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Maternal Smoking and Risk of Childhood Overweight and Obesity: A Meta-Analysis

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***Abstract*—**The purpose of this study was to determine the significance of maternal smoking for the development of childhood overweight and/or obesity. Accordingly, a systematic literature review of English-language studies published from 1980 to 2012 using the following data bases: MEDLINE, PsychINFO, Cochrane Database of Systematic Reviews, and Dissertation Abstracts International was conducted. The following terms were used in the search: pregnancy, overweight, obesity, smoking, parents, childhood, risk factors. Eighteen studies of maternal smoking during pregnancy and obesity conducted in Europe, Asia, North America, and South America met the inclusion criteria. A meta-analysis of these studies indicated that maternal smoking during pregnancy is a significant risk factor for overweight and obesity; mothers who smoke during pregnancy are at a greater risk for developing obesity or overweight; the quantity of cigarettes consumed by the mother during pregnancy influenced the odds of offspring overweight and/or obesity. In addition, the results from moderator analyses suggest that part of the heterogeneity discovered between the studies can be explained by the region of world that the study occurred in and the age of the child at the time of weight assessment.

***Keywords*—**Childhood obesity, overweight, smoking, parents, risk factors.

I. Introduction

HISTORICALLY, maternal smoking during pregnancy has been associated with low-birth weight in offspring [1], [2]. Over the ten to fifteen years, interest appears to have shifted from the short-term effects of maternal smoking during pregnancy, namely low birth weight, to the more long-term effects, including catch-up growth of offspring, and even the development of subsequent overweight and/or obesity. Indeed, current evidence suggests that children born to mothers who smoked during pregnancy may be at an increased risk for the subsequent development of overweight/obesity during childhood [3]-[5].

Despite the empirically-supported hypothesis that prenatal exposure to nicotine appears to increase the likelihood of the subsequent development of childhood overweight and/or obesity, the research surrounding maternal smoking during pregnancy and its influence on the development of childhood overweight/obesity has produced some conflicting results, particularly with regards to the degree of association [6]. One potential explanation for the variation in findings rests in how the dependent variable, namely child weight status, is operationalized. Some researchers for example have used overweight as a dependent variable, categorizing all children with BMI over the 85th percentile as overweight, failing to distinguish obesity [7]-[9]. On the other hand, researchers of another study did not examine overweight status, only including children with a BMI greater than the 95th percentile in their analyses [10]. Moreover, some researchers have examined both overweight and obesity in offspring [11]-[13].

Another issue is the potential impact of the quantity of cigarettes smoked by the mother. For example, some researchers have treated maternal smoking as a dichotomous variable with mothers only providing information about whether they smoked or did not smoke during pregnancy [12], [14]. Other researchers, on the other hand, have treat the variable of maternal smoking as continuous, with mothers indicating in their studies the number of cigarettes consumed per day. Interestingly, when dose-effect is taken into consideration, conflicting results have been discovered. Indeed, while some research suggests that the odds of offspring obesity and/or overweight tend to increase as the number of cigarettes smoked increase [5], others have discovered limited increased risk [15], or increased risk only when greater than 19 cigarettes were smoked per day [9], [16]. Given the variation in findings, a consolidation of findings, or in other words a systematic review is thus necessary to bring better clarity with respect to such discrepancies in findings.

II. Purpose of the Study

The purpose of this current study is to provide a synthesis of the research with respect to maternal smoking as a risk factor for childhood overweight and obesity. The specific questions to be addressed are: (1) Is maternal smoking during pregnancy a significant risk factor of overweight and/or obesity in offspring? (2) Are the offspring of mothers who smoke during pregnancy at a greater risk for developing obesity or a greater risk for being overweight?, and (3) Does the quantity of cigarettes consumed by the mother during pregnancy influence the odds of offspring overweight and/or obesity?

III. Method

Meta-analysis is the research design for this study. Within the context of this study, childhood overweight has been operationalized as BMI between the 85th and the 95th percentile, while BMI greater than the 95th percentile will be used to signify obesity; childhood overweight has been operationalized as BMI between the 85th and the 95th

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percentile, while BMI greater than the 95th percentile will be used to signify obesity. In this study, maternal smoking during pregnancy has been operationalized as 'any' exposure to maternal smoking during pregnancy. Dose-response will be operationalized as a mother who smoked greater than ten cigarettes per day.

A. Criteria for Inclusion of Studies

Studies for this meta-analysis were selected based on a set of detailed criterion that were based on age of participants, date of publication, demographics of the participants, research design, and measurement techniques. They were as follows; (a) the study must involve at least one follow-up visit where the child's weight is measured, (b) obesity and/or overweight must be measured by a medically acceptable measurement technique, including BMI for age or sex growth charts [17], [18], (c) studies must focus only on singleton births, (d) at the time of the final follow-up visit, children must be no more than 12 years of age [17], [19]. According to Barlow [17] BMI growth charts categorize children at several distinct at children from 2-5 and then 6-12 thus making the age selection conducive with current growth charts, (e) children must have been born greater than 28 weeks gestation, with no known birth defects or abnormalities, (f) studies must have been published within the last 30 years, and (g) studies must report sufficient data including means, standard deviations, odds ratios, and confidence intervals.

B. Search Strategies

In order to avoid publication bias, the literature search included both published and non-published studies. A publication bias may over-estimate the total effect size since negative results or results that failed to reach statistical significance are often not published. A key way to mitigate this issue is to include both published and unpublished studies in the meta-analysis [20], [21]. To be comprehensive it is important to search multiple electronic databases when doing meta-analyses [22]. As such, searches were performed on the computerized databases PsycINFO (1967 to March 2012), Medline (1946 to March 2012), Cochrane Database of Systematic Reviews, and Dissertation Abstracts International. Key words for search were identified by examining existing literature in childhood obesity. All computer searches were conducted using the following key words and phrases, in various combinations: 'pregnancy', 'overweight or obesity', 'smoking', 'parents', 'risk factors', and 'childhood'. In an effort to be comprehensive, the tables of contents for journals that commonly publish articles in this area, including *Obesity*, *International Journal of Obesity*, *Obesity Research*, *International Journal of Obesity and Related Metabolic Disorders*, *The Journal of Nutrition*, *Pediatrics*, and *International Journal of Epidemiology* were reviewed for relevant studies, along with the reference sections of all identified articles, past reviews, and books in this area.

