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Formula and breast feeding in infant food allergy: a population-based study

Original Article

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Abstract

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Aim

To determine whether infant feeding practices, including duration of exclusive breastfeeding and use of partially hydrolysed formula, modify the risk of developing infant food allergy.

Method

In an observational population-based study one year olds were recruited from community immunisation clinics in Melbourne, Australia. Parent-reported data on infant feeding practices and potential confounders were collected, prior to infant skin prick testing for four food allergens. Sensitised infants attended hospital-based oral food challenges to establish food allergy status. Multiple logistic regression was used to investigate associations between breastfeeding and formula feeding and infant food allergy adjusting for possible confounding variables.

Results

A total of 5276 (74% response) infants participated. Of the 4537 for whom food allergy status was determined, 515 (11.3%) were food allergic (challenge-proven in the context of SPT positive (≥2mm). After adjusting for confounding variables there was no association between duration of exclusive breastfeeding and food allergy. Use

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of partially hydrolysed formula did not reduce the risk of food allergy compared to cow's milk formula in the general population (adjusted OR 1.03 [CI 0.67-1.50]).

Conclusions

Duration of exclusive breastfeeding and use of partially hydrolysed formula were not associated with food allergy at one year of age in this large population-based study. These findings have implications for population-based infant feeding guidelines and do not support the use of partially hydrolysed formula for food allergy prevention.

Key words

Food allergy, breastfeeding, infant formula, infant feeding, allergy prevention.

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What is already known about this topic

- The effect of duration of breastfeeding on the risk of developing food allergy is controversial.
- Randomised controlled trials of partially hydrolysed formula for the prevention of allergic disease in high-risk infants have produced conflicting results. None have examined the relationship between partially hydrolysed formula and food allergy in infants without a family history of allergy.
- Infant feeding guidelines have recommended partially hydrolysed formula for high-risk bottle-fed infants in the first 4-6 months, despite limited evidence.

What this paper adds

- Duration of exclusive breastfeeding was not associated with infant food allergy after adjusting for all known important confounding variables.
- Partially hydrolysed formula was not associated with infant food allergy in infants with or without a family history of allergic disease.
- Use of partially hydrolysed formula was common in infants with and without a family history of allergic disease, despite guidelines recommending partially hydrolysed formula only for a subset of high-risk infants.

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Introduction

Food allergy is an important health problem in Australian children. Australia has amongst the highest prevalence of allergic disease in the developed world[1]. Allergic diseases, including asthma, eczema, allergic rhinitis and food allergy, have a significant burden and major health, economic and quality of life impact for Australia's children[2–4]. Food allergy has risen rapidly in recent decades. Australian hospitalisations for food-related anaphylaxis have dramatically increased since 1990, particularly in the 0-4 years age group[5,6] in line with trends in the US[7] and UK[8]. We have previously shown that food allergy affects around 10% of one-year-old infants in Melbourne, Australia[9].

Identifying the modifiable determinants of food allergy is important to address the economic, social and pathophysiological burden in children. Early childhood factors such as the type and duration of infant feeding have been postulated as likely to be important in the development of childhood allergies[10]. Infant feeding is a modifiable factor that can be targeted through population guidelines. Current guidelines lack strong evidence to inform infant feeding recommendations with regards to allergy prevention, specifically prevention of food allergy[11–13].

Whilst breastfeeding is widely accepted as the food of choice for infants, its relationship to the development of allergic disease is controversial[11]. Various studies have shown either a protective benefit, no effect or increased risk[14,15]. There is also limited evidence to substantiate current guidelines, both nationally and

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internationally, that advocate the use of partially hydrolysed formula for allergy prevention in high-risk bottle fed infants in the first 4-6 months[11,13,16,17]. Randomised controlled trials examining partially hydrolysed formula for the prevention of allergic disease in high-risk infants have produced conflicting results. In addition, none have examined the relationship between partially hydrolysed formula and food allergy in infants without a family history of allergy.

This article focuses on the impact of breastfeeding and formula feeding food allergy at one year of age. Using data from a large population-based study, we examine whether food allergy is associated with (1) duration of exclusive breastfeeding and (2) the type of infant formula used, in those with and without a family history of allergy.

