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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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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 keywords 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.

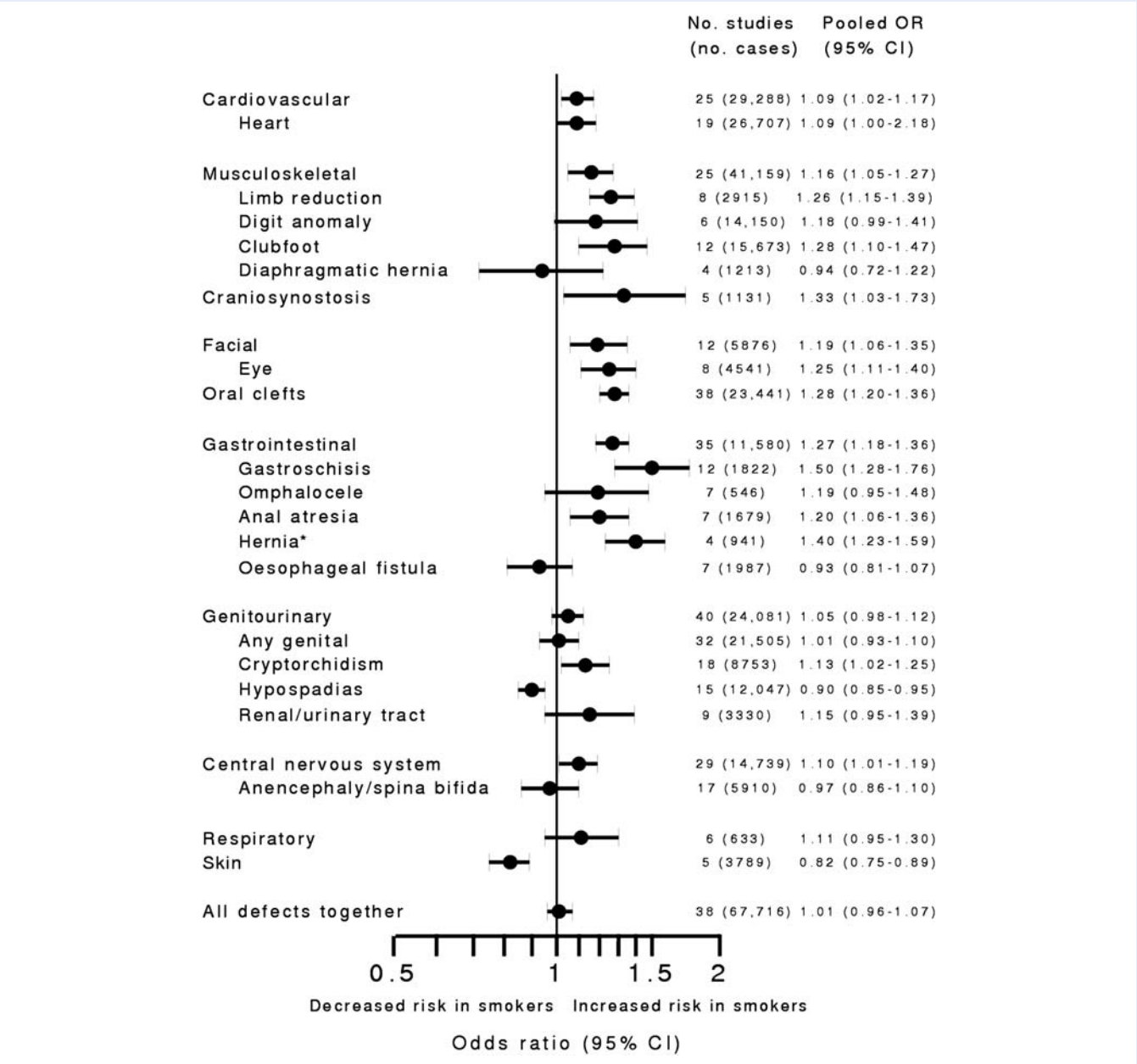


