Maternal smoking during pregnancy and birth defects in children: a systematic review with meta-analysis

Tabagismo materno na gestação e malformações congênitas em crianças: uma revisão sistemática com meta-análise

El tabaquismo materno durante el embarazo y las malformaciones congénitas en niños: una revisión sistemática y meta-análisis

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Abstract

This systematic review aimed to investigate the association between maternal smoking during pregnancy and birth defects in children. We performed an electronic search of observational studies in the databases ovid MEDLINE (1950 to April 2010), LILACS and SciELO. We included 188 studies with a total of 13,564,914 participants (192,655 cases). Significant positive associations were found between maternal smoking and birth defects in the following body systems: cardiovascular (OR: 1.11; 95%CI: 1.03-1.19), digestive (OR: 1.18; 95%CI: 1.07-1.30), musculoskeletal (OR: 1.27; 95%CI: 1.16-1.39) and face and neck (OR: 1.28; 95%CI: 1.19-1.37). The strength of association between maternal smoking and birth defects measured by the OR (95%CI) is significantly related to the amount of cigarettes smoked daily (χ^2 = 12.1; df = 2; p = 0.002). In conclusion, maternal smoking during pregnancy is associated with congenital malformations in children and this association is dose-dependent.

Smoking; Pregnancy; Congenital Abnormalities

Resumo

Esta revisão sistemática teve como objetivo investigar a associação entre fumo materno na gestação e as malformações congênitas em crianças. Uma busca eletrônica dos estudos observacionais foi realizada nas bases de dados ovid MEDLINE (1950 até abril de 2010), SciELO e LILACS. Foram incluídos nesta revisão 188 estudos com um total de 13.564.914 participantes (192.655 casos). Foram encontradas associações positivas significativas entre fumo materno e malformações dos sistemas: cardiovascular (OR: 1,11; IC95%: 1,03-1,19), digestivo (OR: 1,18; IC95%: 1,07-1,30), musculoesquelético (OR: 1,27; IC95%: 1,16-1,39) e face e pescoço (OR: 1,28; IC95%: 1,19-1,37). A força de associação entre fumo materno e malformações medida pelo OR (IC95%) está relacionada significativamente com a quantidade diária de cigarros consumidos (χ^2 = 12,1; df = 2; p = 0,002). Concluímos que fumo materno na gestação está associado com maior risco de malformações congênitas em crianças e essa associação é dose-dependente.

Hábito de Fumar; Gravidez; Anormalidades Congênitas

Introduction

Birth defects are the cause of high mortality and morbidity in children. It is estimated that about 5% of live births present some abnormality in their development [1]. Over the past decades, birth defects have increasingly contributed to child mortality [2,3]. In Brazil, the rate of child deaths due to birth defects rose from 9.7% in 1996 to 18.2% in 2008, representing an annual average increase of 0.71% [3]. This increase may be due to a better management of infections and contagious, and nutrition-related diseases, which reduced child deaths from these conditions [1,3].

Most birth defects are of multifactorial etiology. In addition to the genetic component, their occurrence may be related to exposure of the child, even before birth, or the parents to toxic substances, including tobacco [4]. While this investigation was being carried out, a systematic review with 101 observational studies was published, and showed an association between maternal smoking during pregnancy and different birth defects in children [5]. This review, however, did not include a considerable number of relevant studies [6,7,8,9,10,11,12,13,14]. Moreover, defects of the abdominal wall, such as congenital diaphragmatic and inguinal hernia, gastroschisis, and omphalocele, which should be considered musculoskeletal abnormalities, according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [15] were classified as gastrointestinal defects.

The purpose of this systematic review is to investigate maternal smoking during pregnancy and birth defects in children. The possible dose-response relation in that association was also studied.

Methods

A systematic review with meta-analysis was conducted. The procedures for the review and reporting of the results were based on the recommendations by MOOSE (*Meta-analysis of Observational Studies in Epidemiology*) [16]. The protocol for the review was assessed and approved by a panel that included two experts in Pediatrics and one in Epidemiology, in 2010.

Studies that investigated the association between maternal smoking during pregnancy and birth defects in children were considered eligible for the review. Studies that contemplated the association between maternal smoking and chromosomal abnormalities were ruled out.

The electronic search of the studies was made on databases Ovid MEDLINE (1950 until April 2010), SciELO, and LILACS. The strategy to search potentially relevant studies for the review on the databse Ovid MEDLINE is composed of two parts (Figure 1): the first (from line #1 to line #4) is the search strategy to identify studies on maternal smoking, and the secons part (from line #5 to line #20) is the strategy to find birth-defects-related studies. The bibliographic references of articles whose full text was obtained were reviewed, in order to identify additional studies. The Google Translator (https://translate.google.com.br/) was used to translate two articles, one in Lithuanian and other in French.

Study selection was independently made by four investigators (two teams of two). Selection process was made in two stages: in the first, the title and abstract of the articles identified during the electronic search were reviewed to select potential studies for this review. The full text of articles was obtained for which information from the title and the abstract met the inclusion criteria, or in cases where there was not enough information to decide about their inclusion. In the second stage, the articles were read in full for a final selection of the studies, with the inclusion and exclusion criteria being checked. Discrepancies among the investigators were resolved by consensus. Data extraction was performed by four investigators using a standard form. The extracted data were checked by the investigators.

Meta-analysis was performed using the software Stata, version 11.0 (Stata Corp., College Station, United States). A random effects model was applied. The association between maternal smoking during pregnancy and the presence of any kind of birth defects in children was evaluated by means of odds ratios (OR) and 95% confidence intervals (95%CI). When the original studies indicated the presence of more than one defect, the results of each defect were combined to obtain data of any type of defect. Whenever possible, adjusted OR was used.

The pre-defined sub-group analyses were performed to investigate the association between maternal smoking during pregnancy and birth defects in children, according to the organ systems involved. The classification of birth defects was based on the ICD-10. The pre-defined sub-group analyses were also used to assess the potential influence of the following methodological aspects in the results of the meta-analyses: design of the investigation (prospective *vs.* retrospective); size of the sample (cases) (≤ 200; 200-1,000; 1,000-5,000; > 5,000); adjustment/matching of confounding factors, including age of the mother (yes *vs.* no). Two *post hoc* subgroup analyses were performed to assess the potential impact of exposure definition (maternal smok-

Figure 1

Search strategy of studies in the Ovid MEDLINE database.

1. Smoking/
2. maternal smoking.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
3. maternal tobacco.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
4. maternal tobacco smoking.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. birth defects.mp. or exp Congenital Abnormalities/
6. congenital heart defects.mp. or exp Heart Defects, Congenital/
7. exp Cleft Lip/ or exp Cleft Palate/
8. congenital anomalies.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
9. congenital malformation.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
10. oral cleft.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
11. congenital digital anomalies.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
12. neural tube defect.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. esophageal atresia.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. agenesis.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
15. hypoplasia.mp. [mp=title, original title, abstract, name of substance word, subject heading wd, unique identifier]
16. congenital cryptorchidism.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
17. birth anomalies.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
18. congenital heart disease.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
19. congenital urogenital anomalies.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
20. congenital gastrointestinal anomalies.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
21. or/1-4
22. or/5-20
23. 21 and 22

ing), and the period of exposure during pregnancy in the meta-analysis results. To investigate the dose-response relation between maternal smoking during pregnancy and birth defects in children, the analysis was stratified in three categories according to the number of cigarettes smoked per day (1-9, 10-19 and > 20).

Heterogeneity of results among the studies was assessed through the I^2 statistic. $I^2 > 75\%$ indicates significant heterogeneity [17]. Possible causes for heterogeneity were examined through the above mentioned sub-group analyses. The publication bias was investigated with the use of the funnel plot and the Egger test [17].

Results

Out of the 1,043 citations identified by the electronic search, 129 studies were selected. Fifty-nine additional studies were included, found in reviews of original articles and from the systematic review. Therefore, a total of 188 studies (153 projects or independent databases) [6,7,8,9,10,11,12,13,14,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163.164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196] with a total of 13,564,914 subjects (192,655 birth defect cases, and 13,372,259 controls with no defects) were included in this review (Figure 2). Twenty-nine were prospective studies (cohort, or nested-case control studies), and 159 were retrospective (case-control, or cross-sectional studies). The overall characteristics of the 188 studies included are shown in Table 1.

Figure 2

Flowchart of the selection of studies included in the review.

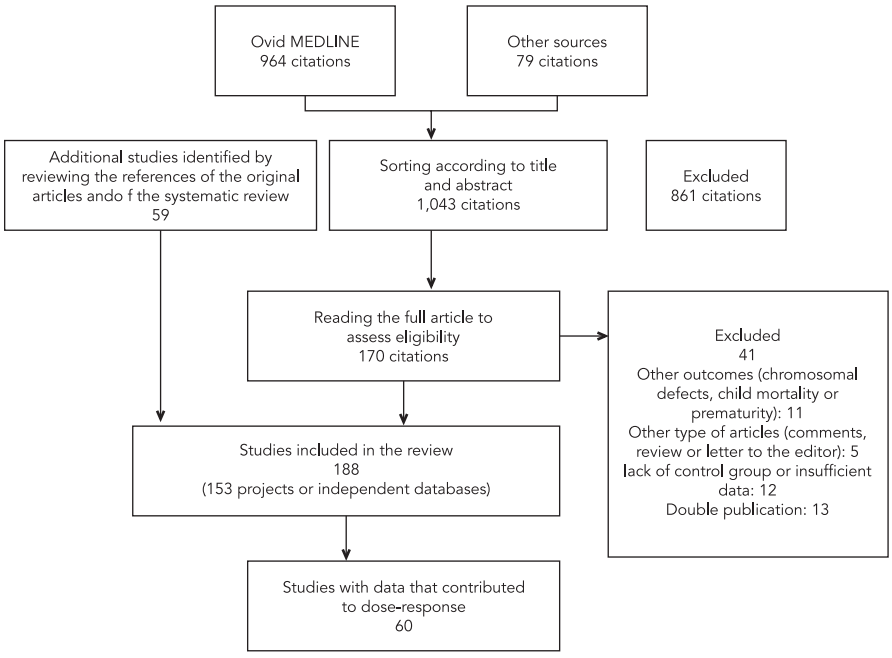

Table 2 presents individual and combined results of the 188 studies about the association between maternal smoking during pregnancy and birth defect of any type in children. The meta-analysis of the 188 studies showed that children of smoking mother had a higher chance of presenting any type of birth defects (OR: 1.18; 95%CI: 1.14-1.22; $p < 0.001$; I^2: 77.2%).

