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REVISÃO
REVIEW

Maternal smoking during pregnancy and offspring body mass index and overweight: a systematic review and meta-analysis

Tabagismo materno durante a gravidez e índice de massa corporal e excesso de peso entre os filhos: uma revisão sistemática e metanálise

Tabaquismo materno durante el embarazo e índice de masa corporal y sobrepeso en los hijos: una revisión sistemática y metaanálisis

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Abstract

The present study aimed to conduct a systematic review and meta-analysis to evaluate the evidence on the association of maternal smoking during pregnancy with offspring body composition in childhood, adolescence and adulthood. MEDLINE, Web of Science and LILACS databases were searched. Reference lists were also screened. We included original studies, conducted in humans, that assessed the association of maternal smoking during pregnancy with offspring body mass index (BMI) and overweight in childhood, adolescence and adulthood, published through May 1st, 2018. A meta-analysis was used to estimate pooled effect sizes. The systematic review included 64 studies, of which 37 evaluated the association of maternal smoking during pregnancy with overweight, 13 with BMI, and 14 evaluated both outcomes. Of these 64 studies, 95 measures of effect were extracted and included in the meta-analysis. We verified that the quality of evidence across studies regarding maternal smoking in pregnancy and overweight and BMI of offspring to be moderate and low, respectively. Most studies (44 studies) were classified as moderate risk bias. Heterogeneity among studies included was high and, in the random-effects pooled analysis, maternal smoking during pregnancy increased the odds of offspring overweight (OR: 1.43, 95%CI: 1.35; 1.52) and mean difference of BMI (β: 0.31, 95%CI: 0.23; 0.39). In conclusion, offspring of mothers who smoked during pregnancy have higher odds of overweight and mean difference of BMI, and these associations persisted into adulthood.

Smoking; Pregnancy; Overweight; Body Mass Index; Meta-Analysis

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Introduction

The epidemic of overweight and obesity is a public health problem, worldwide [1]. Among the early life factors associated with overweight, it has been suggested that maternal smoking during pregnancy may increase offspring body mass index (BMI) and the risk of overweight [2]. However, it has been emphasized that some demographic, socioeconomics and lifestyle factors may contribute to the observed association between maternal smoking and offspring overweight. Mothers who smoke during pregnancy tend to weigh more, to have lower socioeconomic status and achieved schooling, which are also associated with a higher risk of offspring overweight [2]. In addition, offspring of smokers tend to be less physically active and have poor diet quality, which in turn could be mediators in the association of maternal smoking during pregnancy with offspring overweight [3].

Moreover, it has also been reported that maternal smoking during pregnancy is positively associated with BMI in childhood [4,5,6,7], and some studies have reported that the impact of maternal smoking on offspring body composition would last until adulthood [8,9].

Two previously published systematic reviews and meta-analyses [3,10] have reported that maternal smoking is associated with offspring overweight and obesity in childhood. In the more recent paper, it was evaluated data published until January 1, 2015 [3], and in the meta analyses conducted for Oken et al. [3] and Rayfield & Plugge [10] was included 14 and 39 studies, respectively. Nevertheless, these reviews have not evaluated whether the consequences of exposure to maternal smoking persists into adolescence and adulthood, as well as its association with mean BMI.

Therefore, in order to update the previously published meta-analysis and evaluate consequences of maternal smoking in pregnancy on body composition in adolescence and adulthood, we carried out the present meta-analysis.

Methods

Protocol and registration

This systematic review and meta-analysis were reported in accordance with PRISMA guidelines [11]. The protocol for systematic review and meta-analysis was registered in PROSPERO (registration number: CRD42018080334).

Data source and search strategy

MEDLINE, Web of Science and LILACS databases were searched for studies that evaluated the association of maternal tobacco smoking during pregnancy with offspring BMI and overweight. Databases were search from inception to May 1, 2018. There was no language restriction. In the literature search, each of the terms for exposure were combined with each of the outcomes terms described as follows.

• MEDLINE: (cigarette smoke pregnancy OR cigarette smoking pregnancy OR intrauterine tobacco smoke exposure OR maternal smoking during pregnancy OR maternal smoking pregnancy OR nicotine pregnancy OR nicotine pregnant OR prenatal smoke OR prenatal smoking OR prenatal smoke exposure OR prenatal smoking exposure OR prenatal tobacco OR prenatal tobacco exposure OR prenatal tobacco smoke OR smoke pregnancy OR smoke pregnant OR smoking pregnancy OR smoking pregnant OR smoke pregnancy effect OR smoking pregnant effects OR smoking pregnancy offspring OR tobacco pregnancy OR tobacco pregnant OR tobacco smoke pregnancy OR tobacco smoking pregnancy) AND (adiposity OR adiposity risk OR body adiposity OR body mass index OR body mass index obesity OR bmi OR bmi obesity OR obese overweight OR obesity OR obesity body mass index OR obesity bmi OR obesity overweight OR obesity risk OR overweight OR overweight obesity OR overweight obese) [All Fields];

• Web of Science: TS=((((((((((((((((((((((((cigarette smoke pregnancy) OR cigarette smoking pregnancy) OR intrauterine tobacco smoke exposure) OR maternal smoking during pregnancy) OR maternal smoking pregnancy) OR nicotine pregnancy) OR nicotine pregnant) OR prenatal smoke) OR prenatal smoking) OR prenatal smoke exposure) OR prenatal smoking exposure) OR prenatal tobacco) OR prenatal tobacco exposure) OR prenatal tobacco smoke) OR smoke pregnancy) OR smoke pregnant) OR smoking pregnancy) OR smoking pregnant) OR smoke pregnancy effect) OR smoking pregnant effects) OR smoking pregnancy offspring) OR tobacco pregnancy) OR tobacco pregnant) OR tobacco smoke pregnancy) OR tobacco smoking pregnancy)) AND TS=(((((((((((((((((adiposity) OR adiposity risk) OR body adiposity) OR body mass index) OR body mass index obesity) OR bmi) OR bmi obesity) OR obese overweight) OR obesity) OR obesity body mass index) OR obesity bmi) OR obesity overweight) OR obesity risk) OR overweight) OR overweight obesity) OR overweight obese)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years;

• LILACS: ((((((CIGARRETTE-SMOKING) or "NICOTINE") or "SMOKE") or "SMOKE-EXPOSURE") or "SMOKE/TOBACCO") or "SMOKING") or "SMOKING/NICOTINE" and ((("PREGNANCY") or "PREGNANT") or "PREGNANT WOMEN") or "PRENATAL" and (((((((("ADIPOSITY") or "BODY MASS INDEX") or "OBESE") or "OBESE/OVERWEIGHT") or "OBESITY") or "OBESITY-OVERWEIGHT") or "OVERWEIGHT") or "OVERWEIGHT-OBESE") or "OVERWEIGHT-OBESITY" [Words].