In all, the search yielded 91 references involving maternal smoking during pregnancy and childhood overweight or obesity; 73 were excluded based on the previously established inclusion criteria, which resulted in a total of 18 studies.

C. Coding of Included Studies

Each study was coded with respect to a variety of study features and statistical findings. Primary categories of study features that were coded included: 1) study design, 2) research question(s), 3) independent variables, 4) dependent variables, 5) population targeted, 6) overweight or obesity measurement, 7) smoking measurements, 8) moderator variables, and 9) statistical analyses. To ensure that the coding of the studies was accurate and consistent, the primary author initially coded all eligible studies using a detailed coding scheme. From there, a second, independent coder coded all eligible studies using the same scheme. When a difference between the two coders arose surrounding the inclusion or exclusion of a particular study, the difference was reconciled by reviewing the study together.

D. Quality Assessment of Studies

The *Center for Evidence Based Medicine, Levels of Evidence* [23], provides "levels of evidence" criteria which includes five different levels of study quality (The Oxford 2011 Levels of Evidence). Within the five different levels, levels one and two also have an additional three sub-levels, while level three has two sublevels. Level one suggests the highest quality of study and includes systematic reviews, case-controlled studies, and cohort studies with 80 percent follow-up. Level two includes cohort studies, including retrospective cohort study or follow-up of untreated control patients in a randomized controlled trial, as well as ecological studies. Level three includes case controlled studies, while level four focusing on case series research or poor quality cohort or case controlled studies. Finally, level five involves expert opinion type reports. The CEBM "levels of evidence" were first introduced in 1998, as a means of providing researchers with a tool to help them determine the most appropriate forms of research and evidence to include in their research. Currently the "levels" are essentially a heuristic or shortcut to finding the likely best evidence.

The CEBM levels of evidence were employed in the present meta-analysis to assess the overall quality of the studies included (The Oxford 2011 Levels of Evidence). Studies were initially reviewed based on the design tree as proposed by Bennett and Emberson [24]. This design tree provided a guide as to where on the levels of evidence each study would be categorized. Studies are originally classified as either descriptive or analytic. Analytic studies, which were the studies included in the present meta-analysis, attempt to quantify the relationship between two factors, while descriptive studies on the other hand provide a picture of what is occurring in a given population. Once the studies were properly categorized, each was then assigned a level based on the CEMB levels of evidence.

E. Analyses

Data analysis in this meta-analysis involved a sequence of steps. The first step was descriptive statistics. Specifically, the studies included in the meta-analysis were described with regards to participant characteristics (e.g., age, sex), study characteristics (e.g., research design, sample size), and

outcome constructs (e.g., individual effect sizes). Whatever the set of effect sizes under investigation, it is often of interest to examine the characteristics of those studies that yield statistically significant results. Descriptive analysis essentially describes the key results and various important attributes of the studies under investigation. Indeed, it can be argued that providing a broad description and appraisal of the nature and quality of the body of research under examination is fundamental to all other analyses [25]. Descriptive analyses were conducted by creating participant characteristic and study characteristic tables to look for trends and access ranges. Furthermore, the means for participants' age, sample size, smoking prevalence, and overweight status were calculated.

The next step involved expressing individual results in a standardized format. According to Egger and colleagues [21], in order to synthesize the studies included in a meta-analysis, results from individual studies must be expressed in a standardized format. In general, results from a meta-analysis are analyzed in terms of effect sizes. An effect size is a measure of the strength (magnitude) and direction of the relationship between two variables, and necessitates either a control group or pre- and post-test for comparison [26]. While there are numerous different types of effect sizes, one particular example is odds ratio (OR). OR is an effect size that is used when the outcome is binary (e.g., obesity versus average weight). This particular effect size facilitates ease in the combination of data, and in testing overall significance [27]. Closely tied with OR is relative risk (RR). While OR examines the number of participants who fulfill the criteria for a given endpoint, divided by the total number of participants who do not, RR, on the other hand, calculates the number of participants who fulfill the criteria for the outcome, divided by all participants [21].

In the present meta-analysis, the effect size of focus was OR but the RR was also provided to assist with overall interpretation. ORs were calculated through the use of the Comprehensive Meta-analysis program [28]. Raw data from each study on the prevalence of overweight and/or obese, as well as non-overweight offspring were compared for mothers who both smoked and did not smoke during pregnancy. Results from each trial were graphically displayed with their confidence intervals in a forest plot. The 95% confidence interval would contain the true underlying effect in 95% of the instances, if the study was to be repeated multiple times.

The effect sizes calculated in the present meta-analysis were used to answer the research questions. Specifically, with regards to maternal smoking during pregnancy, the effect sizes were used to answer the research questions including whether or not maternal smoking was a significant risk factor for the development of offspring overweight and/or obesity, whether offspring of mothers who smoked during pregnancy were more likely to become overweight or obese and whether the quantity of cigarettes smoked by the mother during pregnancy influenced the odds of offspring overweight and/or obesity.

The third step involved examining the potential homogeneity or heterogeneity between study results. The Q statistic test for heterogeneity was calculated to assess whether the individual study results were likely to reflect a single underlying effect, as opposed to a distribution of effects. In other words, the Q statistic was used to explore whether the observed variability in the distribution of effect size estimates was greater than would be expected from sampling error. If the Q statistic fails to detect heterogeneity among results, then it is assumed that the differences observed between individual studies are a result of the sampling variation and chance. If the Q statistic is significant, further analyses are then warranted to identify the sources of this observed variability. The forest plots of the effect sizes were examined to identify potential moderating variables.