In the sub-group analyses, according to the organ systems involved, there were significant positive associations between maternal smoking and defects in the cardiovascular system (OR: 1.11; 95%CI: 1.03-1.19), digestive system (OR: 1.18; 95%CI: 1.07-1.30), musculoskeletal system (OR: 1.27; 95%CI: 1.16-139), and face and neck (OR: 1.28; 95%CI: 1.19-1.37) (Figure 3). Other subgroup analyses showed that retrospective studies and those with smaller sample size (≤ 1.000 cases) has higher combined OR values. Using or not adjustment/matching in the original studies to control confounding factors, particularly the age of the mother did not significantly affect the meta-analysis results (Table 3). Two *post hoc* sub-group analyses were performed to assess the potential impact of the definition of maternal smoking, and the period of pregnancy the pregnant mother was exposed to smoking in the meta-analysis results. There was no statistically significant difference between studies in which maternal smoking during pregnancy was explicitly defined as daily smoking (n = 91; OR: 1.21; 95%CI: 1.16-1.26) and those studies with no clear definition (n = 97; OR: 1.17; 95%CI: 1.11-1.23) ($\chi^2 = 1.0$; $p = 0.32$). In addition, there was no statistically significant difference between studies in which exposure to smoking occurred in the first quarter of the pregnancy (n = 80; OR: 1.22; 95%CI: 1.17-1.29) and those studies with no clear definition (n = 108; OR: 1.16; 95%CI: 1.10-1.21) ($\chi^2 = 2.1$; $p = 0.15$).

Figure 4 shows the dose-response relation between maternal smoking during pregnancy and birth defects in children. Sixty studies [6,7,8,9,11,12,16,21,24,32,43,44,47,48,49,51,57,58,64,65,69,74,80,82,85,88,89,90,91,92,99,100,101,103,104,107,108,113,115,119,121,122,123,124,132,135,144,150,151,157,163,169,172,173,187,188,189,190,192] with a total of 12,137,944 subjects (103,107 cases) contributed their data to the analysis, of which 11 were prospective studies. The power of association between maternal smoking and defects measured by OR (95%CI) is significantly related with the daily amount of cigarettes smoked

Table 1

General characteristics of the studies included.

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Adams et al. [18] (1989)	Case-control	Five metropolitan areas of Atlanta (United States)	Conotruncal heart defect	Interview	First quarter	83	1,303	Matching: race, month of birth, place of birth
Akre et al. [19] (1999)	Nested case-control	Medical birth record and admission records (Sweden)	Cryptorchidism; hypospadias	Interview	Unspecified	2,576 (cryptorchidism); 1,137 (hypospadias)	12,910 (cryptorchidism); 5,687 (hypospadias)	Adjusted: maternal factors (age, height, parity, preeclampsia) and perinatal factors (plurality, Apgar, other defects); Matching: sex, month and place of birth
Alderman et al. [20] (1991)	Case-control	Birth defects registry, Washington State (United States)	Crooked foot at birth	Birth certificate data	Unspecified	124	1,438	Adjusted or stratified: sex of the child, stillborn, plurality, marital status
Alderman et al. [21] (1994)	Case-control	Colorado Craniosynostosis Registry (United States)	Craniosynostosis	Phone interview	Any period	212	291	Adjusted or stratified: maternal age, race, multiparity, sex of the child, type of craniosynostosis period of exposure
Ananijevic-Pandey et al. [22] (1992)	Case-control	Belgrade Study (Serbia)	General malformations	Interview	Unspecified	113	195	Matching: sex, gestational age, maternal age, place of birth
Aro et al. [23] (1983)	Case-control	The Finnish registry of congenital malformations	Limb reduction	Structured questionnaire	Unspecified	453	453	Adjusted: maternal age, alcohol intake; Matching: month/year and place of birth
Bailey et al. [24] (1970)	Cohort	Christchurch Women's Hospital (New Zealand)	Birth defects	Interview	Unspecified	58	1,116	-
Batra et al. [25] (2007)	Case-control	Comprehensive Hospital Abstract Reporting System, Washington State (United States)	Ventricular septal defect	Birth certificate data	Unspecified	2,898	11,186	Matching: year of birth
Beard et al. [26] (1984)	Case-control	Rochester Study, Minnesota (United States)	Cryptorchidism	-	Unspecified	113	226	Adjusted: maternal age, birth weight, parity, year of birth

(continues)

Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Beaty et al. [27] (2008)	Case-control	Maryland State Birth Defects Reporting and Information System (United States)	Oral fissures	Interview	Unspecified	121	86	-
Beaty et al. [28] (2001)	Case-control	Maryland State Birth Defects Reporting and Information System (United States)	Oral fissures	Interview	Conception and first quarter	135	152	Adjusted: maternal age, maternal/paternal schooling
Bell & Lumley [29] (1989)	Cross-sectional	Statistics of perinatal morbidity. Victoria (Austrália)	Birth defects	Interview or medical records	Second half of pregnancy	7	5,550	-
Berkowitz & Lapinski [30] (1996)	Case-control	Study of the city of New York (United States)	Cryptorchidism	-	Unspecified	63	219	Matching: month/year of birth, sex, place of birth
Biggs et al. [31] (2002)	Case-control	Birth certificate data, Washington State (United States)	Cryptorchidism	Birth certificate data	Unspecified	2,395	9,580	Matching: month/year of birth, sex
Bille et al. [32] (2007)	Nested case-control	Danish National Birth Cohort Data	Oral fissures	Questionnaire and phone interview	First quarter	189	836	Adjusted: maternal age, social class
Bird et al. [6] (2009)	Case-control	National Birth Defects Prevention Study (United States)	Musculoskeletal	Interview	Pre-conception exposure and in the first quarter	653	4,967	Adjusted: place of birth, folic acid supplementation, BMI, maternal diabetes
Bitsko et al. [33] (2007)	Case-control	Birth Defects Risk Factor Surveillance, Iowa (United States)	Birth defects	-	Unspecified	142	243	Matching: month/year of birth, place of birth
Blatter et al. [34] (1996)	Case-control	Hospitals of the Netherlands	CNS defects	Questionnaire and phone interview	Unspecified	274	314	Matching: place of birth
Botto et al. [35] (2001)	Case-control	Atlanta Congenital Defects Program (United States)	Heart defects	Phone interview	Pre-conception exposure and in the first quarter	905	3,029	Matching: month/year of birth, place of birth, race
Bracken et al. [7] (1978)	Case-control	Hospitals of Connecticut (United States)	Birth defects	Interview	First quarter	1,369	2,967	-

(continues)

Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Brouwers et al. [36] (2007)	Case-control	Pediatric urology center (Netherlands)	Hypospadias	Question-naire	Pre-conception exposure and in the first quarter	583	251	Adjusted: maternal/ paternal schooling, place of birth, paternal hypospadias, infertility treatment, exposure to DES, multiparity, vitamin supplements prior to conception, exposure to pesticides, use of medication by the father; Matching: month/year of birth, place of birth, sex
Brouwers et al. [37] (2010)	Case-control	University Hospital, Netherlands	Hypospadias	Question-naire	Unspecified	305	629	Adjusted: year of birth
Browne et al. [38] (2007)	Case-control	National Birth Defects Prevention Study (United States)	Heart defects	Phone interview	Pre-conception exposure and in the first quarter	403	131	Adjusted: race, place of birth
Carbone et al. [39] (2007)	Case-control	Ragusa Study (Italy)	Cryptorchidism; hypospadias	-	Unspecified	91	203	Matching: month/place of birth, place of birth, sex
Cardy et al. [40] (2007)	Case-control	Talipes Study (United Kingdom)	Congenital equinovarus	Interview	Unspecified	194	60	Adjusted: year of birth, sex
Carmi-chael & Shaw [41] (2000)	Case-control	California Birth Defects Monitoring Program (United States)	Anencephaly	Phone interview	Pre-conception exposure and in the first quarter	122	464	-
Carmi-chael et al. [42] (2003)	Case-control	California Birth Defects Monitoring Program (United States)	Malformations (cardiovascular defects and facial cleft)	Phone interview	Pre-conception exposure and in the first quarter	696	734	-
Carmi chael et al. [43] (2005)	Case-control	National Birth Defects Prevention Study (United States)	Hypospadias	Interview	Any period	437	1,225	Adjusted: maternal age, race, maternal schooling, parity, history of subfertility
Carmi chael et al. [44] (2008)	Case-control	National Birth Defects Prevention Study (United States)	Craniosynostosis	Interview	Any period	531	5,008	Adjusted: maternal age, race, maternal/paternal schooling, parity, history of subfertility, folic acid intake, Maternal BMI, place of the study

(continues)

Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Caton et al. [45] (2008)	Case-control	National Birth Defects Prevention Study (United States)	Hypospadias	Phone interview	Pre-conception exposure and in the first quarter	755	2,044	-
Cedergren et al. [8] (2002)	Case-control	Southeastern region of Sweden	Heart defects	Medical records	Beginning of pregnancy	264	515	-
Chambers et al. [46] (2007)	Case-control	Southern region of California (United States)	Gastroschisis	Medical records	First quarter	102	117	-
Chevrier et al. [47] (2008)	Case-control	Hospitals of France	Oral fissures	Question-naire	First quarter	240	236	Adjusted: place of birth, sex, race
Chew et al. [48] (1994)	Cohort	Collaborative perinatal project (United States)	Eye defects	Interview	Unspecified	1,658	37,133	Adjusted: maternal age, race, birth weight, place of birth
Christen-sen et al. [9] (1999)	Case-control	Danish national study	Oral fissures	Interview	First quarter	296	551	Adjusted: maternal alcohol intake, periconcepcional vitamin supplementation, place of birth, month/year of birth
Christian-son [49] (1980)	Cohort	Kaiser Foundation health plan (United States)	Anomalies in all systems	Interview	First quarter	2,547	12,138	-
Chung & Myrianthopoulos [50] (1975)	Cohort	Collaborative perinatal project (United States)	Inguinal hernia	-	Unspecified	713	51,482	-
Chung et al. [51] (2000)	Case-control	Natality database (United States)	Cleft lip; cleft palate	Interview and database	The entire pregnancy	2,207	4,414	Adjusted: maternal age, race, maternal/ paternal schooling, maternal hypertension, birth weight , maternal diabetes, sex
Cordier et al. [52] (1992)	Case-control	Study in hospitals of Marseille and Paris (France)	Major defects	Interview	Unspecified	325	325	Adjusted: place of birth
Correy et al. [53] (1991)	Cohort	Cigarette smoking, alcohol consumption and fetal outcome in Tasmania (Australia)	Malformations in general	Interview	First quarter	1,095	54,942	-

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Croen et al. [54] (2000)	Case-control	California Birth Defects Monitoring Program (United States)	Holoprosen-cephaly	Phone interview	Pre-conception exposure and in the first quarter	48	106	Matching: month/year of birth, place of birth, sex
Czeizel & Vitez [55] (1981)	Case-control	Hungarian congenital abnormalities registry	Omphalocele	Interview	Unspecified	134	134	Matching: month/year of birth, place of birth, sex, pregnancy outcome
Czeizel & Nagy [56] (1986)	Case-control	Hungarian congenital abnormalities registry	Cleft lip; cleft palate	Interview	The entire pregnancy	1,088	752	Adjusted: maternal/ paternal schooling, parity; Matching: month/year of birth, place of birth, sex
Czeizel et al. [57] (1994)	Case-control	Hungarian congenital abnormalities registry	Limb reduction	Question-naire	Pre-conception exposure and the entire pregnancy	537	537	Matching: month/year of birth, place of birth, sex
Czeizel et al. [58] (2004)	Case-control	Hungarian congenital abnormalities registry	Orofacial clefts; limb malformations	Interview	The entire pregnancy	1,346	1,346	Matching: month/year of birth, place of birth, sex
Costa et al. [59] (2006)	Case-control	Rio de Janeiro hospital study (Brazil)	Birth defects	Question-naires	Unspecified	149	9,223	-
Damgaard et al. [60] (2008)	Cohort	University hospitals of Denmark and Finland	Cryptorchidism	Question-naire and interview	The entire pregnancy	127	2,368	Adjusted: place of birth, classe social; Matching: sex
Davies et al. [61] (1986)	Case-control	Addenbrookes Hospital Study (United Kingdom)	Cryptorchidism	Medical records	Unspecified	83	129	Matching: month/year of birth, place of birth, sex
De Roo et al. [10] (2003)	Cohort	Washington State Birth Defects Registry (United States)	Oral fissures	Birth certificate data	The entire pregnancy	608	297,530	Adjusted: race, maternal age, marital status, sex
Dickinson et al. [11] (2008)	Case-control	North Carolina Birth Defects Monitoring Program (United States)	Crooked foot at birth	Birth certificate data	The entire pregnancy	443	4,492	Adjusted: maternal age, race, sex, time until commencement of antenatal care

