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REVIEW ARTICLE

The Association between Maternal Folate Status and Childhood Obesity-Systematic Review and Meta-Analysis

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PURPOSE: Maternal nutrition plays a crucial role in fetal growth and lifelong health outcomes. Folate is an essential methyl donor in the epigenetic programming of offspring. This review and meta-analysis was conducted to compile the evidence reported thus far to identify associations between maternal folate status and childhood obesity.

METHODS: A keyword/reference search was performed in EBSCOhost and Web of Science databases. A CMA program was used for a meta-analysis to estimate the pooled effect of maternal folate status on childhood obesity in offspring and to examine the influence of moderating variables on the overall effect.

RESULTS: Better maternal folate intake was associated with a lower risk of childhood obesity: the overall effect size (ES; Hedges' g) was 0.168 (95% CI=0.075 to 0.260, $p<.001$; small effects; cf., Cohen's criteria). Moderator analysis revealed that the ≥Q statistic for the age group was statistically significant ($Q_b=4.730$, df=1. $p=.030$; heterogeneity of ES). In offspring <7 years and >7 years, the ES was 0.277 (95% CI=0.151, 0.404) and 0.089 (95% CI=-0.025, 0.202), respectively. The study design was a statistically significant variable ($Q_b=4.310$, df=1. $p=.038$; heterogeneity of ES). In cohort studies, ES was 0.251 (95% CI=0.135, 0.367), whereas in randomized controlled trial group, ES was 0.062 (95% CI=-0.073, 0.197).

CONCLUSIONS: Maternal folate intake significantly affects childhood obesity, and the effect of maternal folate status is stronger in children younger than 7 years.

Key words: Folate, Folic acid, Child obesity, Meta-analysis, Review

INTRODUCTION

Maternal nutrition plays a crucial role in fetal growth and lifelong health outcomes [1]. Among several maternal nutrients, folate constitutes an essential micronutrient for nucleic acid synthesis and methylation as well as amino acid metabolism. Inadequate dietary folate intake can lead to folate deficiency. Other factors, such as pregnancy or neoplastic diseases; poor absorptive conditions; use of antifolate drugs and metabolic inhibitors; and alcohol consumption, can cause folic acid deficiency. Folate functions as a methyl donor to primarily provide the methyl groups that are required for DNA methylation to establish the structure and function of the fetal genome [2]. Thus, folate contributes to the epigenetic programming of offspring, and adequate folate intake helps prevent neural tube defects [3].

Maternal folate deficiency is associated with obesity, which results in altered insulin resistance and elevated blood pressure, in adult male offspring [4] as well as increased central fat mass and liver steatosis in the progeny [5]. A recent study showed that sufficient maternal folate concentrations could attenuate the detrimental effects of maternal obesity in the offspring [6]. In the past 35 years, the prevalence of childhood obesi-

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ty has increased more than twofold, from 7% in 1980 to nearly 18.5% in 2016, and has affected 13.7 million children and adolescents [7]. Childhood obesity is a critical issue because it likely leads to obesity in adulthood and can cause metabolic disorders that affect the entire life cycle. Despite the logical connection between maternal folate status and obesity of offspring, the actual impact of this association tends to be underestimated due to the difficulties in proving causality and the limitations associated with follow-up studies. Therefore, efforts to identify the association between maternal folate status and childhood obesity have generated controversial results and maternal folate intake, which affects childhood obesity, remains a debatable critical issue. Several studies have revealed that maternal folate deficiency is associated with childhood obesity [6,8], and some studies have shown that excess folate intake is also related to childhood obesity [9,10]. However, other studies indicated that there is no association between maternal folate levels and childhood obesity [11,12].

To our knowledge, there is limited literature indicating the association between maternal folate intake and childhood obesity using a meta-analytic approach. Therefore, in this study, we aimed to elucidate the possible basis and to understand the relationship between maternal folate status and childhood obesity by undertaking a systematic review with meta-analysis.

METHODS

1. Study Design

We used EBSCOhost to search for relevant studies in the Academic Search Complete, Health Source-Nursing Academic Edition, Medline, SPORTDiscus database, and CINAHL. Moreover, the Web of Science database was searched to identify all relevant studies. All reports were retrieved from inception to September 27, 2020. For EBSCOhost and Web of Science, the search terms were: "maternal folate" OR "maternal folic acid" AND "obesity". Additionally, in order to identify studies in Google Scholar, three groups of search terms were combined as follows: (1) "folate" OR "maternal folate" OR "maternal folic acid"; (2) "obesity" OR "body mass index (BMI)"; and (3) "offspring" OR "child*" The reference lists of selected studies were further investigated to identify relevant articles. This systematic review was performed in conformance with the Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines.