Two independent literature searches, using the same search strategy, were carried out. The searches were compared, and any disagreement was solved by a third reviewer.

Eligibility criteria

We included original studies, conducted in humans, that assessed the association of maternal tobacco smoking during pregnancy with offspring BMI and overweight in childhood (from the age of two years), adolescence and adulthood.

Review articles, editorials, comments, studies conducted with animals, that evaluated the intrauterine exposure to smoking of other drugs such as marijuana, or that assessed the exposure to second-hand smoke on pregnancy, or that evaluated children under two years of age were excluded from the review. Furthermore, we excluded those studies that reported only crude estimates, as well as, those that did not report the confidence interval or the standard error of the association between maternal smoking and offspring anthropometry, or did not provided data that allowed the calculation of these parameters. For these studies that did not provide sufficient data for the inclusion in the review, we tried to contact the authors and requested the information needed for including them.

Selection of studies

Two reviewers, independently, carried out the selection of the studies. After excluding the duplicates, titles and abstracts they were perused to exclude those studies that were obviously irrelevant for the review. The full-texts of the remaining studies were retrieved and those studies that were eligible for this review were identified. In addition to the electronic search, reference lists of the selected articles were examined to identify manuscripts that had not been captured by the database search. Disagreements were solved by a third reviewer.

Data extraction

Using a standardized protocol, two reviewers independently extracted the data from the included studies, and the forms were compared. Of each study, besides to data on exposure and outcome, we extracted the following information: publication year, country of data collection, study design, type of population studied (only one gender or both genders), sample size, maternal smoking recall time, source of information on maternal smoking, losses to follow-up, age at outcome assessment, anthropometric measures (e.g. techniques and methods of measurement, type of equipment), definition of overweight, control for confounding (adjust for variables socioeconomics, demographic and maternal anthropometry), control for potential mediators (birth conditions, breastfeeding/complementary feeding and lifestyle variables).

For those studies reporting more than two categories of maternal smoking during pregnancy (e.g., non-smoker/light smoker/heavy smoker), the effect measure reporting the comparison of the most extreme categories was included in the meta-analysis. For those studies that evaluated overweight and obesity separately, we extracted the effect measure for obesity. In the case of studies reporting effect measures at various ages, the outcome at the later age was considered. When the study results were stratified by gender and ethnicity, the effect measures of each of these strata was considered in the meta-analysis. For those studies that presented estimates adjusted for different settings of confounding variables, we considered the measure of effect adjusted for the greatest number of variables and that did not adjusted for potential mediators.

Assessment of quality of the evidence across studies

The GRADE (*Grading of Recommendations Assessment, Development, and Evaluation*) methodology was used to assess the quality of the body of retrieved evidence [12].

Assessment of risk of bias

Likelihood of risk of bias of individual studies was evaluated through *Risk Of Bias In Non-randomized Studies – of Exposures* (ROBINS-E) tool, developed by Morgan and colleagues [13,14].

Statistical analysis

We used Stata 14.0 (https://www.stata.com/) for the analyses, and analysed separately those studies that reported the mean difference in BMI and those that reported the odds ratio (OR) for overweight/obesity. Because the studies were carried out in different settings, using different designs and evaluated the subjects at different ages, a common effect size could not be assumed and the estimates were pooled using the random effects models [15]. Meta-regression was used to assess the contribution of co-variables (sample size, study design, age at outcome assessment, adjustment for confounders) to the heterogeneity among the studies, and we estimated the percentage of the heterogeneity that was explained by the co-variables. If the inclusion of a co-variable increased the heterogeneity, the estimate on the change in the measure of heterogeneity was truncated to zero. Funnel plot and Egger test were used to investigate the possibility of publication bias [16].

Departures from original review protocol

In the original review protocol, risk of bias would be evaluated by adapted *Newcastle-Ottawa Quality Assessment Scale*. However, the use of scores to assess the quality of studies in meta-analysis has been criticized because most of the scores evaluate possible sources of bias as well as aspects linked quality of reporting, that are not directly linked to susceptibility to bias [17,18]. Thus, we assessed the risk of bias using an instrument that is not based on scores, the ROBINS-E.

Results

In the literature search, 6,818 records were identified and, after duplicates were excluded, 4,364 titles and abstracts were perused. Of these, 98 texts were selected for full-text reading and 63 manuscripts were included in our review. Additionally, we included one of four papers identified in the search of reference lists and studies citing the manuscripts identified in the electronic search. Therefore, 64 studies were included in the meta-analysis, 37 evaluated the association of maternal smoking during pregnancy with overweight/obesity [19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55], whereas 13 evaluated the association with BMI [4,5,6,7,56,57,58,59,60,61,62,63,64], and 14 evaluated both outcomes [8,9,65,66,67,68,69,70,71,72,73,74,75,76]. Because some studies reported more than one effect measure, 95 effect measures were extracted and included in the meta-analysis. Figure 1 shows the study selection flow chart.

Table 1 presents the main characteristics of the included studies. Thirteen studies had been published in the last five years, 52 were carried out in high income countries, 43 were cohort studies,

Figure 1

Flow diagram of studies evaluating maternal smoking during pregnancy and overweight/body mass index offspring.

