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Maternal Smoking during Pregnancy and Offspring Overweight: Is there a Dose Response Relationship? An Individual Patient Data Meta-Analysis

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Conflict of interest

All authors declare that they have no competing financial interests in relation to the work.

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ABSTRACT

Background/Objectives: A number of meta-analyses suggest an association between any maternal smoking in pregnancy and offspring overweight obesity. Whether there is a dose-response relationship across number of cigarettes and whether this differs by sex remains unclear.

Subject/Methods: Studies reporting number of cigarettes smoked during pregnancy and offspring BMI published up to May 2015 were searched. An individual patient data meta-analysis of association between the number of cigarettes smoked during pregnancy and offspring overweight (defined according to the International Obesity Task Force reference) was computed using a generalized additive mixed model with non-linear effects and adjustment for confounders (maternal weight status, breastfeeding, maternal education) and stratification for sex.

Results: Of 26 identified studies, 16 authors provided data on a total of 238 340 mother-child-pairs. A linear positive association was observed between the number of cigarettes smoked and offspring overweight for up to 15 cigarettes per day with an OR increase per cigarette of 1.03, 95%-CI=[1.02-1.03]). The OR flattened with higher cigarette use. Associations were similar in males and females. Sensitivity analyses supported these results.

Conclusions: A linear dose response relationship of maternal smoking was observed in the range of 1-15 cigarettes per day equally in boys and girls with no further risk increase for doses above 15 cigarettes.

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INTRODUCTION

Several recent meta-analyses showed a strong associations between maternal smoking during pregnancy and offspring overweight and obesity with pooled odds ratios (OR) ranging from 1.33 to1.60 [1–4]. Therefore smoking abstinence during pregnancy might have substantial benefit for prevention of offspring obesity in addition to the avoidance of multiple tobacco-related harms to the mother and the child (i.e., preterm delivery, sudden infant death (SIDS), or birth defects). Although plausibility of a causal association between maternal smoking in pregnancy is supported by some animal [5–9] and DNA methylation studies [10–13] there remains concern regarding residual confounding in the observational studies. For example: several studies have shown that children exposed to paternal, or other second-hand smoke in utero or following pregnancy, were at increased risk of overweight, although risk was lower than that for maternal smoking [14–17]. While associations of both maternal and paternal smoking with offspring overweight remained present despite controlling for parental weight and social class, this may reflect residual confounding by unmeasured neighborhood or family factors accounting for both.

Addressing potential residual confounding, one study within families where one child was exposed to maternal smoking and the other was not yielded inconclusive results [18], whereas another study using conditional fixed-effect models among siblings to control for unmeasured confounding confirmed an effect of maternal smoking on overweight [19]. A recent meta-analysis suggested a much smaller specific effect of maternal smoking in pregnancy than reported in previous meta-analyses when taking account of the effect of paternal smoking as a negative control reflecting unmeasured family factors [2]. The association with paternal smoking however, might not only be a reflection of residual confounding. There might be a genuine effect of paternal smoking in pregnancy related to intrauterine exposure to small nicotine doses resulting from maternal inhalation of father's smoke. This hypothesis would be

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supported by a dose response relationship for maternal smoking in pregnancy, if even small doses of maternal smoking are associated with offspring overweight. Indeed cotinine has been detected in newborns' hair with paternal smoking exposure alone which could arise from passive inhalation by the mother and transfer to fetus. These cotinine concentrations were within the range seen with maternal smoking [20,21]. A dose response relationship of maternal smoking and offspring overweight or obesity was detected in some [22–33], but not in all studies [19,34–36], which may be due to different confounders considered and difference in categorization of the dose of maternal smoking. An individual patient data (IPD) meta-analysis allows for uniform assessment of the dose-response in all included studies.

There are several meta-analyses of the association between maternal smoking in pregnancy and offspring overweight or obesity [1–4], however, none has previously explored the dose-response relationship between maternal number of cigarettes during pregnancy and offspring obesity/overweight. Information on whether the risk of overweight/obesity increases with the level of fetal nicotine exposure or whether there is a threshold below which there is no association can provide needed insight into the etiology of offspring overweight/obesity and information to further refine smoking cessation efforts during pregnancy not only for the mother, but potentially all household members. A valid assessment of the dose response requires meta-analysis with uniform assessment of the dose-response in all included studies. Since the reported studies on dose-response assessed the effect in different smoking categories, this is only possible in IPD meta-analyses and could be materialized as many studies ascertained maternal smoking exposures in more detail than reported in the published papers.

Here we undertook an IPD meta-analysis designed to test the hypothesis that there was a linear relationship between the number of cigarettes smoked during pregnancy and risk for child overweight. Since animal studies suggested that changes in the intrauterine milieu

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AUTHOR VERSION

affecting body composition in the offspring may be different by sex, we stratified by offspring sex [37].

METHODS

Potentially eligible studies were identified in a systematic literature search [38] (Figure 1) using the following search term: (offspring OR children OR toddlers OR child OR infant OR adolescen* OR adult*) AND (overweight OR obesity OR obese OR adipose OR adiposity) AND (maternal smoking during pregnancy OR maternal smoking in pregnancy OR mother smoked during pregnancy OR mother smoked in pregnancy OR in utero nicotine exposure OR in utero exposure OR nicotine exposure during pregnancy OR nicotine exposure in pregnancy OR cigarettes during pregnancy OR cigarettes in pregnancy) AND (dose-response OR dose-effect OR dose OR amount of cigarettes OR number of cigarettes OR volume of cigarettes OR volume of nicotine). All studies (retrospective and prospective) that included data on the number of cigarettes mothers smoked during pregnancy and the weight and height of children ≥ three years were considered for inclusion in our IPD. Outcome had to be reported as overweight or obesity or BMI differences in the offspring of mothers who smoked during pregnancy compared to offspring of mothers who did not smoke during pregnancy. Studies were excluded if the manuscript language was neither English nor German, or if the study population was already reported in another included study. All studies published before May 2015 were considered. The literature search was performed independently by two investigators (CS and RvK).

Authors of the selected studies were sent an invitation letter via email. If no response was received after about two months, a second reminder email was sent. Collaboration and data transfer agreements were signed by authors cooperating in this project.

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The study was approved by the Ethics Committee of the LMU Munich (UE Nr. 024-14). For all included studies individual ethical approval is documented in the respective original publications.

The study is registered at PROSPERO international register of systematic reviews with registration number CRD4201502475.

Assessment of study quality

Study quality was assessed based on the quality assessment criteria for observational cohort and cross-sectional studies of the National Institute of Health (http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort). Eight questions out of 14 were appropriate for this analysis (Table S1). We excluded questions regarding sample size/power estimate, sufficient timeframe to observe effect, different levels for exposure, quality of exposure measure, several measures of exposure and adjustment for confounding variables, as the answers were obvious, or they were already considered in the inclusion criteria. Quality assessment was conducted independently by two investigators (RvK and LA) with each study rated as poor, fair, or good by mutual agreement.

