supplemento 1
numero 3/4
anno 42
maggio
agosto
2018

EPIDEMIOLOGIA & PREVENZIONE

Rivista dell'Associazione italiana di epidemiologia

Consiglio Nazionale delle Ricerche
IFC - Istituto di Fisiologia Clinica

Silvia Baldacci
Francesca Gorini
Michele Santoro
Anna Pierini
Fabrizio Minichilli
Fabrizio Bianchi

ENVIRONMENTAL AND INDIVIDUAL EXPOSURE AND THE RISK OF CONGENITAL ANOMALIES: A REVIEW OF RECENT EPIDEMIOLOGICAL EVIDENCE

ESPOSIZIONE AMBIENTALE E INDIVIDUALE E RISCHIO DI ANOMALIE CONGENITE: UNA RASSEGNA DELLE EVIDENZE EPIDEMIOLOGICHE RECENTI

EDIZIONI inferenze

Inferenze, via Ricciarelli 29, 20148 Milano. Poste Italiane spa - Sped. in abb. post. Dl. 353/2003 convertito in legge 27.02.04 n.46 - art.1, com.1, DCB Milano - Una copia 13,50 euro issn 1120-9763 maggio-agosto 2018

EPIDEMIOLOGIA & PREVENZIONE

Rivista dell'Associazione italiana di epidemiologia

Rivista fondata da Giulio A. Maccacaro

ANNO 42 (3-4) 2018

Epidemiologia & Prevenzione
è indicizzata in Medline, Scopus,
Science Citation Index Expanded,
Journal Citation Reports/Science Edition

Pubblicazione bimestrale Registrazione
del Tribunale di Milano
n. 239/1977 Spedizione in AP - 45% - art. 2 comma 20b
legge 662/96 - Milano

Iscrizione al Registro degli Operatori
di Comunicazione (ROC) n. 11747

Una copia: 13,50 euro

Abbonamento annuo: informazioni e condizioni sul sito
www.epiprev.it

Gestione abbonamenti: ufficio abbonamenti
tel. 02 48702283, fax 02 48706089

I dati necessari per l'invio della rivista sono trattati elettronicamente e utilizzati dall'editore Inferenze scarl per la spedizione della presente pubblicazione e di altro materiale medico-scientifico.
Ai sensi dell'art.13 Legge 675/96 è possibile in qualsiasi momento e gratuitamente consultare, modificare e cancellare i dati, o semplicemente opporsi al loro utilizzo scrivendo a:
Inferenze scarl, responsabile dati, via Ricciarelli 29, 20148 Milano.

IVA assolta dall'editore ai sensi dell'art. 74 lettera C del DPR 26/10/1972 n.633 e successive modificazioni e integrazioni nonché ai sensi del DM 29/12/1989. Non si rilasciano quindi fatture (art. 1 c. 5 DM 29/12/1989).

Testata associata
A.N.E.S.
ASSOCIAZIONE NAZIONALE
EDITORIA PERIODICA SPECIALIZZATA

Stampa
Arti grafiche Ancora srl - Milano

EDIZIONI inferenze

via Ricciarelli 29, 20148 Milano
segreteria@inferenze.it

Modalità di abbonamento
Fai tutto con PayPal sul sito web della rivista:
www.epiprev.it/abbonamenti
Pagamento con carta di credito (American Express, Carta Sì, VISA, Eurocard, Master Card) telefonando allo 02-48702283 dal lunedì al venerdì dalle 9 alle 13
Versamento su conto corrente postale n. 55195440
intestato a Inferenze scarl, via Ricciarelli n. 29, 20148 Milano (segnalare la causale del versamento).
Accredito tramite c/c bancario presso: UNIPOL BANCA
Piazza Wagner n. 8, 20145 Milano,
IBAN: IT53P 03127 01600 000000003681
intestato all'impresa editoriale Inferenze scarl,
via Ricciarelli n. 29, 20148 Milano.

e&p

SUPPLEMENTO

ENVIRONMENTAL AND INDIVIDUAL EXPOSURE AND THE RISK OF CONGENITAL ANOMALIES: A REVIEW OF RECENT EPIDEMIOLOGICAL EVIDENCE

ESPOSIZIONE AMBIENTALE E INDIVIDUALE E RISCHIO DI ANOMALIE CONGENITE: UNA RASSEGNA DELLE EVIDENZE EPIDEMIOLOGICHE RECENTI

Silvia Baldacci, Francesca Gorini, Michele Santoro, Anna Pierini, Fabrizio Minichilli, Fabrizio Bianchi
Unit of Environmental Epidemiology and Disease Registries, Institute of Clinical Physiology, National Research Council, Pisa (Italy)

Corresponding author: Silvia Baldacci; silviab@ifc.cnr.it
Conflicts of interest: the authors decleare they have no conflicts of interest

Consiglio Nazionale delle Ricerche
IFC - Istituto di Fisiologia Clinica

CONTENTS
INDICE

ABSTRACT / RIASSUNTO **3**

BACKGROUND / PREMESSA **5**

METHODS / METODI **6**

1. CONGENITAL ANOMALIES AND ENVIRONMENTAL EXPOSURES /
ANOMALIE CONGENITE ED ESPOSIZIONI AMBIENTALI

- **Industries** / Industrie **9**
- **Mines** / Miniere **11**
- **Landfills** / Discariche **12**
- **Incinerators** / Inceneritori **14**

2. CONGENITAL ANOMALIES AND INDIVIDUAL EXPOSURES /
ANOMALIE CONGENITE ED ESPOSIZIONI INDIVIDUALI

- **Cigarette smoke** / Fumo **16**
- **Alcohol** / Alcol **20**
- **Socioeconomic status** / Livello socioeconomico **20**
- **Occupational exposure** / Esposizione occupazionale **22**
- **Air pollution** / Inquinamento atmosferico **25**

3 DISCUSSION AND CONCLUSIONS /
DISCUSSIONE E CONCLUSIONI

DISCUSSION / DISCUSSIONE **29**

Environmental exposures / Esposizioni ambientali **29**

- **Industries** / Industrie **29**
- **Mines** / Miniere **29**
- **Landfills** / Discariche **29**
- **Incinerators** / Inceneritori **30**

Individual exposures / Esposizioni individuali **30**

- **Cigarette smoke** / Fumo **30**
- **Alcohol** / Alcol **30**
- **Socioeconomic status** / Livello socioeconomico **30**
- **Occupational exposure** / Esposizione occupazionale **30**
- **Air pollution** / Inquinamento atmosferico **31**

CONCLUSIONS / CONCLUSIONI **31**

REFERENCES / BIBLIOGRAFIA **32**

ABSTRACT

INTRODUCTION

Congenital anomalies (CAs) represent one of the main cause of foetal death, infant mortality and morbidity, and long-term disability. CAs have been object of systematic registration activity for a long-time in many geographical areas in Europe and worldwide. CAs are often associated with disabilities of different types and severity, including the developed Countries worldwide. According to the World Health Organization (WHO), each year approximately 3,2 million of children worldwide are born with a CA and approximately 300,000 newborns with a diagnosis of birth defect die within the first 28 days of life. In Europe, CAs are the leading cause of perinatal mortality: the European Surveillance of Congenital Anomalies (EUROCAT) network estimated a perinatal mortality associated with CAs of 9.2 per 10,000 births in 2008-2012. In Italy, the Ministry of Health estimates that, on the average of 500,000 births each year, about 25,000 present at least one CA. Moreover, approximately 25% of infant mortality is due to CAs and about 50% of infant mortality is attributable to perinatal morbidity, almost always of prenatal origin. Regarding long-term survival, a recent population study conducted between 1985 and 2003 in the UK estimated a 20.5-year survival of 85.5% of children born with at least one CA. According to the Centre for Disease Control and Prevention, approximately 3.3% of live births in the United States have a severe birth defect. Since CAs represent a significant public health issue, an effective primary prevention strategy should be a priority for public policies and healthcare system.

Regarding aetiology, although in many cases the cause is still unknown, it has been hypothesized that CAs may be developed during the first trimester of pregnancy as a result of hereditary polygenic defects or of a gene-environment interaction. The aetiology is predominantly multifactorial, caused by complex interactions between genes and environment, which modify the normal embryo-foetal development, especially during the organogenesis phase.

In particular, environmental factors (e.g., chemical toxicants, infection agents, maternal disease, and exogenous factors) can have preconceptional mutagenic action, postconceptional teratogenic effects, periconceptional endocrine disruption or epigenetic action. Regarding genetic causes, there are genetic-chromosomal aberrations or dysgeneses. Furthermore, socioeconomic factors affect reproductive health by differentiating the exposure to the other risk factors as well as the access to prevention measures.

In recent years, the importance of the environment as a major factor of reproductive risk has been highlighted.

An individual may be exposed to pollutants present in the workplace and the population may be exposed to multiple sources of environmental contamination of water, soil, and air matrices. Pregnant women and the developing foetus are particularly sensitive to the effects of environmental exposure.

OBJECTIVE

The aim of the present working paper is to produce an updated review of the epidemiological evidence on the risk of CAs associated with environmental exposures, socioeconomic, and main individual risk factors, such as cigarette smoking and alcohol consumption, according to the approach proposed by Pirastu et al. 2010 in the framework of the SENTIERI Project (the Italian Epidemiological Study of Residents in National Priority Contaminated Sites).

DESIGN AND METHODS

Literature search was carried out in PubMed, following the SENTIERI project criteria to evaluate evidence, by selecting articles in English or Italian language published from 2011 to 2016 regarding human studies. For this review, descriptive and analytical epidemiological studies (cohort, case-control, cross-sectional, and ecological), systematic reviews, and metanalyses reporting association estimates between the outcome and at least one of the risk factors were selected.

As in Pirastu et al., the sources of environmental exposure have been classified into four macrocategories: industries, mines, landfills, and incinerators. The sources of individual exposure considered were: active and passive cigarette smoking, alcohol consumption, socioeconomic status (SES), occupational and environmental exposures related to air pollutants from vehicular traffic only. The obtained results were assessed according to the evaluation criteria on the epidemiological evidence related to the association between the outcome and exposures predefined and published by the SENTIERI working group (WG). For the evidence assessment, the SENTIERI WG criteria favoured firstly primary sources and quantitative metanalyses, secondly, consistency among sources. The evaluation of the epidemiological evidence for the association between outcome and the exposure has been classified into three categories: sufficient (S), limited (L), inadequate (I).

RESULTS

Industries: during the period under review, six single studies evaluating the association between industrial sites exposure and the risk of CAs were found. The epidemiological evidence of association between outcome and exposure has been considered limited.

Mines: from the bibliographic research, three single studies investigating possible cause-effect relationship between maternal residential proximity to mines and the risk of CAs have been collected providing inadequate epidemiological evidence.

Landfills: during the period under review, one systematic review and one literature review evaluating the causal associations between maternal residential proximity to landfills and CAs were identified. The epidemiological evidence is limited and concerns almost exclusively sites containing industrial or hazardous waste.

Incinerators: a systematic review has been selected; it concludes that the evidence for the association between maternal residential proximity to incinerators and CAs are inadequate.

Cigarette smoking: the literature search identified eight systematic reviews with metanalysis, five multicentre studies, and ten single studies assessing the causal association between maternal and/or paternal exposure to smoking and the risk of CAs in the offspring providing sufficient evidence for a causal association between maternal exposure to cigarette smoke and the risk of congenital heart defects, oro-facial clefts, neural tube defects, and gastrointestinal malformations.

Alcohol: three systematic reviews with metanalysis, two metanalyses, one multicentre study, and four single studies were collected for the period under review. The acquired literature has provided limited epidemiological evidence for associations between alcohol consumption and CAs in the nervous system, particularly for anencephaly and spina bifida.

Socioeconomic status: the evidence of an association with socioeconomic factors was inadequate due to an insufficient number of studies selected during the period under consideration.

Occupational exposure: the literature search collected one metanalysis, eight multicentre studies, and five single studies. The epidemiological evidence for associations between paternal occupational exposure to solvents and neural tube defects and between maternal pesticide exposure and gold-facial clefts were judged limited.

Air pollution: two systematic reviews with metanalyses, two multicentre studies, and nine single studies were selected by literature search; the epidemiological evidence for a causal association between air pollutants exposure and the risk of CAs is still to be considered limited.

CONCLUSIONS

For future epidemiological studies, a better exposure assessment, using in particular more accurate spatial measurements or models, a standardized case definition, a larger sample and more accurate control of the recognized or presumed confounding variables are needed.

Keywords: congenital anomalies, risk factors, epidemiological evidence

RIASSUNTO

INTRODUZIONE

Le anomalie congenite (AC) sono considerate tra le principali cause di mortalità neonatale e infantile, nonché tra le principali fonti di disabilità a lungo periodo. Le AC sono da lungo tempo oggetto di attività sistematica di registrazione in molte aree geografiche, in Europa e a livello internazionale. Queste patologie, oltre a essere associate molto spesso a disabilità di varia natura e gravità, sono responsabili di una quota considerevole di mortalità infantile anche nei Paesi sviluppati.
Secondo l'organizzazione mondiale della sanità (OMS), le AC colpiscono nel mondo circa 3,2 milioni di nati per anno e circa 300.000 neonati affetti da AC muoiono ogni anno entro i primi 28 giorni di vita.
In Europa, le AC rappresentano la principale causa di morte perinatale: il network europeo di sorveglianza delle anomalie congenite "European Surveillance of Congenital Anomalies" (EUROCAT) ha registrato una mortalità perinatale del 9,2 per 10.000 nati nel periodo 2008-2012.
Il Ministero della salute stima che, in Italia, su 500.000 nati mediamente ogni anno, circa 25.000 presentino almeno un'AC. Sempre in Italia, circa il 25% della mortalità infantile è dovuta ad AC e circa il 50% a stati morbosi perinatali, quasi sempre di origine prenatale.
Per quanto riguarda la sopravvivenza a lungo termine, un recente studio di popolazione condotto nel Regno Unito ha stimato una sopravvivenza a 20 anni dell'85,5% per i bambini nati con almeno una AC tra il 1985 e il 2003. Secondo il Centre for Disease Control and Prevention, approssimativamente il 3,3% dei nati vivi negli Stati Uniti ha un grave difetto congenito.
Il costo sociale ed economico delle AC è, dunque, elevato e la loro prevenzione primaria rappresenta una priorità di sanità pubblica.
Riguardo all'eziologia, si ipotizza che le AC possano essere originate durante il primo trimestre di gravidanza come risultato di difetti poligenici ereditari o di un'interazione gene-ambiente, ma in molti casi la causa è ancora sconosciuta. L'eziologia è prevalentemente multifattoriale, determinata da complesse interazioni tra geni e ambiente che alterano il corretto sviluppo embrio-fetale, soprattutto nella fase di organogenesi. In particolare, i fattori ambientali (sostanze chimiche, agenti infettivi, malattie della madre e altri fattori esogeni) possono avere azione mutagena preconcezionale, azione teratogena postconcezionale, azione d'interferenza endocrina e azione epigenetica. Per le cause genetiche, si tratta di aberrazioni genico-cromosomiche o di disgenesie. I fattori socioeconomici agiscono, invece, differenziando l'esposizione ai fattori di rischio e l'accesso alle misure di prevenzione.
Negli ultimi anni e stata messa in evidenza l'importanza dell'ambiente come uno dei maggiori fattori di rischio riproduttivo.
L'individuo può essere esposto a inquinanti presenti sul luogo di lavoro, ma la stessa popolazione locale può essere esposta a molteplici fonti di contaminazione attraverso le matrici ambientali acqua, suolo e aria. La donna in gravidanza e il feto in via di sviluppo sono particolarmente vulnerabili agli effetti delle aggressioni ambientali.

OBIETTIVO

Lo scopo principale di questo lavoro è di produrre una revisione aggiornata delle evidenze epidemiologiche sul rischio di AC associato alle esposizioni ambientali e ai fattori di rischio socioeconomici e individuali, quali il fumo di sigaretta e il consumo di alcol, in linea con il metodo utilizzato da Pirastu et al. 2010 nell'ambito del Progetto SENTIERI.

DISEGNO E METODO

La ricerca bibliografica è stata eseguita su PubMed selezionando gli articoli in inglese e in italiano di studi condotti sull'uomo e pubblicati nel periodo 2011-1016. Per la rassegna, sono stati selezionati sia gli articoli originali di studi descrittivi e analitici epidemiologici (di coorte, caso-controllo, trasversali ed ecologici) sia le revisioni sistematiche e le metanalisi che presentavano stime di associazione tra l'esito (AC) e almeno uno dei fattori di rischio considerati.
Come in Pirastu et al., le fonti di esposizione ambientale sono state classificate in quattro macrocategorie: industrie, miniere, discariche e inceneritori. Le fonti di esposizione individuale considerate sono state: il fumo di sigaretta attivo e passivo, il consumo di alcol, lo stato socioeconomico (SES), le esposizioni occupazionali e ambientali riferite ai soli inquinanti atmosferici da traffico veicolare.
I risultati ottenuti sono stati valutati secondo i criteri di valutazione sull'evidenza epidemiologica relativa all'associazione tra l'esito e le esposizioni stabiliti e pubblicati dal gruppo di lavoro SENTIERI.
I criteri messi a punto dal gruppo di lavoro SENTIERI per la valutazione dell'evidenza epidemiologica privilegiano le fonti primarie e la metanalisi quantitativa e, in seconda istanza, la coerenza tra le fonti. L'evidenza epidemiologica relativa all'associazione tra esito ed esposizione è stata classificata in tre categorie: sufficiente (S), limitata (L) e inadeguata (I).

RISULTATI

Industrie: nel periodo in esame sono stati raccolti sei studi singoli che esaminano l'associazione tra esposizione a siti industriali e rischio di AC. L'evidenza epidemiologica relativa all'associazione tra esito ed esposizione è da considerarsi limitata.
Miniere: dalla ricerca bibliografica sono stati raccolti tre studi singoli che valutano la possibile relazione causa-effetto tra la prossimità residenziale materna a miniere e l'insorgenza di AC, fornendo evidenze epidemiologiche inadeguate.
Discariche: nel periodo in esame sono state individuate una revisione sistematica e una rassegna relative a studi che valutano le associazioni causali tra la prossimità residenziale materna a discariche e le AC. Le evidenze epidemiologiche risultano limitate e riguardano quasi esclusivamente siti contenenti rifiuti industriali o pericolosi.
Inceneritori: è stata individuata una revisione sistematica che conclude che le evidenze relative all'associazione tra la prossimità residenziale materna a inceneritori e l'insorgenza di AC risultano inadeguate.
Fumo: la ricerca bibliografica ha individuato otto revisioni sistematiche con metanalisi, cinque studi multicentrici e dieci studi singoli che hanno esaminato l'associazione causale tra l'esposizione materna e/o paterna al fumo e il rischio di AC nella prole fornendo evidenze sufficienti sulla presenza di un'associazione causale tra l'esposizione materna al fumo di sigaretta e il rischio di cardiopatie congenite, schisi oro-facciali, difetti del tubo neurale e malformazioni gastrointestinali.
Alcol: nel periodo in esame sono state raccolte 3 revisioni sistematiche con metanalisi, due metanalisi, uno studio multicentrico e tre studi singoli. La letteratura esaminata fornisce evidenze epidemiologiche limitate di associazione tra il consumo di alcol e le AC del sistema nervoso, in particolare l'anencefalia e la spina bifida.
Livello socioeconomico: le evidenze di associazione con i fattori socioeconomici risultano inadeguate a causa di un numero insufficiente di studi individuati nel periodo in esame.
Esposizione occupazionale: la ricerca bibliografica ha selezionato una metanalisi, otto studi multicentrici e cinque studi singoli. Emergono evidenze epidemiologiche limitate di associazione tra l'esposizione occupazionale paterna a solventi e i difetti del tubo neurale e tra l'esposizione materna pesticidi e le schisi oro-facciali.
Inquinamento atmosferico: in letteratura sono state selezionate due revisioni sistematiche con metanalisi, due studi multicentrici e nove studi singoli. Le evidenze epidemiologiche relative all'associazione tra l'esposizione a inquinanti atmosferici e il rischio di AC sono da considerarsi ancora limitate.

CONCLUSIONI

Per i futuri studi epidemiologici sono auspicabili migliori metodi di valutazione dell'esposizione, in particolare misure o modelli spaziali più accurati, una definizione standardizzata dei casi, un campione più ampio e un controllo più accurato dei fattori confondenti principali o presunti.

