Life-course epidemiology

Parental smoking and childhood obesity: higher effect estimates for maternal smoking in pregnancy compared with paternal smoking—a meta-analysis

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Abstract

Background: Some studies reported similar effect estimates for the impact of maternal smoking in pregnancy and paternal smoking on childhood obesity, whereas others suggested higher effects for maternal smoking. We performed a meta-analysis to compare the effect of in utero exposure to maternal smoking and that of paternal or household smoking exposure in utero or after birth with mutual adjustment.

Methods: Meta-analysis of observational studies identified in MEDLINE, EMBASE and Web of Knowledge published in 1900–2013. Study inclusion criterion was assessment of the association of maternal smoking during pregnancy and paternal or household smoking (anyone living in the household who smokes) at any time with childhood overweight and obesity. The analyses were based on all studies with mutually adjusted effect estimates for maternal and paternal/household smoking applying a random-effects model.

Results: Data for 109,838 mother/child pairs were reported in 12 studies. The pooled odds ratios (ORs) for overweight 1.33 [95% confidence interval (CI) 1.23;1.44] (n = 6, I² = 0.00%) and obesity 1.60 (95% CI 1.37;1.88) (n = 4, I² = 32.47%) for maternal smoking during pregnancy were higher than for paternal smoking: 1.07 (95% CI 1.00;1.16) (n = 6, I² = 41.34%) and 1.23 (95% CI 1.10;1.38) (n = 4, I² = 14.61%), respectively. Similar estimates with widely overlapping confidence limits were found for maternal smoking during pregnancy and childhood overweight and obesity: 1.35 (95% CI 1.20;1.51) (n = 3,
$I^2 = 0.00\%$) and 1.28 (95% CI 1.07;1.54) ($n = 3$, $I^2 = 0.00\%$) compared with household smoking 1.22 (95% CI 1.06;1.39) ($n = 3$, $I^2 = 72.14\%$) and 1.31 (95% CI 1.15;1.50) ($n = 3$, $I^2 = 0.00\%$).

**Conclusions:** Higher effect estimates for maternal smoking in pregnancy compared with paternal smoking in mutually adjusted models may suggest a direct intrauterine effect.

**Key words:** Maternal smoking, paternal smoking, household smoking, obesity, overweight, meta-analysis

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**Key Messages**

- Maternal smoking during pregnancy is associated with overweight and obesity in the offspring.
- The effect estimates of maternal smoking during pregnancy on childhood overweight and obesity are higher than the effect estimates of paternal smoking any time.
- The observed differences in the effect estimates of maternal and paternal smoking may suggest an intrauterine effect of maternal smoking in pregnancy.

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**Introduction**

A positive association between maternal smoking in pregnancy and having children who are overweight or have higher body mass index (BMI) values was confirmed in a number of meta-analyses\(^1\)\(^-\)\(^3\) of observational studies. Nicotine traverses the placenta and the duration of the exposure in the fetus is longer than in the mother due to slower nicotine metabolism in the fetus.\(^4\) A number of randomized animal studies reported higher weight gain in rats with intrauterine nicotine exposure.\(^5\)-\(^7\) The biological mechanism accounting for weight gain related to intrauterine nicotine exposure is, however, yet to be understood.\(^8\)

Causal inference on the association between intrauterine exposure to nicotine and childhood overweight however, has been questioned because of potential residual confounding.\(^9\),\(^10\) Major concerns regarding possible residual confounding were based on the observation that children who were exposed to paternal or household smoking *in utero* or in infancy also had an increased risk of being overweight, and that this risk was similar in magnitude to that of children with intrauterine exposure to maternal smoking.\(^11\)-\(^14\) Larger effect estimates would be anticipated for maternal smoking in pregnancy than for paternal smoking with regard to the higher fetal nicotine exposure.\(^15\)

Studies of the effect of paternal/household smoking on childhood overweight reported inconsistent results: some studies found no association between paternal or household smoking and childhood overweight\(^16\),\(^17\) whereas other studies observed positive associations.\(^11\),\(^18\),\(^19\) These equivocal findings point to the need for a meta-analysis to assess and compare the strength of mutually adjusted associations of maternal smoking in pregnancy and paternal/household smoking on childhood overweight.

In the present study, we conducted a meta-analysis to estimate and compare effects of maternal smoking in pregnancy with effects of paternal and household (anyone living in the household who smokes) smoking at any time on childhood overweight and obesity by a meta-analysis of studies that mutually adjusted for maternal and paternal/household smoking. The reason for selecting studies that used mutually adjusted maternal and paternal smoking was to allow for better (or easier) comparisons: since the maternal effect needs to be adjusted for paternal smoking, the effect of paternal smoking also needs to be adjusted for maternal smoking.

