Current Diabetes Reports (2019) 19: 1
https://doi.org/10.1007/s11892-019-1121-x

PEDIATRIC TYPE 2 AND MONOGENIC DIABETES (O PINHAS-HAMIEL, SECTION EDITOR)

# Breastfeeding and Type 2 Diabetes: Systematic Review and Meta-Analysis

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Published online: 14 January 2019


## Abstract

**Purpose of Review** Breastfeeding has short- and long-term benefits for child health. In this systematic review, we updated a review on the association between breastfeeding and type 2 diabetes.

**Recent Findings** A meta-analysis published in 2015 reported that breastfeeding protects against type 2 diabetes (pooled odds ratio, 0.65 (95% confidence interval, 0.48; 0.86)). In the present update, we identified three recently published studies. An internet-based study reported that at a mean age of 25.6 years, exclusive breastfeeding in the first 6 months protected against type 2 diabetes (odds ratio, 0.63 (95% confidence interval, 0.41; 0.95)). In a retrospective cohort, those subjects who had been breastfed before hospital discharge were less likely of presenting diabetes (odds ratio, 0.83 (95% confidence interval, 0.69; 0.99)). In a case-control study, the odds of type 2 diabetes in adolescents was lower for those exclusively breastfed at hospital discharge (odds ratio, 0.52 (95% confidence interval, 0.36; 0.74)). In the meta-analysis, the pooled odds ratio was 0.67 (95% confidence interval, 0.56; 0.80).

**Summary** The updated systematic review and meta-analysis suggests that breastfeeding protects from type 2 diabetes.

**Keywords** Breastfeeding · Human milk · Glycemia · Type 2 diabetes

## Introduction

Breastfeeding has short- and long-term benefits. In childhood, mortality and morbidity from infectious diseases are lower among those of breastfed subjects [1]. Breastfeeding has also long-term benefits, improving human capital and protecting against noncommunicable diseases. With respect to human capital, a meta-analysis reported that the intelligence quotient was 3.44 points higher among subjects who had been breastfed [2]. Furthermore, breastfeeding would also be positively associated with adult earnings [3, 4]. Concerning noncommunicable diseases, breastfeeding reduces the odds of overweight, and this association has been reported among high-quality studies, i.e., those with a large sample size, that controlled for confounding and with a short-term maternal recall of breastfeeding [5]. Moreover, it has also been reported that the association between genetic variants in the *FTO* gene and obesity would be moderated by breastfeeding [6•, 7, 8]. Breastfeeding would also protect against type 2 diabetes (pooled odds ratio, 0.65 (95% confidence interval, 0.48; 0.86)), but the small number of studies included in the review reinforced the relevance of carrying out further studies on this subject.

Several mechanisms have been proposed to explain the association between breastfeeding and type 2 diabetes. Breastmilk has a higher content of long-chain polyunsaturated fatty acids (LCPUFAs), which would increase LCPUFA levels in the cell membrane. And, it has been reported that increased LCPUFA levels in skeletal muscle membrane are inversely related to fasting glucose [9]. Breastfeeding is also associated with a decrease in the odds of obesity, and this association could be another causal mechanism for the association with type 2 diabetes. It has also been proposed that the faster postnatal growth among formula-fed infants would program the development of metabolic cardiovascular risk factors, including type 2 diabetes [10].

This article is part of the Topical Collection on *Pediatric Type 2 and Monogenic Diabetes*

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Finally, insulin concentration is higher among formula-fed infants, which would led to beta-cell failure and the development of type 2 diabetes [11].

Because the studies included in the previous meta-analysis were observational and most of them were carried out in high-income countries, where breastfeeding duration tends to be positively associated with socioeconomic status [12], residual confounding should be taken into consideration in the evaluation of the evidence on the association between breastfeeding and type 2 diabetes. Moreover, some studies have adjusted the estimates to body mass index (BMI) in adulthood, a possible mediator in the relationship between breastfeeding and diabetes. By controlling for a mediator in traditional regression models, a causal pathway is blocked, and the association is underestimated. Moreover, a collider bias is introduced because the traditional regression methods conditioned the analysis on a collider and the estimates are biased by the mediator outcome confounders [13]. Therefore, residual confounding and the strategies used to adjust for confounding should be taken into consideration in the evaluation of the evidence on the association between breastfeeding and type 2 diabetes.

