

# Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls

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## TABLE OF CONTENTS

- Introduction
- Methods
- Results
  - Cardiovascular/heart defects
  - Musculoskeletal defects and craniosynostosis
  - Facial defects (face, eyes or ears)
  - Defects of the gastrointestinal system
  - Defects of the genitourinary system
  - Defects of the CNS
  - Defects of the respiratory system and skin
  - All congenital abnormalities considered together
  - Study quality, heterogeneity and publication bias
- Discussion

**BACKGROUND:** There is uncertainty over whether maternal smoking is associated with birth defects. We conducted the first ever comprehensive systematic review to establish which specific malformations are associated with smoking.

**METHODS:** Observational studies published 1959–2010 were identified (Medline), and included if they reported the odds ratio (OR) for having a non-chromosomal birth defect among women who smoked during pregnancy compared with non-smokers. ORs adjusted for potential confounders were extracted (e.g. maternal age and alcohol), otherwise unadjusted estimates were used. One hundred and seventy-two articles were used in the meta-analyses: a total of 173 687 malformed cases and 11 674 332 unaffected controls.

**RESULTS:** Significant positive associations with maternal smoking were found for: cardiovascular/heart defects [OR 1.09, 95% confidence interval (CI) 1.02–1.17]; musculoskeletal defects (OR 1.16, 95% CI 1.05–1.27); limb reduction defects (OR 1.26, 95% CI 1.15–1.39); missing/extra digits (OR 1.18, 95% CI 0.99–1.41); clubfoot (OR 1.28, 95% CI 1.10–1.47); craniosynostosis (OR 1.33, 95% CI 1.03–1.73); facial defects (OR 1.19, 95% CI 1.06–1.35); eye defects (OR 1.25, 95% CI 1.11–1.40); orofacial clefts (OR 1.28, 95% CI 1.20–1.36); gastrointestinal defects (OR 1.27, 95% CI 1.18–1.36); gastroschisis (OR 1.50, 95% CI 1.28–1.76); anal atresia (OR 1.20, 95% CI 1.06–1.36); hernia (OR 1.40, 95% CI 1.23–1.59); and undescended testes (OR 1.13, 95% CI 1.02–1.25). There was a reduced risk for hypospadias (OR 0.90, 95% CI 0.85–0.95) and skin defects (OR 0.82, 0.75–0.89). For all defects combined

the OR was 1.01 (0.96–1.07), due to including defects with a reduced risk and those with no association (including chromosomal defects).

**CONCLUSIONS:** Birth defects that are positively associated with maternal smoking should now be included in public health educational materials to encourage more women to quit before or during pregnancy.

**Key words:** maternal smoking / pregnancy / birth defects / malformations / fetal development

## Introduction

Maternal smoking during pregnancy is an established risk factor for miscarriage/perinatal mortality, low birthweight, premature births and small fetuses (DiFranza and Lew, 1995; Royal College of Physicians 2010; Shah and Bracken, 2000; US Surgeon General, 2001, 2004). The biological mechanisms of how tobacco smoke affect fetal development have been examined in extensive human and laboratory studies, which show that many of the 7000 chemicals can cross the placental barrier and have a direct harmful effect on the unborn baby (BMA, 2004; Werler et al., 1985; Quinton et al., 2008; Talbot, 2008; Rogers, 2009).

Despite the risks, many women still smoke during pregnancy; 17% in England and Wales (ONS, 2006) and 14% in the USA (Tong et al., 2009). The prevalence varies considerably with maternal age and educational/professional level. In the UK, the smoking prevalence during pregnancy was 45% among those aged <20 years compared with 9% in those aged ≥35 years; and 29% in those in routine/manual work, compared with 7% classified as managerial/professional (ONS, 2006). In the USA, 20% of pregnant women aged <25 years smoked versus 9% among those aged ≥35 years (Tong et al., 2009); and it was 22% in those with <12 years of education versus 6.5% with >12 years (Williams et al., 2006).

In England and Wales, 3759 babies were born with a non-chromosomal congenital anomaly in 2008; the five most common defects were of the heart/cardiovascular system (27%), limbs (22%), urinary (17%) and genital (11%) systems, and orofacial clefts (11%) (ONS, 2010). In the USA there are >120 000 babies born with a birth defect each year (March of Dimes, 2010): an annual incidence of 3% (Parker et al., 2010).

Relatively few public health educational materials mention birth defects as a possible outcome among pregnant women who smoke, and those that do are hardly ever specific. This is probably because of uncertainty over whether congenital defects are causally associated with maternal smoking. Surprisingly, despite research studies spanning 50 years, there has never been a comprehensive systematic review of smoking and congenital defects, except for orofacial clefts (Wyszynski et al., 1997; Little et al., 2004). The purpose of our review is to establish which specific defects are associated with maternal smoking.

## Methods

We conducted a systematic literature review of English articles published 1959 to February 2010 in Medline, using the PRISMA guidelines. The key-words used were (abnormalit\$ or defect\$ or malformation\$ or anomal\$ or deficienc\$ or gastroschisis or omphalocele or atresia or cleft or craniosynostosis or clubfoot/talipes equinovarus or cryptorchidism or hypospadias or spina bifida or anencephaly or strabismus or esotropia or exotropia or polydactyly or syndactyly or adactyly or finger\$ or toe\$) AND (birth\$ or pregnanc\$ or infant\$ or congenital or offspring) AND (maternal or mother\$ or women) AND (smok\$ or cigarette\$ or factor\$ or indicator\$

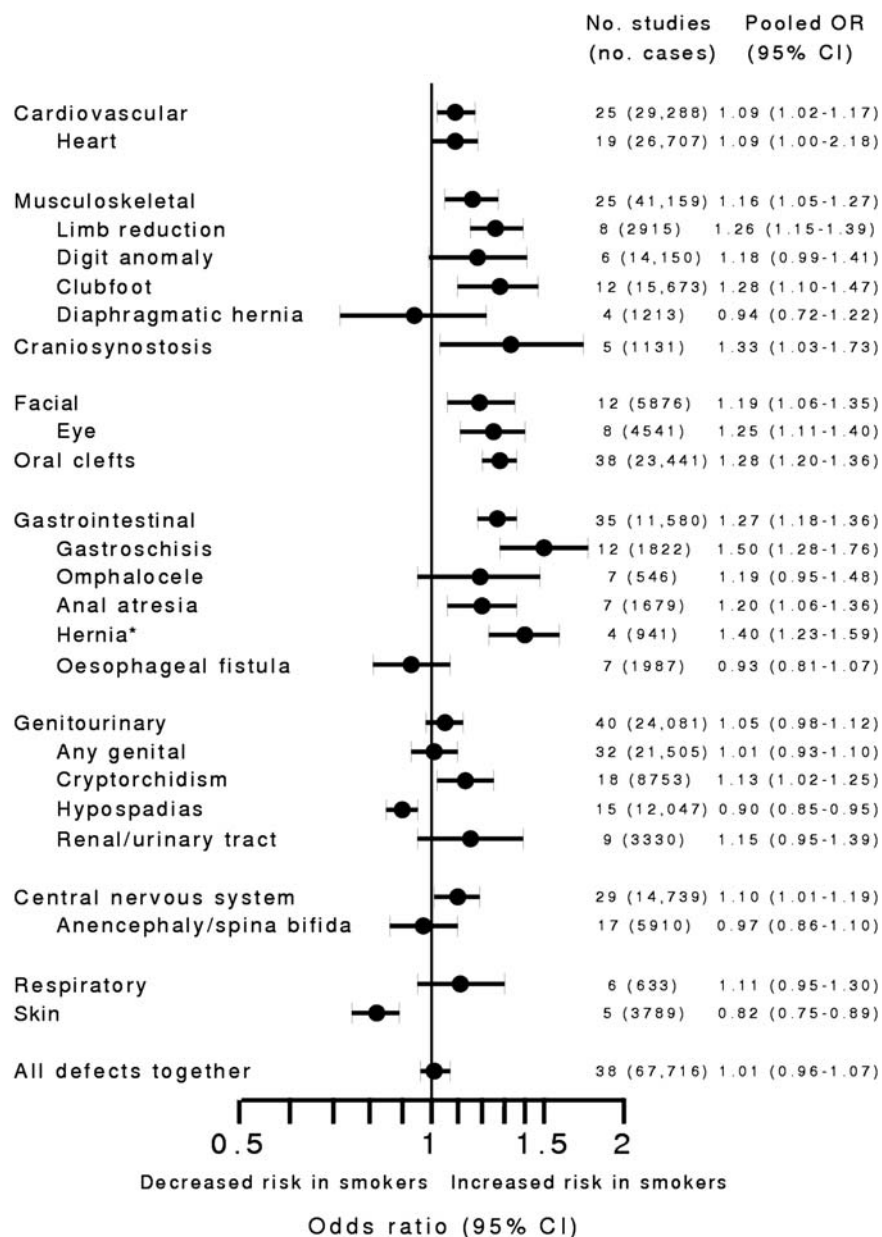
or exposure\$). References were also checked with two US Surgeon General's reports (US Surgeon General, 2004, 2010). We also examined articles in Embase, and found no additional article to those already identified using the above searches.

Any full paper when the abstract referred to maternal smoking or risk factors was obtained. A total of 9328 abstracts were examined (S.B. and A.H. independently), and 768 full papers were obtained, including those identified from article references (see Supplementary data, Flow Chart Figure). The inclusion criteria were: any observational study based on women who smoked during pregnancy (the exposure); the article reported the odds ratio (OR) or relative risk of having a defect among pregnant smokers compared with non-smokers (the outcome), whether adjusted for confounding or not, or it provided data that allowed the calculation of the OR; and there must have been a control group (usually of unaffected births).

After excluding 91 articles that contained duplicate data, there were 177 eligible articles, of which 172 were included in the analyses, covering 101 different research studies. Five articles were not included in the analyses because all controls had malformations other than the one of interest (and so could possibly dilute an association with smoking). Instead, they are summarized in the Supplementary data, table footnotes.

S.B. and A.H. extracted design characteristics and data from each paper. The ORs were sometimes adjusted for potential confounders (e.g. maternal age), either in the reported statistical analysis or by using matched controls. Unadjusted estimates were used when adjusted ORs were unavailable. Of the 101 studies, the affected cases were: live births ( $n = 74$ ), only stillbirths ( $n = 4$ ) or mainly live births with some stillbirths or elective abortions ( $n = 23$ ). In 12 studies the comparison group included all other births unaffected by the defect of interest (i.e. those without the defect plus those with other defects, though this is unlikely to affect the ORs because the vast majority did not have an anomaly, and would only slightly dilute an effect). In one study all controls had chromosomal defects. For several disorders, such as musculoskeletal defects, orofacial clefts and gastrointestinal disorders (e.g. gastroschisis and omphalocele), diagnoses were largely made at birth (or within the first week). However, for others, such as cardiovascular defects, craniosynostosis, facial defects (e.g. of the eye), other gastrointestinal defects, and genitourinary defects, many studies ascertained affected cases up to 1 year after birth or beyond, or when diagnoses were made in infancy (including referrals for corrective treatment).

The study designs were cohort, case–control or surveys. Important study characteristics for each defect are provided in the online supplementary data: such as geographical location, year of recruitment of study subjects, time period following birth during which cases were ascertained (for defects that might not be detected at birth), and matching or confounding factors allowed for. Maternal smoking status and other characteristics were obtained by questionnaires or interviews during early pregnancy (prospectively), or shortly after birth using surveys, interviews or birth certificates (retrospectively). The 101 studies were therefore classified as prospective cohort ( $n = 16$ ), prospective case–control ( $n = 3$ ), retrospective case–control ( $n = 62$ ) or retrospective surveys ( $n = 20$ ). Several case–control studies were matched for factors such as maternal age and birth year, while others without matching reported that characteristics of cases and controls were similar.