**Methods**

**Search strategy**

Studies were identified through searches of the three databases MEDLINE (1950–December 2013), EMBASE (1974–December 2013) and Web of Knowledge (1900–December 2013) by the following search terms: (offspring or children or toddlers or child or infant or adolescent\(^a\) or adult\(^a\)) AND (overweight or obesity or obese or adipose or adiposity or BMI) AND (smoke\(^a\) or nicotine or ‘second-hand smoke’ or ‘second-hand smoking’ or ‘household smoke’ or ‘household smoking’ or cigarette\(^a\) or fume or tobacco) AND (parents or parental or prenatal or (paternal and maternal) or (father and mother) or...
‘second-hand’ or household). We also performed manual searches of cited references of electronically identified articles to further identify all relevant studies.

Data extraction

All search hits were exported to EndnoteX7, which was used to organize the references and eliminate duplicates. Two (C.R. and K.S.) of us independently assessed titles and abstracts by manual scrutiny according to the inclusion criteria: any study published in English if reporting odds ratios (ORs) / BMI differences / BMI z-score differences for maternal smoking during pregnancy and paternal / household smoking at any time on excess weight or obesity or BMI in their offspring. Disagreement regarding the relevance of specific articles prompted a second review of the titles and abstracts and was resolved by consensus. Additional inclusion criteria applied in the full text analyses as follows:

- No evident over-adjustment of parental smoking: Studies were considered as over-adjusted if the OR or BMI increment for maternal smoking during pregnancy and/or paternal/household smoking were not only mutually adjusted but further adjusted for maternal smoking before or after pregnancy or paternal/household smoking at different additional time points.
- Duplicate publication of the same cohort (the most recent publication meeting the inclusion criteria was used).

All studies with mutual adjustment for maternal and paternal/household smoking were included. For studies reporting associations between both maternal smoking during pregnancy and paternal/household smoking and childhood overweight/obesity without mutual adjustment for maternal smoking during pregnancy and paternal/ household smoking, the corresponding author was contacted to provide mutually adjusted estimates.

Quality assessment

Quality assessment was based on AHRQ (Agency for Healthcare Research and Quality) quality assessment criteria for observational studies and was supplemented by specific criteria related to our research question. The included studies were evaluated as high quality if the study population was clearly described or if information about the study population was available elsewhere (in another article), the losses to follow-up were ≤20%, all anthropometric data were measured by investigators, maternal, paternal or household smoking was assessed close to the time of smoking or later, parental smoking status was measured based on cotinine and the effect estimates were at least adjusted for maternal obesity/BMI at any time and parental education, two important confounders of the effect of maternal smoking during pregnancy.20-22 To be considered of high quality, studies could only be deficient in up to two of these criteria and to be considered of moderate quality in four of these criteria.

Statistical analyses

For meta-analyses we used ORs for overweight (including obesity) and/or obesity associated with exposure to maternal smoking during pregnancy and paternal smoking at any time or ORs for overweight (including obesity) and/or obesity associated with maternal smoking during pregnancy and any household smoking (father, mother or other) exposure at any time. For BMI differences, only two studies provided data. Regarding BMI z-score difference, there was only one study providing information on two birth cohorts. Pooled ORs were estimated using random-effects as defined by DerSimonian and Laird.23 This method is based on the inverse-variance approach, making an adjustment to the study weights according to the extent of variation, or heterogeneity.24 Heterogeneity between the studies was estimated by Higgins’ I2 that describes the percentage of total variation across studies due to heterogeneity rather than chance (categorization: 25% low, 50% moderate, 75% high heterogeneity).25 We have assessed to what extent potentially important study-level covariates such as age, classifications of overweight or obesity, prevalence of maternal or paternal/household smoking and time of assessment of maternal or paternal/household smoking, account for the heterogeneity in mixed effect models by comparing the amount of heterogeneity in the random-effects and mixed-effect models.26 We used funnel plots to detect potential publication bias27 and tested the hypothesis that the number of missing studies is zero by a method introduced by Duval and Tweedie.24,26 We performed several sensitivity analyses: (i) excluding studies with a higher risk of bias because of insufficient adjustment for established confounders; (ii) excluding studies that did not adjust for birthweight; (iii) excluding studies without high quality; (iv) excluding studies with ages < 5 years; (v) including studies with potential over-adjustment. All analyses were carried out with the statistical software R28 and the add-on package metafor.26

Results

Electronic search yielded 2578 results. After title and abstract scan we excluded 2558 studies that did not assess both maternal smoking during pregnancy and paternal or household smoking and offspring’s overweight or obesity
later in life. The full texts of the remaining 20 articles were reviewed and 5 studies were excluded for various reasons (see Figure 1). Eight articles reported the effect of maternal smoking during pregnancy and paternal/household smoking but did not adjust these factors mutually. The authors of these studies were contacted to supplement their analyses with mutually adjusted estimates (see Supplementary Table 1, available as Supplementary data at IJE online). From these studies, five authors (G.K.,17 S.Y.,29 Y.C.C.,18 B.G.,30 and R.v.K.19) provided unpublished additional data. In total, we included 12 studies in our meta-analysis.11,12,14,17,18,19,29–34

Study characteristics

Table 1 shows the characteristics of the included studies.