This systematic review was aimed at updating the available evidence of the association between breastfeeding and type 2 diabetes.

## Methods

We updated systematic reviews on the association between breastfeeding and type 2 diabetes that had been carried out in 2006, 2011, and 2014 [5]. The literature search tried to identify as many relevant articles as possible and two independent searches were carried out independently (BLH and NPL), and any disagreement was solved by consensus. We searched the MEDLINE, LILACS, and Web of Science databases for studies that evaluated the association between breastfeeding and type 2 diabetes. Because the previous systematic review covered articles published before August 2014 [5], we searched for manuscripts that had been published between August 2014 and August 2018. In the literature search, we used the following terms for breastfeeding: breastfeeding; breast-feeding; breast feeding; breastfed; breastfeed; bottle feeding; bottle fed; bottle feed; infant feeding; human milk; formula milk; formula feed; formula fed; and weaning. Each one of the breastfeeding terms were combined with the following terms for type 2 diabetes: diabetes; glucose; or glycaemia. The search was not restricted to any language.

After excluding duplicates, titles and abstracts were scanned to exclude clearly irrelevant studies. Full text of the remaining manuscripts was retrieved, and relevant articles were identified. We also searched reference lists of the identified articles and perused the Web of Science Citation Index for manuscripts citing the identified articles to detect published studies that had not been identified in the literature search. We contacted the authors of the identified manuscripts that did not provide sufficient data to estimate the pooled effect, or to clarify any query on the study methodology.

Studies restricted to infants were excluded, as well as those that did not differentiate type 1 from type 2 diabetes. Studies without an internal comparison group were also excluded. But, the type of comparison group was not considered as an exclusion criterion. Two reviewers evaluated the included studies, using a standardized protocol, and the forms were compared, and any disagreement was solved by consensus. The following information was extracted from each study: author name; publication year; sample size; study design; year of birth of subjects; mean age at type 2 diabetes assessment; length of recall of breastfeeding duration (time from weaning to collect of information on infant feeding); control for confounding (we evaluated whether the study adjusted the estimates for each one of the following variables: socioeconomic status; birthweight; maternal gestational diabetes; and body mass index at assessment of type 2 diabetes). As mentioned previously, the control to BMI in adulthood may bias the estimate. For this reason, for studies that adjusted for BMI, we tried to obtain an estimate that was not adjusted for this variable, either retrieving from the manuscript or contacting the authors. Subjects were classified as either breastfed or non-breastfed according to the definition used in each study. The pooled odds ratio and its 95% confidence interval were estimated, and an odds ratio $< 1$ means that the odds of type 2 diabetes was lower among breastfed subjects. Heterogeneity among studies was assessed using the Cochran $Q$ test and $I$ square, and if $p$ value for the $Q$ test was $< 0.1$ or the $I$ square was $\geq .5$, a random effects model was used to pool the estimates [14]. Funnel plot and Egger's test were used to evaluate the presence of publication bias [15]. We also stratified the analysis according to sample size to estimate the influence of publication bias on the pooled effect.

We did not use a score to evaluate the quality of the studies. On the other hand, we evaluated several study characteristics (sample size, study design, year of birth of studied subjects, mean age at type 2 diabetes assessment, length of recall of breastfeeding duration, and control for confounding). The analysis was stratified according to the categories of these variables to evaluate whether they were modifying the association of breastfeeding with type 2 diabetes. Finally, the contribution of these study characteristics to the between-study variability was assessed using meta-regression [16].

## Results

After excluding duplicates, 1959 abstracts were screened, 45 full-text manuscripts were evaluated for eligibility, and 3 were included in the update of the systematic review [17••, 18, 19].