Parola chiave: anomalie congenite, fattori di rischio, evidenza epidemiologica

BACKGROUND
PREMESSA

Congenital anomalies (CAs), also known as congenital malformations or birth defects, can be defined as functional or structural anomalies that occur during intrauterine life. It is estimated that each year 8 million babies – 6% of total births worldwide – are born with a severe congenital birth defect. At least 3.3 millions of children aged 0 to 5 years die as a consequence of severe birth defects and each year approximately 300,000 newborns with a diagnosis of birth defect die within the first 28 days of life.[1-3] In the United States, where over 3.0% of live births present with a congenital defect, CAs represent the leading cause of paediatric hospitalization and infant mortality.[4] In Europe, CAs are the leading cause of perinatal mortality: the European Surveillance of Congenital Anomalies (EUROCAT) network estimated a perinatal mortality associated with CAs of 9.2 per 10,000 births in 2008-2012.[5] The live birth prevalence of CAs does not represent the total CAs prevalence. It is necessary to consider all the cases that do not result in birth in relation to the premature death of the malformed foetus (spontaneous abortion) and therapeutic abortions. In 2010, in Europe, there were 49.16 per 10,000 births recorded as termination of pregnancy following prenatal diagnosis of CA, as reported by EUROCAT surveillance system.[6] In summary, CAs are considered a major cause of foetal death, infant mortality and morbidity, and long-term disability. CAs are diseases with high impact on the affected individuals, on their families, and on the community in terms of quality of life and healthcare service needs.[7] As a consequence, CAs represent a significant public health issue and an efficacy primary prevention strategy should be a priority for public policies and healthcare system. CAs vary widely in severity, organs affected, and aetiopathogenesis. The causes of many CAs are complex and multifactorial, but in most cases their aetiology remains unknown. Most CAs are caused by complex gene-environment interactions, mainly still unknown. It is estimated that about 20% of all CAs are due to gene-chromosomal causes, another 10% to exogenous factors, and the remaining 70% to interactions between the two factors.[8,9] Although genetic factors play an important role, some congenital anomalies might be preventable through interventions addressed to reduce environmental exposures. Environmental factors (such as chemical toxicants, infection agents, maternal diseases, and exogenous factors) can have mutagenic effects before conception, teratogenic effects, endocrine disruption, and epigenetic action. According to the World Health Organization (WHO), approximately 5% (ranging from 1% to 10%) of CAs are attributable to environmental exposures. Genetic causes are attributable to genetic-chromosomal aberration or dysgenesis.[8] Pregnant women and their foetuses may be exposed to multiple contaminants present in environmental matrices (water, soil, air) in the living and working environment, as well as to numerous lifestyle risk factors and socioeconomic determinants.[7,10] Epidemiological studies suggested associations with CAs of various types of environmental exposure, such as air pollutants, cigarette smoke, pesticides, solvents, metals, radiations, contaminants, and chemicals.[11-15]

The main mechanisms of action of exposure to chemical pollutants are DNA methilation,[16,17] oxidative stress,[18,19] inflammatory processes,[20,21] and epigenetic mechanisms.[22,23]

Harmful nicotine and other chemicals in cigarettes have teratogenic and carcinogenic effects on human germ cells and are known to have adverse effects on the development of the embryo, especially during organogenesis.[24,25] Alcohol may enhance the formation of oxygen free radical by inducing apoptosis and modify growth factors by inhibiting or stimulating cell proliferation.[26]

A previous literature review including CAs (carried out on articles published from 1998 to 2009) had been performed by Pirastu el al.,[27] in the framework of the SENTIERI project (the Italian Epidemiological Study of Residents in National Priority Contaminated Sites).[28]

The aim of the present study was to make available a literature review of the recent epidemiological evidence on the risk of CAs associated with environmental and individual exposures.

Since we addressed a very wide topic, namely all CAs associated to many kind of exposure, a non-systematic review was performed.

METHODS
METODI

Our literature review was carried out in PubMed selecting English and Italian articles regarding human studies which were published between 2011 and 2016, maintaining the conceptual framework of SENTIERI methodology and continuing the evaluation of the epidemiological evidence performed by Pirastu et al.[27]

The PubMed search term were:

- **for environmental exposures:** [(residence OR municipality OR mines OR industry OR facilities OR estates OR landfill OR incinerator OR waste OR natural gas OR shale gas OR chemical OR harbor OR asbestos OR power plant) AND ("congenital anomalies" OR" congenital malformations" OR "birth defects" OR "birth outcomes")];
- **for individual exposure:** [(tobacco smoke pollution OR smoking OR alcohol drinking OR "alcohol consumption" OR occupational diseases OR occupations OR job OR workplace OR "work place" OR "work location" OR worksite OR "work site" OR jobsite OR "job site" OR socioeconomic factors OR "health status disparities" OR "standard of living" OR "living standard" OR inequality OR inequalities OR air pollution OR air pollutants OR "particulate matter" OR gases OR urban pollution) AND ("congenital malformation" OR "congenital malformations" OR "congenital anomaly" OR "congenital anomalies" OR "congenital defect" OR "congenital defects" OR "birth defect" OR "birth defects" OR "malformative syndrome" OR "malformative syndromes" OR congenital abnormalities OR deformity OR deformities) AND (birth OR parturition OR delivery OR pregnancy OR pregnancy outcome OR birth certificate OR prenatal OR perinatal OR "maternal exposure" OR "paternal exposure")].

From our initial literature search, we selected 1,566 papers. The abstracts were screened by two researchers to identify potentially relevant articles to be included according to the objective of the present working paper. The identified full papers were reviewed by all the authors and only systematic reviews, metanalyses, and observational epidemiological studies with cohort, case-control, cross-sectional, and ecological design, which reported estimates of association between the outcome (CAs) and at least one of the risk factors of interest, were included in the present review. According to the SENTIERI methodology,[27] the environmental sources of exposure were divided into four macroclasses:

1. industries (refineries, petrochemicals, and metals);
2. mines;
3. landfills;
4. incinerators.

The considered individual exposures were:

- cigarette smoke (active and passive);
- alcohol consumption;
- socioeconomic status (SES);
- occupational exposure;
- air pollution.

To evaluate the evidence of the collected epidemiological literature, we applied the criteria developed by SENTIERI Working Group (WG),[27] which identified a hierarchy in the literature sources to classify each combination of outcome and exposure in terms of strength of association. According to the international consensus of the epidemiological community, SENTIERI WG classified the literature sources in **primary sources** (which express evaluations based on standardized criteria), and in **other sources**, such as quantitative metanalyses, systematic reviews, multicentre studies, and singular studies. Therefore, for the evidence assessment, the SENTIERI WG criteria firstly favoured primary sources and quantitative metanalysis and, secondly, consistency among sources. The evaluation of the epidemiological evidence for the association between outcome and exposure has been classified into three categories, as synthesized in table 1: • sufficient; • limited; • inadequate. The lack of an indication of the category implies the lack of epidemiological data on the association between outcome and risk factor both in primary sources and in quantitative metanalyses, reviews, multicentre studies, or observational studies.

In our review, in the assessment of the epidemiological evidence, we took into account also the results of the evaluation performed by Pirastu et al. 2010.[27]

TYPE OF EVIDENCE	CHARACTERISTICS
SUFFICIENT sufficient to infer the presence of a causal association	One or more of the **primary sources** report the evaluation of sufficient evidence of a causal association or provide data for this evaluation OR metanalyses provide quantitative data for the evaluation of sufficient evidence of a causal association
LIMITED limited but not sufficient to infer the presence of a causal association	one or more **primary sources** / metanalysis / reviews / multicentre studies / two or more studies report the existence of an association, but do not express the evaluation of sufficient evidence of a causal association or do not provide data for this evaluation
INADEQUATE inadequate to infer the presence or the absence of a causal association	several **primary sources** examine the association, but do not agree on the evaluation (conflicting evidence) OR quantitative metanalyses / reviews / multicentre studies / two or more studies examine the association, but do not agree on the evaluation (conflicting evidence) OR **primary sources** / quantitative metanalyses / reviews / multicentre studies / two or more studies examine the association, but none reports its existence OR several studies which do not agree on the evaluation are available (conflicting evidence) OR only one study investigating the association is available

Table 1. Evaluation of the epidemiological evidence by Pirastu et al. 2010.[27]
Tabella 1. Valutazione dell'evidenza epidemiologica dal lavoro di Pirastu et al. 2010.[27]

CONGENITAL ANOMALIES AND ENVIRONMENTAL EXPOSURES

ANOMALIE CONGENITE
ED ESPOSIZIONI AMBIENTALI

INDUSTRIES
INDUSTRIE

A retrospective cohort study performed in Colorado between 1996 and 2009 investigated the maternal exposure to emissions from natural gas wells (within a 10-mile radius from residence), comparing the exposed population with the unexposed population based on both the number of wells within the 10-miles radius and the proximity to the mother's residence. Results revealed a monotonic increase in the prevalence of congenital heart defects (CHDs) in babies, correlating with increasing density and proximity of shale gas to the mother's residence (table 2). Infants born to exposed mothers had a 30% higher risk of CHDs compared to the offspring of unexposed mothers in a similar area without wells. Infants born to exposed mothers showed increased risks compared with the unexposed group; namely, a 400% increase of the tricuspid valve defects, 60% increase of pulmonary valve stenosis (PVS), and 50% increase of ventricular septal defects (VSDs) were observed. A slight increase of neural tube defects (NTDs) among babies born to the most exposed mothers (over 125 wells per mile) was found.[29]

In Texas, association between maternal residential proximity to emissions of chlorinated solvents and selected CAs in their offspring (CHDs, NTDs, cleft lip/palate, limb reductions) was assessed in a case-control study performed on births occurring between 1996 and 2008. The study investigated effects linked to the maternal residential distance from industrial areas or linked to the amount of solvents released from each source on a yearly basis.[30] Results detected a slight increase in risk of cardiac septal defects (CSDs) in babies born to mothers exposed to solvents (any type) compared to the unexposed group. An increase was found for NTDs, especially for spina bifida among babies born to mothers exposed to several chlorinated solvents (e.g., carbon tetrachloride, chloroethane, chloroform). Weak associations were also observed between propylene dichloride and cleft palate and between perchloroethylene and limb reduction defects. Among mothers aged 35 years or older, the associations between maternal residential exposures to chlorinated solvents emissions and development of CAs, especially cleft lip and palate and obstructive cardiac defects, were higher, suggesting that mother's age may increase susceptibility of the developing foetus to the adverse effects of chemical pollutants.[30]

The results from an ecological study on babies born to mothers resident close to an industrial site with power plants and a port in the city of Brindisi (Apulia Region, Southern Italy) reported a higher prevalence rate of total CAs, in particular of CHDs, than those reported by the 2011 pool of EUROCAT registries.[31,32] Specifically, the study observed an increased risk for VSDs and PVS, but not for atrial septal defects (ASDs). The overall risk for CHDs was higher in the city of Brindisi compared to the surrounding municipalities within the same province.[31] A further case-control study in Brindisi reported a risk association between the maternal residence exposure to SO_2 during weeks 3-8 of pregnancy and the occurrence of CHDs and VSDs, with an excess in the 2nd tertile and no trend from the 1st to the 3rd tertile. In the same study, no correlation between mother's exposure to fine particle and CHDs or VSDs emerged.[33]

A descriptive study on the municipality of Gela (Sicily Region, Southern Italy) – an industrial site with chemical plants, a thermoelectric plant, and a large refining plant – carried out between 2003 and 2008 detected an excess compared to the mean value obtained from Italian and European registries for genital organs malformations and for urinary tract defects, including non-specified diagnoses. The study showed an increase of cases with hypospadias compared to the European and Italian reference values, as well as an increase in limb malformations (including non-specified clubfoot), which was higher when compared with data from other areas of Italy. On the contrary, a decrease of lip and cleft palate in comparison to the European data was reported, even if it is difficult to explain and could be indicative of a failure to report or of a loss of documentation (table 2).[34]

LOCATION	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	EXPOSURE ASSESSMENT	CONFOUNDING VARIABLES	REFERENCE
INDUSTRIES							
Colorado (USA)	Cohort LB	124,842 live births (1996-2009)	aOR: 1.2 (1.0-1.3) aOR: 1.3 (1.2-1.5) aOR: 1.5 (1.1-2.1) aOR: 1.5 (1.1-2.1) aOR: 1.6 (1.1-2.2) aOR: 3.9 (1.3-11) aOR: 4.2 (1.3-13) aOR: 2.0 (1.0-3.9)	CHD CHD VSD PVS PVS Tricuspid valve defects Tricuspid valve defects NTD	Average High High Average High Average High High	Newborn gender, maternal age, active smoking, educational level, smoking, alcohol consumption, number of births	McKenzie 2014[29]
Texas (USA)	Case-control LB; FD; ET	60,613 cases 244,927 controls (1996-2008)	aOR: 1.13 (1.04-1.22) aOR: 1.23 (1.10-1.37) aOR: 1.21 (1.07-1.38) aOR: 1.19 (1.06-1.32) aOR: 1.14 (1.02-1.28) aOR: 1.13 (1.05-1.21) aOR: 1.13 (1.02-1.24) aOR: 1.12 (1.01-1.24) aOR: 1.10 (1.01-1.19) aOR: 1.06 (1.02-1.10) aOR: 1.06 (1.04-1.09) aOR: 1.56 (1.11-2.18) aOR: 1.49 (1.08-2.06) aOR: 1.42 (1.09-1.86) aOR: 1.40 (1.04-1.87) aOR: 1.39 (1.08-1.79) aOR: 1.29 (1.01-1.63) aOR: 1.28 (1.01-1.62) aOR: 1.94 (1.32-2.84) aOR: 1.78 (1.22-2.59) aOR: 1.78 (1.12-2.82) aOR: 1.70 (1.06-2.71) aOR: 1.64 (1.24-2.16)	CSD CSD CSD CSD CSD CSD CSD CSD CSD CSD CSD NTD NTD NTD NTD NTD NTD NTD Spina bifida Spina bifida Spina bifida Spina bifida Spina bifida	Carbon tetrachloride 1,1-etylene dichloride Propylene dichloride 1,2-dichloroethylene Tetrachlororethane Ethylchloride 1,2,3-trichloropropane 1,1,2-trichloroethane Chloroform Trichloroethylene Any type of solvent 1,1,2- trichloroethane 1,2,3-trichloropropane Carbon tetrachloride Cloroformium Ethylchloride Metilchloroform 1,2-etylene diclhoride 1,1,2- trichloroethane 1,2,3-trichloropropane Tetrachlororethane 1,1-ethylene dichloride 1,2-ethylene dichloride		Brender 2014[30]
Texas (USA)	Case-control LB; FD; ET	60,613 cases 244,927 controls (1996-2008)	aOR: 1.60 (1.01-2.53) aOR: 1.59 (1.18-2.14) aOR: 1.58 (1.15-2.19) aOR: 1.56 (1.18-2.07) aOR: 1.55 (1.10-2.20) aOR: 1.77 (1.05-2.9) aOR: 1.21 (1.01-1.45) **Mother's age >35 years** aOR: 1.27 (1.01-1.58) aOR: 1.13 (1.04-1.22) aOR: 1.43 (1.08-1.88) aOR: 1.13 (1.03-1.23) aOR: 2.46 (1.23-4.91) aOR: 2.49 (1.09-5.72) aOR: 1.66 (1.04-2.65) aOR: 1.93 (1.05-3.94) aOR: 1.50 (1.00-2.26) aOR: 1.81 (1.06-3.07) aOR: 2.50 (1.11-5.63) aOR: 1.66 (1.07-2.56) aOR: 1.53 (1.21-1.93) aOR: 1.38 (1.14-1.67) aOR: 1.92 (1.11-3.32) aOR: 1.22 (1.03-1.46) aOR: 1.37 (1.10-1.70)	Spina bifida Spina bifida Spina bifida Spina bifida Spina bifida Cleft palate Transversal limb reductions Obstructive heart defects CHD Obstructive heart defects CSD NTD Spina bifida Oro-facial clefts Cleft palate Oral clefts CL ± CP Spina bifida Oro-facial clefts CL ± CP Oro-facial clefts Oro-facial clefts Oro-facial clefts CL ± CP	1,2-dichloroethylene Ethylchloride Carbon tetrachloride Methylchloroform Chloroform Propylene dichloride Tetrachloroethylene Any type of solvent Trichloroethylene Trichloroethylene Trichloroethylene Carbon tetrachloride Carbon tetrachloride Carbon tetrachloride 1,2-etylene diclhoride 1,2-etylene diclhoride Ethylchloride Ethylchloride Ethylchloride Methylchloride Methylchloride 1,2,3-trichloropropane Any type of solvent Any type of solvent		Brender 2014[30]
Brindisi (Italy)	Ecological LB	8,503 live births 194 cases (2001-2010)	RR: 1.42 (1.07-1.89) RR: 2.68 (1.33-5.33) RR: 1.80 (1.34-2.41) RR: 1.49 (1.20-1.85) ***vs.* outlying municipalities** aOR: 1.85 (1.36-2.50)	CAs PVS VSD CHD CHD		Maternal age, deprivation index	Gianicolo 2012[31]
Brindisi (Italy)	Case-control LB	189 cases, up to 4 controls per case (2001-2010)	cOR: 1.74 (1.07-2.81) cOR: 3.21 (1.42-7.25) cOR: 1.60 (0.70-3.62) cOR: 4.57 (1.31-15,96) cOR: 2.54 (0.62-7.40)	CAs CHD CHD VSD VSD	90th percentile SO_2 2nd tertile 3rd tertile 2nd tertile 3rd tertile		Gianicolo 2014[33]
Gela (Italy)	Ecological LB	5,993 live births 178 cases (2003-2008)	RR: 1.41 (1.21-1.63) *vs.* European value RR: 1.97 (1.69-2.27) *vs.* Italian value RR: 0.50 (0.23-0.95) *vs.* Italian value RR: 1.80 (1.19-2.53) *vs.* European value RR: 0.51 (0.23-0.97) *vs.* Italian value RR: 2.04 (1.43-2.76) *vs.* European value RR: 2.97 (2.08-4.02) *vs.* Italian value RR: 2.70 (1.86-3.70) *vs.* European value RR: 3.01 (2.07-4.13) *vs.* Italian value RR: 3.25 (1.05-7.58) *vs.* Italian value RR: 2.73 (1.81-3.84) *vs.* European value RR: 3.29 (2.18-4.62) *vs.* Italian value RR: 0.25 (0.03-0.90) *vs.* European value RR: 1.61 (1.20-2.08) *vs.* Italian value	CAs CAs Limbs (except for club foot n.s.) Limbs (including club foot n.s.) Urinary (except for pielectasia n.s.) Urinary (including pielectasia n.s.) Urinary (including pielectasia n.s.) Genitals (total) Genitals (total) Genitals (except hypospadias) Hypospadias Hypospadias CL CHD			Bianchi 2014[34]

aOR: adjusted odds ratio / *odds ratio aggiustato;* **CAs:** congenital anomalies / *anomalie congenite;* **CHD:** congenital heart defects / *difetti cardiaci congeniti*; **CI:** confidence interval / *intervallo di confidenza*; **CL:** cleft lip / *labioschisi*; **CP:** cleft palate / *palatoschisi*; **CSD:** cardiac septal defects / *difetti cardiaci del setto*; **ET:** elective termination / *interruzione volontaria di gravidanza*; **FD:** foetal death / *morte fetale*; **LB:** live birth / *nato vivo*; **n.s.:** not specified / *non specificato*; **NTD**: neural tube defects / *difetti del tubo neurale*; **PVS:** pulmonary valve stenosis / *stenosi valvolare polmonare*; **RR:** relative risk / *rischio relativo*; **VSD:** ventricular septal defects / *difetti del setto ventricolare*

Table 2. Proximity to industrial areas and risk of congenital anomalies.
Tabella 2. Prossimità residenziale a siti industriali e rischio di anomalie congenite.

MINES
MINIERE

Coal mining activities are widespread across the Appalachian region of the United States (Kentucky, Tennessee, Virginia, and West Virginia) and they largely employ mountain-top mining (MTM) technique with ammonium-nitrate based explosives that causes the seepage of many metals such as arsenic (As), chromium (Cr), mercury (Hg), and lead (Pb) into the groundwater.[35] An ecological study performed within this area for the years 1996-2003 observed an increased prevalence rate ratio (PRR) of total anomalies and for six specific groups (central nervous system, circulatory/respiratory apparatus, gastrointestinal system, urogenital system, musculoskeletal system, "other CAs") in the counties with marked MTM activities. Other mining sites showed an increasing in PRR values compared with unexposed areas exclusively for urogenital anomalies and "other CAs" (table 3).[36] A hospital-based case-control study carried out in West Virginia suggested a higher PRR value in the MTM counties compared with the non-mining areas, when data were not adjusted for the delivery hospital, suggesting that the increase in CAs prevalence was a consequence of the bias introduced by the birth centre.[37]
A small cross sectional study performed in Bolivia in 2006 aimed to evaluate whether the local Weenhayek population, living in proximity to lead and cadmium mine, had an increased risk for reproductive adverse outcomes including CAs (especially, hemangiomas and lymphangiomas) and development disorders compared with the control population. The study did not observe increased risk of CAs.[38]

LOCATION	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	CONFOUNDING VARIABLES	REFERENCE
MINES						
Kentucky, Tennessee, Virginia, West Virginia (USA)	Ecological LB	1,889,071 live births 28,701 cases (1996-2003)	**MTM areas *vs.* control areas** aPRR: 1.26 (1.21-1.32) **non MTM areas *vs.* control areas** aPRR: 1.10 (1.05-1.16) **MTM areas *vs.* control areas** aPRR: 1.93 (1.73-2.15) aPRR: 1.36 (1.11-1.67) aPRR: 1.41 (1.17-1.71) aPRR: 1.35 (1.19-1.54) aPRR: 1.30 (1.20-1.41) aPRR: 1.13 (1.04-1.23) **non MTM areas *vs.* control areas:** aPRR: 1.32 (1.15-1.51) aPRR: 1.12 (1.03-1.22)	CAs CAs Cardio respiratory system Central nervous system Gastrointestinal system Urogenital system Musculoskeletal system Other CAs Urogenital system Other CAs	Maternal age, active smoking, newborn gender, years of schooling, folic acid intake, alcohol consumption, smoking, gestational diabetes, maternal residence in a metropolitan area	Ahern 2011[36]
West Virginia (USA)	Ecological LB	418,385 live births (1990-2009)	**Analysis on 44 hospitals:** cPRR: 1.43 (1.35-1.51); p<0.001 aPRR: 1.08 (0.97-1.20); p=0.16 **Analysis on 6 hospitals with more than 1,000 births:** cPRR: 2.39 (2.15-2.65); p<0.001 aPRR: 1.01 (0.69-1.17); p=0.87	CAs	Hospital birthplace	Lamm 2015[37]
Pilcomayo river (Bolivia); Bermejo river (Argentina)	Cross-sectional LB; FD	191 cases 107 controls (2006)	aOR: 2.60 (0.7-9.2)	CAs	Maternal age	Stassen 2012[38]

aOR: adjusted odds ratio / *odds ratio aggiustato*; **aPRR:** adjusted prevalence rate ratio / *tasso di prevalenza aggiustato*; **CAs:** congenital anomalies / *anomalie congenite*; **CI:** confidence interval / *intervallo di confidenza*; **cPRR:** crude prevalence rate ratio / *tasso di prevalenza crudo*; **FD:** foetal death / *morte fetale*; **LB:** live birth / *nato vivo*

Table 3. Proximity to mines areas and risk of congenital anomalies.
Tabella 3. Prossimità residenziale a miniere e rischio di anomalie congenite.