The studies were published between 2008 and 2013 in children from Taiwan, Australia, the USA, The Netherlands, the UK, Germany, Brazil, Finland and Belarus. Five of these were cross-sectional,12,17,18,19,30, six were cohort studies11,29,31–34 and one study pooled four population-based studies.14 The age varied between 3 and 18 years. Ten studies11,12,14,17,18,19,29–31,34 reported adjusted OR for childhood overweight (including obesity) and/or obesity. Definition of overweight/obesity varied across studies. Five studies12,19,30,31,34 used the international cut-off values from the International Obesity Task Force (IOTF).35 Another three studies17,18,25 defined overweight (including obesity) and obesity as exceeding the 85th and 95th age-specific BMI percentiles, respectively based on the World Health Organization (WHO) cut-off values36 or the United States Centers for Disease Control and Prevention (CDC) cut-off values.37 One study14 reported only overweight (including obesity) as outcome as defined by exceeding the 90th BMI percentile of the German cut-off values.38 Two studies29,32 reported BMI differences between offspring of smoking and non-smoking mothers and one reported BMI z-score differences analyzing two different cohorts.33 In eight studies11,17,19,29,31–34 we could measure the effect of maternal smoking during pregnancy and compare with that of paternal smoking at any time, and in four studies12,14,18,30 we could compare with that of household smoking at any time. The earliest years of birth were 1945–6411 the latest 2002–06.31 The prevalence of maternal smoking during pregnancy varied from 2.1%29 to 33.5%,33 the prevalence of paternal smoking from 20.5%19 to 61%29 and for household smoking from 23.3%30 to 51.7%.12

Table 2 presents study quality assessment for each of the 12 studies included in our meta-analysis.