(continues)

Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Draper et al. [62] (2008)	Case-control	Birth defects registry in three regions of the United Kingdom	Gastroschisis	Interview	First quarter	144	432	Adjusted: use of illicit drugs by the mother, use of vasoconstrictive drugs, maternal BMI, marital status, maternal use of aspirin, parental home ownership, maternal diseases; Matching: maternal age, place of birth
Erickson [63] (1991)	Case-control	Atlanta Birth Defects Risk Factor Surveillance (United States)	General malformations	Interview	Unspecified	4,908	3,024	Adjusted: race, place of birth, month/year of birth
Ericson et al. [64] (1979)	Case-control	Swedish National Board of Health	CNS defects; orofacial clefts	Hospital records	First quarter	132	261	Matching: month/year of birth, place of birth, maternal age, parity
Evans et al. [65] (1979)	Retrospective cohort	Cardiff Births Survey (United Kingdom)	All birth defects	Birth records	Any period	2,266	653,443	-
Fredrick et al. [66] (1971)	Case-control	Assessment of perinatal mortality (United Kingdom)	Congenital heart diseases	Questionnaire	Second and third quarter	290	15,719	-
Feldkamp et al. [12] (2008)	Case-control	Utah Birth Defect Network (United States)	Gastroschisis	Birth certificate	First quarter	189	423,588	-
Felix et al. [67] (2008)	Case-control	Pediatric surgery reference center, Netherlands	Esophageal atresia; diaphragmatic hernia	Questionnaire	Pre-conception exposure and in the first quarter	105	192	Adjusted: maternal age; Matching: month/year of birth, sex
Ferencz et al. [68] (2008)	Case-control	Baltimore-Washington Infant Study (United States)	Cardiovascular defects	Questionnaire	Unspecified	1,541	3,572	-
Garcia et al. [69] (1999)	Case-control	Data from 8 public hospitals of a community in Valencia (Spain)	Birth defects	Phone interview	Pre-conception exposure and in the first quarter	261	161	Matching: month/year of birth, place of birth

(continues)

Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Goldbaum et al. [70] (1990)	Case-control	Birth records, Washington State (United States)	Gastroschisis	Birth records	Unspecified	62	617	Adjusted: month/year of birth, sex, maternal age, race, marital status, maternal occupation, rural/urban, pre-natal care, previous miscarriage, previous induction of abortion, paternal occupation; Matching: month/year of birth
Golding & Butler [71] (1983)	Case-control	Assessment of perinatal mortality (United Kingdom)	Anencephaly	Birth records	Beginning of pregnancy	483	19,172	-
Grewal et al. [72] (2008)	Case-control	Hospitals of California (United States)	All birth defects	Interview	Pre-conception exposure and in the first two months	1,351	620	-
Haddow et al. [73] (1983)	Cohort	Maternal serum alpha-fetoprotein screening programs (United States)	Gastroschisis	Interview	Second quarter	21	59,919	Adjusted: maternal age, month/year of birth
Hakin & Tielsch [74] (1992)	Case-control	Pediatric Ophthalmology Centers in Baltimore (United States)	Esotropia; exotropia	Interview and medical data	The entire pregnancy	377	377	Adjusted: maternal age, paternal age, maternal schooling, alcohol intake, marital status, race, birth weight, Apgar, gestational age
Hearey et al. [75] (1984)	Case-control	Antioch-Pittsburg, California (United States)	CNS defects	Medical records	Unspecified	9	27	-
Heinonen [76] (1977)	Case-control	Collaborative perinatal project (United States)	Malformations	Medical records	Unspecified	1,393	4,889	Matching: month/year of birth, place of birth, sex
Hemminki et al. [77] (1981)	Case-control	The Finnish registry of congenital malformations	CNS defects	Interview	Unspecified	3,300	3,300	Matching: sex
Himmel-berger et al. [78] (1978)	Case-control	Survey of American Healthcare Workers (United States)	Defects	Interview	First quarter	1,369	9,724	Adjusted: age, parity, exposures to anesthetic gases

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Honein et al. [80] (2000)	Case-control	Data from the Atlanta Birth Defects Study (United States)	Craniosynostosis	Interview	Pre-conception exposure and in the first quarter	44	3,029	Adjusted: race, month/ year of birth, place of birth
Honein & Rasmussen [81] (2000)	Case-control	Data from the Atlanta Birth Defects Study (United States)	Crooked foot at birth	Interview	Pre-conception exposure and in the first quarter	346	3,029	Adjusted: sex, parity
Honein et al. [82] (2001)	Case-control	National Vital Statistics (United States)	17 defects: CNS; digestive; musculoskeletal; urogenital; face and neck	Birth certificate data	Unspecified	24,014 (CNS: 4,352; digestive: 1.312; musculo-skeletals: 12,293; urogenital: 819; face and neck: 5,238)	6,134,773	Adjusted: maternal age, race, maternal schooling
Honein et al. [83] (2007)	Case-control	National Birth Defects Prevention Study (United States)	Oral fissures	Phone interview	Pre-conception exposure and in the first quarter	1,461	3,390	Adjusted: maternal age, race, parity, alcohol intake in the first quarter, birth control with folic acid, sex
Hoobs et al. [79] (2006)	Case-control	Arkansas Reproductive Health Monitoring System (United States)	Heart defects	Interview	Pre-conception exposure and in the first primeiro month of pregnancy	275	118	-
Hougland et al. [84] (2006)	Cross-sectional	Children's Medical Center (United States)	Gastroschisis	Medical records	Unspecified	82	47,146	-
Jensen et al. [85] (2007)	Cohort	Birth cohort, 1984-1987 (Denmark)	Cryptorchidism	Question-naire and medical records	The entire pregnancy	270	5,716	Adjusted: maternal age, paternal age, infertility treatment, parity, social class, maternal alcohol intake, birth weight, gestational age, weight of the placenta
Johansen et al. [86] (2009)	Case-control	Norway medical birth records	Cleft lip; cleft palate	Question-naire	First quarter	573	763	-
Jones et al. [87] (1998)	Case-control	Oxford study (United Kingdom)	Cryptorchidism	Medical records	Beginning of pregnancy	1,499	10,811	Matching: month/year of birth, place of birth, sex

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Kallen [88] (1999)	Cohort	Swedish birth defects registry	Craniosynostosis	Interview	First quarter	303	1,413,585	Stratified: place of birth, maternal age, parity, maternal schooling
Kallen [89] (2000)	Cohort	Swedish birth defects registry and birth medical records (1983-1996)	44 defects: CNS; heart; face and neck; musculoskeletal; digestive; urogenital; other	Interview	First quarter	27,670 (CNS: 856; heart: 13,266; face and neck: 3,345; musculo-skeletal: 4,342; diges-tive: 1,241; urogenital: 4,502; other: 118)	1,413,811	Adjusted: month/ year of birth, maternal age, parity, maternal schooling
Kelsey et al. [90] (1978)	Case-control	Birth data from 5 Connecticut hospitals (United States)	Malformations	Interview	First quarter	1,370	2,968	-
Khoury et al. [91] (1989)	Case-control	Atlanta Birth Defects Case-Control Study (United States)	Cleft lip; cleft palate	Phone interview	Pre-conception and first quarter exposure	345	2,809	Adjusted: maternal age, schooling, alcohol intake, use of tranquilizers, use of contraceptives, pregnancy planning, race
Krapels et al. [92] (2006)	Case-control	Dutch university medical centers	Cleft lip with or without cleft palate	Interview	Pre-conception exposure e first quarter	349	222	-
Krauss et al. [93] (2003)	Case-control	Missouri Birth Defects Registry (United States)	Microcephaly	Interview	Unspecified	360	3,600	-
Kricker et al. [93] (1986)	Case-control	Two states of Australia	Limb reduction	Interview	First quarter	155	2,274	Matching: data of birth, place of residency
Kuciene & Dulskiene [95] (2009)	Case-control	Medical records of hospitals and clinics of the city of Kaunas (Lithuania)	Heart defects	Interview	Unspecified	187	643	-
Kullander & Kallen [96] (1971)	Cohort	Study in the Malmö hospital (Sweden)	Defects	Question-naire	First quarter	192	5,548	-
Kurahashi et al. [97] (2005)	Case-control	Hokkaido University Hospital and Chukyo Hospital (Japan)	Hypospadias	Question-naire	Unspecified	31	64	-

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Kurahashi et al. [98] (2005)	Case-control	Hokkaido University Hospital and Chukyo Hospital (Japan)	Cryptorchidism	Question-naire	Unspecified	96	116	Adjusted: maternal age, maternal schooling, year of birth
Lam & Torfs [99] (2006)	Case-control	California Birth Defects Monitoring Program (United States)	Gastroschisis	Interview	Pre-conception exposure and in the first quarter	55	94	-
Leite & Koifman [100] (2009)	Case-control	Hospitals of Rio de Janeiro (Brazil)	Oral fissures	Interview	Pre-conception exposure and in the first quarter	274	548	-
Li et al. [101] (1996)	Case-control	Birth Defects Registry, Washington State (United States)	Urinary tract defects	Interview	The entire pregnancy	118	369	Adjusted: family income, paternal schooling, periconceptional vitamin supplementation, maternal use of illicit drugs, parity, place and year of birth
Li et al. [102] (2006)	Case-control	Birth difects surveillance system in the province of Shanxi (China)	Neural tube defects	Interview	Pre-conception exposure and in the first quarter	158	226	-
Lie et al. [103] (2008)	Case-control	Birth records of Norway	Oral fissures	Question-naire	First quarter	573	763	-
Lieff et al. [104] (1999)	Case-control	Birth defects study, Boston University (United States)	Oral fissures	Interviews	The entire pregnancy	1,479	2,295	-
Linn et al. [105] (1983)	Case-control	Women's hospital, Boston (United States)	Defects	Interview	Unspecified	579	11,861	Adjusted: parity, use of oral contraceptive, previous miscarriage, social class, maternal/ paternal age/, race, maternal/paternal schooling, maternal religion
Little et al. [106] (2004)	Case-control	Scotland, Manchester and Merseyside (United Kingdom)	Oral fissures	Interview	First quarter	190	248	Adjusted: sex, race, month of birth, maternal schooling
Liu et al. [107] (2009)	Case-control	City hospitals in the province of Shandong (China)	Heart defects	Interview	Pre-conception exposure and in the first quarter	164	328	-

