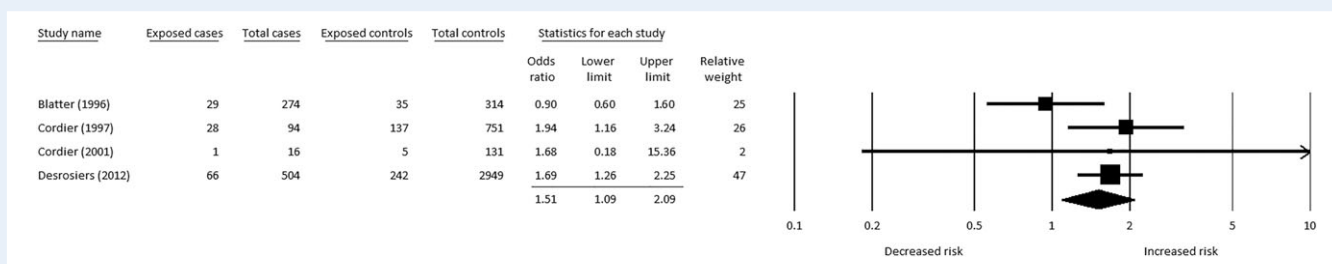
Figure 2 **Forest plot of maternal occupational exposure to solvents and risk of neural tube defects in offspring**.
Heterogeneity: $\chi^2 = 5.54$, df $= 3$, $P = 0.21$, $I^2 = 35\%$.

publication bias could not be assessed, because only two studies were included.

Five studies assessed the relation between occupational exposure to pesticides and neural tube defects (Blatter *et al.*, 1996; Shaw *et al.*, 1999; Brender *et al.*, 2002; Makelarski *et al.*, 2014; Pettigrew *et al.*, 2016). We excluded Pettigrew *et al.* from the meta-analysis because they used the same study population as Makelarski *et al.*, and this last study had a larger sample size. No association was found between pesticide exposure and neural tube defects (pooled estimate OR: 0.93, 95%CI: 0.76–1.15, Supplementary Figure S3). Egger's test indicated that publication bias is likely (Supplementary Figure S4).

Three studies investigated the association between exposure to metals and neural tube defects (Blatter *et al.*, 1996; Brender *et al.*, 2002, 2006). Two studies retrieved the cases from the Texas Neural Tube Defect project (Brender *et al.*, 2002, 2006). We included Brender *et al.* (2006) in the meta-analysis because it assessed several classes of heavy metals compared to Brender *et al.* (2002), which only assessed maternal occupational exposure to lead. The study of Blatter *et al.* showed an association in the opposite direction between exposure to metals and neural tube defects. Because the results were heterogeneous, no pooled estimate could be calculated ($\chi^2 = 5.6$, df $= 1$, $P = 0.02$, $I_2 = 82\%$, Supplementary Figure S5). This heterogeneity and publication bias could not be assessed because only two studies are included.

Congenital heart defects

Six papers assessed the relation between occupational exposure to solvents and congenital heart defects in the (Tikkanen *et al.*, 1988; Cordier *et al.*, 1992, 1997, 2001; Garlantézec *et al.*, 2009; Gilboa *et al.*, 2012). None of the studies in the meta-analysis found an association between exposure to solvents and congenital heart defects as a group (Tikkanen *et al.*, 1988; Cordier *et al.*, 1992, 1997, 2001; Garlantézec *et al.*, 2009; Gilboa *et al.*, 2012). However, several studies found increased ORs for specific phenotypes of congenital heart defects (Cordier *et al.*, 1997, 2001; Gilboa *et al.*, 2012), and the forest plot in Figure 3 showed an association between maternal occupational exposure to solvents and congenital heart defects in the offspring (OR: 1.31, 95% CI: 1.06–1.63). Egger's test indicated that publication bias was unlikely (Supplementary Figure S6). A subgroup analysis was performed on two studies that reported on glycol ethers as exposure (Cordier *et al.*, 1997, 2001). The pooled estimate of maternal

occupational exposure to glycol ethers and congenital heart defects in the offspring showed no significant association (OR: 1.63, 95% CI: 0.94–2.84, Supplementary Figure S7). The likelihood of publication bias could not be assessed.

