

Association of breast milk fatty acids with allergic disease outcomes—A systematic review

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Abstract

Introduction: Dietary polyunsaturated fatty acids (PUFAs) have immunoregulatory properties. Breast milk is rich in PUFA, and it has been hypothesized that these PUFAs may be important in the aetiology of allergic diseases. Despite a growing body of evidence, the associations between breast milk PUFA and allergic disease have not previously been systematically reviewed.

Methods: The search was performed in PubMed and EMBASE databases using breastfeeding, fatty acid and allergic disease terms. Two authors were involved in selecting papers for review according to the inclusion criteria and extracting information on study characteristics and measures of association. Only studies that reported numeric associations between concentration of breast milk fatty acids and allergic disease outcomes were included.

Results: A total of 18 papers met the inclusion criteria, reporting results from 15 study populations. The majority were cohort studies (n=11), with data from only two case-control and two cross-sectional studies. Sample size varied between 30 and 352 participants, and follow-up time of the cohorts varied between 3 months and 14 years. Nine studies reported on eczema, seven reported on sensitization, and only five reported on asthma/wheeze. There was heterogeneity among studies in terms of presenting the association between PUFA and allergy; therefore, estimates could not be pooled. Only a few studies observed associations between n-3 and n-6 PUFAs and allergic disease, and the magnitude of this effect varied greatly.

Conclusions: There is insufficient evidence to suggest that colostrum or breast milk polyunsaturated fatty acids influence the risk of childhood allergic diseases.

KEYWORDS

allergic disease, breast milk, colostrum, polyunsaturated fatty acids

1 | INTRODUCTION

There has been a substantial increase in the prevalence of allergic diseases throughout the world. This increase varies between and

within countries, suggesting that the reasons behind the allergy “epidemic” may be linked with environmental exposures.^{1,2} Many theories have been proposed in relation to the pathogenesis of allergic diseases, but effective preventive strategies for these conditions

remain elusive.^{3,4} Early-life dietary exposure has been proposed as a key determinant of allergic disease outcomes.³

Breast milk is the first dietary exposure for most newborns and contains many immunomodulatory substances,⁵ including polyunsaturated fatty acids (PUFA).⁶ PUFAs can be categorized as n-3 or n-6 PUFA based on the location of the first double bond. Counting from the methyl end of the carbon chain, in n-3 the first double bond is placed in the C-3 position for n-3 and the C-6 position for n-6. N-3 PUFA has the ability to reduce the production of anti-inflammatory substances. It also stabilizes T-cell membranes, which in turn reduces allergic inflammation.⁷⁻⁹ In contrast, n-6 PUFA enhances the inflammatory response.¹⁰

Based on these inflammatory properties, it has been hypothesized that colostrum and breast milk PUFA may influence the risk of allergic disease. Although a number of papers have been published on the relationship between colostrum and breast milk fatty acids and allergic disease outcomes, the evidence has not been systematically reviewed and synthesized.

Dietary intervention in early life to modify the levels of fatty acids has been proposed as a means of allergic disease prevention^{11,12} but the evidence from intervention trials is inconclusive.¹³ The outcomes of intervention trials cannot be directly compared with the associations obtained from breast milk PUFA observational studies as the intervention doses are much larger than the normal biological doses.

The aim of this systematic review was to appraise all available literature on the relationship between colostrum/breast milk fatty acids and allergic disease outcomes. This may aid understanding of the impact of breast milk PUFA on the prevalence of allergic disease outcomes, and inform the design of future intervention trials.

2 | METHODS

2.1 | Search strategy

Publications related to fatty acids in breast milk and allergic disease outcome were identified using Medline (PubMed) and EMBASE platforms. The last search was performed on 27th May 2016, and both key and MeSH terms were used (see online supplement for full search details). The key words used for the search were as follows: (i) breast milk terms—"breast milk" "human milk" "colostrum"; (ii) fatty acid terms—"poly unsaturated fatty acids" "n-3" "n-6"; (iii) outcome terms—"allergic disease" "asthma" "wheeze" "sensitization" "allergic rhinitis" "eczema" and "lung function" (further details in online supplementary material). This review was prospectively registered in PROSPERO systematic review registry (No 2015023420).

2.2 | Inclusion and exclusion criteria

Only those studies that (i) reported original data; (ii) included a quantitative assessment of fatty acids in breast milk and/or colostrum; and (iii) reported associations with at least one allergic disease,

Key Points

- It is proposed that allergic diseases are mediated via passive immunity as well as active immune-mediated pathways.
- Maternal nutrition status can modify the status of breast milk.
- Colostrum and breast milk PUFA may help to improve the immune function of the newborn.
- This systematic review of the published literature on the association between colostrum and breast milk fatty acids and allergic disease outcomes was unable to confirm that PUFA has beneficial effects on allergic disease outcomes.
- It is plausible that methodological issues have contributed to our results.
- Further research is needed using larger samples to clearly explore these associations.

allergic sensitization or lung function outcome in the child were included in this review.

2.3 | Selection of articles

Title and abstract review was performed by two reviewers independently (NW and GB). If either reviewer considered the paper potentially eligible, both reviewers examined the full text for inclusion. Any disagreements were resolved by involvement of a third reviewer (AL).

2.4 | Data extraction

Study design, sample size, details of the exposure categorization and outcomes measured were recorded. Details of available potential confounders, and the measures of association with allergic disease, were also extracted.

2.5 | Statistical analysis

Due to the heterogeneity of exposure classification between the included studies, it was not possible to undertake a meta-analysis. Most common method of expressing the outcome was per weight percentage increase in individual fatty acid (w%—percentage of the individual fatty acid forms total fatty acids). However, results are presented in forest plots to visualize associations. The study name, the age at which the outcome was assessed and the family history of allergic diseases were included in the forest plots. Associations were grouped according to the type of fatty acid (n-3, n-6 and n-6/n-3 ratio) in breast milk. STATA 13 was used for the analysis (version 13; Stata Corp, College Station, TX, USA).

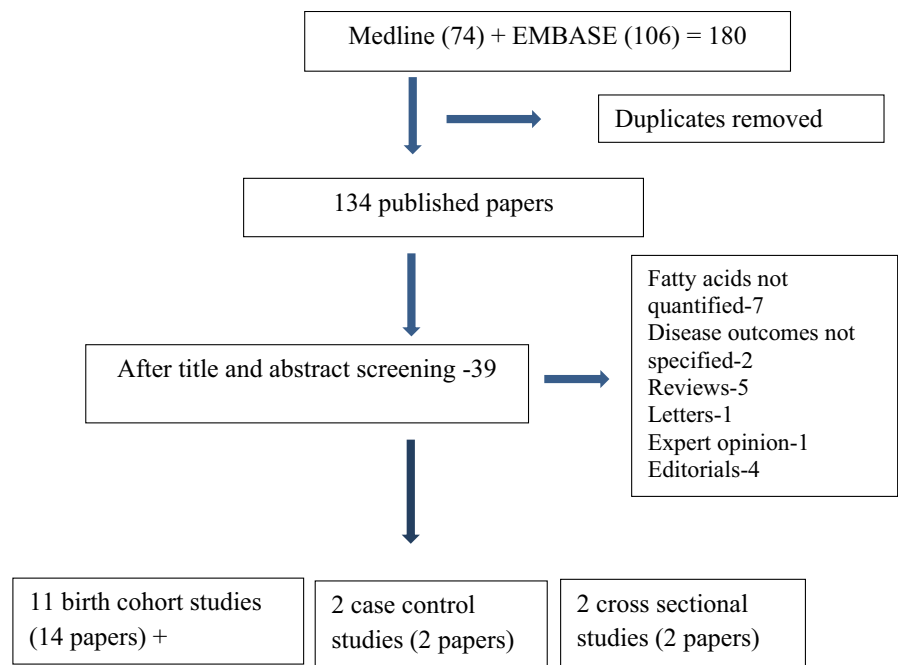


FIGURE 1 Selection of the studies for the review [Colour figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

The Medline and EMBASE search identified 180 published papers. After reviewing the titles and the abstracts, 39 papers were identified for the full-text review. From the 39 papers, 18 published papers met the inclusion criteria, from 15 unique study populations (Figure 1). In addition to these, another paper was captured from journal alerts. Therefore, this review contains 14 papers from 11 birth cohort studies,^{7,9,14-24} with three of these cohorts (MACS,^{7,9} PIAMA^{19,20} and Swedish cohort^{23,24}) generating two publications each. Two papers were from case-control studies^{25,26} and two were from cross-sectional studies.^{27,28} As some studies reported the same outcome at multiple time points in different publications, we summarized the results according to the study population ($n = 15$), rather than by publication ($n = 18$). This has resulted in instances where the number of citations exceeds the number of studies with a given result.