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Methods

HealthNuts study methods have been detailed previously[18]. HealthNuts is a population-based, observational study investigating modifiable risk factors for paediatric food allergy. 12-month-old infants were recruited from immunisation clinics in Melbourne. Written informed consent was obtained from parents. Parents completed a questionnaire ascertaining infant feeding practices and potential confounding variables. Infants underwent skin prick testing (SPT) using single-tine lancets to four foods (hen's egg, peanut, sesame, and either cow's milk [n=2725] or shrimp [n=2551]) with a positive histamine and negative saline control. Infants with any detectable wheal on SPT were invited to attend the Royal Children's Hospital allergy clinic for repeat SPT with an extended panel of foods (egg, peanut, sesame, milk, shrimp, hazelnut, almond, cashew, soy and wheat) and oral food challenge (OFC). OFCs were performed to egg, peanut and sesame using predetermined stopping criteria of objective allergic signs occurring within two hours of the last dose of allergen. Challenges were called positive if an infant developed one or more of the following: ≥3 concurrent non-contact urticaria lasting 5 minutes or more; perioral/periorbital angioedema; vomiting; or circulatory or respiratory compromise, within 2 hours of ingestion of a challenge dose. Details of reactions occurring during challenge have been published previously. [19]

Definitions

Food allergic: A positive OFC in the context of a positive SPT (wheal ≥2mm) to that food or ≥8mm to unchallenged foods (tree nuts, shrimp, soy or wheat).

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Not food allergic: A negative SPT in the community to all four foods in the context of a positive histamine control, or a negative OFC in sensitised infants.

Cow's milk allergic: A parent-reported immediate (<1 hour) reaction (urticaria, angioedema, vomiting or anaphylaxis) to cow's milk in the context of a positive SPT (≥2mm).

High risk of allergy: parent-reported allergic disease (asthma, eczema, allergic rhinitis or food allergy) in at least one first-degree family member (parent or sibling).

Low risk of allergy: parent-report of no allergic disease in first-degree family members.

Exclusive breastfeeding: Breastfeeding without concurrent infant formula, solids or semi-solids.

Formula type: Formula use was categorized as cow's milk, partially hydrolysed, or soy. Other formula types were excluded due to heterogeneity of types, relevance to population guidelines, and small numbers (n<50). Extensively hydrolysed and amino acid formulas are available by specialist prescription for allergic infants, and thus are of limited population relevance.

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Statistical analysis

We used a separate multivariable logistic regression model for each of the two primary exposures (duration of exclusive breastfeeding and type of formula) to quantify the association with food allergy reported as odds ratios (OR) and 95% CIs. Each model was adjusted for confounders identified from published literature: family history of allergy, infant eczema status during breastfeeding, parent reported reactions to cow's milk in the infant and age of introduction of egg[20–22]. Additional potential confounders were retained if they changed the magnitude of the association between either of the exposures and food allergy by more than 10% or were associated with both the exposure and the outcome with a P value <0.05. These included maternal smoking during pregnancy, household smoking, preterm delivery (≤36 weeks), number of siblings, maternal country of birth, socioeconomic status via SEIFA (a summary measure of socio-economic conditions developed by the Australian Bureau of Statistics[23]) and infant eczema status during formula feeding. Only data that was complete for all exposures, important confounders, and outcomes were included.

A sample size of 5000 infants was calculated to provide sufficient power to detect risk factors present in at least 10% of the population given a prevalence of food allergy of 5-10%. This sample sizeprovides 98% power to detect an OR of 1.75 assuming food allergy prevalence of 10%. In our study, 10.5% of infants used partially hydrolysed formula.

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Analyses investigated the relationship between infant feeding and food allergy separately among low and high-risk infants based on an *a priori* decision. We also tested for interactions by comparing models with and without interaction terms using the likelihood ratio test.

Stata software (release 12.0; StataCorp, College Station, Texas) was used for all analyses.

Ethics approval

Ethics approval was obtained from the Victorian State Government Office for Children (reference no. CDF/07/492), Victorian State Government Department of Human Services (reference no. 10/07), Royal Children's Hospital Melbourne (reference no. 27047A) and University of Notre Dame Australia (reference no. 012043S) ethics committees.