In the final step, results were then interpreted by estimating an overall effect by combining the data from all studies. Although different statistical methods exist for combining the data, the method employed for this meta-analysis was a weighted average of the results. In a weighted average, the results from large sample studies tend to have more weight than smaller ones; inversely, results from smaller studies are more susceptible to chance and should be given less weight [21]. The statistical technique of calculating the weighted average can be generally classified into fixed-effect model, and random-effect model. Fixed-effect model considers the variability of the results as a random variation, and individual studies are simply weighted by their precision, meaning that the fixed-effect model only looks at within-study variations. Random-effect model, on the other hand, assumes a different underlying effect for each study, and accounts for this as an additional source of variation, being randomly distributed. In other words, random-effect model takes into account both between-study and within-study variations. Overall, the random-effect model leads to more weight being given to smaller studies and also to wider confidence intervals than the fixed-effect model [21]. In fact, the use of the random-effect model has been advocated for when there is heterogeneity between study results. Furthermore, the random-effects model allows for increased generalization of the findings to other studies with differing characteristics. This meta-analysis calculated the weighted average of the studies using a random-effect model.

F. Moderator Analysis

A moderator variable is essentially an independent variable that interacts with another independent variable in predicting scores on and accounting for variance in a dependent variable [29]. In the case of the present meta-analysis, a potential moderator variable would be one that interacts with maternal smoking thus accounting for at least some of the variance in childhood obesity. Several factors including age of the participants and place of study were hypothesized to have potential effects on the homogeneity of studies. Indeed, individual studies where the weight of children has been examined at multiple ages have demonstrated higher odds ratios for obesity at younger ages than at older ages [10], [30]. Further, in the examination of individual studies, varying odds ratios have been discovered depending on the country where the study was conducted.

Two factors (age of children and location of study) were

chosen at the beginning of the study as potential moderator variables as previous research had shown varying findings in individual studies. For example, research examining offspring at age four, five, and six discovered that six year old offspring were at an greater risk of being classified as overweight and/obese as four year old offspring [31]. In terms of location of the study, research indicates that the cultural values of a given region may influence factors such lifestyle choices, including smoking-related behaviour, dietary choices, and physical activity intake which may ultimately influence the results of a given study. When statistical tests suggest heterogeneity in results, moderator analyses are justified [29].

Moderator analyses were conducted by grouping the studies into categories related to each moderator variable. Specifically, in examining age of the offspring, studies were grouped as either including participants over six or six and under. In terms of location of the study, each study was grouped into one of four categories, North America, South America, Europe, or Asia. In the case of moderator analyses, the Q statistic, instead of the OR will be examined. A significant Q statistic suggests that the variable in question appears be moderating the overall effect sizes, thus partially explaining the heterogeneity in the findings.

IV. Results

A. Prevalence

The literature review yielded 18 studies eligible for inclusion in the meta-analysis of risk for overweight and obesity in childhood resulting from maternal smoking during pregnancy. The studies included 74,393 children, and represent pregnancies that occurred from 1986 to 2006 in Europe, Asia, North America, and South America. The prevalence of smoking during pregnancy ranged from 8% to 43%, with an average of 19% of mothers smoking during pregnancy. The prevalence of childhood overweight ranged from 8% to 32%, with an average of 15% of children being classified as overweight. Lower prevalence rates were discovered when specifically examining childhood obesity, with ranges from 2% to 22%, and an overall average of 8% of children being classified as obese. The children were between the ages of three and 12 at the time their BMI status was assessed.

B. Quality Assessment of Included Studies

As per the CEBM levels of evidence [23] all of the included studies were coded based their assessed quality. As all of the studies were cohort or retrospective studies, they were classified under the second level of quality. Variations in the sublevels, however, were discovered. Of the 18 maternal smoking articles included in the meta-analysis, three of the studies, were assessed as having level two sub-levels ‘a’. The remaining 15 studies were assessed as having sublevel ‘b’ quality. While level one is considered to be studies of the highest quality, given the nature of this research and the unlikelihood of being able to assess maternal smoking during pregnancy during randomized control studies (the type of studies included in level one), the results of this quality assessment suggest that all of the articles included for maternal smoking during pregnancy were of strong quality therefore likely to lead to reliable findings.

C. Effect Size Results

The Comprehensive Meta-Analysis [28] software program was used to assist in the calculation, storage and analysis of effect size estimates. Several different effect size estimates for maternal smoking during pregnancy, including risk for offspring overweight and obesity, risk for offspring obesity versus risk for overweight, as well as the dose response effect of maternal smoking during pregnancy and risk for offspring overweight and obesity were calculated.

D. Is Maternal Smoking During Pregnancy a Significant Risk Factor of Overweight and/or Obesity in Offspring?

The first research question of this meta-analysis was to determine whether the offspring of mothers who smoke during pregnancy are at a greater risk for developing obesity or overweight. Based on the present meta-analysis, children whose mothers smoked during pregnancy were at an elevated risk for overweight and obesity (pooled adjusted odds ratio (OR) 1.69, 95% CI: 1.49- 1.92, P for heterogeneity < 0.001 compared with mothers who did not smoke during pregnancy (See Fig. 1). The pooled relative risk (RR) was 1.56, 95% CI: 1.40-1.73. Such information suggests that offspring of mothers who smoke during pregnancy are over one and a half times more likely to become overweight and/or obese than offspring of mothers who did not smoke. As illustrated by the Forest plot in Fig. 1, 17 of the 18 studies showed that offspring of mothers who smoked during pregnancy were significantly more likely than offspring of mothers who did not smoke during pregnancy to be identified as overweight or obese. Only one non-significant OR of less than 1.0 was reported by Tome and colleagues [8] (OR) 0.98, 95% CI: 0.77-1.24. The study by Adams and colleagues [6] yielded the greatest effect (OR) 3.99, 95% CI: 2.08-7.68, but excluding that study only slightly influenced the pooled odds ratio (OR) 1.66, 95% 1.46,-1.87.

E. Are the Offspring of Mothers Who Smoke during Pregnancy at a Greater Risk for Developing Obesity or Developing Overweight?