Five studies assessed the association between maternal occupational exposure to pesticides and congenital heart defects (Tikkanen *et al.*, 1988; Shaw *et al.*, 1999; Snijder *et al.*, 2012b; Rocheleau *et al.*, 2015; Wang *et al.*, 2015). Shaw *et al.* (1999) included only cases with conotruncal congenital heart defects. None of the studies showed an increased OR. The pooled estimate showed no association between mothers who were occupationally exposed to pesticides and congenital heart defects in the offspring (OR: 0.81, 95% CI: 0.54–1.21, Supplementary Figure S8). Egger's test indicated publication bias is likely (Supplementary Figure S9).

Three studies assessed the relation between exposure to metals and congenital heart defects (Jackson *et al.*, 2004; Snijder *et al.*, 2012b; Wang *et al.*, 2015). Jackson *et al.* (2004) only included cases with one specific congenital heart disease: total anomalous pulmonary venous return. Only the study of Wang *et al.* showed an association between occupational exposure to metals and congenital heart defects in the offspring (Wang *et al.*, 2015). The pooled estimate showed no significant association (OR: 1.83, 95% CI: 0.65–5.20, Supplementary Figure S10). Egger's test indicated that publication bias is unlikely (Supplementary Figure S11).

Orofacial clefts

Eight studies investigated the association between maternal occupational exposure to solvents and oral clefts in the offspring (Cordier *et al.*, 1992, 1997, 2001; Lorente *et al.*, 2000; Chevrier *et al.*, 2006; Garlantézec *et al.*, 2009; Desrosiers *et al.*, 2012; Spinder *et al.*, 2017). We excluded Lorente *et al.* from the meta-analysis because they used the same study population as Cordier *et al.* (1997). Cordier *et al.* (1997) included all solvent subclasses whereas Lorente *et al.* only studied exposure to glycol ethers. Three studies reported a positive association between solvent exposure and oral clefts in the offspring (Cordier *et al.*, 1997; Chevrier *et al.*, 2006; Garlantézec *et al.*, 2009). These results were too heterogeneous to calculate a pooled estimate ($\chi^2 = 17.3$, df $= 6$, $P = 0.01$, $I^2 = 65\%$) and the source of this heterogeneity could not be explored (Supplementary Figure S12). Egger's test indicated publication bias was likely (Supplementary Figure S13). We performed a subgroup analysis on data from five studies that
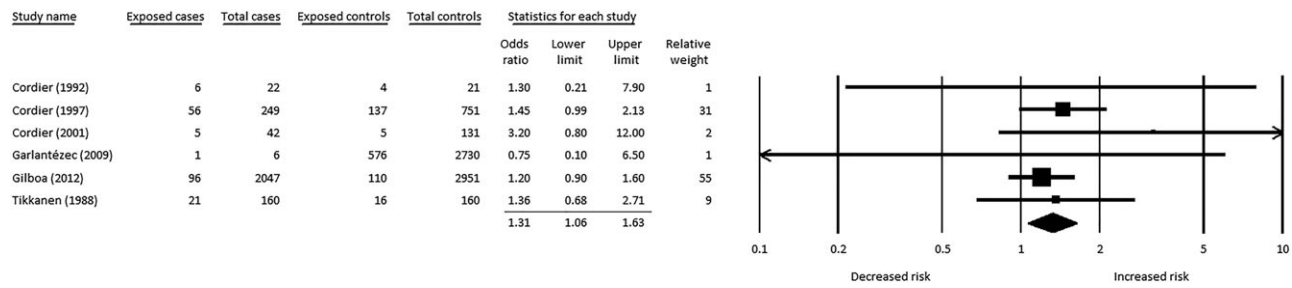
Figure 3 Forest plot of maternal occupational exposure to solvents and risk of congenital heart defects in offspring.
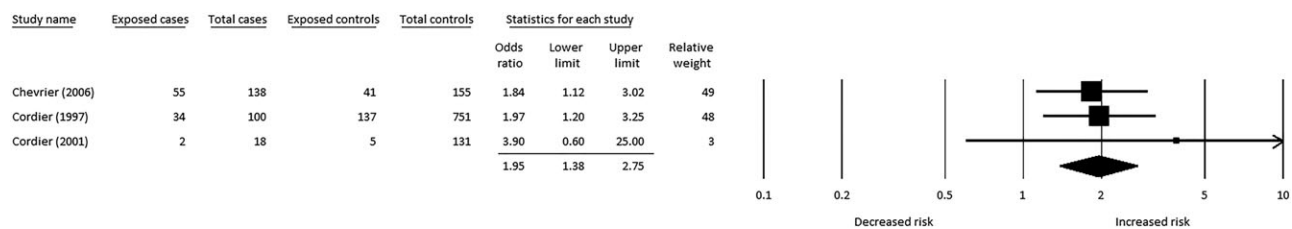Heterogeneity: $\chi2 = 2.58$, df $= 5$, $P = 0.76$, $I^2 = 0\%$.