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Results

Study population

Of 7134 infants approached at community immunisation clinics, 5276 (74%) participated. Of these, 1089 infants were invited for hospital-based allergy testing. 928 (85%) attended and completed further SPT and OFC. Overall, food allergy status was determined for 4537 (86%) infants. Of these, 515 (11.3%) were food allergic (456 egg allergic, 153 peanut allergic, 35 sesame allergic) and 27 classified as cow's milk allergic. Table 1 details characteristics of the study population.

Rates of any breastfeeding were high with 94.3% breastfed in the first month and 64.9% at six months (Figure 1). Formula feeding was also common with 67.3% (3066) infants being fed formula, either alone or concurrently with breastfeeding, at some stage during the first 12 months. The majority (82%) of formula fed infants used cow's milk formula, however 16% of high-risk and 13% of low risk formula fed infants used partially hydrolysed formula. Use of formula alone rose from 6.4% in the first month, to 37.1% at six months, and 37.5% at 12 months.

Duration of exclusive breastfeeding and infant food allergy

There was no evidence of a relationship between the duration of exclusive breastfeeding and infant food allergy after adjusting for confounding variables. Stratification by family history of allergy showed that food allergy was more common in the high-risk cohort, as would be expected. However duration of exclusive breastfeeding was not associated with food allergy in either the high or low risk group

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either before or after adjustment (Table 2). There was no evidence of an interaction between allergy risk and the exclusive breastfeeding and food allergy relationship (P = 0.459).

Type of formula and infant food allergy

Use of partially hydrolysed formula did not alter the risk of infant food allergy, compared to cow's milk formula. Unadjusted ORs suggested soy formula increased the risk of food allergy relative to cow's milk formula, however no association was evident after adjusting for confounding variables. The association between soy formula and food allergy in the unadjusted analysis was explained by confounding due to infant history of allergic disease. Infants with eczema and those with parent reported reactions to cow's milk formula were both more likely to use soy formulas and to have a food allergy (data not shown). Adjustment for these factors reduced the magnitude of the association between soy formula and food allergy by >20%. Stratification according to low versus high-risk infants yielded similar results with aORs close to 1.00 (not significant) in both risk categories (Table 3). Family history of allergy did not significantly interact with the relationship between food allergy and formula type (p=0.72).

Infant feeding and cow's milk allergy

Of the 2,725 infants who underwent SPT to cow's milk, 2.2% had a SPT ≥ 2mm. Of these 45% had a parent reported history of reaction to cow's milk consistent with an IgE-mediated reaction, thus 1.0% (n=27/2725) were considered cow's milk allergic.

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There was no evidence of an association between duration of breastfeeding, or type of infant formula used, and cow's milk allergy at one year of age after adjusting for confounding variables (Tables 4&5).

Discussion

In a large population-based study of one year old infants, neither duration of exclusive breastfeeding nor use of partially hydrolysed formula were associated with food allergy. Contrary to infant feeding recommendations, the use of partially hydrolysed formula was common, even for infants without a family history of allergic disease. For soy formula, the apparent increased risk of food allergy was significantly reduced after adjusting for confounders. This is the first large, population-based study to investigate the relationship between use of partially hydrolysed formula and the gold standard measure of challenge-proven infant food allergy in the general population.

Failure to adjust for confounders of the relationship between breastfeeding and food allergy can lead to the reporting of potentially spurious associations, in particular an increased risk of food allergy or sensitisation in breastfed infants[24–27]. An analysis of breastfeeding and nut allergy, which did not adjust for any recognised confounders, found an increase in parent-reported nut allergy in breastfed infants[27]. Our unadjusted findings also found a spurious, although weak, association between longer breastfeeding and an increased risk of food allergy. Adjusting for confounders eliminated the association. Our data is consistent with a meta-analysis of breastfeeding and eczema, which found that any protective benefit of longer duration

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of breastfeeding for childhood allergic disease was lost after adjusting for other confounding factors[28].