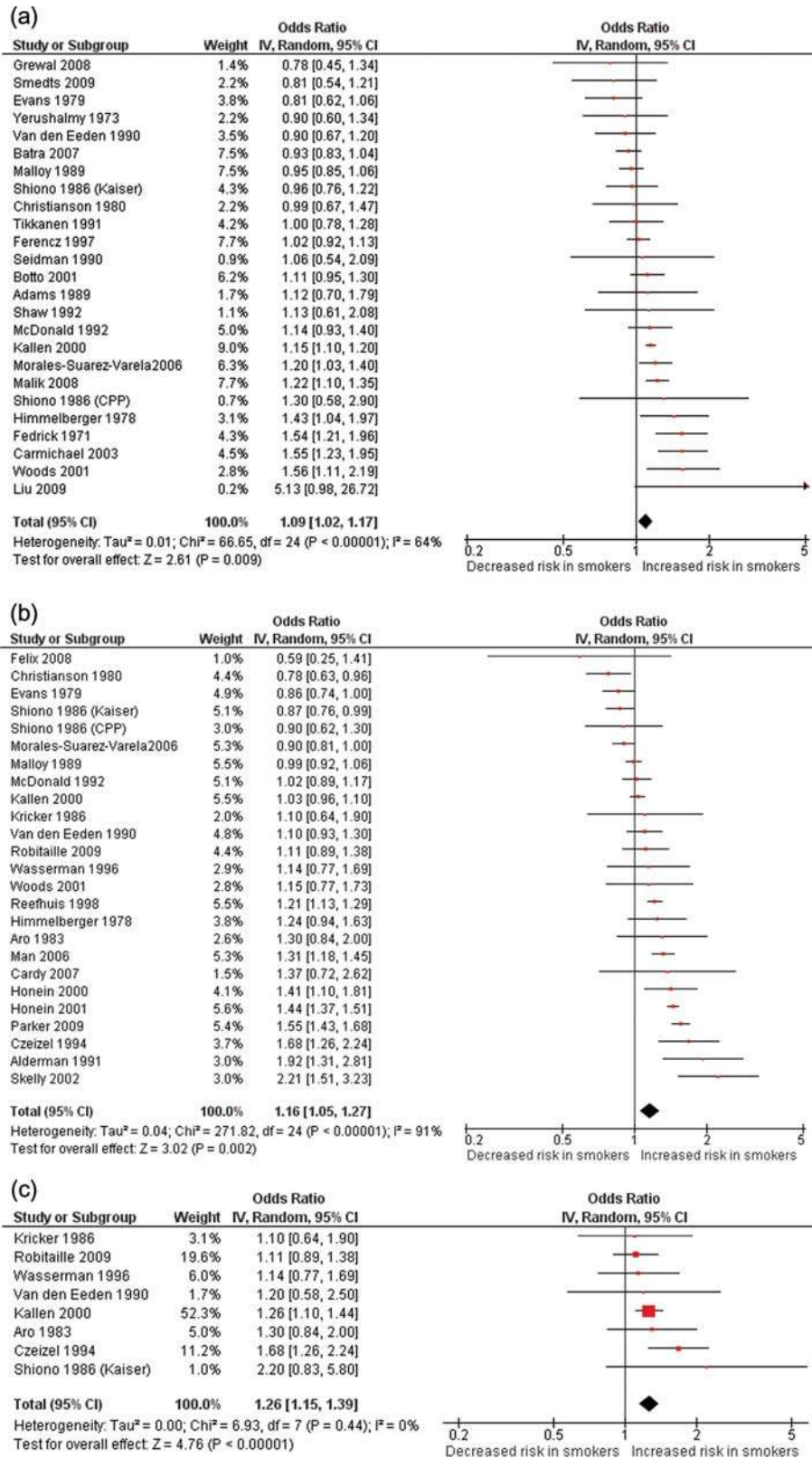
**Figure 1** Summary of the meta-analyses for maternal smoking in pregnancy and birth defects. The pooled ORs are shown for each body system and specific defects (total number of malformed cases in brackets). CI: confidence interval

\*Umbilical, inguinal or ventral hernia. 'Oesophageal fistula' is 'oesophageal atresia/tracheoesophageal fistula'.

Analyses were conducted using a random effects model, allowing for heterogeneity (REVMAN, 2008), based on adjusted ORs from each study (allowing for a range of potential confounders; see Supplementary data), and if not available, the unadjusted estimate. In addition, analyses were performed using only the adjusted estimates, and also where at least allowance was made for maternal age and alcohol use (two main potential confounders). Further subgroup analyses were restricted to studies where smoking status was collected prospectively to avoid misreporting bias, in which smokers with an affected baby might be more likely to report themselves as non-smokers. Heterogeneity between studies was assessed by a test for heterogeneity and  $I^2$  (Higgins *et al.*, 2003). Publication bias was examined using funnel plots.

## Results

The 172 reports together contain 173 687 cases with a congenital defect and 11 674 332 unaffected controls (see reference list for all 177 eligible articles). Figure 1 and Supplementary data, Table S1 summarizes the pooled ORs from the meta-analysis for each body system or specific defect, including ORs adjusted for potential confounders. Maternal smoking is associated with a significant increased risk for defects of the cardiovascular, musculoskeletal and gastrointestinal systems, the face including orofacial clefts, and cryptorchidism. There appears to be a decreased risk for hypospadias and



**Figure 2** Forest plots for (a) cardiovascular/heart defects (Kelsey 1978 had no standard error, OR = 1.08), (b) all musculoskeletal defects (two studies had no standard error: Kelsey 1978 OR = 0.93, and Hemminki 1981 OR = 1.35), (c) limb reduction defects, (d) digit anomaly (ie polydactyly, syndactyly and adactyly), (e) clubfoot (Kelsey 1978 had no standard error, OR = 1.22; and the pooled OR excluding Shiono 1986 Kaiser is 1.35, 95% CI 1.17–1.54), and (f) craniosynostosis. Studies are ranked according to size of the odds ratio.

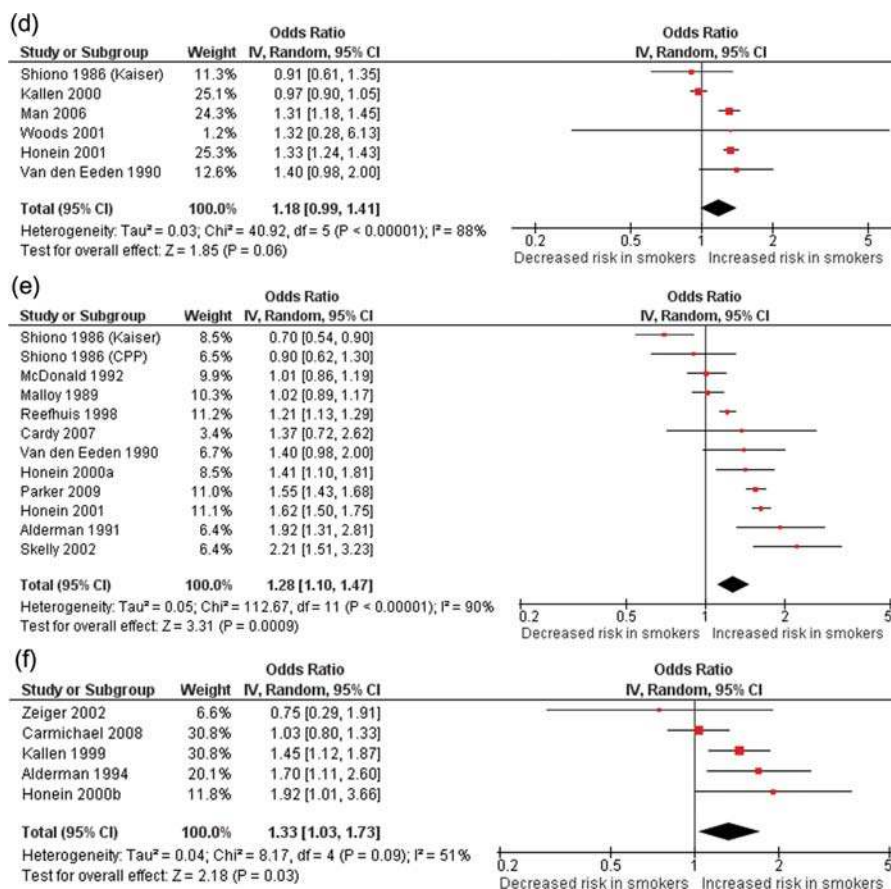


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skin defects among smokers. There is probably no association with defects of the genitourinary, respiratory or central nervous systems (CNS).

### Cardiovascular/heart defects

There is a modest (9%) but significant increased risk, OR 1.09 [95% confidence interval (CI) 1.02–1.17,  $P = 0.009$ ] from 25 studies (29 288 malformed cases, 2.09 million controls); Supplementary data, Table S2a and Fig. 2a. Seven studies each had significant excess risks. The pooled OR from 19 studies of heart defects only is also 1.09 (Supplementary data, Table S2b and Fig. S1); 5 were statistically significant. When we restricted the analyses to only those studies that had at least 1-year follow-up to ascertain affected cases, the pooled OR was similar: 1.10 (95% CI 1.02–1.18).

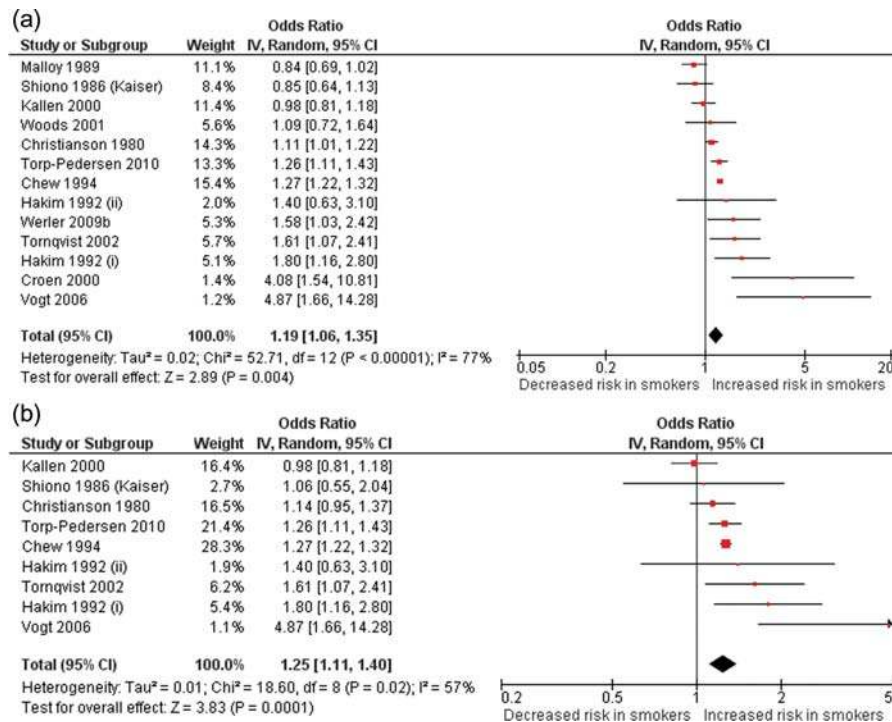
It was not clear whether any specific heart anomaly (e.g. ventricular septal defects) had a greater association with maternal smoking. The study with the largest number of affected cases ( $n = 3067$ ; Malik *et al.*, 2008) suggested that the strongest effect could be on ventricular septal defects (OR 1.34, 95% CI 1.08–1.65), and atrial septal defects (OR 1.98, 95% CI 1.53–2.57). The ORs for other types were: 1.26 (right ventricular outflow tract obstruction), 0.96 (left ventricular outflow tract obstruction) and 1.00 (conotruncal defects).

### Musculoskeletal defects and craniosynostosis

Musculoskeletal defects include a range of problems associated with the muscles, bones and limbs. There is a significant 16% increase in risk associated with maternal smoking (OR 1.16, 95% CI 1.05–1.27,  $P = 0.002$ ) from 25 studies (41 159 malformed cases, 1.2 million controls); Supplementary data, Table S3 and Fig. 2b. There was evidence of heterogeneity, but this was not present in some subgroup analyses. Six studies reported evidence of a dose–response relationship (Alderman *et al.*, 1991; Czeizel *et al.*, 1994; Honein *et al.*, 2001; Skelly *et al.*, 2002; Man and Chang, 2006; Parker *et al.*, 2009).

Eight studies of limb reduction defects (2915 malformed cases, 2.4 million controls)—the absence or severe underdevelopment of the hands or feet (transverse limb reductions), or of the radius, tibia, ulna or fibula (longitudinal limb reductions)—all reported increased risks; Supplementary data, Table S4 and Fig. 2c. Two studies each had significant results (Czeizel *et al.* 1994; Kallen, 2000), one with a dose–response relationship (Czeizel *et al.*, 1994). The excess risk is 26% (OR 1.26, 95% CI 1.15–1.39,  $P < 0.00001$ ), and no heterogeneity ( $P = 0.44$ ,  $I^2 = 0\%$ ).

Among six studies of digit anomalies (missing, fused or extra fingers or toes; 14 150 malformed cases, 7.6 million controls), two were each significant, and the pooled OR is 1.18 (95% CI 0.99–1.41); Supplementary data, Table S5 and Fig. 2d.