Figure 4 Forest plot of maternal occupational exposure to glycol ethers and risk of oral clefts in offspring.
Heterogeneity: $\chi2 = 0.58$, df $= 2$, $P = 0.75$, $I^2 = 0\%$.

reported separately on cases with cleft lip with or without cleft palate and cleft palate (Cordier *et al.*, 1997, 2001; Chevrier *et al.*, 2006; Desrosiers *et al.*, 2012; Spinder *et al.*, 2017). The studies of Chevrier *et al.* and Cordier *et al.* (1997) concluded that there was an association between exposure to solvents and cleft lip with or without cleft palate. The pooled estimate in our meta-analyses did show an association as well (OR: 1.35, 95% CI: 1.10–1.66, Supplementary Figure S14). Egger's test indicated publication bias was unlikely (Supplementary Figure S15). None of the studies reporting on the exposure to solvents and cleft palate in offspring did show an association, nor did the pooled estimate show a significant association (OR: 1.25, 95% CI: 0.94–1.65, Supplementary Figure S16). Egger's test indicated publication bias was unlikely (Supplementary Figure S17).

Furthermore, we performed subgroup analyses on three studies that reported on glycol ethers, a subgroup of solvents (Cordier *et al.*, 1997, 2001; Chevrier *et al.*, 2006). The pooled estimate of maternal occupational exposure to glycol ethers showed an association with orofacial clefts in the offspring (OR: 1.95, 95% CI: 1.38–2.75, Figure 4). Publication bias was likely (Supplementary Figure S18). Additionally, separate analyses on cleft lip with or without cleft palate and cleft palate alone with these same studies were performed. Both analyses showed an association when mothers are occupationally exposed to glycol ethers (OR: 1.95, 95% CI: 1.31–2.92; OR: 1.85, 95% CI: 1.10–3.05, respectively) (Supplementary Figure S19 and S21). Egger's test indicated publication bias was unlikely for cleft lip with or without cleft palate, and likely for cleft palate alone (Supplementary Figure S20 and S22).

Two studies assessed the association between maternal occupational exposure to pesticides and oral clefts in the offspring (Shaw *et al.*, 1999; Spinder *et al.*, 2017). Only the study of Spinder *et al.* found a positive association. The results were too heterogeneous to calculate a pooled estimate ($\chi^2 = 2.3$, df $= 1$, $P = 0.13$, $I^2 = 57\%$, Supplementary Figure S23). Heterogeneity and publication bias could not be assessed, because only two studies were included. When a separate analysis on cleft lip with or without cleft palate was performed the pooled estimate with these two studies estimate showed no significant association (OR: 1.30, 95% CI: 0.84–2.01, Supplementary Figure S24). The results for cleft palate were too heterogeneous to calculate a pooled estimate ($\chi^2 = 3.4$, df $= 1$, $P = 0.07$, $I^2 = 70\%$, Supplementary Figure S25). The source of this heterogeneity could not be assessed because only two studies were included.