The sample sizes of the cohort studies ranged from 34 to 352 participants (Table 1). All of the case-control and cross-sectional studies had less than 50 participants (Table 1). The maximum age of follow-up was 14 years after birth for the cohort studies (Table 1).¹⁹ Only two studies assessed allergic disease outcomes beyond pre-school age.^{9,19}

Three studies measured PUFA levels in both colostrum and breast milk.^{7,9,17,23} Of the remaining studies, PUFA was measured either in colostrum^{16,22} or in breast milk.^{8,14,15,18,19,21,25-28}

Gas chromatography was used in all of the studies to quantify fatty acids from colostrum and breast milk. The concentration of fatty acids was expressed as lipid based (% of lipids) for 16 studies,^{7-9,14,16,18-20,22-28} while one reported results as wet-based technology (% of total weight).¹⁷ Further details of the method used and how the individual fatty acids were expressed are given in Table S1. While the concentrations of individual fatty acids were

higher with the lipid-based analysis method compared to wet-based method, but the strength and direction of associations were similar.¹⁷ Method of exposure categorization was also different among studies. These included outcomes expressed as per weight%,^{9,19} per interquartile range (IQR) increase.^{14,18,22} Some studies provided the mean^{8,16,21} or median²⁵ fatty acid levels between affected and unaffected groups. Outcomes were generally defined by clinical diagnosis,^{14,18-21} parent report^{7,9,26} or based on the ISAAC (The international Study of Asthma and Allergies in Childhood) study questionnaire.¹

From the ten birth cohort studies included in the review, only seven adjusted for confounding factors.^{7,9,14,16-20,23} These included maternal and paternal factors as well as factors related to the child and the environment (Table 1). The KOALA birth cohort study and the PIAMA birth cohort study adjusted for a range of confounding factors¹⁸⁻²⁰ (Table 1), including the children's BMI¹⁹ and vaccination schedule.¹⁸

3.1 | Associations between breast milk PUFA and eczema

3.1.1 | N-3 and eczema

Of the nine studies (ten publications) that reported the associations between total n-3 either in breast milk or in colostrum and eczema, only three found that increased levels of n-3 were associated with a decreased odds of eczema in childhood.^{8,18,21} The remaining four studies found no association (Table 2/Figure 2).^{9,15,16,19,20,22,26}

3.1.2 | N-6 and eczema

Of the eight studies (nine publications) that reported the association between total n-6 levels and eczema, one study observed increased

TABLE 1 Details of studies included in this review

Study name, country, citation(s)	Sample size & exposure type (n/N) and how the exposure was ascertained	Age at the follow-up	Confounding factors adjusted during analysis
Birth cohort studies			
ALADDIN birth cohort Sweden Rosenlund et al ¹⁴	225/330 Breast milk: 2 mo postpartum, hand-expressed	6, 12 and 24 mo	Lifestyle, maternal smoking during pregnancy, sex, number of siblings or other children in the household at the time of birth, exclusive breastfeeding at 2 mo, parental education, living on a farm with animals during pregnancy and parental sensitization.
INMA Spain Morales et al ¹⁶	352/657 Colostrum: 2-4 d postpartum, expressed using a breast pump and collected in the morning	6 and 14 mo	Eczema: gender of the child, maternal atopy and maternal pre-pregnancy BMI. Wheeze: gender of the child, maternal social class, siblings at birth, maternal smoking in pregnancy and DDE ^a levels in cord blood
BACH & PEACH USA Soto-Ramirez et al ¹⁷	33/231 Colostrum: 2 d postpartum 115/231 Breast milk 2 wk postpartum, expressed using a breast pump in the morning	6 and 12 mo	Child's sex, maternal age during pregnancy, maternal race, smoking during pregnancy, vaginal or urinary infection during pregnancy, maternal history of asthma, consumption of antibiotics during pregnancy, season of child's birth, any respiratory tract infection during infancy and household cigarette use at the age of 6 and 12 mo.
KOALA birth cohort Netherlands Thijs et al ¹⁸	315/2343 Breast milk: 1 mo postpartum expressed either manually or using a breast pump in the morning	7, 12 and 24 mo	Maternal age, maternal education, infant's gender, number of older siblings and their atopic history, parental atopic history, maternal smoking during pregnancy, smoking in the presence of infant, place of birth, season of breast milk collection, duration and exclusivity of breastfeeding, maternal n-3 fatty acid supplement use, maternal probiotic supplement use, maternal probiotic dairy use, maternal antibiotic use during lactation, vaccination schedule, dampness of the home and pet animals in the home
COPSAC birth cohort Denmark Giwerzman et al ¹⁵	314/411 Breast milk: 1 mo postpartum at clinic visit	2 y	Day care, mother's smoking during third trimester.
MACS Australia Lowe et al ⁹	224/620 Colostrum: 194 as close to delivery, hand-expressed in the morning	4 mo and at 6 and 7 y	Maternal and paternal history of allergy, infant gender, presence of older siblings, parental smoking and parental education, parental age, use of gas heating and cooking, pet exposure within first year of life
Stony et al ⁷	Breast milk: 118 3 mo postpartum, using a breast pump in the morning Both: 88	6, 12 and 24 mo	Maternal atopy
PIAMA Netherlands Wijga et al ²⁰	265/4146 Breast milk: 3 mo postpartum, collection method and time depending on mother's preference	1 and 4 y	Children of mothers with and without allergy were compared. Models adjusted for sex, number of older siblings, maternal age, maternal smoking during pregnancy, maternal BMI before pregnancy
van Elton ¹⁹		12 and 14 y	Models adjusted in addition to the above-mentioned variables maternal and paternal education status, gestation weight gain of the mother, duration of any breastfeeding, child's gender, parental allergy, allergic family member, birth weight of the child, caesarean section delivery complementary feeding before or after 4 mo, BMI of the child, pet exposure and smoking of the child.
CAS Australia Oddy et al ⁸	91/263 Breast milk 6 wk and 6 mo postpartum at the clinic visit	6 mo and 5 y	No adjustments were made

(Continues)

TABLE 1 (Continued)

Study name, country, citation(s)	Sample size & exposure type (n/N) and how the exposure was ascertained	Age at the follow-up	Confounding factors adjusted during analysis
Finland Hoppu et al ²¹	34/34 Breast milk: 1 mo postpartum by manual expression in the morning	12 mo	No adjustments were made
LARS Germany Reichardt et al ²²	Colostrum: 218/429 collected in the morning (a subsample of the LARS cohort)	1 y	No adjustments were made
Sweden Duchen et al ²³	160/160 Colostrum and 1 and 3 mo breast milk	3, 6, 12 and 18 mo	Heredity. Smoking habits, exposure to pets, number of children breastfed for more than 3 mo
Sweden Duchen et al ²⁴	160/160 Colostrum and 3 breast milk colostrum 2-4 d postpartum and breast milk at 1 and 3 mo with a mechanical breast pump in the morning	6 and 12 mo	-
Case-control studies			
Finland Laitinen et al ²⁵	30/30 Breast milk 5.6 mo postpartum by manual expression in the morning	1 y	Matched for age
Zimbabwe Wright and Bolton et al ²⁶	47/47 Breast milk collected 2-6 mo postpartum between 10.00 and 12.00 h	2 and 6 mo	Matched for age and early skin manifestations
Cross-sectional studies			
Italy Businco et al ²⁷	41/41 Breast milk 6 mo postpartum between 10.00 and 12.00 h	6 mo	No adjustments were made
Finland Kankaanpää et al ²⁸	40/40 Breast milk after 3 mo postpartum between 10.00 and 12.00 h	3 mo	No adjustments were made

EBM, expressed breast milk.