**Figure 3** Forest plots for (a) facial defects, (b) eye defects only, and (c) cleft lip or palate. Studies are ranked according to size of the odds ratio.

Among 12 studies of clubfoot (15 673 malformed cases, 6.6 million controls) seven were statistically significant, but one with a decreased risk. Four reported evidence of a dose–response relationship (Alderman *et al.*, 1991; Honein *et al.*, 2001; Skelly *et al.*, 2002; Parker *et al.*, 2009). The pooled excess risk is 28% (OR 1.28, 95% CI 1.10–1.47,  $P = 0.0009$ ); Supplementary data, Table S6 and Fig. 2e. However, examination of the five statistically significant positive studies suggests that the effect could be greater ( $\geq 40\%$ ).

Four studies of diaphragmatic hernia did not show an association with maternal smoking; Supplementary data, Table S7 and Fig. S2. The pooled OR is 0.94 ( $P = 0.63$ ).

Craniosynostosis is where sutures of the skull have fused prematurely, deforming the shape of the head. Of the five studies (1 131 malformed cases, 1.4 million controls), three were each significant, with evidence of a dose–response relationship (Alderman *et al.*, 1994; Kallen, 1999; Honein and Rasmussen, 2000); Supplementary data, Table S8 and Fig. 2f. The pooled OR is 1.33 (95% CI 1.03–1.73,  $P = 0.03$ ), with no heterogeneity ( $P = 0.09$ ).

### Facial defects (face, eyes or ears)

Twelve studies together show a 19% increased risk of a facial defect (OR 1.19, 95% CI 1.06–1.35,  $P = 0.004$ ), excluding orofacial clefts, and seven were each significant; Supplementary data, Table S9 and Fig. 3a (5876 malformed cases, 2.6 million controls). Two reported evidence of a dose–response relationship (Chew *et al.*, 1994; Tornqvist *et al.*, 2002). When results for eye defects only were examined (e.g. anophthalmia, microphthalmia, esotropia, exotropia and optic nerve hypoplasia), the excess risk is 25% (OR 1.25, 95% CI 1.11–1.40,  $P = 0.0001$ ); Supplementary data, Table S10 and Fig. 3b. Five

of the nine studies on eye defects (4541 malformed cases, 2.3 million controls) were each significant, and one reported evidence of a dose–response relationship (Chew *et al.*, 1994).

Thirty-eight studies have examined the risk of cleft lip or palate (23 441 malformed cases, 8.1 million controls), and 13 were each significant. The pooled OR is 1.28 (95% CI 1.20–1.36,  $P < 0.00001$ ); Supplementary data, Table S11 and Fig. 3c. Six reported evidence of a dose–response relationship (Khoury *et al.*, 1987; Shaw *et al.*, 1996a; Chung *et al.*, 2000; Honein *et al.*, 2001; Little *et al.*, 2004; Shi *et al.*, 2007). The effects of cleft lip and palate were not separated because a previous systematic review (25 cohort and case–control studies) indicated that the risks are not too dissimilar: pooled ORs were 1.34 (95% CI 1.25–1.44) for cleft lip, with or without cleft palate, and 1.22 (95% CI 1.10–1.35) for cleft palate alone (Little *et al.*, 2004).

### Defects of the gastrointestinal system

Gastrointestinal defects include abdominal wall defects and a range of abnormalities of the pharynx, oesophagus, intestine, colon, bile ducts, gallbladder and liver. Although there are 35 studies in the meta-analysis (11 580 malformed cases, 9.7 million controls), the degree of heterogeneity was not great ( $P = 0.02$ ,  $I^2 = 36\%$ ); Supplementary data, Table S12 and Fig. 4a. One reported evidence of a dose–response relationship (Chung and Myrianthopoulos, 1975). The excess risk is 27% (OR 1.27, 95% CI 1.18–1.36,  $P < 0.00001$ ); or OR = 1.22 (95% CI 1.14–1.31) excluding gastroschisis/omphalocele.

Five specific types of defect could be reliably examined. There is a clear association with gastroschisis, OR 1.50 (95% CI 1.28–1.76), and

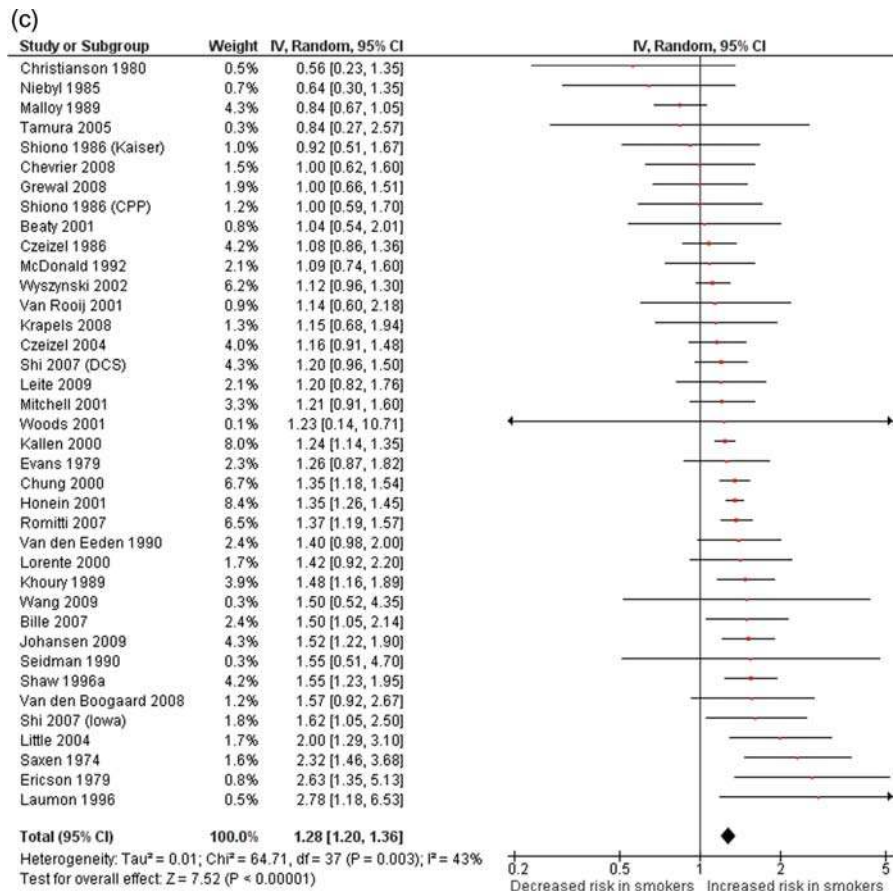


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$P < 0.00001$ , from 12 studies (1822 malformed cases, 2.68 million controls); Supplementary data, Table S13, Fig. 4b). All but one showed an increased risk, and five studies were each significant. The effect on omphalocele is less and not statistically significant, OR 1.19 (95% CI 0.95–1.48), and  $P = 0.14$  from seven studies; Supplementary data, Table S14 and Fig. S3.

There is an association with anal atresia (OR 1.20, 95% CI 1.06–1.36, and  $P = 0.005$ , from seven studies (1679 malformed cases, 7.8 million controls); Supplementary data, Table S15, Fig. 4c, and umbilical/inguinal/ventral hernias, OR 1.40 (95% CI 1.23–1.59, and  $P < 0.00001$ ) from four studies, 941 malformed cases and 374 086 controls; Supplementary data, Table S16, Fig. 4d. All four studies of hernias showed an increased risk. There is no evidence for oesophageal atresia/tracheoesophageal fistula, OR 0.93 (95% CI 0.81–1.07 and  $P = 0.32$ ) from seven studies, Supplementary data, Table S17 and Fig. S4.

### Defects of the genitourinary system

These defects included those of the genital organs, urinary bladder, kidney, ureter and urethra. When considered together, there does not seem to be a clear association with maternal smoking, OR 1.05 (95% CI 0.98–1.12, and  $P = 0.20$ ), from 40 studies, with 24 081 malformed controls and 8.2 million controls; Supplementary data, Table S18, Fig. 4e. An analysis of non-specific genitourinary defects produced

an OR of 1.02 95% CI 0.91–1.14; which became 0.93 (95% CI 0.84–1.04) when based only on studies that had at least 1-year follow-up during which cases were ascertained. The OR for the genital system alone is 1.01, 95% CI 0.93–1.10,  $P = 0.76$  (based on 32 studies; Supplementary data, Table S19 and Fig. S5).

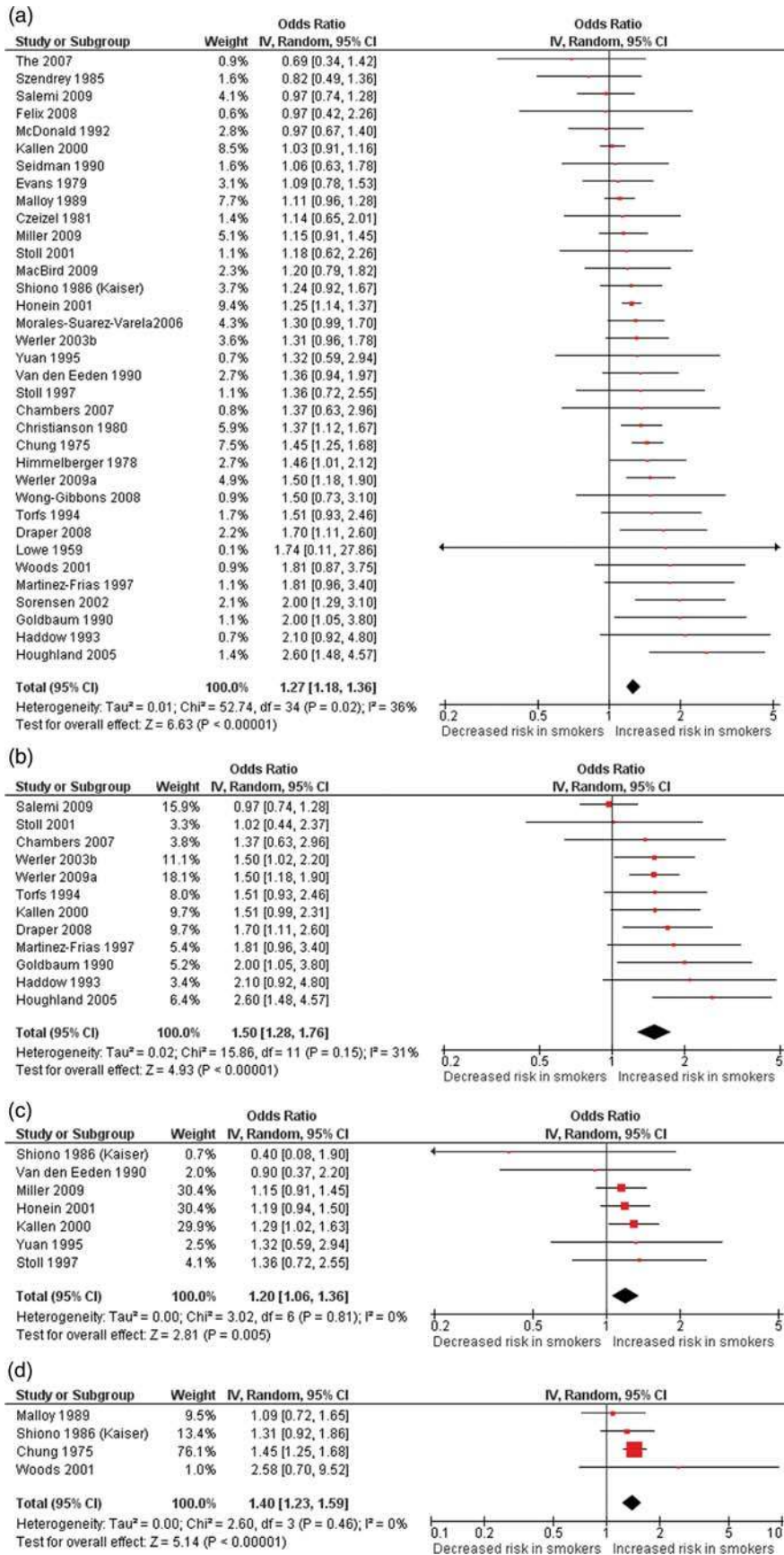
The OR for cryptorchidism (undescended testes), based on 18 studies (8753 malformed cases, 98 627 controls) is 1.13 (95% CI 1.02–1.25,  $P = 0.02$ ); Supplementary data, Table S20, Fig. 4f.