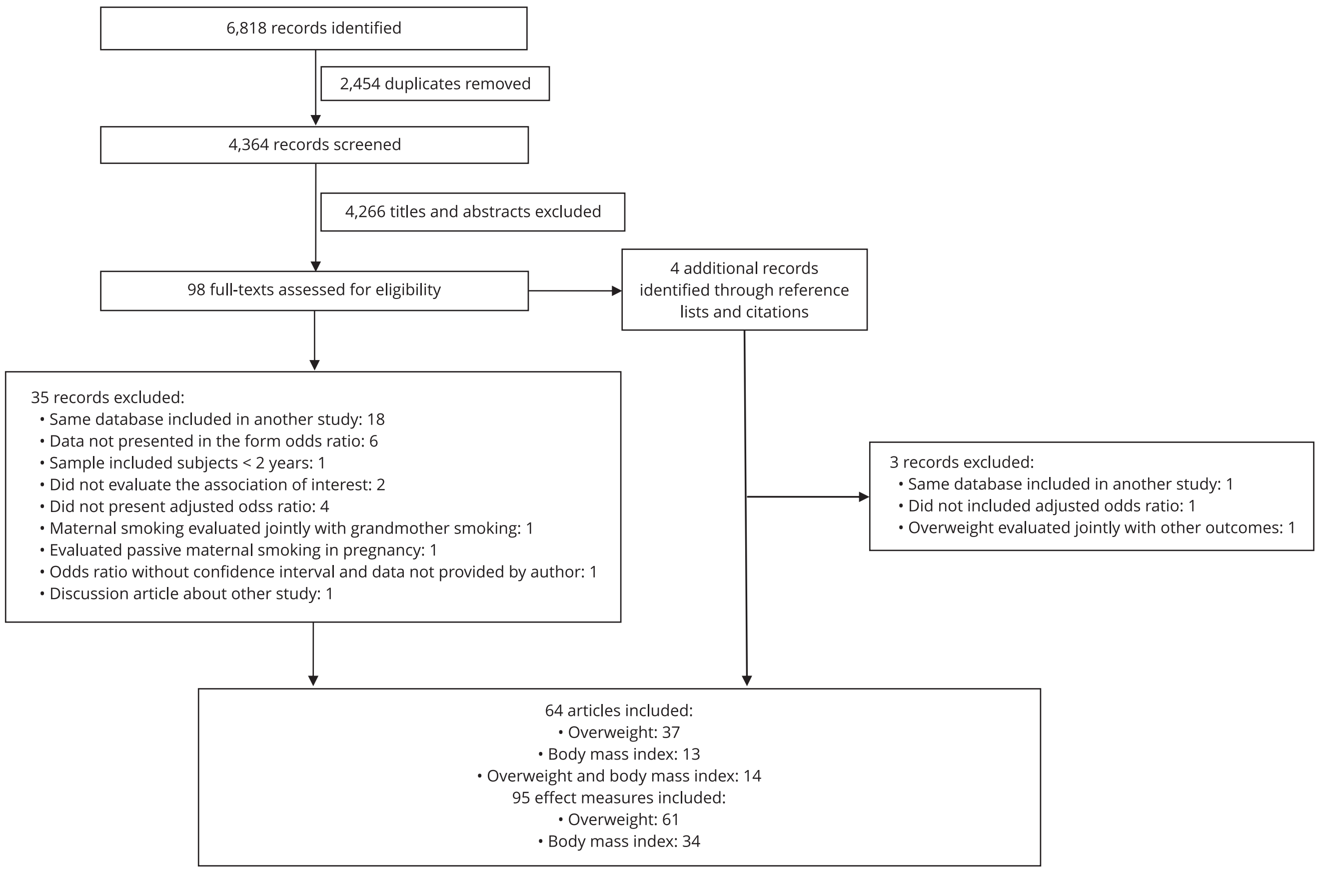


Table 1

Summary of studies included in systematic review and meta-analyses.

Study (Year)	Origin	Study design	Gender	Sample (N)	Age group (years)	Outcome
Toschke et al. [19] (2002)	Germany	Cross-sectional	All	8,765	< 10	Overweight and obesity
von Kries et al. [20] (2002)	Germany	Cross-sectional	All	6,483	< 10	Overweight and obesity
Bergmann et al. [21] (2003)	Germany	Cohort	All	918	< 10	Overweight and obesity
Toschke et al. [22] (2003)	Germany	Cross-sectional	All	4,974	< 10	Overweight and obesity
Widerøe et al. [23] (2003)	Norway and Sweden	Cohort	All	482	< 10	Overweight or obesity

(continues)

Table 1 (continued)

Study (Year)	Origin	Study design	Gender	Sample (N)	Age group (years)	Outcome
Oken et al. [65] (2005)	United States	Cohort	All	746	< 10	Overweight or obesity and BMI (Z score)
Reilly et al. [24] (2005)	United Kingdom	Cohort	All	7,758	< 10	Obesity
Chen et al. [66] (2006)	United States	Cohort	All	Male: 6,298; Female: 6,362	< 10	Overweight or obesity and BMI (kg/m^2)
Dubois & Girard [25] (2006)	Canada	Cohort	All	1,450	< 10	Overweight or obesity
Leary et al. [56] (2006)	England	Cohort	All	5,689	< 10	BMI (SD units)
Macías Gelabert et al. [26] (2007)	Cuba	Case-control	All	172	< 10	Obesity
Goldani et al. [57] (2007)	Brazil	Cohort	Male	1,189	10-19	BMI (kg/m^2)
Mizutani et al. [27] (2007)	Japan	Cohort	All	1,417	< 10	Overweight and obesity
Salsberry & Reagan [28] (2007)	United States	Cohort	All	3,368	10-19	Overweight or obesity
Tomé et al. [29] (2007)	Brazil	Cohort	All	2,797	< 10	Overweight or obesity
Koupil & Toivanen [67] (2008)	Sweden	Cohort	Male	1,103	10-19	Overweight or obesity and BMI (kg/m^2)
Moschonis et al. [30] (2008)	Greece	Cohort	All	1,667	< 10	Overweight or risk of overweight
Sharma et al. [31] (2008)	United States	Cohort	All	NHW: 82,361; NHB: 31,704; H: 34,378; AIAN: 2,228; API: 4,740	< 10	Obesity
von Kries et al. [32] (2008)	Germany	Cross-sectional	All	5,899	< 10	Overweight and obesity
Fasting et al. [68] (2009)	Norway	Cohort	All	711	< 10	Overweight or obesity and BMI (kg/m^2)
Hawkins et al. [33] (2009)	United Kingdom	Cohort	All	13,188	< 10	Overweight or obesity
Hesketh et al. [58] (2009)	Australia	Cohort	All	1,373	10-19	BMI (Z score)
Braun et al. [69] (2010)	United States	Cohort	All	356	< 10	Overweight or obesity and BMI (kg/m^2)
Iliadou et al. [70] (2010)	Sweden	Cohort	Male	124,203	≥ 20	Overweight or obesity and BMI (kg/m^2)
Koshy et al. [34] (2010)	United Kingdom	Cross-sectional	All	3,038	< 10	Overweight and obesity
Kuhle et al. [35] (2010)	Canada	Cross-sectional	All	3,426	10-19	Overweight or obesity
Mangrio et al. [36] (2010)	Sweden	Cross-sectional	All	9,009	< 10	Overweight and obesity

(continues)

Table 1 (continued)