Statistical methods

The primary outcome variables were overweight (including obesity) or obesity only (defined according to the International Obesity Task Force (IOTF) reference [39]) and were analyzed in two separate models. If data on BMI measurements at different ages were available, the measurement at the oldest available age was used in the analysis, since tracking of BMI increases by age [40–42].

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The main explanatory variable was the number of cigarettes smoked by the mother during pregnancy of the child, who was included in the analysis. If the study provided multiple measures at different stages of pregnancy, we used the maximum number of cigarettes at any time point. In studies where the number of cigarettes was observed only in categories (e.g. none, 1-10, 11-20, >20 cigarettes per day), the actual numbers of cigarettes smoked during pregnancy were generated by randomly imputing a number from an assumed uniform distribution in the respective category for each mother. For the last, open categories (i.e., >20 cigarettes per day), numbers were imputed from an exponential distribution where the parameters of this distribution were estimated from the observations from all remaining studies using the actual observations above the lower category bound.

Potential confounders considered in the analysis were identified using a directed acyclic graph (Figure 2). The number of potential confounders included in the models was driven by their availability in the studies included in the meta-analysis. In the main analysis we considered a) maternal weight status (underweight (BMI<18 kg/m²), overweight (25 kg/m²≤ BMI<30 kg/m²), obese (BMI≥30 kg/m²) or normal weight (18 kg/m²≤ BMI<25 kg/m²; which was used as reference)) (if available pre-pregnancy weight was used; if not available, then maternal weight at assessment of child's BMI was used); b) breastfeeding (for at least one month if available, else ever breastfeeding) (yes vs. no); c) maternal education (at least high school completed or 10 years of school education vs. no high school completed or less than 10 years of school education).

We also considered size at birth including small for gestational age (SGA; weight <10th percentile) or large for gestational age (LGA; weight >90th percentile) with reference to appropriate for gestational age (AGA; weight for gestational age between 10th and 90th percentile) as defined in the original studies or applying country specific percentiles if not reported, and preterm delivery (<37 weeks of gestation) to be of substantial interest. First,

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effect modification was examined by stratifying for SGA, AGA and LGA. Then, models with adjustment for SGA, LGA and preterm delivery were provided in a supplementary analysis. These models would give the direct effect of smoking on overweight/obesity (beyond the effects working through SGA, LGA or preterm delivery), whereas the main analysis gives the best estimate from the data of the overall causal effect of maternal smoking, namely the effect of a hypothetical intervention reducing maternal smoking on offspring overweight/obesity [43].

Missing values for the potential confounders/mediating variables were imputed by a model-based single imputation step (PROC MI, SAS, V.9.4), the imputation model included the exposure, the confounders, and a categorical study effect. As the percentage of missing values was small (<2.2% of the observations for maternal weight status, child's birth weight for gestational age, preterm delivery, breastfeeding, maternal education) and the sample size large we did not correct the analysis results by applying Rubin's rules [44].

In a first step, the dichotomized effect of maternal smoking (yes vs. no) during pregnancy on either offspring overweight including obese children, overweight excluding obese children, or obesity excluding overweight children was analyzed in logistic regression models with adjustment for potential confounders (maternal weight status, breastfeeding, maternal education) and stratification for infant sex. A random intercept term for the respective study was included to account for variation between and correlation within studies. Family variations could not be taken into account in these models, thus sibling/twin data were excluded.

To analyze the dose response relationship of number of cigarettes smoked during pregnancy, a generalized additive mixed model was used as described by Lin and Zhang for binary outcomes [45]. Such models use additive non-parametric functions to model the effect of covariates, while they additionally account for correlation of children-mother pairs within studies by adding a random study effect to the predictor. We used P-splines (smoothed linear

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AUTHOR VERSION

functionals) for the estimation of the nonlinear effect, with data-driven estimation of the smoothness of the effect by restricted maximum likelihood (REML). The analysis was performed separately for boys and girls since some previous studies reported gender-specific differences of the association between maternal smoking in pregnancy and overweight in the offspring [24,46–49]. Furthermore age-stratified models for the age groups <3, ≥3 to <5 years, ≥5 to <8, and ≥8 years (chosen to achieve as similar as possible numbers per stratum) were estimated.

In sensitivity analyses further potential confounders (with data not available in all studies) were considered: A) paternal smoking (yes vs. no), B) child TV watching/video games (high = '≥ 1 hr per day'; moderate/low = '<1 hr per day') at obesity assessment, C) child physical activity (sufficient = '≥ 1 h per day', low = '<1 h per day') at obesity assessment.

Two additional sensitivity analyses were performed; one in which observations with imputed data (number of cigarettes and potential confounders) were excluded and another which only included studies where the study quality was rated good.

RESULTS

The results of the literature search are shown in Figure 1 with 26 studies meeting the inclusion criteria. Their investigators were invited to participate in the present IPD meta-analysis and 16 provided data [19,22–28,46,50–56]. Study characteristics are shown in Table 1: The included studies (13 prospective studies and 3 retrospective studies) were undertaken in eight different countries with the assessment of BMI carried out in children of age five or older in most studies. In two studies younger children with mean ages of 4.7 and 3.8 years were included [23,26]. Thirteen of the 16 studies provided information on the precise number of maternal

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AUTHOR VERSION

cigarettes smoked. For the remaining studies with interval censored data (with assessments in 4-5 dose categories) [28,46,52] imputation was performed. Paternal smoking during pregnancy was assessed in eight studies. Different definitions for small (and large) for gestational age were used across studies. Most studies used country specific percentiles; two Brazilian studies used the Williams percentiles [57] to define small (large) for gestational age. Another study used population specific percentiles (10^{th} and 90^{th}) defined as cut-off points [22], whereas two studies used a web-calculator [23,25]. Children were assumed to be breastfed if the mother reported at least 1 month of breastfeeding, in one study this was at least 1.5 months [27], in another at least three months exclusive breastfeeding [51], and in four studies any breastfeeding ever was assessed at time or at interview [23,25,26,56]. Maternal pre-pregnancy BMI was assessed in nine studies, at interviews after pregnancies ended in five studies [19,23,27,50,51] and imputed in two studies by using the conditional distributions of the complete datasets [25,50]. High maternal education was defined as completed high school or ≥9-10 years of school except for one study where ≥12 years of schooling was assumed as high education, and one study where a combination of education and occupation was assessed [22,26]. The study quality was rated good in eleven studies and fair in five studies (Table S2 of the supplemental material).