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Lorente et al. [108] (2000)	Case-control	European registry of congenital anomalies (France, Italy, Netherlands and United Kingdom)	Oral fissures	Interview	First quarter	161	1,134	Adjusted: place of birth, maternal age, maternal alcohol intake, social class; Matching: month/ year of birth, place of birth
Lowe [109] (1959)	Cohort	Maternity, Birmingham Hospital (United Kingdom)	Malformations	Question-naire	Any period	23	1,800	-
Lubs [110] (1973)	Retrospec-tive cohort	Yale Hospital Study, New Haven (United States)	Major anomalies	Interview	Unspecified	102	4,067	-
Lumley et al. [111] (1985)	Cohort	Cigarette smoking, alcohol consumption study in Tasmania (Australia)	Malformations	Interview	Unspecified	251	10,112	Adjusted: maternal age, maternal alcohol intake, parity, social class
MacBird et al. [112] (2009)	Case-control	National Birth Defects Prevention Study (United States)	Omphalocele	Interview	Any period	168	4,967	Adjusted: place of birth, maternal diabetes, maternal BMI, folic acid intake materna
Malik et al. [113] (2008)	Case-control	National Birth Defects Prevention Study (United States)	Heart defects	Interview	Any period	3,067	3,947	Adjusted: sex, race, maternal age, maternal BMI, folic acid and periconceptional vitamines intake, alcohol and caffeine maternal intake, family history of malformation, place of birth
Malloy et al. [114] (1989)	Case-control	Missouri Birth Defects Registry (United States)	Malformations	Birth certificate	Unspecified	10,223	277,844	Adjusted: maternal age, race, marital status, parity, maternal schooling
Man & Chang [115] (2006)	Case-control	Natality database (United States)	Digital anomaly	Interview	Unspecified	5,171	10,342	Adjusted: marital status, maternal diseases, maternal diabetes, maternal hypertension, previous premature delivery, maternal chronic disease, Rh sensitivity
Mandira-cioglu et al. [116] (2004)	Case-control	Study in Izmir hospital (Turkey)	Neural tube defects	Interview	Unspecified	44	88	Matching: place of birth, month/year of birth

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Martinez-Frias et al. [117] (2008)	Case-control	Birth defects study in Spain	Gastroschisis	Phone interview	Pre-conception exposure and in the first quarter	45	690	Matching: month/year of birth, sex
McBride et al. [118] (1991)	Case-control	Birth Defects Registry (Canada)	Cryptorchidism	Phone interview	Pre-conception exposure and in the first quarter	244	488	Adjusted: maternal age, maternal/paternal schooling, race, maternal alcohol intake, caffeine
McDonald et al. [119] (1992)	Case-control	Assessment of occupational factors in pregnancy in Montreal (Canada)	Birth defects	Interview	First quarter	1,928	87,389	Matching: sex
McGlynn et al. [120] (2006)	Nested case-control	Collaborative perinatal project (United States)	Cryptorchidism	Interview	Unspecified	424	23,994	-
Miller et al. [121] (2009)	Case-control	National Birth Defects Prevention Study (United States)	Anorectal atresia	Phone interview	Pre-conception exposure and in the first quarter	464	4,940	-
Miller et al. [122] (2010)	Case-control	National Birth Defects Prevention Study (United States)	Holoprosen-cephaly	Phone interview	Pre-conception exposure and in the first quarter	59	4,999	-
Mitchell et al. [123] (2001)	Case-control	Danish case-control study	Oral fissures	Interview	First quarter	296	559	Matching: month/year of birth, place of birth
Morales-Suarez-Varela et al. [124] (2006)	Cohort	Danish national birth cohort Denmark	Birth defects	Interview	First quarter	3,767	73,001	Adjusted: maternal age, maternal alcohol intake
Morgana et al. [125] (2008)	Case-control aninhado	Child Health and Development Studies of California (United States)	Cryptorchidism	Interview	Unspecified	84	250	Matching: race, month/ year of birth, sex
Mori et al. [126] (1992)	Case-control	University Hospital of Sapporo (Japan)	Cryptorchidism	Interview	Beginning of pregnancy	104	104	Matching: age, sex
Mossey et al. [127] (2007)	Case-control	Regions of England	Oral fissures	Phone interview	First quarter	191	247	-

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Munoz et al. [128] (2006)	Case-control	Neural tube defects epidemiological surveillance system (Mexico)	Anencephaly	Interview	Pre-conception exposure and in the first month of pregnancy	151	151	Matching: month/year of birth, place of birth
Mygind et al. [129] (2002)	Cross-sectional	Denmark	Birth defects	Interview	First quarter	342	9,284	Adjusted: maternal age, gestational age
Niebyl et al. [130] (1985)	Case-control	Children's Hospital, Baltimore (United States)	Cleft lip; cleft palate	Interview	Unspecified	59	59	Matching: race, maternal age
Noorgaard et al. [131] (2009)	Case-control	National Patient Regsitry of Denmark	Hypospadias	Database	Pre-conception exposure and in the first quarter	1,591	14,900	-
Oddsberg et al. [132] (2008)	Case-control	Swedish Registry of Birth Defects	Esophagus atresia	Prenatal data	First quarter	722	3,610	
Ormond et al. [133] (2009)	Case-control	Southeastern England Study (United Kingdom)	Hypospadias	Phone interview	First quarter	468	485	Adjusted: family income gestational age, birth weight, folic acid intake; Matching: month/year of birth, place of birth, sex
Parikh et al. [134] (2002)	Case-control	Birth records of the State of Colorado (United States)	Renal agenesis	Birth certificate data	Unspecified	188	940	Matching: month/year of birth
Parker et al. [135] (2009)	Case-control	Birth Defects Surveillance Program (United States)	Crooked foot at birth	Birth certificate data	Unspecified	6,139	61,390	Adjusted: race, maternal age, parity, maternal/ paternal schooling; Matching: month/year of birth, place of birth
Pierik et al. [136] (2004)	Nested case-control	Cohorte of infants in the city of Rotterdam (Netherlands)	Cryptorchidism; hypospadias	Interview	Unspecified	134	313	-
Porter et al. [137] (2006)	Case-control	Hospitais, Washington State (United States)	Hypospadias	Birth certificate data	Unspecified	2,006	10,084	Matching: month/year of birth, sex
Preiksaet al. [138] (2006)	Cohort	Hospital-based study in the city of Panevęžys (Lithuania)	Cryptorchidism	Question-naire	Unspecified	69	1,135	Matching: sex

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Queissur-Luft et al. [139] (2002)	Cohort	Birth defects monitoring system of Mainz (Germany)	Major birth defects	Interview	Unspecified	2,144	28,796	-
Ramirez et al. [13] (2007)	Case-control	Population-based study in California (United States)	Oral fissures	Phone interview	Pre-conception exposure and in the first quarter	431	299	-
Rantakallio [140] (1978)	Nested case-control	Birth cohort, Northern Finland	Malformations	Interview	Unspecified	95	3,549	Matching: parity, marital status, maternal age, place of birth, multiparity
Reefhuis et al. [141] (1998)	Case-control	EUROCAT Study (Europe)	Crooked foot at birth	Interview and hospital records	Any period	2,905	7,829	Adjusted: maternal age, place of birth, parity, month/year of birth
Robitaille et al. [142] (2009)	Case-control	National Birth Defects Prevention Study (United States)	Limb reduction	Phone interview	Unspecified	527	4, 956	-
Rodriguez-Pinilla et al. [143] (2008)	Case-control	Collaborative birth defects study (Spain)	Hypospadias	Interview	Unspecified	2,393	12,465	Adjusted: maternal age, maternal/paternal schooling, maternal epilepsy, maternal chronic disease, race, family history of malformations, fever during pregnancy, maternal alcohol intake mother, periconceptional vitamin supplementation, maternal use of medication; Matching: month/year of birth, place of birth, sex
Romitti et al. [144] (2007)	Case-control	National Birth Defects Prevention Study (United States)	Cleft lip with or without cleft palate	Phone interview	Pre-conception exposure and in the first quarter	1,748	4,094	-
Salemi et al. [145] (2009)	Retrospe-ctive cohort	Florida Registry of Birth Defects (United States)	Gastroschisis	Birth records	Unspecified	394	117,8147	Adjusted: maternal age, marital status, race, maternal/paternal schooling, parity, place of birth

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Saxen [146] (1974)	Case-control	The Finnish registry of congenital malformations	Cleft lip with or without cleft palate	Interview	The entire pregnancy	599	590	Matching: month/year of birth, place of birth
Schmidt et al. [147] (2009)	Case-control	National Birth Defects Prevention Study (United States)	CNS defects	Phone interview	Pre-conception exposure and in the first quarter	768	4,143	-
Seidman et al. [148] (1990)	Cross-sectional	Hospitals of Jerusalem (Israel)	Malformations	Interview	The entire pregnancy	1,296	15,856	-
Shaw et al. [149] (1992)	Case-control	California Birth Defects Monitoring Program (United States)	Cardiovascular defects	Phone interview	Pre-conception exposure and in the first quarter	141	176	Adjusted: race, maternal age, maternal/ paternal schooling, maternal alcohol intake; Matching: month/year of birth, place of birth
Shaw et al. [150] (1996)	Case-control	California Birth Defects Monitoring Program (United States)	Neural tube defects	Phone interview	Pre-conception exposure and in the first quarter	538	539	Adjusted: periconceptional vitamin supplementation, race, maternal schooling, maternal age, maternal alcohol intake
Shaw et al. [151] (1996)	Case-control	California Birth Defects Monitoring Program (United States)	Cleft lip with or without cleft palate	Phone interview	Pre-conception exposure and in the first quarter	728	731	Matching: month/year of birth, place of birth
Shaw et al. [152] (1999)	Case-control	California Birth Defects Monitoring Program (United States)	Malformations	Phone interview	Pre-conception exposure and in the first quarter	1,299	734	Matching: month/year of birth, place of birth
Shaw et al. [153] (2000)	Case-control	California Birth Defects Monitoring Program (United States)	Multiple congenital anomalies	Phone interview	Pre-conception exposure and in the first quarter	112	194	Matching: month/year of birth, place of birth
Shi et al. [154] (2007)	Case-control	Case-control study (United States and Denmark)	Orofacial cleft	Interview	The entire pregnancy	1,378	1,435	-
Shiono et al. [155] (1986)	Cohort	Kaiser Permanente Birth Defects Study (United States)	Major malformations	Interview	Unspecified	592	28,810	Adjusted: maternal age, race, maternal alcohol intake