The evidence that hydrolysed formula reduces the risk of allergic disease, including food allergy, remains weak. However infant feeding guidelines internationally have recommended hydrolysed formula for bottle-fed, high-risk infants. Two randomised controlled trials have addressed the impact of hydrolysed formulas on allergic manifestations yielding contradictory results. A German randomised controlled trial (GINI) comparing three hydrolysed formulas with cow's milk formula in 2252 high-risk infants found both extensively hydrolysed casein formula and partially hydrolysed whey formula were protective for atopic dermatitis and a diagnosis of any allergic manifestation in the first year of life[29]. In contrast, a recently published Australian randomised controlled trial (MACS) in 620 high-risk infants comparing partially hydrolysed formula and cow's milk formula found no difference in allergic outcomes in the first two years[30]. Neither study measured food allergy using the gold standard OFC and both were limited to high allergy risk cohorts. The Cochrane review of hydrolysed formulas, conducted prior to publication of the MACS findings, concluded that there is some evidence, although limited, that use of a hydrolysed formula compared to a cow's milk formula reduces infant cow's milk allergy [36].

It has been hypothesised that hydrolyzing cow's milk formula, through enzymatic breakdown of proteins reduces exposure to intact proteins and, may reduce sensitisation and thus development of allergic disease[31]. Our findings are consistent

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with recent evidence suggesting that allergen avoidance may not be effective in preventing allergy. The new concept of a window of opportunity[31] proposes that early exposure to potentially allergenic foods may promote persistent oral tolerance. Evidence supporting this concept has been reported for egg[22], peanut[32] and cow's milk[33]. Katz et al. found lower rates of cow's milk allergy amongst Israeli infants who were exposed to cow's milk formula within the first 14 days of life, suggesting early exposure to cow's milk protein might promote tolerance[34]. It is possible that very early exposure may modify the development of cow's milk allergy and that the timing of the window of opportunity for promoting tolerance is earlier for milk compared with egg[22,34]. This is supported by the findings that infants introduced to milk at 4-6 months were more likely to be milk allergic[34], while in a separate study, introduction of egg at 4-6 months was found to be protective[22].

A possible explanation for our findings is that most infants were predominantly breastfed for the first 4-6 months of life and exposure to cow's milk protein was not at sufficient amounts at the appropriate developmental opportunity to develop tolerance. That is to say, the protective effect of formula might relate to the timing, rather than type, of formula exposure. Similarly both the GINI and MACS study cohorts had a high rate of breastfeeding in the first six months which may also explain the null effect of formula for the protection of allergic disease[29,30].

Key strengths of this study include a high community recruitment rate, large sample size, and standardised, well-defined food allergy criteria including OFC. The study

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included a representative population sample,[18] and infants across the spectrum of allergy risk (ie infants with and without a family history of allergic disease), thus enabling translation of findings to the general population.

Observational studies offer the only practical and ethically feasible approach to studying breastfeeding associations since breastfeeding is the preferred infant food. Compared to a randomised trial, our observational study is ethically feasible and likely to be more representative of population infant feeding practices. Randomised controlled trials comparing different formula types for the prevention of food allergy among those who choose not to exclusively breastfeed are feasible, however to date these have only been conducted in high risk infants. A large population-based randomised controlled trial of partially hydrolysed formula compared with cow's milk formula could theoretically be undertaken, however this would require a very large sample size to investigate the effect among low-risk infants and infants without a family history of allergy are likely to be difficult to recruit to an allergy study.

The use of parent-reported questionnaire (completed at recruitment when the child was 11-15months) is subject to recall error. Questionnaire data was collected prior to food allergy testing, therefore recall is likely to be non-differential between the allergic and non-allergic groups. Family history of food allergy or infant eczema might also impact on recall, however we have adjusted for these factors in our analysis.

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Our analysis of cow's milk allergy was likely underpowered to detect associations as Ig-E mediated cow's milk allergy was rare at twelve months, however this was not the primary outcome and was included as a secondary analysis.

Our study examined food allergy at one year. How breastfeeding practices affect the development of allergic disease, particularly asthma, in the longer term remains unclear. Further follow-up of the HealthNuts cohort, which is currently underway, may yield further insights. Previous studies have found that associations change during childhood. In a population based longitudinal study of 8280 Australian infants, exclusive breastfeeding for the first three months was associated with a reduced risk of parent reported food allergy at seven years, but an increased risk in adult life[35].