There is a reduction in risk for hypospadias (abnormal urethra), based on 15 studies (12 047 malformed cases and 1.5 million controls); OR 0.90 (95% CI 0.85–0.95,  $P = 0.0004$ ), with little heterogeneity,  $P = 0.28$  and  $I^2 = 16\%$ . Two of the 15 studies on hypospadias were significant (Supplementary data, Table S21 and Fig. S6).

The pooled OR is 1.15, 95% CI 0.95–1.39, for renal/urinary tract defects, which is not statistically significant ( $P = 0.15$  from 9 studies, 3330 malformed cases and 7.7 million controls; Supplementary data, Table S22 and Fig. S7).

### Defects of the CNS

When all CNS defects were considered together, there seems to be a modest excess risk; OR 1.10 (95% CI 1.01–1.19,  $P = 0.02$ ); Supplementary data, Table S23 and Fig. S8a. Seven of the 29 studies (14 739 malformed cases, 8.2 million controls) were each significant,



**Figure 4** Forest plots for (a) all gastrointestinal defects (Kelsey 1978 had no standard error, OR = 1.55), (b) gastroschisis, (c) anal atresia, (d) umbilical/ventral/inguinal hernias, (e) all genitourinary defects, and (f) cryptorchidism. Studies are ranked according to size of the odds ratio.



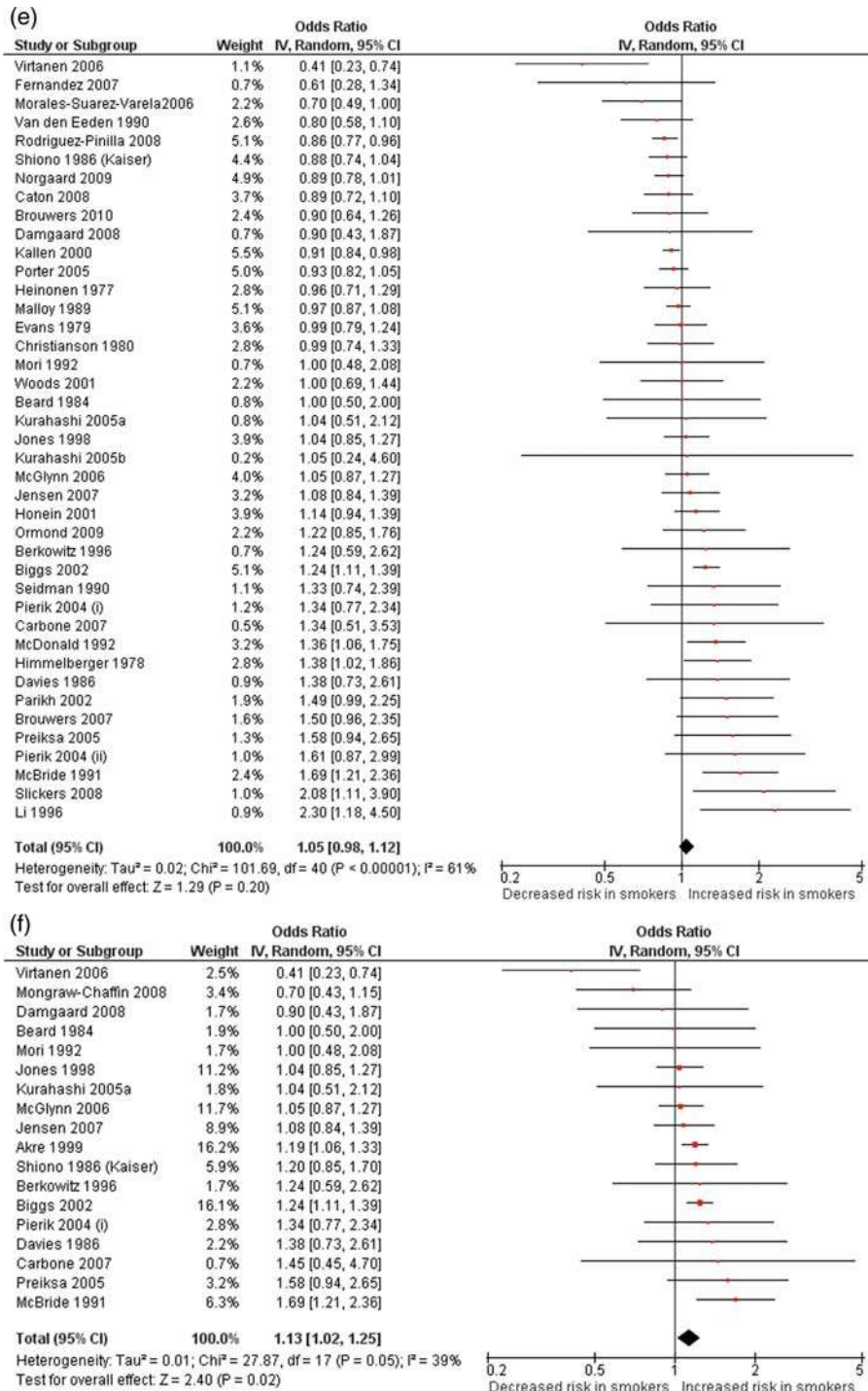


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one with a decreased risk. However, among 17 studies of spina bifida and anencephaly (the most common CNS defects) there is no evidence of an association (5910 malformed cases, 7.9 million controls); OR 0.97, 95% CI 0.86–1.10, and  $P = 0.66$ ; Supplementary data, Table S24 and Fig. S8b. While it is possible that there may be an effect of maternal smoking on some CNS defects, the evidence is not sufficiently clear.

### Defects of the respiratory system and skin

There were six studies of defects of the respiratory system, i.e. nasal passage, larynx and lungs (633 malformed cases, 415 653 controls). The OR is 1.11, 95% CI 0.95–1.30, but not significant,  $P = 0.18$ ; Supplementary data, Table S25 and Fig. S9. There is a clear reduction in risk for defects of the skin (e.g. pigmentation disorders and moles) among five studies (3789 malformed cases, 386 576 controls). All

showed a decreased risk and two were each significant. The pooled OR is 0.82, 95% CI 0.75–0.89 ( $P < 0.00001$ ), with little heterogeneity ( $I^2 = 0\%$ ); Supplementary data, Table S26 and Fig. S10.

## All congenital abnormalities considered together

There are 38 studies in which the OR for all birth defects combined was reported (67 716 malformed cases, 2.2 million controls). Only five were each significant, one of which had a decreased risk. The pooled OR of 1.01 (95% CI 0.96–1.07) suggests no effect; Supplementary data, Table S27 and Fig. S11. Initially, this seems inconsistent with the sections above. However, while smoking is positively associated with several disorders (and sometimes only modestly), it also appears to be protective for hypospadias and skin defects, and there is probably no effect on diaphragmatic hernia, genital defects (except cryptorchidism), and defects of the CNS, renal/urinary tract and respiratory systems. Furthermore, maternal smoking is not associated with chromosomal disorders such as Down syndrome (Rudnicka et al., 2002), but studies often include these when reporting on all abnormalities. Therefore, by examining all defects together a diluted effect is expected. By applying the pooled ORs estimated for each body system to the distribution of types of birth defects (ONS, 2010) and assuming a maternal smoking prevalence of 17% (ONS, 2006), an OR of about 1.10 is expected. This assumes that an affected case has only one defect, but there is evidence that women who smoke are more likely to have a baby with  $\geq 2$  defects: excess risks 15% (Kallen, 2000), 19% (Yushkiv et al., 2005) and 61% (Bitsko et al., 2007), compared with non-smokers. Therefore, to allow for 'double counting', the OR for all defects together is probably between 1.05 and 1.10. Most studies would be underpowered to detect this effect size. Furthermore, under-reporting bias in retrospective studies might be more likely to influence an OR as low as 1.05–1.10. The pooled OR among the three largest prospective studies, each with  $>2000$  cases (Kallen 2000; Queisser-Luft et al., 2002; Morales-Suarez et al., 2006) was 1.04 (95% CI 1.01–1.07), consistent with expectation.

## Study quality, heterogeneity and publication bias

The pooled ORs where smoking status was obtained prospectively were similar to those given above, e.g. cardiovascular disease (OR 1.14 versus 1.09 based on all studies), limb reduction defects (OR 1.28 versus 1.26), gastrointestinal defects (OR 1.38 versus 1.27), gastroschisis (OR 1.65 versus 1.50) and oral clefts (OR 1.24 versus 1.28). The main concern is adjustment for confounding, another indicator of study quality. Supplementary data, Table S1 compares the pooled ORs from the main analysis with those only based on studies that allowed for potential confounders (by including them as matching variables in case-control studies, or in the statistical analysis). The ORs were similar, and those that were statistically significant remained so, indicating that the effect of confounding was minimal. Pooled ORs only from studies that allowed for at least maternal age and alcohol use (perhaps the two most important potential confounders) were also examined. The point estimates were again generally similar to those given in the sections above, e.g. cardiovascular disease (OR 1.20 versus 1.09), limb reduction defects (OR 1.30 versus 1.26), oral

clefts (OR 1.40 versus 1.28), gastrointestinal defects (OR 1.30 versus 1.27), gastroschisis (OR 1.50 versus 1.50), cryptorchidism (OR 1.12 versus 1.13), hypospadias (OR 0.87 versus 0.90) and skin defects (OR 0.82 versus 0.82). Sometimes, adjusted estimates were not reported, but the authors stated that the results were similar to the unadjusted ones. Recreational drug use was not often measured, and so could not be reliably addressed.

There is some evidence that folic acid or other multivitamins could reduce the birth prevalence of defects other than of the neural tube (Czeizel, 2005), though the evidence is not consistent (Bower et al., 2006). Multivitamins would be a potential confounder if non-smoking women were more likely to use them than smokers and multivitamins were protective for many defects, because this could create a spurious association between smoking and birth defects. Few studies included in our meta-analyses adjusted for peri-conceptual multivitamin use (including folic acid), but those that did still reported an increased risk for maternal smoking (e.g. Malik et al., 2008 for cardiovascular disease, Wasserman et al., 1996 for limb reduction defects, and Van Rooij et al., 2001 and Shi et al., 2007 for orofacial clefts). Similarly, if there was a significant confounding effect of multivitamin use, looking only at studies that recruited subjects after say 1992 should produce a clear excess risk for all defects. However, when we did this, the pooled OR was only 1.06 (compared with 1.01 for all studies).

There was evidence of significant heterogeneity for some defects/body systems but not all. For cardiovascular defects and orofacial clefts, the test for heterogeneity became non-significant ( $P = 0.48$  and  $P = 0.10$ , respectively) when the subgroup analysis was based on prospective studies only, even though the pooled estimates were not materially different from all studies. There was heterogeneity for all gastrointestinal defects considered together, but not when analysed according to specific sub-type (i.e. gastroschisis, omphalocele, anal atresia and hernias). We could not find factors that explained the heterogeneity for all musculoskeletal defects, but what is of note is that 18 out of 25 studies showed an increased risk, of which eight were each statistically significant. When examining subgroups of musculoskeletal defects the number of studies in the meta-analyses was insufficient to evaluate heterogeneity reliably (for example, digit anomalies, club-foot, facial defects and eye defects).

Publication bias would occur if studies that found little or no association between maternal smoking and birth defects were less likely to be published, so a meta-analysis would be skewed by studies that did find an association. We examined funnel plots for all of the meta-analyses, and none indicated significant asymmetry, which is a sign of publication bias. We therefore concluded that this bias was not present to a material extent. Furthermore, the observation that most studies reported results that were not statistically significant (often interpreted to be a 'negative' study), provides further evidence that studies were likely to be published, regardless of what they found.

## Discussion

This first ever comprehensive systematic review of congenital birth defects shows which are associated with maternal smoking during pregnancy. There are modest effects on digit anomalies, cryptorchidism and defects of the heart and musculoskeletal system (ORs 1.09–1.19); and larger effects (ORs 1.25–1.50) on limb reduction defects,

clubfoot, oral clefts and defects of the eyes and gastrointestinal system (especially gastroschisis and abdominal hernias). These defects should now be referred to by clinicians or other health professionals when providing advice to women planning a pregnancy, or early on in pregnancy.

Maternal smoking appears to have a protective effect for hypospadias and skin defects (ORs 0.82–0.90); not unexpected given that active smoking reduces the risk for some adult disorders (Wald and Hackshaw, 1996).

There is unlikely to be an effect (positive or negative) on defects of the CNS, respiratory and genitourinary (except cryptorchidism and hypospadias) systems.