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Skelly et al. [156] (2002)	Case-control	Hospitais, Washington State (United States)	Crooked foot at birth	Interview	Unspecified	239	356	Adjusted: maternal age, race, family history of birth defects
Slickers et al. [157] (2008)	Case-control	National Birth Defects Prevention Study (United States)	Renal agenesis or hypoplasia	Interview	Pre-conception exposure and in the first quarter	73	859	-
Smedts et al. [158] (2009)	Case-control	HAVEN Study (Netherlands)	Congenital heart defects	Question-naire	Pre-conception exposure and in the first quarter	276	324	-
Sorensen et al. [159] (2002)	Case-control	North Justland, Denmark	Hypertrophic pyloric stenosis	Birth certifi-cate data	Unspecified	78	57,918	-
Stein-berger et al. [160] (2002)	Case-control	Baltimore-Washington Infant Study (United States)	Heart defects	Interview	Unspecified	48	3,572	Matching: month/year of birth, place of birth, sex
Stoll et al. [161] (1997)	Case-control	Strasbourg Study (France)	Anal atresia	Hospital records	Unspecified	108	225,644	Matching: sex, gestational age
Stoll et al. [162] (2001)	Case-control	Strasbourg Study (France)	Musculoskeletal	Hospital records	Unspecified	105	105	Matching: sex, gestational age
Suarez et al. [163] (2008)	Case-control	Texas neural tube defects project (United States)	Neural tube defects	Interview	Pre-conception exposure and in the first quarter	175	221	Adjusted: maternal age, schooling, maternal BMI, use of folic acid
Szendrey et al. [164] (1985)	Case-control	Hungarian Birth Defects Registry	Esophageal atresia	Interview	Unspecified	160	160	Matching: month/year of birth, place of birth, sex
Tamura et al. [165] (2006)	Case-control	Study in the Province of Cebu (Philippines)	Facial clefts	Interview	Unspecified	74	283	-
Targett et al. [166] (1977)	Cohort	Maternity of the Mercy hospital (Australia)	Major defects	Interview	Unspecified	122	2,878	-
Tata et al. [167] (2008)	Case-control	Health network database (United Kingdom)	Birth defects	Birth records	The entire pregnancy	3,995	23,156	Matching: month/year of birth, place of birth, multiparity
The et al. [168] (2007)	Case-control	National Birth Defects Prevention Study (United States)	Biliary atresia	Phone interview	Unspecified	62	4,094	-

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Tikkanen & Heinonen [169] (1991)	Case-control	The Finnish registry of congenital malformations/ children's cardiac registry (Finland)	Cardiovascular defects	Interview	First quarter	573	1,055	-
To & Tang [170] (1999)	Case-control	Department of Gynecology and Obstetrics of a Hong Kong hospital (China)	Birth defects	Prenatal records	Pre-conception exposure until the second quarter of pregnancy	1,678	57,714	-
Torfs et al. [171] (1994)	Case-control	California Birth Defects Monitoring Program (United States)	Gastroschisis	Interview	First quarter	110	220	Matching: maternal age
Tornquist et al. [172] (2002)	Case-control	Registry of visual impaired children (Sweden)	Optic nerve hypoplasia	Interview	Beginning of pregnancy	125	2,109,316	Matching: maternal age, race
Torp-Pedersen et al. [173] (2010)	Cohort	Danish national birth cohort	Strabismus	Interview	The entire pregnancy	1,299	95,543	Adjusted: month/year of birth, social class, maternal age, caffeine
Tuohy et al. [174] (1993)	Retrospective cohort	Plunket National Child Health Study (New Zealand)	Birth defects	Medical records	Unspecified	169	3,759	-
Underwood et al. [175] (1965)	Retrospective cohort	Hospitals of South Carolina (United States)	Major malformations	Hospital records	Unspecified	68	16,090	-
van den Boogaard et al. [176] (2008)	Case-control	Study of cleft palate defects (Netherlands)	Cleft lip with or without cleft palate	Questionnaire	Pre-conception exposure and in the first quarter	181	132	-
van den Eeden et al. [177] (1990)	Case-control	Birth records, Washington State (United States)	General malformations	Medical records	Unspecified	3,163	4,323	Adjusted: maternal age, parity. Matching: month/ year of birth, sex
van Rooij et al. [178] (2001)	Case-control	Population-based study in Nijimegen (Netherlands)	Cleft lip with or without cleft palate	Questionnaire	Pre-conception exposure and in the first quarter	113	104	-
van Rooij et al. [179] (2002)	Case-control	Population-based study in Nijimegen (Netherlands)	Malformations	Phone interview	Unspecified	84	72	-

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Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Verkerk et al. [180] (1994)	Case-control	Dutch obstectrics study (Netherlands)	Birth defects	Medical records	First quarter	40	2,320	-
Virtanen et al. [181] (2006)	Case-control	Central University Hospital of Turku (Finland)	Cryptorchidism	Interview and medical records	Unspecified	125	1,159	Matching: sex
Wang et al. [182] (2009)	Case-control	Study in the city of Shenyang (China)	Cleft lip with or without cleft palate	Interview	Pre-conception exposure and in the beginning of pregnancy	586	1,172	-
Wasserman et al. [183] (1996)	Case-control	California Birth Defects Monitoring Program (United States)	Limb reduction	Phone interview	First quarter	178	481	Matching: month/year of birth, place of birth
Watkins et al. [184] (1996)	Case-control	Study of birth defects in Atlanta (United States)	Spina bifida; Anencephaly	Interview	Pre-conception exposure and in the first quarter	307	2,755	Matching: month/year of birth, place of birth, race
Watkins et al. [185] (2003)	Case-control	Atlanta Birth Defects Risk Factor Surveillance (United States)	Malformations	Interview	Unspecified	644	330	-
Werler et al. [186] (2003)	Case-control	29 hospitals in the United States and Canada	Malformations (Gastroschisis and intestinal atresia)	Phone interview	First quarter	332	416	Adjusted: use of vasoconstrictor drugs, maternal/paternal schooling, family income maternal use of medication, maternal alcohol intake, use of illicit drugs by the mother, maternal age; Matching: month/year of birth, place of birth
Werler et al. [187] (2009)	Case-control	26 cities in the United States and Canada	Hemifacial microsomia	Phone interview	First quarter	230	678	Adjusted: maternal age, maternal schooling, family income, parity, race, maternal use of medication, maternal diabetes and hypertension
Werler et al. [188] (2009)	Case-control	National Birth Defects Prevention Study (United States)	Transverse limb reduction	Phone interview	Pre-conception exposure and in the first quarter	367	5,886	-

(continues)

Table 1 (continued)

Reference (year)	Type of study	Site/Source of data	Type of defect	Exposure (maternal smoking)		Case	Controls	Control of confounders (adjustment/ matching)
				Data collection	Stage of pregnancy			
Werler et al. [189] (2009)	Case-control	National Birth Defects Prevention Study (United States)	Gastroschisis	Phone interview	Pre-conception exposure and in the first quarter	514	3,277	Adjusted: maternal age, maternal schooling, family income, parity, race, maternal use of medication, place of birth, maternal BMI, maternal alcohol intake, folic acid intake, use of oral contraceptives
Williams et al. [14] (2004)	Case-control	Atlanta Birth Defects Case-Control Study (United States)	Ventricular septal defects	Phone interview	Pre-conception exposure and in the first quarter	122	3,029	-
Wong-Gibbons et al. [190] (2008)	Case-control	National Birth Defects Prevention Study (United States)	Esophageal atresia with or without tracheoe-sophageal fistula	Phone interview	Pre-conception exposure and in the first quarter	334	4,967	Adjusted: multiparity, maternal age, race, maternal/paternal schooling, maternal diabetes, infertility treatment, maternal alcohol intake, duration of maternal smoking, place of birth
Woods & Raju [191] (2001)	Cohort	Data of the TriHealth health system (United States)	Malformations	Interview	Unspecified	2,066	15,950	Adjusted: maternal age, race, maternal diabetes
Wyszynski & Wu [192] (2002)	Case-control	Birth database (United States)	Oral fissures	Database	First quarter	2,029	4,050	Adjusted: maternal age; Matching: month/year of birth, place of birth, sex, race
Yerush-almy [193] (1971)	Cohort	Child Health and Development Studies (United States)	Malformations	Question-naire	Unspecified	1,329	11,754	-
Yerush-almy [194] (1973)	Cohort	Child Health and Development Studies (United States)	Congenital heart disease	Question-naire	Unspecified	115	14,616	-
Yuan et al. [195] (1995)	Case-control	Kanagawa Birth Defects Monitoring Program (Japan)	Anal atresia	Interview	Unspecified	84	176	Matching: maternal age, sex, parity, month/year of birth
Zeiger et al. [196] (2002)	Case-control	Metropolitan area of Baltimore-Washington (United States)	Craniosynos-tosis	Phone interview	Unspecified	42	182	Adjusted: race, sex; Matching: sex

DES: diethylstilbestrol ; BMI: body mass index; CNS: central nervous system.

Table 2

Association between maternal smoking during pregnancy and birth defects in children: results of the 188 studies with birth defect of any type.

Reference (year)	Type of defect	OR	95%CI	Weight (%) *
Adams et al. [18] (1989)	Conotruncal heart defect	1.13	0.71-1.81	0.35
Akre et al. [19] (1999)	Cryptorchidism	1.19	1.06-1.33	0.99
Alderman et al. [20] (1991)	Crooked foot at birth	1.92	1.31-2.81	0.46
Alderman et al. [21] (1994)	Craniosynostosis	1.70	1.11-2.60	0.40
Ananijevic-Pandey et al. [22] (1992)	General malformations	1.58	0.96-2.60	0.32
Aro et al. [23] (1983)	Limb reduction	1.30	0.89-1.90	0.46
Bailey et al. [24] (1970)	Birth defects	0.75	0.43-1.32	0.27
Batra et al. [25] (2007)	Ventricular septal defect	0.93	0.83-1.04	0.98
Beard et al. [26] (1984)	Genitourinary defect	1.00	0.50-2.00	0.19
Beaty et al. [27] (2008)	Oral fissures	1.04	0.51-2.12	0.19
Beaty et al. [28] (2001)	Oral fissures	1.77	0.86-3.65	0.18
Bell & Lumley [29] (1989)	Birth defects	0.80	0.44-1.46	0.24
Berkowitz & Lapinski [30] (1996)	Cryptorchidism	1.24	0.59-2.61	0.17
Biggs et al. [31] (2002)	Cryptorchidism	1.24	1.11-1.38	1.00
Bille et al. [32] (2007)	Oral fissures	1.50	1.05-2.14	0.50
Bird et al. [6] (2009)	Musculoskeletal	1.44	1.04-2.00	0.54
Bitsko et al. [33] (2007)	Birth defects	1.61	1.00-2.60	0.33
Blatter et al. [34] (1996)	Central nervous system defects	0.95	0.68-1.32	0.54
Botto et al. [35] (2001)	Heart defects	1.11	0.95-1.30	0.90
Bracken et al. [7] (1978)	Birth defects	1.09	0.96-1.25	0.95
Brouwers et al. [36] (2007)	Hypospadias	0.90	0.61-1.32	0.45
Brouwers et al. [37] (2010)	Hypospadias	1.50	0.97-2.32	0.39
Browne et al. [38] (2007)	Heart defects	1.16	1.03-1.31	0.98
Carbone et al. [39] (2007)	Cryptorchidism; hypospadias	1.33	0.55-3.18	0.13
Cardy et al. [40] (2007)	Congenital equinovarus	1.37	0.72-2.61	0.22
Carmichael et al. [42] (2003)	Cardiovascular defects and facial cleft	1.70	1.35-2.14	0.73
Carmichael & Shaw [41] (2000)	Anencephaly	0.81	0.49-1.33	0.32
Carmichael et al. [44] (2008)	Craniosynostosis	1.03	0.80-1.33	0.68
Carmichael et al. [43] (2005)	Hypospadias	1.00	0.76-1.31	0.64
Caton et al. [45] (2008)	Hypospadias	0.88	0.72-1.10	0.77
Cedergren et al. [8] (2002)	Heart defects	1.19	0.86-1.66	0.54
Chambers et al. [46] (2007)	Gastroschisis	1.37	0.63-2.96	0.16
Chevrier et al. [47] (2008)	Oral fissures	1.00	0.62-1.61	0.55
Chew et al. [48] (1994)	Eye defects	1.27	1.22-1.32	1.10
Christensen et al. [9] (1999)	Oral fissures	1.16	0.73-1.83	0.37
Christianson [49] (1980)	Anomalies in all systems	1.05	0.96-1.15	1.03
Chung & Myrianthopoulos [50] (1975)	Inguinal hernia	1.45	1.25-1.68	0.95
Chung et al. [51] (2000)	Cleft lip; cleft palate	1.35	1.18-1.54	0.92
Cordier et al. [52] (1992)	Major defects	0.80	0.53-1.20	0.42
Correy et al. [53] (1991)	Defects	0.94	0.82-1.08	0.94
Croen et al. [54] (2000)	Holoprosencephaly	4.08	1.54-10.80	0.11
Czeizel et al. [58] (2004)	Orofacial clefts; Congenital limb defects	1.27	1.11-1.45	0.95
Czeizel et al. [57] (1994)	Limb reduction	1.68	1.26-2.24	0.61
Czeizel & Nagy [56] (1986)	Cleft lip; cleft palate	1.08	0.86-1.36	0.73
Czeizel & Vitez [55] (1981)	Omphalocele	1.14	0.64-2.01	0.26
Costa et al. et al. [59] (2006)	Birth defects	1.15	0.73-1.81	0.36
Damgaard et al. [60] (2008)	Cryptorchidism	0.88	0.53-1.47	0.31
Davies et al. [61] (1986)	Cryptorchidism	1.38	0.73-2.61	0.22
De Roo et al. [10] (2003)	Oral fissures	1.10	0.73-1.66	0.41