All studies described their study population in detail. Three29,31,34 of the six11,29,31–34 longitudinal studies had losses to follow-up ≤20%, and in three11,32,33 studies this information was not reported. In all but one study,11 the anthropometric data were objectively measured by investigators. The main study variables—maternal smoking during pregnancy and paternal/household smoking—were proxy-reported by mother or father in four studies,12,29,30,32 reported by mother in three studies11,31,33 and assessment was not clearly described in five
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Type of study</th>
<th>Size of study population</th>
<th>Age in years</th>
<th>Country of study</th>
<th>Definition of outcome and respective BMI percentile cut-off</th>
<th>Reference percentile</th>
<th>Exposure and prevalence of maternal smoking</th>
<th>Exposure and prevalence of paternal smoking</th>
<th>Exposure and prevalence of household smoking</th>
<th>Year of birth (cohort studies) or study enrolment (cross-sectional studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al.</td>
<td>2012</td>
<td>Cross-sectional study</td>
<td>7930</td>
<td>9–14</td>
<td>Taiwan</td>
<td>Overweight (incl. obesity): 85th percentile, obesity: 95th percentile</td>
<td>WHO</td>
<td>Any smoking during pregnancy 25% (198)</td>
<td>–</td>
<td>Any current smoking (father, mother or other family members) in the child’s house at 12-year interview 29.3% (2396)</td>
<td>2007 and 2010*</td>
</tr>
<tr>
<td>Gopinath</td>
<td>2012</td>
<td>Cross-sectional study</td>
<td>2353</td>
<td>12</td>
<td>Australia</td>
<td>Overweight (incl. obesity): extrapolated from adult BMI of 25 kg/m² at age 18</td>
<td>IOTF</td>
<td>Any smoking during pregnancy</td>
<td>–</td>
<td>Any current smoking (father, mother or other family members) in the child’s house at 12-year interview 23.3% (512)</td>
<td></td>
</tr>
<tr>
<td>Harris et al.</td>
<td>2013</td>
<td>Cohort study</td>
<td>35 370</td>
<td>18</td>
<td>USA</td>
<td>Overweight (incl. obesity): BMI &gt;25 kg/m², BMI &gt;30 kg/m²</td>
<td>–</td>
<td>15.0% (319) Smoking 1–14 (light), 15–24 (moderate) and 25+ (heavy) cigarettes/day during pregnancy</td>
<td>58.8% (19 943)</td>
<td></td>
<td>1945–64 (years of birth)</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Year</td>
<td>Type of study</td>
<td>Size of study</td>
<td>Age in years</td>
<td>Country of study</td>
<td>Definition of outcome and respective BMI percentile cut-off</td>
<td>Reference</td>
<td>Exposure and prevalence of smoking</td>
<td>Exposure and prevalence of smoking</td>
<td>Exposure and prevalence of smoking</td>
<td>Year of birth (cohort studies) or study enrolment (cross-sectional studies)</td>
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<tr>
<td>Heppe et al.</td>
<td>2012</td>
<td>Birth cohort</td>
<td>3610</td>
<td>4</td>
<td>Netherlands</td>
<td>Overweight (incl. obesity): extrapolated from adult BMI of 25 kg/m² at age 18</td>
<td>IOTF</td>
<td>Any smoking during pregnancy</td>
<td>23.0% (829)</td>
<td>Any smoking during pregnancy</td>
<td>38.0% (1371)</td>
</tr>
<tr>
<td>Howe et al.</td>
<td>2012</td>
<td>Birth cohort</td>
<td>8887</td>
<td>10</td>
<td>UK</td>
<td>BMI-difference</td>
<td>–</td>
<td>Any smoking during pregnancy</td>
<td>20.5% (3209)</td>
<td>Any smoking during pregnancy</td>
<td>36.1% (1824)</td>
</tr>
<tr>
<td>Kleiser et al.</td>
<td>2009</td>
<td>Cross-sectional study</td>
<td>10 021</td>
<td>3–17</td>
<td>Germany</td>
<td>Obesity: extrapolated from adult BMI of 30 kg/m² at age 18</td>
<td>IOTF</td>
<td>Any smoking during pregnancy</td>
<td>17.5% (2273)</td>
<td>Any current smoking (mother, father) at interview</td>
<td>1998 and 2003</td>
</tr>
<tr>
<td>Koshy et al.</td>
<td>2011</td>
<td>Cross-sectional study</td>
<td>3038</td>
<td>5–11</td>
<td>UK</td>
<td>Overweight (incl. obesity): 85th percentile, obesity: 95th percentile BMI z-score</td>
<td>WHO</td>
<td>Any smoking during pregnancy</td>
<td>30.3% (991)</td>
<td>42.5% (875)</td>
<td>51.7% (6796)</td>
</tr>
<tr>
<td>Matijasevich</td>
<td>2011</td>
<td>Birth cohort (1993 cohort)</td>
<td>1450</td>
<td>4</td>
<td>Brazil</td>
<td>BMI z-score g</td>
<td>WHO</td>
<td>Any smoking during pregnancy</td>
<td>33.5% (1993 cohort)</td>
<td>Any smoking during pregnancy</td>
<td>44.8% (1993 cohort)</td>
</tr>
<tr>
<td>et al.</td>
<td></td>
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<tr>
<td>Author(s)</td>
<td>Year</td>
<td>Type of study</td>
<td>Size of study</td>
<td>Age in years</td>
<td>Country of study</td>
<td>Definition of outcome and respective BMI percentile cut-off</td>
<td>Exposure and prevalence of smoking</td>
<td>Exposure and prevalence of smoking</td>
<td>Exposure and prevalence of smoking</td>
<td>Year of birth (cohort studies) or study enrolment (cross-sectional studies)</td>
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<tr>
<td>Plachta-</td>
<td>2012</td>
<td>4 population-based studies (cross-sectional and birth cohort studies)</td>
<td>11 121</td>
<td>3–18</td>
<td>Germany</td>
<td>Overweight (incl. obesity): 90th percentile</td>
<td>KH</td>
<td>Any smoking during pregnancy</td>
<td>–</td>
<td>Any current smoking (at least 1 parent smokes) at interview</td>
<td>1996–2008</td>
</tr>
<tr>
<td>Danielzik</td>
<td>et al., 14</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>von Kries, 2008</td>
<td>Cross-sectional</td>
<td>5899</td>
<td>5–7</td>
<td>Germany</td>
<td>Overweight (incl. obesity): extrapolated from adult BMI of 25 kg/m² at age 18, obesity: extrapolated from adult BMI of 30 kg/m² at age 18 examinations</td>
<td>IOTF</td>
<td>Any smoking during pregnancy</td>
<td>Any current smoking at 6.5-year interview</td>
<td>–</td>
<td>2005 school</td>
<td></td>
</tr>
<tr>
<td>Yang et al., 2013</td>
<td>Birth cohort study</td>
<td>12 192</td>
<td>6.5</td>
<td>Belarus</td>
<td>Overweight (incl. obesity): 85th percentile</td>
<td>CDC</td>
<td>Any smoking during and after pregnancy</td>
<td>Any current smoking at 6.5-year interview</td>
<td>–</td>
<td>1996–97</td>
<td></td>
</tr>
</tbody>
</table>

CDC, United States Centers for Disease Control and Prevention; IOTF, International Obesity Task Force; KH, Kromeyer-Hauschild; WHO, World Health Organization.