LANDFILLS
DISCARICHE

A review of epidemiological studies[39] – which followed the International Agency for Research on Cancer (IARC) criteria in the attempt to evaluate the evidence of cause-effect relation between landfills exposure and the risk of CAs[40] – concluded that the reviewed literature provided limited evidence. Overall, this review collected 18 papers published in the years 1992-2010 (table 4). The review covered 10 ecological studies, 1 cohort study, and 7 case-control studies (2 of which were multicentre studies). Three single-site ecological studies were conducted in England. Whilst an increase in prevalence of CAs in babies born to mothers residing in proximity of a landfill was reported in the first of these 3 studies, the risk increased similarly both before and after the opening of the landfill site, suggesting possible involvement of other sources of exposure.[41] In the second study, an increase in CAs prevalence among newborns in proximity of a landfill treating hazardous, domestic, and commercial wastes emerged.[42] The third study did not find any association between CAs in newborns and distance of residence from chromium-contaminated site.[43] In two multisite ecological studies conducted in England, a weak increase in NTDs, hypospadias and epispadias, abdominal wall defects, surgical correction of gastroschisis and exomphalos, and a weak prevalence decrease of CHDs were reported among babies born to mothers living less than 2 km from special and non-special waste landfills. For specific anomalies, especially for hospital admissions for abdominal wall defects, risks were higher in the period before the opening of a landfill site compared with the period after the opening.[44,45] A multisite ecological study carried out in the UK did not observe any associations between CA risk and residential proximity to 61 sites of hazardous waste landfills.[46]

Another multiple-site ecological study carried out in Washington State showed an increased overall risk of CA and skin anomalies in offspring of communities living less than 8 km from landfills processing hazardous waste.[47] Palmer's study found that the number of observed CA cases, compared with the expected, increased by 40% after the opening of landfill sites located within 4 km from residence.[48] A multisite ecological study conducted in Denmark on people residing less than 2 km from one of the 48 landfill sites showed a slight increase in the risk of CHDs, compared with the populations living 2-4 km or 4-6 km away from the landfill sites.[49] This result was not confirmed after the normalization of aggregated data, except for an increased risk of nervous system defects.[49] A Brazilian ecological study performed on the areas surrounding the 15 landfills in San Paolo did not observe any increase in the risk of total CAs among children up to one year of age born to mothers residing within 2 km from a landfill.[50] The lack of an association was reported in a cohort study conducted in an area with 196 landfill sites in Cumbria (England).[51] The multicentre case-control study EUROHAZCON – which aimed to study the risk of congenital anomalies near hazardous-waste landfill sites in Europe – detected a moderate increase for transposition of great arteries (TGA), CSDs, and NTDs among babies born to mothers living within 3 km from landfill sites containing hazardous chemical waste compared with those of mothers living within a 3-7 km radius from the same sites.[52] In a further multicentre study, no association was found even if at each study area was attributed a specific risk coefficient based on the site characteristics.[53] A case-control study carried out in California on 48 sites stocking hazardous waste did report no CAs increases among offspring.[54] Similarly, an Irish case-control study did not observe associations between proximity to landfill of urban waste and CAs prevalence.[55]

An American case-control multisite study showed an increase in the risk of anomalies of CNS, musculoskeletal disorders, and skin malformations among newborns to mothers residing within a 1.6 km radius from one of the 590 landfills containing toxic wastes. The study reported a dose-response relationship.[56] In contrast, a United States case-control study reported a weak association for CNS defects and musculoskeletal system disorders in offspring of mothers living nearby sites producing dangerous emissions (solvents, metals, pesticides).[57] A previous case-control study conducted in the United States did not show any increase in risk of NTDs as a group or of oro-facial clefts in babies born to mothers living within 0,4 km from at least one of the 764 hazardous waste sites.[58]

The review by Triassi et al. relating to the effects of waste disposal on human health found only 2 studies published in 2008-2009 concerning the risk of CAs associated with both legal and illegal disposal of waste. These studies investigated areas in the provinces of Naples and Caserta (Campania Region, Southern Italy), characterized by illegal waste disposal and by the presence of other environmental contaminant sources (intensive agriculture, industrial activities, high population density), and concluded that further studies were needed to detect any possible causal relation.[59] The first study reported the presence of clusters with an excess of prevalence of total CAs (five clusters), urogenital malformations (three cluster), CHDs (two clusters), and limb malformations (one cluster).[60] A second ecological study carried out in the same provinces reported a negative trend between the risk of CHDs and exposure, while observed a positive association with the socioeconomic deprivation index. An excess of urogenital cases and CNS defects for the highest percentile levels of exposure was also detected.[61]

LANDFILLS

LOCATION (NUMBER)	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	EXPOSURE ASSESSMENT	CONFOUNDING VARIABLES	REFERENCE
LANDFILLS							
UK (No. 8) Europe (No. 2) USA (No. 5) Ireland (No. 1) Brazil (No. 1) Denmark (No. 1)	**Systematic review:** • ecological (No. 10) • case-control (No. 2) **Multicentre:** • case-control (No. 5) • cohort (No. 1)	18 studies (1992-2010)	**Single site study:** RR: 1.9 (1.30-2.85) RR: 1.9 (1.23-2.95) RR: 1.9 (1.30-2.90) **Multisite studies:** RR 1.39 (1.12-1.72) aOR: 1.33 (1.11-1.59) RR: 1.07 (1.04-1.09)* RR: 1.02 (1.01-1.03)* aOR: 1.33 (1.27-1.40) aOR: 1.28 (1.22-1.35) aOR: 1.26 (1.20-1.32) aOR: 1.15 (1.10-1.21) aOR: 1.08 (1.02-1.13) aOR: 2.46 (2.27-2.68) aOR: 2.39 (2.16-2.65) aOR: 1.86 (1.24-2.79) RR: 1.05 (1.01-1.10)* RR: 1.06 (1.01-1.12)* aOR: 1.49 (1.09-2.04) aOR: 1.81 (1.02-3.20) RR: 0.96 (0.93-0.99)* aOR: 1.16 (1.00-1.33) RR: 1.18 (1.03-1.34)* RR: 1.08 (1.01-1.15)* RR: 1.07 (1.04-1.10)* aOR: 1.12 (1.02-1.22)	CAs CAs CAs CAs CAs CAs CAs CAs CAs Skin anomalies Skin anomalies NTD NTD NTD CSD TGA CHD CHD Gastroschisis and omphafalocele Abdominal wall defects Hypospadias and epispadias Hypospadias and epispadias	Urban and industrial waste (before/after the opening of the plants) Urban and industrial waste (after the opening of the plants) Urban, commercial, and industrial waste Urban and Industrial waste (before/after the opening of the plants) Hazardous waste < 3 km Special waste and non-special waste Hazardous waste d < 0,8 km Hazardous waste 0.8 < d < 1.6 km Hazardous waste 0.6 < d < 3.2 km Hazardous waste 3.2 < d < 8.0 km Special waste (3rd quartile *vs.* 1st quartile) Low risk sites All sites Hazardous waste < 3 km Special and non-special waste Special and non-special waste Hazardous waste < 3 km Hazardous waste < 3 km Special and non-special waste special waste (3° quartile) Special and non-special waste Special and non-special waste Special and non-special waste Special waste Special waste (4th quartile *vs.* 1st quartile)	Newborn gender, maternal age, smoking, weight at birth, length of pregnancy, complications during pregnancy, alcohol consumption, smoking, parity, folic acid intake, employment status, family income, town of residence	Mattiello 2013[39]
UK (No. 8) Europe (No. 2) USA (No. 4) Ireland (No. 1) Brazil (No. 1) Denmark (No. 1)	**Systematic review:** • ecological (No. 10) • case-control (No. 2) **Multicentre:** • case-control (No. 5) • cohort (No. 1)	18 studies (1992-2010)	aOR: 1.12 (1.06-1.18) aOR: 1.63 (1.34-1.99) aOR: 1.09 (1.04-1.15) aOR: 1.29 (1.05-1.59) aOR: 1.32 (1.18-1.48) aOR: 2.63 (1.31-2.49) aOR: 1.22 (1.08-1.38) aOR: 1.16 (1.06-1.26) aOR: 1.75 (1.31-2.34) aOR: 1.09 (1.00-1.18) aOR: 1.27 (1.03-1.57) aOR: 1.36 (1.08-1.72) **Risk ratio:** 1 (zone 0-2 km); 0.926 (zone 2-4 km); 0.854 (zone 4-6 km) p trend: 0.16	CAs CAs CAs CNS Skin anomalies Skin anomalies Skin anomalies Musculoskeletal system Musculoskeletal system Musculoskeletal system CNS CNS CHD	Hazardous waste Hazardous waste (high exposure) Hazardous waste (low exposure) Hazardous waste Hazardous waste Hazardous waste (high exposure) Hazardous waste (low exposure) Hazardous waste Hazardous waste (high exposure) Hazardous waste (low exposure) Hazardous waste + emissions industrial solvents Hazardous waste + emissions industrial metals Hazardous waste	Newborn gender, maternal age, smoking, weight at birth, length of pregnancy, complications during pregnancy, alcohol use, smoking, parity, folic acid intake, employment status, family income, town of residence	Mattiello 2013[39]
Campania (Southern Italy) (No. 2)	**Review:** • ecological (No. 2)	2 studies (2008-2009)	RR: 1.28-5.85 RR: 2.38-4.29 RR: 1.30 ERR: 82.7 (25.6-155.7) ERR: 83.5 (24.7-169.9) RR: 1.54-2.04 ERR: -5.3 (-9.4;-1.0) ERR: 12.5 (6.9-12.4)	CAs Urogenital system Limb reduction Urogenital system CNS CHD CHD CHD	Landfills + illegal waste landfills	Deprivation index, exposure Index	Triassi 2015[59]

***** 99% confidence interval / *intervallo di confidenza al 99%*

aOR: adjusted odds ratio / *odds ratio aggiustato*; **CAs:** congenital anomalies / *anomalie congenite*; **CHD:** congenital heart defects / *difetti cardiaci congeniti*; **CI:** confidence interval / *intervallo di confidenza*; **CNS:** central nervous system / *sistema nervoso centrale*; **CSD:** cardiac septal defects / *difetti cardiaci del setto*; **ERR:** excess relative risk / *eccesso di rischio relativo*; **NTD:** neural tube defects / *difetti del tubo neurale*; **RR:** relative risk / *rischio relativo*; **SES:** socioeconomic status / *livello socioeconomico*; **TGA:** transposition of great arteries / *trasposizione dei grossi vasi*

Table 4. Proximity to landfills and risk of congenital anomalies.
Tabella 4. Prossimità residenziale a discariche e rischio di anomalie congenite.

INCINERATORS
INCENERITORI

The association between maternal residential proximity to incinerators and CA risk was evaluated in a review of 7 published studies conducted between 1998 and 2010. The review found associations only for selected CA subgroups and concluded that literature provided limited evidence and that further studies were necessary (table 5).[62] In particular, a French ecological study observed an excess of risk for cleft lip/palate and kidney dysplasia among the population living in proximity to solid waste incinerators. An increase of relative risk of conotruncal heart malformations and other CHDs was observed.[63] Another French study reported an increased risk for urinary tract defects in the offspring of exposed mothers. This study investigated maternal exposure to airborne dioxins and dioxin deposits starting a month before conception until the last trimester of pregnancy.[64] In a Swedish ecological study, no association between maternal exposure to dioxins and the risk of cleft lip and palate among offspring were observed.[65]

An ecological study carried out in England in a population residing close to a waste combustion plant did not report any increase in CAs as a group.[66] In contrast, a cohort study found a slight increase in risk for CHDs and NTDs (particularly spina bifida and anencephaly) among offspring of mothers living in proximity to incinerators or cremating incinerators.[67] Lastly, two studies carried out in Italy (a cohort study and a case-control study) showed no increased risk of CAs, both as CAs overall and as specific anomaly subgroups, among newborns born to mothers exposed to municipal urban solid waste incinerator emissions.[68,69]

LOCATION (NUMBER)	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	EXPOSURE ASSESSMENT	CONFOUNDING VARIABLES	REFERENCE
INCINERATORS							
France (No. 2) UK (No. 2) Italy (No. 2) Sweden (No. 1)	**Systematic review:** • cohort (No. 2) • case-control (No. 2) • ecological (No. 3)	7 studies (1998-2010)	RR: 1.30 (1.06-1.59) RR: 1.55 (1.10-2.20) aOR: 1.83 (1.13-2.96) aOR: 2.95 (1.47-5.92) aOR: 1.99 (1.17-3.40) aOR: 2.84 (1.32-6.09) aOR: 1.13 (1.04-1.23) aOR: 1.17 (1.07-1.28) aOR: 1.23 (1.01-1.50) aOR: 1.12 (1.03-1.22) aOR: 1.12 (0.90-1.40) aOR: 1.02 (0.87-1.20)	Oro-facial cleft Renal dysplasia Urinary anomalies Urinary anomalies Urinary anomalies Urinary anomalies NTD Spina bifida Anencephaly CHD Conotruncal CHD	Solid urban waste Solid urban waste Dioxin deposits Dioxin deposits – above the median Airborne dioxins Airborne dioxins – above the median After the opening of the incinerator After the opening of the incinerator ≤3 km from the cremating ovens After the opening of the incinerator Solid urban waste Solid urban waste	Newborn's year of birth, newborn gender, town of birth, maternal age, maternal ethnicity, educational level, parity, maternal job, folic acid intake, treatment of chronic disease during first trimester, obesity, smoking, antiepileptic drugs, tobacco use, consanguinity, alcohol consumption, population density, deprivation index, multiple births, average family income, other sources of dioxin, car traffic, previous exposure to incinerator emissions	Ashworth 2014[62]

aOR: adjusted odds ratio / *odds ratio aggiustato*; **CHD:** congenital heart defects / *difetti cardiaci congeniti*; **CI:** confidence interval / *intervallo di confidenza*; **NTD:** neural tube defects / *difetti del tubo neurale*; **RR:** relative risk / *rischio relativo*

Table 5. Proximity to incinerators and risk of congenital anomalies.
Tabella 5. Prossimità residenziale a inceneritori e rischio di anomalie congenite.

CONGENITAL ANOMALIES AND INDIVIDUAL EXPOSURES

ANOMALIE CONGENITE
ED ESPOSIZIONI INDIVIDUALI

2

CIGARETTE SMOKE
FUMO

A systematic review with metanalysis selected 33 studies published in the period 1971-2011. The metanalysis suggested for smoking mothers a moderate increase of CHDs in offspring (table 6). The effect of smoke was observed for CHDs overall, as well as for specific CHD subgroups. The strongest association was reported for in full CSDs. Women who had smoked during pregnancy were 44% more likely to have a child with CSDs compared with non-smokers. No association was found for conotruncal heart malformations, TGA, total anomalous pulmonary venous return (TAPVR), left ventricular outflow tract obstruction (LVOTO), coartation of aorta (CoA), and aortic valve stenosis.[70]

Another systematic review and metanalysis identified 172 studies published between 1959 and 2009 in order to investigate the associations between maternal smoking during pregnancy and the risk of CAs overall as well as of selected CA subtypes. The pooled analysis showed slight associations between maternal smoking and CHDs, CNS, and musculoskeletal defects, while moderate associations with gastrointestinal disorders, lip/palate clefts, eye and facial defects were found. Pooled analysis detected also moderate increases in the risk of gastroschisis, inguinal/umbilical hernia, clubfoot, limb reductions for smoking mothers, while an inverse association for hypospadias and skin diseases were observed.[71]

A systematic review and metanalysis identified 28 studies aimed at examining the association between several risk factors and the incidence of cleft lip with or without cleft palate. The metanalysis of 6 papers published between 2000 and 2010 evaluated the effect of maternal smoking in pregnancy. Pooled results revealed a modest increased risk for cleft lip/palate in offspring of mothers who smoked during pregnancy (table 6).[72]

A more recent systematic review and metanalysis collected 14 epidemiological studies published in the years 2001-2011 to analyse the associations between maternal exposure to passive smoking and the risk of cleft lip/palate, both overall and in two subtypes (cleft lip with or without cleft palate, cleft palate only). An increased risk of both oro-facial clefts overall and the two subtypes under examination was observed.[73]

In Denmark, a population-based cohort study carried out between 1997 and 2010 analysed the association between maternal smoking during pregnancy and the risk of CAs both overall and of specific subtypes. Detailed information on exposure also allowed studying the dose-response association and the effect of smoking cessation. The results showed an increased risk for major artery malformations, pulmonary and tricuspid valve malformations, CSDs, and total CHDs. The results also reported an increase not only of the risk of oro-facial clefts, but also of the respiratory system and of the digestive system among offspring. No association for urinary system defects was found. Conversely, results showed a decreased risk of musculoskeletal malformations. Increased risks were observed for clubfoot, pyloric stenosis, and cleft lip with or without cleft palate.[74]

The association between maternal smoking during pregnancy and the risk of oro-facial clefts is also reported in a Swedish cohort study conducted on over a million births which took place between 1999 and 2009. The study showed that the increased risk of oro-facial clefts is not associated to cigarette smoking alone, but also to sniffing tobacco, though the associations were modest.[75]

A case-control study conducted in Canada on patients with CAs aged 18 years or younger for the period 2008-2011 suggested an increased risk for CHDs as group and for all the considered CHD subgroups. However, the small size of the control group may have reduced the statistical power to detect associations, even if the main interest of the authors was to compare specific CHD rather than the overall CHD group (table 6).[76]

The association between paternal periconceptional smoking and the risk of CHDs was investigated in a case-control study performed in 4 Chinese delivery hospitals between 2010 and 2011. The study reported increased risk of conotruncal heart malformations (isolated and not) associated with low exposure (<10 cigarettes/day), with a dose-response relationship. In addition, an increased risk of CSDs and LVOTO for moderate to severe exposures (10-19, ≥20 cigarettes/day) was observed, although calculated on a small sample.[77]

In Brazil, a cross-sectional study conducted between 2009 and 2012 examined the relationship between smoking and the gender of the baby and the risk of cleft lip and/or palate. The binary logistic regression analysis showed that both variables considered were associated to oro-facial clefts.[78]

A Chinese case-control study for the years 2006-2009 investigated whether the exposure to both maternal and paternal smoking increased the risk of oro-facial clefts among offspring. Results demonstrated a threefold increase in risk for cleft lip and palate among infants born to mothers who had smoked before pregnancy, and an almost fivefold increased for risk of cleft lip alone. The risk for both malformations increased markedly when mothers had continued smoking during the first trimester of gestation. Lastly, periconceptional exposure to father smoking was also associated with all the examined types of clefts (table 6).[79]

A recent systematic review and metanalysis of 13 articles published between 1983 and 2011 assessed the association between

maternal smoking during pregnancy and NTDs. Five studies included only spina bifida and anencephaly; 4 studies involved only spina bifida; 3 studies involved anencephaly, spina bifida, and encephalocele; and one study anencephaly alone. The metanalysis, performed with fixed effect and random-effect models, did not show any association with NTDs overall, but a positive association for spina bifida was reported.[80]

In North America, a multicentre case-control study conducted between 1988 and 2012 found no association between low to moderate smoking exposure in the first trimester of pregnancy and the risk of spina bifida in offspring.[81]

Zwink's systematic review and metanalysis of 22 studies published during 1981-2010 examined the association between anorectal malformations and the maternal and paternal exposure to different risk factors. The metanalysis of 8 studies on smoking showed no association between maternal exposure and the risk of ano-rectal malformations, while a weak association with paternal smoking was demonstrated.[82]

A positive association between periconceptional maternal smoking exposure and the risk of isolated choanal atresia was observed in a multicentre case-control study, using the National Birth Defects Prevention Study (NBDPS) data, although the authors suggest caution in interpreting the findings, because of the large number of associations that had been tested without Bonferroni correction for multiple tests.[83]

A recent multicentre study carried out in Germany during the period 1993-2008 also found a positive association between maternal periconceptional smoking exposure and the risk of ano-rectal malformations. Dose-response relationships have also been reported.[84]

A systematic review and metanalysis identified 19 studies published between 1969 and 2009 to assess whether secondhand smoke exposure during pregnancy increased the risk of CAs, spontaneous abortion, and perinatal mortality. Exposure was analysed exclusively in non-smoking pregnant women. Secondhand smoke exposure was defined as contact with passive smoke from any source (domestic, occupational, or other sources). According to the metanalysis of 7 epidemiological studies, the exposure to seconhand smoke was associated with a 13% increase in risk of only CAs as group, while no positive association for selected CA subgroups (musculoskeletal, genitourinary, central nervous system, face, eyes, and ears) was found (table 6).[85]