As it was determined that offspring of mothers who smoked were at a significant greater risk for developing overweight and/or obesity, the second research question sought to investigate whether offspring of mothers who smoked during pregnancy were at a greater risk for becoming overweight or obese. Of the 18 studies included in the meta-analysis, 16 (84%) provided specific effect sizes for maternal smoking during pregnancy and the risk of overweight, while 11 (61%) provided specific effect sizes for maternal smoking during pregnancy and risk for obesity. As such, due to a sufficient number of studies providing data for overweight and obesity status in offspring, a subgroup analysis was performed to compare the risk for childhood overweight versus the risk for obesity. The pooled odds ratio for maternal smoking during pregnancy and risk for obesity (OR) 1.86, 95% CI: 1.46-2.35,

P for heterogeneity < 0.001 (see Fig. 2) was greater than the pooled odds ratio for maternal smoking during pregnancy and risk for overweight (OR) 1.60, 95% CI: 1.37-1.87, P for heterogeneity < 0.001 (see Fig. 3). The pooled relative risk for maternal smoking during pregnancy and risk for obesity (RR) 1.70, 95% CI: 1.39-2.02, P for heterogeneity < 0.001 was greater than the pooled odds ratio for maternal smoking during pregnancy and risk for overweight (OR) 1.45, 95% CI: 1.27-1.64, P for heterogeneity < 0.001 Providing support for the second hypothesis that children of mother who smoked during pregnancy are at greater risk for becoming obese than they are overweight. It should be noted, however, the risk for overweight remained statistically significant.

F. Does the Quantity of Cigarettes Consumed by the Mother during Pregnancy Influence the Odds of Offspring Overweight and/or Obesity?

The third research question sought to investigate whether the quantity of cigarettes also referred to as the dose-response of the cigarettes impacted the odds of offspring overweight and/or obesity. Of the 18 studies included in the meta-analysis, five (28%) reported data on the effects of dose response and maternal smoking during pregnancy, and the risk for offspring overweight and obesity. As shown in Fig. 4, all of the studies revealed a statistically significant increase in the risk for childhood overweight and obesity as the number of cigarettes the mother smoked during pregnancy increased. The pooled odds ratio for dose response of maternal smoking (OR) was found to be 2.50, 95% CI 1.53-4.06, P for heterogeneity < 0.001. The pooled relative risk for dose response of maternal smoking (RR) was found to be 2.10, 95% CI: 1.39-3.11, P for heterogeneity < 0.001. These results provide support for the third hypothesis. As the number of cigarettes smoked during pregnancy increased so too did the risk for offspring overweight and/or obesity.

G.Moderator Analyses and Heterogeneity

The effect sizes calculated suggested that maternal smoking during pregnancy increased the odds of children being classified as overweight and/or obese. Despite these noteworthy findings, the Q test suggested heterogeneity of results both maternal smoking. A significant Q test suggests that the differences observed between studies were due to something other than chance. As a result of the detection of heterogeneity, moderator analyses for age at the time of overweight and/or obesity measurement and region of the study were conducted. It is important to note that while variables such as SES status, level of parental education, and dietary patterns were investigated in some studies, due to inconsistencies between the studies; those variables were unable to be investigated as potential moderator variables. The following sections will explain the results of the moderator analyses.

H.Age of the Child at Overweight and/or Obesity Measurement

An analysis of variance was calculated to determine whether there was a difference between the odds of offspring of mothers who had smoked during pregnancy being classified as overweight and/or obese at six years of age and under versus over six years of age. Results suggest a statistically significant difference between the odds of offspring whose mothers smoked during pregnancy being identified as overweight and/or obesity when they were assessed at age six years and under versus when the assessment was done when the child was older than six ($Q = 10.35$, $p < 0.001$). This would suggest that maternal smoking during pregnancy appears to have the greater impact on the overweight and/or obesity status of their offspring when they are six years and under than when they are older than six years old.

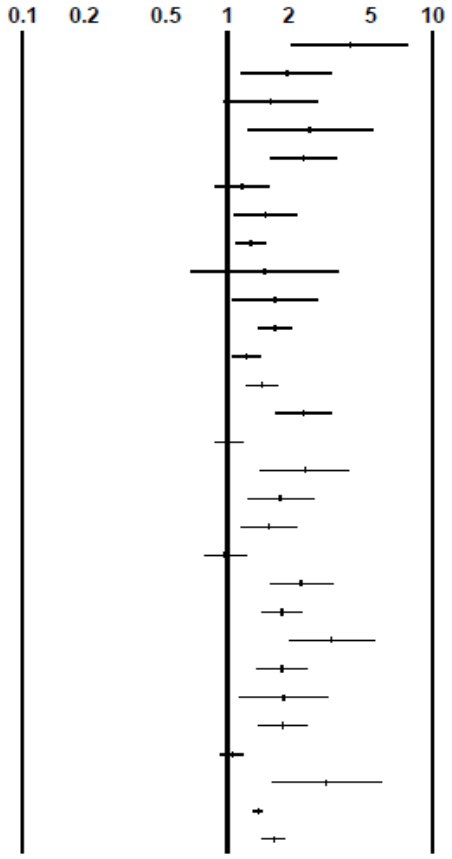
I. Region of the Study

An analysis of variance was calculated to determine whether there was a difference between the odds of offspring of mothers who smoked during pregnancy being classified as overweight and/or obese depending on the region of the world where the study was conducted. The studies were grouped into four categories of region which included Asia, Europe, North America, and South America. There was a significant difference in the odds ratio of offspring being identified as overweight and/or obesity depending on the region where the study took place ($Q = 54.52$, $p < .0001$). Specifically, the North American region produced the largest effect sizes; offspring of mothers who smoked during pregnancy were over two times more likely to become overweight and/or obese than offspring of mothers who did not smoke during pregnancy. The effect sizes discovered in the regions of Asia and Europe were almost identical, with the offspring of mothers who smoked during pregnancy being just over one and a half times more likely than offspring of non-smoking mothers to be classified as overweight and/or obese. Studies conducted in the region of South America discovered the lowest overall effect sizes; offspring of mothers who smoked during pregnancy were just over one time more likely to develop overweight and/or obesity than offspring of non-smoking mothers. This information suggests that the region where the study took place impacted the odds that offspring of mothers who smoked during pregnancy would develop overweight and/or obesity.