Table 1 here

In total N=422 064 BMI measurements (including multiple measurements per child) of children/adolescents years were available. After excluding twins and siblings (only first child was included), observations with missing data on maternal number of cigarettes, and observations where sex and age specific weight class according to the IOTF reference [39] could not be assigned (excluding children aged <2 years with no such reference data, or children

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with missing data on gender) N=238 340 mother-child pairs were available for analysis (boys N=121 254, girls N=117 086) (Figure 3).

The prevalence of offspring overweight (including obesity) was 18.50% (N=44 088), of which obesity counted for 5.07% (N=12 081). 21.77% (N= 51 887) of mothers reported to have smoked during pregnancy with a mean number of cigarettes per day of 11.06 (SD=9.06). The overall odds ratios (OR) in offspring of mothers who smoked compared with offspring of mothers who did not smoke during pregnancy was 1.26 (95% CI=[1.22-1.29]) for overweight (including obesity) (girls: 1.22 with 95% CI=[1.18-1.27]; boys: 1.30 with 95% CI=[1.25-1.35]) and 1.24 (95% CI=[1.18-1.29]) (girls: 1.25 with 95% CI=[1.17-1.37]; boys: 1.22 with 95% CI=[1.14-1.51]) for obesity in the adjusted (for maternal weight status, breastfeeding, maternal education) random effect model that included data for all 16 studies. For overweight excluding obesity, the corresponding OR was 1.26 (95% CI=[1.22-1.30]). In the sub-sample where paternal smoking was assessed (N=58 812) the OR for the global association between maternal smoking and both overweight (including obesity) and obesity only without adjustment for paternal smoking was higher (overweight: 1.46, 95% CI=[1.39-1.55]; obesity: 1.54, 95% CI=[1.39-1.71])); after adjusting for paternal smoking OR were 1.37 (95% CI=[1.29-1.45]) for overweight (including obesity) and 1.40 (95% CI=[1.26-1.57]) for obesity only.

We analyzed the number of cigarettes on a continuous scale to assess a dose response relationship for both overweight and obesity overall and stratified by sex. The odds of a child being overweight or obese increased linearly up to 10-15 cigarettes per day and levelled out for doses higher than 15 cigarettes per day (Figure 4). For example for 12 cigarettes per day, odds ratios were 1.29 (95% CI=[1.25-1.33]) for overweight (including obesity) and 1.26 (95% CI=[1.20-1.33]) for obesity only, reflecting an OR per additional cigarette of 1.02 [1.02-1.02] for overweight (including obesity) and 1.02 [1.02-1.02]) for obesity only. The

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AUTHOR VERSION

association for overweight appeared to be slightly more pronounced in boys than in girls but with widely overlapping 95% confidence intervals (Figure 4).

Stratified analysis by age at BMI assessment showed an increase of the effect size by age, with the largest ORs observed for those aged 5-8 years (Figure 5).

For birth weight for gestational age, stratified analysis did not suggest effect modification (associations between maternal smoking and offspring overweight (including obesity) was OR=1.26 with 95% CI=[1.17-1.36] in SGA children, OR=1.33 with 95% CI= [1.29-1.37] in AGA children and OR=1.29 with 95% CI= [1.18-1.42] in LGA children). Models with adjustment for small for gestational age (Figure S1) and large for gestational age (Figure S2) both showed a general increase in effect compared to the main model. In the model with adjustment for preterm delivery nearly no change in the association was seen (Figure S3).

Sensitivity analyses, adjusting for additional potential confounding variables - assessed only in some of the included studies - yielded very similar results compared to models without additional adjustment for these variables. With adjustment for paternal smoking (N=58 812; eight studies) a similar pattern was observed compared to the model not adjusted for paternal smoking: for overweight (including obesity) the increasing risk per cigarette was OR=1.02 (95% CI=[1.02-1.03]) compared to OR=1.03, 95%-CI=[1.02-1.03] for the model not adjusted for paternal smoking; for obesity OR=1.02 (95% CI=[1.02-1.03]) compared to OR=1.03 (95% CI=[1.02-1.04]) (Figure S4). In the sample where child TV watching/video games was assessed (N=18 850; six studies) additional adjustment did not change the results for the association with overweight (including obesity) (Figure S5). For obesity only in general confidence intervals were very wide precluding any conclusions. When adjusting the original model additionally for child physical activity (N=12 338; eight studies) the magnitude of the dose-response effect for both overweight (including obesity) and obesity only for the main analysis was unchanged (Figure S6).

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Restricting the analysis to the eleven studies with good quality (excluding also retrospective studies except one with validation of exposure in medical records), showed essentially no change in the association of the number of cigarettes smoked during pregnancy with offspring overweight (including obesity) and obesity only. Associations were of slightly smaller magnitude with a linear effect up to 20 cigarettes per day. However confidence limits were widely overlapping (Figure S7). Including only completely assessed data without imputation (for the interval censured, maternal smoke dose exposures, or missing values for confounder variables) showed very similar dose-response effects for both overweight (including obesity) and obesity only compared with the main analysis (Figure S8).

DISCUSSION

Our data show a linear increase in offspring risk for becoming overweight and obese by number of cigarettes smoked during pregnancy for up to 10-15 cigarettes per day. This relationship was most pronounced in children aged 5-8 years, which accords with previous evidence that the effect emerges in the preschool years [49]. Thus, even few maternal cigarettes smoked per day may confer risk for subsequent offspring overweight and obesity. With further increments in smoking frequency beyond 15 cigarettes per day, there was no apparent increased additional risk.

Most previous studies attempting to assess dose response relationships for maternal smoking did not analyze the number of cigarettes smoked on a continuous scale, but compared categories using 5-10 cigarette groupings (reference none smoking) thus yielding imprecise estimates of the dose response relationship [17,23–29,29–33,58,59]. Some of these studies did not detect a dose response relationship [19,34,36,60]. Only two studies assessed dose response

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relationships by number of cigarettes on a continuous scale [22,35] and these assumed a linear association over the whole range of frequency of cigarette use. In the present analysis, applying P-splines for the estimation of non-linear effects, with data-driven estimation of the smoothness of the effect by generalized cross-validation minimization, no fixed linear association was forced on the data. Indeed, a linear association was only observed for up to 10-15 cigarettes. The observation of flattening of the effect with very high number of cigarettes smoked by the mother might be due to reporting bias, which might arise if heavy smoking mothers lose awareness of the number of cigarettes smoked. Assuming selective underreporting of excessive smoking, however, would rather account for an upward shift of the curve.