Two studies assessed the relation between exposure to metals and oral clefts (Lorente *et al.*, 2000; Spinder *et al.*, 2017). The pooled estimate showed no significant association between occupational exposure to metals and oral clefts in the offspring (OR: 1.62, 95% CI: 0.91–2.86, Supplementary Figure S26). Publication bias could not be assessed, because only two studies were included. When a separate analysis on cleft lip with or without cleft palate and cleft palate alone was performed with these two studies, the pooled estimate showed no significant association (OR: 1.45, 95% CI: 0.70–3.01; OR: 2.06, 95% CI: 0.63–6.75, respectively) (Supplementary Figure S27 and S28).

Hypospadias
Only one study assessed the association between maternal occupational exposure to solvents and hypospadias in the offspring (Kalfa

et al., 2015). This study found an association between exposure to solvents and hypospadias in the offspring (OR: 3.63, 95%CI: 1.94–7.17).

Eight studies assessed the association between maternal occupational exposure to pesticides and hypospadias (Vrijheid *et al.*, 2003; Pierik *et al.*, 2004; Carbone *et al.*, 2007; Giordano *et al.*, 2010; Nassar *et al.*, 2010; Morales-Suarez-Varela *et al.*, 2011; Rocheleau *et al.*, 2011; Kalfa *et al.*, 2015). We excluded one study from the meta-analysis because an OR could not be calculated due to zero exposed mothers in the control group (Giordano *et al.*, 2010). Only the study of Kalfa *et al.* showed an association between exposure to pesticides and hypospadias. The pooled estimate showed no association (OR: 0.97, 95%CI: 0.75–1.24, Supplementary Figure S29). Egger's test indicated publication bias is unlikely (Supplementary Figure S30).

Four studies assessed the association between maternal exposure to metals and hypospadias (Vrijheid *et al.*, 2003; Giordano *et al.*, 2010; Nassar *et al.*, 2010; Morales-Suarez-Varela *et al.*, 2011). Only one of these showed an increased risk when mothers were occupationally exposed to metals (Nassar *et al.*, 2010). The results were heterogeneous ($\chi^2 = 9.20$, df = 3, $P = 0.03$, $I^2 = 67\%$, Supplementary Figure S31), which meant that no pooled estimate could be calculated. The heterogeneity in results between studies could be explained by differences in recruitment of cases. Giordano *et al.* recruited children with a congenital anomaly at the hospital while the other studies retrieved their cases from registries. The heterogeneity in results might also be explained by variations in methodological quality. One study scored high in risk of bias on control definition because there was no definition of controls stated (Vrijheid *et al.*, 2003). Three studies had high risk of bias because the non-response rate between cases and controls was either not described or not comparable (Vrijheid *et al.*, 2003; Giordano *et al.*, 2010; Morales-Suarez-Varela *et al.*, 2011). Egger's test indicated publication bias was unlikely (Supplementary Figure S32).

Discussion

Main findings

The aim of this systematic review and meta-analysis was to summarise the current evidence about maternal occupational exposure and congenital anomalies in the offspring. Our meta-analysis showed that maternal occupational exposure to solvents is positively associated with neural tube defects in the offspring, especially exposure to glycol ethers. Maternal occupational exposure to solvents also appeared to be positively associated with congenital heart anomalies in the offspring. Furthermore, we found an association between an increased risk of orofacial clefts in the offspring and maternal occupational exposure to glycol ethers. This was also seen for cleft lip with or without cleft palate and cleft palate alone. Hypospadias in the offspring was also positively associated with maternal exposure to solvents, however this result was only based on one study. For maternal exposure to pesticides and metals no evidence for an association was found for the congenital anomalies considered.

Strengths and limitations

Our study has several strengths. This is the first review that has summarised and evaluated literature of both different subtypes of congenital anomalies and different subtypes of occupational exposures.