2 Of 34 413 including those who quit smoking during pregnancy (n = 1385).
3 Of 33 894.
4 % of total population including missing values for outcome, exposure variable and other confounders.
5 Data only available depending on group [gestational diabetes mellitus (normal weight, overweight), oral glucose tolerance test normal (normal weight, overweight), control].
6 % of origin population at birth (5304 and 4287 births in the 1993 and 2004 cohorts, respectively).
7 BMI-for-age z-scores according to the growth curves published by WHO in 2006.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population clearly describes study population?</th>
<th>Losses of follow-up</th>
<th>Data collection / Outcome</th>
<th>Method of assessment of exposure data (interview, questionnaire)</th>
<th>Smoking status defined from measured cotinine level, self report or proxy report</th>
<th>Time of reporting of maternal smoking during pregnancy</th>
<th>Time of reporting of paternal/household smoking during pregnancy at interview</th>
<th>Method adjusted for main potential confounders (maternal obesity/BMI and parental education)?</th>
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</thead>
<tbody>
<tr>
<td>Chen et al. 18</td>
<td>Yes</td>
<td>NA</td>
<td>Measured (recorded during school visits)</td>
<td>Questionnaire</td>
<td>Not clear a</td>
<td>At a later time</td>
<td>Contemporary</td>
<td>No b</td>
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<tr>
<td>Gopinath et al. 30</td>
<td>Yes</td>
<td>NA</td>
<td>Measured</td>
<td>Questionnaire</td>
<td>Self-reported by mother and/or father</td>
<td>At a later time</td>
<td>Contemporary</td>
<td>No b,c</td>
</tr>
<tr>
<td>Harris et al. 11</td>
<td>Yes</td>
<td>Not reported d</td>
<td>Reported</td>
<td>Questionnaire</td>
<td>Reported by mother only</td>
<td>At a later time</td>
<td>At a later time</td>
<td>Yes</td>
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<td>Heppe et al. 31</td>
<td>Yes</td>
<td>15%</td>
<td>Measured at the research centre</td>
<td>Questionnaire</td>
<td>Reported by mother only</td>
<td>Contemporary</td>
<td>Contemporary</td>
<td>Yes</td>
</tr>
<tr>
<td>Howe et al. 32</td>
<td>Yes</td>
<td>Not reported</td>
<td>Measured in clinics</td>
<td>Questionnaire</td>
<td>Self-reported by mother and father</td>
<td>At a later time</td>
<td>Contemporary</td>
<td>Yes</td>
</tr>
<tr>
<td>Kleiser et al. 12</td>
<td>Yes</td>
<td>NA</td>
<td>Measured by trained staff</td>
<td>Interview</td>
<td>Self-reported by mother and/or father</td>
<td>At a later time</td>
<td>Contemporary</td>
<td>Yes</td>
</tr>
<tr>
<td>Koshy et al. 17</td>
<td>Yes</td>
<td>NA</td>
<td>Measured</td>
<td>Questionnaire</td>
<td>Not clear a</td>
<td>At a later time</td>
<td>At a later time</td>
<td>No b</td>
</tr>
<tr>
<td>Matijasevich et al. 33</td>
<td>Yes</td>
<td>Not reported (1993 cohort and 11.4% (2004 cohort)</td>
<td>Measured by trained interviewers</td>
<td>Interview</td>
<td>Not clear a</td>
<td>At a later time</td>
<td>At a later time</td>
<td>No b</td>
</tr>
<tr>
<td>Pirkola et al. 34</td>
<td>Yes</td>
<td>20%</td>
<td>Measured by trained nurses</td>
<td>Questionnaire</td>
<td>Not clear a</td>
<td>Contemporary</td>
<td>Contemporary</td>
<td>No c</td>
</tr>
<tr>
<td>Plachta-Danielzik et al. 14</td>
<td>Yes</td>
<td>NA</td>
<td>Measured</td>
<td>Not described</td>
<td>Not described</td>
<td>At a later time</td>
<td>Contemporary</td>
<td>Yes</td>
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<tr>
<td>von Kries et al. 19</td>
<td>Yes</td>
<td>NA</td>
<td>Measured by public health nurses</td>
<td>Questionnaire</td>
<td>Not clear a</td>
<td>At a later time</td>
<td>Contemporary</td>
<td>Yes</td>
</tr>
<tr>
<td>Yang et al. 29</td>
<td>Yes</td>
<td>18.8%</td>
<td>Measured by polyclinic pediatricians</td>
<td>Interview</td>
<td>Usually reported by mother</td>
<td>Contemporary</td>
<td>Contemporary</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NA, not applicable.