Implications of study findings

Since cotinine concentrations in the offspring related to paternal cigarette smoke exposure alone [61] can be similar to concentrations when only a few cigarettes are smoked by the mother, the linear dose response relationship up to 10-15 cigarettes may have implications for the understanding of the role of paternal smoking for offspring overweight [2]. The paternal smoking effect might be a reflection of low doses by passive smoking; exposing the pregnant mother to environmental tobacco smoke (ETS) may have a genuine effect on the child's risk for overweight. Cotinine values in urine of neonates from non-smoking mothers increase in relation to number of daily cigarettes smoked by the father during pregnancy [62]. Interestingly, two studies reported a dose response relationship for the risk of overweight and obesity for paternal smoking during pregnancy [17,25]. Whether this effect of paternal smoking is mediated by passive smoking of the mother during pregnancy, or is transmitted via the spermatozoal genome (meaning the preconceptional toxical exposure of the father) as explored in a recent methylation study [63] is unknown. A low exposure to maternal smoking, which appears to have

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AUTHOR VERSION

an effect on offspring overweight/obesity, may be mimicked by ETS. Therefore one implication of our findings is, that any environmental smoke exposure during pregnancy might causally related to overweight/obesity in offspring.

Mechanistic pathways linking prenatal exposure to cigarette smoking to obesity are not well understood. One potential pathway may involve exposure-related effects on the developing brain-reward system. The system processes hedonic properties of food (as well as drugs of abuse) and includes brain structures, such as the amygdala [64]. In a brain-imaging study of adolescents, prenatal exposure to maternal cigarette smoking was associated with higher adiposity and preference for fatty foods and lower volume of the amygdala; further, amygdala volume correlated inversely with fat intake [65]. Diets high in fats are considered rewarding [66] and obesogenic [67], as fats compared with other macronutrients (i.e. carbohydrates and proteins) are of higher energy density and efficiency [68]. The amygdala has been studied extensively in the context of both drug addiction and the regulation of fat preference. With respect to the former, lower amygdala volume has been observed in individuals with alcohol addiction in whom it was associated with greater alcohol craving and more likely relapse into alcohol consumption [69]. With respect to the regulation of fat preference, activation of the amygdala by intra-amygdala administrations of neuropeptide Y and enterostatin decreases dietary preference for fat in experimental animals [70,71]. In human brain-imaging studies, the amygdala is activated by high-fat versus low-fat food stimuli [72]. These observations are consistent with the possible role of the prenatal exposure-induced reduction of the amygdala size in increasing fat preference and, in turn, risk for obesity.

Strengths and Limitations

The major strengths of this study are the large sample size and application of a dose response model allowing assessment of dose response in a uniform analysis by number of cigarettes

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AUTHOR VERSION

smoked and confounding factors. In contrast to previous studies, this study did not restrict estimates to a linear association, but instead employed P-splines to examine possible non-linear effects.

The validity of the findings is supported by the robustness of these results confirmed by sensitivity analyses considering paternal smoking and other possible confounding variables.

The dose response relationship observed in the main analysis might still reflect residual confounding due to imprecise measurement and limited information on potential confounders. However, the sensitivity analysis, based on studies, which provided more extensive information on confounders including paternal smoking, physical activity, and TV watching/video games, yielded very similar risk estimates and strengthens the main conclusion. Confounding by unknown risk factors e.g. nutrition and eating patterns [73] cannot be excluded.

Furthermore, we showed that size for gestational age is not an effect modifier for the association between maternal smoking during pregnancy and offspring overweight. Hence, it might act as mediator. Adjustment for size at birth and gestational age, (Figure 2) yielded generally higher estimates with a similar pattern as the main analysis results. These estimates can be interpreted as the direct effect of smoking on overweight or obesity (independent of the effects working through SGA, LGA or preterm delivery), whereas the models without adjustment for these potential mediating variables estimates the total effect of maternal smoking. These higher estimates might imply that there are two oppositely acting pathways from maternal smoking during pregnancy through offspring overweight and obesity: one reducing child adiposity by reducing birth weight and another increasing child adiposity through another pathway.

Selection bias due to non-participation of eligible studies, whose authors did not contribute data to the IPD analyses [17,18,29,32,33,35,36,59,60,74] might be an issue. We summarized study

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441 characteristics and dose-response results for the number of cigarettes smoked during
442 pregnancy or overall results for the association between smoking in pregnancy and offspring
443 anthropometric outcome in studies not providing data for the IPD meta-analysis in Table S3
444 of the supplemental material. Unfortunately it was impossible to provide a summary estimate
445 of the dose response relationship reported in the studies which had not provide data, because
446 units, outcomes, statistics differed between studies. In studies reporting odds ratios for the
447 association between overweight/obesity and maternal smoking, the strength of the effects
448 were comparable with the main findings.

449 It would have been ideal to use also repeated BMI outcome measures of the same child for the
450 analysis. Therefore, we tried to estimate such models with an additional random effect for the
451 child's identification number, but unfortunately these models did not converge irrespective of
452 which statistical software was used (neither R nor SAS).

453 A concern for validity is that mothers may have under-reported the number of cigarettes
454 smoked during pregnancy due to negative social stigma associated with smoking in
455 pregnancy. In cases where under-reporting was selective, meaning that only those reporting
456 the lowest number of cigarettes were misreporting and those who reported smoking more
457 cigarettes gave the true numbers, this could be an explanation for the flattening of the dose
458 response effect. However, there is no ideal biomarker for early pregnancy smoking exposure.
459 Cotinine concentration in the newborn's hair constitutes a very precise measure for the
460 cumulative smoke exposure during pregnancy during the last three months of the pregnancy
461 [75]. Such data have demonstrated a close association between the self-reported number of
462 maternal cigarettes smoked and the measured newborn hair cotinine concentration [76].
463 However, maternal smoking in the third trimester might not be the best indicator for overall
464 smoke exposure of the fetus [77]. Good markers for early pregnancy smoke exposure are
465 required. End-tidal breath carbon monoxide (ETCO) levels and urine cotinine levels in the

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mother do provide more accurate measurements for recent nicotine and carbon monoxide exposure [78], but may indicate transient exposures rather than chronicity during pregnancy. Substantial within-person fluctuation may exist if women repeatedly try to quit or cut-down. This may explain why confidence intervals widen at doses >15 cigarettes. Pickett et al. suggest that where timing, intensity and duration of exposure are critical, self-reported history of cigarette consumption may be a better measure for fetal exposure [79]. Maternal smoking status at different stages of pregnancy was only reported in few studies, therefore in our study we could not assess whether the duration of smoking is also important for child overweight and obesity. If a longer duration is stronger associated with offspring overweight and obesity, as suggested by a large study from the United States [26], our current results would be an underestimate of the true association among continued smokers.