**Table 1** Breastfeeding and type 2 diabetes in later life: studies included in ascending order of subjects' age at which outcome was measured

| Author, year | Study design | Mean age at assessment | Gender | Categorization of breastfeeding | Odds ratio of type 2 diabetes among breastfed subjects |
|---|---|---|---|---|---|
| Young, 2002 [20] | Case-control | 13 years | All | Breastfed ≥ 6 months vs. vreastfed < 6 months | 0.36 (0.13; 0.99) |
| Izadi, 2013 [21] | Cross-sectional | 14 years | All | Breastfed ≥ 18 months vs. breastfed ≤6 months | 0.57 (0.26; 1.22) |
| Halipchuk, 2018 [18] | Case-control | 14 years | All | Exclusively breastfed at hospital discharge vs. formula fed at hospital discharge | 0.52 (0.36; 0.74) |
| Mayer-Davis, 2008 [22] | Case-control | 15 years | All | Ever breastfed vs. never breastfed | 0.43 (0.19; 0.99) |
| Evenhouse, 2005 [23] | Cross-sectional | 15 years | All | Ever breastfed vs. never breastfed | 0.40 (SE, 0.24) |
| Fall, 2011 [24] | Cohort | 25 years | All | Ever breastfed vs. never breastfed | 1.26 (0.63; 2.50) |
| Petit, 1997 [25] | Cohort | 25 years | All | Exclusively breastfed vs. exclusively bottle-fed at 2 months | 0.41 (0.18; 0.93) |
| Baldassarre, 2017 [19] | Cross-sectional | 26 years | All | Exclusively breastfed ≥ 6 months vs. not exclusively breastfed < 6 months | 0.63 (0.41; 0.95) |
| Martens, 2016 [17••] | Cohort | 27 years | All | Breastfed before hospital discharge vs. not breastfed before hospital discharge | 0.83 (0.69; 0.99) |
| Parikh, 2009 [26] | Cohort | 41 years | All | Ever breastfed vs. never breastfed | 0.40 (0.09; 1.70) |
| Ravelli, 2000 [27] | Cohort | 50 years | All | Exclusively breastfed vs. bottle-fed during hospital stay | 0.51 (0.30; 0.90) |
| Martin, 2005 [28] | Cross-sectional | 52 years | Male | Ever breastfed vs. never breastfed | 2.89 (0.65; 12.83) |
| Rich-Edwards, 2004 [29] | Cohort | 59 years | Female | Ever breastfed vs. never breastfed | 0.79 (0.74; 0.85) |
| Martin, 2005 [30] | Cohort | 71 years | All | Ever breastfed vs. never breastfed | 0.97 (0.41; 2.30) |