^adichlorodiphenyl dichloroethene.

risk with increased levels of n-6⁸ and all the other studies did not observe an association.^{9,15,16,19-22,26}

3.1.3 | N-6/n-3 ratio and eczema

Of the five studies (six publications) that reported the association between the ratio of total n-6 to total n-3 and eczema, one found increased ratio increasing the risk of eczema⁸ and the others did not find an association.^{9,19-22}

3.2 | Association between breast milk PUFA and sensitization

3.2.1 | N-3 and sensitization

Of the seven studies (eight publications) that reported the association between total n-3 and sensitization,^{7,8,14,17-20,22} three reported no association.^{8,19,20} Four studies found that increased n-3 was

associated with reduced risk of sensitization.^{14,17,18,22} From the three studies that assessed sensitization at the age of 1 year, two studies showed a reduced odds with increasing n-3 PUFA (highest vs lowest quartile OR 0.17 [95% CI: 0.04, 0.77]¹⁸ and 0.14 [0.05, 0.39]¹⁷). The third study found that the median value of n-3 in maternal milk of sensitized infants was lower than that found in nonsensitized (2.66 vs 2.88, $P < .05$).²² From the two studies that assessed the outcome at 2 years, comparing the highest vs lowest quartile of n-3, in one study the association was not apparent (OR 0.89 [0.32, 2.50]),¹⁸ while the other showed nonsignificant trend towards a protective effect (0.49 [0.23, 1.05]).¹⁴ In a high-risk birth cohort, Stoney et al⁷ found that increased n-3 was associated with an increased risk of sensitization at both 6 and 24 months of age (Table 3/Figure 3).

3.2.2 | N-6 and sensitization

Of the six studies (seven publications) that reported the total n-6 levels and sensitization, five reported no association.^{7,8,14,19,22}

TABLE 2 The association between colostrum/breast milk fatty acids and eczema

The association between n-3 and eczema							
Study	Exposure	Exposure categorization	Age at which the outcome was tested	Results			Effect
KOALA birth cohort Thijs et al 2011 (18)	EBM	Fatty acid quartiles in w%	2 y	Fatty acid quartile 0.30-0.56 0.56-0.65 0.65-0.78 0.78-2.55	OR (95% CI) Ref 0.80 (0.37, 1.71) 0.89 (0.43, 1.88) 0.62 (0.30, 1.29)	<i>P</i> for trend .040	n-3 protective
COPSAC birth cohort Giwercman et al 2010 (15)	EBM	Effect per w% increase	2 y	HR 0.625 ^a	<i>P</i> value >.1		No association
MACS Lowe et al 2008 (9)	Colostrum EBM	Effect per w% increase	2 y	OR 95% CI Colostrum: 1.11 (0.82, 1.48) EBM: 1.42 (0.96, 2.09)	<i>P</i> value .503 .076		No association
PIAMA birth cohort Wijga et al 2006 (20)	EBM	Effect per IQR increase in w%	1 y 4 y 14 y	With allergy* OR (95% CI) per IQR 0.74 (0.45, 1.21) 0.84 (0.54, 1.30) 0.83 (0.60, 1.15)	Children of mothers Without allergy* OR (95% CI) per IQR — — 0.89 (0.74, 1.07)		No association
van Elton (19)							No association
Hoppu et al 2005 (21)	EBM	Mean w% (95% CI) in children with and without eczema	1 y	With eczema Mean (95% CI) 1.61 (1.21, 2.00)	No eczema Mean (95% CI) 2.17 (1.77, 2.56)	<i>P</i> value .05	n-3 protective
CAS Oddy et al 2006 (8)		Mean values of fatty acid composition (weight per cent of total fatty acids—wt%)	6 mo 5 y 6 mo 5 y	Without eczema* Mean fatty acid level (SD) 2.44 (0.12) 2.28 (0.09) 2.32 (0.11) 2.26 (0.09)	With eczema* Mean fatty acid level (SD) 2.12 (0.08) 2.25 (0.13) 2.05 (0.08) 2.25 (0.13)	<i>P</i> value .04	n-3 protective
LARS cohort Reichardt et al 2004 (22)	Colostrum	Median w% (IQR) in children with and without eczema	1 y	With eczema Median (IQR) 2.77 (0.36)	No eczema Median (IQR) 2.73 (0.45)	<i>P</i> value Not reported	No association
INMA Morales et al 2012 (16)	Colostrum	Effect per w% increase in fatty acid of tertiles	14 mo (recurrent eczema)	Fatty acid level Lowest tertile Highest tertile	OR (95% CI) Ref 0.54 (0.11-2.64)	<i>P</i> value Not reported	No association
Wright & Bolton 1989 (26)	EBM	Mean w% in children with and without eczema	6 mo	Children with eczema mean 1.6 ^b	Children without eczema mean 1.6 ^b	<i>P</i> value Not reported	No association
The association between n-6 and eczema							
Study	Exposure	Exposure categorization	Age at which the outcome was tested	Results			Effect
COPSAC birth cohort Giwercman et al 2010 (15)	EBM	Effect per w% increase	2 y	HR 0.958 ^a	<i>P</i> value >.1		No association

(Continues)

Table 2 (Continued)

MACS Lowe et al 2008 (9)	Colostrum EBM	Effect per w% increase	2 y	OR (95% CI) (per w%) Colostrum: 1.10 (0.82, 1.47) EBM: 1.23 (0.84, 1.78)	<i>P</i> value .520 .284	No association	
PIAMA birth cohort Wijga et al 2006 (20) van Elton (19)	EBM	Effect per IQR increase in w%	1 y 4 y 14 y	Children of mothers With allergy* OR (95% CI) per IQR 1.12 (0.67, 1.90) 1.11 (0.66, 1.85) 1.24 (0.90, 1.71)	Without allergy* OR (95% CI) per IQR — — 1.11 (0.83, 1.48)	No association	
CAS Oddy et al 2006 (8)	EBM: 6 wk EBM: 6 mo	Mean values of fatty acid composition (weight percentage of total fatty acids—wt%)	6 mo 5 y 6 mo 5 y	Without eczema* Mean fatty acid level (SD) 12.80 (0.56) 13.61 (0.35) 13.13 (0.47) 13.44 (0.41)	With eczema* Mean fatty acid level (SD) 14.60 (0.47) 13.90 (0.59) 14.06 (0.59) 13.98 (0.83)	<i>P</i> value .010	n-6 increases the risk
Hoppu et al (21)	EBM	Mean w% (95% CI) in children with and without eczema	1 y	Children with eczema Mean (95% CI) 9.7 (8.7, 10.8)	Children without eczema Mean (95% CI) 10.6 (9.7, 11.2)	<i>P</i> value .21	No association
LARS cohort Reichardt et al 2004 (22)	Colostrum	Median w% (IQR) in children with and without eczema	1 y	Children with eczema Median (IQR) 11.26 (4.18)	Children without eczema Median (IQR) 12.02 (2.93)	<i>P</i> value Not reported	No association
INMA Morales et al 2012 (16)	Colostrum	Effect per w% increase in fatty acid of tertiles	14 mo (recurrent eczema)	Fatty acid level Lowest tertile Highest tertile	OR (95% CI) Ref 0.60 (0.17-2.14)	<i>P</i> value Not reported	No association
Wright & Bolton et al 1989 (26)	EBM	Mean w% in children with and without eczema	6 mo	Children with eczema mean 14.6 ^b	Children without eczema mean 12.5 ^b	<i>P</i> value Not reported	No association
The association between n-3/n-6 ratio and eczema							
Study	Exposure	Exposure categorization	Age at which the outcome was tested	Results		Effect	
MACS Lowe et al 2008 (9)	Colostrum EBM	Effect per w% increase	2 y	OR (95% CI) (per w%) Colostrum: 0.96 (0.72, 1.29) EBM: 0.85 (0.51, 1.24)	<i>P</i> value .807 .391	No association	
PIAMA birth cohort Wijga et al 2006 (20) van Elton (19)	EBM	Effect per IQR increase in w%	1 y 4 y 14 y	Children of mothers With allergy* OR (95% CI) per IQR 0.82 (0.52, 1.27) ^α 0.81 (0.52, 1.26) 0.78 (0.54, 1.13) ^α	Without allergy* OR (95% CI) per IQR — — 0.82 (0.65, 1.03)	No association	
CAS Oddy et al 2006 (8)	EBM: 6 wk	Mean values of fatty acid composition (weight percentage of	6 mo 5 y	Without eczema* Mean fatty acid level (SD) ^c 5.54 (0.28) 6.28 (0.23)	With eczema* Mean fatty acid level (SD) ^c 7.21 (0.38) 6.46 (0.46)	<i>P</i> value .001	Increases the risk