Figure 1 Summary of the meta-analyses for maternal smoking in pregnancy and birth defects. The pooled ORs are shown for each body system and specific defects (total number of malformed cases in brackets). CI: confidence interval
*Umbilical, inguinal or ventral hernia. 'Oesophageal fistula' is 'oesophageal 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

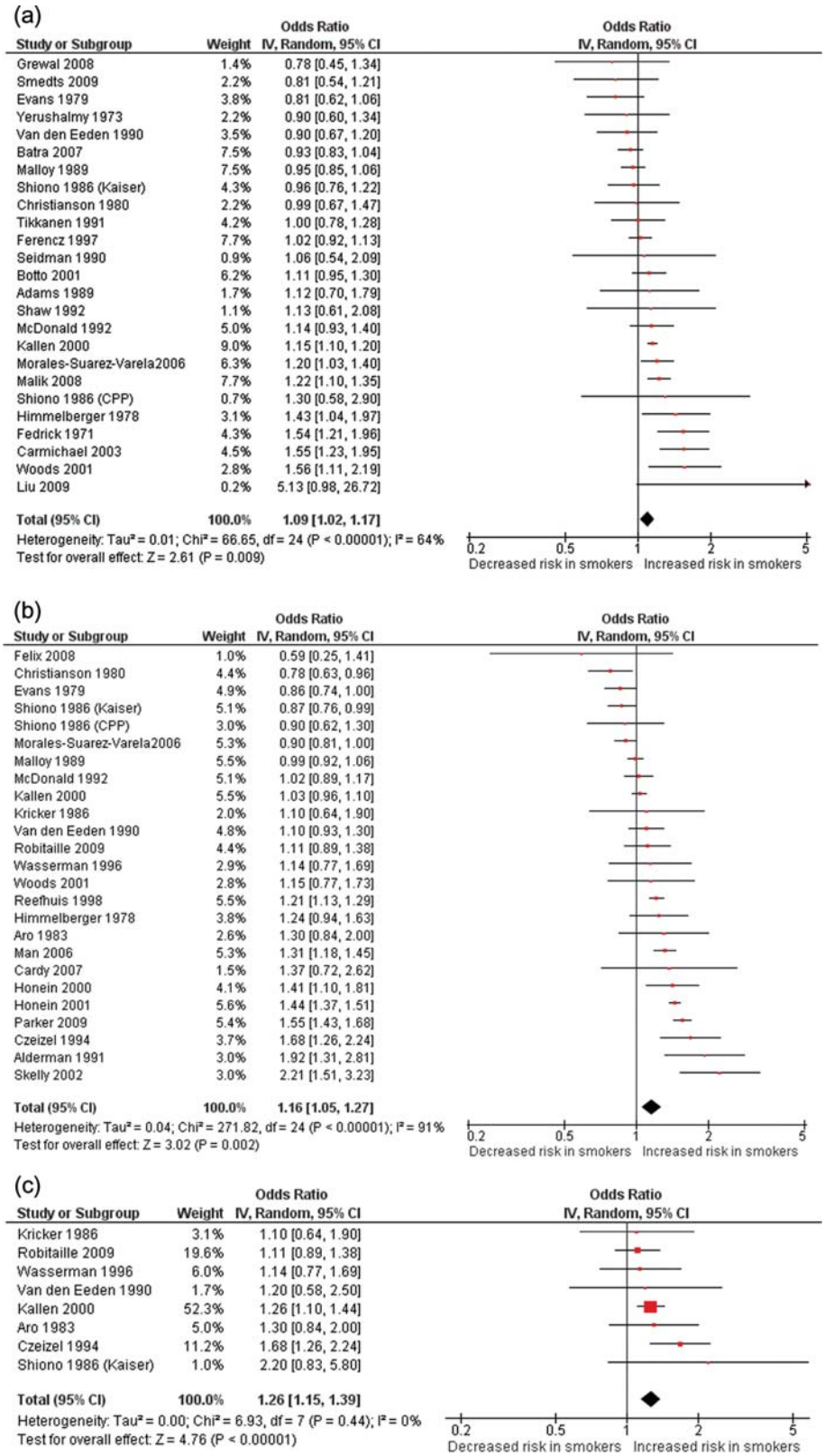
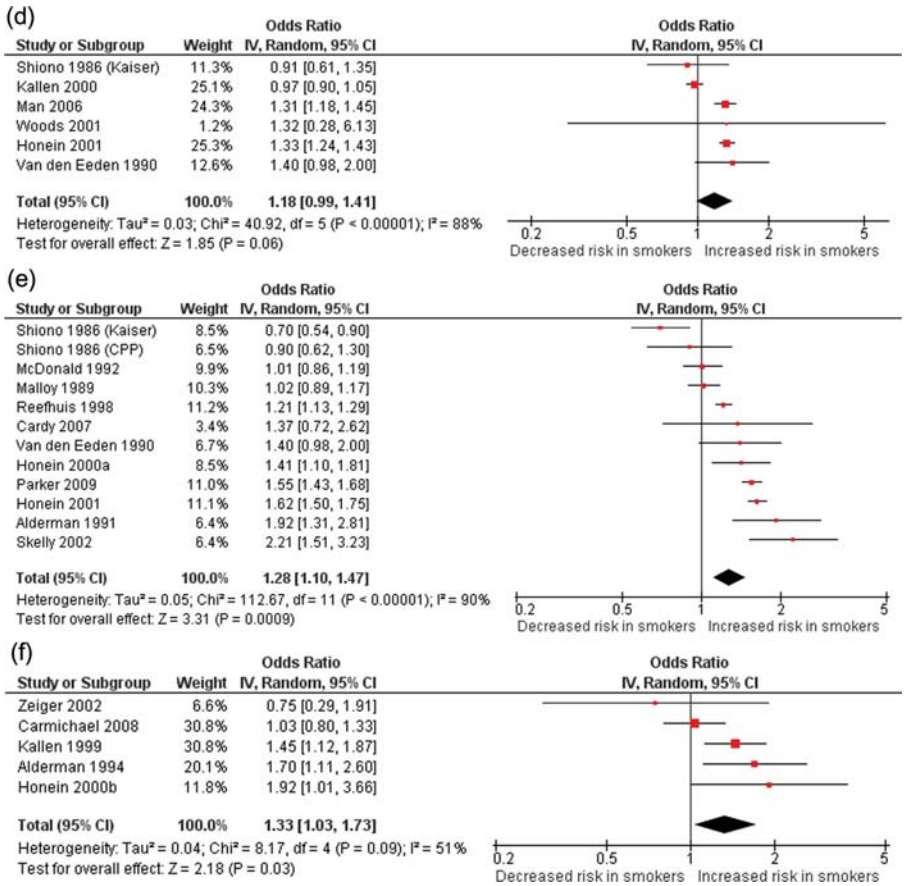


Figure 2 Forest plots for (**a**) cardiovascular/heart defects (Kelsey 1978 had no standard error, OR = 1.08), (**b**) all musculoskeletal defects (two studies had no standard error: Kelsey 1978 OR = 0.93, and Hemminki 1981 OR = 1.35), (**c**) limb reduction defects, (**d**) digit anomaly (ie polydactyly, 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.