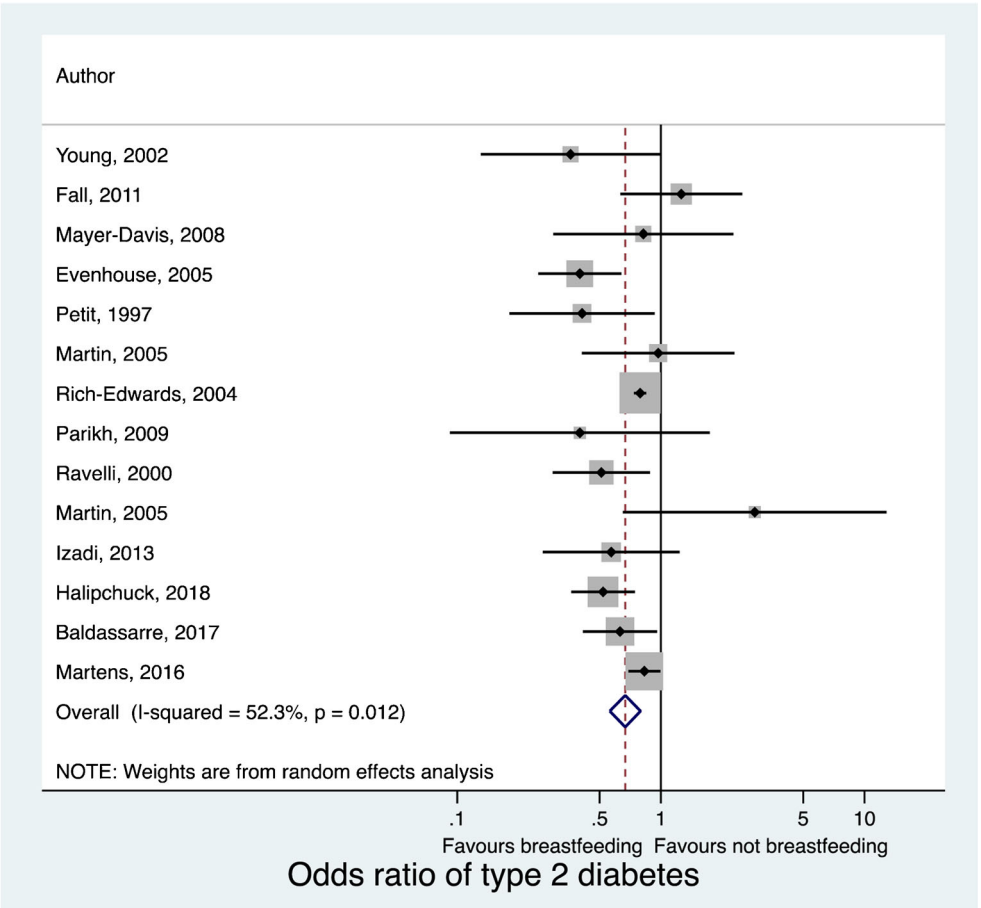


**Fig. 1** Odds ratio and 95% confidence interval of having type 2 diabetes, comparing breastfed vs. non-breastfed subjects

The meta-analysis included 14 studies that evaluated the association between breastfeeding duration and type 2 diabetes (Table 1). Figure 1 shows that the majority of the included studies reported that breastfeeding decreased the odds of type 2 diabetes, and for 9 studies the confidence interval did not include the reference (1). The pooled odds ratio was 0.67 (95% confidence interval, 0.56; 0.80), using a random effects model.

Table 2 shows that the protective effect of breastfeeding was higher among adolescents (pooled odds ratio, 0.49 (95% confidence interval, 0.38; 0.63)) and that age at diabetes assessment explained 81.1% of the heterogeneity among the studies. Study design also modified the association between breastfeeding and type 2 diabetes, and the benefit of breastfeeding was higher among the case-control studies (pooled odds ratio, 0.52 (95% confidence interval, 0.38; 0.72)). Study design explained 50.6% of the heterogeneity. Those studies that compared ever vs. never breastfed subjects reported a smaller benefit of breastfeeding than those studies that used different durations of breastfeeding to consider the subjects as breastfed. With respect to the study setting, 12 studies were carried out in high-income settings and the studies carried out in this setting tended to report a higher benefit of breastfeeding. The other variables did not provide a contribution to the heterogeneity among studies.

Concerning publication bias, Table 2 shows that sample size did not modify the association between breastfeeding and type 2 diabetes, and the Egger test was not statistically significant ($p = 0.16$).

**Table 2** Breastfeeding and the odds ratio of type 2 diabetes in later life: random effects meta-analyses by subgroup

| Subgroup analysis | Number of estimates | Pooled odds ratio (95% confidence interval) | Heterogeneity explained (%) |
|---|---|---|---|
| Age group | | | |
| 10–19 years | 5 | 0.49 (0.38; 0.63) | 81.1 |
| ≥ 20 years | 9 | 0.77 (0.66; 0.90) | |
| Study size | | | |
| < 500 participants | 4 | 0.59 (0.36; 0.95) | 0.0 |
| ≥ 500 participants | 10 | 0.68 (0.56; 0.82) | |
| Study design | | | |
| Cohort | 7 | 0.78 (0.68; 0.90) | 50.6 |
| Case-control | 3 | 0.52 (0.38; 0.72) | |
| Cross-sectional | 4 | 0.61 (0.37; 0.99) | |
| Length of recall of breastfeeding | | | |
| < 3 years | 4 | 0.71 (0.50; 0.99) | 0.0 |
| ≥ 3 years | 10 | 0.63 (0.48; 0.82) | |
| Study setting | | | |
| High-income country | 10 | 0.65 (0.54; 0.78) | 0.0 |
| Low/middle-income country | 2 | 0.87 (0.40; 1.88) | |
| Categorization of duration of breastfeeding | | | |
| Breastfed for a given number of months | 7 | 0.60 (0.47; 0.77) | 0.0 |
| Ever breastfed | 7 | 0.77 (0.54; 1.12) | |
| Control for confounding by socioeconomic status | | | |
| No | 8 | 0.66 (0.47; 0.93) | 0.0 |
| Yes | 6 | 0.68 (0.54; 0.84) | |
| Control for confounding by birthweight | | | |
| No | 8 | 0.67 (0.53; 0.84) | 0.0 |
| Yes | 6 | 0.65 (0.43; 0.99) | |
| Control for confounding by gestational diabetes mellitus | | | |
| No | 9 | 0.69 (0.53; 0.89) | 0.0 |
| Yes | 5 | 0.61 (0.43; 0.87) | |
| Control for confounding by body mass index | | | |
| No | 13 | 0.67 (0.56; 0.81) | * |
| Yes | 1 | 0.63 (0.41; 0.96) | |
| Total | 14 | 0.67 (0.56; 0.80) | |