(Continues)

Table 2 (Continued)

	EBM: 6 mo	total fatty acids—wt%)	6 mo 5 y	5.87 (0.19) 6.26 (0.26)	7.09 (0.38) 6.29 (0.31)	.005	
Hoppu et al (21)	EBM	Mean w% (95% CI) in children with and without eczema	1 y	Children with eczema Mean (95% CI) 7.1 (5.0,9.1)	Children without eczema Mean (95% CI) 5.5 (4.4,6.6)	<i>P</i> value .11	No association
LARS cohort Reichardt et al (22)	Colostrum	Median w% (IQR) in children with and without eczema	1 y	Children with eczema Median (IQR) 4.12 (1.55)	Children without eczema Median (IQR) 4.53 (1.29)	<i>P</i> value >.05	No association

**P* value reported only for some comparisons in the original paper.

^a95% CI was not reported.

^bSD not reported.

^cThe original paper reported n-6/n-3 ratio.

However, Wijga et al²⁰ and Soto-Ramirez et al¹⁷ found that increased n-6 was associated with decreased odds of sensitization, but in one study the association was apparent only in children of mothers without allergy (OR 0.42, 95% CI: 0.18, 1.02 [$P \leq .05$]).²⁰

3.2.3 | N-6/n-3 ratio and sensitization

Of the four studies (five publications) that investigated the association between the n-6/n-3 ratio and sensitization,^{7,8,20,22,26} only one⁷ observed that an increased ratio was associated with decreased food sensitization. The other studies did not observe an association.

3.3 | Association between breast milk PUFA and asthma/wheeze

3.3.1 | N-3 and asthma/wheeze

Five studies (six publications) reported the association between total n-3 levels and wheeze or asthma.^{9,15-17,19,20} One cohort found that increased n-3 was associated with reduced risk of childhood asthma at both 4 and 14 years,^{19,20} with the protective effect at 14 years only among the children of mothers with allergy.¹⁹ Two did not find any association between n-3 levels and asthma.^{9,17} Two studies reported the outcome of childhood wheezing,^{15,16} and neither found an association (Table 4/Figure 4).

3.3.2 | N-6 asthma/wheeze

Of the five studies (six publications) that reported on n-6 levels and asthma or wheeze, two found an increased risk with increased levels of n-6^{17,19} and three did not find any associations. Morales et al¹⁶ assessed the association between n-6 and wheezing and found no effect between 7 and 14 months of age (OR 1.14, 95% CI: 0.57, 2.27).

3.3.3 | N-6/n-3 ratio and asthma/wheeze

Two studies (three publications) reported the association between the n-6/n-3 ratio and asthma. One found no association,⁹ while the other found an association between increased ratio and reduced risk of asthma.^{19,20}

3.4 | Allergic rhinitis

Only one study⁹ reported on allergic rhinitis. In this study, n-3 levels were not associated with allergic rhinitis (colostrum OR: 1.08 [95% CI: 0.75, 1.55]) and EBM (expressed breast milk OR: 1.11 [95% CI: 0.71, 1.74]), nor was n-6/n-3 ratio (colostrum OR: 1.32; 95% CI: 0.96, 1.82; EBM OR: 1.02; 95% CI: 0.66, 1.57). However, higher levels of n-6 in colostrum were associated with an increased risk of allergic rhinitis (OR: 1.59; 95% CI: 1.12, 2.25, $P = .01$) but there was no association between the EBM and total n-6 fatty acids (OR: 1.21; 95% CI: 0.78, 1.88).

3.4.1 | Studies with composite outcomes

Four of the included studies reported on composite outcomes.^{23-25,27,28} Duchon et al²³ reported fatty acid concentrations in colostrum and breast milk according to the atopic status of the child (a composite of skin prick test [SPT] reactivity and symptoms) at 12²⁴ and 18 months.²³ Up to the age of 12 months,²⁴ mean n-3 in breast milk was lower among the children with atopy compared to the nonatopic children (mean 1.5 and SD 0.3 and 1.8 and 0.5, respectively). The ratio between n-6 and n-3 was high in breast milk of atopic children compared to the nonatopic children (6.9 ± 1.3 and 5.8 ± 1.2 , respectively). By 18 months, there was no difference in PUFA concentration in colostrum according to the atopic status of the child, but differences were observed for specific subtypes of PUFA (C20:5 n-3 and C22:5 n-3) in breast milk at 1 and 3 months. At 1 month, C20:5