2. Population and Sample

This review included only studies that met all of the following criteria: (1) study design: observational studies (e.g., longitudinal studies, case-control studies, or cross-sectional studies) or qualitative studies; (2) study subjects: offspring age from 2 to 15 years, also 47 years (one study); (3) intervention: maternal folic acid or folate supplementation; (4) outcomes: obesity status (e.g., BMI, BMI z-score, fat mass, or % fat); (5) article type: peer-reviewed publications; (6) time window of search: from the inception of an electronic bibliographic database to September 27, 2020; (7) geographical location: worldwide; and (8) language: only articles written in English. We excluded studies from this review if they met any of the following criteria: (1) studies without an outcome pertaining to children's obesity status; (2) interventions without maternal folic acid or folate; (3) articles not written in English; or (4) letters, editorials, study/review protocols, and review articles.

For the quantification of maternal folate status, folate analysis was performed by chemiluminescence-based immunoassay of serum samples. Folic acid can be measured even in erythrocytes or plasma; however, we excluded analyses that used this type of sample from the final analysis dataset.

3. Types of participants and interventions

Pregnant women and their children participated in studies that utilized folic acid supplementation or measured maternal folate status (either from serum folate concentration or daily folate intake). The results were based on the amount of daily dietary folate intake that was calculated from the responses to the nutritional survey. In cases where supplements were used, the amount of folate in the supplement was added to the value of dietary folate intake. Dietary assessments were conducted during regular antenatal checkups. Therefore, based on the timing of the dietary assessment, the cohort could be divided into two groups: less than or more than 13 weeks of gestation. These were evaluated as moderator variables.

4. Study Variables: Data Extraction and Preparation

Two investigators independently obtained and screened data from the included studies. A standardized data extraction form was used to collect the following methodological and outcome variables from each study: first author, publication year, study design, sample age group, sample size, folate concentration range, amount of dietary folate intake, method of dietary folate intake, periods of folate intake, obesity status

measurement, and estimated effects of maternal overweight and obesity. The mean and standard deviation (SD) of obesity indices in the study, including BMI or fat mass, from the folate intake group and placebo as well as indices of adequate or low serum folate concentration were recorded. From studies that reported data for several age groups during the developmental period, we obtained data from each point to assess the effect in different age groups. Moreover, if an investigation had used different concentrations or amounts of folic acid, the comparison of data for each concentration or amount with that of the control was considered a separate study.

5. Operational Definition of Variables: Methodological Quality Assessment

Using the modified Downs and Black Checklist [13], which was developed for both randomized and non-randomized comparative studies, we reviewed the full-texts of studies in order to assess the methodological quality. The checklist comprises 27 criteria across four domains - reporting, external validity, internal validity, and power - to provide an overall study quality score. Discrepancies in quality ratings between the reviewers were resolved by consensus. We revised the final question from a 5-point to a 1-point rating to avoid confusion in the power calculation, and assigned a score of 1 if the authors reported power or sample-size calculation and a score of 0 if there was no power calculation or a description of whether the number of participants was appropriate for the research design. The Modified Downs and Black Checklist has been successfully used previously, validating its use in the abovementioned approach [14]. Therefore, the total maximum score is 28, with a higher score representing higher methodological quality.

6. Data Analysis

Comprehensive Meta-Analysis, Version 3.0 was used to calculate effect sizes (ES) that represented the magnitude of the maternal folic acid status on the child's obesity status. The ES values that we used for the meta-analysis were adjusted for various confounding factors by the authors. This study employed a random-effects model to calculate the mean ES and 95% confidence interval (CI) [15,16]. Based on Cohen's criteria, ES values were described as small (0.2), moderate (0.5), or large (0.8) [17]. Under the null hypothesis of homogenous weighted mean ES, the heterogeneity of the weighted mean ES was examined through moderator analyses using Cochran's Q statistic (Q_b) [18], which is a measure of heterogeneity, among the sublevels of each moderator on the child's obesity. Furthermore, publication bias was analyzed via a visual inspection of a funnel plot and Egger's test of the regression intercept. For Egger's test statistics, two-sided *p*-values are reported.