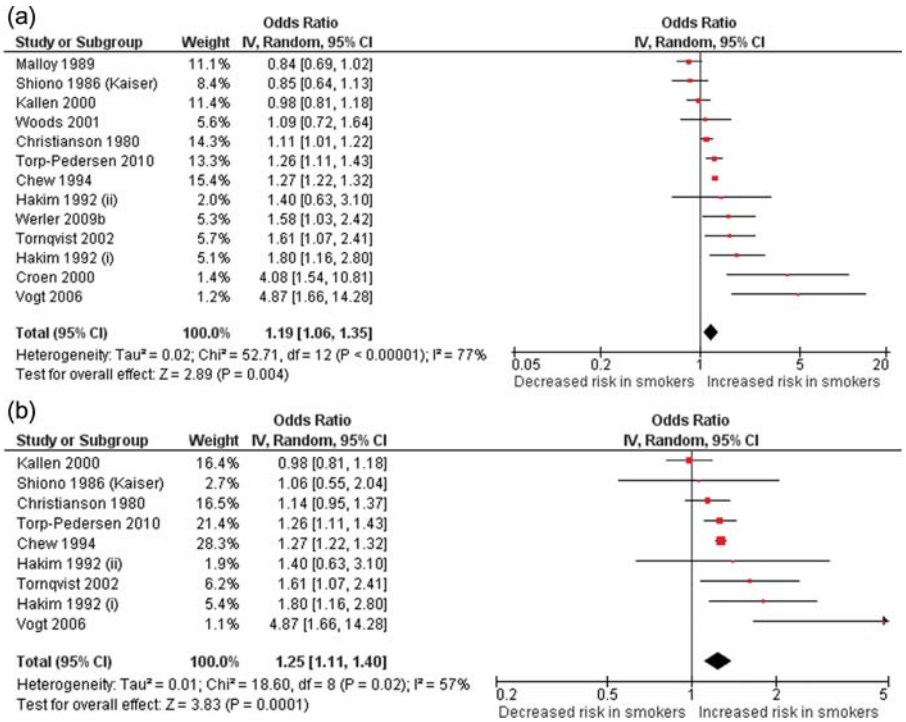


Figure 3 Forest plots for (**a**) facial defects, (**b**) eye defects only, and (**c**) cleft lip or palate. Studies are ranked according to size of the odds ratio.

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 (≥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 (1131 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)

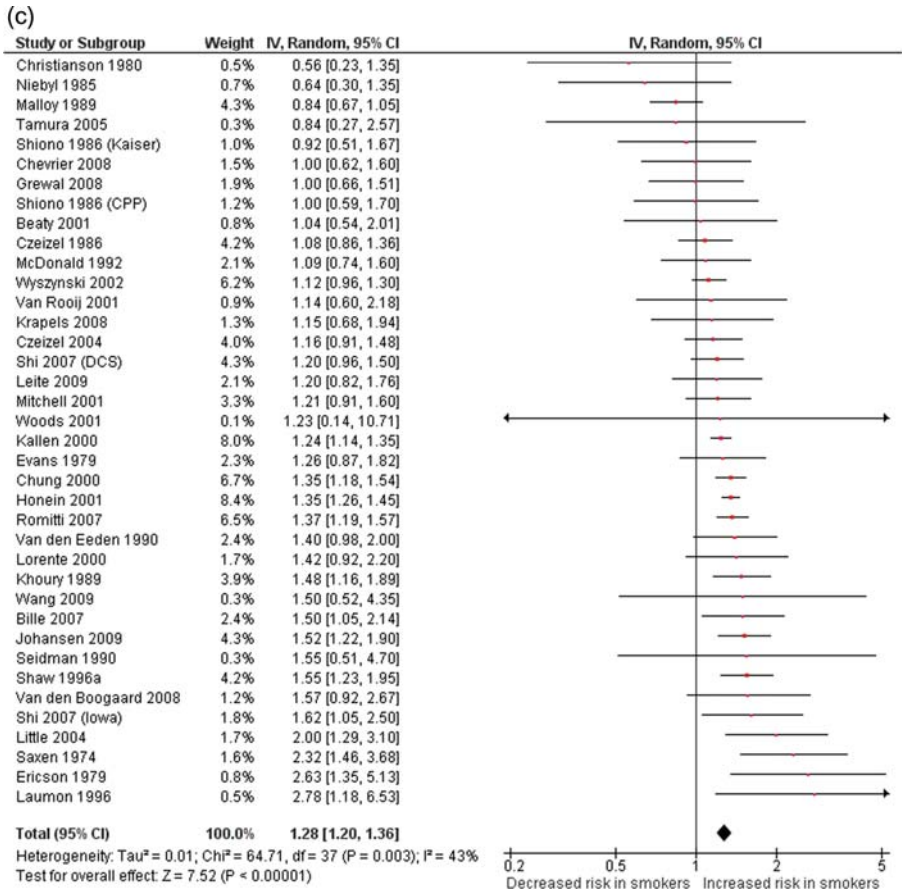