Early signs of atopic disease (ie visible infant eczema) are known to have an important influence on maternal infant feeding decisions[20]. This study was able to control for this, thus taking into account the potential for reverse causation. This study also adjusted for other important known potential confounders including family history of allergy, parental smoking history, timing of introduction of solids, and parent report of infant food reactions. As in all observational studies, we are unable to completely exclude the possibility of confounding by unknown factors.

In conclusion although partially hydrolysed formula is currently recommended for high-risk bottle-fed infants, uptake of guidelines appears to be variable. Although use of partially hydrolysed formula is common, it is not restricted to the recommended

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high-risk population. This supports the likelihood that infant feeding choices are informed by numerous influences, including community beliefs, understandings of allergy risk, formula types and guidelines, health professional advice, and advertising influences**.** Thus our data on the use of infant formula, and effect of partially hydrolysed formula on allergic disease at a population level, have important implications for population based infant feeding guidelines.

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Figure legends

FIGURE 1. Formula use and breastfeeding in the first 12 months†
†percentages do not add up to 100% because some infants were no longer breastfeeding or formula feeding.

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Tables

TABLE 1. Demographic, infant feeding and allergy risk variables of the study cohort defined by food allergy status (column percentages)

Characteristic	Not food allergic, n (%)	Food allergic, n (%)
Total	4044 (88.7)	515 (11.3)
Infant feeding variables		
Completed months of exclusive breastfeeding (n=3841)		
0	1007(29.6)	116(26.7)
1	219(6.4)	20(4.6)
2	138(4.1)	19(4.4)
3	200(5.9)	23(5.3)
4	464(13.6)	62(14.3)
5	606(17.8)	96(22.1)
6	710(20.9)	91(21.0)
>6m	63(1.9)	7(1.6)
Use of formula (n=2958)		
Cows milk formula	2225(82.5)	255(76.8)
Partially hydrolysed	421(15.6)	57(17.2)
Soy	51(1.9)	20(6.0)
Allergy risk variables		
Family history (n=4559)		
Immediate family history of allergy	2754(68.1)	397(77.1)

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(asthma, food allergy, allergic rhinitis or eczema in a first degree relative)		
No immediate family history of allergy	1290(31.9)	118(22.9)
Eczema status and breastfeeding (n=4267)		
No eczema	3082(81.3)	192(40.2)
Eczema while breastfeeding	452(11.9)	234(49.1)
Eczema after breastfeeding	256(6.8)	51(10.7)
Eczema and formula use (n=4274)		
No eczema	3082(81.1)	192(40.3)
First eczema before formula feeding started	360(9.48)	171(35.9)
First eczema after formula feeding started	356(9.37)	113(23.7)
Other infant variables		
Gender (n=4515)		
Male	2017(50.2)	297(57.8)
Female	2003(49.8)	217(42.2)
Preterm delivery (n=4330)		
Preterm delivery (≤36weeks)	249(6.5)	17 (3.5)
>36 weeks gestation	3595(93.5)	469(96.5)
Number of siblings (n=4515)		
No siblings	1937(48.4)	290(56.7)
1 sibling	1349(33.7)	159(31.1)

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2 siblings	532(13.3)	51(10.0)
3 or more siblings	185(4.6)	11(2.2)
Mother's country of birth (n=4451)		
Australia	2942(74.5)	320(63.5)
Europe	367(9.3)	47(9.3)
East Asia	303(7.7)	94(18.7)
Other	335(8.5)	43(8.5)
SES via SEIFA quintiles (n=4545)		
1 (least disadvantaged)	828(20.5)	76(14.8)
2	792(19.6)	117(22.8)
3	855(21.2)	101(19.7)
4	787(19.5)	110(21.4)
5 (most disadvantaged)	769(19.1)	110(21.4)
Maternal smoking during pregnancy (n=4429)		
Yes	197(5.0)	12(2.4)
No	3734(95.0)	486(97.6)
Parent reported reaction to cow's milk formula (n=4453)		
Yes	186(4.7)	89(17.8)
No	3766(95.3)	412(82.2)
Age at first introduction of egg products (n=4353)		
<4 months	35(0.9)	6(1.2)
4-6 months	989(25.4)	92(18.9)
7-9 months	1575(40.5)	178(36.5)
10-12 months	1170(30.1)	154(31.6)