RESULTS

1. Sample Characteristics

1) Search Results

The flowchart shows the literature search process (Fig. 1). The computerized searches yielded 4,722 articles; among these, 2,620 were eliminated due to duplication, and 2,102 articles were screened for inclusion in the meta-analysis. After the initial screening of 2,102 titles and abstracts, 421 articles were selected for full-text review, of which 409 were ineligible (not meeting the inclusion criteria or insufficient data to calculate ES). In total, 12 studies met our inclusion criteria for the systematic review, and 8 studies were eligible for the quantitative meta-analysis.

2) Study Characteristics

Detailed information on study characteristics is displayed in Table 1. Sample sizes ranged from 63 to 5,783 participants, with age varying from 2 to 15 years, and 47 years in only one study. Among the 8 studies, 3 (37%) were randomized controlled trials and 5 (63%) were cohort studies. The folate status varied, including, for example, folate intake volume, folate supplement intake, and serum folate concentration. The childhood obesity indices varied and included fat mass, BMI mean, BMI median, and BMI Z-score. Among the 8 studies, 3 (37%) were carried out in the United Kingdom, 2 (25%) in the United States, and the remainder in India, Nepal, and the Netherlands.

2. Bivariate Analysis

1) Study Quality

Based on the Modified Downs and Black Checklist, the methodological quality of the included studies was rated as being relatively robust (mean ± SD: 23.25 ± 2.71 [range 20-27]), considering a maximum score of 28.

2) Overall Strength of ES

The results revealed a significantly positive effect of maternal folate intake on the childhood obesity status of the children: the overall ES (Hedges'g) was 0.168 (95% CI = 0.075, 0.260, $p < .001$; small effects; cf., Cohen's criteria). The 95% CI did not include zero, which indicates that

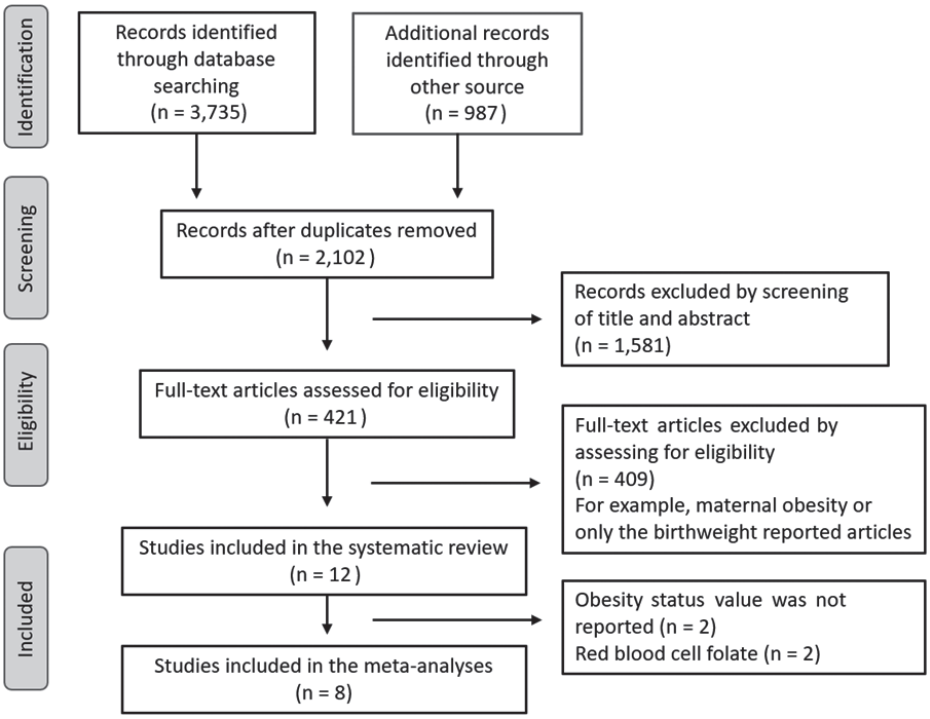

Fig. 1. PRISMA flow chart.