It is uncertain what proportion of the study populations had ultrasound screening for malformations during pregnancy. This can influence the results when studies are based on live births only because, if widely used, ultrasound can lead to termination of pregnancy for some defects and thus reduce the prevalence at birth. However, it might increase the detection of some internal abnormalities, e.g. cardiac and renal, which could be missed at birth.

The studies were conducted or published between 1959 and 2010 with different designs, so they are expected to be of variable quality. The intention of this review was to be inclusive, and objective assessment of quality was made by subgroup analyses based on features that could be associated with bias or confounding. Women, especially those with an affected baby, could misreport their smoking status when based on self-reports (compared with blood cotinine measurements; Shipton *et al.*, 2009), but this bias would tend to underestimate the ORs. When the meta-analyses only included studies in which smoking status was obtained prospectively, similar pooled ORs were found. Potential confounding does not seem to be an issue; similar point estimates were found when only adjusted ORs were pooled, including allowance for both maternal age and alcohol (some individual studies made the same conclusion). Only English language articles were included in the review. However, examination of non-English language articles for a sample of the publication years did not produce additional studies. Furthermore, we examined 768 full papers and included 177 articles, so any missed studies are likely to have a negligible effect. Follow-up is an important consideration for defects that may not be readily observed at birth, because if too short, then defects could be missed and an association becomes diluted or not detected. Many studies had at least 1-year follow-up, and analysis restricted to such studies (e.g. for cardiovascular or genitourinary defects) produced almost identical pooled ORs.

Much of the literature on the harmful effects of smoking in pregnancy concentrates on other complications, such as fetal death, fetal growth restriction and prematurity. The mechanisms (Werler *et al.*, 1985; Talbot, 2008; Rogers, 2009) are not precisely understood but are thought to include: the vasoconstrictor action of nicotine causing reduced blood flow to the placenta; carbon monoxide binding to haemoglobin so that less oxygen is available for placental and fetal tissues, leading to fetal hypoxia; disruption of vascular neogenesis; and disturbance of endothelial function in the maternal (Quinton *et al.*, 2008) as well as, presumably, in the fetal circulations. How some or all of these mechanisms can cause a variety of congenital malformations is unknown. Abnormal morphogenesis can certainly be produced by toxins and/or hypoxia/ischemia interfering with cell proliferation or migration or both. The timing of such an insult relative to sensitive

or critical periods of organogenesis, which may present only small windows of opportunity (a few days or even hours), combined with different thresholds for damage in fetal tissues, could determine which organ or system is affected. Interaction between constituents of tobacco smoke and other chemicals, particularly recreational drugs, are likely to be quite common. Some of these (e.g. cocaine and dexamphetamine) also have vasoconstrictor actions and may be important in the aetiology of gastroschisis (Morrison *et al.*, 2005) but these data were not collected in most studies so it was not possible to examine the potential confounding effect reliably.

There are several reasons why the associations found are likely to be causal (consistent with the Bradford–Hill criteria for causality). There is biological plausibility, including laboratory experiments, and established harm in children and adults for a wide range of disorders. In many studies (i.e. the prospective ones) we can establish that the exposure (smoking) occurred before the pregnancy outcome. The ORs were statistically significant, and there was an effect after allowing for potential confounders. Although many individual studies did not have sufficient statistical power to reliably examine (and therefore report) dose–response relationships, several found evidence that the risk of the defect of interest increased with increasing cigarette consumption, for the abnormalities for which significant pooled ORs were found. There is a general consistency in the ORs estimated from studies conducted in different geographical regions (where the birth defect prevalence could vary), even though women have different lifestyle habits and medical care, either of which could affect the birth defect prevalence.

Most of the malformations associated with maternal smoking have physical and psychological morbidity for the infant and parents, often lifelong and with significant healthcare service costs for hospitalizations and length of stay (Russo and Elizhauser, 2004; Robbins *et al.*, 2007; Wehby and Cassell, 2010). The estimated total hospital charges for treating the defects for which there are positive associations was ~\$2.1 billion in the USA in 2003 (Robbins *et al.*, 2007). Of this, around \$46 million could be crudely attributed to maternal smoking, after applying population attributable risk proportions (using our estimated ORs and the US smoking prevalence during pregnancy) to the 2003 US costs. Congenital heart defects are a common and serious birth anomaly, and infants often require several operations during their lifetime. Similarly, limb reduction defects, hand and foot anomalies, including clubfoot, and oral clefts are all visible, and despite surgical treatment (sometimes painful), may result in disability. Disorders of the gastrointestinal system also require corrective treatments.

It is worthwhile considering the use of nicotine replacement therapy (NRT) during pregnancy. It is available in several different forms (patches, gum, and spray) and has been shown to be effective in giving up smoking. There is some evidence that it is safe in pregnancy, with respect to stillbirth and fetal growth restriction, and it is being used increasingly, with the support of national guidelines (for example, in the UK). However, there is little information on congenital malformations and a cautious attitude is advisable. The view that NRT is safer than smoking is widely held but of special concern are those women who take NRT and continue to smoke as well, especially in the first trimester.

Further studies could examine in more detail the financial and other healthcare and societal costs for the defects identified here. While the

risk of miscarriage and low birthweight has had some effect on smoking habits, many women still smoke just before and during pregnancy. Other research could be conducted to ascertain whether the risk of lifelong physical abnormalities to the child might encourage more women to quit, especially younger ones. In England and Wales (ONS 2008) the prevalence of a birth defect was 139.8 per 10 000 among women aged <20 years, higher than those aged 30–34 years (116.5 per 10 000). Some of this difference will be related to the much higher smoking prevalence in the younger age group (45%), acknowledging less use of peri-conceptual folic acid (because there are more unplanned pregnancies), and a much lower risk of a chromosomal defect.

In conclusion, maternal smoking in pregnancy is an important risk factor for several major birth defects. These specific defects should be included in public health educational information to encourage more women to quit smoking before or early on in pregnancy, and to particularly target younger women and those from lower socio-economic groups, in which smoking prevalence is greatest.

## Supplementary data

Supplementary data are available at <http://humup.oxfordjournals.org/>.

## Authors' roles

A.H. had the original concept for the study, which was subsequently developed and planned by A.H. and C.R.; S.B. performed the literature searches and analyses, with A.H. All three authors were involved in interpreting the results, writing the paper and approving the final version.

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## References

- Adams MM, Mulinare J, Dooley K. Risk factors for conotruncal cardiac defects in Atlanta. *J Am Coll Cardiol* 1989; **14**:432–442.
- Akre O, Lipworth L, Cnattingius S, Sparen P, Ekbohm A. Risk factor patterns for cryptorchidism and hypospadias. *Epidemiology* 1999; **10**:364–369.
- Alderman BW, Takahashi ER, LeMier MK. Risk indicators for talipes equinovarus in Washington State, 1987–1989. *Epidemiology* 1991; **2**:289–292.
- Alderman BV, Bradley CM, Greene C, Fernbach SK, Baron AE. Increased risk of craniosynostosis with maternal cigarette smoking during pregnancy. *Teratology* 1994; **50**:13–18.
- Ananjevic–Pandey J, Jarebinski M, Kastratovic B, Vlajinac H, Radojkovic Z, Brankovic D. Case–control study of congenital malformations. *Eur J Epidemiol* 1992; **8**:871–874.
- Aro T. Maternal diseases, alcohol consumption and smoking during pregnancy associated with reduction limb defects. *Early Hum Dev* 1983; **9**:49–57.
- Batra M, Heike CL, Phillips RC, Weiss NS. Geographic and occupational risk factors for ventricular septal defects: Washington State, 1987–2003. *Arch Pediatr Adolesc Med* 2007; **161**:89–95.
- Beard CM, Melton LJ, O'Fallon WM, Noller KL, Benson RC. Cryptorchidism and maternal estrogen exposure. *Am J Epidemiol* 1984; **120**:707–716.
- Beaty TH, Wang H, Hetmanski JB, Fan YT, Zeiger JS, Liang KY, Chiu YF, Vanderkolk CA, Seifert KC, Wulfsberg EA et al. A case–control study of nonsyndromic oral clefts in Maryland. *Ann Epidemiol* 2001; **11**:434–442.
- Bell R, Lumley J. Alcohol consumption, cigarette smoking and fetal outcome in Victoria, 1985. *Community Health Stud* 1989; **13**:484–491.
- Berkowitz GS, Lapinski RH. Risk factors for cryptorchidism: a nested case–control study. *Paediatr Perinat Epidemiol* 1996; **10**:39–51.
- Biggs ML, Baer A, Critchlow CW. Maternal, delivery, and perinatal characteristics associated with cryptorchidism: a population–based case–control study among births in Washington State. *Epidemiology* 2002; **13**:197–204.
- Bille C, Olsen J, Vach W, Knudsen VK, Olsen SF, Rasmussen K, Murray JC, Andersen AM, Christensen K. Oral clefts and life style factors—a case–cohort study based on prospective Danish data. *Eur J Epidemiol* 2007; **22**:173–181.
- Bitsko RH, Reefhuis J, Romitti PA, Moore CA, Honein MA. Periconceptional consumption of vitamins containing folic acid and risk for multiple congenital anomalies. *Am J Med Genet A* 2007; **143A**:2397–2405.
- Blanco Munoz J, Lacasana M, Borja Aburto VH, Torres Sanchez LE, Garcia Garcia AM, Lopez Carrillo L. Socioeconomic factors and the risk of anencephaly in a Mexican population: a case–control study. *Public Health Rep* 2005; **120**:39–45.
- Blatter BM, Roeleveld N, Zielhuis GA, Gabreels FJ, Verbeek AL. Maternal occupational exposure during pregnancy and the risk of spina bifida. *Occup Environ Med* 1996; **53**:80–86.
- Botto LD, Lynberg MC, Erickson JD. Congenital heart defects, maternal febrile illness, and multivitamin use: a population–based study. *Epidemiology* 2001; **12**:485–490.
- Bower C, Miller M, Payne J, Serna P. Folate intake and the primary prevention of non–neural birth defects. *Aust N Z J Public Health* 2006; **30**:258–261.
- Brouwers MM, Feitz WF, Roelofs LA, Kiemeny LA, de Gier RP, Roeleveld N. Risk factors for hypospadias. *Eur J Pediatr* 2007; **166**:671–678.
- Brouwers MM, van der Zanden LF, de Gier RP, Barten EJ, Zielhuis GA, Feitz WF, Roeleveld N. Hypospadias: risk factor patterns and different phenotypes. *BJU Int* 2010; **105**:254–262.
- British Medical Association (BMA). *Smoking and Reproductive Life: The Impact of Smoking on Sexual, Reproductive and Child Health*. London: BMA, 2004.
- Butler NR, Alberman ED, (eds). *Perinatal Problems: The second report of the 1958 British Perinatal Mortality Survey*. Edinburgh & London: E&S Livingstone Ltd; 1969.
- Carbone P, Giordano F, Nori F, Mantovani A, Taruscio D, Lauria L, Figà-Talamanca I. The possible role of endocrine disrupting chemicals in the aetiology of cryptorchidism and hypospadias: a population–based case–control study in rural Sicily. *Int J Androl* 2007; **30**:3–13.
- Cardy AH, Barker S, Chesney D, Sharp L, Maffulli N, Miedzybrodzka Z. Pedigree analysis and epidemiological features of idiopathic congenital talipes equinovarus in the United Kingdom: a case–control study. *BMC Musculoskelet Disord* 2007; **8**:62.
- Carmichael SL, Shaw GM. Maternal life event stress and congenital anomalies. *Epidemiology* 2000; **11**:30–35.
- Carmichael SL, Nelson V, Shaw GM, Wasserman CR, Croen LA. Socio–economic status and risk of conotruncal heart defects and orofacial clefts. *Paediatr Perinat Epidemiol* 2003; **17**:264–271.
- Carmichael SL, Ma C, Rasmussen SA, Honein MA, Lammer EJ, Shaw GM. Craniosynostosis and maternal smoking. *Birth Defects Res* 2008; **82**:78–85.
- Caton AR, Bell EM, Druschel CM, Werler MM, Mitchell AA, Browne ML, McNutt LA, Romitti PA, Olney RS, Correa A. Maternal hypertension, antihypertensive medication use, and the risk of severe hypospadias. *Birth Defects Res* 2008; **82**:34–40.
- Chambers CD, Chen BH, Kalla K, Jernigan L, Jones KL. Novel risk factor in gastroschisis: change of paternity. *Am J Med Genet A* 2007; **143**:653–659.
- Chevrier C, Bahuau M, Perret C, Iovannisci DM, Nelva A, Herman C, Vazquez MP, Francannet C, Robert–Gnansia E, Lammer EJ, Cordier S. Genetic susceptibilities in the association between maternal exposure to tobacco smoke and the risk of nonsyndromic oral cleft. *Am J Med Genet A* 2008; **146A**:2396–2406.
- Chew E, Remaley NA, Tamboli A, Zhao J, Podgor MJ, Klebanoff M. Risk factors for esotropia and exotropia. *Arch Ophthalmol* 1994; **112**:1349–1355.
- Christianson RE. The relationship between maternal smoking and the incidence of congenital anomalies. *Am J Epidemiol* 1980; **112**:684–695.
- Chung CS, Myrianthopoulos NC. Factors affecting risks of congenital malformations. I. Analysis of epidemiologic factors in congenital malformations. Report from the Collaborative Perinatal Project. *Birth Defects: Orig Artic Ser* 1975; **11**:1–22.
- Chung KC, Kowalski CP, Kim HM, Buchman SR. Maternal cigarette smoking during pregnancy and the risk of having a child with cleft lip/palate. *Plast Reconstr Surg* 2000; **105**:485–491.
- Cordier S, Ha MC, Ayme S, Goujard J. Maternal occupational exposure and congenital malformations. *Scand J Work, Environ Health* 1992; **18**:11–17.