Another strength of this review is that we used strict criteria on the definition of congenital anomalies. We used EUROCAT guidelines and definitions for major congenital anomalies because of their reliability (European Surveillance of Congenital Anomalies, 2013). EUROCAT has been registering congenital anomalies since 1979 and has strict inclusion criteria for major congenital anomalies. Furthermore, we included studies that used ICD codes for inclusion of congenital anomalies. Most studies included in our review retrieved case information from birth registries and birth defect registries. Those studies used EUROCAT guidelines or ICD codes as inclusion criteria for congenital anomalies. Other studies used hospital charts or diagnoses by medical experts. Particular birth defects may have been included in some studies and excluded from other studies depending upon which classification method was used. From the study of Hansen *et al.*, it is known that this results in similar estimates of birth defect risks (Hansen *et al.*, 2013). Parental self-reporting can introduce misclassification of congenital anomalies because of low reliability due to low recognition and recall bias of the anomaly (Shi and Chia, 2001), which is why we excluded studies that used parental reporting on congenital anomalies. Another strength is that we have only included studies that used expert assessment for defining occupational exposures or expert judgement, as the basis for assignment at the job level, via a JEM. Studies included in other reviews often used self-reported occupational exposure for exposure assessment or job title as a proxy of occupational exposure. Self-reported occupational exposure can introduce misclassification of exposure (Fritschi *et al.*, 1996). Using job description as proxy for exposure can introduce non-differential misclassification (Snijder *et al.*, 2012a). Occupational hygienists assess occupational exposure on an individual level, whereas JEMs designed by experts can describe exposures on a group level. Studies using those methods reduce the risk of recall bias and differential misclassification of exposure compared to studies based on self-reported exposure (Kromhout and Vermeulen, 2001; Mannetje and Kromhout, 2003). Furthermore, a strength of our review is that most included studies in this systematic review used an adequate exposure time window. This is important, because the critical period for the development of most congenital anomalies is the first month before conception until the end of the first trimester. During the month before conception, maternal oocytes are vulnerable to chemical exposure. In the first trimester after conception, chemical exposure can affect the developing embryo. After this period, organogenesis is completed and the foetus is less vulnerable to chemical exposure for developing most congenital anomalies (Shi and Chia, 2001). Finally, a strength of this review is that only includes studies reporting on major congenital anomalies. Studies reporting minor congenital anomalies were excluded because they have fewer medical, functional, societal and cosmetic consequences, and the definitions, diagnoses and reporting of minor anomalies are very variable (European Surveillance of Congenital Anomalies, 2013). Additionally, several studies have combined all major congenital anomalies in their analysis. Aetiology differs between congenital anomalies of different organ systems, which makes combining congenital anomalies of different organ origins unrealistic and analysis meaningless. For this reason, we excluded studies that did not report on congenital anomalies in separate categories.

We had to group birth defects by anatomical region. This could have been a limitation for congenital heart defects in particular. This review shows a positive association between occupational exposure

to solvents and congenital heart defects but, because congenital heart defects are a heterogeneous group of birth defects, it is possible that this association is true for some types of heart defects and not for others. Also we did not find an association between occupational exposure to pesticides or metals and congenital heart defects overall, however it is still possible that specific types of heart defects might have been associated with these exposures. Our study has also some other limitations. It is possible that we missed relevant publications. Our original search was performed in January 2017, with an additional search performed in October 2017 that identified one additional study (Spinder et al., 2017). During further preparation of the manuscript, we carefully have tracked publications in the field of this systematic review. Another limitation is that it was not possible to calculate pooled estimates for some specific congenital anomalies because too few included studies reported on the congenital anomaly or the occupational exposure. Furthermore, it is a limitation that it was not possible to analyse individual chemicals, we examined only generic occupational exposure classes in this review. It was also not possible to study exposure–response relations as not all included studies reported levels of exposure. Even when studies did report on level of exposure, it is questionable whether categories of exposure are comparable between studies because studies do not handle strict criteria for categorising levels of exposure. Dichotomising exposure could have masked the effect of a specific exposure on the development of congenital anomalies. Some studies found associations only at high doses, but not for 'any exposure' (Chevrier et al., 2006; Rocheleau et al., 2015). Those studies were included in our meta-analysis with the non-significant 'any exposure' OR. Another limitation is that little is known about the association between occupational exposure and multiple congenital anomalies (i.e. major congenital anomalies in more than one organ system). It is possible that one occupational exposure contributes to anomalies in multiple organ systems. Furthermore, eight studies did not correct for any confounding factors such as maternal age, folic acid use or maternal education. Not correcting for confounding factors leads to a high risk of bias and may result in an overestimation of the effect of occupational exposure on the development of congenital anomalies in the offspring (Blair et al., 2007). Finally, it is important to interpret the results with caution due to the likelihood of publication bias. Although Egger's test did not indicate the presence of publication bias in most meta-analyses, our funnel plots and Egger's tests are based on fewer than ten studies. It is known that Egger's test is more reliable when at least ten studies are included in the meta-analysis (Ioannidis and Trikalinos, 2007; Higgins and Green, 2011). Furthermore, Egger's test did indicate that publication bias is likely in the meta-analysis on occupational exposure to pesticides and congenital heart defects. This could be a false positive finding, because all included studies are non-significant studies, which makes Egger's less reliable (Ioannidis and Trikalinos, 2007; Higgins and Green, 2011). In addition, the positive Egger's test regarding the meta-analysis on occupational exposure to solvents and oral clefts could be a false positive finding, because the included studies were heterogeneous ($I^2 > 50\%$) (Ioannidis and Trikalinos, 2007; Higgins and Green, 2011).