A recent Chinese case-control paediatric study performed between 2004 and 2013, based on the Guangdong Registry of Congenital Heart Disease, reported that maternal exposure to passive smoking and paternal smoking was associated with an increased risk of multiple and isolated CHDs. In particular, the study showed a strong association between exposure to paternal smoke and TGA, a moderate association with ASDs, and a weak association with VSDs.[86]

A cross-sectional Chinese study realized in 2010-2013 evaluating the association between maternal exposure to passive smoking and the prevalence of CAs among offspring reported an increasing prevalence of births with both eyes, ears, face, neck defects, and respiratory system defects.[87]

In Canada, a cohort study conducted between 2006 and 2012, which used data from two national population registries (the Canadian Paediatric Surgery Network and the Canadian Community Health Survey), assessed the association between several maternal risk factors and gastroschisis. A multivariate analysis revealed an association between maternal smoking and the risk of gastroschisis in offspring.[88]

A multicentre case-control study carried out in the United States over the period 1997-2007 using the NBDPS data examined the association between maternal passive and active smoking during the periconceptional period and the risk of both isolated and multiple (associated with other CAs) omphalocele cases. Results showed a weak association between passive smoking and the risk of multiple omphalocele and an inverse association among smoking mothers.[89]

In Norway, a cohort study carried out between 1999 and 2008 detected an association between the risk of club foot and smoking exposure both in the periconceptional period and in the first trimester of pregnancy (table 6).[90]

A positive association between maternal smoking and clubfoot was also reported by a multicentre case-control study conducted in the United States for the years 2007-2011. Findings showed that the risk of club foot increased by 40% in women who stopped smoking only after the first month of pregnancy, while the risk doubled between mothers who continued smoking during the first trimester of pregnancy.[91]

Finally, a recent review identified 32 articles in order to evaluate the association between several maternal risk factors (diabetes, obesity, smoking, alcohol consumption) and cryptorchidism. The pooled analysis of 25 studies published in the period 1984-2013 showed that smoking during pregnancy increased the risk of cryptorchidism in offspring.[92]

CIGARETTE SMOKE

LOCATION (NUMBER)	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	CONFOUNDING VARIABLES	REFERENCE
SMOKING						
USA (No. 17) Europe (No. 14) Canada (No. 1) China (No. 1)	Systematic review and metanalysis: • case-control (No. 23) • cohort (No. 5) • cross-sectional (No. 5)	33 studies (1971-2011)	RR pooled: 1.11 (1.02-1.21) RR: 1.44 (1.16-1.79) RR: 1.20 (1.03-1.40) RR: 1.34 (1.12-1.60) RR: 1.34 (1.02-1.75) RR: 1.35 (1.01-1.81) RR: 1.21 (1.01-1.44) RR: 1.09 (0.98-1.20) RR: 1.09 (0.84-1.42) RR: 1.19 (0.83-1.71) RR: 0.95 (0.80-1.13) RR: 0.91 (0.75-1.10) RR: 0.89 (0.60-1.32)	CHD CSD RVOTO PVS ASD AVSD (no Down syndrome) PDA Conotruncal TGA TAPVR LVOTO CoA Aortic valve stenosis	Mother's age, educational level, alcohol consumption, BMI, smoking, coffee, marital status, folic acid intake, gestational diabetes, baby's sex, job, CHD consanguinity	Lee 2013[70]
Europe (No. 63) USA (No. 87) Israel (No. 3) Canada (No. 4) Asia (No. 6) Brazil (No. 1) Lithuania (No. 1) Mexico (No. 1) Australia (No. 1)	Systematic review and metanalysis	172 studies (1959-2010)	OR pooled: 1.27 (1.19-1.35); 37 studies OR pooled: 1.27 (1.18-1.36); 35 studies OR pooled: 1.16 (1.05-1.27); 25 studies OR pooled: 1.10 (1.01-1.19); 29 studies OR pooled: 1.19 (1.06-1.35); 12 studies OR pooled: 1.05 (0.98-1.12); 40 studies OR pooled: 1.11 (0.95-1.30); 6 studies OR pooled: 1.26 (1.15-1.39); 8 studies OR pooled: 1.50 (1.28-1.76); 12 studies OR pooled: 1.28 (1.10-1.47); 12 studies OR pooled: 1.33 (1.03-1.73); 5 studies OR pooled: 1.25 (1.11-1.40); 8 studies OR pooled: 1.20 (1.06-1.36); 7 studies OR pooled: 1.40 (1.23-1.59); 4 studies OR pooled: 1.13 (1.02-1.25); 18 studies OR pooled: 0.90 (0.85-0.95); 15 studies OR pooled: 0.82 (0.75-0.89); 5 studies aOR pooled: 1.10 (1.02-1.20); 25 studies cOR pooled: 1.09 (1.02-1.17); 25 studies	CL±CP Gastrointestinal system defects Musculoskeletal system defects CNS Face Defects Urogenital system defects Respiratory system defects Limb reduction Gastroschisis Clubfoot Craniosynostosis Eye defects Anal atresia Umbilical/inguinal hernia Cryptorchidism Hypospadias Skin diseases CHD CHD	Maternal age, BMI, active smoking, maternal ethnicity, social class, alcohol consumption, coffee consumption, marital status, folic acid intake, maternal diabetes, newborn gender, educational level, parity, pregnancy type, foetal death, induced abortion, mother's chronic disease, consanguinity, fever during pregnancy, medicine intake, preterms, twins, weight of placenta, mother's exposure to X-rays	Hackshaw 2011[71]
USA (No. 2) Europe (No. 2) Brazil (No. 1) China (No. 1)	Systematic review and metanalysis: • case-control (No. 6)	6 studies (2000-2010)	OR pooled: 1.48 (1.36-1.61)	CL±CP	Mother's age, active smoking, educational level, health status, obesity, alcohol consumption, folic acid intake	Molina-Solana 2013[72]
China (No. 6) Europe (No. 4) USA (No. 2) Brazil (No. 1) Iran (No. 1)	Systematic review and metanalysis: • case-control (No. 14)	14 studies (2001-2011)	OR pooled: 2.11 (1.54-2.89) OR pooled: 2.05 (1.27-3.3) OR pooled: 2.11 (1.23-3.62)	Oro-facial clefts CL±CP CP	Mother's age, educational level, occupation, obesity, folic acid intake, alcohol consumption, newborn gender	Sabbagh 2015[73]
Denmark	Cohort LB	838,265 live births (1997-2010)	aOR: 1.29 (1.14-1.46) aOR: 1.25 (1.11-1.41) aOR: 1.24 (1.14-1.36) aOR: 1.15 (1.07-1.14) aOR: 1.58 (1.40-1.78) aOR: 1.56 (1.35-1.81) aOR: 1.36 (1.18-1.56) aOR: 0.90 (0.87-0.93) aOR: 1.13 (1.07-1.19) aOR: 1.37 (1.17-1.60) aOR: 1.37 (1.14-1.65) aOR: 1.13 (1.05-1.21)	Oro-facial clefts Respiratory system defects Other malformations Digestive system defects Club foot Pyloric stenosis CL±CP Muscoloskeletal defects CHD Great arteries anomalies Pulmonary and tricuspid Valve anomalies CSD	Mother's age, marital status, newborn's year of birth	Leite 2014[74]
Sweden	Cohort LB	1,086,213 live births (1999-2009)	aOR: 1.48 (1.00-2.21) aOR: 1.19 (1.01-1.41)	CL/CP	Mother's age, mother's citizenship, gestational diabetes, hypertension, pre-eclampsia, newborn gender, parity, pregnancy type, living with father	Gunnerbeck 2014[75]
Ontario (Canada)	Case-control LB	2,339 cases 199 controls (2008-2011)	cOR: 2.8 (1.4-5.4) cOR: 2.6 (1.0-4.2) cOR: 3.2 (0.98-6.4) cOR: 3.0 (1.4-4.2) cOR: 2.2 (1.01-3.8) cOR: 3.0 (1.01-3.6) cOR: 2.6 (1.4-4.2) cOR: 2.6 (1.6-8.0) cOR: 2.6 (1.4-5.0) cOR: 2.4 (1.0-4.0)	CHD ECD LATDIS LHL PDA RHL CSD SV TGA TVA		Fung 2013[76]
Shenzhen, Fuzhou, Wuhan, Zhengzhou (China)	Case-control LB	267 cases 386 controls (2010-2011)	aOR: 2.23 (1.05-4.73) aOR: 1.75 (1.04-2.95) aOR: 2.48 (1.04-5.95) aOR: 2.04 (1.05-3.98) aOR: 13.12 (2.55-67.39) aOR: 8.16 (1.13-58.84) aOR: 5.46 (1.09-27.43)	Conotruncal isolated Conotruncal associated LVOTO CSD LVOTO Conotruncal isolated Conotruncal associated	Maternal residence, maternal age, BMI, folic acid intake, educational level, mother and father's alcohol consumption, parental consanguinity	Deng 2013[77]
State of Minas Gerais (Brazil)	Case-control LB	843 cases 676 controls (2009-2012)	cOR: 2.08 (1.58-2.75) cOR: 1.92 (1.26-2.92) cOR: 2.02 (1.54-2.63)	CL±CP CP Any clefts		Martelli 2015[78]

→

Table 6. Exposure to cigarette smoke and risk of congenital anomalies.
Tabella 6. Esposizione a fumo di sigaretta e rischio di anomalie congenite.

LOCATION (NUMBER)	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	CONFOUNDING VARIABLES	REFERENCE
China	Case-control LB	304 cases 453 controls (2006-2009)	aOR: 4.97 (1.39-17.76) before and after conception aOR: 3.37 (1.04-10.88) before and after conception aOR: 7.0 (1.44-34.13) till first trimester aOR: 5.1 (1.30-20.12) till first trimester	CL CL±CP CL CL±CP	Mother and father's age, parent's educational level, newborn gender, vaginal discharge, abdominal pain	Zhang 2011[79]
USA (No. 9) Europe (No. 3) China (No. 1)	Metanalysis: • case-control (No. 11) • cohort (No. 2)	13 studies (1983-2011)	OR pooled: 1.03 (0.80-1.33) OR pooled: 1.55 (1.06-2.26)	NTD Spina bifida		Wang 2014[80]
Massachusetts, Philadelphia, Toronto, San Diego, New York State	Multicentre case-control LB; FD; ET	776 cases 8,756 controls (1988-2012)	**Period 1988-1997** aOR: 1.2 (0.8.-2.0) 1-9 cigarette/day aOR: 1.3 (0.9.-1.7) >10 cigarette/day **Period 1997-2012** aOR: 1.1 (0.7-1.8) 1-9 cigarette/day aOR: 1.0 (0.7.-1.6) >10 cigarette/day	Spina bifida	Educational level, use of folic antagonists and anti-inflammatory drugs, study centre	Benedum 2013[81]
USA (No. 3) Europe (No. 4) JApan (No. 1)	Systematic review and metanalysis: • case-control (No. 8)	8 studies (1981-2010)	OR pooled: 1.53 (1.04-2.26) paternal smoking OR pooled: 1.03 (0.83-1.29) maternal smoking	Ano-rectal	Mother's age, educational level, smoking, race/ethnicity, season of conception, parity	Zwink 2011[82]
Arkansas, Iowa, Massachusetts, California, Georgia, New York, North Carolina, Texas, Utah (USA-NBDPS)*	Multicentre case-control LB; FD; ET	117 cases 8,350 controls (1997-2007)	aOR: 2. 3 (1.1-4.7)	Choanal atresia	Newborn gender, gestational age, smoking, maternal ethnicity, diabetes, hypertension, parity, season of conception	Kancherla 2014[83]
Germany	Multicentre case-control LB	158 cases 474 controls (1993-2008)	aOR: 2.23 (1.04-4.79) aOR: 2.36 (1.03-5.41) 6-10 cigarette/day aOR: 5.62 (2.66-11.89) >10 cigarette/day	Ano-rectal malformations	Maternal age, BMI, baby's age and year of birth	Zwink 2016[84]
USA (No. 4) Europe (No. 2) China (No. 1)	Metanalysis: • case-control (No. 6) • cross-sectional (No. 1)	7 Studies (1992-2008)	Passive smoking OR pooled:1.13 (1.01-1.26)	CAs	Maternal age, ethnicity, alcohol consumption, educational level	Leonardi-Bee 2011[85]
Guandong (China)	Matched case-control LB	4,034 cases 4,034 controls (2004-2013)	aOR: 1.76 (1.4-2.2) paternal smoking aOR: 7.95 (1.0-61.3) passive smoking aOR: 28.34 (1.5-505.3) paternal smoking aOR: 2.48 (1.4-4.1) paternal smoking aOR: 1.69 (1.1-2.3) paternal smoking	CHD Isolated CHD Multiple TGA ASD VSD		Ou 2016[86]
Shaanxi Province (China)	Cross-sectional LB	29,098 live births (2010-2013)	PRR: 1.95 (1.15-3.33) PRR: 1.70 (1.25-2.31) PRR: 9.94 (2.37-41.76)	Eye, nose, face, neck Cardiovascular system Respiratory system defects	Sociodemographic factors	Pei 2015[87]
Canada	Cohort LB; SB; TP	5,400 pregnant women (2006-2012)	aOR: 2.86 (2.22-3.66)	Gastroschisis	Maternal age	Skarsgard 2015[88]
Arkansas, Iowa, Texas Massachusetts, Utah California, Georgia, New York, North Carolina (NBDPS)*	Multicentre case-control LB; SB; TP	301 cases, 8,135 controls (1997-2007)	aOR: 1.70 (0.98-2.95) passive smoking aOR: 0.87 (0.54-1.40) active smoking	Multiple omphalocele cases All omphalocele cases	Maternal active smoking, maternal ethnicity, BMI, alcohol consumption	Feldkamp 2014[89]
Norway	Cohort LB	108,353 pregnancies (1999-2008)	aOR: 1.82 (1.05-3.18) 3 months before pregnancy aOR: 2.67 (1.28-5.55) 1st trimester	Club foot	Mother's age, education level, BMI, number of births, active smoking, gender of newborn	Dodwell 2015[90]
Massachusetts, North Carolina, New York (USA)	Multicentre case-control LB	646 cases 2,037 controls (2007-2011)	**1st month** aOR: 2.13 (1.33-3.41) >10 cigarette/day aOR: 1.73 (1.37-2.21) ≤10 cigarette/day **1st trimester** aOR: 2.58 (1.38-4.81) >10 cigarette/day aOR: 2.21 (1.61-3.02) ≤10 cigarette/day	Club foot	Maternal age, education level, smoking, ethnicity, BMI, gender of newborn, number of births, centre, alcohol consumption, coffee consumption, fertility treatments	Werler 2015[91]
USA (No. 7) Europe (No. 14) Japan (No. 2) Egyptian (No. 1) Lithuania (No. 1)	Systematic review and metanalysis: • case-control (No. 12) • cohort (No. 9) • nested (No. 4)	25 studies (1984-2013)	OR pooled: 1.17 (1.11-1.23)	Cryptorchidism	Maternal age, educational level, smoking, ethnicity, season of conception, parity	Zhang 2015[92]

aOR: adjusted odds ratio / *odds ratio aggiustato*; **ASD:** atrial septal defects / *difetti del setto atriale*; **AVSD:** atrial ventricular septal defects / *difetti del setto atrio-ventricolare*; **BMI:** body mass index / *indice di massa corporea;* **CAs:** congenital anomalies / *anomalie congenite*; **CoA:** coartation of aorta / *coartazione dell'aorta*; **cOR:** crude odds ratio / *odds ratio crudo*; **CHD:** congenital heart defects / *difetti cardiaci congeniti*; **CI:** confidence interval / *intervallo di confidenza*; **CL:** cleft lip / *labioschisi*; **CNS:** central nervous system / *sistema nervoso centrale*; **CP:** cleft palate / *palatoschisi*; **CSD:** cardiac septal defects / *difetti cardiaci del setto*; **ECD:** endocardial cushion defects / *difetti del cuscinetto endocardico*; **ET:** elective termination / *interruzione volontaria di gravidanza*; **FD:** foetal death / *morte fetale*; **LATDIS:** laterality disorders / *malattie della lateralità*; **LB:** live birth / *nato vivo*; **LHL:** left heart lesions / *lesioni al cuore sinistro*; **LVOTO:** left ventricular outflow tract obstruction / *ostruzione del flusso del ventricolo sinistro*; **NTD:** neural tube defects / *difetti del tubo neurale*; **PDA:** patent ductus arteriosus / *dotto arterioso pervio*; **PRR:** prevalence rate ratio / *rapporto dei tassi di prevalenza*; **PVS:** pulmonary valve stenosis / *stenosi della valvola polmonare*; **RHL:** right heart lesions / *lesioni al cuore destro*; **RR:** relative risk / *rischio relativo*; **RVOTO:** right ventricular outflow tract obstruction / *ostruzione del flusso del ventricolo destro*; **SB:** still birth / *nato morto*; **SV:** single ventricle / *ventricolo unico*; **TAPVR:** total anomalous pulmonary venous return / *ritorno venoso polmonare anomalo totale*; **TGA:** transposition of great arteries / *trasposizione dei grossi vasi*; **TVA:** thoracic vessel anomalies / *anomalie dei vasi toracici*; **VSD:** ventricular septal defects / *difetti del setto ventricolare*; **WG:** week of gestation / *settimana di gestazione*

* National Birth Defects Prevention Study

Table 6. Exposure to cigarette smoke and risk of congenital anomalies.
Tabella 6. Esposizione a fumo di sigaretta e rischio di anomalie congenite.

ALCOHOL
ALCOL

A recent metanalysis of 23 studies published over the period 1989-2014 aimed to examine the association between alcohol consumption and/or binge drinking (the consumption of five or more drinks within a short period of time) and the risk of CHDs in offspring. The metanalysis, conducted through fixed and random effect models, did not reveal any association (table 7).[93]

Another recent pooled analysis of 8 papers published between 1992 and 2013 showed no association between the risk of NTDs in the offspring and maternal alcohol consumption during the periconceptional period and the first trimester of pregnancy. No association was found for both NTDs overall and for the specific NTD subgroup of the spina bifida. Even in the case of binge drinking, no association was reported.[94]

In a systematic review, Zhang et al. conducted a metanalysis of 15 epidemiological studies published in the years 1986-2012 to investigate the relationship between maternal moderate alcohol consumption during pregnancy and the risk of cryptorchidism in the offspring. The metanalysis did not find any association between maternal gestational drinking and the risk of cryptorchidism.[92]

A systematic review and metanalysis selected 33 studies published in 1971-2011 to evaluate the association between alcohol consumption and the risk of oro-facial clefts, both as a group and in different subtypes. The metanalysis of 31 studies examined any alcohol consumption, level of binge drinking, and heavy and moderate levels of consumption. Findings from random effects metanalysis suggested no association between quantity of alcohol consumption and the risk of oro-facial clefts in offspring.[95]

Differently, the metanalysis of 5 articles published between 2007 and 2009 reported a slight association between alcohol consumption in pregnancy and the risk of oro-facial clefts among offspring.[72]

According to a cohort study conducted on the Danish National Birth Cohort data in 1996-2002, prenatal exposure to low-to-moderate levels of alcohol on a weekly basis or occasional binge drinking during the early pregnancy was not associated with the prevalence of isolated VSD and ASD in offspring (table 7).[96]

A multicentre case-control study conducted in the period 1997-2005 using the data of the NBDPS evaluated the association between the periconceptional alcohol consumption and the risk of NTDs overall as well as in NTD subtypes (anencephaly, spina bifida, encephalocele, and other rare diseases) both in the isolated form and in the associated form. The exposure was divided into 4 categories and binge drinking was also considered (≥ 4 glasses per occasion). The study suggests no association both for NTDs combined and for specific subtypes.[97]

Another case-control study carried out in the United States in the period 1987-2009 examined the association between the risk of diaphragmatic hernia (overall, isolated, and complex) and several risk factors, including maternal alcohol consumption. Multivariate analysis found that alcohol consumption was associated with the increased risk of diaphragmatic hernia, for both complex and isolated form (table 7).[98]

In Mexico, a case-control study performed between 2009 and 2013 investigated the association between the risk of gastroschisis in offspring and maternal alcohol consumption during the periconception period and the first trimester of pregnancy. Findings reported increased risk of gastrostroschisis among mothers who consumed alcohol during the first trimester of pregnancy.[99]

Cross-sectional study by Pei et al., conducted in China in 2010-2013, found that mothers who consumed alcohol during pregnancy showed a higher prevalence ratio of newborns affected by nervous system defects, oro-facial clefts, and CHDs.[87]

SOCIOECONOMIC STATUS
LIVELLO SOCIOECONOMICO

A recent case-control study carried out in the United States between 1999 and 2008 using data from the Texas Birth Defects Registry evaluated the association between maternal neighbourhood socioeconomic position (SEP) and the risk of cleft lip with or without cleft palate or cleft palate alone in offspring. The study suggested that mothers living in areas with adverse neighbourhood SEP factors were more likely to have offspring with cleft lip with or without cleft palate than mothers living in areas with favourable neighbourhood SEP factors, and the association was strongest among Hispanic mothers. No association for cleft palate alone were observed (table 7).[100] Another USA case-control study examined the association between neighbourhood socioeconomic level and the risk of gastroschisis in offspring. As cases, live-born infants with gastroschisis during 1998-2004 were extracted from the "North Carolina Birth Defects Monitoring Program", while matched normal-live births were selected as controls from birth certificates. The residential address of mothers was geocoded in high or low socioeconomic neighbourhoods using 2000 Census data, which took in consideration 4 variables (education, poverty, unemployment, and racial composition). Association was investigated at various geographic scales (from 1,000 up to 5,500 km radius). Results revealed a modest association between living in a more disadvantage neighbourhood characterized by high poverty and unemployment and an enhanced risk of gastroschisis among offspring.[101]

