Review

international lactation consultant association®

Journal of Human Lactation
1–11

DOI: 10.1177/0890334417737038
journals.sagepub.com/home/jhl
SAGE

Breastfeeding and Risk of Metabolic Syndrome in Children and Adolescents: A Systematic Review

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Abstract

Background: The beneficial effect of breastfeeding on individual components of the metabolic syndrome in children and adolescents has been reported, but it is unknown if there is an association between being breastfed and metabolic syndrome as a whole.

Research aim: This systematic review was performed to assess quality and strength of evidence for the association between being breastfed and the development of metabolic syndrome in children and adolescents.

Methods: Articles were obtained from searches using PubMed and Embase databases, as well as from secondary searches through reference lists. Study quality was assessed using a three-level quality rating system.

Results: Of 11 studies reviewed, 7 found a protective association between breastfeeding and metabolic syndrome and 4 found no association. There was no clear dose–response relationship between duration of breastfeeding and metabolic syndrome risk and insufficient evidence to demonstrate an added effect of being exclusively breastfed. The overall quality of the articles was moderate. In general, lower quality articles found no significant association, whereas higher quality articles found a significant association.

Conclusion: Our review demonstrated a limited amount of high-quality research on the relationship between being breastfed and development of metabolic syndrome in children and adolescents. The evidence presented in this review suggests that being breastfed may be protective against metabolic syndrome, but further research with improvements in study design, such as improved measurement of breastfeeding and the use of prospectively collected data, will improve our understanding of this relationship.

Keywords

breastfeeding, breastfeeding duration, breastfeeding initiation, bottle feeding, exclusive breastfeeding, formula feeding

Background

Metabolic syndrome is defined by the presence of multiple risk factors, including central obesity, high blood concentrations of triglycerides, low blood concentrations of high-density lipoprotein cholesterol, hypertension, and high fasting blood glucose concentrations (American Heart Association, 2016). Although global prevalence statistics for children and adolescents are unavailable (International Diabetes Federation [IDF], 2015), the prevalence of metabolic syndrome components, particularly obesity and type 2 diabetes, has increased globally in children and adolescents over the last few decades (Europe PMC Funders Group, 2014). Children and adolescents diagnosed with metabolic syndrome are at higher risk for metabolic syndrome in adulthood and also other conditions, including cardiovascular disease (Halfon, Verhoef, & Kuo, 2012).

Research suggests that being breastfed may reduce risk of several components of metabolic syndrome. Hormones present in human milk are important in regulation of appetite, growth, and weight, and it has been suggested that infant

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Date submitted: January 19, 2017; Date accepted: September 24, 2017.

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intake of human milk hormones may prevent obesity by affecting food intake and food preferences later in life (Hassiotou & Geddes, 2014). These hormones, including leptin and ghrelin, influence energy balance regulation by altering glucose-insulin metabolism and hypothalamic development, thereby reducing excess weight gain (Savino, Benetti, Liguori, Sorrenti, & Cordero Di Montezemolo, 2013). Some studies report that children who are breastfed have lower risk of obesity (Jwa, Fujiwara, & Kondo, 2014; McCrory & Layte, 2012; Yan, Liu, Zhu, Huang, & Wang, 2014; Yin, Quinn, Dwyer, Ponsonby, & Jones, 2012), improved blood pressure (de Beer et al., 2016), improved cholesterol (Izadi et al., 2013), and reduced risk of diabetes (Horta, Loret de Mola, & Victoria, 2015) compared to children not breastfed, although not all findings are consistent (Djalalinia et al., 2015; Estévez-González, Pino, Henríquez-Sánchez, Peña-Quintana, & Saavedra-Santana, 2016; Li, Parsons, & Power, 2016). Interpretation of these studies can be challenging due to lack of breastfeeding randomization and potential for the influence of unmeasured variables. Although obesity and insulin resistance are often considered the primary risk factors for metabolic syndrome (Praasad, Ryan, Celzo, & Stapleton, 2012), poor diet, lack of exercise, smoking, and genetic predisposition also increase risk (Morrell, Lofgren, Burke, & Reilly, 2012; Pattyn, Cornelissen, Eshghi, & Vanhees, 2013; Rajaie, Azadbakht, Saneei, Khazaei, & Esmaillzadeh, 2013; Sun, Liu, & Ning, 2012; Vattikuti, Guo, & Chow, 2012). In sum, there is considerable literature on the association between breastfeeding and the components of metabolic syndrome in children and adolescents but fewer investigations into associations between breastfeeding and metabolic syndrome as a whole. The rising prevalence of both the individual components of metabolic syndrome as well as complete metabolic syndrome indicates a need to identify potential preventive interventions for at-risk populations. If breastfeeding were to reduce the risk of metabolic syndrome, interventions that increase breastfeeding length and exclusivity may be even more strongly warranted than current recommendations suggest.