Comparison with existing literature

Several earlier reviews have summarised the literature regarding occupational exposure and congenital anomalies in offspring. In particular, two meta-analyses have been performed on the association between maternal occupational pesticide exposure and congenital anomalies (Romitti et al., 2007; Rocheleau et al., 2009). The first meta-analysis focused on children with hypospadias and found that maternal occupational exposure to pesticides is not associated with hypospadias in the offspring, when only studies using JEMs were included (OR: 0.93, 5% CI: 0.24–3.65, based on two studies using a JEM) (Rocheleau et al., 2009). This result is in line with the results of our study, where we did not find an association between maternal occupational exposure to pesticides and hypospadias in the offspring (OR: 0.87, 95% CI: 0.73–1.05, based on seven studies). Both studies included in the review of Rocheleau were included in our review. We included an additional five studies assessing the association between maternal occupational pesticide exposure and hypospadias that were published since March 2008.

Another meta-analysis, Romitti et al. (2007), studied the association between maternal occupational pesticide exposure and oral clefts in the offspring (Romitti et al., 2007). They suggested that maternal occupational exposure to pesticides can lead to a modest increase in the risk of having a child with an oral cleft (OR: 1.37; CI: 1.04–1.81). In our meta-analysis, we were unable to estimate a pooled OR, because the studies were too heterogeneous and we included only two papers. The difference between our review and Romitti et al. is that we were restricting our review to those studies with expert assessment of maternal occupational exposure.

Conclusions and implications

Our meta-analysis included 27 studies, examining the association between maternal occupational exposure and congenital anomalies in the offspring, each of which used expert assessment to assess occupational exposure. We concluded that maternal occupational exposure to solvents is associated with an increased risk of neural tube defects, congenital heart anomalies and orofacial clefts in the offspring. Occupational health specialists, employers and female employees should be aware of the possible teratogenic effects of solvent exposure at the workplace. Clinicians should provide women with preconception advice on exposure to solvents at the workplace to prevent neutral tube defects, congenital heart defects and orofacial clefts. Further research should focus on specific chemicals, use expert-based exposure assessment, and perform dose-response evaluation.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Acknowledgements

Authors' roles

NSp wrote the first draft of the manuscript and was responsible for the search in MEDLINE/EMBASE, for selection based on title and abstract and full text, for inclusion and exclusion of articles, for the data extraction and quality assessment, for interpretation of the data, and the for revisions of the manuscript. JP contributed to the selection based on title and abstract and full text, to the inclusion and exclusion of articles, and to data extraction and quality assessment. NSm assisted and guided with the study design and reviewed data extraction. HdW verified the selection process of articles and reviewed the data extraction. HK verified the occupational exposure categories. JB reviewed the data extraction and verified the categories of congenital anomalies. HdW, HMB and HK initiated the study. All authors critically revised the protocol and manuscript.

Funding

Conflict of interest

The authors report no conflict of interest.

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