(continues)

Table 2 (continued)

Reference (year)	Type of defect	OR	95%CI	Weight (%) *
Dickinson et al. [11] (2008)	Crooked foot at birth	1.39	1.06-1.82	0.65
Draper et al. [62] (2008)	Gastroschisis	1.70	1.11-2.61	0.39
Erickson [63] (1991)	General malformations	1.12	1.05-1.20	1.07
Ericson et al. [64] (1979)	Central nervous system defects; orofacial clefts	1.88	1.22-2.90	0.39
Evans et al. [65] (1979)	All birth defects	0.96	0.88-1.04	1.04
Fredrick et al. [66] (1971)	Congenital heart diseases	1.54	1.22-1.95	0.72
Feldkamp et al. [12] (2008)	Gastroschisis	2.56	1.75-3.75	0.46
Felix et al. [67] (2008)	Esophageal atresia; diaphragmatic hernia	0.58	0.30-1.13	0.21
Ferencz et al. [68] (2008)	Cardiovascular defects	1.02	0.92-1.13	1.01
Garcia et al. [69] (1999)	Birth defects	4.25	1.57-11.50	0.10
Goldbaum et al. [70] (1990)	Gastroschisis	2.00	1.05-3.80	0.22
Golding & Butler [71] (1983)	Anencephaly	1.34	1.12-1.60	0.85
Grewal et al. [72] (2008)	Defects	0.81	0.57-1.17	0.49
Haddow et al. [73] (1983)	Gastroschisis	2.10	0.92-4.80	0.14
Hakin & Tielsch [74] (1992)	Esotropia; exotropia	1.56	1.15-2.12	0.58
Hearey et al. [75] (1984)	Central nervous system defects	4.00	0.64-24.99	0.03
Heinonen [76] (1977)	Defects	0.94	0.8-1.054	0.99
Hemminki et al. [77] (1981)	Central nervous system defects	1.61	1.27-2.04	0.72
Himmelberger et al. [78] (1978)	Defects	1.32	1.14-1.53	0.92
Honein et al. [82] (2001)	Defects	1.25	1.13-1.38	1.01
Honein et al. [83] (2007)	Oral fissures	1.20	0.98-1.47	0.79
Honein et al. [80] (2000)	Craniosynostosis	1.92	1.01-3.65	0.22
Honein & Rasmussen [81] (2000)	Crooked foot at birth	1.41	1.10-1.81	0.69
Hoobs et al. [79] (2006)	Heart defects	1.72	0.95-3.13	0.25
Hougland et al. [84] (2006)	Gastroschisis	2.61	1.49-4.57	0.27
Jensen et al. [85] (2007)	Cryptorchidism	1.08	0.84-1.39	0.68
Johansen et al. [86] (2009)	Cleft lip; cleft palate	1.52	1.21-1.91	0.74
Jones et al. [87] (1998)	Cryptorchidism	1.04	0.85-1.27	0.80
Kallen [88] (1999)	Craniosynostosis	1.45	1.12-1.87	0.68
Kallen [89] (2000)	Defects	1.03	1.00-1.06	1.11
Kelsey e tal. [90] (1978)	Defects	1.09	0.96-1.25	0.70
Khoury et al. [91] (1989)	Cleft lip; cleft palate	1.48	1.16-1.89	0.43
Krapels et al. [92] (2006)	Cleft lip; cleft palate	1.12	0.75-1.67	0.41
Krauss et al. [93] (2003)	Microcephaly	1.90	1.00-3.60	0.22
Kricker et al. [93] (1986)	Limb reduction	1.10	0.67-1.81	0.32
Kuciene & Dulskiene [95] (2009)	Heart defects	1.48	0.82-2.67	0.25
Kullander & Kallen [96] (1971)	Defects	1.14	0.85-1.52	0.61
Kurahashi et al. [97] (2005)	Cryptorchidism	1.04	0.50-2.12	0.19
Kurahashi et al. [98] (2005)	Hypospadias	1.04	0.24-4.45	0.05
Lam & Torfs [99] (2006)	Gastroschisis	1.96	0.98-3.92	0.20
Leite & Koifman [100] (2009)	Oral fissures	1.19	0.82-1.75	0.43
Li et al. [102] (2006)	Neural tube defects	1.44	0.35-5.85	0.05
Li et al. [101] (1996)	Urinary tract defects	2.30	1.18-4.49	0.21
Lie et al. [103] (2008)	Oral fissures	1.60	1.15-2.23	0.53
Lieff et al. [104] (1999)	Defects	1.27	1.10-1.46	0.94
Linn et al. [105] (1983)	All defects	0.93	0.71-1.21	0.66
Little et al. [106] (2004)	Oral fissures	2.00	1.29-3.10	0.38
Liu et al. [107] (2009)	Heart defects	5.13	0.98-26.71	0.04
Lorente et al. [108] (2000)	Oral fissures	1.42	0.92-2.20	0.39
Lowe [109] (1959)	All defects	1.30	0.57-2.99	0.14
Lubs [110] (1973)	Major defects	0.75	0.50-1.12	0.43

(continues)

Table 2 (continued)

Reference (year)	Type of defect	OR	95%CI	Weight (%) *
Lumley et al. [111] (1985)	All defects	1.04	0.80-1.35	0.67
MacBird et al. [112] (2009)	Omphalocele	1.20	0.79-1.82	0.41
Malik et al. [113] (2008)	Heart defects	1.22	1.10-1.35	1.01
Malloy et al. [114] (1989)	Defects	0.98	0.94-1.03	1.09
Man & Chang [115] (2006)	Congenital digital anomaly	1.31	1.18-1.45	1.01
Mandiracioglu et al. [116] (2004)	Neural tube defects	1.25	0.50-3.13	0.12
Martinez-Frias et al. [117] (2008)	Gastroschisis	1.81	0.96-3.41	0.23
McBride et al. [118] (1991)	Cryptorchidism	1.69	1.21-2.36	0.53
McDonald et al. [119] (1992)	Birth defects	1.07	0.98-1.17	1.04
McGlynn et al. [120] (2006)	Cryptorchidism	1.05	0.87-1.27	0.82
Miller et al. [121] (2009)	Anorectal atresia	1.15	0.91-1.45	0.73
Miller et al. [122] (2010)	Holoprosencephaly	0.90	0.47-1.71	0.22
Mitchell et al. [123] (2001)	Oral fissures	1.21	0.91-1.60	0.62
Morales-Suarez-Varela et al. [124] (2006)	Birth defects	1.10	1.00-1.20	1.03
Morgana et al. [125] (2008)	Cryptorchidism	0.71	0.46-1.10	0.38
Mori et al. [126] (1992)	Cryptorchidism	1.00	0.49-2.05	0.18
Mossey et al. [127] (2007)	Oral fissures	2.40	1.59-3.62	0.42
Munoz et al. [128] (2006)	Anencephaly	0.65	0.23-1.88	0.09
Mygind et al. [129] (2002)	Birth defects	1.19	0.94-1.51	0.72
Niebyl et al. [130] (1985)	Cleft lip; cleft palate	0.64	0.30-1.36	0.17
Noorgaard et al. [131] (2009)	Hypospadias	0.87	0.77-0.99	0.96
Oddsberg et al. [132] (2008)	Esophageal atresia	0.89	0.70-1.13	0.71
Ormond et al. [133] (2009)	Hypospadias	1.22	0.85-1.76	0.48
Parikh et al. [134] (2002)	Renal agenesis	1.49	0.99-2.25	0.42
Parker et al. [135] (2009)	Crooked foot at birth	1.53	1.18-1.99	0.67
Pierik et al. [136] (2004)	Cryptorchidism; hypospadias	1.45	0.92-2.29	0.37
Porter et al. [137] (2006)	Hypospadias	0.93	0.82-1.05	0.97
Preiksa et al. [138] (2006)	Hypospadias	1.58	0.94-2.65	0.31
Queissur-Luft et al. [139] (2002)	Major birth defects	1.00	0.83-1.20	0.84
Ramirez et al. [13] (2007)	Oral fissures	0.76	0.56-1.03	0.58
Rantakallio [140] (1978)	All defects	0.86	0.55-1.33	0.38
Reefhuis et al. [141] (1998)	Crooked foot at birth	1.21	1.13-1.29	1.07
Robitaille et al. [142] (2009)	Limb reduction	1.11	0.89-1.38	0.76
Rodriguez-Pinilla et al. [143] (2008)	Hypospadias	0.86	0.77-0.96	1.00
Romitti et al. [144] (2007)	Cleft lip; cleft palate	1.37	1.20-1.57	0.95
Salemi et al. [145] (2009)	Gastroschisis	0.97	0.74-1.28	0.64
Saxen [146] (1974)	Cleft lip; cleft palate	2.32	1.46-3.68	0.36
Schmidt et al. [147] (2009)	Central nervous system defects	0.90	0.73-1.10	0.80
Seidman et al. [148] (1990)	Malformations	1.04	0.89-1.21	0.90
Shaw et al. [149] (1992)	Cardiovascular defects	1.13	0.61-2.09	0.24
Shaw et al. [150] (1996)	Neural tube defects	0.85	0.61-1.18	0.53
Shaw et al. [151] (1996)	Cleft lip with or without cleft palate	1.55	1.12-2.14	0.55
Shaw et al. [152] (1999)	Neural tube defects	1.31	1.06-1.62	0.78
Shaw et al. [153] (2000)	Multiple defects	0.98	0.48-2.01	0.18
Shi et al. [154] (2007)	Cleft lip; cleft palate	1.28	1.09-1.51	0.89
Shiono et al. [155] (1986)	Malformations	0.90	0.83-0.98	1.04
Skelly et al. [156] (2002)	Crooked foot at birth	2.21	1.51-3.23	0.46
Slickers et al. [157] (2008)	Renal agenesis or hypoplasia	2.12	1.27-3.51	0.32
Smedts et al. [158] (2009)	Heart defects	0.81	0.54-1.21	0.43
Sorensen et al. [159] (2002)	Hypertrophic pyloric stenosis	2.00	1.29-3.10	0.38