- Correy JF, Newman NM, Collins JA, Burrows EA, Burrows RF, Curran JT. Use of prescription drugs in the first trimester and congenital malformations. *Aust NZ J Obstet Gynaecol* 1991;**31**:340–344.
- Croen LA, Shaw GM, Lammer EJ. Risk factors for cytogenetically normal holoprosencephaly in California: a population-based case-control study. *Am J Med Genet* 2000; **90**:320–325.
- Czeizel A, Vitez M. Etiological study of omphalocele. *Hum Genet* 1981;**58**:390–395.
- Czeizel A. The primary prevention of birth defects: multivitamins or folic acid? *Int J Med Sci* 2005; **1**: 50–61.
- Czeizel A, Nagy E. A recent aetiological study on facial clefting in Hungary. *Acta Paediatr Hung* 1986;**27**:145–166.
- Czeizel AE, Kodaj I, Lenz W. Smoking during pregnancy and congenital limb deficiency. *BMJ* 1994;**308**:1473–1476.
- Czeizel AE, Petik D, Puho E. Smoking and alcohol drinking during pregnancy. The reliability of retrospective maternal self-reported information. *Cent Eur J Public Health* 2004;**12**:179–183.
- da Silva Costa CM, da Gama SGN, do Carmo Leal M. Congenital malformations in Rio de Janeiro, Brazil: prevalence & associated factors. *Cad Saude Publica* 2006; **22**:2423–2431.
- Damgaard IN, Jensen TK; Nordic Cryptorchidism Study Group, Petersen JH, Skakkebaek NE, Toppari J, Main KM. Risk factors for congenital cryptorchidism in a prospective birth cohort study. *PLoS ONE [Electronic Resource]* 2008;**3**: e3051.
- Davies TW, Williams DR, Whitaker RH. Risk factors for undescended testis. *Int J Epidemiol* 1986;**15**:197–201.
- DiFranza JR, Lew RA. Effect of maternal cigarette smoking on pregnancy complications and sudden infant death syndrome. *J Fam Pract* 1995;**40**: 385–394.
- Draper ES, Rankin J, Tonks A, Boyd P, Wellesley D, Tucker D, Budd J; BINOCAR Management Committee. Recreational drug use: a major risk factor for gastroschisis? *Am J Epidemiol* 2008 Feb 15;**167**:485–491.
- Ericson A, Kallen B, Westerholm P. Cigarette smoking as an etiologic factor in cleft lip and palate. *Am J Obstet Gynecol* 1979;**135**:348–351.
- Erickson JD. Risk factors for birth defects: data from the Atlanta Birth Defects Case-Control Study. *Teratology* 1991;**43**:41–51.
- Evans DR, Newcombe RG, Campbell H. Maternal smoking habits and congenital malformations: a population study. *Br Med J* 1979;**2**:171–173.
- Fedrick J, Alberman ED, Goldstein H. Possible Teratogenic Effect of Cigarette Smoking. *Nature* 1971;**231**:529–530.
- Felix JF, van Dooren MF, Klaassens M, Hop WC, Torfs CP, Tibboel D. Environmental factors in the etiology of esophageal atresia and congenital diaphragmatic hernia: results of a case-control study. *Birth Defects Res* 2008; **82**:98–105.
- Ferencz C, Loffredo CA, Correa-Villasenor A. *Genetic and Environmental Risk Factors of Major Cardiovascular Malformations: The Baltimore-Washington Infant Study 1981–1989*. Armonk, New York: Futura Publishing Co., 1997.
- Fernandez MF, Olmos B, Granada A, López-Espinosa MJ, Molina-Molina JM, Fernandez JM, Cruz M, Olea-Serrano F, Olea N. Human exposure to endocrine-disrupting chemicals and prenatal risk factors for cryptorchidism and hypospadias: a nested case-control study. *Environ Health Perspect* 2007; **115**(Suppl 1):8–14.
- Garcia AM, Fletcher T, Benavides FG, Orts E. Parental agricultural work and selected congenital malformations. *Am J Epidemiol* 1999;**149**:64–74.
- Goldbaum G, Daling J, Milham S. Risk factors for gastroschisis. *Teratology* 1990; **42**:397–403.
- Golding J, Butler NR. Maternal smoking and anencephaly. *Br Med J Clin Res Ed* 1983; **287**:533–534.
- Grewal J, Carmichael SL, Ma C, Lammer EJ, Shaw GM. Maternal periconceptional smoking and alcohol consumption and risk for select congenital anomalies. *Birth Defects Res* 2008;**82**:519–526.
- Haddow JE, Palomaki GE, Holman MS. Young maternal age and smoking during pregnancy as risk factors for gastroschisis. *Teratology* 1993;**47**:225–228.
- Hakim RB, Tielsch JM. Maternal cigarette smoking during pregnancy. A risk factor for childhood strabismus. *Arch Ophthalmol* 1992;**110**:1459–1462.
- Hearley CD, Harris JA, Usatin MS, Epstein DM, Ury HK, Neutra RR. Investigation of a cluster of anencephaly and spina bifida. *Am J Epidemiol* 1984;**120**:559–564.
- Heinonen OP. *Birth Defects and Drugs in Pregnancy*: Publishing Sciences Group, Inc.; 1977.
- Hemminki K, Mutanen P, Saloniemi I, Luoma K. Congenital malformations and maternal occupation in Finland: multivariate analysis. *J Epidemiol Community Health* 1981;**35**:5–10.
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–560.
- Himmelberger DU, Brown BW Jr., Cohen EN. Cigarette smoking during pregnancy and the occurrence of spontaneous abortion and congenital abnormality. *Am J Epidemiol* 1978;**108**:470–479.
- Honein MA, Paulozzi LJ, Moore CA. Family history, maternal smoking, and clubfoot: an indication of a gene-environment interaction. *Am J Epidemiol* 2000a; **152**:658–665.
- Honein MA, Rasmussen SA. Further evidence for an association between maternal smoking and craniosynostosis. *Teratology* 2000b;**62**:145–146.
- Honein MA, Paulozzi LJ, Watkins ML. Maternal smoking and birth defects: validity of birth certificate data for effect estimation. *Public Health Rep* 2001;**116**:327–335.
- Houglund KT, Hanna AM, Meyers R, Null D. Increasing prevalence of gastroschisis in Utah. *J Pediatr Surg* 2005;**40**:535–540.
- Hwang SJ, Beaty TH, Panny SR, Street NA, Joseph JM, Gordon S, McIntosh I, Francomano CA. Association study of transforming growth factor alpha (TGF alpha) TaqI polymorphism and oral clefts: indication of gene-environment interaction in a population-based sample of infants with birth defects. *Am J Epidemiol* 1995;**141**:629–636.
- Jensen MS, Toft G, Thulstrup AM, Bonde JP, Olsen J. Cryptorchidism according to maternal gestational smoking. *Epidemiology* 2007;**18**:220–225.
- Johansen AM, Wilcox AJ, Lie RT, Andersen LF, Drevon CA. Maternal consumption of coffee and caffeine-containing beverages and oral clefts: a population-based case-control study in Norway. *Am J Epidemiol* 2009;**169**:1216–1222.
- Jones ME, Swerdlow AJ, Griffith M, Goldacre MJ. Prenatal risk factors for cryptorchidism: a record linkage study. *Paediatr Perinat Epidemiol* 1998; **12**:383–396.
- Kallen B, Winberg J. An epidemiological study of hypospadias in Sweden. *Acta Paediatr Scand Suppl* 1982;**293**:1–21.
- Kallen K. Maternal smoking and craniosynostosis. *Teratology* 1999;**60**:146–150.
- Kallen K. Multiple malformations and maternal smoking. *Paediatr Perinat Epidemiol* 2000;**14**:227–233.
- Kallen K. Role of maternal smoking and maternal reproductive history in the etiology of hypospadias in the offspring. *Teratology* 2002;**66**:185–191.
- Kelsey JL, Dwyer T, Holford TR, Bracken MB. Maternal smoking and congenital malformations: an epidemiological study. *J Epidemiol Community Health* 1978; **32**:102–107.
- Khoury MJ, Weinstein A, Panny S, Holtzman NA, Lindsay PK, Farrel K, Eisenberg M. Maternal cigarette smoking and oral clefts: a population-based study. *Am J Public Health* 1987;**77**:623–625.
- Khoury MJ, Gomez-Farias M, Mulinare J. Does maternal cigarette smoking during pregnancy cause cleft lip and palate in offspring? *Am J Dis Child* 1989; **143**:333–337.
- Krapels IP, Rajmakers-Eichhorn J, Peters WH, Roelofs HM, Ras F, Steegers-Theunissen RP; Eurocran Gene-Environment Interaction Group. The I105V polymorphism in glutathione S-transferase P1, parental smoking and the risk for nonsyndromic cleft lip with or without cleft palate. *Eur J Hum Genet* 2008; **16**:358–366.
- Krauss MJ, Morrissey AE, Winn HN, Amon E, Leet TL. Microcephaly: an epidemiologic analysis. *Am J Obstet Gynecol* 2003;**188**:1484–1489; discussion 9–90.
- Kricker A, Elliott JW, Forrest JM, McCredie J. Congenital limb reduction deformities and use of oral contraceptives. *Am J Obstet Gynecol* 1986;**155**:1072–1078.
- Kullander S, Kallen B. A Prospective Study of Smoking and Pregnancy. *Acta Obstet Gynec Scand* 1971;**50**:83–94.
- Kurahashi N, Kasai S, Shibata T, Kakizaki H, Nonomura K, Sata F, Kishi R. Parental and neonatal risk factors for cryptorchidism. *Med Sci Monit* 2005a; **11**:CR274–CR283.
- Kurahashi N, Sata F, Kasai S, Shibata T, Moriya K, Yamada H, Kakizaki H, Minakami H, Nonomura K, Kishi R. Maternal genetic polymorphisms in CYP1A1, GSTM1 and GSTT1 and the risk of hypospadias. *Mol Hum Reprod* 2005b;**11**:93–98.
- Laumon B, Martin JL, Collet P, Bertucat I, Verney MP, Robert E. Exposure to organic solvents during pregnancy and oral clefts: a case-control study. [Erratum appears in *Reprod Toxicol* 1996 May-Jun;10(3):vi]. *Reprod Toxicol* 1996;**10**:15–19.