a The questionnaire was distributed to parents by class teachers or was sent by post.  
b Did not adjust for maternal obesity/BMI.  
c Did not adjust for parental education.  
d The Nurses’ Health Study II was established in 1989; 116430 female nurses participated. In 2001, mothers of these nurses were asked to complete a questionnaire regarding their daughter. Information on pregnancy and early-life exposure were obtained for 35 794 participants with a response rate of 76.5%.  

studies.\textsuperscript{14,17,18,19,34} Five studies\textsuperscript{29,31–34} assessed maternal smoking during pregnancy or after delivery and seven\textsuperscript{11,12,14,17,18,19,30} at a later time in childhood. Ten studies\textsuperscript{12,14,18,19,29–34} assessed paternal/household smoking at interview and two studies by recall of earlier smoking\textsuperscript{11,17} at a later time. Eight studies\textsuperscript{11,12,14,19,29,31–33} adjusted for both maternal obesity/BMI and parental education, and four studies\textsuperscript{17,18,30,34} did so only for one\textsuperscript{17,18,34} or none\textsuperscript{30} of these factors.

Maternal smoking during pregnancy vs paternal smoking at any time

For childhood overweight and/or obesity, pooled ORs were greater for maternal smoking during pregnancy (vs no maternal smoking during pregnancy) than those for paternal smoking (vs no paternal smoking) (Figure 2a). Children of mothers who smoked during pregnancy had an increased risk of overweight and obesity later in life with a pooled OR of 1.33 (95% CI 1.23;1.44) and 1.60 (95% CI 1.37;1.88), respectively. Compared with effect sizes associated with maternal smoking during pregnancy, the magnitude of associations with paternal smoking was lower [pooled OR 1.07 (95% CI 1.00;1.16) for overweight and pooled OR 1.23 (95% CI 1.10;1.38) for obesity]. Low to moderate heterogeneity was suggested by the Higgins I\textsuperscript{2} in all models. Mean BMI differences yielded similar magnitudes of the strength of the associations for maternal [0.14 (95% CI –0.17;0.46)] and paternal smoking [0.15 (95% CI 0.13;0.26)] with a high heterogeneity of 84.11\% (Figure 2b). There was only one study reporting the impact of maternal and paternal smoking on BMI z-scores for two cohorts followed up to the age of 4 years and yielding higher pooled effect estimates for maternal smoking during pregnancy compared with paternal smoking during pregnancy.

The funnel plots did not suggest selective reporting of studies with high effect sizes (see Figures S1 and S2, available as Supplementary data at IJE online).

Maternal smoking during pregnancy vs household smoking anytime

Comparing the effect estimates for maternal smoking in pregnancy (vs no maternal smoking during pregnancy) and household smoking any time (vs no household smoking any time) yielded similar effect estimates with widely overlapping confidence limits (Figure 3): 1.35 (95% CI 1.20;1.51) and 1.22 (95% CI 1.06;1.39) for overweight and 1.28 (95% CI 1.07;1.54) and 1.31 (95% CI 1.15;1.50) for obesity. High heterogeneity was estimated for ‘anytime household smoking’ and overweight. The funnel plots did not indicate evident publication bias (Figure S3, available as Supplementary data at IJE online).

Sensitivity analyses

For paternal smoking, four sensitivity analyses were performed. One excluded studies with failure to adjust for maternal smoking and paternal/paternal education.\textsuperscript{17,34} Higher effect estimates for paternal smoking in pregnancy compared with paternal smoking were confirmed (Figure S4, available as Supplementary data at IJE online). Excluding studies that did not adjust for birthweight\textsuperscript{29,32,33} in the second sensitivity analysis or studies with ages of children <5 years\textsuperscript{31} in the third sensitivity analysis yielded identical results (Figures S5 and S6, available as Supplementary data at IJE online). The last sensitivity analysis excluded studies with moderate or poor quality.\textsuperscript{11,17} Restriction to studies with high quality did not reverse higher effect estimates for paternal smoking in pregnancy compared with paternal smoking although the 95\% CIs for maternal smoking in pregnancy and paternal smoking were no longer disjunctive (Figure S7, available as Supplementary data at IJE online).