Table 1. Baseline characteristics of the included studies

Author	Sample size	Age	Folate status information	Indices	Study type	Location	Confounding adjusted
Krikke et al. (2015)	2,892	5-6	Serum concentration	BMI Mean	Cohort	Netherlands	Gender, gestational age at birth, birthweight, BMI of child, age, maternal age, pre-pregnancy BMI, parity, non-Western ethnicity, smoking, alcohol use
Krishnaveni et al. (2013)	1,650	5-13.5	Serum concentration	BMI median, % Fat	Cohort	India	Baby's sex and gestational age
Lewis et al. (2009)	5,783	9	Intake volume	Fat mass, % Fat	Cohort	U.K.	Age, sex, height, height squared, maternal education and mother's social class
McNulty et al. (2019)	109	3, 7	Intake volume	BMI Z-score	RCT	U.K.	Maternal age and education attainment, child's sex, birth weight, and breastfeeding
Richmond et al. (2018)	63	47	Intake volume	BMI Mean	RCT	U.K.	Methylation array batch, gestational age at booking and age of the offspring at the time of data and sample collection in the main analysis
Stewart et al. (2009)	1,393	6-8	Intake volume	BMI Mean	RCT	Nepal	Child's age at the time of the follow-up, which ranged from 6-8 years, and cholesterol, triglycerides, glucose, and metabolic syndrome models
Wang et al. (2016)	2,263	2-9	Serum concentration	BMI Z-score, OWO	Cohort	U.S.	Maternal BMI categories (overweight/obese vs. normal weight)
Wang et al. (2019)	214	2-15	Serum concentration	BMI Z-score, OWO	Cohort	U.S.	Maternal educational level, race/ethnicity, smoking status, parity, diabetes, hypertensive disorder, preterm birth, fetal growth, and breastfeeding

the mean ES is different from a zero value. The forest plot shows the weighted mean ES and 95% CIs of the studies included in the current meta-analysis (Fig. 2).

3) Variation of ES

The Q-statistics was 43.793 (df=14; $p<.001$), indicating that the true ES was not identical across the studies (i.e., the variability of outcomes

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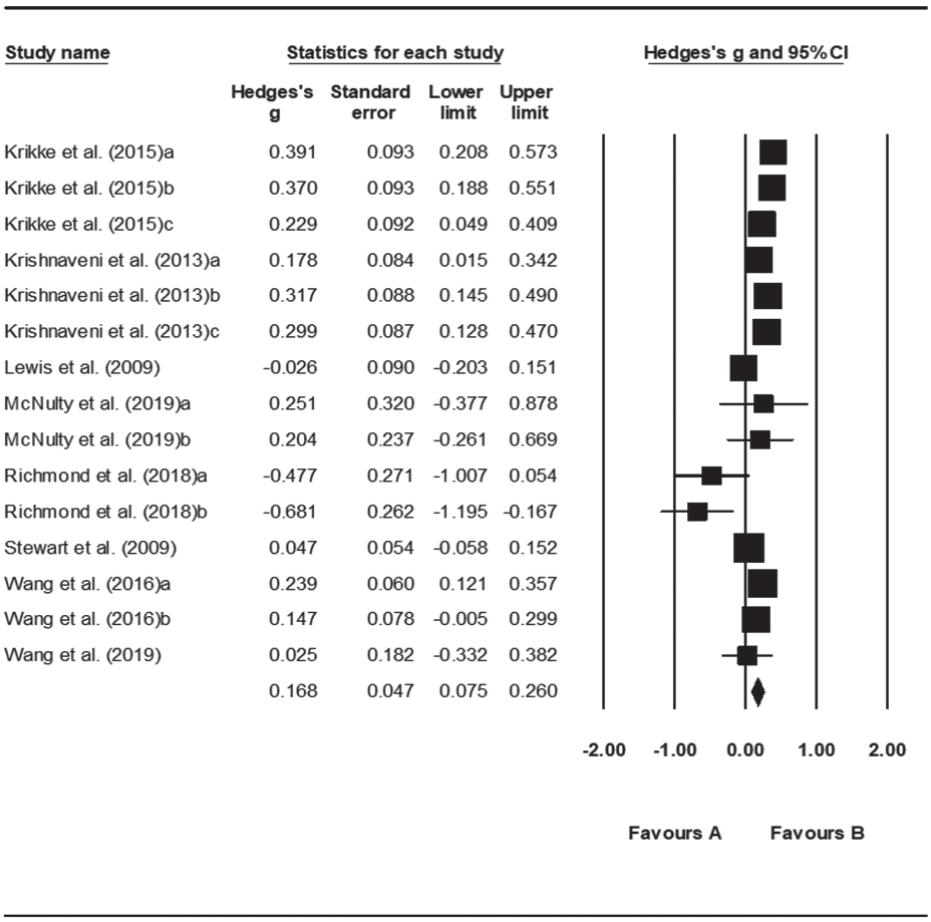

Fig. 2. Forest plot for effect of maternal folate status on offspring's obesity.