Twelve studies together show a 19% increased risk of a facial defect (OR 1.19, 95% CI 1.06–1.35, $P = 0.004$), excluding orofacial clefts, and seven were each significant; Supplementary data, Table S9 and Fig. 3a (5876 malformed cases, 2.6 million controls). Two reported evidence of a dose–response relationship (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,

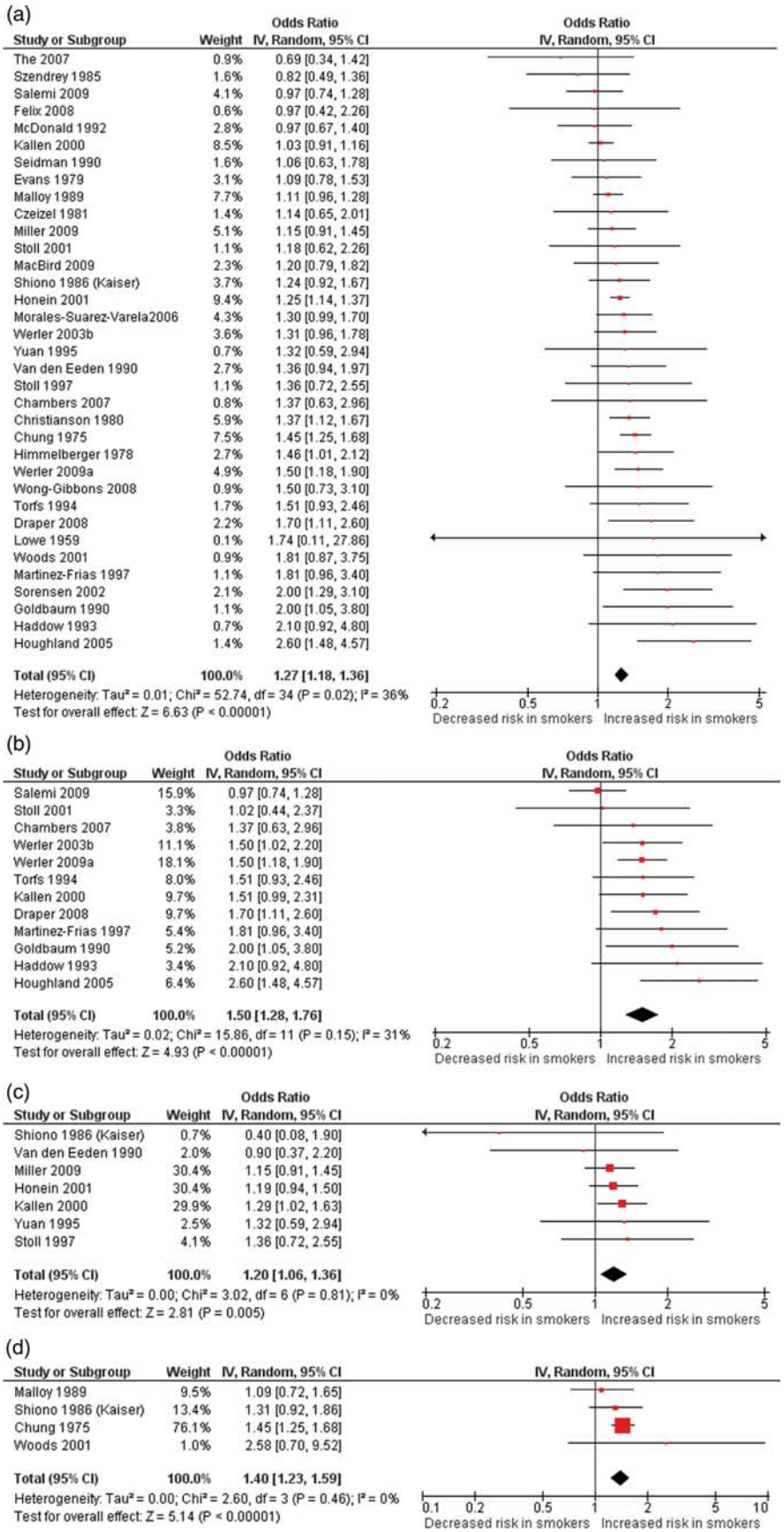