CONCLUSION

A linear dose-response relationship between maternal smoking during pregnancy and the child's risk for overweight was observed for mothers who smoked one to 15 cigarettes per day. Since these findings suggest that even very low doses of cigarette smoke exposure during pregnancy may increase the risk of offspring overweight and obesity, family smoking cessation programs and recommendations about avoiding passive smoke exposure are warranted.

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Conflict of interest

All authors declare that they have no competing financial interests in relation to the work.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

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Supplementary information is available at International Journal of Obesity's website.

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Figure Legends

Figure 1: Flow chart displaying the process of literature search and study selection

Figure 2: Directed acyclic graph on potential confounders

Figure 3: Flow chart on mother-child pairs included in our final study population

Figure 4: Association of maternal number of cigarettes smoked per day and risk of offspring overweight (includingobesity) and obesity only stratified by gender (____ =odds ratio (OR) for the association between maternal number of cigarettes and offspring overweight/obesity; _ _ _ =

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95%-CI of the OR; the vertical dashes above the x-axis indicate the density of the observations underlying the model;)

Figure 5: Association of maternal number of cigarettes smoked per day and risk of offspring overweight (including obesity) and obesity only stratified for age groups (two to younger than three years (N=82 572/ N=70 054), three to younger than five year old children (N=85 019/ N=72 805), five to younger than eight year old children (N=78 954/ N=71 997), over eight year old children (N=17 936/ N=15 458) (____ =odds ratio (OR) for the association between maternal number of cigarettes and offspring overweight/obesity; _ _ _ = 95%-CI of the OR; ……. = OR with 95%-CI for the overall effect of the main model; the vertical dashes above the x-axis indicate the density of the observations underlying the model;

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741 **Table 1: Study characteristics**

Author, Year, County	Study, study type	N cases include in our IPD	Children's age in years (mean ± SD)	Continuous assessment of number of cigarettes	Assessment of paternal smoking	Potential mediators		Potential confounder variables assessed				Study quality (assessed with NIH tool[a]
						SGA/LGA	Pre-term	Breastfeeding	Maternal BMI after pregnancy	Maternal BMI before pregnancy	Maternal education	
Møller, 2014 Denmark	Danish National Birth Cohort, prospective study	44544	7.0 ± 0.3	yes	yes	yes, defined in study population, as <10th respectively >90th percentile adjusted for gestational age and gender	yes	yes (≥1month)	yes	yes	yes, combination of education and occupation (low, medium, high)[b]	fair
Bettiol, 2010 Brazil	Ribeirão Preto birth cohort, prospective study	723	10.6 ± 0.3	yes	yes	yes, based on the Williams curve (Williams et al., 1982)	yes	yes (≥1month)	no	no	yes, at least 9-10 years school (assessed in categories)	good
Da Silva, 2010 Brazil	São Luís birth cohort	672	8.2 ± 0.3	yes	yes	yes, based on the Williams curve (Williams et al., 1982)	yes	yes (≥1month)	yes	no	yes, at least 9-10 years school (assessed in categories)	good
Gilman, 2008 United States	Collaborative Perinatal Project (CPP), prospective study	12516	Ca. 7	yes	no	yes, based on United States percentiles (Talge, 2014)	yes	no	yes	no	yes, at least 10 years school	good
Grzeskowiak, 2015 Australia	Women's and Children's Health	6877	4.7 ± 0.3	yes	no	yes, calculated with generic birth weight	yes	yes (any breastfeeding yes/no)	yes	no	no	good

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	Network, prospective study					centile calculator from gestation.net						
Howe, 2012 United Kingdom	ALPAC, prospective study	9127	15 ± 3.6	yes	yes	yes, based on British percentiles (Cole 1998)	yes	yes (≥1month)	yes	yes	yes, at least A level	good
Boerschmann, 2010 Germany	German GDM offspring study, prospective study	492	13.5 ± 4.6	yes	yes	yes, based on German percentiles (Voigt, 1996)	yes	yes (Fully breastfed ≥3 months)	yes	no	no	fair, because of limited external validity
Jones, 1999 Australia	"live births in Tasmania", prospective study	390	ca. 8	no, categorical assessment "null" "1-10", "11-20", "21-40", ">40" (cig. per day)	no	Yes, based on Australian percentiles (Dobbins 2012)	yes	yes (≥1month)	yes	yes	yes, completed high school	fair, because of limited external validity
Koshy, 2010 United Kingdom	"15 primary schools in Merseyside", retrospective study	1829	7.9 ± 1.9	yes	yes	only sga, IUGR computed	yes	yes (any breastfeeding yes/no)	no	no	yes, secondary education and above	fair
Oken, 2005 United States[c]	Project Viva, prospective study	970	7.9 ± 0.8	no, categorical assessment "Never smoker", "<1", "1-4", "5-14", "15-24", "≥25" (cig. per day)	no	yes, based on US percentiles (Oken, 2003)	yes	yes (≥1month)	yes	yes	yes, completed high school	good
Syme, 2010	Saguenay Youth Study	478	13.7 ± 1.2	yes	yes	yes, based on US percentiles	yes	yes (total duration in	yes	yes	yes, completed	good

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Canada	(SYS), retrospective cohort study of prenatal exposure to maternal cigarette smoking					(Talge, 2014)		months)			high school	
Sharma, 2008 United States	Prevention's Pregnancy Nutrition Surveillance System (PNSS), prospective study	71270	3.8 ± 0.5	yes	no	yes, based on United States percentiles (Talge, 2014)	yes	yes (any breastfeeding yes/no)	yes	yes	yes, ≥12 years school	good
Thiering, 2011 Germany	GINI LISA, prospective study	6323	13.0 ± 3.9	yes	no	yes, using German percentiles (Voigt, 1996)	yes	yes (≥1 month exclusively breastfed)	yes	yes	yes, ≥10 years school	good
Prabhu, 2010 United Kingdom	SEATON, prospective study	841	7.7 ± 2.7	yes	yes	yes, using British percentiles (Cole 1998)	yes	yes, (breastfeeding at 4th month after birth)	no	yes	yes (age at leaving education at least 16)	good
Widerøe, 2003 Norway	Trondheim and Bergen (Norway), and Uppsala (Sweden), prospective study	515	5.3 ± 0.2	yes	no	yes, defined in study population, as $<10^{th}$ respectively $>90^{th}$ percentile adjusted for sex, parity	yes	yes (≥1.5 months)	yes	no	yes, at least 9 years school + 1-2 years further education	good
Von Kries, 2002 Germany	"six Bavarian communities", retrospective study	5594	6.2 ± 0.4	no, categorical assessment "no cigarettes", "1-10", "11-20", ">20"	no	yes, using German percentiles (Voigt, 1996)	yes	yes (≥1 months fully breastfed)	no	yes	yes, at least >9 years school	fair

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				(cig. per day)								

[a] Detailed quality assessment in online supplement Table S1

[b] Socio-occupational status based on the current or most recent job within 6 months, or, if the woman was attending school, on the type of education. Women in training were categorized according to the type of education they headed for. The category "high" included women in management jobs or in jobs requiring higher education (generally more than 4 years beyond high school). Office workers, service workers, skilled manual workers, and women in the military constituted the "middle" category. The "low" category included unskilled workers and unemployed women. Women with no connection to the labour market (not in training, not disability-retired, not house wife, not on public support) were also categorized in the "low" category.