Study (Year)	Origin	Study design	Gender	Sample (N)	Age group (years)	Outcome
Pirkola et al. [37] (2010)	Finland	Cohort	All	4,168	10-19	Overweight or obesity
Power et al. [8] (2010)	United Kingdom	Cohort	All	8,815	≥ 20	Obesity and BMI (kg/m^2)
Seach et al. [38] (2010)	Australia	Cohort	All	307	10-19	Overweight or obesity
Beyerlein et al. [4] (2011)	Germany	Cross-sectional	All	12,383	10-19	BMI (SD score)
Gorog et al. [39] (2011)	Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia	Cross-sectional	All	8,926	10-19	Overweight and obesity
Matijasevich et al. [59] (2011)	Brazil	Cohort	All	1993 cohort: 1,450; 2004 cohort: 3,799	< 10	BMI (Z score)
Raum et al. [40] (2011)	Germany	Cross-sectional	All	1,954	< 10	Overweight or obesity
Chen et al. [41] (2012)	Taiwan	Cross-sectional	All	7,930	10-19	Overweight and obesity
Cupul-Uicab et al. [42] (2012)	Norway	Cross-sectional	Female	74,023	≥ 20	Obesity
Gopinath et al. [43] (2012)	Australia	Cross-sectional	All	4,094	10-19	Overweight and/or obesity
Janjua et al. [44] (2012)	United States	Cohort	All	740	< 10	Overweight and obesity
Mamun et al. [9] (2012)	Australia	Cohort	All	2,038	≥ 20	Overweight, obesity and BMI (kg/m^2)
Messiah et al. [45] (2012)	United States	Cross-sectional	All	H: 1,416; NHB: 1,090; NHW: 1,138	< 10	Overweight and obesity
Plachta-Danielzik et al. [46] (2012)	Germany	Cross-sectional	All	34,240	< 10	Overweight or obesity
Risvas et al. [47] (2012)	Greece	Cross-sectional	All	2,093	10-19	Overweight or obesity
Bingham et al. [48] (2013)	Portugal	Cross-sectional	All	17,136	< 10	Overweight and/or obesity
Harris et al. [49] (2013)	United States	Cohort	Female	35,020	≥ 20	Overweight and obesity
Mattsson et al. [50] (2013)	Sweden	Cohort	Female	54,012	≥ 20	Obesity
Pei et al. [71] (2013)	Germany	Cohort	All	Male: 1,588; Female: 1533	10-19	Overweight or obesity and BMI (Z score)
Shi et al. [51] (2013)	Canada	Cross-sectional	All	968	< 10	Overweight and obesity
Wang et al. [52] (2013)	United States	Cohort	All	1,041	10-19	Overweight or obesity
Yang et al. [72] (2013)	Belarus	Cohort	All	13,889	< 10	Overweight or obesity and BMI (kg/m^2)

(continues)

Table 1 (continued)

Study (Year)	Origin	Study design	Gender	Sample (N)	Age group (years)	Outcome
Durmuş et al. [73] (2013)	Netherlands	Cohort	All	5,243	< 10	Overweight, obesity and BMI (kg/m^2)
Ehrenthal et al. [60] (2013)	United States	Cohort	All	3,302	< 10	BMI (Z score)
Dior et al. [61] (2014)	Israel	Cohort	All	1,440	≥ 20	BMI (kg/m^2)
Florath et al. [5] (2014)	Germany	Cohort	All	609	< 10	BMI (kg/m^2)
Huang et al. [53] (2014)	United States	Cohort	All	5,156	10-19	Obesity
Moller et al. [54] (2014)	Denmark	Cohort	All	32,747	< 10	Overweight or obesity
Riedel et al. [6] (2014)	Germany	Cohort	All	Male: 540; Female: 509	10-19	BMI (Z score)
Suzuki et al. [74] (2014)	Japan	Cohort	All	Male: 1,134; Female: 1,096	< 10	Overweight or obesity and BMI (kg/m^2)
Timmermans et al. [75] (2014)	Netherlands	Cohort	All	1,730	< 10	Overweight or obesity and BMI (Z score)
Fairley et al. [62] (2015)	United Kingdom	Cohort	All	987	< 10	BMI (Z score)
Grzeskowiak et al. [7] (2015)	Australia	Cohort	All	7,658	< 10	BMI (Z score)
Mourtakos et al. [55] (2015)	Greece	Cross-sectional	All	5,125	< 10	Obesity
Thurber et al. [63] (2015)	Australia	Cohort	All	682	< 10	BMI (Z score)
Li et al. [64] (2016)	Portugal	Cross-sectional	All	Male: 8,798; Female: 8,488	< 10	BMI (kg/m^2)
Robinson et al. [76] (2016)	Spain	Cohort	All	INMA subcohorts: 1,866; Menorca subcohort: 427	INMA subcohorts: 10; Menorca subcohort: 10-19	Overweight or obesity and BMI (Z score)

AIAN: American Indian or Alaska Native; API: Asian or Pacific Islander; BMI: body mass index; H: Hispanic; INMA: Infancia y Medio Ambiente; NHB: Non-Hispanic Black; NHW: Non-Hispanic White; SD: standard deviation.

and 57 evaluated the outcomes at childhood and adolescence. Regarding the assessment of maternal smoking, 24 studies gathered the information on tobacco smoking during pregnancy, and three studies used biochemical markers to verify intrauterine exposure to tobacco. In addition, considering the relevance of further discussing the likelihood of residual confounding, Supplementary Table 1 (http://cadernos.ensp.fiocruz.br/site/public_site/arquivo/suppl-e00176118_7666.pdf) provide information on the variables included by each study in the multivariable model.

We verified that the quality of evidence across studies regarding maternal smoking in pregnancy and overweight and BMI of offspring to be low. Details of assessment of quality are presented in Supplementary Table 2 (http://cadernos.ensp.fiocruz.br/site/public_site/arquivo/suppl-e00176118_7666.pdf).

With respect assessment of risk of bias, in classification for overall bias, no study presented a risk of serious or critical bias. Most studies (44 studies) were classified as moderate risk bias. A detailed assessment of risk bias is presented in Supplementary Table 3 (http://cadernos.ensp.fiocruz.br/site/public_site/arquivo/suppl-e00176118_7666.pdf).

Figure 2 shows that most of the studies that evaluated the association of maternal smoking with overweight/obesity, reported higher odds among offsprings of smoking mothers. In the pooled analysis, maternal smoking during pregnancy increased the odds of offspring overweight/obesity [random-effects pooled OR: 1.43 (95%CI: 1.35; 1.52)] and heterogeneity was high (I^2: 73.9%). For BMI, the heterogeneity was also high (I^2: 88.9%) and the pooled mean difference in BMI, using random-effects model, was 0.31kg/m^2 (95%CI: 0.23; 0.39) in the comparison between offspring of smoking and non-smoking mothers (Figure 3).