*We did not estimate the contribution of this variable to the heterogeneity among studies because the categories had only one study

## Discussion

In this manuscript, we updated the meta-analysis on the association between breastfeeding duration and type 2 diabetes. In the previous study, we observed that the odds of diabetes was 35% lower among subjects who had been breastfed (pooled odds ratio, 0.65 (95% confidence interval, 0.49; 0.86)). After incorporating three new studies [17••, 18, 19], the pooled odds ratio was similar, and the confidence interval narrowed (pooled odds ratio, 0.67 (95% confidence interval, 0.56; 0.80)).

The magnitude of the protection against type 2 diabetes was larger among adolescents, suggesting that the benefit of breastfeeding may decrease overtime. But even among adults, breastfeeding protected against type 2 diabetes (pooled odds ratio, 0.77 (95% confidence interval, 0.66; 0.90)). In another review, we also observed that the protection of breastfeeding against overweight/obesity diluted over time [5]. Because overweight/obesity increases the risk of type 2 diabetes [31], the moderation of the association of breastfeeding with overweight could be an explanation for the decrease in the protection among adults.

Because most of the studies were carried out in high-income countries, where breastfeeding is positively associated with breastfeeding duration, adjustment for confounding by socioeconomic status should decrease the magnitude of the association of breastfeeding with type 2 diabetes. Initially, we observed that adjustment for socioeconomic status, as well as birthweight and gestational diabetes, did not modify the association. But, when we examined the pooled effect among those three studies that adjusted for socioeconomic status and birthweight, we observed that the pooled effect among these studies was 0.81 (95% confidence interval, 0.69; 0.97). Suggesting, therefore, that residual confounding by socioeconomic status and birthweight could overestimate the benefit of breastfeeding, residual confounding did not introduce a spurious association.

Concerning publication bias, the benefit of breastfeeding was slightly higher among those studies with a sample size < 500 participants (pooled odds ratio, 0.59 (95% confidence interval, 0.36; 0.95)), but the pooled effect among larger studies was similar to the estimate observed for the overall studies. Therefore, publication bias did not overestimate the pooled effect. In our review, length of recall of breastfeeding did not modify the association. Because a longer recall time tends to be associated with classification errors in the information of duration of breastfeeding [32], a stronger association would be expected among those studies with a short recall time. A possible explanation for this finding is that half of the studies compared ever vs. never breastfed and for this categorization, classification error is unlikely.

## Conclusion

In the previous review, we have already reported that breastfeeding could protect against type 2 diabetes, and even after incorporating three new studies, with a study population of about 250,000 individuals, the pooled estimate showed a small variation. Therefore, this new evidence reinforces the likelihood that breastfeeding has a benefit on protecting against type 2 diabetes. But, further studies with a high quality are needed. These studies should adjust the estimates for confounding by socioeconomic status and birthweight, as well as collect data on duration of breastfeeding with a short recall time.

**Funding Information** Bernardo Lessa Horta has a Scientific Productivity Scholarship (Level 1A) from the Brazilian Research Council (CNPq). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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