- Leite IC, Koiffman S. Oral clefts, consanguinity, parental tobacco and alcohol use: a case-control study in Rio de Janeiro, Brazil. *Pesqui Odontol Bras* 2009; **23**:31-37.
- Li DK, Mueller BA, Hickok DE, Daling JR, Fantel AG, Checkoway H, Weiss NS. Maternal smoking during pregnancy and the risk of congenital urinary tract anomalies. *Am J Public Health* 1996;**86**:249-253.
- Lieff S, Olshan AF, Werler M, Strauss RP, Smith J, Mitchell A. Maternal cigarette smoking during pregnancy and risk of oral clefts in newborns. *Am J Epidemiol* 1999;**150**:683-694.
- Linn S, Schoenbaum SC, Monson RR, Rosner B, Stubblefield PG, Ryan KJ. Lack of association between contraceptive usage and congenital malformations in offspring. *Am J Obstet Gynecol* 1983;**147**:923-928.
- Little J, Cardy A, Arslan MT, Gilmour M, Mossey PA. Smoking and orofacial clefts: a United Kingdom-based case-control study. *Cleft Palate Craniofac J* 2004; **41**:381-386.
- Little J, Cardy A, Munger RG. Tobacco smoking and oral clefts: a meta-analysis. *Bull World Health Organ* 2004;**82**:213-218.
- Liu S, Liu J, Tang J, Ji J, Chen J, Liu C. Environmental risk factors for congenital heart disease in the Shandong Peninsula, China: a hospital-based case-control study. *J Epidemiol* 2009;**19**:122-130.
- Lorente C, Cordier S, Goujard J, Aymé S, Bianchi F, Calzolari E, De Walle HE, Knill-Jones R. Tobacco and alcohol use during pregnancy and risk of oral clefts. *Am J Public Health* 2000;**90**:415-419.
- Lowe CR. Effect of mothers' smoking habits on birth weight of their children. *Br Med J* 1959;**2**:673-676.
- Lubs ML. Racial differences in maternal smoking effects on the newborn infant. *Am J Obstet Gynecol* 1973;**115**:66-76.
- Lumley J, Correy JF, Newman NM, Curran JT. Cigarette smoking, alcohol consumption and fetal outcome in Tasmania 1981-82. *Aust N Z J Obstet Gynaecol* 1985;**25**:33-40.
- Mac Bird T, Robbins JM, Druschel C, Cleves MA, Yang S, Hobbs CA. Demographic and environmental risk factors for gastroschisis and omphalocele in the National Birth Defects Prevention Study. *J Pediatr Surg* 2009;**44**:1546-1551.
- Malik S, Cleves MA, Honein MA, Romitti PA, Botto LD, Yang S, Hobbs CA. Maternal smoking and congenital heart defects. *Pediatrics* 2008;**121**:e810-e816.
- Malloy MH, Kleinman JC, Bakewell JM, Schramm WF, Land GH. Maternal smoking during pregnancy: no association with congenital malformations in Missouri 1980-83. *Am J Public Health* 1989;**79**:1243-1246.
- Man LX, Chang B. Maternal cigarette smoking during pregnancy increases the risk of having a child with a congenital digital anomaly. *Plast Reconstr Surg* 2006; **117**:301-308.
- Mandiracioglu A, Ulman I, Luleci E, Ulman C. The incidence and risk factors of neural tube defects in Izmir, Turkey: a nested case-control study. *Turk J Pediatr* 2004; **46**:214-220.
- March of Dimes. <http://www.marchofdimes.com/birthdefectsresearch.html> (accessed December 2010).
- Martinez-Frias ML, Rodriguez-Pinilla E, Prieto L. Prenatal exposure to salicylates and gastroschisis: a case-control study. *Teratology* 1997;**56**:241-243.
- McBride ML, Van den Steen N, Lamb CW, Gallagher RP. Maternal and gestational factors in cryptorchidism. *Int J Epidemiol* 1991;**20**:964-970.
- McDonald AD, Armstrong BG, Sloan M. Cigarette, alcohol, and coffee consumption and congenital defects. *Am J Public Health* 1992;**82**:91-93.
- McGlynn KA, Graubard BI, Klebanoff MA, Longnecker MP. Risk factors for cryptorchidism among populations at differing risks of testicular cancer. *Int J Epidemiol* 2006;**35**:787-795.
- Meyer MB, Tonascia JA. Maternal smoking, pregnancy complications, and perinatal mortality. *Am J Obstet Gynecol* 1977;**128**:494-502.
- Miller EA, Manning SE, Rasmussen SA, Reefhuis J, Honein MA, National Birth Defects Prevention Study. Maternal exposure to tobacco smoke, alcohol and caffeine, and risk of anorectal atresia: National Birth Defects Prevention Study 1997-2003. *Paediatr Perinat Epidemiol* 2009;**23**:9-17.
- Mitchell LE, Murray JC, O'Brien S, Christensen K. Evaluation of two putative susceptibility loci for oral clefts in the Danish population. *Am J Epidemiol* 2001; **153**:1007-1015.
- Mongraw-Chaffin ML, Cohn BA, Cohen RD, Christianson RE. Maternal smoking, alcohol consumption, and caffeine consumption during pregnancy in relation to a son's risk of persistent cryptorchidism: a prospective study in the Child Health and Development Studies cohort, 1959-1967. *Am J Epidemiol* 2008;**167**:257-261.
- Morales-Suarez-Varela MM, Bille C, Christensen K, Olsen J. Smoking habits, nicotine use, and congenital malformations. *Obstet Gynecol* 2006;**107**:51-57.
- Mori M, Davies TW, Tsukamoto T, Kumamoto Y, Fukuda K. Maternal and other factors of cryptorchidism—a case-control study in Japan. *Kurume Med J* 1992; **39**:53-60.
- Morrison JJ, Chitty LS, Peebles D, Rodeck CH. Recreational drugs and fetal gastroschisis: maternal hair analysis in the periconceptional period and during pregnancy. *Br J Obstet Gynaecol* 2005;**112**:1022-1025.
- Mygind H, Thulstrup AM, Pedersen L, Larsen H. Risk of intrauterine growth retardation, malformations and other birth outcomes in children after topical use of corticosteroid in pregnancy. *Acta Obstet Gynecol Scand* 2002;**81**:234-239.
- Niebyl JR, Blake DA, Rocco LE, Baumgardner R, Mellits ED. Lack of maternal metabolic, endocrine, and environmental influences in the etiology of cleft lip with or without cleft palate. *Cleft Palate J* 1985;**22**:20-28.
- Nørgaard M, Wogelius P, Pedersen L, Rothman KJ, Sørensen HT. Maternal use of oral contraceptives during early pregnancy and risk of hypospadias in male offspring. *Urology* 2009;**74**:583-587.
- Oddsberg J, Jia C, Nilsson E, Ye W, Lagergren J. Maternal tobacco smoking, obesity, and low socioeconomic status during early pregnancy in the etiology of esophageal atresia. *J Pediatr Surg* 2008;**43**:1791-1795.
- Office for National Statistics (ONS). The Information Centre. Statistics on smoking: England 2006. Office for National Statistics, 2006. <http://www.ic.nhs.uk/pubs/smokingeng2006/report/file>.
- Office for National Statistics (National Congenital Anomaly System). Congenital anomaly statistics: notifications England and Wales 2008 (series MB3 no. 23); 2010.
- Ormond G, Nieuwenhuijsen MJ, Nelson P, Toledano MB, Iszatt N, Geneletti S, Elliott P. Endocrine disruptors in the workplace, hair spray, folate supplementation, and risk of hypospadias: case-control study. *Environ Health Perspect* 2009;**117**:303-307.
- Parikh CR, McCall D, Engelman C, Schrier RW. Congenital renal agenesis: case-control analysis of birth characteristics. *Am J Kidney Dis* 2002 **39**:689-694.
- Parker SE, Mai CT, Strickland MJ, Olney RS, Rickard R, Marengo L, Wang Y, Hashmi SS, Meyer RE. Multistate study of the epidemiology of clubfoot. *Birth Defects Res* 2009;**85**:897-904.
- Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, Correa A: for the National Birth Defects Prevention Network. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol* 2010 Sep 28. <http://www.cdc.gov/ncbddd/features/birthdefects-keyfindings.html>.
- Pierik FH, Burdorf A, Deddens JA, Juttman RE, Weber RF. Maternal and paternal risk factors for cryptorchidism and hypospadias: a case-control study in newborn boys. *Environ Health Perspect* 2004;**112**:1570-1576.
- Porter MP, Faizan MK, Grady RW, Mueller BA. Hypospadias in Washington State: maternal risk factors and prevalence trends. *Pediatrics* 2005;**115**:e495-499.
- Preiksa RT, Zilaitiene B, Matulevicius V, Skakkebaek NE, Petersen JH, Jorgensen N, Toppari J. Higher than expected prevalence of congenital cryptorchidism in Lithuania: a study of 1204 boys at birth and 1 year follow-up. *Hum Reprod* 2005;**20**:1928-1932.
- PRISMA guidelines for reporting meta-analyses of observational studies - <http://www.prisma-statement.org/>
- Quinton AE, Cook CM, Peek MJ. The relationship between cigarette smoking, endothelial function and intrauterine growth restriction in human pregnancy. *BJOG* 2008;**115**:780-784.
- Queisser-Luft A, Stolz G, Wiesel A, Schlaefler K, Spranger J. Malformations in newborn: results based on 30,940 infants and fetuses from the Mainz congenital birth defect monitoring system (1990-1998). *Arch Gynecol Obstet* 2002;**266**:163-167.
- Rantakallio P. Relationship of maternal smoking to morbidity and mortality of the child up to the age of five. *Acta Paediatr Scand* 1978;**67**:621-631.
- Reefhuis J, de Walle HE, Cornel MC. Maternal smoking and deformities of the foot: results of the EUROCAT Study. European Registries of Congenital Anomalies. *Am J Public Health* 1998;**88**:1554-1555.
- REVMAN. Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.
- Robbins JM, Bird TM, Tilford JM, Cleves MA, Hobbs CA. Hospital stays, hospital charges, and in-hospital deaths among infants with selected birth defects - United States, 2003. *Morb Mortal Wkly Rep* 2007;**56**:25-29.