The aim of this review was to systematically evaluate evidence for the association between being breastfed and the later development of metabolic syndrome in children and adolescents. In addition to summarizing and reviewing results, we aimed to assess the quality of included studies using a three-level rating system. Causal criteria, including dose–response and exclusivity, were investigated in addition to overall evidence.

Key Messages

- The amount and direction of evidence for the association between being breastfed and the development of metabolic syndrome in children and adolescents are unknown.
- Seven of 11 studies reviewed found a protective association between breastfeeding and metabolic syndrome, and 4 failed to find an association. Overall, article quality was moderate, and lower quality articles failed to find a significant association, whereas higher quality articles found a significant association.
- The results from this systematic review suggest a possible protective association between breastfeeding and metabolic syndrome and offer specific improvements in study design that are needed to truly assess this research question.

Methods

Design

We performed a systematic review to collect and review evidence for the association between being breastfed and development of metabolic syndrome in children and adolescents. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, 2015) guidelines were followed.

Sample

A systematic search was conducted between December 2016 and April 2017 using PubMed and Embase electronic databases (see Figure 1). The search terms *breastfeeding, infant feeding*, and *infant formula* were used in combination with the term *metabolic syndrome*. We obtained relevant articles by examining the titles and abstracts of search results. In addition, we searched reference lists of the selected articles to ensure that no relevant articles were missed. Additional searches with the term *syndrome X* instead of *metabolic syndrome* did not improve results.

Inclusion criteria were determined prior to the literature search and were designed to capture a wide array of studies, due to the small number of articles on this topic. There were no study design restrictions. The articles were required to be available in English, but no study location restriction was put in place. In addition, no criteria were implemented regarding publication year. Only articles that assessed metabolic syndrome in children and adolescents ages 3 through 19 were included. This age range ensured that children and adolescents were both represented, and this is compliant with the definitions of children and adolescents used by the Centers for Disease Control and Prevention (2015) and the World Health Organization (2016). We included studies examining only metabolic syndrome as a whole and not just one or some of the components of metabolic syndrome. Breastfeeding was not required to be the primary exposure of interest; however, studies had to report an association between breastfeeding and metabolic syndrome.