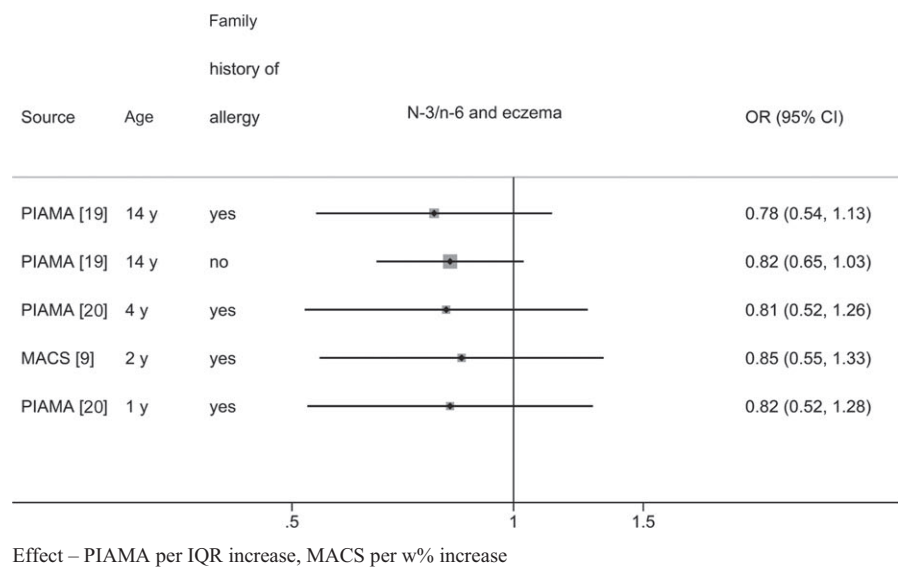
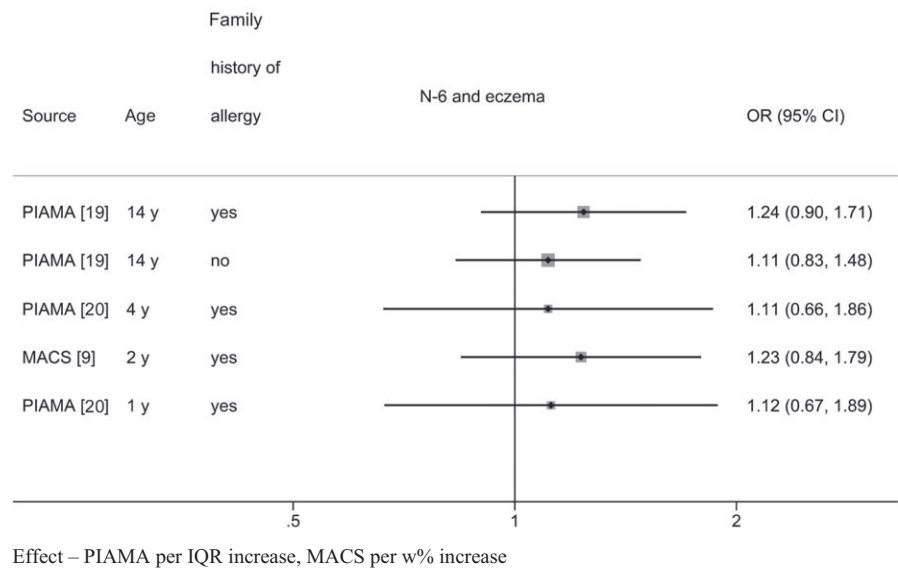
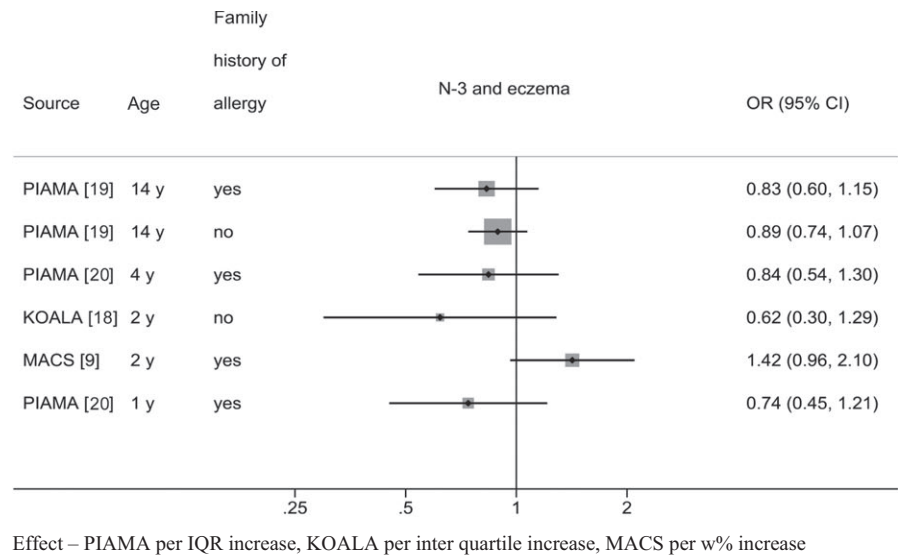


FIGURE 2 The association between breast milk PUFA and eczema

TABLE 3 The association between colostrum/breast milk fatty acids and sensitization

The association between n-3 and sensitization							
Study	Exposure	Exposure categorization	Age at which the outcome was tested	Results			Effect
ALADDIN birth cohort Rosenlund et al 2016 (14)	EBM	Quartiles of w% (g in 100 g)	6, 12 and 24 mo	Fatty acid quartile 1 (lowest) 2 3 4 (highest)	RR (95% CI) Ref 0.89 (0.44-1.80) 0.49 (0.23-1.04) 0.49 (0.23-1.05)	<i>P</i> value for trend .024	n-3 is protective
BACH & PEACH Soto-Ramirez et al 2012 (17)	Colostrum	Above the median as high level of exposure and below the median as low level of exposure in nmol/mg	12 mo	No evidence—data not shown			No association
	EBM			Fatty acid level Low High	RR (95% CI) Ref 0.15 (0.02, 1.05) 0.14 (0.05, 0.39)	<i>P</i> value .05 (lipid based) .0002 (wet based)	n-3 is protective
KOALA birth cohort Thijs et al 2011 (18)	EBM	Fatty acid quartiles in w%	1 y 2 y	Fatty acid quartiles 0.30-0.56 0.56-0.65 0.65-0.78 0.78-2.55 0.30-0.56 0.56-0.65 0.65-0.78 0.78-2.55	OR (95% CI) Ref 0.80 (0.21, 3.08) 0.68 (0.21, 2.20) 0.17 (0.04, 0.77) Ref 1.29 (0.45, 3.68) 1.32 (0.47, 3.72) 0.89 (0.32, 2.50)	<i>P</i> for trend .029 .92	n-3 protective effect at 1 y
PIAMA birth cohort Wijga et al 2006 (20)	EBM	Effect per IQR increase in w%	4 y	With allergy* OR (95% CI) (per IQR)	Children of mothers Without allergy* OR (95% CI) (per IQR)		No association
van Elton (19)			12 y	0.86 (0.52, 1.41)	1.11 (0.86, 1.42)		No association
CAS Oddy et al 2006 (8)		Mean values of fatty acid composition		Without sensitization* Mean fatty acid level (SD)	With sensitization* Mean fatty acid level (SD)		No association
	EBM:	(weight	6 mo	2.44 (0.12)	2.14 (0.19)		
	6 wk	percentage of	5 y	2.28 (0.09)	2.49 (0.48)		
	EBM:	total fatty	6 mo	2.32 (0.11)	2.29 (0.21)		
	6 mo	acids—wt%)	5 y	2.26 (0.09)	1.81 (0.82)		
MACS Stony et al 2004 (7)	Colostrum	Effect per w% increase	6 mo	Food Aero	Atopics Mean (SD) 2.05 (0.34) 1.96 (0.37)	Nonatopics Mean (SD) 1.82 (0.34) 1.86 (0.35)	<i>P</i> value .004 .70
			2 y	Food Aero	2.03 (0.37) 1.99 (0.38)	1.80 (0.32) 1.78 (0.31)	.04 .009
	EBM			No evidence—data not shown			No association
LARS Reichardt et al 2004 (22)	Colostrum	Median w%(IQR)	1 y	With sensitization Median (IQR)	Without sensitization Median (IQR)	<i>P</i> value 2.66 (0.42) 2.88 <.05	n-3 protective
The association between n-6 and sensitization							
Study	Exposure	Exposure categorization	Age at which the outcome was tested	Results			Effect

(Continues)

Table 3 (Continued)