(continues)

Table 2 (continued)

Reference (year)	Type of defect	OR	95%CI	Weight (%) *
Steinberger et al. [160] (2002)	Heart defects	2.49	1.23-5.03	0.19
Stoll et al. [161] (1997)	Musculoskeletal	1.18	0.61-2.26	0.22
Stoll et al. [162] (2001)	Anal atresia	1.36	0.72-2.56	0.23
Suarez et al. [163] (2008)	Neural tube defects	2.65	1.40-5.00	0.22
Szendrey et al. [164] (1985)	Esophageal atresia	0.82	0.49-1.36	0.31
Tamura et al. [165] (2006)	Oral fissures	0.84	0.28-2.56	0.08
Targett et al. [166] (1977)	Major malformations	1.33	0.92-1.92	0.48
Tata et al. [167] (2008)	Birth defects	0.99	0.92-1.06	1.06
The et al. [168] (2007)	Biliary atresia	0.70	0.34-1.43	0.19
Tikkanen & Heinonen [169] (1991)	Cardiovascular defects	1.00	0.78-1.27	0.70
To & Tang [170] (1999)	Birth defects	1.32	0.94-1.85	0.53
Torfs et al. [171] (1994)	Gastroschisis	1.51	0.93-2.46	0.33
Tornquist et al. [172] (2002)	Optic nerve hypoplasia	1.61	1.08-2.40	0.43
Torp-Pedersen et al. [173] (2010)	Strabismus	1.26	1.11-1.42	0.97
Tuohy et al. [174] (1993)	Birth defects	1.18	0.85-1.63	0.54
Underwood et al. [175] (1965)	Major malformations	0.78	0.46-1.33	0.29
van den Boogaard et al. [176] (2008)	Cleft lip	1.57	0.92-2.67	0.29
van den Eeden et al. [177] (1990)	General malformations	1.00	0.91-1.10	1.02
van Rooij et al. [179] (2002)	Spina bifida/facial cleft	1.92	0.90-4.12	0.17
van Rooij et al. [178] (2001)	Cleft lip; cleft palate	1.12	0.58-2.16	0.21
Verkerk et al. [180] (1994)	Birth defects	1.12	0.59-2.11	0.22
Virtanen et al. [181] (2006)	Cryptorchidism	0.41	0.23-0.72	0.26
Wang et al. [182] (2009)	Cleft lip; cleft palate	1.50	0.52-4.34	0.09
Wasserman et al. [183] (1996)	Limb reduction	1.14	0.77-1.69	0.44
Watkins et al. [184] (1996)	Spina bifida; anencephaly	1.09	0.85-1.39	0.69
Watkins et al. [185] (2003)	Birth defects	1.36	0.96-1.93	0.50
Werler et al. [187] (2009)	Hemifacial microsomia	1.62	0.86-3.06	0.22
Werler et al. [189] (2009)	Gastroschisis	1.50	1.18-1.90	0.71
Werler et al. [186] (2003)	Gastroschisis; intestinal atresia	1.31	0.96-1.78	0.57
Werler et al. [188] (2009)	Transverse limb reduction	1.10	0.85-1.42	0.68
Williams et al. [14] (2004)	Ventricular septal defects	1.26	0.86-1.84	0.46
Wong-Gibbons et al. [190] (2008)	Esophageal atresia; tracheoesophageal fistula	1.68	0.99-2.86	0.29
Woods & Raju [191] (2001)	Birth defects	1.16	1.02-1.32	0.95
Wyszynski & Wu [192] (2002)	Oral fissures	1.12	0.96-1.30	0.91
Yerushalmy [193] (1971)	Birth defects	0.51	0.45-0.58	0.96
Yerushalmy [194] (1973)	Heart defects	0.90	0.61-1.34	0.45
Yuan et al. [195] (1995)	Anal atresia	1.32	0.59-2.95	0.15
Zeiger et al. [196] (2002)	Craniosynostosis	0.75	0.29-1.95	0.11
Meta-analysis		1.18	1.14-1.22	100.00

95%CI: 95% confidence interval; OR: *odds ratio*.

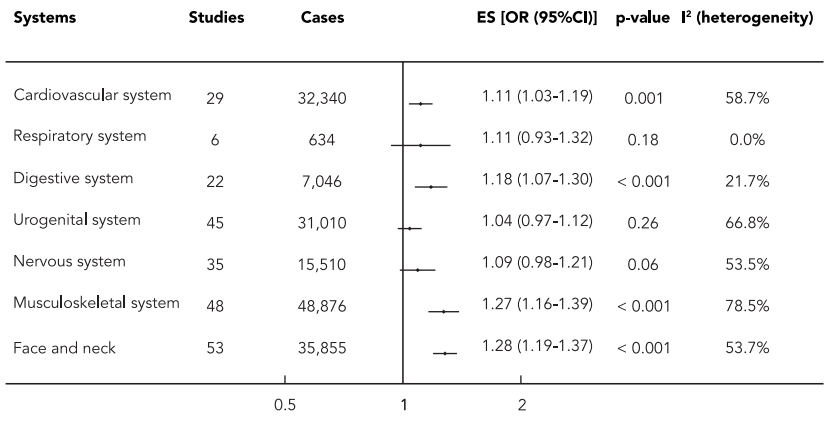
* Weight of each study that contributed to the final result of the meta-analysis.

($\chi^2 = 12.1$; p = 0.002). *Post hoc* sub-group analyses were performed according to the design of the investigation, control of confounders, and size of the sample (cases). The statistically significant dose-response relation was seen in sub-groups of studies that had controlled confounder factors and in studies where the number of cases ranged between 200 and 5,000 (Table 4). The design of the investigation did not substantially affect the results of the dose-response relation.

The cumulative meta-analysis showed a statistically significant association between maternal smoking during pregnancy and birth defects in children when 40 studies published until 1990, with a total of 26,827 were included in the analysis (OR: 1.09; 95%CI: 1.001-1.19; p = 0.035). The

Figure 3

Maternal smoking during pregnancy and birth defects in children according to the body systems involved.



Note: weights are of random effect analysis.

95%CI: 95% confidence interval; ES: effect size; OR: odds ratio.

Table 3

Analysis of subgroups about the association between maternal smoking during pregnancy and birth defects in children.

	OR	95%CI	I² (%) *	Difference among subgroups
1. Study design				$\chi^2 = 21.2$; $p < 0.00001$
Restrospective studies (n = 159)	1.21	1.17-1.26	69.70	
Prospective studies (n = 29)	1.08	1.01-1.17	90.20	
2. Adjustment/matching according to the age of the mother				$\chi^2 = 0.06$; $p = 0.81$
No (n = 127)	1.19	1.13-1.25	76.50	
Yes (n = 61)	1.18	1.13-1.24	78.80	
3. Sample size (cases)				$\chi^2 = 16.5$; $p = 0.0009$
≤ 200 (n = 81)	1.31	1.20-1.43	49.60	
> 200-1,000 (n = 61)	1.23	1.16-1.31	60.90	
> 1,000-5,000 (n = 40)	1.09	1.03-1.15	89.00	
> 5,000 (n = 6)	1.11	1.01-1.22	91.30	

95%CI: 95% confidence interval; OR: *odds ratio*.

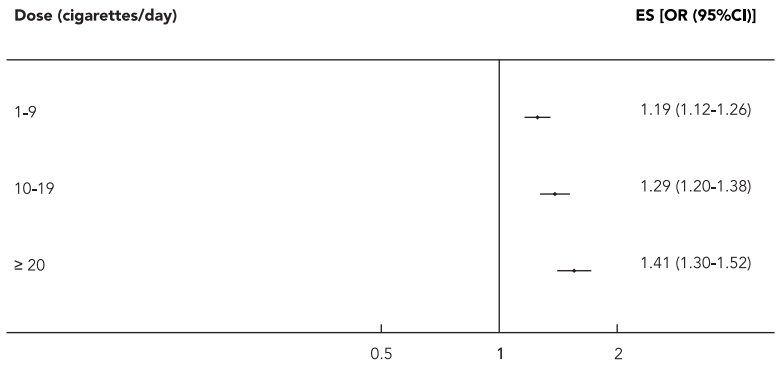
* I^2 measures the heterogeneity of the results among the sutdies (> 75% indicates significant heterogeneity).

OR (95%CI) and the p value were respectively 1.16 (1.10-1.23) and < 0.001, when 87 studies published until 2000, with a total of 95,556 cases were included in the meta-analysis. The result of the meta-analysis remained almost unchanged when 101 studies (97,099 cases) published between 2001 and 2010 were included (Figure 5).

In the funnel plot (Figure 6), a slight asymmetry in the lower left corner was observed due to lack of studies, which suggested that studies with small samples demonstrating protective effects of maternal smoking against defects in children had not been published. The Egger test also showed evidence of the "small studies" effect, which suggests the presence of publication bias ($p < 0.001$).

Figure 4

Dose-response relation between maternal smoking and birth defects in children.



Note: weights are of random effect analysis.

Test for differences among sub-groups (χ^2 = 12; df = 2; p = 0.002).

95%CI: 95% confidence interval; ES: effect size; OR: odds ratio.

Table 4

Post hoc subgroup analysis amout the dose-response relation between maternal smoking during pregnancy and birth defects in children.

	1-9 cigarettes/day OR (95%CI)	10-19 cigarettes/day OR (95%CI)	≥ 20 cigarettes/day OR (95%CI)	Difference among the 3 dose groups *
1. Study design				
Retrospective studies (n = 49)	1.25 (1.18-1.33)	1.31 (1.22-1.39)	1.47 (1.33-1.61)	χ^2 = 7.95; p = 0.002
Prospective studies (n = 11)	1.05 (0.98-1.14)	1.19 (0.96-1.48)	1.28 (1.10-1.50)	χ^2 = 5.63; p = 0.06
2. Adjustment/matching according to the age of the mother				
No (n = 32)	1.15 (1.05-1.26)	1.22 (1.12-1.33)	1.34 (1.18-1.53)	χ^2 = 0.89; p = 0.64
Yes (n = 28)	1.22 (1.15-1.30)	1.35 (1.24-1.48)	1.49 (1.31-1.68)	χ^2 = 9.37; p = 0.009
3. Sample size (cases)				
≤ 200 (n = 14)	1.60 (1.34-1.91)	1.66 (1.09-2.51)	1.76 (1.41-2.21)	χ^2 = 0.43; p = 0.81
> 200-1,000 (n = 28)	1.21 (1.10-1.34)	1.39 (1.26-1.54)	1.45 (1.24-1.69)	χ^2 = 5.42; p = 0.07
> 1,000-5,000 (n = 14)	1.10 (0.93-1.30)	1.19 (1.09-1.31)	1.42 (1.25-1.61)	χ^2 = 7.14; p = 0.03
> 5,000 (n = 4)	1.22 (1.00-1.25)	1.28 (1.17-1.41)	1.20 (0.98-1.46)	χ^2 = 3.25; p = 0.20

95%CI: 95% confidence interval; OR: odds ratio.