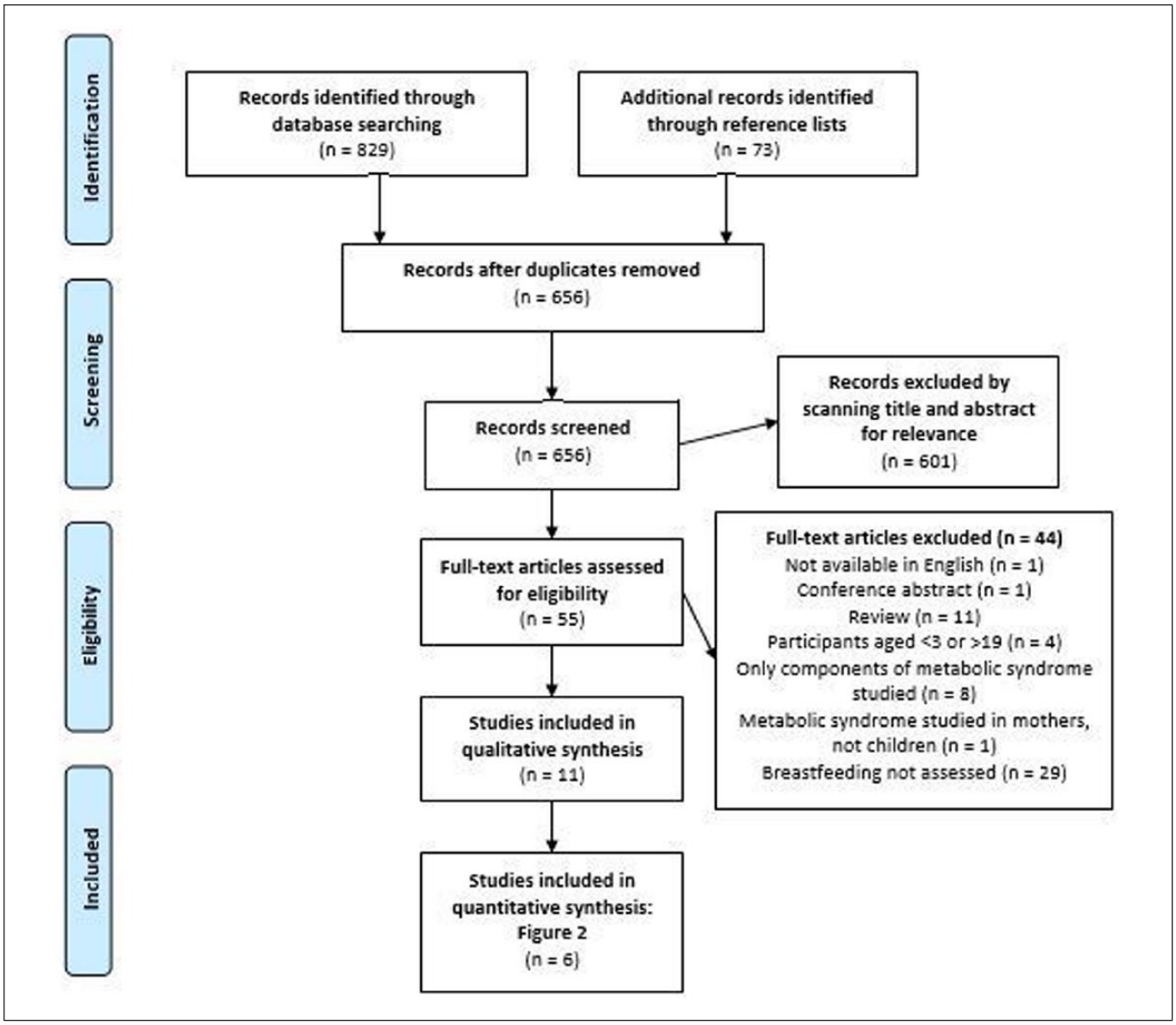

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

Measurement

One reviewer (L.W.) extracted the following information from each article: study design, sampling strategy, study population, detection of metabolic syndrome, measurement of breastfeeding, covariates, sample size, and results (see Table 1). Results were organized by breastfeeding definition (e.g., ever breastfed, duration of breastfeeding, exclusivity of breastfeeding, participation in a breastfeeding promotion trial).

Quality Assessment

Two reviewers (L.W. and J.K.) independently determined quality ratings of the articles. Quality of articles was assessed using five categories, as described in Table 2: study design, handling of missing information/data, detection of metabolic syndrome, measurement of breastfeeding, and adjustment for control variables. Articles were judged on individual topics within each of the five categories on a 3-point scale (3 being the highest) and an average score for each category was calculated. Articles then received an overall qualitative rating of good, moderate, or fair, based on the average of scores across categories. Quality ratings were based only on the ability of the study to assess the relationship between being breastfed and development of metabolic syndrome in children and adolescents and did not evaluate overall quality or other aims of the included articles.

Study design. The study design score was based on the following criteria:

Table 1. Description of Studies Examining the Association Between Breastfeeding and Metabolic Syndrome in Children and Adolescents.

First author, year	Location	Study design	Study participants	Age at outcome (years)	Categorization of breastfeeding	Sample size (cases, controls)
Ekelund, 2009	Estonia, Denmark, Portugal	Cross-sectional	Sampled from the EYHS	10 and 15	Ever breastfed	3,193 (27, 3,166)
Esfarjani, 2013	Iran	Cross-sectional	Participants from a field trial of a family-based intervention for childhood obesity	7 (*M* = 6.65)	Ever breastfed, and less than 6 months or 6 months or greater	150 (20, 130)
Folic, 2015	Serbia	Case-control	Patients treated on an inpatient basis at an endocrine department of a pediatric clinic center	10-16 (*M* = 12.93 in cases, 12.43 in controls)	Ever breastfed during first 6 months of life	84 (28, 56)
González-Jiménez, 2015	Spain	Cross-sectional	Sixth grade of primary school to the 3rd year of secondary school from 18 schools	10-15	Duration in months (categorical)	976 (43, 933)
Jamoussi, 2012	Tunisia	Cross-sectional	Participants recruited from the research unit of the National Institute of Nutrition	6-18 (*M* = 13.50)	Ever breastfed	186 (64, 122)
Khuc, 2012	Chile	Retrospective cohort	Participants from a randomized controlled trial of iron supplementation	16-17 (*M* = 16.6 in males, 16.7 in females)	Breastfeeding as sole source of milk for 90 days or more	357 (37, 320)
Martin, 2014	Belarus	Retrospective cohort	Participants followed up from the PROBIT breastfeeding promotion trial	11.5	Intervention arm vs. control arm, and duration of exclusive breastfeeding	13,616 (475, 13,141)
Sen, 2008	Turkey	Cross-sectional	Participants referred from a pediatric endocrinology division of a hospital	2-19 (median = 11.8)	Duration in months	352 (147, 205)
J. Wang, 2015	China	Cross-sectional	Ten schools selected in an urban area of a large city	7-17 (*M* = 11.3)	Duration in months and exclusively breastfed 30 days or more	1,770 (19, 1,751)
S. Wang, 2015	China	Cross-sectional	Participants randomly selected from urban and rural areas	Unavailable (*M* = 9.6)	Ever breastfed	624 (42, 582)
Yakubov, 2015	Israel	Retrospective cohort	Participants enrolled who visited an outpatient clinic for hypertension and obesity	3-18	Duration in months (categorical)	123 (58, 65)

Note. EYHS = European Youth Heart Study; PROBIT = Promotion of Breastfeeding Intervention Trial.

