CONGENITAL ANOMALIES AND INDIVIDUAL EXPOSURES

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CIGARETTE SMOKE
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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]

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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

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