For household smoking, two sensitivity analyses were performed. Restriction to high quality studies\textsuperscript{12,14,30} yielded almost identical results as did inclusion of studies with potential over-adjustment\textsuperscript{30–41} for smoking at different time points (Figures S8 and S9, available as Supplementary data at IJE online).

Discussion

In studies with mutual adjustment for maternal smoking in pregnancy and paternal smoking any time, higher effect estimates for childhood overweight or obesity were observed for maternal smoking in pregnancy, whereas the effect estimates appear similar for maternal smoking in pregnancy and household smoking. Regarding BMI and BMI z-scores, the differences between maternal and paternal smoking were inconsistent. To our knowledge, this is the first meta-analysis comparing the effects of maternal smoking during pregnancy and paternal/household smoking on childhood overweight and obesity with mutual adjustment.

The main objective of our meta-analyses is not to quantify the independent effects of maternal and paternal/household smoking on the risk of overweight or obesity in the offspring but to compare differences of their effect estimates as a negative control approach with paternal smoking acting as a negative control.\textsuperscript{42,43} We therefore included different age levels, different classifications of obesity and different levels of smoking in the analyses if they applied both to maternal and paternal/household smoking.

The higher effect differences between maternal smoking during pregnancy and paternal smoking any time than for maternal smoking during pregnancy and household smoking anytime are likely to reflect that maternal and paternal
smoking can be clearly disentangled whereas postnatal maternal smoking is included in the case definitions for household smoking. Therefore similar effect estimates for maternal and household smoking appear plausible. The inconsistent differences between maternal and paternal smoking on BMI z-score and BMI may be a reflection of the small numbers of studies included.

Although the higher mutually adjusted effect estimates of maternal smoking in pregnancy than for paternal smoking provide a strong argument for a specific intrauterine...
effect of maternal smoking, alternative explanations must be considered in face of the persistent effect of paternal smoking. The latter could be explained by: (i) uncontrolled, residual confounding of the association of both maternal smoking during pregnancy and paternal smoking and childhood overweight/obesity; (ii) a genuine effect of exposure to passive smoking in pregnancy; (iii) a genuine effect of postnatal smoking of father or mother.43

On item (i), some residual confounding is supported by a sibling study in 8445 women with two subsequent male births between 1983 and 1988 by Iliadou et al.10 In the focus of this study were sibling pairs where one sibling was exposed to maternal smoking in pregnancy, whereas the other was not. In an analysis stratified by maternal smoking habits across the first and second pregnancies, an increased risk for overweight in young men could only be detected if the mother smoked during both pregnancies. Smoking in either pregnancy only was not associated with overweight in the exposed son. Similar findings were reported by Gilman et al.9 who assessed the effects of maternal smoking during pregnancy on children's growth and development in 16 619 siblings by conditional likelihood methods. BMI in offspring of mothers who had been smoking during pregnancy was higher in the unconditional analyses. With adjustment for unmeasured family conditions by conditional-on-family specific intercepts which provided effect estimates that were free from bias due to potentially confounding factors to which both siblings were exposed, the effects of maternal smoking in pregnancy decreased and were no longer significant.

On item (ii), cotinine concentrations, irrespective of the substrate analysed, are by far higher in active than in passive smokers.15,44 This also pertains to a measure for the cumulative nicotine exposure in utero: the amount of cotinine in the hair of newborns of actively smoking mothers was considerably higher (2.8 ± 0.8 ng/mg) than in the hair of newborns of mothers exposed to passive smoke only (0.6 ± 0.15 ng/mg) or in newborns who were unexposed to environmental tobacco smoke (ETS) and had non-smoking mothers (0.26 ± 0.04 ng/mg).45,46

Higher effect estimates for maternal smoking during pregnancy compared with paternal smoking would be compatible with a linear dose effect. There are some studies suggesting a linear dose effect of maternal smoking during pregnancy on overweight and/or obesity in childhood19,47 whereas other studies48,49 suggest a threshold effect, with a steep increase in effect size at low exposure levels flattening at higher exposure levels. Assuming a threshold effect, exposure to paternal smoking levels above the threshold might yield effects similar to those of maternal smoking exposure in pregnancy.

On item (iii), the effects for both paternal and maternal smoking on childhood overweight/obesity may reflect a causal relationship between postnatal smoking of either

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**Figure 3.** Odds ratios in meta-analyses of association between maternal smoking during pregnancy (vs no maternal smoking during pregnancy) and household smoking any time (vs no household smoking any time) and overweight or obesity in childhood. Squares represent the point of estimate of each study; square size corresponds to the weight of the study in the meta-analysis. Horizontal lines denote the respective 95% CIs. The diamond represents the overall pooled estimate of the smoking effect.
parent and childhood overweight/obesity since most parents will continue smoking after pregnancy.