Type of epidemiological study. Studies that used a cohort design were rated higher than case-control and cross-sectional studies. Measurement of breastfeeding occurred years after breastfeeding cessation in case-control and cross-sectional studies; therefore, results may be subject to recall bias. Cases and controls may recall exposure differently because knowledge of the disease may alter the individuals' perception and reporting of past exposures.

Sample selection. Articles were rated a high score if a random sampling scheme was used. For case-control studies, however, articles were required to use a sampling scheme to

Table 2. Quality Assessment Scoring System.

Category	Subcategory	Scoring system[a]
Study design	Type of epidemiological study	Cohort = 3, case-control or cross-sectional = 1
	Sample selection	Random sampling scheme used (yes = 3, no = 1)
	Population source	Multiple locations, wide inclusion criteria, justification of sample size and statistical power, generalizable location (met three or more criteria = 3, met two criteria = 2, met one or fewer criteria = 1)
Missing information	NA	Participation rates, loss to follow-up (cohort studies only), or missing data (included a measure for missing data, measure was of high quality (≥75%) or handled missing information well[b] = 3; included a measure, measure was of low quality (<75%) but did not handle missing data sufficiently = 2; did not include a measure = 1)
Detection of metabolic syndrome	Criteria included	Measured/collected most components of the IDF (2016) definition for metabolic syndrome = 3, measured some of the components = 3, measured few of the components = 1
	Quality of methods	Measured central obesity as waist circumference, repeat measurements for central obesity and blood pressure, reported fasting status of patients, methods used for assays, and instruments used (missed two or fewer criteria = 3, missed three criteria = 2, missed four or more criteria = 1)
Breastfeeding data	Definition of breastfeeding	Assessed duration and exclusivity = 3, assessed either duration or exclusivity = 2, did not assess duration or exclusivity (e.g., reported ever breastfed) = 1
	Breastfeeding data source	Prospectively collected breastfeeding data = 3, retrospectively collected data but consulted medical records = 2, retrospectively collected data = 1
Adjustment for control variables[c]	Child/adolescent demographics	Gender, race or ethnicity, and age (controlled for at least two = 3, controlled for one = 2, controlled for none = 1)
	Maternal factors	Maternal BMI or weight, age, income, education, gestational diabetes, and smoking status during pregnancy (controlled for two or more = 3, controlled for one = 2, controlled for none = 1)
	Birth characteristics	Gestational age, birth order, and birth weight (controlled for at least one = 3, controlled for none = 1)

Note. NA = not applicable; IDF = International Diabetes Federation; BMI = body mass index.
[a]Articles were given an average score per category and an overall score based on the categories' averages. [b]Articles used statistical analyses such as sensitivity analyses, comparison of those with and without complete data, or data imputation. [c]Adjustment for control variables was defined as either including control variables in the final analysis or matching participants on control variables.

select controls, not cases, from the population, as this is the general methodology used to conduct case-control studies.

Population source. Number of sites, inclusion criteria, justification of sample size and statistical power, and location of recruitment (e.g., health centers) were evaluated to determine the generalizability of the results. The criteria for this category are as follows: recruitment from multiple locations, wide inclusion criteria, justification of sample size and statistical power, and recruitment from a more generalizable location. A more generalizable location in this case is a school or the community, instead of a specialty clinic or a randomized controlled trial, since participants who are recruited from specialty clinics or from randomized controlled trials may be different from the general population, reducing generalizability of the results.

Missing information. Missing information included low participation rates, loss to follow-up, and missing data. The studies were scored based on whether they reported a measure of missing data, the quality of the measure, and how missing information was handled if the quality of the measure was low (less than 75%). Measures were considered high quality if participation rates were at 75% or greater. In addition, studies were considered to have handled missing information well if they used statistical analyses to investigate potential implications of missing information (e.g., sensitivity analyses, comparison of participants who completed the study with those who did not, or data imputation).

Detection of metabolic syndrome. The score for detection of metabolic syndrome was based on measurement of metabolic syndrome components as well as the quality of the measurements.

Criteria included. The articles were scored on whether they collected the required components of the IDF definition for metabolic syndrome in children and adolescents, which included a measurement of central obesity, triglycerides, high-density lipoprotein cholesterol, blood pressure,

Table 3. Article Results and Rating by Quality Assessment Score.