J. Publication Bias

The effect size of each study was plotted to assess for publication bias. Plotting the natural logarithms of the odds ratio of studies with smaller sample sizes (which biases are more likely to occur) against their standard error is common practice (21). The funnel plot analyses used to test for asymmetry between main and subgroup effect size calculations suggests that studies with smaller sample sizes scattering more widely in the lower portion of the graph reflecting less precision in the estimation of odds ratio thus supporting a non-publication bias in the development of offspring overweight and/or obesity as it pertains to maternal smoking during pregnancy.

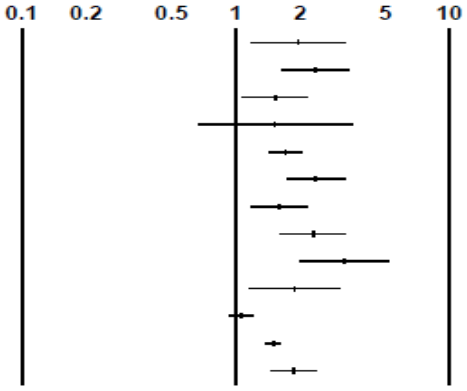
Study Citation	Year	OR (Random) 95% CI
[6]	2006	3.99 (2.08 – 7.67)
[31]	2003	1.95 (1.17 – 3.25)
[31]	2003	1.63 (0.96 – 2.76)
[7]	2010	2.53 (1.25 – 5.09)
[15]	2004	2.36 (1.63 – 3.39)
[15],	2004	1.18 (0.87 – 1.61)
[33]	2011	1.53 (1.08 – 2.18)
[33]	2011	1.30 (1.09 – 1.55)
[11]	2011	1.53 (0.66 – 3.49)
[11]	2011	1.71 (1.05 – 2.76)
[3]	2010	1.71 (1.43 – 2.05)
[3]	2010	1.24 (1.06 – 1.45)
[34]	2010	1.48 (1.24 – 1.77)
[34]	2010	2.37 (1.73 – 3.23)
[12]	2007	1.01 (0.87 – 1.20)
[32]	2005	2.40 (1.46 – 3.95)
[13]	2011	1.83 (1.27 – 2.63)
[16]	2005	1.60 (1.17 – 2.18)
[8]	2007	0.98 (0.77 – 1.24)
[4]	2002	2.30 (1.62 – 3.26)
[4]	2002	1.85 (1.47 – 2.32)
[4]	2003	3.23 (2.00 – 5.21)
[5]	2003	1.85 (1.38 – 2.47)
[5]	2002	1.89 (1.15 – 3.09)
[10]	2002	1.86 (1.41 – 2.45)
[9]	2004	1.06 (0.93 – 1.20)
Fixed Combined (27)	2003	3.05 (1.36 – 5.27)
Random Combined (27)		**1.43 (1.33 – 1.47)**
		1.69 (1.49 – 1.92)



Test for heterogeneity: $x2$ = 134.7,df = 26 (P<.0001). Test for overall effect: Z = 8.14 (P <.0001)

Fig. 1 Meta-analysis of random combined ORs - maternal smoking and risk for childhood overweight and obesity

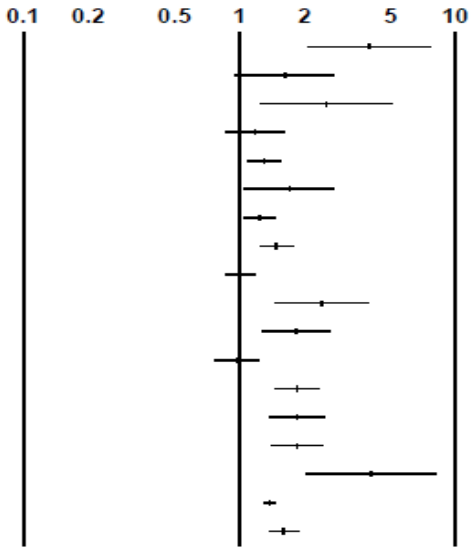
Study Citation	Year	OR (Random) 95% CI
[31]	2003	1.95 (1.17 – 3.25)
[15]	2004	2.36 (1.63 – 3.39)
[33]	2011	1.53 (1.08 – 2.18)
[11]	2011	1.53 (0.66 – 3.49)
[3]	2010	1.71 (1.43 – 2.05)
[34]	2010	2.37 (1.73 – 3.23)
[16]	2005	1.60 (1.17 – 2.18)
[4]	2002	2.30 (1.62 – 3.26)
[4]	2003	3.23 (2.00 – 5.21)
[5]	2002	1.89 (1.15 – 3.09)
[10]	2004	1.06 (.93 – 1.20)
Fixed Combined (11)		**1.50 (1.35 – 1.59)**
Random Combined (11)		**1.86(1.46 – 2.35)**



Test for heterogeneity: $x2$ = 62.71,df = 9 (P<.0001).Test for overall effect: Z = 4.82 (P <.0001)

Fig. 2 Meta-analysis of random combined ORs - maternal smoking and risk for childhood obesity

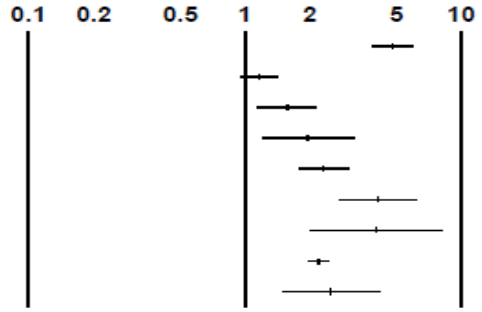
Study Citation	Year	OR (Random) 95% CI
[6]	2006	3.99 (2.08 – 7.68)
[31]	2003	1.63 (0.96 – 2.76)
[7]	2010	2.53 (1.25 – 5.09
[15]	2004	1.18 (0.87 – 1.61)
[33]	2011	1.30 (1.09 – 1.55)
[11]	2011	1.71 (1.05 – 2.76)
[3]	2010	1.24 (1.06 –1.45)
[34]	2010	1.48 (1.24 – 1.77)
[12]	2007	1.02 (0.87 – 1.20)
[32]	2005	2.40 (1.46 – 3.95)
[13]	2011	1.83 (1.27 – 2.63)
[8]	2007	0.98 (0.77 – 1.24)
[4]	2002	1.85 (1.47 – 2.32)
[4]	2003	1.85 (1.38 – 2.47)
[5]	2002	1.86 (1.41 – 2.45)
[9]	2003	4.06 (1.36 – 5.27)
Fixed Combined (16)		**1.38 (1.28 – 1.46)**
Random Combined (16)		**1.60 (1.37 – 1.87)**