ALADDIN birth cohort Rosenlund et al 2016 (14)	EBM	Quartiles of w% (g in 100 g)	6, 12 and 24 mo	Fatty acid quartile	RR (95% CI)	<i>P</i> value for trend	No association
				1 (lowest)	Ref		
				2	1.39 (0.72-2.67)	.315	
				3	0.62 (0.27-1.42)		
				4 (highest)	0.89 (0.41-1.92)		
BACH & PEACH Soto-Ramirez et al 2012 (17)	Colostrum EBM	Above the median as high level of exposure and below the median as low level of exposure in nmol/mg	12 mo	No evidence—data not shown	RR (95% CI)	<i>P</i> value	No association
				Fatty acid level	Ref		n-6 is protective
				Low	0.76 (0.26,2.20)	.72 (lipid based)	
				High	0.30 (0.10, 0.92)	.03 (wet based)	
CAS Oddy et al 2006 (8)		Mean values of fatty acid composition		Without sensitization* Mean fatty acid level (SD)	With sensitization* Mean fatty acid level (SD)		No association
	EBM: 6 wk	(weight percentage of	6 mo	12.80 (0.56)	13.27 (0.56)		
		total fatty acids—wt%)	5 y	13.61 (0.35)	15.16 (0.56)		
	EBM: 6 mo		6 mo	13.13 (0.47)	12.91 (0.85)		
			5 y	13.44 (0.41)	11.00 (0.43)		
PIAMA birth cohort Wijga et al 2006 (20)	EBM	Effect per IQR increase in w%		Children of mothers			n-6 is protective among children of mothers without allergy
				With allergy* OR (95% CI) (per IQR)	Without allergy* OR (95% CI) (per IQR)		
			4 y	0.78 (0.43, 1.41)	0.42 (0.18, 1.02)		
			12 y	0.87 (0.56, 1.33)	0.86 (0.59, 1.24)		No association
LARS Reichardt et al 2004 (22)	Colostrum	Median w% (IQR) in children with and without sensitization	1 y	With sensitization Median (IQR)	Without sensitization Median (IQR)	<i>P</i> value	No association
				11.64 (2.41)	12.21 (2.89)	>.05	
MACS Stony et al 2004 (7)	Colostrum	Effect per w% increase		Atopics Mean (SD)	Nonatopics Mean (SD)	<i>P</i> value	No association
			6 mo	Food 13.8 (3.2)	14.7 (3.9)	.33	
				Aero 15.6 (4.0)	14.5 (3.8)	.59	
			24 mo	Food 15.8 (3.9)	14.3 (3.7)	.20	
				Aero 15.4 (4.6)	14.2 (4.6)	.25	
	EBM			No evidence—data not shown			No association
The association between n-3/n-6 ratio and sensitization							
Study	Exposure	Exposure categorization	Age at which the outcome was tested	Results			Effect
CAS Oddy et al 2006 (8)		Mean values of fatty acid composition		Without sensitization* Mean fatty acid level (SD) ^a	With sensitization* Mean fatty acid level (SD) ^a		No association
	EBM: 6 wk	(weight percentage of	6 mo	5.54 (0.28)	6.75 (0.69)		
		total fatty acids—wt%)	5 y	6.28 (0.23)	7.21 (2.04)		
	EBM: 6 mo		6 mo	5.87 (0.19)	5.79 (0.32)		
			5 yr	6.26 (0.26)	6.21 (0.82)		
PIAMA birth cohort	EBM	Effect per IQR increase in w%		Children of mothers			No association

(Continues)

Table 3 (Continued)

Wijga et al 2006 (20)				With allergy* OR (95% CI) (per IQR)	Without allergy* OR (95% CI) (per IQR)		
			4 yr	1.12 (0.70, 1.77) ^a	1.29 (0.85, 1.95) ^a		
van Elton (19)			12 yr	0.91 (0.69, 1.20)	1.12 (0.92, 1.36)		No association
MACS	Colostrum	Effect per w% increase		Atopic Mean (SD)	Nonatopic Mean (SD)	<i>P</i> value	At 6 mo, increased ratio is associated with food sensitization.
Stony et al 2006 (7)			6 mo	Food 6.84 (1.8)	8.37 (3.1)	.027	
				Aero 7.95 (1.5)	8.13 (3.0)	.95	
			24 mo	Food 8.10 (3.1)	8.24 (3.0)	.99	
				Aero 8.11 (3.9)	8.25 (2.7)	.82	
EBM				No evidence—data not shown			No association
LARS	Colostrum	Median w% (IQR) in children with and without eczema	5 mo	With sensitization Median (IQR) 4.62 (1.51)	Without sensitization Median (IQR) 4.21 (1.15)	<i>P</i> value	No association
Reichardt et al 2004 (22)						>.05	

**P* values were available only for some comparisons.

^aThe original paper reported n-6/n-3 ratio.

n-3 was higher among nonatopic children (0.07 ± 0.5 and 0.06 ± 0.03 , $P < .05$) and the ratio between total n-6 and n-3 was lower among the atopic children (5.60 ± 1.3 and 6.40 ± 2.15 , $P < .05$). In the 1-month breast milk samples, C22:5 n-3 was higher among the nonatopics (0.16 ± 0.08 and 0.12 ± 0.04 , $P < .05$) and the ratio was lower among atopic children (5.80 ± 1.2 and 6.80 ± 1.4 , $P < .01$).

Kankaapaa et al also reported the outcome as the child's atopic status (eczema or food allergy in the context of a positive SPT) and found that the n-6/n-3 ratio in 3-month breast milk samples was significantly higher among atopic children compared to healthy children ($P < .05$).²⁸ Businco et al reported on the associations between mature breast milk PUFA (2-8.8 months) and eczema (atopic dermatitis), but did not present results for total n-3, n-6 or their ratio. This study identified that two n-6 fatty acids (20:3n-6 and 22:4 n-6) were significantly lower in the breast milk of mothers of children with eczema, while one n-3 (22:6 n-3) was lower in the breast milk of mothers of children without eczema.²⁷ Laitinen et al²⁵ reported eczema and sensitization as a combined outcome in a small sample of children ($n = 31$), and found that none of the breast milk PUFAs were associated with this outcome.

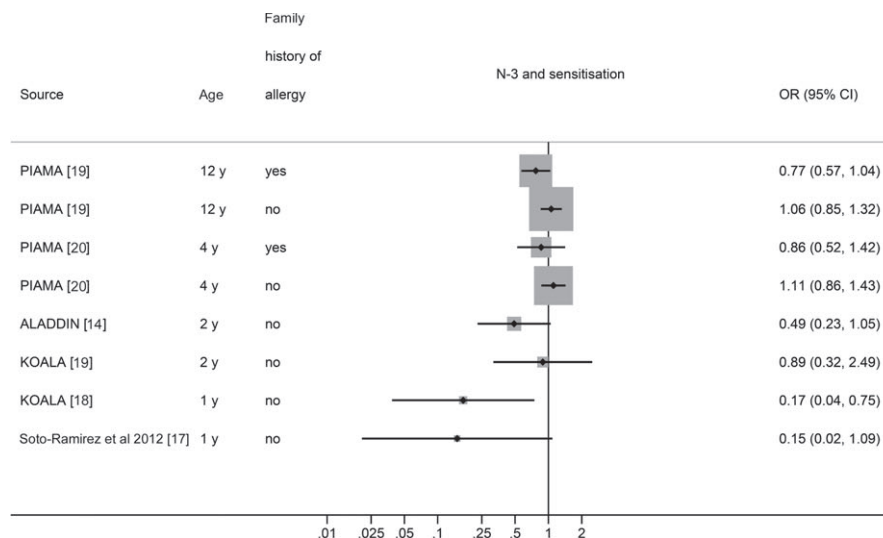
4 | DISCUSSION

A number of studies have investigated the association of colostrum or breast milk fatty acids and allergic disease outcomes with mixed results and no clear evidence of an association. Given the relatively small sample sizes of many of the studies included, and the associated imprecision of effect estimates, it would have been beneficial to pool results to obtain a combined estimate. However due to substantial differences in the reporting of exposures, we were unable to pool results to perform a meta-analysis.

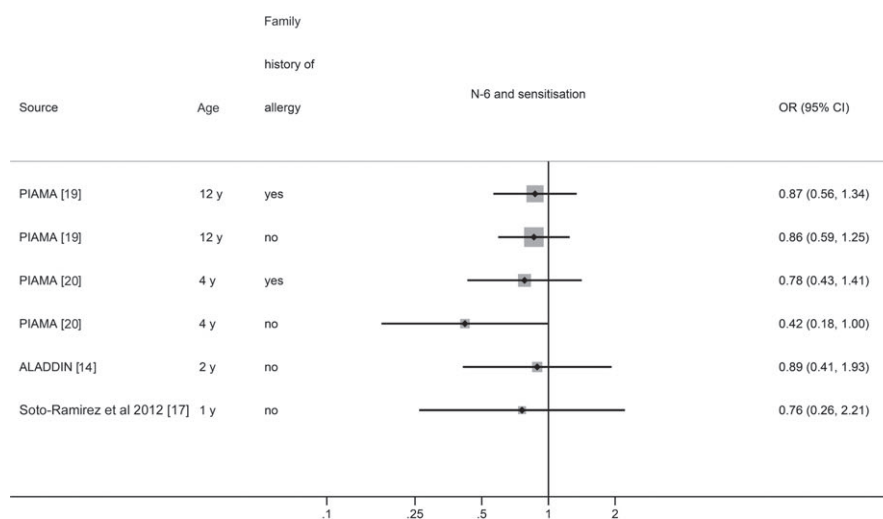
This paper identified several key strengths and limitations in the available literature. While all the studies included in this review quantitatively assessed PUFA levels, the timing of breast milk sample collection varied from colostrum^{16,22} through to mature breast milk^{26,27} collected when the infant was up to 6 months old. While it is plausible that the timing of collection of breast milk (particularly colostrum vs mature milk) may impact on the associations between PUFA and allergic disease outcomes, few studies have reported the associations with allergic disease outcomes with breast milk PUFA collected at multiple times^{7-9,23,24} and these studies have produced conflicting evidence. Further studies that compare associations with PUFA from breast milk collected at different times and allergy outcomes are required. Although a wide range of allergic disease outcomes were assessed in these studies, there were differences in the definitions used between the papers, and some outcomes were rarely reported. For example, only two studies^{9,19} assessed asthma as an outcome (which has the highest burden for all the allergic diseases) and three¹⁵⁻¹⁷ reported associations with wheeze.