First author, year	Category 1: study design	Category 2: missing information	Category 3: detection of metabolic syndrome	Category 4: breastfeeding data	Category 5: adjustment for control variables	Total average score	Rating[a]	Found protective association
Ekelund, 2009	2.3	3.0	3.0	1.0	2.0	2.3	Moderate	Yes
Esfarjani, 2013	2.0	1.0	3.0	1.5	2.5	2.0	Moderate	Yes
Folic, 2015	1.7	1.0	2.0	1.0	2.0	1.5	Fair	Yes
González-Jiménez, 2015	1.7	1.0	3.0	2.0	2.3	2.0	Moderate	Yes
Jamoussi, 2012	1.0	1.0	3.0	1.0	1.0	1.4	Fair	No
Khuc, 2012	2.3	3.0	3.0	2.5	2.7	2.7	Good	No
Martin, 2014	3.0	3.0	2.0	3.0	2.7	2.7	Good	Yes
Sen, 2008	1.0	1.0	3.0	1.5	1.0	1.5	Fair	No
J. Wang, 2015	2.0	3.0	3.0	2.0	2.3	2.5	Good	Yes
S. Wang, 2015	2.3	1.0	3.0	1.0	2.7	2.0	Moderate	Yes
Yakubov, 2015	1.7	1.0	2.0	1.5	1.0	1.4	Fair	No
Average	1.9	1.7	2.7	1.6	2.0	2.0	Moderate	—

[a]Articles were given qualitative ratings based on the following scale: good (≥2.5), moderate (2.0 to <2.5), or fair (<2.0).

and glucose. In addition, the articles were graded on whether they collected any disease or treatment history related to at least one of the following: diabetes, lipid abnormalities, or hypertension.

Quality of methods. Articles were rated based on how well components of metabolic syndrome were measured and how well methods were reported. Articles received a high score if investigators reported the following: the measurement of central obesity as waist circumference (instead of body mass index), repeat measurements for central obesity and blood pressure, fasting status of patients, methods used for assays, and most of the instruments/equipment used (e.g., mercury sphygmomanometer, self-calibrating floor scale, stadiometer).

Breastfeeding data

Definition of breastfeeding. Clearly defining exposure is instrumental in determining associations. Articles were rated highest if they measured duration of breastfeeding and recorded information on length of exclusive breastfeeding.

Breastfeeding data source. The validity of recalled breastfeeding duration has been shown to substantially decrease as soon as 2 years after birth (Burnham et al., 2014). Articles were rated highest if they collected breastfeeding information through examinations or self-report questionnaires throughout infancy, and lower if they retrospectively collected self-report breastfeeding data and did not consult medical records.

Adjustment for control variables. Adjustment for control variables, either by including control variables in the final analysis or by matching participants on control variables, was assessed. The studies were rated on the following categories of control variables: child/adolescent demographics, maternal factors, and birth characteristics. Child/adolescent demographics included gender, race or ethnicity, and age. Maternal factors included maternal characteristics such as age, income, and smoking status during pregnancy. Last, birth characteristics included gestational age, birth order, and birth weight.

Data Analysis

Qualitative synthesis. Results of the articles were summarized based on breastfeeding definition (e.g., ever breastfed, 6 or more months) and exclusivity to assess support for the association between breastfeeding and development of metabolic syndrome. We assessed risk of publication bias by descriptively comparing the quality of articles that had published significant versus nonsignificant results (see Table 3).

Quantitative synthesis. Articles that reported odds ratios were included in the quantitative synthesis. We plotted the odds ratios for the relationship between being breastfed and metabolic syndrome against study quality, and we compared confidence interval estimates to assess whether studies of low versus high quality resulted in different conclusions (see Figure 2). Evidence for a dose–response relationship was determined by visually inspecting odds ratios that corresponded with different durations of breastfeeding (see Figure 2).

Results

Our search strategy identified a total of 902 studies (see Figure 1). Of these, 11 studies met our inclusion criteria. The study characteristics are described in Table 1.