ALCOHOL AND SOCIOECONOMIC STATUS

LOCATION (NUMBER)	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	CONFOUNDING VARIABLES	REFERENCE
ALCOHOL						
USA (No. 15) Europe (No. 7) Australia (No. 1)	Metanalysis: • case-control (No. 19) • cohort (No. 4)	23 studies (1989-2014)	RR pooled: 1.11 (0.96-1.29)	CHD	Maternal age, alcohol consumption, BMI, smoking, race/ethnicity, coffee consumption, marital status, folic acid intake, vitamins, stress, educational level, infant's year/month of birth, maternal residence, socioeconomic status	Wen 2016[93]
USA (No. 5) Canada (No. 1) Europe (No. 2)	Metanalysis	8 studies (1992-2013)	OR pooled: 1.01 (0.71-1.45) OR pooled: 1.03 (0.65-1.64) **Binge drinking** OR pooled: 1.01(0.71-1.43) OR pooled: 1.07(0.81-1.41)	NTD Spina bifida NTD Spina bifida	Maternal age, alcohol consumption, BMI, smoking, maternal race/ethnicity, coffee consumption, marital status, folic acid intake, vitamins, stress, educational level, infant's year/month of birth, maternal residence, socioeconomic status	Leng 2016[94]
USA (No. 3) Europe (No. 10) Japan (No. 2)	Systematic review and metanalysis: • case-control (No. 8) • cohort (No. 6) • nested (No. 1)	15 studies (1986-2012)	OR pooled: 0.97 (0.87-1.07)	Cryptorchidism	Mother's age, educational level, parity, smoking, maternal ethnicity, season of conception	Zhang 2015[92]
USA (No. 11) Europe (No. 18) Australia (No. 1) India (No. 1) Brazil (No. 1) Japan (No. 1)	Systematic review and metanalysis: • case-control (No. 23) • cohort (No. 10)	33 studies (1974-2013)	No association	Oro-facial clefts	Smoking and other covariates	Bell 2014[95]
USA (No. 2) Europe (No. 2) Brazil (No. 1)	Systematic review and metanalysis: • case-control (No. 4) • cohort (No. 1)	5 studies (2007-2009)	aOR pooled: 1.28 (0.98-1.66)	CL±CP	Mother's age, active smoking, educational level, health status, obesity, folic acid intake	Molina-Solana 2013[72]
Denmark	Cohort LB	80,346 pregnant women (1996-2002)	aPR: 1.10 (0.54-2.23) aPR: 0.66 (0.27-1.62) aPR: 1.33 (0.72-2.46) aPR: 1.15 (0.57-2.35)	VSD: +3 glasses/die ASD: +3 glasses/die VSD: +3 binge drinking ASD: +3 binge drinking	Mother's age, smoking, socioeconomic status, parity, time before conception	Strandberg-Larsen 2011[96]
Arkansas, Iowa, Texas, California Massachusetts, Utah, Georgia, New York, North Carolina (USA-NBDPS)*	Multicentre case-control LB; FD; ET	1,223 cases, 6,807 controls (1997-2005)	aOR: 0.9 (0.8-1.2) aOR: 1.0 (0.8-1.2) aOR: 0.8 (0.5-1.3) aOR: 0.9 (0.6-1.4) aOR: 1.0 (0.8-1.3) aOR: 1.1 (0.8-1.4)	NTD associated NTD isolated Anencephaly associated Anencephaly isolated Spina bifida associated Spina bifida isolated	Smoking/ethnicity, BMI, education level, study centre	Makelarski 2013[97]
Washington State (USA)	Case-control LB	492 cases, 4,920 controls (1987-2009)	aOR 3.65 (1.36-9.83) aOR: 4.02 (1.36-11.94)	Diaphragmatic hernia Diaphragmatic hernia-isolated	Mother's age, marital status, smoking, BMI, gender of newborn, parity	McAteer 2014[98]
Western Mexico	Case-control LB	90 cases, 180 controls (2009-2013)	aOR: 3.4 (1.6-7.3)	Gastroschisis	Mother's age, BMI, anaemia, smoking, passive smoking	Robledo-Aceves 2015[99]
Shaanxi Province (China)	Cross-sectional LB	29,098 births (2010-2013)	PRR: 14.67 (1.94-110.92) PRR: 3.22 (1.02-10.16) PRR: 9.02 (2.08-39.10)	CNS CHD Oro-facial clefts	Sociodemographics characteristics	Pei 2015[87]
SOCIOECONOMIC STATUS						
Texas (USA)	Case-control LB	3,367 cases 14,735 controls (1999-2008)	aOR 1.20 (1.05-1.37) aOR: 1.32 (1.07-1.62) Hispanics aOR: 0.95 (0.64-1.42)	CL±CP CL±CP CP	Newborn's year of birth, gender of newborn, mother's age, smoking, education level	Lupo 2015[100]
North Carolina (USA)	Case-control LB	264 cases 12,488 controls (1998-2004)	aOR: 1.85 (1.19-2.83) 3rd quartiles of poverty aOR: 1.89 (1.25-2.94) 2nd and 3rd quartiles of unemployment	Gastroschisis Gastroschisis	Mother's age, marital status, race/ethnicity, smoking, parity, Medicaid status	Root 2011[101]

aOR: adjusted odds ratio / *odds ratio aggiustato*; **aPR:** adjusted prevalence ratio / *rapporto di prevalenza aggiustato*; **ASD:** atrial septal defects / *difetti del setto atriale*; **BMI:** body mass index / *indice di massa corporea*; **CHD:** congenital heart defects / *difetti cardiaci congeniti*; **CI:** confidence interval / *intervallo di confidenza*; **CL:** cleft lip / *labioschisi*; **CNS:** central nervous system / *sistema nervoso centrale*; **CP:** cleft palate / *palatoschisi*; **ET:** elective termination / *interruzione volontaria di gravidanza*; **FD:** foetal death / *morte fetale*; **LB:** live birth / *nato vivo*; **NTD:** neural tube defects / *difetti del tubo neurale*; **PRR:** prevalence rate ratio / *rapporto dei tassi di prevalenza*; **RR:** relative risk / *rischio relativo*; **VSD:** ventricular septal defects / *difetti del setto ventricolare*
* National Birth Defects Prevention Study

Table 7. Alcohol consumption, socioeconomic status, and risk of congenital anomalies.
Tabella 7. Consumo di alcol, livello socioeconomico e rischio di anomalie congenite.

OCCUPATIONAL EXPOSURE
ESPOSIZIONE OCCUPAZIONALE

A review of a recent metanalysis of epidemiological studies examined the association between several environmental risk factors and CAs. Three metanalyses published between 2005 and 2010 examined the association between occupational exposure of either or both parents to organic solvents or pesticides and the risk of CAs among the offspring. The pooled odds ratio of 6 studies reported an association between paternal occupational exposure to solvents and both NTDs overall and anencephaly. Another metanalysis of 5 papers showed an increased risk of oro-facial clefts in infants born to mothers exposed to pesticides. Finally, a pooled analysis of 9 epidemiological studies on hypospadias observed a weak increased risk for hypospadias and both maternal and paternal occupational exposure to pesticides (table 8).[102]

A prospective cohort of 3,421 pregnant women living in Brittany (France) during 2002-2006 investigated maternal occupational exposure to solvents during pregnancy. Exposure was assessed from a self-administered questionnaire and a job-exposure matrix. In a nested case-control sample, urinary concentrations of 10 metabolites of glycol ethers and chlorinated solvents were measured in maternal samples collected during early pregnancy. A dose-response relationship was reported for oro-facial clefts, urinary system malformations, and male genital malformations. The presence of specific metabolites of glycol ethers and trichloroacetic acid in urine was associated with a greater risk of limb defects and male genital malformations.[103]

A prospective cohort study of newborns born to employed women and delivered in Mončegorsk (Russia) in the period 1973 and 2005 examined the association between maternal exposure to acetone, toluene, xylene, and Stoddard solvent – a straight-run petroleum naphtha fraction of low flammability containing principally aliphatic hydrocarbons and conforming to specifications (such as water-white colour, distillation range 300° to 400° F, and flash point over 100° F) for use chiefly in dry cleaning – and the overall risk of CHDs, genitourinary tract malformations, digestive and musculoskeletal system anomalies among offspring. Results showed increased risk among employed mothers exposed to organic solvents compared to the unexposed group.[104]

A prospective cohort study in Denmark assessed the association between exposure to pesticides and the risk of cryptorchidism. The exposed population included all newborns from single pregnancy between 1980 and 2007, having at least one parent employed in agriculture or floriculture, while the unexposed population had parents employed in non-hazardous jobs. Data were collected from three population-based registries: the civil registration system, which had been active since 1968 covering the entire Danish population, the national patient registry, and the birth registry. The study reported a higher risk of cryptorchidism for mothers exposed to pesticides. In the case of paternal exposure, a slight increase was found.[105]

A study by Rocheleau et al., using the data of the NBDPS, investigated the association between maternal occupational exposure to three pesticides (fungicides, insecticides, and herbicides) and the risk of CHDs among the offspring. No association between exposure to pesticides and the risk of CHDs overall was found, neither with herbicides nor in the case of multiple exposures. These findings suggested associations for concurrent occupational exposure to the three pesticides and ASDs, and for combined exposure to both insecticides and herbicides and hypoplastic left heart syndrome (HLHS).[106]

In an American case-control multicentre study carried out between 1997 and 2002, maternal exposure to insecticide, herbicide, and fungicide was moderately associated with gastroschisis, but only among babies born to mothers aged twenty years or older. No association for craniosynostosis, diaphragmatic hernia, and limb reduction defects was observed (table 8).[107]

Rocheleau's multicentre case-control study carried out in the United States during 1997-2002 using data from the NBDPS investigated the increase risk of hypospadias among cases born to women exposed to insecticides, fungicides, and herbicides in the periconceptional period. Findings showed a reduced risk of hypospadias. Moreover, no evidence of a dose-response relationship was observed.[108]

A case-control study performed in the Netherlands did not reveal any association between maternal occupational exposure to pesticides, phthalates, alkylphenolic compounds, heavy metals and risk of CHDs overall. Positive associations between paternal occupational exposure to phthalates and polychlorinated compounds and the risk of CHDs overall were observed. Analysing specific CHDs subtypes, paternal jobs with exposure to phthalates and polychlorinated compounds had increased risk of perimembranous ventricular septal defect (VSDpm) and atrial ventricular septal defects (AVSDs) in offspring. Paternal occupational exposure to alkylphenolic compounds was associated with CoA.[109]

Another NBDPS study by Desrosiers et al. examined the relationship between maternal occupational exposure to aromatic, chlorinated, and solvent "Stoddard" and the risk for both NTDs overall and in specific subtypes (anencephaly, spina bifida, and encephalocele) and the risk of oro-facial clefts and selected subgroups (cleft lip with/without cleft palate and isolated palatoschisis). Findings reported a positive association between occupation-

al exposure to chlorinated solvents during early pregnancy and NTDs. Employed women had a doubled risk of having a child with spina bifida compared with unexposed mothers, while the risk of anencephaly and encephalocele was moderately raised. No association for total oro-facial clefts was reported.[110]

A more recent multicentre case-control study conducted in the United States between 1997 and 2002, using NBDPS data, detected a weak increased risk for craniosynostosis among offspring to women professionally exposed to polycyclic aromatic hydrocarbons (PAH).[111]

Another multicentre case-control study examined the association between PAH exposure and the risk of CHDs subtypes among offspring. Results suggested slight positive associations with VSDs, ASDs, CSDs, LVOTO, CoA, HLHS, and Tetralogy of Fallot (ToF). Also, slight negative associations for conotruncal defects, PVS, and right ventricular outflow tract obstruction (RVOTO) were found.[112]

Lupo's multicentre case-control study carried out on the population enrolled in the American NBDPS evaluated the association between maternal occupational exposure to PAH and the risk of gastroschisis in offspring. Findings reported a positive association between exposure to PAH and the risk of gastroschisis, but only in employed women aged 20 years or older, although young maternal age is the strongest known risk factor for gastroschisis.[113]

Lim's multicentre case-control study assessed the increase in the risk for 39 CAs among women occupationally exposed to ionizing radiation during the periconceptional period. Findings demonstrated that mothers exposed to ionizing radiation had higher odds ratios for hydrocephalus, anotia/microtia, omphalocele, and colon atresia compared to unexposed women. Decreased risks for anencephaly and hypospadias were observed.[114]

According to a recent Chinese matched case-control study, using the data from the Guangdong Registry of Congenital Heart Disease (GRCHD) during the years 2004-2013, women employed as manual worker or housekeeper had an increased risk of isolated CHDs subtypes (PVS, ASDs, and VSDs) in offspring compared to mothers employed in agriculture. The study also reported a reduced risk among unemployed women.[86]

LOCATION	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	EXPOSURE ASSESSMENT	CONFOUNDING VARIABLES	REFERENCE
OCCUPATIONAL							
USA, Europe, Canada	Metanalysis review	3 metanalyses (2005-2010)	OR pooled: 2.18 (1.52-3.11) OR pooled: 1.86 (1.40-2.46) OR pooled: 1.59 (0.99-2.56) OR pooled: 1.37 (1.04-1.81) RR: 1.36 (1.04-1.77) RR: 1.19 (1.00-1.41)	Anencephaly NTD Spina bifida Oro-facial clefts Hypospadias Hypospadias	Paternal solvents Paternal solvents Paternal solvents Maternal pesticides Maternal pesticides Paternal pesticides	Mother's age, SES, parity, alcohol consumption, drug use	Nieuwenhuijse 2013[102]
Brittany (France)	Cohort LB; SB; ET	3,421 pregnant women (2002-2006)	aOR: 4.3 (1.0-18.2) aOR: 12.0 (2.3-60.0) aOR: 3.6 (1.1-12.0)	Oro-facial clefts Oro-facial clefts Male genital defects	Solvents	Mother's age, smoking, alcohol consumption, folic acid intake, educational level	Cordier 2012[103]
Mončegorsk (Russia)	Cohort LB; SB	712 exposed 10,561 non-exposed (1973-2005)	aOR: 2.24 (0.95-5.31) aOR: 1.12 (0.62-2.02) aOR: 1.65 (0.50-5.46) aOR: 1.06 (0.33-3.43) aOR: 2.03 (0.85-4.84)	Genital defects Muscoloskeletal defects Digestive system defects Urinary defects CHD	Organic solvents	Mother's age <18 years, smoking, newborn's year of birth	Vaktskjold 2011[104]
Denmark	Cohort LB	600,000 births (1980-2007)	aHR: 1.31 (1.12-1.53) aHR: 1.04 (0.96-1.12)	Cryptorchidism Cryptorchidism	Maternal pesticides Paternal pesticides	Parental age, newborn's year and place of birth, parity	Jørgensen 2014[105]
Arkansas, Iowa, Texas, California Massachusetts, Utah, Georgia, New York, North Carolina (USA-NBDPS)*	Multicentre case-control LB; SB; ET	3,328 cases 2,988 controls (1997-2002)	aOR: 3.15 (1.27-7.82) aOR: 1.66 (1.04-2.66)	HLHS ASD	Insecticides, herbicides Insecticides, herbicides fungicides	Education level, BMI, residence, alcohol consumption, interview language	Rocheleau 2015[106]
USA (NBDPS)*	Multicentre case-control LB; SB; ET	871 cases 2,857 controls (1997-2002)	aOR: 1.88 (1.16-3.05) matenal age ≥20 years No association	Gastroschisis Craniosynostosis, diaphragm hernia, limb reduction	Insecticides, herbicides fungicides	Mother's age, BMI, diabetes, smoking, study centre, educational level	Kielb 2014[107]
USA (NBDPS)*	Multicentre case-control LB; SB; ET	646 cases 1,493 controls (1997-2002)	aOR: 0.78 (0.61-1.01)	Hypospadias	Pesticides	Mother's age, smoking, parity, gestation age	Rocheleau 2011[108]
Western Netherlands	Case-control LB	424 cases (and their parents) 480 controls (and their parents) (2003-2010)	aOR: 2.08 (1.27-3.40) aOR: 2.84 (1.37-5.92) aOR: 3.85 (1.17-12.67) aOR: 4.22 (1.23-14.42)	CHD VSDpm CoA AVSD	Phthalates Phthalates Alkyphenols Biphenyls	Mother's/father's age, urban density, educational level, smoking, alcohol consumption, folic acid intake, consanguinity	Snijder 2012[109]
Arkansas, Iowa, Texas, California, New York Massachusetts, Utah, Georgia, North Carolina (USA-NBDPS)*	Multicentre case-control LB; SB; ET	511 NTDs 1,163 OFCs 2,977 controls (1997-2002)	aOR: 1.96 (1.34-2.87) aOR: 2.26 (1.44-3.53) aOR: 2.22 (0.84-5.82) aOR: 1.25 (0.58-2.71)	NTD Spina bifida Encephalocele Anencephaly	Chlorinated solvents	Mother's age, educational level, smoking, BMI, parity, folic acid intake, study centre	Desrosiers 2012[110]
USA (NBDPS)*	Multicentre case-control LB; SB; ET	316 cases 2,993 controls (1997-2002)	aOR: 1.75 (1.01-3.05)	Craniosynostosis	PAH	Mother's age, educational level	O'Brien 2016[111]
USA (NBDPS)*	Multicentre case-control LB; SB; ET	3,339 cases 2,993 controls (1997-2002)	aOR: 1.84 (0.72-4.68) aOR: 1.66 (0.70-3.93) aOR: 1.56 (0.85-2.86) aOR: 1.39 (0.72-2.66) aOR: 1.30 (0.58-2.90) aOR: 1.31 (0.74-2.30) aOR: 1.19 (0.68-2.10) aOR: 0.98 (0.58-1.67) aOR: 0.54 (0.23-1.24) aOR: 0.51 (0.19-1.42)	VSDm CoA ToF ASD HLHS LVOTO VSDpm Conotruncal RVOTO PVS	PAH	Mother's age, BMI, educational level, smoking, gestational diabetes, study centre	Lupo 2012[112]
USA (NBDPS)*	Multicentre case-control LB; SB; ET	299 cases 2,993 controls (1997-2002)	aOR: 2.53 (1.27-5.04) aged ≥20 years	Gastroschisis	PAH	Mother's age, BMI, study centre, smoking, educational level, gestational diabetes	Lupo 2012[113]
USA (NBDPS)*	Multicentre case-control LB; SB; ET	18,621 cases 6,820 controls (1997-2009)	aOR: 2.18 (1.11-4.25) aOR: 2.03 (1.03-4.00) cOR: 7.51 (2.53-22.30) aOR: 2.32 (1.15-4.69) cOR: 0.23 (0.06-0.94) aOR: 0.62 (0.40-0.94)	Hydrocephalus Isolated anotia/microzia Isolated colonic atresia Omphalocele Anencephaly Hypospadias	Ionizing radiations	Mother's age, BMI, educational level, location of school, family income, drug abuse	Lim 2015[114]
China	Matched case-control LB	4,034 cases 4,034 controls (2004-2013)	aOR: 1.72 (1.44-2.21) aOR: 1.30 (1.03-1.64) aOR: 1.34 (1.01-1.76) aOR: 0.77 (0.6-0.95)	Isolated CHD ASD VSD Isolated CHD	Employees Manual worker Housekeeper Unemployed		Ou 2016[86]

aHR: adjusted hazard ratio / *rapporto di rischio aggiustato*; **aOR:** adjusted odds ratio / *odds ratio aggiustato*; **ASD:** atrial septal defects / *difetti del setto atriale*; **AVSD:** atrial ventricular septal defects / *difetti del setto atrio-ventricolare*; **BMI:** body mass index / *indice di massa corporea*; **CHD:** congenital heart defects / *difetti cardiaci congeniti*; **CI:** confidence interval / *intervallo di confidenza*; **CoA:** coartation of aorta / *coartazione dell'aorta*; **cOR:** crude odds ratio / *odds ratio crudo*; **ET:** elective termination / *interruzione volontaria di gravidanza*; **HLHS:** hypoplastic left heart syndrome / *syndrome del cuore sinistro ipoplasico*; **LB:** live birth / *nato vivo*; **LVOTO:** left ventricular outflow tract obstruction / *ostruzione del flusso del ventricolo sinistro*; **NTD:** neural tube defects / *difetti del tubo neurale*; **PVS:** pulmonary valve stenosis / *stenosi della valvola polmonare*; **RVOTO:** right ventricular outflow tract obstruction / *ostruzione del flusso del ventricolo destro*; **SB:** still birth / *nato morto*; **ToF:** tetralogy of Fallot / *tetralogia di Fallot*; **VSD:** ventricular septal defects / *difetti del setto ventricolare*; **VSDm:** muscular ventricular septal defects / *difetti muscolari del setto ventricolare*; **VSDpm:** perimembranous ventricular septal defects / *difetti perimembranosi del setto ventricolare*
* National Birth Defects Prevention Study

Table 8. Occupational exposure and risk of congenital anomalies.
Tabella 8. Esposizione occupazionale e rischio di anomalie congenite.