The exposure categorization varied across the studies, which prevented us pooling effect estimates. Some studies expressed outcomes as per weight percentage increase,^{7,9,19,20} and some studies expressed outcomes as per interquartile range (IQR).^{14,18} A number of studies expressed the results as mean^{8,16,21} or median²² fatty acid levels between the affected and unaffected groups, while other reported relative risk estimates (ORs or RRs) for the clinical outcomes per unit increase in fatty acid level. In addition, the majority of studies assessed fatty acid levels in a relatively small number of participants, limiting the statistical power to detect associations.

There are a range of potential biases that may have influenced the results of this review. As breastfeeding is an important public health issue, it is possible that some studies with negative findings might not have been published. This would result in publication bias and an overestimate of the beneficial effect of breast milk PUFA.



Effect – PIAMA per IQR increase, ALADDIN and KOALA per quartile increase, Soto Ramirez nmol/mg



Effect – PIAMA per IQR increase, ALADDIN per quartile increase, Soto Ramirez nmol/mg above median

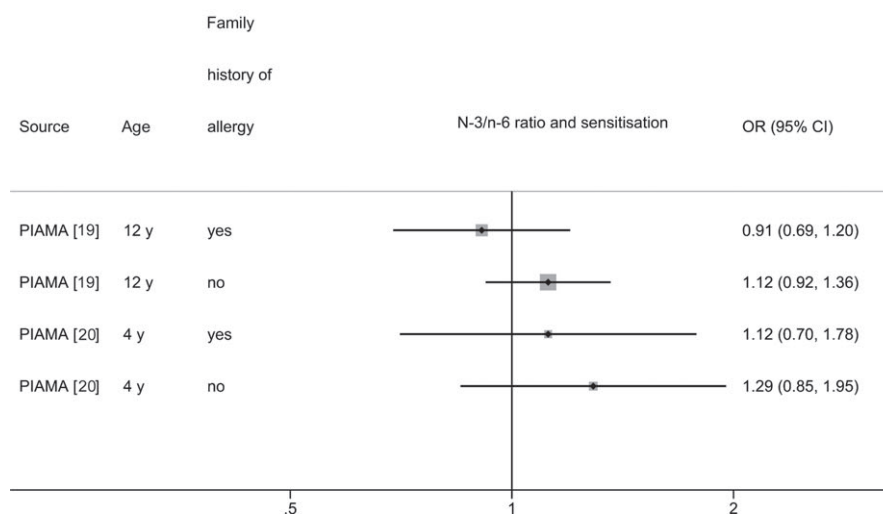


FIGURE 3 The association between breast milk PUFA and sensitisation

TABLE 4 The association between colostrum/breast milk fatty acids and asthma/wheeze

The association between n-3 and asthma/wheeze							
Study	Exposure	Exposure categorization	Age at which the outcome was tested	Results		Effect	
INMA study Morales et al 2013 (16)	Colostrum	Effect per w% increase in fatty acid of tertiles	14 mo (recurrent wheeze)	Fatty acid level	OR (95% CI)	No association	
				Lowest tertile	Ref		
				Highest tertile	1.08 (0.37-3.18)		
BACH & PEACH Soto-Ramirez et al 2012 (17)	EBM	Above the median as high level of exposure and below the median as low level of exposure in nmol/mg	6 or 12 mo	Fatty acid level	RR (95% CI)	<i>P</i> value	No association
				Low	Ref	.92	
				High	0.94 (0.30, 2.94)		
COPSAC birth cohort Giwerzman et al 2010 (15)	EBM	Effect per w% increase	2 y	—		No association ^a	
MACS Lowe et al 2008 (9)	Colostrum	Effect per w% increase	7 y	OR (95% CI)	<i>P</i> value	No association	
	EBM			Colostrum: 0.96 (0.69, 1.32)	.794		
				EBM: 0.74 (0.45, 1.20)	.224		
PIAMA Wijga et al 2006 (20)	EBM	Effect per IQR increase in w%		Children of mothers		n-3 protective	
			4 y	with allergy* OR (95% CI) per IQR	without allergy* OR (95% CI) per IQR	<i>P</i> value	
				0.50 (0.22, 1.13)	—	<.05	
van Elton (19)			14 y	0.50 (0.31, 0.79) <i>P</i> <.01	1.13 (0.94, 1.36)	<.01	n-3 is protective among the children mothers with allergy
The association between n-6 and asthma/wheeze							
Study	Exposure	Exposure categorization	Age at which the outcome was tested	Results		Effect	
INMA Morales et al 2013 (16)	Colostrum	Effect per w% increase in tertiles	14 mo	Fatty acid level	OR (95% CI)	No association	
				Lowest tertile	Ref		
				Highest tertile	0.44 (0.14, 1.37)		
BACH & PEACH Soto-Ramirez et al 2012 (17)	EBM	Above the median as high level of exposure and below the median as low level of exposure in nmol/mg	6 or 12 mo	Fatty acid level	RR (95% CI)	<i>P</i> value	n-6 increased the risk
				Low	Ref	.005	
				High	2.91 (1.37, 6.18)		
COPSAC birth cohort Giwerzman et al 2010 (15)	EBM	Effect per w% increase	2 y	—		No association ^a	
MACS study Lowe et al 2008 (9)	Colostrum	Effect per w% increase	7 y	OR (95% CI) (per w%)	<i>P</i> value	No association	
	EBM			Colostrum: 0.93 (0.67, 1.29)	.662		
				EBM: 1.07 (0.69, 1.67)	.751		

(Continues)

Table 4 (Continued)

PIAMA study Wijga et al 2006 (20)	EBM	Effect per IQR increase in w%		Children of mothers		P value	No association
				With allergy* OR (95% CI) (per IQR)	Without allergy* 95%(CI) (per IQR)		
			4 y	1.40 (0.71,2.76)	-		
van Elton (19)			14 y	1.00 (0.57, 1.78)	1.86 (1.14,3.03)	<.05	n-6 increased the risk among the children mothers without allergy
The association between n-3/n-6 and asthma/wheeze							
Study	Exposure	Exposure categorization	Age at which the outcome was tested	Results		Effect	
MACS Lowe et al 2008 (9)	Colostrum EBM	Effect per w% increase	7 y	OR (95% CI) Colostrum: 0.94 (0.68, 1.31) EBM: 1.31 (0.88, 1.96)	P value .712 .187	No association	
PIAMA study Wijga et al 2006 (20)	EBM	Effect per IQR increase in w%		Children of mothers		P value	n-3/n-6 ratio protective
				Mothers with allergy* OR (95% CI) (per IQR)	Mothers without allergy* OR (95% CI) (per IQR)		
			4 y	0.39 (0.16, 1.00) ^b	-	<.05	
van Elton (19)			14 y	0.55 (0.33, 0.92)	1.01 (0.82, 1.24)	<.05	n-3/n-6 ratio is protective among the children mothers with allergy

*P values were available only for some comparisons.