Test for heterogeneity: $x2$ = 71.64,df = 15 (P<.0001). Test for overall effect: Z = 5.90 (P <.0001)

Fig. 3 Meta-Analysis of Random Combined ORs - Maternal Smoking and Risk for Childhood Overweight

Study Citation	Year	OR (Random) 95% CI
[15]	2004	4.82 (3.85 – 6.03)
[15]	2004	1.17 (0.97 – 1.42)
[16]	2005	1.56 (1.14 – 2.16)
[16]	2005	1.96 (1.20 – 3.22)
[5]	2002	2.31 (1.78 – 3.00)
[5]	2002	4.11 (2.73 – 6.12)
[9]	2003	4.06 (1.65 – 5.63)
Fixed Combined (6)		**2.20 (1.99 – 2.46)**
Random Combined (6)		**2.50 (1.53 – 4.06)**



Test for heterogeneity: $x2$ = 105.82,df = 26 (P<.0001). Test for overall effect: Z = 3.05 (P <.0001)

Fig. 4 Meta-analysis of random combined ORs – dose response of maternal smoking and risk for childhood overweight and obesity

V. Discussion

Based on the participant characteristic, and the means calculated, it was discovered that the prevalence of smoking during pregnancy ranged from 8% to 43%, with an average of 19% of mothers smoking during pregnancy. The highest prevalence of maternal smoking of 43% was reported by a study in the United States and involved American Indian women [6].

The prevalence rates of maternal smoking did not appear to be related to year in which the study was conducted. Specifically, both low (under 15% and high above 30 % prevalence rates) were observed in studies conducted within the past ten years and ones conducted prior to ten years ago. The prevalence of childhood overweight ranged from 8% to 32%, with an average of 15% of children being classified as overweight. Lower prevalence rates were discovered when specifically examining childhood obesity, with ranges from 2% to 22%, and an overall average of 8% of children being classified as obese. This finding corresponds with Canadian Childhood Obesity prevalence, which suggests that 8% of Canadian children are classified as obese [32]. Further, worldwide prevalence estimates suggest that as many as 25% of children under the age of 18 are overweight [33]. The children in the studies were between the ages of three and 12 at the time their BMI status was assessed. Upon visual inspection of the characteristic table, the younger the children were at the time of the overweight and/or obesity measurement, the higher the prevalence rates for overweight and/or obesity were reported. Childhood obesity prevalence research has suggested that as children get older their prevalence rates for overweight and/or obesity increase [32]. The finding that indicates that younger children had higher prevalence of overweight and/or obesity rates in the present meta-analysis may ultimately highlight the importance of

socialization and lifestyle factors in children's weight as they age [34].

According to the CEBM levels of evidence, provide researchers with a tool to help them determine the most appropriate forms of evidence to include in their research [23]. In terms of maternal smoking, the use of randomized controlled studies was neither practical nor ethical. Specifically, it would be unethical to assign participants to two different groups and have one group smoke during pregnancy and the other not smoking. As such, the studies included in the meta-analysis were immediately precluded from being assigned the highest level of study quality. Still, all of the studies included, were classified as possessing the second highest level quality. In terms of maternal smoking during pregnancy, two studies were classified falling under as sublevel 'a' of level two. The remaining 15 studies were assessed as having sublevel 'b' quality

From a research and practical standpoint, the studies included in the present meta-analysis, were each conducted using sound research procedures and methodology, such as adequate sample sizes and parallel cohort groups where those with the condition in the first group were compared to those without the condition in the second group. The distinguishing feature that impacted the sublevel assigned to the included studies was the degree of follow-up that the study had. Those studies classified as having sublevel 'b' quality had less than 80% follow-up, which had the potential to somewhat altered the overall findings of these studies Overall, however, based on the CEBM criteria each of the studies included would be given an overall grade of B in terms of their quality. Indicating that they have reasonable internal and external validity to be generalized to the population of interest, namely, offspring of mothers who smoke during pregnancy [23].

The results of the present meta-analysis show that maternal smoking during pregnancy is a significant risk factor in the development of offspring overweight and/or obesity. With the exception of the study conducted by Tome and colleagues (8), all other studies included in the present meta-analysis found that maternal smoking during pregnancy increased the odds of offspring subsequently becoming overweight and/obese. When individual studies included in the meta-analysis were examined independently, the offspring of mothers who smoked during pregnancy were discovered to be between one to just under four times more likely to become overweight and/or obese than the offspring of mothers who did not smoke during pregnancy. Even when the study that produced the largest effect size was removed from the equation, the odds of a child whose mother smoked during pregnancy becoming overweight and/or obese were over one-and-a-half times greater than for children whose mothers did not smoke during pregnancy. These findings suggest that maternal smoking during pregnancy is significantly associated with the development of overweight and/or obesity in offspring.

Maternal smoking during pregnancy has been repeatedly established as an important risk factor for low birth-weight in infants [9], [35]-[37]. Indeed, in a comprehensive review of the risk factors for low birth-weight, offspring of mothers who smoked during pregnancy were, on average, 149g lighter than mothers who did not smoke [38], with some studies documenting birth-weights 300g lighter. Due to the vast research in this particular area, understanding that maternal smoking during pregnancy is associated with low birth-weight in offspring has become almost common knowledge. The long-term effects of maternal smoking on the weight of offspring, however, have been less investigated. The relation between maternal smoking and low birth-weight is thought to be the result of vasoconstriction of the nicotine and hypoxemia (oxygen deficiency) by the carbon monoxide [38]. Biological mechanisms may explain the observed association between maternal smoking during pregnancy and offspring overweight and/or obesity. Two possible mechanisms have been hypothesized to account for how maternal smoking during pregnancy may lead to offspring who are overweight and/or obese. One involves hypothalamic function and the other involves abnormalities in fat [39], [40]. Experimental studies involving rats have shown that gestational starving of the mother is associated with offspring obesity [41]. Studies involving rats have found larger fat pads in the offspring of the mothers who were starved rather than those whose total body weight increased during their pregnancies. These studies suggest that the obesity of the offspring of starved mothers is due to altered hypothalamic regulatory mechanisms of energy intake and expenditure, rather than abnormalities in fat cells [41]. Other animal studies have discovered that the administration of nicotine to pregnant mothers resulted in offspring that were smaller at birth but had increased body fat [42], [43].