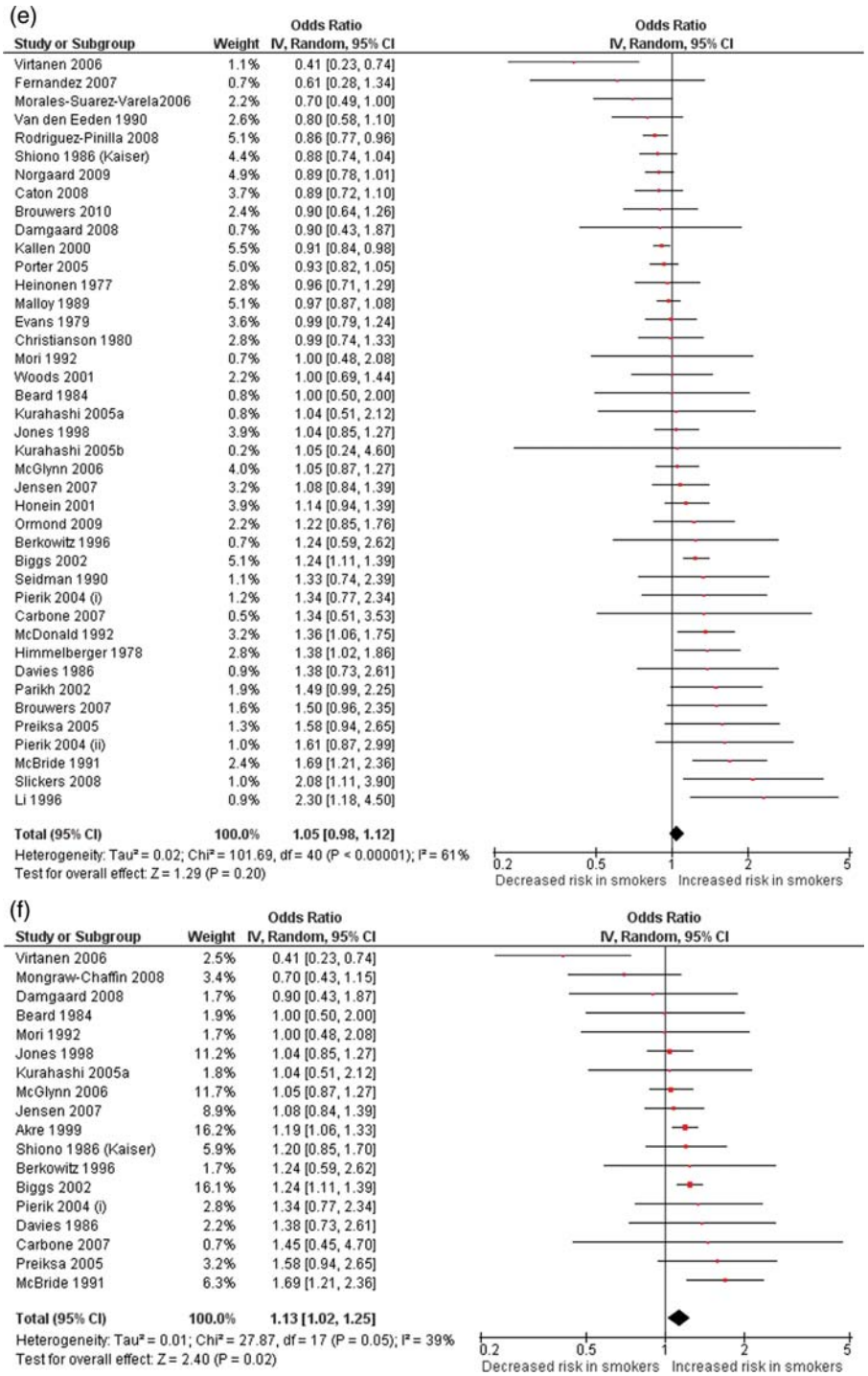


Figure 4 Forest plots for (**a**) all gastrointestinal defects (Kelsey 1978 had no standard error, OR = 1.55), (**b**) gastroschisis, (**c**) anal atresia, (**d**) umbilical/ventral/inguinal hernias, (**e**) all genitourinary defects, and (**f**) cryptorchidism. Studies are ranked according to size of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