AIR POLLUTION
INQUINAMENTO ATMOSFERICO

A systematic review and metanalysis selected 17 studies to examine the association between traffic air pollutants sulfur dioxide (SO_2), nitrogen dioxide (NO_2), particulate matter (PM_{10} and $PM_{2.5}$), carbon monoxide (CO), and ozone (O_3) exposures and the risk of CAs among offspring. The distance between the monitoring units and the maternal residence ranged from a minimum of 10 km to a maximum of 50 km. The metanalysis of 10 studies published between 2011 and 2014 evaluated the association between exposure to air pollutants and the risk of CHDs among offspring and highlighted a single association between exposure to NO_2 and CoA. The pooled analysis of 7 studies published between 2005 and 2013 evaluated the association between exposure to air pollutants and the risk of oro-facial clefts among offspring, but no association was seen (table 9).[115]
The review and metanalysis by Vrijheid et al. showed a slight increased risk of CoA and ToF with exposure to NO_2, but also an increased risk of ASDs with exposure to PM_{10}. Weak associations between CoA and ToF with SO_2 exposure were observed.[116]
A recent retrospective cohort study conducted in China between 2010 and 2012 investigated whether maternal exposure to PM_{10}, SO_2, and NO_2 before and after conception and during each of the three trimesters of pregnancy increased the risk of CHDs in offspring. Results observed a positive association between exposure to SO_2 and the risk of CAs in offspring, both in the preconceptional period and during the first and third trimesters of pregnancy.[117]
A recent retrospective cohort study conducted on babies born in Florida for the years 2000-2009 assessed whether maternal exposure to $PM_{2.5}$ and benzene during the first three months of pregnancy increased the risk of selected congenital defects, including oro-facial clefts and spina bifida, among offspring. Exposure was categorised into quartiles. Mothers exposed in the 4th quartile of benzene exposure showed an increased risk of any oro-facial clefts as well as isolated cleft palate compared to mothers with exposures in the 1st quartile of benzene exposure.[118]
Another cohort study in the USA for the period 2002-2008 evaluated the association between air pollutants – specifically CO, NO_x, O_3, $PM_{2.5}$, PM_{10}, and SO_2 – and oro-facial defects. The study analysed the exposure to pollutants during the first trimester before conception, through the second trimester, and during the first 3-8 weeks of gestation. Positive associations were found between CO and PM_{10} and the risk of cleft palate, while SO_2 was associated only with cleft lip with or without cleft palate. In addition, the results of the study showed elevated odds ratio of cleft palate with CO, NO, and $PM_{2.5}$ exposures during the first 3-8 weeks of pregnancy.[119]
A cohort study carried out in Israel on 216,730 live births (207,825 of which were conceived naturally and 8,905 conceived through assisted reproduction techniques) assessed the association between air pollutants and CAs between 1997 and 2005. The exposure assessment included the first and second trimesters and the entire pregnancy. For each pollutant, the monthly average was calculated and exposure was considered both as a continuous and categorical variable. There was a modest association between exposure to high concentrations of PM_{10} and NO_x throughout pregnancy and risk of any CHDs, and between exposure in the first and second trimesters of pregnancy and risk of VSDs. The results of the study showed a slight increase in the risk of genital malformations in mothers exposed to NO_x for each period considered among babies conceived naturally.[120]
A multicentre case-control study was performed on subjects enrolled in NBDPS to evaluate the association between maternal exposure to air pollutants between the 2nd and the 8th week of pregnancy and several isolated CHD subgroups. The exposure assessment was carried out using a single-pollutant-based model and a multifactorial model. Exposure was also assessed on the basis of three categories of exposure estimated by model using daily maximum pollutant levels and exploring individual-exposure weeks. The results of statistical analyses on single pollutants revealed increases in risk for CoA and PVS in association with high concentrations of NO_2, for PVS and medium and high concentrations of SO_2, and for HLHS and high concentrations of $PM_{2.5}$. On the contrary, a negative association was found between ASDs and particulate matter. The analysis by week identified the 2nd and 3rd weeks as the most sensitive periods of exposure. Multifactorial analysis revealed an inverse association between high concentrations of SO_2 and ASDs or VSDs.[121]
A recent American case-control study, based on the Massachusetts Birth Defects Registry and conducted for the years 2001-2008, assessed the association between maternal exposure to $PM_{2.5}$ and the risk of CHDs, NTDs, and oro-facial defects. The study examined both special exposure by means of a satellite detection system and exposure related to vehicular traffic calculated on the basis of the distance between the residence and the high traffic-density road. Association estimates were calculated using a logistic regression model, while additive models were used to evaluate spatial patterns. Positive associations were observed for VSDpm, patent foramen ovale (PFO), and patent doctus arteriosus (PDA). The study also found an inverse association between $PM_{2.5}$ and the risk of cleft lip, with or without cleft lip, isolated cleft lip and NTDs.[122]
A matched case-control study conducted in Italy between 1998

and 2006, based on the Emilia-Romagna population registry (IMER-Registry, Northern Italy), examined whether maternal exposure during pregnancy to PM_{10} and benzene from vehicular traffic was associated with the risk of CAs. Results highlighted a slight association between PM_{10} and the overall risk of birth defects, while no association was observed for benzene exposure (table 9).[123]
A case-control study in the US used both cases enrolled in NBDPS and the Texas Birth Defects registry in 2002 and 2006 to examine the association between selected CAs and maternal exposure to $PM_{2.5}$ and O_3 during the first trimester of pregnancy. The exposure assessment was carried out based on both single and co-pollutant models. The results showed a positive association between high O_3 concentrations and risk of craniosynostosis. Inverse associations between CSD and obstructive cardiac defects and $PM_{2.5}$ were reported.[124]

A case-control study carried out in Taiwan matched for month and year of conception reported a weak association between the risk of limb reductions and exposure to SO_2 during the first trimester of pregnancy, and between exposure to O_3 in the first month of pregnancy and the risk of limb deficiencies among preterm births.[125]
Finally, an ecological study carried out on a hospital cohort in Hong Kong during the period 2002-2009 evaluated the association between the incidence of oro-facial clefts and the exposure to atmospheric pollutants (means of monthly solar radiation, UVR, NO_x, NO, NO_2, SO_2, O_3) during the first month and at the first 4-8 weeks of gestation. The monthly rate of oro-facial clefts was correlated with exposure at NO_x during the first month of pregnancy. When exposure was evaluated during the first 8 weeks of pregnancy, an inverse correlation was observed between NO_x and cleft lip and between NO and cleft lip and palate.[126]

LOCATION (NUMBER)	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	EXPOSURE ASSESSMENT	CONFOUNDING VARIABLES	REFERENCE
AIR POLLUTION							
USA (No. 13) Europe (No. 2) Taiwan (No. 1) Australia (No. 1)	Systematic review and metanalysis: • case-control (No. 15) • cohort (No. 2)	17 studies (2005-2013)	OR pooled: 1.08 (0.94-1.24) OR pooled: 0.92 (0.76-1.14) OR pooled: 1.04 (0.80-1.35) OR pooled: 1.17 (0.98-1.41) OR pooled: 1.06 (0.89-1.27) aOR pooled: 1.20 (1.02-1.41)	CL CL CL CL CL CoA	PM_{10}: high *vs.* low quartile NO_2: high *vs.* low quartile CO: high *vs.* low quartile O_3: high *vs.* low quartile NO_2/10 ppb NO_2/10 ppb	Mother's age, smoking, season of conception, folic acid intake, SES, alcohol consumption, marital status, sex of newborn, newborn's year of birth	Chen 2014[115]
USA (No. 3) Europe (No. 4) Australia (No. 1)	Systematic review and metanalysis: • case-control (No. 6) • cohort (No. 2)	8 studies (2001-2011)	aOR pooled: 1.20 (1.02-1.44) aOR pooled: 1.17 (1.00-1.36) aOR pooled: 1.14 (1.01-1.28) aOR pooled: 1.07 (1.01-1.13) aOR pooled: 1.03 (1.01-1.05)	ToF CoA ASD CoA ToF	NO_2/10 ppb NO_2/10 ppb PM_{10}/10 μg/m^3 SO_2/1 ppb SO_2/1 ppb	Mother's age, smoking, season of conception, folic acid intake, marital status, SES, newborn's year of birth	Vrijheid 2011[116]
China	Cohort LB	16,332 births (2010-2012)	aOR: 1.20 (1.09-1.29) aOR: 1.26 (1.15-1.36) aOR: 1.12 (1.03-1.22)	CAs	SO_2/10 μg/m^3	Mother's age, sex of newborn, parity, two of three pollutants	Yao 2016[117]
Florida (USA)	Cohort LB	1,917,155 births (2000-2009)	aPR: 1.52 (1.13-2.04) aPR: 1.29 (1.08-1.56)	CP Oro-facial clefts	Benzene	Mother's age, smoking, ethnicity, educational level, marital status, sex of newborn, parity	Tanner 2015[118]
USA	Cohort LB; FD	188,102 live births and foetal deaths (2002-2008)	aOR: 2.24 (1.21-4.16) aOR: 1.72 (1.12-2.66) aOR: 1.93 (1.16-3.21) aOR: 2.74 (1.62-4.62) aOR: 3.64 (1.73-7.66) aOR: 1.74 (1.15-2.64)	CP CP CL±CP CP CP CP	CO before and after conception PM_{10} before and after conception SO_2 before and after conception CO 3-8 week NO_x 3-8 week $PM_{2.5}$ 3-8 week	Mother's age, smoking, ethnicity, educational level, alcohol consumption, BMI, insurance, season of conception, pregnancy type, parity	Zhu 2015[119]
Israel	Cohort LB	216,730 births (207,825 spontaneous conception; 8,905 with MAP) (1997-2004)	aOR: 1.06 (1.02-1.10) full pregnancy aOR: 1.57 (1.27-1.93) full pregnancy aOR: 1.07 (1.00-1.14) 1,445 cases aOR: 1.03 (1.01-1.04) 1,643 cases aOR: 1.16 (1.01-1.33) 1,445 cases aOR: 1.18 (1.01-1.39) 1,022 cases aOR: 1.04 (1.01-1.07) 1,161 cases aOR: 1.16 (1.00-1.34) 1,161 cases aOR: 1.18 (1.02-1.38) 1st trimester aOR: 1.18 (1.01-1.38) 2nd trimester	Genital defects Genital defects CHD CHD CHD VSD VSD VSD VSD VSD	NO_x10 ppb NO_x: high *vs.* low tertile PM_{10}/10 μg/m^3 NO_x/10 μg/m^3 PM_{10}: high *vs.* low quartile PM_{10}: high *vs.* low quartile NO_x/10 μg/m^3 NO_x: high *vs.* low quartile NO_x: high *vs.* low quartile NO_x: high *vs.* low quartile	Mother's age, smoking, mother's place of birth, education level, season of conception, newborn's year of birth, type of conception, sex of newborn	Farhi 2014[120]

Table 9. Air pollution and risk of congenital anomalies.
Tabella 9. Esposizione a inquinanti atmosferici e rischio di anomalie congenite.

LOCATION (NUMBER)	STUDY DESIGN	STUDY SAMPLE (PERIOD)	MAIN RESULTS (95%CI)	ASSESSED OUTCOME	EXPOSURE ASSESSMENT	CONFOUNDING VARIABLES	REFERENCE
AIR POLLUTION							
Arkansas, Iowa, Texas, New York, Georgia, California, Massachusetts, Utah, North Carolina (USA-NBDPS)*	Multicentre case-control LB; SB; TP	3,328 cases 4,632 controls (1997-2006)	**Based on the distance from the main road** aOR: 3.17 (1.21-8.26) aOR: 3.80 (1.47-9.80) aOR: 7.12 (2.53-20.00) aOR: 4.66 (1.08-20.10) aOR: 4.53 (1.05-19.50) aOR: 11.10 (2.39-51.00) aOR: 3.55 (1.25-10.1) aOR: 2.63 (1.14-6.06) aOR: 1.54 (1.01-2.33) aOR: 1.53 (1.01-2.33) aOR: 2.79 (1.19-6.52) aOR: 3.28 (1.41-7.61) aOR: 3.32 (1.30-8.43) aOR: 1.98 (1.19-3.31) aOR: 1.85 (1.08-3.18) aOR: 2.18 (1.08-4.49)	 Conotruncal Conotruncal Conotruncal ToF ToF ToF RVOTO HLHS LVOTO LVOTO CoA CoA CoA RVOTO PVS CoA	 NO_2 (10-50 percentile) NO_2 (50-90 percentile) NO_2 (≥90 percentile) NO_2 (10-50 percentile) NO_2 (50-90 percentile) NO_2 (≥90 percentile) NO_2 (≥90 percentile) PM_{10} (≥90 percentile) NO_2 (10-50 percentile) NO_2 (50-90 percentile) NO_2 (10-50 percentile) NO_2 (50-90 percentile) NO_2 (≥90 percentile) NO_2 (≥90 percentile) NO_2 (≥90 percentile) PM_{10} (10-50 percentile)	Mother's age, smoking, educational level, BMI, folic acid intake, alcohol consumption, study site, place of birth, family income	Stingone 2014[121]
Arkansas, Iowa, Texas, New York, Georgia, California, Massachusetts, Utah, North Carolina (USA-NBDPS)*	Multicentre case-control LB; SB; TP	3,328 cases 4,632 controls (1997-2006)	**Individual pollutant/weekly mean** **2nd week** aOR: 0.37 (0.19-0.70) aOR: 1.96 (1.11-3.46) aOR: 3.43 (1.36-8.66) **3rd week** aOR: 2.15 (1.22-3.78) aOR: 1.98 (1.10-3.56) **5th week** aOR: 1.83 (1.08-3.12) **Multiple analysis** aOR: 0.59 (0.36-0.98) aOR: 0.40 (0.19-0.83)	 PVS ToF AVSD PVS VSDpm PVS VSDpm ASD	 CO (≥90 percentile) $PM_{2.5}$ (≥90 percentile) $PM_{2.5}$ (≥90 percentile) O_3 (75-25 percentile) SO_2 (≥90 percentile) $PM_{2.5}$ (≥90 percentile) SO_2 (50-90 percentile) SO_2 (≥90 percentile)	Mother's age, active smoking, educational level, BMI, folic acid intake, family income, alcohol consumption, study centre, place of birth	Stingone 2014[121]
Massachusetts (USA)	Case-control Births	3,713 cases 7,816 controls (2001-2008)	aOR: 1.34 (0.98-1.83) aOR: 1.24 (0.94-1.62) aOR: 1.23 (0.78-1.90) aOR: 1.19 (0.82-1.72) aOR: 1.18 (0.67-2.09) aOR: 1.18 (0.91-1.53) aOR: 0.76 (0.50-1.10) aOR: 0.89 (0.54-1.46) aOR: 0.77 (0.46-1.05)	VSDpm PDA ASD Common atrium Endocardial cushion defects PFO CL±CP CP NTD	$PM_{2.5}$/10 μg/m^3	Mother's age, active smoking, educational level, twin births, family income, alcohol consumption. **For CHD and NTD:** preferred languages, number of pregnancies, adequate prenatal treatment **For NTD and CL±CP:** smoking **For CL±CP:** season of conception, sex of newborn	Girguis 2016[122]
Reggio Emilia (Northern Italy)	Matched case-control LB; ET	228 cases, 228 controls (1998-2006)	cOR: 1.16 (0.99-1.26)	CAs	PM_{10}		Vinceti 2016[123]
Texas (USA)	Case-control LB	21,351 cases 1,402,132 controls (2002-2006)	aOR: 1.28 (1.04-1.58) aOR: 0.79 (0.75-0.82) aOR: 0.88 (0.79-0.97)	Craniosynostosis CSD Obstructive heart defects	O_3/13.3 ppb /IQR $PM_{2.5}$/5.0 μg/m^3 $PM_{2.5}$/5.0 μg/m^3	Mother's age, smoking, ethnicity, educational level, prenatal treatments, number of live births	Vinikoor-Imler 2015[124]
Taiwan	Case-control LB	1,687 cases 16,870 controls (2001-2007)	aOR: 1.024 (1.000-1.048) aOR: 1.391 (1.064-1.818) preterm	Limb reduction Limb reduction	SO_2/1 ppb 1st trimester O_3/10 ppb 1st month	Mother's age, socioeconomic status	Lin 2014[125]
Hong Kong (China)	Ecological LB	48,404 births (2002-2009)	r = 0.685; p = 0.014 r = 0.75; p = 0.05 r = -0.900; p = 0.018 r = -0.669; p = 0.031	Oro-facial clefts Oro-facial clefts CL CL±CP	NO_x 1st month NO 1st month NO_x 8th week NO 8th week		Chung 2013[126]

aOR: adjusted odds ratio / *odds ratio aggiustato*; **aPR:** adjusted prevalence ratio / *rapporto di prevalenza aggiustato*; **ASD:** atrial septal defects / *difetti del setto atriale*; **AVSD:** atrial ventricular septal defects / *difetti del setto atrio-ventricolare*; **BMI:** body mass index / *indice di massa corporea*; **CAs:** congenital anomalies / *anomalie congenite*; **CoA:** coartation of aorta / *coartazione dell'aorta*; **cOR:** crude odds ratio / *odds ratio crudo*; **CHD:** congenital heart defects / *difetti cardiaci congeniti*; **CI:** confidence interval / *intervallo di confidenza*; **CL:** cleft lip / *labioschisi*; **CP:** cleft palate / *palatoschisi*; **CSD:** cardiac septal defects / *difetti cardiaci del setto*; **ET:** elective termination / *interruzione volontaria di gravidanza*; **FD:** foetal death / *morte fetale*; **HLHS:** hypoplastic left heart syndrome / *syndrome del cuore sinistro ipoplasico*; **LB:** live birth / *nato vivo*; **LVOTO:** left ventricular outflow tract obstruction / *ostruzione del flusso del ventricolo sinistro*; **MAP:** medically assisted procreation / *procreazione medicalmente assistita*; **NTD:** neural tube defects / *difetti del tubo neurale*; **PDA:** patent ductus arteriosus / *dotto arterioso pervio*; **PFO:** persistent forame ovale / *persistenza del forame ovale*; **PVS:** pulmonary valve stenosis / *stenosi valvola polmonare*; **RVOTO:** right ventricular outflow tract obstruction / *ostruzione del flusso del ventricolo destro*; **SB:** still birth / *nato morto*; **ToF:** tetralogy of Fallot / *tetralogia di Fallot*; **VSD:** ventricular septal defects / *difetti del setto ventricolare*; **VSDpm:** perimembranous ventricular septal defects / *difetti perimembranosi del setto ventricolare*
* National Birth Defects Prevention Study

Table 9. Air pollution and risk of congenital anomalies.
Tabella 9. Esposizione a inquinanti atmosferici e rischio di anomalie congenite.

DISCUSSION AND CONCLUSIONS

DISCUSSIONE E CONCLUSIONI

3

DISCUSSION
DISCUSSIONE

Epidemiological studies, as well as experimental studies, are providing a growing amount of information for recognized or potential risk factors for single or groups of CAs and are useful to generate hypotheses for future research investigating the relationship between environmental exposures and the development of birth defects.

Currently, there is no unified monitoring system for birth defects worldwide. Information on the prevalence of CAs come from birth certificates and from State birth defects monitoring systems. CA prevalence data come from population-based registries of CAs, which are the most reliable sources. CA registries are tools used to identify genetic and teratogenic exposures, as well as evaluating and planning health care services and prevention policies.[127,128] In Europe, the European Joint Action EUROCAT considered CA registries an effective tools for epidemiological assessments in polluted areas.[129] Moreover, primary prevention of CAs in the population based on controlling environmental risk factors is a crucial policy priority, including preconceptional care and whole population approaches. An updated on the state of the art on prevention of CAs has recently been published by a EUROCAT and EUROPLAN working group.[130]

ENVIRONMENTAL EXPOSURES
ESPOSIZIONI AMBIENTALI

Industries / Industrie

The epidemiological evidence collected in this review on the association between industrial sources of prenatal exposure and the increased risk of CAs are still limited, as few analytic epidemiological studies have been performed and most of these studies have used an ecological design unable to infer a causal relationship. The ecological design does not allow the exploration of possible individual confounders related to maternal and paternal risk factors. Another limitation that needs to be considered in the interpretation of the results is that evaluating health impact in industrially polluted areas is a very complex process due to the multiple and heterogeneous sources of pollution, the role of non-environmental risk co-factors and the multifactorial aetiology of CAs. Finally, the CA prevalence estimates are highly variable across the different registries due to different diagnostic practices and methods of gathering and coding data. Another important consideration is that the risk estimate may be underestimated since, in several studies, cases were ascertained only in live births. Despite these limitations, slight associations of CAs as a group among offspring to mothers living in proximity to industrial activities – such as chemical, petrochemical, steel and power plants, and ports – were detected. Based on scientific literature, the evidence of association in relation to selected CA subgroups is still inadequate, although the potential teratogenic effect of chlorinated solvents, especially on CHDs and NTDs, have already been reported, suggesting a relationship between maternal occupational exposure to specific chlorinated solvents and the development of birth defects.[110] An excess for genital defects, namely cryptorchidism and hypospadias, were observed suggesting a correlation with the presence of petrochemical plants.[131] In the literature, there is already evidence of the harmful effects of hydrocarbon exposure on spermatogenesis,[132] including reduced sperm mobility[133] and sperm chromosome abnormalities.[134] The hypothesis of cumulative effects to multiple low-dose environmental risk factors exposure with a prevalent endocrine disruptor effect is currently proposed.[135]

Mines / Miniere

Due to sparse epidemiological data collected in the examined period, evidence on the association between maternal residential proximity to mines and the risk of CAs as a group in offspring is inadequate. In addition, the current epidemiological evidence on the causal relationship between residential exposure and increased risk of specific subgroups is inadequate, both due to the limited number of studies and to the ecological approach being unable to estimate individual exposure to specific categories of pollutants. Extraction activities of shale gas with surface techniques are uniquely practiced in the United States, where, according to estimates, 15 millions of Americans live within one mile from unconventional natural gas extraction wells.[136] During 1982-2005, surface mining activities in West Virginia have been increased from 19% up to 42%,[137] while the International Energy Agency reports that unconventional gas production accounts for 18% of gas production.[138] Fracking operations are accountable for the release of BTEX (benzene, toluene, ethylbenzene, xylene), PHA (polyhydroxyalkanoates), volatile organic compounds, ozone, suspended particulate, sulphur and nitrate oxides, and heavy metals seeping into the groundwater.[139-141] Hence, geographic specificity should be addressed by future research assessing the relationship of exposure over time, in addition to adopting surveillance programmes or analytical study designs.