Table 2 shows the results stratified according to study characteristics. The odds ratio for overweight/obesity was not modified by age at the evaluation, whereas for BMI, in spite of the small number of studies that evaluated adolescents and adults, we observed that the difference increased, and age at assessment explained 51.8% of the heterogeneity among the studies. For overweight/obesity, study design explained 12.8% of the heterogeneity and the pooled OR was higher among cross-sectional and case-control studies. Independent of the outcome, a larger simple size was associated with a small magnitude of the association, but even among those studies that evaluated > 1,500 subjects an association with overweight [pooled OR: 1.37 (95%CI: 1.29; 1.43)] and BMI [pooled mean difference: 0.28 (95%CI: 0.18; 0.38)] was observed. Studies that used serum/urinary cotinine to verify the exposure to maternal smoking in pregnancy showed higher pooled OR for overweight and the source of information on maternal smoking explained 11.2% of the heterogeneity. For BMI, studies that used serum cotinine to assess maternal smoking or relied on the information from medical records observed a higher mean difference. Concerning control for confounding, those studies that adjusted for demographic and socioeconomic variables reported a lower pooled OR of overweight, whereas for BMI the pooled mean difference was higher among studies that controlled for socioeconomic status. On the other hand, studies that adjusted for demographic and socioeconomic variables reported a pooled OR that was slightly lower than those that did not adjusted for both confounders, whereas those studies that adjusted for both variables and at least one of the potential mediators reported the lowest pooled OR of overweight, and this methodological aspect explained 33.6% of heterogeneity.

Multivariable meta-regression including the study level variables that had non-zero proportions of heterogeneity explained, showed that these variables explained 57.5% and 75.7% of heterogeneity for the overweight and BMI outcomes, respectively.

The funnel plots suggest a small study effect (Supplementary Figures 1 and 2: http://cadernos.ensp.fiocruz.br/site/public_site/arquivo/suppl-e00176118_7666.pdf), but the Egger tests were not statistically significant (overweight: p = 0.284; BMI: p = 0.596).

Discussion

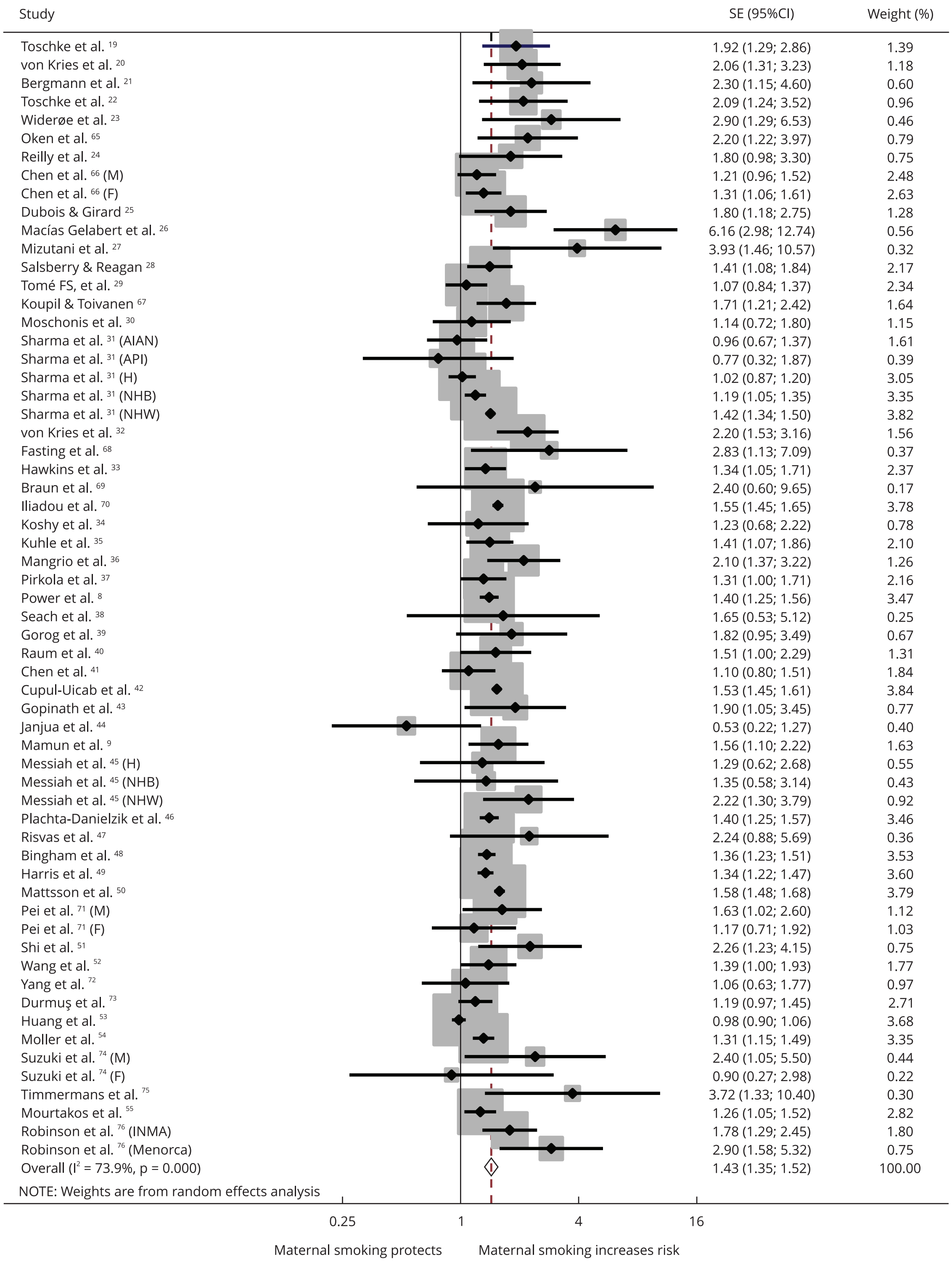
In the present systematic review and meta-analysis, we observed that maternal smoking in pregnancy was associated with a higher odds of offspring overweight/obesity. BMI was also higher among those subjects whose mothers smoked during pregnancy. Previous meta-analyses have also shown that maternal smoking in pregnancy increases the risk of offspring overweight. Oken et al. [3] observed that children whose mothers smoked during pregnancy presented 50% higher risk of overweight (pooled adjusted OR: 1.50; 95%CI: 1.36; 1.65). Rayfield & Plugge [10] reported a pooled adjusted OR of 1.37 (95%CI: 1.28; 1.46) and 1.55 (95%CI: 1.40; 1.73) for childhood overweight and childhood obesity, respectively, among offspring of smoking mothers.