[c] the most recent outcome data (mid-childhood) assessed in that study was used (not included in that publication)

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AUTHOR VERSION

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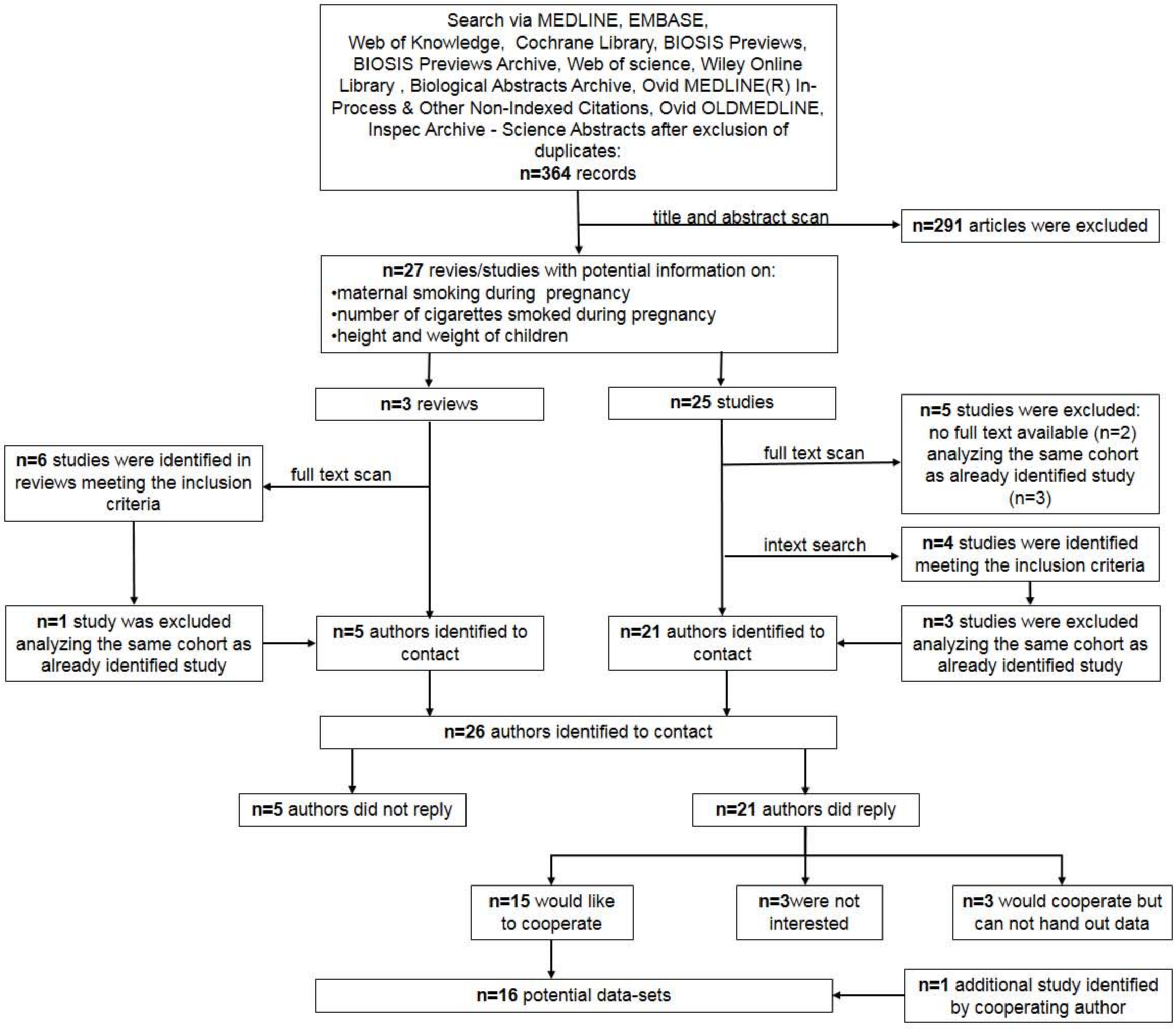

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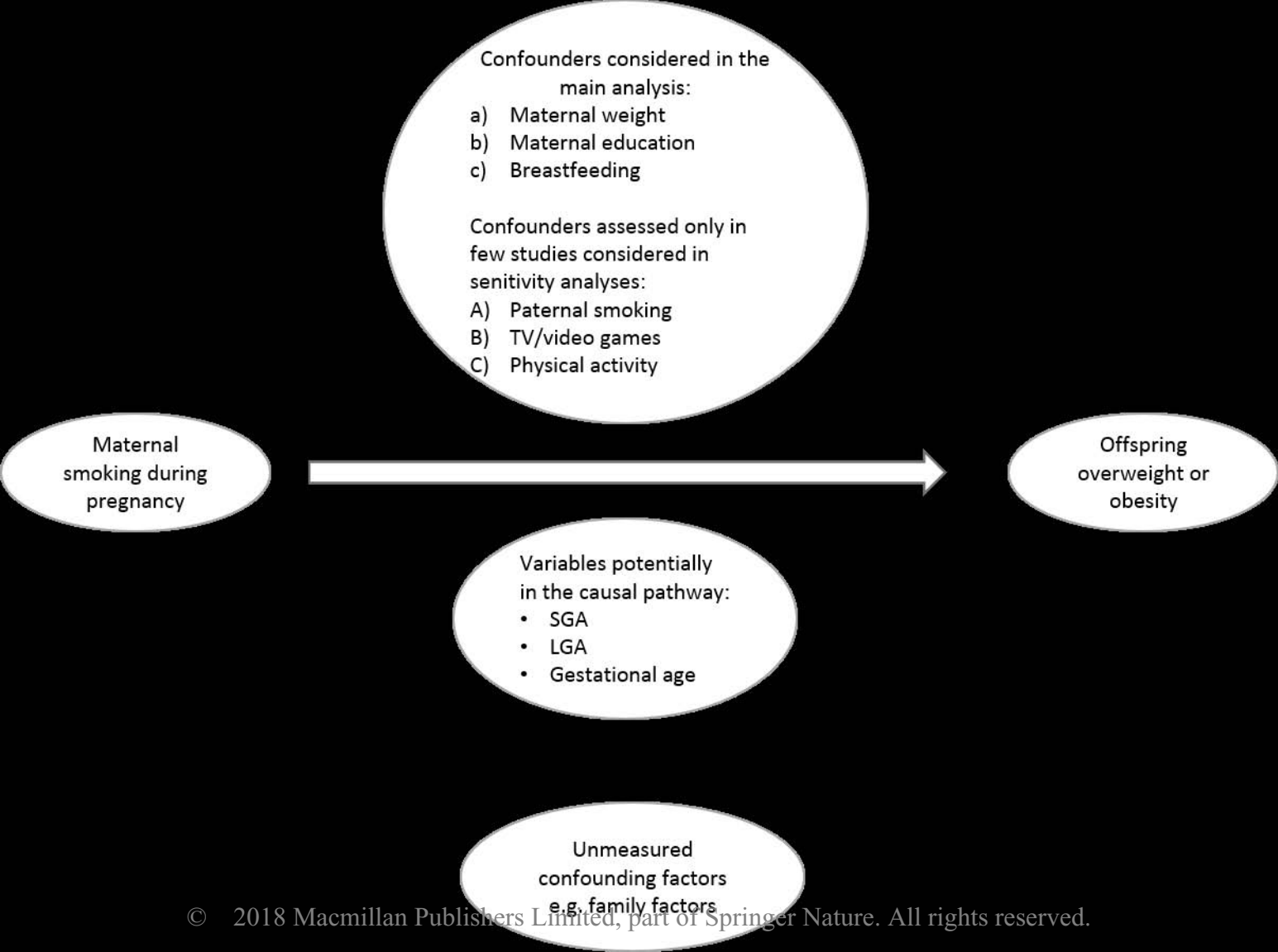