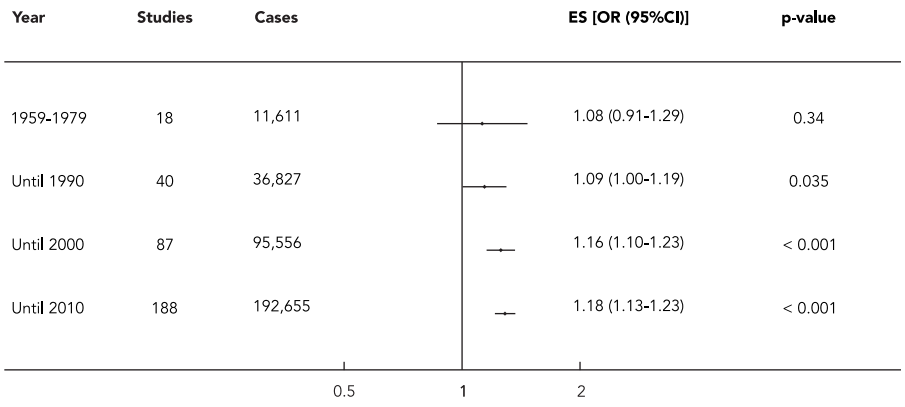
* p-value < 0.10 rather than 0.05 was considered statistically significant in the χ^2 test due to the low statistic value, as there are only 3 dose groups.

Discussion

This systematic review with meta-analysis has shown that children of mothers who smoked during pregnancy are at a higher risk of presenting birth defects of any type. Significant associations between maternal smoking during pregnancy and birth defects of the cardiovascular, digestive, musculoskeletal systems and of the face and neck were evidenced. Positive associations were also observed between maternal smoking and birth defects of the respiratory, nervous, and urogenital systems; however, these associations were not statistically significant.

Figure 5

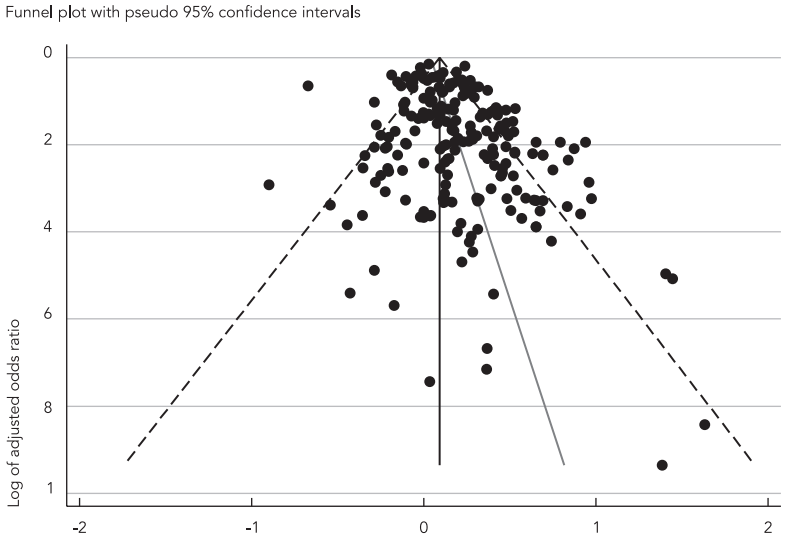
Cumulative meta-analysis about the association between maternal smoking during pregnancy and birth defects in children.



Note: weights are of random effect analysis.
95%CI: 95% confidence interval; ES: effect size; OR: odds ratio.

Figure 6

Funnel plot.



In this systematic review a statistically significant dose-response relation was alsou found between maternal smoking during pregnancy and the risk of birth defects in children; this means, the higher the number of cigarettes a day smoked by the mother, the higher the risk of having babies with some type of birth defects. It was also observed that all the three daily doses of

cigarette-smoking were significantly associated with higher risk of birth defects compared to non-smoking, suggesting that the regular use of cigarettes by the pregnant woman, even in small amounts, may cause adverse impact in the development of the fetus.

The mechanisms of action of tobacco in the increase of abnormalities in babies are not accurately understood. It is believed that the vasoconstrictor effect of nicotine may reduce the uterine and placental blood flow [197]. Carbon monoxide binds to the hemoglobin in such a way that less oxygen is available for the placenta. In addition, the endothelial injury caused by tobacco increases the rupture of blood vessels from neovascularization of the placenta, leading to a decrease in the blood flow to the fetus, causing hypoxia which will likely result in abnormal fetal morphogenesis [198]. Therefore, exposure to toxins in tandem with hypoxia and cellular ischemia results in abnormal cellular proliferation.

Approximately one third of Brazilian adults were smokers by the end of the 1990s; there was, however, a reduction of about 50% (from 34% to 18.2%) in the prevalence of smokers in this population between 1989 and 2008 [199]. A number of factors account for this reduction, including anti-tobacco policies and availability of smoking-cessation treatments. Smoking during pregnancy is of particular concern, as it is associated with many maternal-fetal outcomes, such as low-weight at birth, premature deliveries, perinatal deaths, and birth defects [200,201]. In countries such as the United States and Canada, where anti-tobacco governmental policies are aggressive, and strong investments are made to control smoking during pregnancy, the prevalence of maternal smoking during pregnancy is currently around 10 to 12% [202,203]. A recent study carried out in nine countries, including Latin America (Argentina, Brazil, Ecuador, Guatemala and Uruguay), Asia (India and Pakistan), and Africa (Democratic Republic of Congo and Zambia) showed higher prevalence of maternal smoking during pregnancy in Uruguay (18.3%), followed by Argentina (10.3%) and Brazil (6.1%) [204]. However, some local studies made in Brazil have shown a prevalence of active smoking of around 20% among pregnant women [201,205], a proportion much higher than the reported in this international multicentric study. These data point the need for yet stronger actions against tobacco-use during pregnancy in Latin America, including Brazil.

There are a number of resources available to facilitate smoking cessation, such as anti-smoking patches, and anti-anxiety agents like bupropion [197]. These may be used prior to the patient become pregnant. For this reason, we stress the importance of pre-pregnancy counseling.

A systematic review has also shown an association between maternal smoking during pregnancy and birth defects in children [5]. Compared to that review, this one has included 20 additional studies [6,7,8,9,10,11,12,13,14,24,43,79,83,95,99,102,103,122,125,188] that have added about 10,000 cases of defects, and 800,000 of controls. Another difference between the two reviews is that 19 studies about abdominal wall defects were included in the meta-analysis of the gastro-intestinal system in the previous review, whereas these defects were classified as pertaining to the musculoskeletal system in this review. Despite these methodological differences, the results of these two reviews were similar in regards to the association between maternal smoking during pregnancy and defects of the cardiovascular, respiratory, digestive, nervous, urogenital and musculoskeletal systems. The meta-analysis from the previous review included 38 studies in which all defects were combined together did not show significant association between maternal smoking and birth defects (OR: 1.01; 95%CI: 0.96-1.07). The meta-analysis of the current review has included all the 188 studies in which the defects were both combined or of a particular type, and evidenced a statistically significant association between maternal smoking during pregnancy and the risk of any type of birth defect in children (OR: 1.18; 95%CI: 1.14-1.22).

The cumulative meta-analysis of this current review shows that there was already evidence of the association between maternal smoking during pregnancy and birth defects in children by analyzing the results of 40 studies published until 1990 that included a total of 26,827 cases of defects (OR = 1.09; p = 0.035). The evidence of the association became more robust with the results of 87 studies published until 2000, with a total of 95,556 cases (OR = 1.16; p < 0.0001). Between 2000 and 2010, more than 100 studies were carried out with some 100,000 cases of defects; the inclusion of these studies, however, did not change significantly the results of the meta-analysis. These data indicate that findings about the association between maternal smoking during pregnancy and birth defects in children are convincing, and there is no need of further epidemiological studies to investigate this association.

Some methodological studies should be considered in interpreting the results of this systematic review. The heterogeneity of the results of the studies included in this review is to be expected, considering the differences in the research design, type of defect and method used for diagnosis, definition of maternal smoking and control of the effect of confounders. Some of the confounding factors were investigated

through subgroup analyses, whose results suggest that the type of defect, the design of the research and the size of the sample are possible causes of heterogeneity. The quality of the studies included was not assessed individually due to limitations of the tools currently available [206]; however, the potential influences of the methodological aspects of the studies (research design, sample size, control of the effect of confounders, and definition of exposure) in the results of the meta-analysis were investigated through the sub-group analyses. The influence of passive smoking in the association between maternal smoking during pregnancy and birth defects in children was not investigated due to lack of information in most of the original studies. Future studies should address this issue. The funnel plot and the Egger test suggest the presence of publication bias, due to non-publication of small studies that would demonstrate the protective effect of maternal smoking against defects in children. We believe that the number of this type of study is limited, and the lack of data from these studies does not significantly affect the results of the meta-analysis.

We conclude, from this systematic review with meta-analysis, that maternal smoking during pregnancy is associated with a higher risk of birth defects in children, and that this is a dose-dependent association.

Resumen

Esta revisión sistemática se encargó de investigar la asociación entre el tabaquismo materno durante el embarazo y las malformaciones congénitas en los niños. Se realizó una búsqueda electrónica de los estudios de observación en las bases de datos de ovid MEDLINE (1950 hasta abril de 2010), LILACS y SciELO. 188 estudios con 13.564.914 participantes se incluyeron en esta revisión. Se encontraron asociaciones positivas significativas entre el tabaquismo materno y malformaciones de los sistemas: cardiovascular (OR: 1,11; IC95%: 1.03-1.19), digestivo (OR: 1,18; IC95%: 1,07-1,30), musculoesqueléticos (OR: 1,27; IC95%: 1,16-1,39) y de cara y cuello (OR: 1,28; IC95%: 1,19-1,37). La fuerza de la asociación entre el tabaquismo materno y los defectos de nacimiento, medidos por el OR (IC95%) está significativamente relacionada con la cantidad de cigarrillos fumados diariamente (χ^2 = 12,1; p = 0,002). Llegamos a la conclusión de que el tabaquismo materno durante el embarazo se asocia con un mayor riesgo de malformaciones congénitas en los niños y esta asociación es dosis-dependiente.

Hábito de Fumar; Embarazo; Anomalías Congénitas

Contributors

D. Nicoletti designed the investigation project and the writing of the article; she also participated in the selection and evaluation of the studies, extraction of data and interpretation of results. L. D. Appel, P. Siedersberger Neto and G. W. Guimarães participated in the selection and evaluation of the studies and the extraction of data; they conducted a critical review and approved the final version of the article. L. Zhang was responsible for the idea of the investigation and for data analysis and interpretation; he provided guidance in the design of the project and the writing of the article, and approved the final version of the article.

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