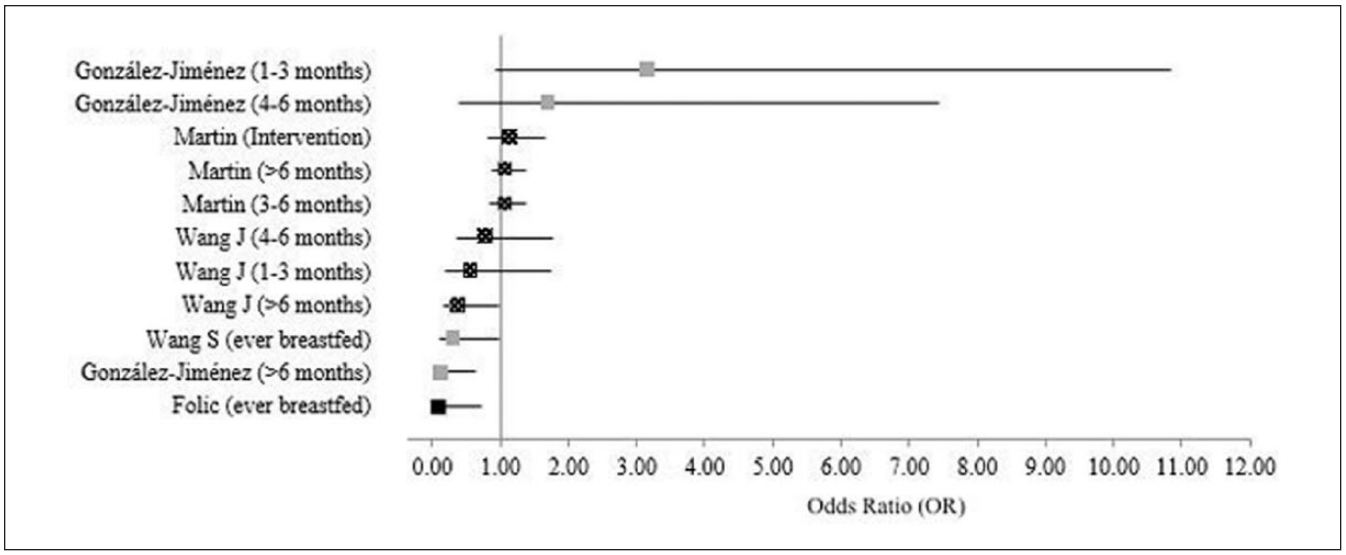

Figure 2. Quantitative synthesis: summary of reported odds ratios. Only 5 of 11 articles included in this review reported odds ratios. Of these, most reported more than 1 odds ratio that corresponded to different lengths or definitions of breastfeeding, which is reflected in the figure. Articles are labeled by quality score: black spotted = good, gray = moderate, black solid = fair. Logistic regression instrumental variable results from Martin et al. (2014) are omitted (and nonsignificant).

Qualitative Results

Overall, 7 of the 11 studies reviewed found a statistically significant inverse relationship between being breastfed and the development of metabolic syndrome in children and adolescents (see Table 3). Reviewed studies examined the risk of metabolic syndrome in relation to ever being breastfed, duration of breastfeeding, duration of exclusive breastfeeding, and group participation in a cluster-randomized breastfeeding promotion trial (see Table 1). Of 5 studies that investigated the association between ever being breastfed and development of metabolic syndrome, 3 found a statistically significant inverse relationship, whereas 2 did not. Of the 6 studies that investigated duration of breastfeeding, 3 found an inverse relationship with metabolic syndrome, and 3 found no association. One study compared the average duration of breastfeeding between those with metabolic syndrome and those without metabolic syndrome and found no significant difference in duration of breastfeeding. The other 5 studies compared different categories based on breastfeeding duration (e.g., less than 1 month, 1 to 3 months, etc.). The categories were not consistent across studies, although some studies used similar categories. For example, 6 or more months of breastfeeding (or at least 6 months) was associated with a reduced risk of metabolic syndrome in 1 study and not associated with risk of metabolic syndrome in 2 studies, whereas more than 6 months of breastfeeding was associated with a reduction of metabolic syndrome in 2 studies. In 1 study, an inverse association was found between being exclusively breasted for 3 months and risk of metabolic syndrome. The only study using a cluster-randomized breastfeeding promotion study design did not find a significant difference between those in the intervention arm of a trial that promoted breastfeeding and those in the control arm.

Quality Assessment Results

The overall quality of the articles was moderate based on our quality assessment scoring system (see Tables 2 and 3). Most articles were vulnerable to measurement error due to breastfeeding data being collected years after infancy, with the exception of Khuc et al. (2012) and Martin et al. (2014). The majority of articles did not report a sample size or power calculation, except Ekelund et al. (2009) and Martin et al. (2014), which both reported sample size calculations. With respect to missing information, the majority of articles failed to provide participation rates or response rates, but when reported, the rates were moderate to high and ranged from 73% to 97% (Ekelund et al., 2009; Martin et al., 2014; J. Wang et al., 2015). Two out of three cohort studies provided follow-up rates that were moderately high at 93% (Khuc et al., 2012) and 81.4% (Martin et al., 2014), respectively. Both of these studies did a follow-up analysis comparing those who completed the study with those who did not, and Martin et al. (2014) also completed a sensitivity analysis. The third cohort study failed to mention follow-up rates (Yakubov, Nadir, Stein, & Klein-Kremer, 2015).

Misclassification (misdiagnosis) of metabolic syndrome was also a potential source of bias because most articles failed to collect disease history (e.g., diabetes, lipid abnormalities, or hypertension) (Esfarjani, Khalafi, Mohammadi, Zamani-Nour, & Kelishadi, 2013; González-Jiménez, Montero-Alonso, Schmidt-RioValle, García-García, & Padez, 2015;

Jamoussi et al., 2012; Khuc et al., 2012; J. Wang et al., 2015; S. Wang et al., 2015; Yakubov et al., 2015) that may have improved the ability of the researchers to correctly identify metabolic syndrome. For instance, if a child/adolescent was previously diagnosed with type 2 diabetes but his or her glucose levels were measured as normal at the time of study outcome ascertainment, he or she would still meet the requirement for abnormal glucose levels if disease history was considered.