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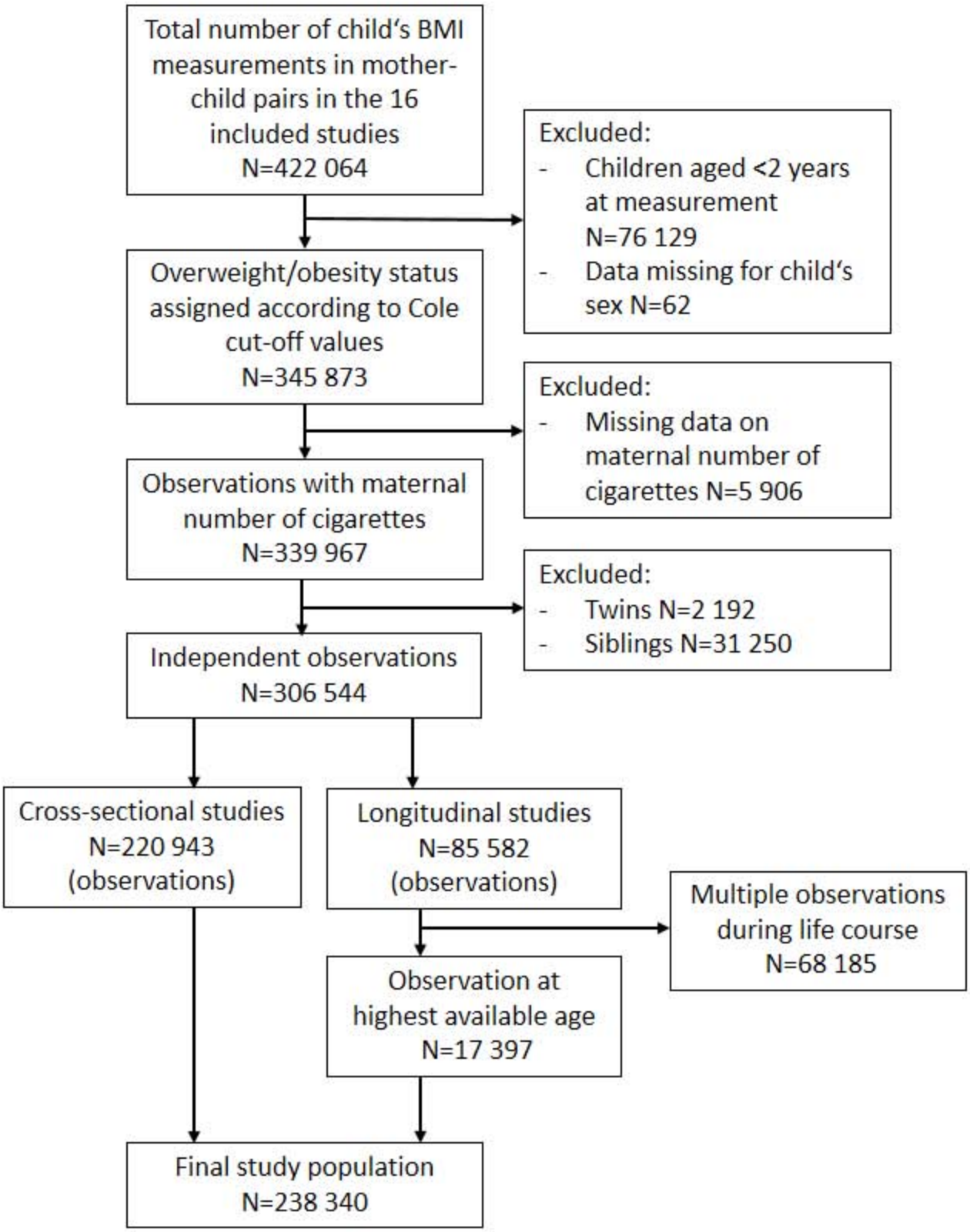