Some plausible mechanisms have been proposed to explain these associations. Studies with humans and animals have appointed that, when crossing the placenta, nicotine acts as a suppressant of appetite and body weight and the postnatal cessation of exposure to nicotine would result in hyperphagia and weight gain in the offspring [77,78]. Exposure to nicotine in pregnancy may also increase body adiposity through modifications in endocrine control of body weight homeostasis [79]. In addition, maternal smoking during pregnancy is causally related with fetal growth restriction and low birth weight [80]. In animals, it has been observed that exposure to nicotine in utero reduce the responsiveness to adrenergic stimuli and promote rapid weight gain [81]. Analogously, prenatal exposure to nicotine in humans may decrease responsiveness to adrenergic stimuli via epinephrine and norepinephrine, which modulate the mobilization of lipids from adipose tissue [82].

Moreover, offspring of smoking mothers tend to have less healthy lifestyle habits, such as poorer diet, physical inactivity [3], and smoking [83]. It has been reported that cigarette smoking is associated

Figure 2

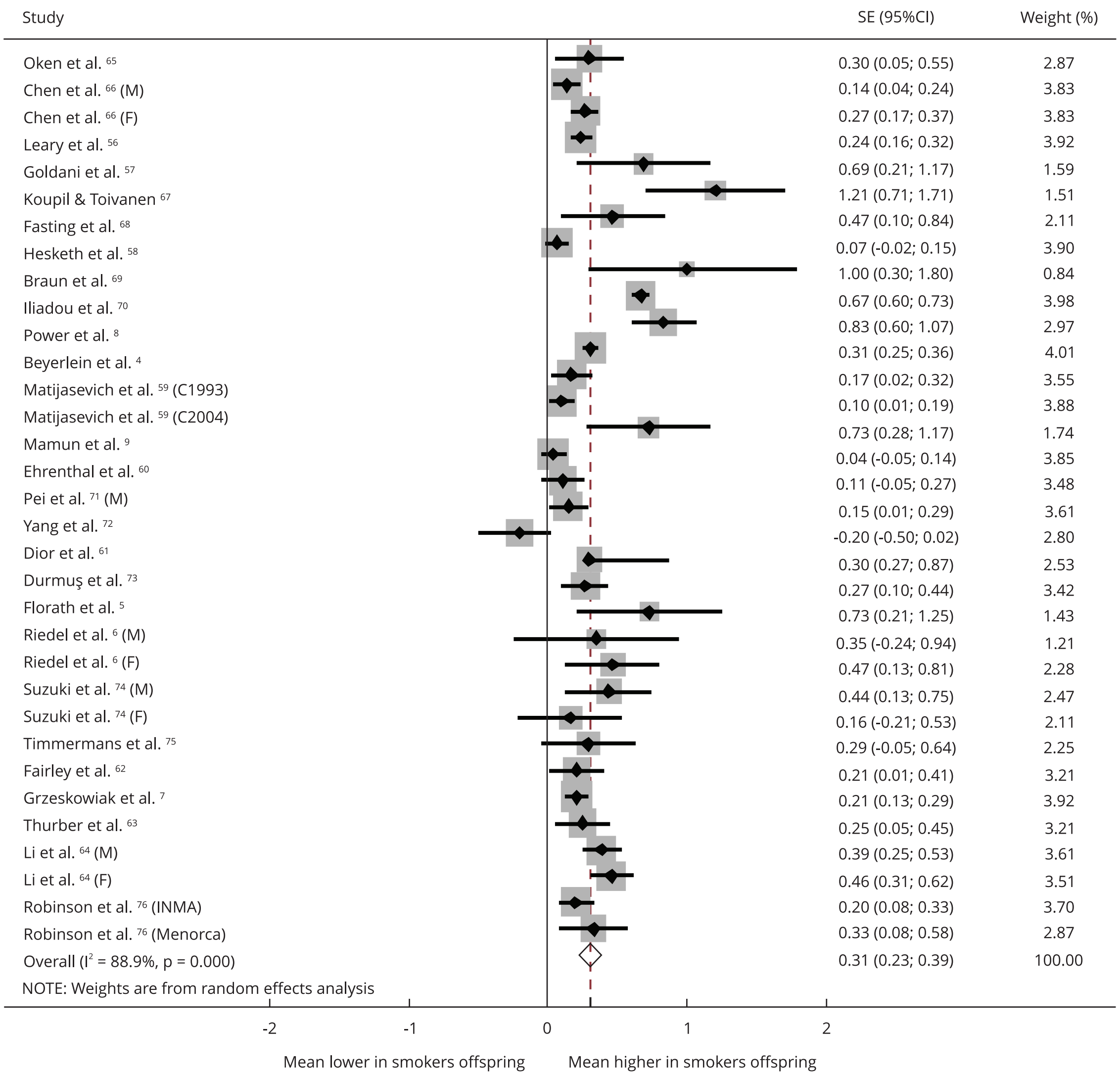
Random effects meta-analysis of odds ratio of overweight/obesity among offspring of mothers who smoked during pregnancy.



95%CI: 95% confidence interval; AIAN: American Indian or Alaska Native; API: Asian or Pacific Islander; F: Female; H: Hispanic; INMA: *Infancia y Medio Ambiente*; M: Male; NHB: Non-Hispanic Black; NHW: Non-Hispanic White; SE: standard error.

Figure 3

Random effects meta-analysis of mean body mass index difference among offspring of mothers who smoked during pregnancy.



95%CI: 95% confidence interval; C1993: 1993 cohort; C2004: 2004 cohort; F: Female; INMA: *Infancia y Medio Ambiente*; M: Male; SE: standard error.

with increased abdominal fat accumulation [84,85]. Nicotine could lead to fat accumulation through increased level of stress hormones like cortisol, which are related to fat depots [86]. Therefore, offspring lifestyle could be a mediator in the association between maternal smoking and offspring overweight.

Because we excluded those studies that reported crude associations, we reduced the likelihood that confounding biased the pooled estimates. But the possibility of unmeasured confounding cannot be completely ruled out because important confounders may not have been included in the regression models. Furthermore, if a confounder was poorly measured or defined in a form that was not perfectly correct, residual confounding will occur. Although the association between maternal smoking and offspring overweight/BMI is fairly consistent across studies, some authors have indicated that unmeasured confounding, as familial factors, for example, may contribute to this association. Iliadou et al. [70] evaluated 124,203 singleton males born between 1983 and 1988 in Sweden to investigate

Table 2

Maternal smoking during pregnancy and risk of overweight/obesity and body mass index (BMI) of offspring: random-effects meta-analysis by subgroup.