[ESs] is beyond sampling error). Moreover, the variance of 68.032% in the observed effects reflects a variation in true effects, rather than a sampling error ($I^2 = 68.032$). T2 (the variance of true effects) and T (the SD of true effects) were 0.019 and 0.138, respectively. The prediction interval was -0.147 to 0.483. Therefore, the true ES could range between a minimum and maximum limit of -0.147 and 0.483, respectively, in the study populations. Therefore, in some populations, there could have been a negative impact of folate intake on childhood obesity.

4) Moderator (Subgroup) Analyses

This study examined the effect of moderators (age, concentration, measure type, ingestion volume, method, and study design) on the overall weighted mean ES. Table 2 shows the results of moderator analyses, including the number of studies, mean ES, 95% CI, *p*-values, and Q_b. The results revealed that the Q statistic for the age group (<7 years or ≥ 7 years) was statistically significant ($Q_b = 4.730$, df = 1. $p = .030$; explaining the heterogeneity of ES). The effect of maternal folate status was more effective in the children who were younger than 7 years. Furthermore. the study design was statistically significant ($Q_b = 4.310$, df = 1. $p = .038$; explaining the heterogeneity of ES). In the cohort study, ES was 0.251 (95% CI = 0.135, 0.367, $p < .001$), whereas the ES of the RCT group was 0.062 (95% CI = -0.073, 0.197. $p = .370$). The heterogeneity of ESs was not identified by other moderators. The subgroup analyses showed that ≤25.1 and >25.1 folate concentration, mean BMI, and BMI Z-score in the quantitative measures and 13 week and ≥30 week as the time point of folate intake have positive effects on childhood obesity and are statistically significant as the value is different from zero.

5) Test for Publication Bias

The studies were symmetrically distributed in the funnel plot, which indicated a marginal possibility of publication bias (Fig. 3). The result of Egger's test statistically supported the finding that there was no evidence of publication bias (regression intercept = -0.972, two-tailed *p*-value = .383). The trim and fill analysis showed no adjustment with the ES,

Table 2. Effect sizes by moderator variables in the meta-analysis on offspring's obesity

Moderator variables	N	ES	95% CI		*p*-value	Q_b
			Lower	Upper		
Age of offspring (yr)						
<7	6	.277	.151	.404	.000*	4.730*
≥7	9	.089	-.025	.202	.126	
Concentration of serum folate (ng/mL)						
≤25.1	2	.309	.136	.482	.000*	.418
>25.1	7	.248	.182	.314	.000*	
Assessment method of obesity status						
BMI mean (Median)	9	.187	.067	.308	.003*	1.375
BMI Z-score	5	.174	-.009	.356	.063	
Fat mass	1	-.026	-.363	.311	.880	
Volume of intake (mg/day)						
≤200	1	-.483	-1.234	.269	.208	1.201
>200	1	-.026	-.581	.529	.927	
≥400	4	-.035	-.373	.302	.837	
Method of intake						
Supplement	5	-.113	-.431	.205	.448	.066
Food + Supplement	1	-.026	.606	.554	.930	
Length of intake						
Midterm-delivery	4	-.185	-.658	.287	.442	.248
Early-3 months after delivery	1	.047	-.735	.829	.906	
Time point of intake						
13 weeks	3	.330	.199	.460	.000*	3.233
≥30 weeks	7	.188	.106	.272	.000*	
Study design						
Cohort	7	.251	.135	.367	.000*	4.310*
RCT	8	.062	-.073	.197	.370	

N = number of effect sizes; ES = weighted mean ES; Q_b = Cochran's Q statistics.
*p < .05.

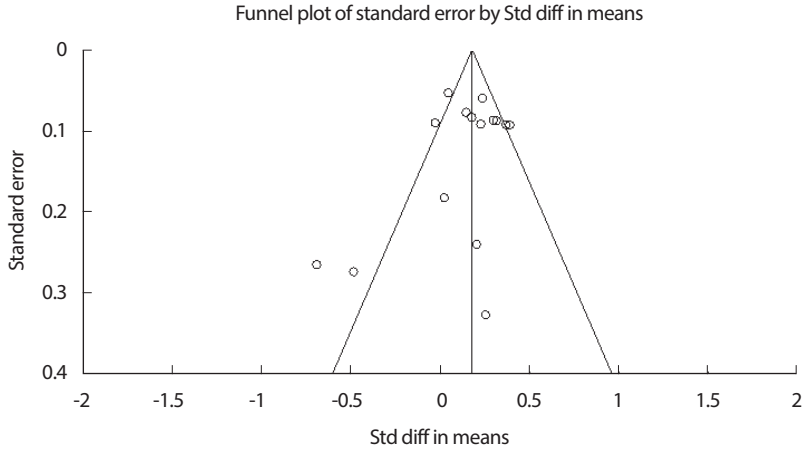

Fig. 3. Funnel plot for checking publication bias.

indicating that there was no need for imputation for additional studies.