^aNumeric values not provided.

^bThe original paper reported n-6/n-3 ratio.

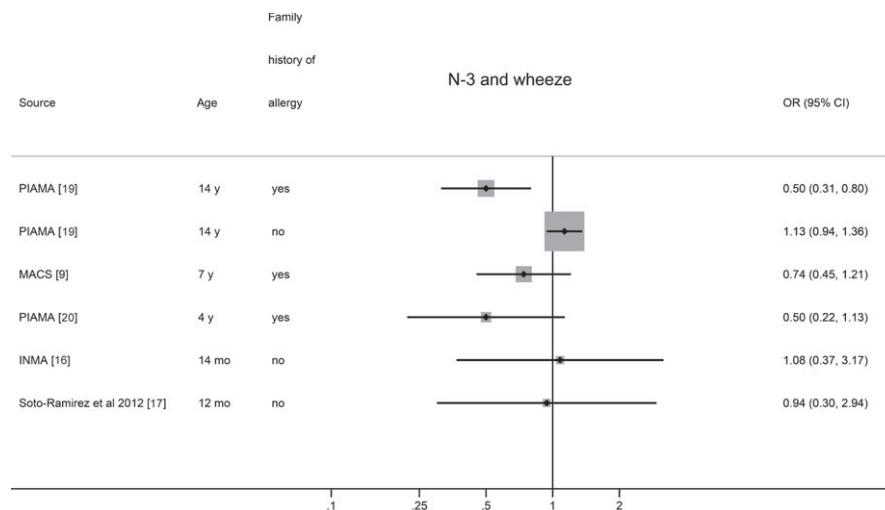
However, given the high proportion of studies of breast milk PUFA which have observed null results, it seems unlikely that strong publication bias is present in this literature.

How potential confounding was dealt with was highly variable between the studies included in this review. A number of publications did not adjust for potential confounding factors at all,^{21,22,24,27,28} leaving them at high risk of potential residual confounding. In contrast, other studies appear to have possibly over-adjusted these associations¹⁸⁻²⁰ by including factors that occur after the exposure of breast milk PUFA, such as children's BMI¹⁹ or respiratory tract infections in infancy.¹⁷ These postbreastfeeding variables are more likely to be mediating factors (pathways via which breast milk PUFA influences allergic disease outcomes), rather than confounding factors. Adjusting for such mediating factors could result in underestimation of the effect of breast milk PUFA on these outcomes. None of the included studies that detected associations formally investigated potential mediators for these associations.

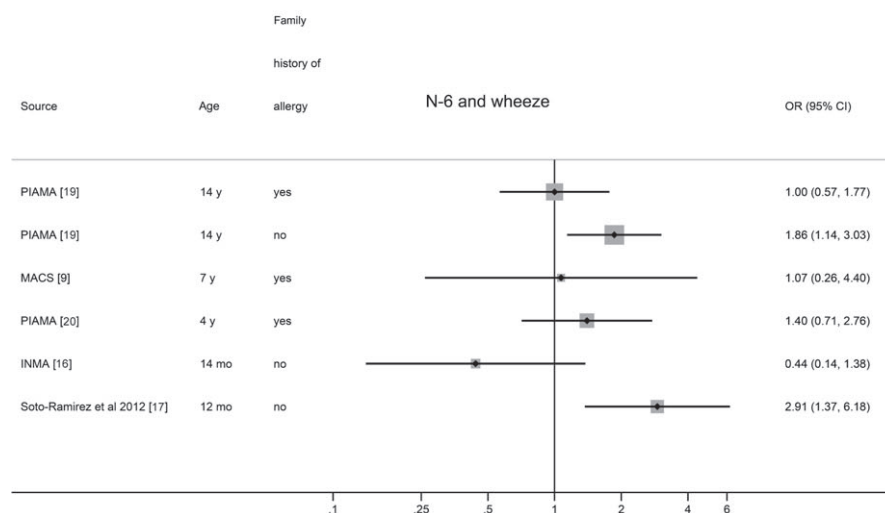
The published randomized controlled trials on early-life PUFA supplementation and childhood allergic disease and the observed effects are inconsistent. Two studies showed a risk reduction in allergic disease with n-3 supplementation,^{29,30} while the other trial³¹ found no benefit. While inconclusive at this time, there seems to be

some limited evidence that maternal supplementation with PUFA may be protective against allergic disease in the child. In contrast, the results of our systematic review based on naturally occurring colostrum and breast milk PUFA did not demonstrate any clear associations. The evidence based on PUFA supplementation trials to pregnant and lactating mothers is not directly comparable to the results reported in the observational studies summarized in this review, as the supplemented dose is far greater than the biological dose that can be obtained from a normal diet.³² Furthermore, there are a number of factors that influence the transfer of maternal dietary supplementation with PUFA into breast milk.³² For example, fatty acid desaturase enzyme level in mammary glands is a rate-limiting step in the metabolism of PUFA pathway.³³ These factors may create a disconnect between associations between maternal intake of PUFA and measured breast milk PUFA, and the associations with outcomes in the child.

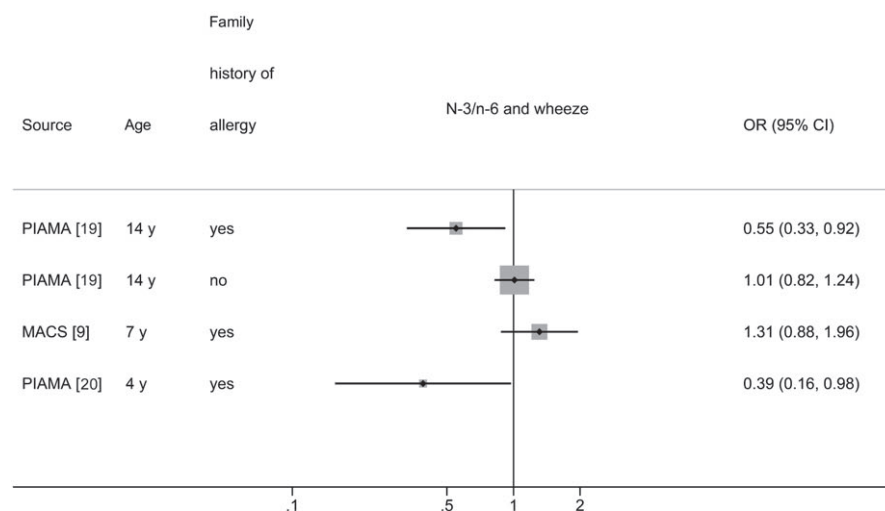
In conclusion, we observed a few associations between levels of PUFAs in breast milk and allergic disease outcomes, and these associations were relatively inconsistent. Therefore, based on this review, there is currently insufficient evidence to warrant modifying the dietary exposures to PUFA to influence the colostrum or breast milk fatty acids as a preventive strategy for later childhood allergic disease outcomes.



Effect – PIAMA per IQR increase, MACS per w% increase, INMA per tertile increase, Soto Ramirez nmol/mg above median



Effect – PIAMA per IQR increase, MACS per w% increase, INMA per tertile increase, Soto Ramirez nmol/mg above median



Effect – PIAMA per IQR increase, MACS per w% increase

FIGURE 4 The association between breast milk PUFA and wheeze

5 | SUMMARY

The evidence available to date is inadequate to determine whether colostrum or breast milk fatty acids influence the risk of allergic diseases in children. During the next 5 years, there will be an increase in the number of studies published with larger sample sizes and longer follow-up time. If researchers can find the biological mechanism for this association, then interventions may help to reduce childhood immune-mediated disorders.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

AJL and NW devised the review protocol and search strategy. NW and GB reviewed all titles and abstracts for eligibility, and confirmed this by examination of full-text papers. NW extracted data from the original papers, and GB checked these data. All authors contributed to interpreting of the data, drafting the manuscript, to the intellectual content, and for the revising of the final draft of the manuscript. The final version of the manuscript was approved by all the authors.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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