Additionally, agents that are associated with cigarettes, including nicotine (which is transported through the placenta) and carbon monoxide (which influences vascular functions) have also been hypothesized to explain the physiological effects of maternal smoking and offspring overweight and/or obesity. In animal and human studies, nicotine has been found to reduce appetite and body weight, while nicotine withdrawal leads to excessive ingestion of food and weight gain [44], [45]. Furthermore, children of smokers tend to be less physically active and have poorer diet quality [5].

Two previous syntheses involving maternal smoking and offspring obesity have been conducted [46], [47]. These previous meta-analyses, however, failed to differentiate between overweight and obesity in offspring, treating these two constructs as one. Thus, while such meta-analyses provide evidence supporting the association between maternal smoking during pregnancy and offspring obesity, overweight status in offspring was not specifically investigated. To overcome the limitations of treating two differing constructs as one, the present meta-analysis conducted a subgroup analysis of the studies to determine whether a difference existed between the risks for the development of overweight versus obesity in the offspring of mothers who smoked during pregnancy. This is the first meta-analysis to synthesize the odds of maternal smoking and future offspring overweight versus obesity. Results from the present meta-analysis suggest that, while offspring of mothers who smoked during

pregnancy have greater odds of becoming obese during childhood than they do overweight, the odds of offspring overweight remain high. Indeed, offspring of mothers who smoked during pregnancy are over one-and-a-half times more likely to become overweight than the offspring of mothers who did not smoke.

The findings of the present meta-analysis are important because, as overweight and obesity are not the same constructs. In fact, although overweight and obesity are often used interchangeably, they are defined differently and therefore should not be treated as identical. According to the National Institute of Health [48], adults with a body mass index (BMI) greater than 30 kg/m² are considered obese, while adults with a BMI between 25 and 29.9 kg/m² are classified as obese. In children, overweight is defined as a BMI between the 85th and less than the 95th percentile is considered overweight, while having a BMI greater than the 95th percentile signifies obesity [49]. It has also been established that obesity is associated with several adverse health conditions, including but not limited to cardiovascular disease, non-insulin-dependent (NIDDM) type 2 diabetes, respiratory diseases such as asthma, and certain cancers [50]. Nevertheless, children who are classified as overweight, not just obese, are also more likely to have risk factors for cardiovascular problems, including high blood pressure and high cholesterol [51], though the specific risks of these overweight children may differ from those who are obese.

Indeed, it must not be forgotten that, much like obesity, being overweight has also been shown to be associated with the negative health implications. In fact, both overweight and obesity identify ranges of weight that have been shown to increase the likelihood of certain diseases [52]. Studies involving childhood populations have discovered that even children classified as overweight are at risk for developing health complications, including metabolic syndrome [53]. Metabolic syndrome has been shown to be an important risk factor in the development of cardiovascular disease in later years. As BMI increases, so does the risk for negative health consequences [35]. Furthermore, just as obese children tend to experience negative psychosocial effects of their weight; overweight children also demonstrate lowered levels of self-esteem, decreased social competence, and higher levels of depressive symptomology [54]. Moreover, children classified as having BMI greater than the 85th percentile tend to utilize health services more often, thus contributing to the growing cost of health care. For example, a recent study suggests that, when comparing the health care costs associated with overweight and/or obese children and normal-weight children, costs were 16% higher in children with measured overweight and/or obesity [55].

Another distinguishing factor between overweight and obesity that highlights the necessity to investigate them independently are prevalence rates. Prevalence rates of overweight, for both children and adults, have consistently been higher than for obesity [56]. Data from the 2004 CCHS Canadian prevalence rate data suggests that children between the ages of two and 17 are almost three times more likely to be classified as overweight than obese, with approximately one in four Canadian children being overweight. Even more alarming, 59% percent of Canadian adults are overweight while 23% are obese [18]. The associated risk for the development of negative health consequences, as well as higher prevalence rates, suggests that overweight status is a distinct construct that must be included as part of prevention and treatment efforts. As such, research must also investigate overweight status, and not simply focus on obesity.

Five of the 18 studies included in the present meta-analysis investigated not only the association between maternal smoking and risk for offspring overweight and/or obesity, but examined whether the number of cigarettes smoked during pregnancy, also referred to as a dose effect, impacted this association. Dose effect was operationalized as smoking greater than ten cigarettes per day. Among studies that reported information regarding the quantity of cigarettes mothers smoked during pregnancy, all found evidence of a dose-response effect [4], [9], [16]. Indeed, children's BMI - as well as risk for overweight and/or obesity - increased along with the increasing numbers of cigarettes smoked during pregnancy. Moreover, when skinfold thickness was assessed in addition to BMI, the more cigarettes the mother smoked during pregnancy, the more children's skinfold thickness increased [9]. Indeed, overall results suggest that the offspring of mothers who smoked more than ten cigarettes per day were two-and-a-half times more likely than mothers who did not smoke during pregnancy to be classified as overweight and/or obese. Comparatively, mothers who smoked less than ten cigarettes per day had offspring who were one-and-a-half times more likely to be classified as overweight and/or obese. Thus, not only does maternal smoking during pregnancy increase the odds that offspring will become overweight and/or obese, but the number of cigarettes that the mother smokes also increases these odds.