Landfills / Discariche

Two reviews concluded that epidemiological evidence on associations between both total CA and selected subtypes, such as

CHDs, NTDs, hypospadias, and skin disorders, and the maternal residential proximity to industrial or hazardous waste landfill sites are still to be considered limited. Though several multiple-site studies supported a plausible linkage between residence near waste disposal sites and adverse reproductive effects, literature investigating links between land contamination and CA risk often provides no consistent results.

Moreover, just recently, a systematic review evaluated the causal relationship between exposure to hazardous waste and risk of CAs, overall and for specific subgroups (i.e., urogenital, connective and musculoskeletal system and neural tube anomalies), as limited.[142]

In the Provinces of Naples and Caserta (Southern Italy), illegal toxic waste disposal is responsible for emissions of dioxins, furans, and polychlorinated biphenyls, but the body of evidence is still inadequate and only slight associations for urogenital system and CNS defects alone were detected.

The difficulty in exactly identifying waste arrangement and locating illegal waste dumping implies that the population at risk is hard to identify. Low-dose exposures affect the relative risk in small increments that are difficult to distinguish from the ones introduced by confounding factors.

Overall, the wide geographical and demographic dimension of these areas, the heterogeneity of the sources of exposure, and the limitation due to the ecological design need to be considered in the interpretation of the results.

Incinerators / Inceneritori

The evidence of a causal relation between residential proximity to incinerators and increased CA risk is still inadequate. Most of the epidemiological studies used an ecological approach based on the distance from the source of emissions or on the exposure to incinerators estimated with dispersion models, but none of the studies included biomonitoring data able to validate the exposure models. Experimental data show that dioxins are highly lipophilic and they partition preferentially in adipose tissue.[143]

Overall, in the field of environmental causes of CAs, evidence is often limited or inadequate. Epidemiological studies are hard to compare since they often differ in the type of population (total births including foetal deaths, stillbirths, pregnancy termination, or only live births), the source of data, and the considered confounding factors.

Therefore, future studies should try to adhere to very strict standards in order to avoid underestimation of the risk estimates.

INDIVIDUAL EXPOSURES
ESPOSIZIONI INDIVIDUALI

Cigarette smoke / Fumo

The analysed literature provides sufficient evidence that maternal smoking is associated with increased risk of CHDs among offspring, in particular for septal defects and right ventricular outflow tract obstruction (RVOTO), especially in the case of maternal exposure before and after conception. Smoking was a significant risk factor even considering potential confounding factors. The calculated pooled risk estimates were homogeneous, despite studies conducted in different geographical areas and on women with different lifestyles factors may influence the prevalence of CHDs. The association between maternal smoking in pregnancy and the risk of CHDs in the foetus had already been demonstrated by previous work.[144,145]

Pooled analyses showed evidence of significant association between maternal smoking exposure during pregnancy and orofacial clefts, NTDs, and gastrointestinal anomalies, above all, when women smoke in the periconceptional period and in the first trimester of pregnancy. Smoking was also a significant risk factor for less severe CAs, such as cryptorchidism. These results further support public health recommendations to completely abstain from smoking both before and during pregnancy.

Alcohol / Alcol

The use of alcohol during pregnancy can lead to multiple health and social problems for both the mother and the child. High alcohol consumption among pregnant women can cause life-long disabilities in the offspring known as foetal alcohol spectrum disorder, together with other adverse pregnancy outcomes.

The Action plan for the prevention and control of non-communicable diseases in the WHO European Region addresses alcohol use and aims to prevent alcohol exposure during pregnancy. Recently, the WHO published a report to give an overview of the literature on interventions to prevent alcohol exposure during pregnancy addressed to pregnant and non-pregnant women.[146,147]

However, collected evidence regarding CAs and maternal mild-to-moderate alcohol consumption during pregnancy is considered too limited to show a causal association. In particular, while the evidence of an association between mild-to-moderate alcohol intake and risk of CHDs is weak, there is more persuasive evidence of the harmful effect of high levels of alcohol consumed either on weekly bases or on a single binge drinking occasion. As to other specific CA subtypes, it appears that anomalies in the nervous system, particularly anencephaly and spina bifida, are more likely to occur in association with high levels of alcohol consumption both on a constant consumption and on binge drinking occasion during the first trimester of pregnancy. However, the statistical analysis of the data collected in this review confirms the association between alcohol consumption and age, smoke, and SES, strengthening its use as a confounding factor.

Socioeconomic status / Livello socioeconomico

To date, few studies have evaluated if socioeconomic inequalities could be associated with the risk of CAs, as the epidemiological evidence of associations between SES and CAs are still limited. In particular, findings suggest that the risk of CAs increases in the most disadvantaged classes. An important consideration is that lower socioeconomic status is associated with health-damaging lifestyles, such as heavy smoking, increased alcohol consumption, and poor health care.

Occupational exposure / Esposizione occupazionale

Concerning occupational exposure, the epidemiological studies collected in this review were suggestive of an association between NTDs and paternal exposures to solvents, although they are not strong enough to infer a causal relationship, as well as between maternal exposure to pesticides and increased risk of oro-facial clefts among offspring.

Conversely, evidence of association between maternal and paternal exposure to pesticides and urogenital defects, such as cryptorchidism and hypospadias, are to be considered inadequate; the evidence of causal relation between occupational exposure of both parental to chemical agents or PAH and increased risk of selected CAs is also inadequate.

In conclusion, even if the evidence is still limited or inadequate, pregnant women at work must be protected from teratogenic exposure as pesticides and organic solvent. This issue should be address in occupation health policies.[130]

Air pollution / Inquinamento atmosferico

A limited number of studies investigated the causal relation between birth defects and prenatal exposure to air pollution, specifically CO, O_3, PM_{10} and $PM_{2.5}$, NO_2, and SO_2. Most of these analytical epidemiological studies have focused on cardiac and oral cleft birth defects; for cardiac defects, only a slight association was detected, for oral cleft defects no evidence was identified. Anyway, evidence of a positive association between specific CHDs and maternal exposure to high concentrations of NO_2 and SO_2 has been reported in a recent pooled analysis. However, inconsistencies and uncertainties concerning the effects of specific pollutants and pollutant mixtures and critical exposure periods remain. In particular, the major limitations of air pollution studies are exposure misclassification, low statistical power, and unmeasured confounding. Further studies which include more accurate exposure assessment and spatial analyses, better case ascertainment, and adjustment for a large number of potentially confounding effects are needed.

CONCLUSIONS
CONCLUSIONI

In conclusion, despite a growing number of studies suggests a link between CAs and specific environmental contaminants and individual risk factors, such association appears to be limited to some birth defect subgroups. Furthermore, environmental epidemiology suffers from limitations leading to inadequate or contrasting results: since most diseases are "rare" in populations, a large number of individuals have to be observed for a long-time period to identify a potential determinant, and studies carried out in small communities for a limited number of years lack statistical power. Hence, improved exposure assessment methods – in particular more accurate spatial measurements or modelling – standardized definition of cases, a more accurate control of the main or putative confounders, and a larger sample size are highly recommended for future epidemiological studies.

REFERENCES
BIBLIOGRAFIA

1. Christianson A, Howson CP, Modell CB. March of Dimes Global Report on Birth Defects: The Hidden Toll of Dying and Disabled Children. New York, March of Dimes Foundation, White Plains, 2006.
2. World Health Organization. Congenital anomalies fact sheet. Geneva, WHO, 2016. Available from: http://www.who.int/news-room/fact-sheets/detail/congenital-anomalies
3. Higashi H, Barendregt JJ, Kassebaum, NJ, Weiser TG, Bickler SW, Vos T. The burden of selected congenital anomalies amenable to surgery in low and middle-income regions: cleft lip and palate, congenital heart anomalies and neural tube defects. Arch Dis Child 2015;100(3):233-38.
4. Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: Final data for 2013. Natl Vital Stat Rep 2016; 64(2):1-119.
5. European Surveillance of Congenital Anomalies (EUROCAT). Perinatal Mortality Associated with Congenital Anomalies in EUROCAT Full Member Registries (n=29^), 2008-2012, by Type of Anomaly. Available from: http://www.eurocat-network.eu/content/EUROCAT-Perinatal-Mortality-Table-1v.pdf (last accessed: 21 July 2014).
6. EUROCAT working group. EUROCAT Special Report: Congenital Anomalies are a Major Group of Mainly Rare Diseases. Newtownabbey, University of Ulster, 2012. Available from: http://www.eurocat-network.eu/content/Special-Report-Major-Group-of-Mainly-Rare-Diseases.pdf (last accessed: 20 January 2014)
7. Prüss-Ustün A, Wolf J, Corvalán C, Bos R, Neira M. Preventing disease through healthy environments. A global assessment of the burden of disease from environmental risks. Geneva, WHO, 2016.
8. Hobbs CA, Cleves MA, Simmons CJ. Genetic epidemiology and congenital malformations: from the chromosome to the crib. Arch Pediatr Adolesc Med 2002;156(4):315-20.
9. Weinhold B. Environmental Factors in Birth Defects: What We Need to Know. Environ Health Perspect 2009;117(10):A440-47.
10. Slama R, Cordier S. Environmental contaminants and impacts on healthy and successful pregnancies. In: Environmental impacts on reproductive health and fertility. Woodruff TJ, Janssen SJ, Guillette LJ, Giudice LC (eds). Cambridge, Cambridge University Press, 2010.
11. Castilla EE, López-Camelo JS, Campaña H, Rittler M. Epidemiological methods to assess the correlation between industrial contaminants and rates of congenital anomalies. Mutat Res 2001;489(2-3):123-45.
12. Shi M, Wehby GL, Murray JC. Review on genetic variants and maternal smoking in the etiology of oral clefts and other birth defects. Birth Defects Res C Embryo Today 2008;84(1):16-29.
13. Nieuwenhuijsen MJ, Martinez D, Grellier J et al. Chlorination disinfection by-products in drinking water and congenital anomalies: review and meta-analyses. Environ Health Perspect 2009;117(10):1486-93.
14. Dolk H, Vrijheid M. The impact of environmental pollution on congenital anomalies. Br Med Bull 2003;68:25-45.
15. Miranda ML, Maxson P, Edwards S. Environmental contributions to disparities in pregnancy outcomes. Epidemiol Rev 2009;31(1):67-83.
16. Yuan Y, Jin L, Wang L et al. Levels of PAH-DNA adducts in placental tissue and the risk of fetal neural tube defects in a Chinese population. Reprod Toxicol 2013;37:70-75.
17. Tang D, Li TY, Chow JC et al. Air pollution effects on fetal and child development: a cohort comparison in China. Environ Pollut 2014;185:90-96.
18. Hansen JM. Oxidative stress as a mechanism of teratogenesis. Birth Defects Res C Embryo Today 2006;78(4):293-307.
19. Pirinccioglu AG, Alyan O, Kizil G, Kangin M, Beyazit N. Evaluation of oxidative stress in children with congenital heart defects. Pediatr Int 2012;54(1):94-98.
20. Giannakoulas G, Mouratoglou SA, Gatzoulis MA, Karvounis H. Blood biomarkers and their potential role in pulmonary arterial hypertension associated with congenital heart disease. A systematic review. Int J Cardiol 2014;174(3):618-23.
21. Mostafavi N, Vlaanderen J, Chadeau-Hyam M et al. Inflammatory markers in relation to long-term air pollution. Environ Int 2015;81:1-7.
22. Stein RA. Epigenetics and environmental exposures. J Epidemiol Community Health 2012; 66(1):8-13.
23. Zhang QJ, Liu ZP. Histone methylations in heart development, congenital and adult heart diseases. Epigenomics 2015;7(2):321-30.
24. Rogers JM. Tobacco and pregnancy. Reprod Toxicol 2009;28(2):152-60.
25. Zalacain M, Sierrasesumaga L, Larrañaga C, Patiño-García A. Effects of benzopyrene-7,8-diol-9,10-epoxide (BPDE) in vitro and of maternal smoking in vivo on micronuclei frequencies in fetal cord blood. Pediatr Res 2006;60(2):180-84.
26. Mancinelli R, Fidente RM, Draisci R (eds). Donna e alcol: aggiornamenti in tema di ricerca clinica e preclinica. Rapporti ISTISAN 13/36. Roma, Istituto Superiore di Sanità, 2013. Available from: http://old.iss.it/binary/alco4/cont/Rapporto_Istisan.pdf
27. Pirastu R, Ancona C, Iavarone I, Mitis F, Zona A, Comba P (eds). SENTIERI Project. Evaluation of the epidemiological evidence Epidemiol Prev 2010;34(5-6) Suppl 3:1-96.
28. Pirastu R, Iavarone I, Ancona C. Il progetto SENTIERI (Studio Epidemiologico Nazionale dei Territori e degli Insediamenti Esposti a Rischio da Inquinamento). ISTISAN congressi 10/C1. Roma, Istituto superiore di Sanità, 2010.
29. McKenzie LM, Guo R, Witter RZ, Savitz DA, Newman LS, Adgate JL. Birth outcomes and maternal residential proximity to natural gas development in rural Colorado. Environ Health Perspect 2014;122(4):412-17.
30. Brender JD, Shinde MU, Zhan FB, Gong X, Langlois PH. Maternal residential proximity to chlorinated solvent emissions and birth defects in offspring: a case-control study. Environ Health 2014;13:96.
31. Gianicolo EAL, Bruni A, Rosati E et al. Congenital anomalies among live births in a polluted area. A ten-year retrospective study. BCM Pregnancy Childbirth 2012;12:165.
32. EUROCAT. Prevalence Tables. Available from: http://www.eurocat-network.eu/accessprevalencedata/prevalencetable
33. Gianicolo EAL, Mangia C, Cervino M, Bruni A, Andreassi MG, Latini G. Congenital anomalies among live births in a high environmental risk area – a case-control study in Brindisi (Southern Italy). Environ Res 2014;128:9-14.
34. Bianchi F, Bianca S, Barone C, Pierini A. Updating of the prevalence of congenital anomalies among resident births in the Municipality of Gela (Southern Italy). Epidemiol Prev 2014;38(3-4):219-26.
35. Lockwood AH, Welker-Hood K, Rauch M, Gottlieb B. Coal's Assault on Human Health. A Report from Physicians for Social Responsibility. 2009. Available from: http://large.stanford.edu/courses/2015/ph240/mcfadden2/docs/psr-coal-fullreport.pdf
36. Ahern MM, Hendryx M, Conley J, Fedorko E, Ducatman A, Zullig KJ. The association between mountain top mining and birth defects among live births in central Appalachia, 1996-2003. Environ Res 2011;111(6):838-46.
37. Lamm SH, Li J, Robbins SA, Dissen E, Chen R, Feinleib M. Are residents of mountain-top mining counties more likely to have infants with birth defects? The West Virginia experience. Birth Defects Res A Clin Mol Teratol 2015;103(2):76-84.
38. Stassen MJM, Preeker NL, Ragas AMJ, van de Ven MW, Smolders AJ, Roeleveld N. Metal exposure and reproductive disorders in indigenous communities living along the Pilomayo River, Bolivia. Sci Total Environ 2012;427-428:26-34.
39. Mattiello A, Chiodini P, Bianco E et al. Health effects associated with the disposal of solid waste in landfills and incinerators in populations living in surrounding areas: a systematic review. Int J Public Health 2013;58(5):725-35.
40. International Agency for Research on Cancer. Preamble to the IARC Monographs. B. Scientific review and evaluation. Available from: http://monographs.iarc.fr/ENG/Preamble/currentb6evalrationale0706.php (last accessed: 22 July 2013)
41. Fielder HM, Poon-King CM, Palmer SR, Moss N, Coleman G. Assessment of impact on health of residents living near the Nant-y-Gwyddon landfill site: retrospective analysis. BMJ 2000;320(7226):19-22.
42. Fielder HM, Palmer SR, Poon-King C, Moss N, Coleman G. Addressing environmental health concerns near Trecatti landfill site, United Kingdom. Arch Environ Health 2001;56(6):529-35.
43. Eizaguirre-García D, Rodríguez-Andrés C, Watt GC. Congenital anomalies in Glasgow between 1982 and 1989 and chromium waste. J Public Health Med 2000;22(1):54-58.
44. Elliott P, Briggs D, Morris S et al. Risk of adverse birth outcomes in populations living near landfill sites. BMJ 2001;323(7309):363-68. Erratum in: BMJ 2001; 323(7322):1182.
45. Elliott P, Richardson S, Abellan JJ et al. Geographic density of landfill sites and risk of congenital anomalies in England. Occup Environ Med 2009;66(2):81-89.
46. Morris SE, Thomson AOW, Jarup L, de Hoogh C, Briggs DJ, Elliott P. No excess risk of adverse birth outcomes in populations living near special waste landfill sites in Scotland. Scott Med J 2003;48(4):105-07.
47. Kuehn CM, Mueller BA, Checkoway H, Williams M. Risk of malformations associated with residential proximity to hazardous waste sites in Washington State. Environ Res 2007;103(3):405-12.
48. Palmer SR, Dunstan FD, Fielder H, Fone DL, Higgs G, Senior ML. Risk of congenital anomalies after the opening of landfill sites. Environ Health Perspect 2005;113(10):1362-65.
49. Kloppenborg SC, Brandt UK, Gulis G, Ejstrud B. Risk of congenital anomalies in the vicinity of waste landfills in Denmark: an epidemiological study using GIS. Cent Eur J Public Health 2005;13(3):137-43.
50. Gouveia N, Prado RR. Spatial analysis of the health risks associated with solid waste incineration: a preliminary analysis. Rev Bras Epidemiol 2010;13(1):3-10.