Subgroups	Overweight			BMI		
	N	Pooled OR (95%CI)	% heterogeneity explained	N	Pooled β (95%CI)	% heterogeneity explained
Age group (years)			0.0			51.8
< 10	41	1.44 (1.33; 1.56)		21	0.23 (0.17; 0.29)	
10-19	14	1.43 (1.21; 1.70)		9	0.30 (0.16; 0.44)	
≥ 20	6	1.50 (1.42; 1.57)		4	0.64 (0.46; 0.83)	
Gender			0.0			0.0
Male	5	1.50 (1.31; 1.73)		5	0.25 (0.10; 0.40)	
Female	6	1.46 (1.36; 1.58)		5	0.30 (0.17; 0.42)	
All	50	1.45 (1.34; 1.56)		24	0.33 (0.23; 0.43)	
Setting			0.5			0.0
Low/Middle income country	9	1.35 (1.12; 1.64)		6	0.24 (0.06; 0.42)	
High income country	52	1.45 (1.36; 1.54)		28	0.32 (0.24; 0.41)	
Study design			12.8			0.0
Cohort	40	1.37 (1.27; 1.47)		31	0.30 (0.22; 0.39)	
Cross-sectional/Case-control	21	1.58 (1.43; 1.73)		3	0.36 (0.27; 0.45)	
Sample size (participants)			34.4			0.0
< 800	8	2.33 (1.44; 3.77)		8	0.36 (0.25; 0.47)	
800-1,500	11	1.74 (1.48; 2.05)		8	0.32 (0.15; 0.49)	
> 1,500	42	1.37 (1.29; 1.43)		18	0.28 (0.18; 0.38)	
Assessment of maternal smoking			0.0			0.0
During pregnancy	28	1.40 (1.30; 1.50)		15	0.30 (0.17; 0.42)	
At maternity hospital	7	1.36 (1.16; 1.59)		12	0.34 (0.18; 0.50)	
In the first year of life	2	1.47 (1.12; 1.93)		3	0.33 (0.14; 0.52)	
Older than 1 year	24	1.53 (1.36; 1.72)		4	0.30 (0.14; 0.46)	
Source of maternal smoking information			11.2			0.0
Interview/Questionnaire	54	1.41 (1.33; 1.51)		26	0.26 (0.20; 0.33)	
Medical record	4	1.55 (1.46; 1.65)		4	0.48 (0.10; 0.86)	
Serum/Urinary cotinine	3	2.00 (1.51; 2.64)		4	0.40 (0.14; 0.66)	
Adjustment for socioeconomic variables			0.4			0.0
No	12	1.61 (1.37; 1.89)		5	0.20 (0.07; 0.33)	
Yes	49	1.40 (1.32; 1.50)		29	0.32 (0.24; 0.41)	
Adjustment for demographic variables			23.2			0.0
No	6	2.12 (1.47; 3.06)		4	0.41 (0.07; 0.75)	
Yes	55	1.40 (1.32; 1.48)		30	0.30 (0.22; 0.38)	
Adjustment for maternal anthropometry			0.0			0.0
No	21	1.46 (1.37; 1.56)		5	0.22 (0.09; 0.36)	
Yes	40	1.44 (1.33; 1.56)		29	0.32 (0.23; 0.40)	
Adjustment for maternal comorbidities			0.0			0.0
No	57	1.44 (1.36; 1.54)		30	0.33 (0.24; 0.41)	
Yes	4	1.34 (1.22; 1.47)		4	0.19 (0.10; 0.32)	
Adjustment for birth conditions			11.9			21.7
No	24	1.51 (1.41; 1.61)		20	0.24 (0.14; 0.34)	
Yes	37	1.37 (1.26; 1.49)		14	0.43 (0.32; 0.54)	
Adjustment for breastfeeding/ complementary feeding			4.2			0.0
No	31	1.46 (1.37; 1.56)		19	0.28 (0.16; 0.39)	
Yes	30	1.42 (1.29; 1.55)		15	0.34 (0.25; 0.43)	

(continues)

Table 2 (continued)

Subgroups	Overweight			BMI		
	N	Pooled OR (95%CI)	% heterogeneity explained	N	Pooled β (95%CI)	% heterogeneity explained
Adjustment for lifestyle variables			0.0			0.0
No	42	1.44 (1.35; 1.53)		22	0.30 (0.20; 0.41)	
Yes	19	1.42 (1.24; 1.62)		12	0.33 (0.19; 0.45)	
Adjustment for socioeconomic and demographic variables			11.2			0.0
No	17	1.66 (1.44; 1.91)		9	0.29 (0.15; 0.44)	
Yes	44	1.38 (1.29; 1.47)		25	0.31 (0.22; 0.40)	
Adjustment for socioeconomic, demographic variables and mediators			33.6			0.0
No adjustment for socioeconomic and demographic variables	17	1.66 (1.44; 1.91)		9	0.29 (0.15; 0.44)	
Adjustment for socioeconomic and demographic variables without adjust for mediators	9	1.52 (1.44; 1.61)		8	0.33 (0.11; 0.54)	
Adjustment for socioeconomic and demographic variables and mediators	35	1.33 (1.23; 1.44)		17	0.30 (0.23; 0.37)	
Overall	61	1.43 (1.35; 1.52)		34	0.31 (0.23; 0.39)	

95%CI: 95% confidence interval; N: number of estimates; OR: odds ratio.

whether familial factors confound the association between maternal smoking during pregnancy and overweight in the offspring at about 18 years of age, and reported an association between maternal smoking during the first trimester of pregnancy and overweight. However, the magnitude of the association was lower within-family analyses, suggesting a partial confounding by familial factors.

Heterogeneity among studies included in this meta-analysis was high, and part of this heterogeneity derived from differences among the studies regarding sample size and other methodological characteristics.

Regarding sample size, the odds ratio and the mean difference were lower among those studies with a large sample size, but even among these studies, the associations were still statistically significant. Suggesting, therefore, that publication bias may be overestimating the magnitude of the associations but not causing it. In the analysis for risk of overweight, the pooled OR using the random effect model is 1.43 and when conducting a sensitivity analysis using the Trim and Fill method, the pooled estimate slightly changed 1.39 (95%CI: 1.33; 1.45) (data no shown). Suggesting that the publication bias had a small impact on the pooled estimate, similar to that indicated by the analysis stratifying by sample size.