The age of the child at the time of the overweight and/obesity assessment appeared to produce some difference in the effects sizes of the studies. Specifically, in studies that examined children six years or age and under, larger effects sizes tended to be reported than in studies that assessed children for overweight and/or obesity after the age of six. Results from the moderator analyses showed that more offspring under the age of six who had smoking mothers were identified as overweight and/or obese than offspring six years and older who had mother who smoked during pregnancy. One potential explanation for this finding may be the associated features or characteristics potentially found in mothers who smoke during pregnancy. Maternal smoking during pregnancy has been found to be associated with other prenatal risk factors for obesity [57]. While the lack of raw data on breastfeeding and maternal weight gain during pregnancy prevented these factors from being examined in separate moderator analysis, previous research would suggest that the offspring of mothers smoked during pregnancy, may have also had numerous other risk factors for overweight and/or obesity [10]. Specifically, mothers who smoke are also more likely to gain excessive weight during pregnancy and

rely more on formula to feed their offspring rather than breast milk that has been shown to have a protective factor against the development of overweight and/or obesity in children [58], [59]. Each of these risk factors occur prenatally or very early in the child's life, thus potentially increasing the likelihood that the child will become overweight and/or obese right from birth.

In addition to prenatal risk factor for childhood overweight and/or obesity, dietary and lifestyle choices such as amount of physical activity may also partially explain the difference the higher effect size for overweight and/or obesity in children under the age of six. Again, the overwhelming majority of the studies included in the meta-analysis did not focus on physical activity or dietary choices or parents, thus preventing their analyses. However, it has been hypothesized that when parents engage in poor dietary or lifestyle choices, these behaviours will be modeled to their children [34]. Further, at a young age, parents are the one that often make diet and lifestyle choices for their children, which increases the likelihood that children will eat the same foods and receive similar amounts of physical activity as their parents [60].

The increasing number of socialization agents that children come into contact with as they age may provide an explanation for why the effect sizes are not as high for children older than six. As children enter school, numerous socialization sources, including their peers or even the social climate of their school begin to influence the lifestyle decision they make [61]. While parents may still largely determine the types of food that children consume, children's opportunity for physical activity increase significantly once they are in the school setting. In fact, many of the current prevention efforts are targeted at school-aged children, with some programs even occurring directly in the school setting [62]. Thus as children get older, they begin to have more opportunities to make their own healthy lifestyle choices, thus suggesting that the influence of prenatal or early childhood risk factors for overweight and/or obesity may decline over time.

Another variable thought to influence the homogeneity of results was the region of the study. Specifically, studies included in the meta-analysis were conducted in the regions of North America, South America, Asia, and Europe. An analysis of variance was calculated to determine whether there was a difference between the risk of offspring of mothers who smoked during pregnancy or who had a family history of obesity being classified as overweight and/or obese depending on the region of the world where the study was conducted. Results from the moderator analysis suggest that the region where the study took place impacted the odds that offspring of mothers who smoked during pregnancy would develop overweight and/or obesity. In particular, studies conducted in North America yielded the largest overall effect sizes; such children were over two times more likely to be classified as overweight and/or obese than offspring of mothers who did not smoke.

This finding may at least be partially explained by the specific cultural norms and expectations, as well as the attitudes towards obesity for the various regions where the studies took place. For example, in some regions (i.e., Europe), smoking is more prevalent and less taboo, compared to regions such as North America, where the prevalence of smoking during pregnancy is declining [63]. Specifically, it has been estimated that over 43 percent of the Greek population over the age of 15 currently smokes, while only 17 percent of the Canadian population over 15 smoke [63]. On the other hand, North America has one of the highest prevalence of obesity, thus increasing the likelihood that offspring will be born into family with such a condition [32]. Furthermore, dietary patterns and lifestyle choices often depend upon the culture that a given population is living in. As lifestyle patterns vary among the varying regions across the world, it should therefore come as no surprise that the region in which a study takes place influence the effect sizes of overweight/ and obesity in children whose mothers smoked during pregnancy.

VI. Conclusion

One potential factor with regards to maternal smoking during pregnancy that requires further research is the timing of maternal smoking. Indeed, while it appears as though smoking during pregnancy can lead to negative outcomes in the development of offspring, understanding the impact of smoking during the first trimester versus the second and third may be particularly useful for prevention efforts. For example, some women may think that they will quit smoking once they become pregnant. However, often a woman may be several weeks pregnant before she even knows it. Should future research suggest that the first trimester is particularly crucial in terms of the impact of smoking, then women will need to learn that smoking cessation must begin before even attempting to become pregnant. Additionally, as smoking during pregnancy becomes increasingly socially unacceptable, a natural progression would be to examine the effects of second-hand exposure to cigarettes. While it may be assumed that, since second-hand smoke exposure can be harmful to people, it should therefore be harmful to a developing fetus, such assumptions require the backing of research. As such, future research should separate the possible effects of maternal smoking during pregnancy from environmental exposure to tobacco.

Another area of future research that is required with regards to maternal smoking during pregnancy and the increased odds of offspring overweight and/or obesity is further investigation relative to the reason for this association. It has been hypothesized that hypothalamic functioning of offspring of mother who smoke during pregnancy are altered and that although children may be smaller at birth, they are at risk for having increased fat [41], [43], more research is needed in this area. The majority of the evidence for these hypotheses comes from animal studies. More research is needed to determine the exact biological mechanism responsible for intrauterine growth retardation yet subsequent overweight and/or obesity status.

The findings of the present meta-analysis serve as not only a useful resource for future research, but also have practical

implications for developing a framework for the prevention of overweight status and obesity in children. Although public health recommendations already discourage smoking in all individuals particularly for the elevated negative health risks (e.g., lung cancer), the public will need to also be educated on the potential lifelong adverse outcomes of smoking not only on themselves, but on their children [64]. The results of this study indicate that prevention programs should target expectant mothers and fathers, rather than just the children themselves. In other words, prevention needs to start before birth. Prevention should provide rigorous assessment of fetal growth, monitor pregnant mothers trying to maintain a healthy BMI, ensure meticulous glucose control for diabetic mothers, encourage moderate exercise for both expectant mothers and father, highlight the benefits of breastfeeding, and focus on smoking cessation during pregnancy. Indeed, raising awareness of childhood overweight and/obesity will surely need to become a critical task for health care providers. Increasingly doctors should include the family in children's health care visits and incorporate assessment of maternal weight status and family functioning into patient care and education [30].

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