The pathophysiology underlying the association between maternal smoking and overweight/obesity in the offspring, however, is far from being understood. There is some evidence that the risk is not mediated by low birthweight, both in animal5,7,30 and human studies.51,52 Catch-up growth, too, does not appear to be in the causal pathway.51,53 Whereas smoking in the last trimester appears to account most for the offspring’s risk for low birthweight,54 first-trimester smoking appears to be more relevant for the offspring’s risk for overweight/obesity.55 Further research with regard to changes in the hypothalamic regulation of energy forth and appetite control might help to elucidate the aetiology of the association between maternal smoking in pregnancy and the risk for overweight/obesity in the offspring.1,56

A strength of our analyses is the search strategy based on using three databases and a broad search term. All but one11 included studies were of high or moderate quality. Studies with potential over-adjustment were excluded.39–41 Over-adjustment may be assumed if adjustment is made for a variable closely related to the exposure of interest;57 because of multicollinearity, it can obscure a true effect or create an apparent effect even if none exists.58 The study by Raum et al.41 for example, was excluded because of concomitant adjustment for maternal smoking during pregnancy, maternal smoking before pregnancy, maternal smoking during the first year after pregnancy, and hand-hand smoke at the age of 6 years: 97.2% of mothers who smoked during pregnancy had already smoked before pregnancy; 92.2% of children who were exposed to tobacco smoke during pregnancy were also exposed to maternal smoking during their first year of life.

A limitation is that our study included only five out of 12 studies reporting maternal and paternal/household smoking exposure status but no mutually adjusted effect estimates. The results could not be shown by sex since only one study32 stratified analyses by gender. Howe et al.32 found similar associations between boys and girls, suggesting there are no substantial differences in the associations of exposure to maternal and paternal/household smoking between sexes. Some, but not all of the studies eligible for this meta-analysis adjusted for birthweight which is associated with weight later in life. Excluding studies that did not adjust for birthweight29,32,33 yielded identical results, suggesting no bias in estimates of our main results. Moderate and high heterogeneity was observed in some models. In the model of paternal smoking any time and childhood overweight, moderate heterogeneity was explained by differences in paternal smoking prevalence and in time of assessment of paternal smoking. In the model of household smoking and childhood overweight, high heterogeneity was explained by the prevalence of maternal smoking. Further variables (age, classifications of overweight or obesity) were taken into account but did not explain any heterogeneity. Different reference criteria to define overweight/obesity across studies might have contributed to a greater heterogeneity in our meta-analysis. However, a previous study suggests that identification of genuine risk factors for overweight or obesity does not depend on the choice of the reference system.59 In fact, ORs associated with maternal smoking during pregnancy and childhood overweight or obesity ranged between 1.15 and 1.30 or 1.10 and 1.59 in studies using WHO, and between 1.27 and 1.52 or 1.37 and 2.30 in studies using IOTF for the reference, indicating similar effect sizes across different references. Mutual adjusted estimates, or interpreting those estimates, assume that there is no interaction between maternal and paternal/household smoking. An interaction may not be very likely, but we have no good evidence as to how the two interact with each other, and empirical studies to test effect modification/interaction of the two are very limited, particularly with pregnancy period involved. It is of note that studies included in our meta-analysis estimated ORs for overweight/obesity that was a common outcome, with a prevalence range of 9–32%. Thus, we should be cautious in interpreting the effect sizes in our study as ORs estimated for a common outcome overestimate risk ratios.60 Finally, underreporting of the perhaps socially undesirable behaviour of smoking during pregnancy could result in underreporting of maternal smoking accounting for smoking mothers classified as non-smoking. In this case the strength of the effect of maternal smoking during pregnancy would be underestimated.61

Conclusion
Higher effect estimates in mutually adjusted models for maternal smoking in pregnancy compared with paternal smoking may suggest a direct intrauterine effect.

Supplementary Data
Supplementary data are available at IJE online.

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Author contributions
C.R. and R.v.K. developed the study hypotheses and contributed to the first and final drafts of the manuscript. C.R. and K.S. conducted title and abstract scans, abstracted the information and evaluated the included studies. C.R. was responsible for data management and performed the statistical analysis. S.Z. contributed to the final draft of the manuscript. S.Y. supported this work by providing new calculations in addition to those in his previously published article, and contributed to subsequent drafts of the manuscript. G.K., B.G. and Y.C.C. supported this work by providing new calculations in addition to those in their previously published articles, and contributed to the final draft of the manuscript. C.R. will act as guarantor for the paper.

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