REFERENCES

51. Dummer TJB, Dickinson HO, Parker L. Adverse pregnancy outcomes near landfill sites in Cumbria, northwest England, 1950-1993. Arch Environ Health 2003;58(11):692-98.
52. Dolk H, Vrijheid M, Armstrong B et al. Risk of congenital anomalies near hazardous-waste landfill sites in Europe: the EUROHAZCON study. Lancet 1998;352(9126):423-27.
53. Vrijheid M, Dolk H, Armstrong B et al. Hazard potential ranking of hazardous waste landfill sites and risk of congenital anomalies. Occup Environ Med 2002;59(11):768-76.
54. Orr M, Bove F, Kaye W, Stone M. Elevated birth defects in racial or ethnic minority children of women living near hazardous waste sites. Int J Hyg Environ Health 2002;205(1-2):19-27.
55. Boyle E, Johnson H, Kelly A, McDonnell R. Congenital anomalies and proximity to landfill sites. Ir Med J 2004;97(1):16-18.
56. Geschwind SA, Stolwijk JA, Bracken M et al. Risk of congenital malformations associated with proximity to hazardous waste sites. Am J Epidemiol 1992;135(11):1197-207.
57. Marshall EG, Gensburg LJ, Deres DA, Geary NS, Cayo MR. Maternal residential exposure to hazardous wastes and risk of central nervous system and musculoskeletal birth defects. Arch Environ Health 1997;52(6):416-25.
58. Croen LA, Shaw GM, Sanbonmatsu L, Selvin S, Buffler PA. Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations. Epidemiology 1997;8(4):347-54.
59. Triassi M, Alfano R, Illario M, Nardone A, Caporale O, Montuori P. Environmental pollution from illegal waste disposal and health effects: a review on the triangle of death. Int J Environ Res Public Health 2015;12(2):1216-36.
60. Fazzo L, Belli S, Minichilli F et al. Cluster analysis of mortality and malformations in the Provinces of Naples and Caserta (Campania Region). Ann Ist Super Sanita 2008;44(1):99-111.
61. Martuzzi M, Mitis F, Bianchi F, Minichilli F, Comba P, Fazzo L. Cancer mortality and congenital anomalies in a region of Italy with intense environmental pressure due to waste. Occup Environ Med 2009;66(11):725-32.
62. Ashworth DA, Elliott P, Toledano MB. Waste incineration and adverse birth and neonatal outcomes: a systematic review. Environ Int 2014;69:120-32.
63. Cordier S, Chevrier C, Robert-Gnansia E, Lorente C, Brula P, Hours M. Risk of congenital anomalies in the vicinity of municipal solid waste incinerators. Occup Environ Med 2004;61(1):8-15.
64. Cordier S, Lehebel A, Amar E et al. Maternal residence near municipal waste incinerators and the risk of urinary tract birth defects. Occup Environ Med 2010;67(7):493-99.
65. Jansson B, Voog L. Dioxin from Swedish municipal incinerators and the occurrence of cleft lip and palate malformations. Int J Environ Stud 1989;34(1-2):99-104.
66. Cresswell PA, Scott JE, Pattenden S, Vrijheid M. Risk of congenital anomalies near the Byker waste combustion plant. J Public Health Med 2003;25(3):237-42.
67. Dummer TJ, Dickinson HO, Parker L. Adverse pregnancy outcomes around incinerators and crematoriums in Cumbria, North West England, 1956-93. J Epidemiol Community Health 2003;57(6):456-61.
68. Vinceti M, Malagoli C, Teggi S et al. Adverse pregnancy outcomes in a population exposed to the emissions of a municipal waste incinerator. Sci Total Environ 2008;407(1):116-21.
69. Vinceti M, Malagoli C, Fabbi S et al. Risk of congenital anomalies around a municipal solid waste incinerator: a GIS-based case-control study. Int J Health Geogr 2009;8:8.
70. Lee LJ, Lupo PJ. Maternal smoking during pregnancy and the risk of congenital heart defects in offspring: a systematic review and metaanalysis. Pediatr Cardiol 2013;34(2):398-407.
71. Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. Hum Reprod Update 2011;17(5):589-604.
72. Molina-Solana R, Yáñez-Vico RM, Iglesias-Linares A, Mendoza-Mendoza A, Solano-Reina E. Current concepts on the effect of environmental factors on cleft lip and palate. Int J Oral Maxillofac Surg 2013;42(2):177-84.
73. Sabbagh HJ, Hassan MH, Innes NP, Elkodary HM, Little J, Mossey PA. Passive smoking in the etiology of non-syndromic orofacial clefts: a systematic review and meta-analysis. PLoS One 2015;10(3):e0116963.
74. Leite M, Albieri V, Kjaer SK, Jensen A. Maternal smoking in pregnancy and risk for congenital malformations: results of a Danish register-based cohort study. Acta Obstet Gynecol Scand 2014;93(8):825-34.
75. Gunnerbeck A, Edstedt Bonamy AK, Wikström AK, Granath F, Wickström R, Cnattingius S. Maternal snuff use and smoking and the risk of oral cleft malformations – a population-based cohort study. PLoS One 2014;9(1):e84715.
76. Fung A, Manlhiot C, Naik S et al. Impact of prenatal risk factors on congenital heart disease in the current era. J Am Heart Assoc 2013;2(3):e000064.
77. Deng K, Liu Z, Lin Y et al. Periconceptional paternal smoking and the risk of congenital heart defects: a case-control study. Birth Defects Res A Clin Mol Teratol 2013;97(4):210-16.
78. Martelli DR, Coletta RD, Oliveira EA et al. Association between maternal smoking, gender, and cleft lip and palate. Braz J Otorhinolaryngol 2015;81(5):514-19.
79. Zhang B, Jiao X, Mao L, Xue J. Maternal cigarette smoking and the associated risk of having a child with orofacial clefts in China: a case-control study. J Craniomaxillofac Surg 2011;39(5):313-18.
80. Wang M, Wang ZP, Gong R, Zhao ZT. Maternal smoking during pregnancy and neural tube defects in offspring: a meta-analysis. Childs Nerv Syst 2014;30(1):83-89.
81. Benedum CM, Yazdy MM, Mitchell AA, Werler MM. Risk of spina bifida and maternal cigarette, alcohol, and coffee use during the first month of pregnancy. Int J Environ Res Public Health 2013;10(8):3263-81.
82. Zwink N, Jenetzky E, Brenner H. Parental risk factors and anorectal malformations: systematic review and meta-analysis. Orphanet J Rare Dis 2011;6:25.
83. Kancherla V, Romitti PA, Sun L et al. Descriptive and risk factor analysis for choanal atresia: The National Birth Defects Prevention Study, 1997-2007. Eur J Med Genet 2014;57(5):220-29.
84. Zwink N, Rissmann A, Pötzsch S, Reutter H, Jenetzky E, CURE-Net Consortium. Parental risk factors of anorectal malformations: Analysis with a regional population-based control group. Birth Defects Res A Clin Mol Teratol 2016;106(2):133-41.
85. Leonardi-Bee J, Britton J, Venn A. Secondhand smoke and adverse fetal outcomes in nonsmoking pregnant women: a meta-analysis. Pediatrics 2011;127(4):734-41.
86. Ou Y, Mai J, Zhuang J et al. Risk factors of different congenital heart defects in Guangdong, China. Pediatr Res 2016;79(4):549-58.
87. Pei L, Kang Y, Cheng Y, Yan H. The Association of Maternal Lifestyle with Birth Defects in Shaanxi Province, Northwest China. PLoS One 2015;10(9):e0139452.
88. Skarsgard ED, Meaney C, Bassil K et al. Maternal risk factors for gastroschisis in Canada. Birth Defects Res A Clin Mol Teratol 2015;103(2):111-18.
89. Feldkamp ML, Srisukhumbowornchai S, Romitti PA et al. Self-reported maternal cigarette smoke exposure during the periconceptional period and the risk for omphalocoele. Paediatr Perinat Epidemiol 2014;28(1):67-73.
90. Dodwell E, Risoe P, Wright J. Factors associated with increased risk of clubfoot: a Norwegian National Cohort Analysis. J Pediatr Orthop 2015;35(8):e104-09.
91. Werler MM, Yazdy MM, Kasser JR et al. Maternal cigarette, alcohol, and coffee consumption in relation to risk of clubfoot. Paediatr Perinat Epidemiol 2015;29(1):3-10.
92. Zhang L, Wang XH, Zheng XM et al. Maternal gestational smoking, diabetes, alcohol drinking, pre-pregnancy obesity and the risk of cryptorchidism: a systematic review and meta-analysis of observational studies. PLoS One 2015;10(3):e0119006.
93. Wen Z, Yu D, Zhang W et al. Association between alcohol consumption during pregnancy and risks of congenital heart defects in offspring: meta-analysis of epidemiological observational studies. Ital J Pediatr 2016;42:12.
94. Leng LY, Wang JW, Cao SS, Wang M. Maternal periconceptional alcohol consumption and the risk of neural tube defects in offspring: a meta-analysis. J Matern Fetal Neonatal Med 2016;29(10):1673-79.
95. Bell JC, Raynes-Greenow C, Turner RM, Bower C, Nassar N, O'Leary CM. Maternal alcohol consumption during pregnancy and the risk of orofacial clefts in infants: a systematic review and meta-analysis. Paediatr Perinat Epidemiol 2014;28(4):322-32.
96. Strandberg-Larsen K, Skov-Ettrup LS, Grønbæk M, Andersen AM, Olsen J, Tolstrup J. Maternal alcohol drinking pattern during pregnancy and the risk for an offspring with an isolated congenital heart defect and in particular a ventricular septal defect or an atrial septal defect. Birth Defects Research A Clin Mol Teratol 2011;91(7):616-22.
97. Makelarski JA, Romitti PA, Sun L et al. Periconceptional maternal alcohol consumption and neural tube defects. Birth Defects Res A Clin Mol Teratol 2013;97(3):152-60.
98. McAteer JP, Hecht A, De Roos AJ, Goldin AB. Maternal medical and behavioral risk factors for congenital diaphragmatic hernia. J Pediatr Surg 2014;49(1):34-38; discussion 38.
99. Robledo-Aceves M, Bobadilla-Morales L, Mellín-Sánchez EL et al. Prevalence and risk factors for gastroschisis in a public hospital from west México. Congenit Anom (Kyoto) 2015;55(2):73-80.
100. Lupo PJ, Danysh HE, Symanski E, Langlois PH, Cai Y, Swartz MD. Neighborhood-Based Socioeconomic Position and Risk of Oral Clefts Among Offspring. Am J Public Health 2015;105(12):2518-25.
101. Root ED, Meyer RE, Emch M. Socioeconomic context and gastroschisis: exploring associations at various geographic scales. Soc Sci Med 2011;72(4):625-33.
102. Nieuwenhuijsen MJ, Dadvand P, Grellier J, Martinez D, Vrijheid M. Environmental risk factors of pregnancy outcomes: a summary of recent meta-analyses of epidemiological studies. Environ Health 2013;12: 6.
103. Cordier S, Garlantézec R, Labat L et al. Exposure during pregnancy to glycol ethers and chlorinated solvents and the risk of congenital malformations. Epidemiology 2012;23(6):806-12.
104. Vaktskjold A, Talykova LV, Nieboer E. Congenital anomalies in newborns to women employed in jobs with frequent exposure to organic solvents – a register-based prospective study. BCM Pregnancy Childbirth 2011;11:83.
105. Jørgensen KT, Jensen MS, Toft GV, Larsen AD, Bonde JP, Hougaard KS. Risk of cryptorchidism among sons of horticultural workers and farmers in Denmark. Scand J Work Environ Health 2014;40(3):323-30.
106. Rocheleau CM, Bertke SJ, Lawson CC et al. Maternal occupational pesticide exposure and risk of congenital heart defects in the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 2015;103(10):823-33.
107. Kielb C, Lin S, Herdt-Losavio M et al. Maternal periconceptional occupational exposure to pesticides and selected musculoskeletal birth defects. Int J Hyg Environ Health 2014;217(2-3):248-54.
108. Rocheleau CM, Romitti PA, Sanderson WT et al. Maternal occupational pesticide exposure and risk of hypospadias in the National Birth Defects Prevention Study. Birth Defects Research A Clin Mol Teratol 2011;91(11):927-36.
109. Snijder CA, Vlot IJ, Burdorf A et al. Congenital heart defects and parental occupational exposure to chemicals. Hum Reprod 2012;27(5):1510-17.
110. Desrosiers TA, Lawson CC, Meyer RE et al. Maternal occupational exposure to organic solvents during early pregnancy and risks of neural tube defects and orofacial clefts. Occup Environ Med 2012;69(7):493-99.

REFERENCES

111. O'Brien JL, Langlois PH, Lawson CC et al. Maternal occupational exposure to polycyclic aromatic hydrocarbons and craniosynostosis among offspring in the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 2016;106(1):55-60.
112. Lupo PJ, Symanski E, Langlois PH et al. Maternal occupational exposure to polycyclic aromatic hydrocarbons and congenital heart defects among offspring in the National Birth Defects Prevention Study. Birth Defects Res A Clin Mol Teratol 2012;94(11):875-81.
113. Lupo PJ, Langlois PH, Reefhuis J et al. Maternal occupational exposure to polycyclic aromatic hydrocarbons: effects on gastroschisis among offspring in the National Birth Defects Prevention Study. Environ Health Perspect 2012;120(6):910-15.
114. Lim H, Agopian AJ, Whitehead LW et al. Maternal occupational exposure to ionizing radiation and major structural birth defects. Birth Defects Res A Clin Mol Teratol 2015;103(4):243-54.
115. Chen EK, Zmirou-Navier D, Padilla C, Deguen S. Effects of air pollution on the risk of congenital anomalies: a systematic review and meta-analysis. Int J Environ Res Public Health 2014;11(8):7642-68.
116. Vrijheid M, Martinez D, Manzanares S et al. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. Environ Health Perspect 2011;119(5):598-606.
117. Yao C, Chen Y, Zhu X et al. Air pollution and the risk of birth defects in Anqing City, China. J Occup Environ Med 2016;58(4):e124-27.
118. Tanner JP, Salemi JL, Stuart AL et al. Associations between exposure to ambient benzene and PM (2.5) during pregnancy and the risk of selected birth defects in offspring. Environ Res 2015;142:345-53.
119. Zhu Y, Zhang C, Liu D, Grantz KL, Wallace M, Mendola P. Maternal ambient air pollution exposure preconception and during early gestation and offspring congenital orofacial defects. Environ Res 2015;140:714-20.
120. Farhi A, Boyko V, Almagor J et al. The possible association between exposure to air pollution and the risk for congenital malformations. Environ Res 2014;135:173-80.
121. Stingone JA, Luben TJ, Julie L et al. Maternal exposure to criteria air pollutants and congenital heart defects in offspring: results from the National Birth Defects Prevention Study. Environ Health Perspect 2014;122(8):863-72.
122. Girguis MS, Strickland MJ, Hu X, Liu Y, Bartell SM, Vieira VM. Maternal exposure to traffic-related air pollution and birth defects in Massachusetts. Environ Res 2016;146:1-9.
123. Vinceti M, Malagoli C, Malavolti M et al. Does maternal exposure to benzene and PM10 during pregnancy increase the risk of congenital anomalies? A population-based case-control study. Sci Total Environ 2016;541:444-50.
124. Vinikoor-Imler LC, Stewart TG, Luben TJ, Davis JA, Langlois PH. An exploratory analysis of the relationship between ambient ozone and particulate matter concentrations during early pregnancy and selected birth defects in Texas. Environ Pollut 2015;202:1-6.
125. Lin YT, Lee YL, Jung CR, Jaakkola JJ, Hwang BF. Air pollution and limb defects: a matched-pairs case-control study in Taiwan. Environ Res 2014;132:273-80.
126. Chung MK, Lao TT, Ting YH, Leung TY, Lau TK, Wong TW. Environmental factors in the first trimester and risk of oral-facial clefts in the offspring. Reprod Sci 2013;20(7):797-803.
127. Dolk H. Epidemiologic approaches to identifying environmental causes of birth defects. Am J Med Genet C Semin Med Genet 2004;125C(1):4-11.
128. EUROCAT – European Surveillance of Congenital Anomalies.
Publication of the EUROCAT statistical monitoring report and updated prevalence tables. Available from: http://www.eurocat-network.eu/ (last accessed: 21 September 2016).
129. Vrijheid M, Bianchi F, Nelen V, Thys G, Rankin J, Martos C. Actions towards European Environmental Surveillance: feasibility of environmental linkage. Available from: http://www.eurocat-network.eu/content/Vrijheid-2013-Environmental-Linkage.pdf (last accessed: 30 August 2016).
130. Taruscio D, Arriola L, Baldi F et al. European recommendations for primary prevention of congenital anomalies: a joined effort of EUROCAT and EUROPLAN projects to facilitate inclusion of this topic in the National Rare Disease Plans. Public Health Genomics 2014;17(2):115-23.
131. Balabani D, Rupnik M, Klemencic AK. Negative impact of endocrine-disrupting compounds on human reproductive health. Reprod Fertil Dev 2011;23(3):403-16.
132. De Celis R, Feria-Velasco A, Gonzalez-Unzaga M, Torres-Calleja J, Pedron-Nuevo N. Semen quality of workers occupationally exposed to hydrocarbons. Fertil Steril 2000;73(2):221-28.
133. Wang SL, Wang XR, Chia SE et al. A study on occupational exposure to petrochemicals and smoking on seminal quality. J Androl 2001;22(1):73-78.
134. Marchetti F, Eskenazi B, Weldon RH et al. Occupational exposure to benzene and chromosomal structural aberrations in the sperm of Chinese men. Environ Health Perspect 2012;120(2):229-34.
135. Thorup J, Nordenskjöld A, Hutson JM. Genetic and environmental origins of hypospadias. Curr Opin Endocrinol Diabetes Obes 2014;21(3):227-32.
136. Gold R, McGinty T. Energy boom puts wells in America's backyards. The Wall Street Journal, online edition, 25 October 2013. Available from: https://www.wsj.com/articles/energy-boom-puts-wells-in-america8217s-backyards-1382756256
137. The West Virginia Geological and Economic Survey. Available from: http://www.wvgs.wvnet.edu (last accessed: 5 June 2009).
138. Stacy SL, Brink LL, Larkin JC et al. Perinatal outcomes and unconventional natural gas operations in Southwest Pennsylvania. PLoS One 2015;10(6):e0126425.
139. Frazier A (ed). Analysis of Data Obtained for the Garfield County Air Toxics Study – Summer 2008. Denver, Colorado Department of Public Health and Environment, 2009. Available from: http://www.garfield-county.com/air-quality/documents/airquality/2008_Targeted_Oil_and_Gas_Monitoring_Report.pdf (last accessed: 22 May 2013).
140. Walther E (ed). Screening Health Risk Assessment Sublette County, Wyoming. SR2011-01-03. Sacramento, Sierra Research, 2011. Available from: http://www.sublettewyo.com/DocumentCenter/Home/View/438 (last accessed: 22 May 2013).
141. Olaguer EP. The potential near-source ozone impacts of upstream oil and gas industry emissions. J Air Waste Manag Assoc 2012;62(8):966-77.
142. Fazzo L, Minichilli F, Santoro M et al. Hazardous waste and health impact: a systematic review of the scientific literature. Environmental Health 2017;16(1):107.
143. Milbrath MO, Wenger Y, Chang CW et al. Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. Environ Health Perspect 2009;117(3):417-25.
144. Malik S, Cleves MA, Honein MA et al. Maternal smoking and congenital heart defects. Pediatrics 2008;121(4):e810-16.
145. Karatza AA, Giannakopoulos I, Dassios TG, Belavgenis G, Mantagos SP, Varvarigou AA. Periconceptional tobacco smoking and isolated congenital heart defects in the neonatal period. Int J Cardiol 2011;148(3):295-99.
146. Nykjaer C, Alwan NA, Greenwood DC et al. Maternal alcohol intake prior to and during pregnancy and risk of adverse birth outcomes: evidence from a British cohort. J Epidemiol Community Health 2014;68(6):542-49.
147. Scholin L (ed). Prevention of harm caused by alcohol exposure in pregnancy. Rapid review and case studies from Member States. Geneva, World Health Organization, 2016. Available from: http://www.euro.who.int/en/publications/abstracts/prevention-of-harm-caused-by-alcohol-exposure-in-pregnancy.-rapid-review-and-case-studies-from-member-states-2016

e&P

ABBONAMENTI 2018
A CIASCUNO IL SUO

PROMOZIONI:

35 €
Abbonamento on-line per **GIOVANI EPIDEMIOLOGI** under 35.

40 €
Per coloro che sono stati **AUTORI** di un contributo nell'anno in corso e non sono abbonati alla rivista da almeno 2 anni.

50 €
Ai **GENEROSI EPIDEMIOLOGI GIÀ ABBONATI,** regalare un abbonamento a E&P per il 2018 costa solo 50 euro per l'edizione on-line e 60 euro per avere anche il cartaceo.

ZERO
Per gli **EPIDEMIOLOGI "CONTAGIOSI"** che fanno sottoscrivere due nuovi abbonamenti a chi non conosce la rivista o non è più abbonato da almeno due anni, l'abbonamento o il rinnovo è **GRATUITO**.

	E&P ON-LINE + SUPPL ON-LINE	E&P ON-LINE + E&P CARTA + SUPPL ON-LINE	E&P ON-LINE + E&P CARTA + SUPPL CARTA
PRIVATI ITALIA			
1 anno	72 €	80 €	95 €
2 anni	135 €	150 €	180 €
3 anni	190 €	210 €	250 €
ENTI ITALIA AD ACCESSO UNICO ENTI ITALIA AD ACCESSO MULTIPLO: ABBONAMENTI DA CONCORDARE CON L'EDITORE			
1 anno	148 €	155 €	170 €
2 anni	275 €	290 €	320 €
3 anni	390 €	410 €	450 €
ENTI ESTERO			
1 anno	165 €	180 €	210 €
2 anni	310 €	335 €	395 €
3 anni	425 €	475 €	555 €
PRIVATI ESTERO			
1 anno	85 €	100 €	130 €
2 anni	160 €	190 €	245 €
3 anni	225 €	265 €	350 €

EPIDEMIOLOGIA & PREVENZIONE

ABBONAMENTO ALLA RIVISTA A PARTIRE DAL PRIMO NUMERO RAGGIUNGIBILE

SCRIVI A: abbonamenti@inferenze.it **TELEFONA:** 02 48702283 **COLLEGATI:** www.epiprev.it/abbonamenti
INFERENZE scarl via Ricciarelli, 29 - 20148 Milano; fax 02 48706089

__/__/__ **DATA** ..... **TIPO DI ABBONAMENTO** ..... **EURO**

MODALITÀ DI PAGAMENTO

☐ Fai tutto on-line con **PAYPAL:** alla pagina www.epiprev.it/abbonamenti

OPPURE

☐ **VERSAMENTO**
a mezzo cc postale n. 55195440 intestato a Inferenze scarl, via Ricciarelli, 29 - 20148 Milano (ricordati di comunicare via mail i tuoi dati personali, p. IVA e/o codice fiscale)

☐ **BONIFICO BANCARIO**
UNIPOL BANCA, P.zza Wagner, 8 - 20145 Milano
IBAN IT 53 P 03127 01600 0000 0000 3681
intestato a Inferenze scarl, via Ricciarelli, 29 20148 Milano (ricordati di comunicare via mail i tuoi dati personali, p. IVA e/o codice fiscale)

☐ **CARTA DI CREDITO** fai tutto on-line oppure:

CARTA DI CREDITO: ☐ American Express ☐ Carta Sì ☐ Master Card ☐ Eurocard ☐ VISA

COGNOME E NOME .....

AZIENDA .....

INDIRIZZO .....

CAP / LOCALITÀ / PROVINCIA .....

TEL. / FAX .....

E-MAIL ..... PARTITA IVA / CODICE FISCALE .....

NUMERO CARTA _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ SCADENZA __/__/__ COD. CV2 ___ (ULTIME TRE CIFRE STAMPATE SUL RETRO DELLA CARTA)

FIRMA .....


e&p