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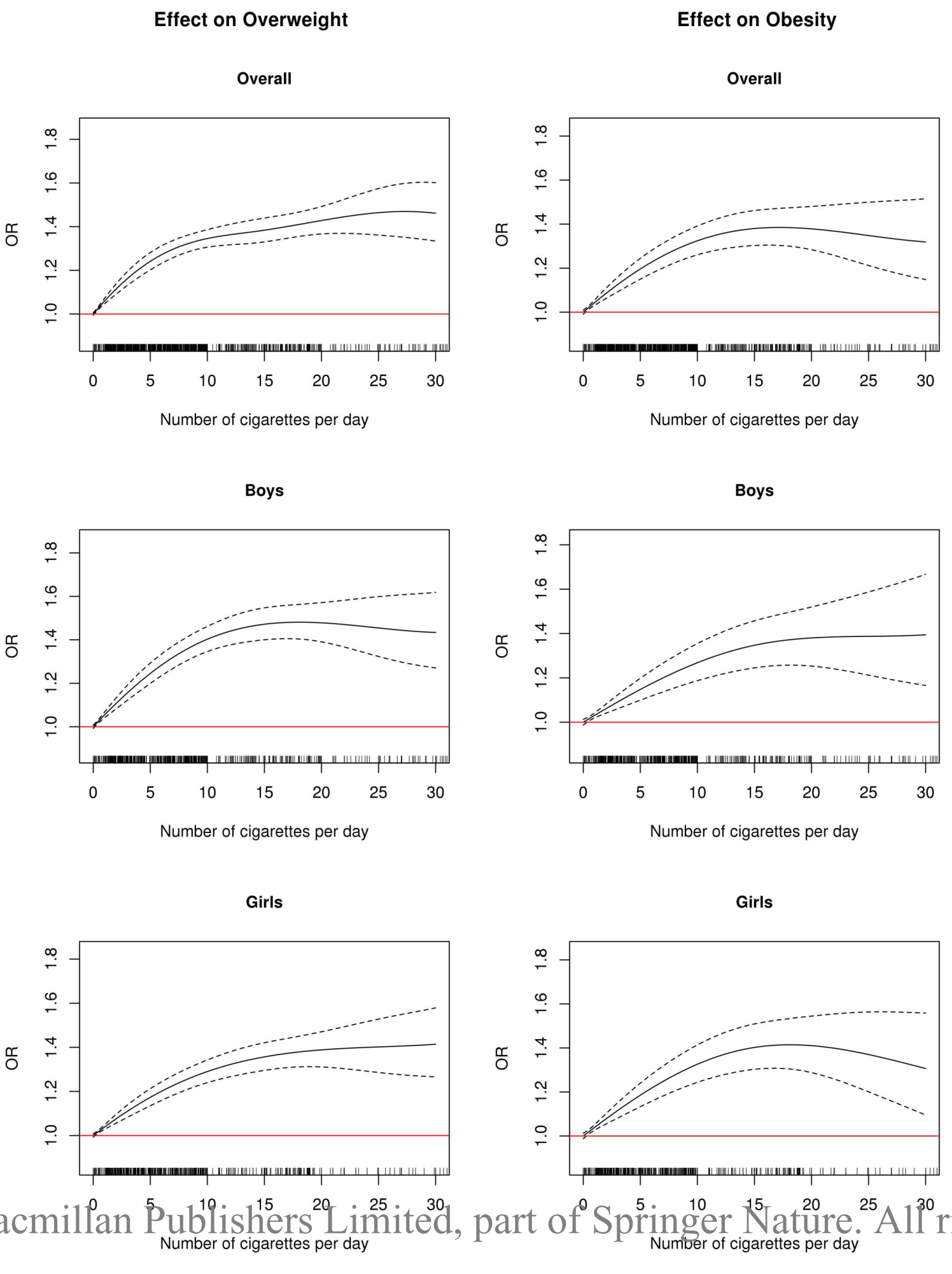

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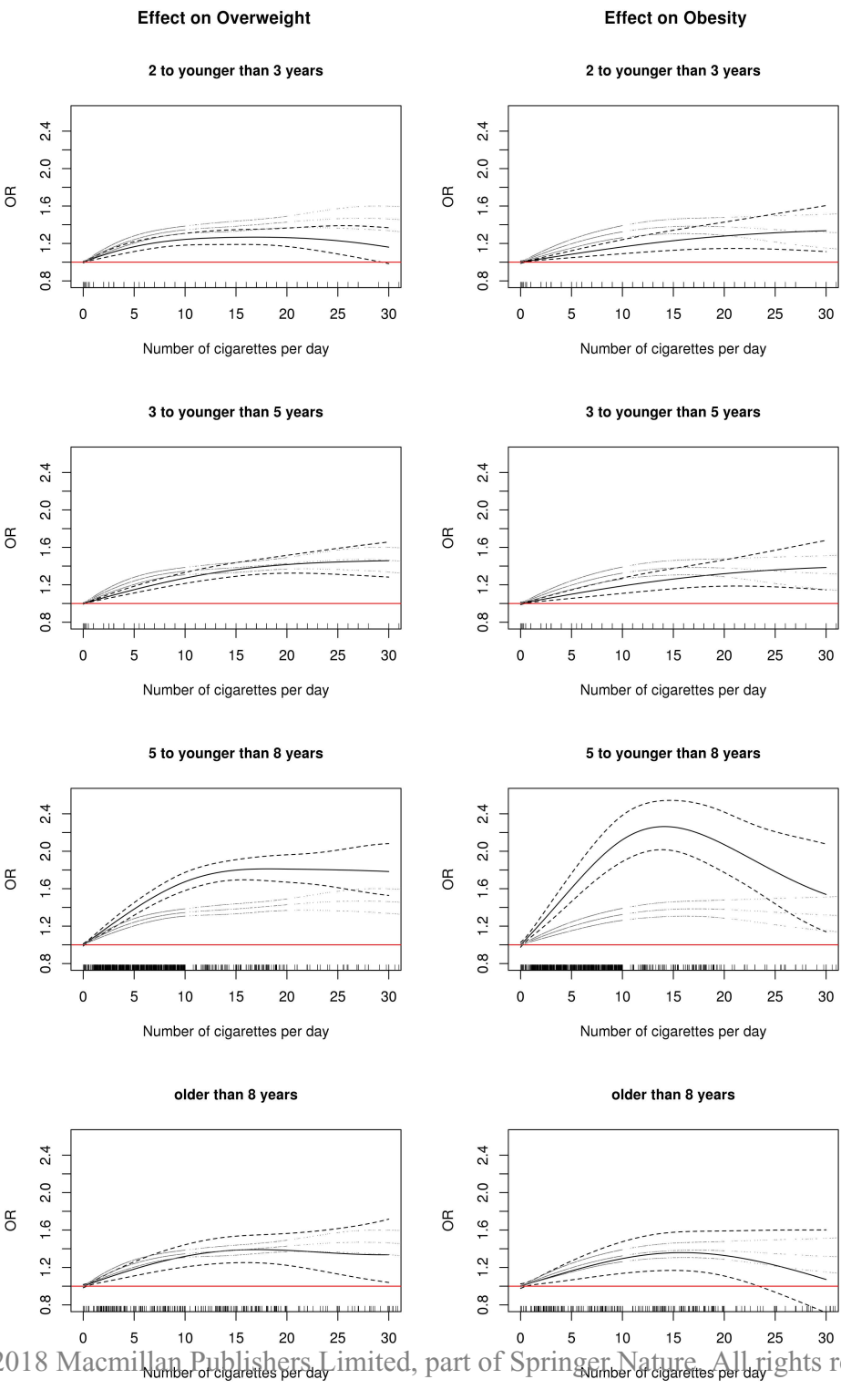

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