- Robitaille J, Carmichael SL, Shaw GM, Olney RS, National Birth Defects Prevention S. Maternal nutrient intake and risks for transverse and longitudinal limb deficiencies: data from the National Birth Defects Prevention Study, 1997–2003. *Birth Defects Res* 2009;**85**:773–779.
- Rodriguez–Pinilla E, Mejias C, Prieto–Merino D, Fernandez P, Martinez–Frias ML, Group EW. Risk of hypospadias in newborn infants exposed to valproic acid during the first trimester of pregnancy: a case–control study in Spain. *Drug Safety* 2008;**31**:537–543.
- Rogers JM. Tobacco and pregnancy. *Reprod Toxicol* 2009;**28**:152–160.
- Romitti PA, Sun L, Honein MA, Reefhuis J, Correa A, Rasmussen SA. Maternal periconceptional alcohol consumption and risk of orofacial clefts. *Am J Epidemiol* 2007;**166**:775–785.
- Royal College of Physicians. Effects of maternal active and passive smoking on fetal and reproductive health. In: Passive smoking and children. A report by the Tobacco Advisory Group of the Royal College of Physicians, Chapter 3, 40–76. Eds: Britton J, Edwards R. Royal College of Physicians 2010.
- Rudnicka A, Wald NJ, Huttly W, Hackshaw AK. Influence of maternal smoking on the birth prevalence of Down syndrome and on second trimester screening performance. *Prenat Diagn* 2002;**22**:893–897.
- Russo C. A. (Thomson Medstat) and Elixhauser, A. (AHRQ). Hospitalizations for Birth Defects, 2004. HCUP Statistical Brief #24. January 2007. U.S. Agency for Healthcare Research and Quality, Rockville, MD. <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb24.pdf>.
- Salemi JL, Pierre M, Tanner JP, Kornosky JL, Hauser KW, Kirby RS, Carver JD. Maternal nativity as a risk factor for gastroschisis: a population–based study. *Birth Defects Res* 2009;**85**:890–896.
- Saxen I. Cleft lip and palate in Finland: parental histories, course of pregnancy and selected environmental factors. *Int J Epidemiol* 1974;**3**:263–270.
- Schmidt RJ, Romitti PA, Burns TL, Browne ML, Druschel CM, Olney RS. Maternal caffeine consumption and risk of neural tube defects. *Birth Defects Res* 2009;**85**:879–889.
- Seidman DS, Ever–Hadani P, Gale R. Effect of maternal smoking and age on congenital anomalies. *Obstet Gynecol* 1990;**76**:1046–1050.
- Shah NR, Bracken MB. A systematic review and meta–analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. *Am J Obstet Gynecol* 2000;**182**:465–472.
- Shaw GM, Malcoe LH, Swan SH, Cummins SK, Schulman J. Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. *Eur J Epidemiol* 1992;**8**:757–760.
- Shaw GM, Wasserman CR, Lammer EJ, O'Malley CD, Murray JC, Basart AM, Tolarova MM. Orofacial clefts, parental cigarette smoking, and transforming growth factor–alpha gene variants. *Am J Hum Genet* 1996a;**58**:551–561.
- Shaw GM, Velie EM, Morland KB. Parental recreational drug use and risk for neural tube defects. *Am J Epidemiol* 1996b;**144**:1155–1160.
- Shaw GM, Wasserman CR, O'Malley CD, Nelson V, Jackson RJ. Maternal pesticide exposure from multiple sources and selected congenital anomalies. *Epidemiology* 1999;**10**:60–66.
- Shaw GM, Croen LA, Todoroff K, Tolarova MM. Periconceptional intake of vitamin supplements and risk of multiple congenital anomalies. *Am J Med Genet* 2000;**93**:188–193.
- Shi M, Christensen K, Weinberg CR, Romitti P, Bathum L, Lozada A, Morris RW, Lovett M, Murray JC. Orofacial cleft risk is increased with maternal smoking and specific detoxification–gene variants. *Am J Hum Genet* 2007;**80**:76–90.
- Shiono PH, Klebanoff MA, Berendes HW. Congenital malformations and maternal smoking during pregnancy. *Teratology* 1986;**34**:65–71.
- Shipton D, Tappin DM, Vadiveloo T, Crossley JA, Aitken DA, Chalmers J. Reliability of self reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study. *BMJ* 2009;**339**:b4347. doi:10.1136/bmj.b4347.
- Skelly AC, Holt VL, Mosca VS, Alderman BW. Talipes equinovarus and maternal smoking: a population–based case–control study in Washington state. *Teratology* 2002;**66**:91–100.
- Slickers JE, Olshan AF, Siega–Riz AM, Honein MA, Aylsworth AS, National Birth Defects Prevention Study. Maternal body mass index and lifestyle exposures and the risk of bilateral renal agenesis or hypoplasia: the National Birth Defects Prevention Study. *Am J Epidemiol* 2008;**168**:1259–1267.
- Smedts HP, de Vries JH, Rakhshandehroo M, Wildhagen MF, Verkleij–Hagoort AC, Steegers EA, Steegers–Theunissen RP. High maternal vitamin E intake by diet or supplements is associated with congenital heart defects in the offspring. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2009;**116**:416–423.
- Sorensen HT, Norgard B, Pedersen L, Larsen H, Johnsen SP. Maternal smoking and risk of hypertrophic infantile pyloric stenosis: 10 year population based cohort study. *BMJ* 2002;**325**:1011–1012.
- Steinberger EK, Ferencz C, Loffredo CA. Infants with single ventricle: a population–based epidemiological study. *Teratology* 2002;**65**:106–115.
- Stoll C, Alembik Y, Roth MP, Dott B. Risk factors in congenital anal atresias. *Ann Genet* 1997;**40**:197–204.
- Stoll C, Alembik Y, Dott B, Roth MP. Risk factors in congenital abdominal wall defects (omphalocele and gastroschisis): a study in a series of 265,858 consecutive births. *Ann Genet* 2001;**44**:201–208.
- Suarez L, Felkner M, Brender JD, Canfield M, Hendricks K. Maternal exposures to cigarette smoke, alcohol, and street drugs and neural tube defect occurrence in offspring. *Maternal Child Health J* 2008;**12**:394–401.
- Szendrey T, Danyi G, Czeizel A. Etiological study on isolated esophageal atresia. *Hum Genet* 1985;**70**:51–8.
- Talbot P. In vitro assessment of reproductive toxicity of tobacco smoke and its constituents. *Birth Defects Res C Embryo Today* 2008;**84**:61–72.
- Tamura T, Munger RG, Corcoran C, Bacayao JY, Nepomuceno B, Solon F. Plasma zinc concentrations of mothers and the risk of nonsyndromic oral clefts in their children: a case–control study in the Philippines. *Birth Defects Res* 2005;**73**:612–616.
- Targett CS, Ratten GJ, Abell DA, Beischer NA. The Influence of Smoking on Intrauterine Fetal Growth and on Maternal Oestriol Excretion. *Aust N Z J Obstet Gynecol* 1977;**17**:126–130.
- Tata LJ, Lewis SA, McKeever TM, Smith CJ, Doyle P, Smeeth L, Gibson JE, Hubbard RB. Effect of maternal asthma, exacerbations and asthma medication use on congenital malformations in offspring: a UK population–based study. *Thorax* 2008;**63**:981–987.
- The NS, Honein MA, Caton AR, Moore CA, Siega–Riz AM, Druschel CM. Risk factors for isolated biliary atresia, National Birth Defects Prevention Study, 1997–2002. *Am J Med Genet A* 2007;**143A**:2274–2284.
- Tikkanen J, Heinonen OP. Maternal exposure to chemical and physical factors during pregnancy and cardiovascular malformations in the offspring. *Teratology* 1991;**43**:591–600.
- Torfs CP, Velie EM, Oechsli FW, Bateson TF, Curry CJ. A population–based study of gastroschisis: demographic, pregnancy, and lifestyle risk factors. *Teratology* 1994;**50**:44–53.
- Tornqvist K, Ericsson A, Kallen B. Optic nerve hypoplasia: Risk factors and epidemiology. *Acta Ophthalmol Scand* 2002;**80**:300–304.
- Tong VT, Jones JR, Dietz PM, D'Angelo D, Bombard JM. Trends in smoking before, during, and after pregnancy – Pregnancy Risk Assessment Monitoring System (PRAMS), United States, 31 sites, 2000–2005. *Morbidity and mortality weekly report. Centers for Disease Control and Prevention*, 2009;**29**:SS–4.
- Torp–Pedersen T, Boyd HA, Poulsen G, Haargaard B, Wohlfahrt J, Holmes JM, Melbye M. In–utero exposure to smoking, alcohol, coffee, and tea and risk of strabismus. *Am J Epidemiol* 2010;**171**:868–875.
- Tuohy PG, Counsell AM, Geddis DC. The Plunket National Child Health Study: birth defects and sociodemographic factors. *N Z Med J* 1993;**106**:489–492.
- Tuthill DP, Stewart JH, Coles EC, Andrews J, Cartledge PH. Maternal cigarette smoking and pregnancy outcome. *Paediatr Perinat Epidemiol* 1999;**13**:245–253.
- Underwood P, Hester LL, Laffitte T Jr., Gregg KV. The relationship of smoking to the outcome of pregnancy. *Am J Obstet Gynecol* 1965;**91**:270–276.
- US Surgeon General. Department of Health and Human Services, Women and smoking. A report of the US Surgeon General. Rockville: DHHS, 2001.
- US Surgeon General. Department of Health and Human Services, The health consequences of smoking. A report of the US Surgeon General. Rockville: DHHS, 2004.
- US Surgeon General. U.S. Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking–Attributable Disease. A Report of the Surgeon General. Public Health Service. Office of the Surgeon General 2010.
- van den Boogaard MJ, de Costa D, Krapels IP, Liu F, van Duijn C, Sinke RJ, Lindhout D, Steegers–Theunissen RP. The MSX1 allele 4 homozygous child exposed to smoking at periconception is most sensitive in developing nonsyndromic orofacial clefts. *Hum Genet* 2008;**124**:525–534.

- Van den Eeden SK, Karagas MR, Daling JR, Vaughan TL. A case-control study of maternal smoking and congenital malformations. *Paediatr Perinat Epidemiol* 1990;**4**:147–155.
- van Rooij IA, Wegerif MJ, Roelofs HM, Peters WH, Kuijpers-jagtman AM, Zielhuis GA, Merkus HM, Steegers-Theunissen RP. Smoking, genetic polymorphisms in biotransformation enzymes, and nonsyndromic oral clefting: a gene-environment interaction. *Epidemiology* 2001;**12**:502–507.
- van Rooij IA, Groenen PM, van Drongelen M, Te Morsche RH, Peters WH, Steegers-Theunissen RP. Orofacial clefts and spina bifida: N-acetyltransferase phenotype, maternal smoking, and medication use. *Teratology* 2002;**66**:260–266.
- Verkerk PH, Buitendijk SE, Verloove-Vanhorick SP. Differential misclassification of alcohol and cigarette consumption by pregnancy outcome. *Int J Epidemiol* 1994;**23**:1218–1225.
- Virtanen HE, Tapanainen AE, Kaleva MM, Suomi AM, Main KM, Skakkebaek NE, Toppari J. Mild gestational diabetes as a risk factor for congenital cryptorchidism. *J Clin Endocrinol Metab* 2006;**91**:4862–4865.
- Vogt G, Horvath-Puho E, Czeizel AE. A population-based case-control study of isolated primary congenital glaucoma. *Am J Med Genet A* 2006;**140**:1148–1155.
- Wang W, Guan P, Xu W, Zhou B. Risk factors for oral clefts: a population-based case-control study in Shenyang, China. *Paediatr Perinat Epidemiol* 2009;**23**:310–320.
- Wasserman CR, Shaw GM, O'Malley CD, Tolarova MM, Lammer EJ. Parental cigarette smoking and risk for congenital anomalies of the heart, neural tube, or limb. *Teratology* 1996;**53**:261–267.
- Watkins ML, Scanlon KS, Mulinare J, Khoury MJ. Is maternal obesity a risk factor for anencephaly and spina bifida? *Epidemiology* 1996;**7**:507–512.
- Watkins ML, Rasmussen SA, Honein MA, Botto LD, Moore CA. Maternal obesity and risk for birth defects. *Pediatrics* 2003;**111**:1152–1158.
- Werler MM, Mitchell AA, Shapiro S, Werler MM, Mitchell AA, Shapiro S. Demographic, reproductive, medical, and environmental factors in relation to gastroschisis. *Teratology* 1992;**45**:353–360.
- Werler MM, Bower C, Payne J, Serna P. Findings on potential teratogens from a case-control study in Western Australia. *Aust N Z J Obstet Gynaecol* 2003a;**43**:443–447.
- Werler MM, Sheehan JE, Mitchell AA. Association of vasoconstrictive exposures with risks of gastroschisis and small intestinal atresia. *Epidemiology* 2003b;**14**:349–354.
- Werler MM, Mitchell AA, Moore CA, Honein MA, National Birth Defects Prevention Study. Is there epidemiologic evidence to support vascular disruption as a pathogenesis of gastroschisis? *Am J Med Genet A* 2009a;**149A**:1399–1406.
- Werler MM, Starr JR, Cloonan YK, Speltz ML. Hemifacial microsomia: from gestation to childhood. *J Craniofac Surg* 2009b;**20** Suppl 1:664–669.
- Wong-Gibbons DL, Romitti PA, Sun L, Moore CA, Reefhuis J, Bell EM, Olshan AF. Maternal periconceptional exposure to cigarette smoking and alcohol and esophageal atresia +/- tracheo-esophageal fistula. *Birth Defects Res* 2008;**82**:776–784.
- Woods SE, Raju U. Maternal smoking and the risk of congenital birth defects: a cohort study. *J Am Board Fam Pract* 2001;**14**:330–334.
- Wald NJ, Hackshaw AK. Cigarette smoking: an epidemiological overview. In: *Tobacco and Health*. Doll R, Crofton J (eds). British Medical Bulletin 1996;**52**:3–11.
- Wehby GL, Cassell CH. The impact of orofacial clefts on quality of life and healthcare use and costs. *Oral Dis* 2010;**16**:3–10.
- Werler MM, Pober BR, Holmes LB. Smoking and pregnancy. *Teratology* 1985;**32**:473–481.
- Williams L, Morrow B, Shulman H, Stephens R, D'Angelo D, Fowler CI. PRAMS 2002 Surveillance Report. Atlanta, GA: Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, 2006. <http://www.cdc.gov/PRAMS/Reports.htm>.
- Wyszynski DF, Duffy DL, Beaty TH. Maternal cigarette smoking and oral clefts: a meta-analysis. *Cleft Palate Craniofac J* 1997;**34**:206–210.
- Yushkiv N, Honein MA, Moore CA. Reported multivitamin consumption and the occurrence of multiple congenital anomalies. *Am J Med Genetics* 2005;**136A**:1–7.
- Wyszynski DF, Wu T. Use of US birth certificate data to estimate the risk of maternal cigarette smoking for oral clefting. *Cleft Palate Craniofac J* 2002;**39**:188–192.
- Yerushalmy J. The relationship of parents' cigarette smoking to outcome of pregnancy – implications as to the problem of inferring causation from the observed associations. *Am J Epidemiol* 1971;**93**:443–456.
- Yerushalmy J. Congenital heart disease and maternal smoking habits. *Nature* 1973;**242**:262–263.
- Yuan P, Okazaki I, Kuroki Y. Anal atresia: effect of smoking and drinking habits during pregnancy. *Jpn J Hum Genet* 1995;**40**:327–332.
- Zeiger JS, Beaty TH, Hetmanski JB, Wang H, Scott AF, Kasch L, Raymond G, Jabs EW, VanderKolk C. Genetic and environmental risk factors for sagittal craniosynostosis. *J Craniofac Surg* 2002;**13**:602–606.