DISCUSSION

We assessed the studies examined in this meta-analysis as "good" (score 20-22) or as "very good" (22-28), with an average score of 23.25 ± 2.71 on the Downs and Black Checklist (range 20-27).

We found a protective effect of maternal folate supplementation on childhood obesity that seemed more effective in age groups below 7 years. The effect of maternal folate status on the offspring will probably

be significant in the prenatal and lactational periods, highlighting the effectiveness of maternal folate in infants and children. As children grow, the influence of environmental factors (such as eating habits and physical activity) on obesity increase; therefore, the ES decreases after 7 years. A major advantage of cohort studies, in general, is the possibility to study multiple exposures and multiple outcomes in one cohort. Several confounders may be related to childhood obesity, such as physiological factors; age, BMI, activity level of the pregnant woman, and social indicators, such as the level of education and income. Critical confounders that influence childhood obesity were addressed and adjusted on the primary studies. However, we did not conduct a separate analysis for these confounders for two reasons. First, since each study considered different types of confounders, we could not adjust for these variables. Second, there is a lack of information regarding confounders, including levels of confounders and types of confounders.

Maternal folate status can be evaluated using serum/plasma folic acid or red blood cell (RBC) folic acid concentration. We did not include two references using RBC folate concentration as the criteria for maternal folate status in this meta-analysis due to the small number of data points and a previously reported limitation [19,20]. Unlike RBC folate levels, serum folic acid is readily available for tissue absorption and can reflect recent folic acid intake [21]. The results revealed a significant positive effect of maternal folate intake on the offspring's obesity status. Possible mechanisms can include epigenetic regulation. Maternal diets or nutritional compositions contribute to establishing the epigenetic profiles that profoundly impact individual susceptibility to childhood obesity in the offspring [22-24]. Folate is especially essential for nucleotide synthesis. Folate deficiency has been reported to cause problems in proliferation, DNA repair, and so on. Therefore, folate intake during pregnancy influences methyl donor availability for methylation during gestation and may play an essential role in the development and disease of offspring [25].

Folate/methionine's dietary restriction in sheep revealed widespread epigenetic alterations and obesity-induced health problems such as vulnerable insulin resistance and elevated blood pressure observed in male offspring [4]. Moreover, maternal folate deficiencies during pregnancy can elicit metabolic disorders in the offspring, including accumulated central fat mass and liver steatosis [5], and is associated with altered gene expression for the metabolic pathways through epigenetic regulation [26]. Besides, a prospective birth cohort study showed that maternal folate deficiency could increase child obesity ratio and metabolic risk; however, they suggest that sufficient maternal folate supplementation can reduce the risk of obesity in the offspring [6].

In contrast, a recent cohort study reported that higher RBC folate contributes to obesity in male offspring. They observed that high folate intake increased the proliferation and differentiation of adipose cells in Sprague-Dawley rats [10]. However, the number of data points is small, and a problem of directional inconsistency between RBC folate and serum folic acid concentrations exists. Elaborately designed studies will need to be carried out in animal models and human pregnancies to prove the effect of maternal folate status on offspring's obesity and to understand the exact mechanism.

Study Limitations

Because of small sample sizes and different confounding factors, a separate analysis was not possible due to the lack of power. Although most of studies adjusted several confounding factors, they are not consistent throughout the studies included in this meta-analysis. The residual confounding may exist due to the observational design of the study. Therefore, the results of this analysis should be interpreted with caution.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: BE Yoon, S Lee ; Data curation: K Kim; Formal analysis: K Kim, BE Yoon, J Park, E Kwon, K Kim; Funding acquisition: BE Yoon, S Lee; Methodology: J Park, E Kwon; Project administration: K Kim, BE Yoon, J Park, E Kwon; Visualization: J Kim, K Kim; Writing-original draft: J Kim, BE Yoon; Writing-review & editing: S Lee.

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