Concerning the variables used to adjust for confounding, we observed that the pooled OR was lower among those studies that adjusted the estimates for demographic, socioeconomic variables, and potential mediators. Considering that, among the 44 studies that adjusted for both socioeconomic and demographic variables, 35 also adjusted for mediators (Supplementary Table 1: http://cadernos.ensp.fiocruz.br/site/public_site/arquivo/suppl-e00176118_7666.pdf), this attenuation, in part, is due to the simultaneous adjustment for socioeconomic and demographic variables and mediators.

Regarding the age, the mean BMI difference was higher in the studies with adults, whereas for overweight the association was not modified by age. This finding may be related to the fact that as the age increases the mean BMI also increases, thus, differences of the same relative magnitude lead to larger absolute values.

An intriguing finding was that those studies that adjusted for demographic and socioeconomic variables showed a lower pooled OR of overweight, whereas for BMI the pooled mean difference was higher among studies that adjusted for socioeconomic variables. We were not able to present a coherent and plausible explanation for this.

For those variables that did not explain the heterogeneity among the studies, in its turn, it is also possible that residual confounding may have had an important role in the non significant results.

One limitation of this study is that the dose-response and of cessation effect of maternal smoking on gestation on overweight/BMI of offspring could not be assessed, since most studies did not present estimates of effect measures stratified by smoking intensity and duration. Thus, new studies and/or meta-analysis evaluating the dose-response effect and cessation of maternal smoking during gestation in overweight/BMI of the offspring would be interesting to investigate in more detail the impact of exposure to tobacco on utero in adiposity later in life.

In conclusion, besides the high heterogeneity among studies, the present systematic review and meta-analysis suggests, as in previous meta-analysis, that offspring of mothers who smoked during pregnancy showed higher odds of overweight and BMI, and these associations persisted into adulthood. Taking into account that rates of prevalence of prenatal maternal smoking among the studies included in present meta-analysis are considerable (reaching up to 51.4% – data not shown), we reinforce the relevance of reducing maternal smoking during pregnancy. Smoking and obesity are among major risk factors for noncommunicable diseases and, their combined effects at young ages may also contribute to increase early morbidity and mortality [87]. Thus, by stimulating pregnant women to stop smoking (and/or by decreasing smoking prevalence rates in the population as a whole), we would also reduce the burden of childhood obesity at the population level.

Contributors

E. I. S. Magalhães designed the study, performed the statistical analysis, interpretation of the results and drafted the manuscript. B. A. Sousa, N. P. Lima, and B. L. Horta designed the study, helped the data analysis and the drafting of the paper. All authors revised and approved the final version of the manuscript.

Additional informations

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Resumo

Este estudo teve como objetivo realizar uma revisão sistemática e metanálise para avaliar as evidências sobre a associação entre tabagismo materno durante a gravidez e composição corporal dos filhos na infância, adolescência e vida adulta. Foram realizadas buscas nas bases de dados MEDLINE, Web of Science e LILACS, além de listas de referências. Incluímos estudos originais em seres humanos que avaliaram a associação entre tabagismo materno durante a gravidez e índice de massa corporal (IMC) e excesso de peso dos filhos na infância, adolescência e vida adulta, publicados até 1º de maio de 2018. A metanálise foi usada para estimar os tamanhos dos efeitos agregados. A revisão sistemática incluiu 64 estudos, dos quais 37 avaliaram a associação entre tabagismo materno durante a gravidez e excesso de peso, 13 com IMC e 14 com ambos os desfechos. Desses 64 estudos, foram extraídas 95 medidas de efeito, incluídas na metanálise. Verificamos que a qualidade das evidências nos estudos sobre o tabagismo materno e excesso de peso e IMC dos filhos era moderada e baixa, respectivamente. A maioria dos estudos (44) foi classificada como risco de viés moderado. A heterogeneidade entre os estudos era alta, e na análise de efeitos aleatórios agrupada, o tabagismo materno durante a gravidez aumentou a probabilidade de excesso de peso nos filhos (OR: 1,43; IC95%: 1,35; 1,52) e a diferença média do IMC (β: 0,31; IC95%: 0,23; 0,39). Conclui-se que filhos de mulheres que fumaram durante a gravidez têm maior probabilidade para excesso de peso e maior diferença média de IMC, e que essas associações persistem na vida adulta.

Fumar; Gravidez; Sobrepeso; Índice de Massa Corporal; Metanálise

Resumen

El objetivo del presente estudio fue llevar a cabo una revisión sistemática y metaanálisis para evaluar la evidencia de asociación del tabaquismo materno durante el embarazo con el índice de masa corporal de los hijos durante la infancia, adolescencia y etapa adulta. Se buscó información en las siguientes bases de datos: MEDLINE, Web of Science y LILACS. También se analizaron listas de referencia. Se incluyeron estudios originales, realizados con humanos, que evaluaron la asociación del tabaquismo materno durante el embarazo con el índice de masa corporal (IMC) en los hijos, así como el sobrepeso en la infancia, adolescencia y etapa adulta, publicado el 1 de mayo de 2018. Se realizó un metaanálisis para estimar el tamaño de los efectos combinados. La revisión sistemática incluyó 64 estudios, donde 37 evaluaron la asociación del tabaquismo materno durante el embarazo con el sobrepeso, 13 con el IMC, y 14 evaluaron ambos resultados. De estos 64 estudios, se obtuvieron 95 medidas de efecto que se incluyeron en el metaanálisis. Verificamos que la calidad de las evidencias en los diferentes estudios, respecto tabaquismo materno durante el embarazo y el sobrepeso, así como el IMC en los hijos, era moderada y baja, respectivamente. La mayor parte de los estudios (44 estudios) estaba clasificada como de riesgo moderado de sesgo. La heterogeneidad entre los estudios incluidos fue alta y, en los análisis agrupados de efectos aleatorios, el tabaquismo materno durante el embarazo incrementó la probabilidad de descendencia con sobrepeso (OR: 1,43; IC95%: 1,35; 1,52) y la diferencia media del IMC (β: 0,31; IC95%: 0,23; 0,39). En conclusión, los hijos de las madres que fumaron durante el embarazo tienen una mayor probabilidad de sobrepeso, así como una diferencia media del IMC, y estas asociaciones persisten en la etapa adulta.

Fumar; Embarazo; Sobrepeso; Índice de Masa Corporal; Metaanálisis

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