Even though most articles used a random sampling scheme, two were secondary analyses of randomized controlled trials, and participants in four studies were from nongeneralizable sources such as specialty clinics, which may have led to selection bias (see Table 1). With respect to control variables, three of the articles did not include a multivariable analysis that included breastfeeding and other control variables (Jamoussi et al., 2012; Sen, Kandemir, Alikasifoglu, Gonc, & Ozon, 2008; Yakubov et al., 2015).

Six articles addressed control variables in all three categories: child/adolescent demographics, maternal factors, and birth characteristics (Esfarjani et al., 2013; González-Jiménez et al., 2015; Khuc et al., 2012; Martin et al., 2014; J. Wang et al., 2015; S. Wang et al., 2015). Four studies did not control for any demographics, including age, gender, and race or ethnicity (Folic, Folic, Markovic, Marija, & Jankovic, 2015; Jamoussi et al., 2012; Sen et al., 2008; Yakubov et al., 2015). Four studies did not control for any maternal factors, including body mass index or weight, age, income, education, gestational diabetes, and smoking status (Jamoussi et al., 2012; Khuc et al., 2012; Sen et al., 2008; Yakubov et al., 2015). Six studies did not control for birth factors, including gestational age, birth order, and birth weight (Ekelund et al., 2009; Folic et al., 2015; Jamoussi et al., 2012; Khuc et al., 2012; Sen et al., 2008; Yakubov et al., 2015). Last, although many articles included duration and exclusivity in their measure of breastfeeding, which increased the specificity of the results, some articles investigated only the effect of ever being breastfed.

Quantitative Results

Figure 2 displays multiple results from the 5 articles that reported odds ratios. Of these, 3 were cross-sectional, 1 was a case-control, and 1 was a retrospective cohort. Odds ratios did not tend to get lower with longer durations of breastfeeding as would be expected with a dose–response relationship; however, odds ratios for 6 months or more of breastfeeding tended to be significant more often than shorter durations of breastfeeding, which is consistent with the American Academy of Pediatrics breastfeeding recommendations. This may suggest a threshold effect at 6 months, instead of a dose–response. Table 3 summarizes results from all 11 studies by quality rating. Three of 4 articles that failed to find a statistically significant inverse association were of lower quality, indicating that lower quality articles were less likely to find an association. However, 1 article with a high-quality rating did not find a statistically significant protective association. There was no evidence for significant differences in odds ratios reported based on article quality and duration of breastfeeding because all confidence intervals reported mostly overlap (see Figure 2).

Discussion

The majority of articles in this review (7 of 11) found a protective association between being breastfed and metabolic syndrome in children and adolescents, and none found that being breastfed increased the risk of metabolic syndrome. When further categorized by breastfeeding definition, we found that 3 of 5 articles that investigated ever being breastfed and development of metabolic syndrome found an inverse association. Three of 6 that investigated duration of breastfeeding and metabolic syndrome found an inverse relationship. Although individually, some articles found a dose–response relationship when investigating duration of breastfeeding (see Tables 1 and 3), there was no clear trend when looking at all articles jointly. However, a threshold effect may be present given that odds ratios for breastfeeding 6 or more months were significant more often than shorter durations of breastfeeding. Only 1 article investigated the association between exclusive breastfeeding and metabolic syndrome; it found a significant inverse association between exclusive breastfeeding for 3 months and development of metabolic syndrome.

Randomized breastfeeding promotion and support trials are needed to reduce the potential influence of other variables. One article assessed the effect of a breastfeeding promotion intervention, the Promotion of Breastfeeding Intervention Trial, on metabolic syndrome. The intervention was modeled on the Baby-Friendly Hospital Initiative and consisted of healthcare worker assistance with breastfeeding initiation and maintenance (Kramer et al., 2001). The authors suggested that their failure to find a significant association between the breastfeeding intervention and metabolic syndrome could be due to substantial overlap in breastfeeding duration and exclusivity in the two study arms, which may also be an issue in future trials (Martin et al., 2014).

Since breastfeeding was expected to be protective for metabolic syndrome, odds ratios below 1 were expected. Of the 5 articles that reported odds ratios, lower quality articles reported odds ratios that were inconsistent and had a large range of values, whereas higher quality articles reported odds ratios closer to 1. Among all 11 studies, the lower quality articles failed to find a significant inverse association between breastfeeding and metabolic syndrome, whereas the higher quality articles reported significant, inverse associations, with the exception of Martin et al. (2014), which assessed the effect of a breastfeeding promotion intervention using an intention-to-treat analysis.

One of the strengths of this review is that wide inclusion criteria were used, resulting in analyses from multiple study

designs and populations. In addition, the quality assessment ratings allowed for assessment of trends between high-quality and low-quality articles.

Limitations

A limitation is that we did not conduct a meta-analysis due to large variation in definitions of breastfeeding (e.g., ever breastfed, exclusively breastfed for 3 months), age ranges of the study samples, and locations of the studies. In addition, publication bias, which may result in a larger proportion of published articles with significant findings irrespective of quality, could artificially increase the amount of evidence for a significant association. However, if publication bias was strong, lower quality articles that found significantly protective associations would be more frequent. In contrast, the results indicated that the articles that were more likely to find an association were of higher quality, which does not suggest strong publication bias. Another potential limitation is that each category and subcategory were given equal weight in the quality assessment scoring system, although some might argue that certain categories are more important than others, such as diagnosis of metabolic syndrome. Last, we did not conduct a formal evaluation of the agreement between the two reviewers who assessed article quality. This would have strengthened the results, given the subjective nature of the quality assessment scoring system.

Future Studies

Our review identified several key improvements in study design for future studies, including the use of longitudinal designs, larger sample sizes, random sampling from a representative population, and assessment of breastfeeding exclusivity, duration, and bottle feeding both human milk and formula. In addition, more rigorous ascertainment of exposure and outcome, and careful attention to control variables, is needed to determine if there is truly a causal relation between being breastfed and metabolic syndrome in children and adolescents. Randomized breastfeeding education trials (similar to the trial in Martin et al. (2014), but with methodological improvements in the diagnosis of metabolic syndrome) and randomized interventions that decrease barriers to breastfeeding (e.g., by providing access to breast pumps) are important additions to this topic area, since breastfeeding itself cannot be randomized due to ethical and practical reasons. Another alternate strategy to randomization is the use of propensity scores, a statistical technique that accounts for other covariates that affect the probability of receiving the "treatment," for example, breastfeeding. Novel methods to account for unmeasured control variables also can be utilized, such as investigating effects of breastfeeding among children from the same family (i.e., sibling analyses), which can reduce the influence of multiple unmeasured factors such as genetics, environment, and diet. In addition, future studies should use the IDF definition to increase consistency when reporting results and include only children 10 years and older to be consistent with current IDF standards.

Furthermore, future studies should be conducted in the United States. Since the United States has lower exclusive breastfeeding rates for the first 6 months of life (19%) compared with various other regions, including the African (36%) and Eastern Mediterranean (40%) World Health Organization regions and even globally (36%), as well as a high prevalence of obesity, research in this location is especially pertinent (World Health Organization, 2015). In addition, the association between breastfeeding and the development of metabolic syndrome could be studied in populations with known high rates of metabolic syndrome and associated conditions (e.g., diabetes, cardiovascular disease). For instance, the population of Pima Indians in Arizona has been extensively studied due to their unusually high rates of diabetes and obesity compared with their parent population in Mexico. This allowed for the identification of environmental and genetic influences on the incidence of these conditions (Schulz & Chaudhari, 2015). Similarly, South Asian migrants may be a suitable study population for studying breastfeeding and metabolic syndrome because they exhibit a greater burden of cardiovascular disease, potentially due to a more sedentary lifestyle and changes to diet after migration (Fernando, Razak, Lear, & Anand, 2015).

A closer look into whether and how the association between being breastfed and metabolic syndrome may differ by factors such as pregnancy and birth outcomes, gender, age, race, socioeconomic status, or puberty status is also needed. The articles reviewed here did not investigate whether the effect of being breastfed is different in subgroups of the population. Last, the authors did not differentiate between bottle feeding human milk and actual breastfeeding in the articles in this review. It has been demonstrated that infants have the ability to self-regulate food intake, but infants tend to consume excess calories when bottle fed (Li, Magadia, Fein, & Grummer-Strawn, 2012; Oddy, 2012), making this an important aspect to include in future studies.

Conclusion

This review aimed to fill current gaps in our understanding of the relationship between being breastfed and metabolic syndrome development in children and adolescents. Our review of the existing literature suggests that there may be a protective relationship between breastfeeding and metabolic syndrome in children and adolescents; however, more research is needed to clarify this relationship. For future studies, methodological improvements—in particular, improved measurement of breastfeeding, longitudinal data, and careful consideration of control variables—are necessary in study design. If a relationship is established, interventions can be put in place to encourage breastfeeding for those populations most at risk for metabolic syndrome. In addition,

more information on the optimal duration and exclusivity of breastfeeding in relation to metabolic syndrome can tailor interventions for those most at risk, including small for gestational age and preterm infants. Designing and implementing effective interventions to reduce risk for metabolic syndrome are important because it is a strong risk factor for chronic cardiovascular disease and diabetes.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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