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>12 months	119(3.1)	57(11.7)

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TABLE 2. Relationship between duration of exclusive breastfeeding and infant food allergy stratified by low risk versus high risk

	Low risk infants (n=977)					High risk infants (n=2236)				
Completed months of exclusive breastfeeding	**Food allergic (%)**	**OR (95% CI)**	**P value**	**aOR (95% CI)†**	**P value**	**Food allergic (%)**	**OR (95%CI)**	**P value**	**aOR (95% CI)†**	**P value**
0	7.19	1.00		1.00		10.74	1.00		1.00	
1	6.25	0.86(0.31-2.36)	0.770	1.09(0.36-3.32)	0.884	8.53	0.77(0.40-1.51)	0.454	0.74(0.37-1.49)	0.399
2	8.33	1.17(0.38-3.58)	0.779	1.17(0.34-3.99)	0.804	13.04	1.24(0.65-2.41)	0.511	1.09(0.54-2.22)	0.804
3	7.69	1.08(0.39-2.97)	0.888	1.10(0.35-3.47)	0.868	11.48	1.08(0.58-1.99)	0.811	1.11(0.57-2.15)	0.756
4	13.07	1.94(1.02-3.70)	0.044	1.52(0.71-3.27)	0.285	9.77	0.90(0.57-1.41)	0.651	0.77(0.47-1.27)	0.303
5	8.18	1.15(0.56-2.36)	0.705	1.10(0.48-2.55)	0.815	14.73	1.44(1.00-2.06)	0.051	1.38(0.92-2.08)	0.126
6	6.67	0.92(0.44-1.92)	0.828	0.59(0.25-1.43)	0.246	13.21	1.27(0.88-1.81)	0.200	1.07(0.72-1.61)	0.728

†Adjusted for infant eczema that occurred during breastfeeding, family history of allergic disease, maternal smoking during pregnancy, preterm delivery (<38weeks), number of siblings, maternal country of birth, SES via SEIFA and age of introduction of egg.

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TABLE 3. Relationship between type of formula and infant food allergy stratified by low risk versus high risk infants

	Low risk infants (n=764)					High risk infants (n=1625)				
Type of Formula	**% Food allergic (n)**	**OR (95%CI)**	**P value**	**aOR (95%CI)†**	**P value**	**% Food allergic (n)**	**OR (95%CI)**	**P value**	**aOR (95% CI) †**	**P value**
Cow's milk	8.29 (54)	1.00		1.00		10.84 (142)	1.00		1.00	
Partially hydrolysed	6.86 (7)	0.81(0.36-1.84)	0.623	0.81 (0.33-1.94)	0.633	12.73(35)	1.20 (0.81-1.78)	0.367	1.09(0.72-1.67)	0.684
Soy	27.27 (3)	4.15(1.07-16.09)	**0.040**	1.06(0.17-6.65)	0.946	22.50 (9)	2.39 (1.11-5.12)	**0.025**	1.32(0.56-3.13)	0.524

†Adjusted for infant eczema that occurred during breastfeeding, infant eczema that occurred before formula feeding, family history of allergic disease, maternal smoking during pregnancy, preterm delivery (<38weeks), parent reported reactions to cow's milk formula, and age of introduction of egg.

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TABLE 4. Relationship between duration of exclusive breastfeeding and cow's milk allergy among 2725 infants who underwent skin prick testing to cow's milk

Completed months of exclusive breastfeeding	**N.**	**Cow's milk allergy**	**OR (95% CI)**	**P value**	**aOR (95% CI)†**	**P value**
0	499	0.6(3)	1.00		1.00	
1	121	0(0)	1.00	-	1.00	-
2	81	0(0)	1.00	-	1.00	-
3	114	0.88(1)	1.46(0.15-14.20)	0.743	1.33(0.12-14.42)	0.815
4	296	0.68(2)	1.12(0.19-6.77)	0.898	0.43(0.06-3.08)	0.400
5	357	1.68(6)	2.83(0.70-11.38)	0.144	1.54(0.33-7.11)	0.582
6	351	2.85(10)	4.84(1.32-17.75)	**0.017**	3.19(0.76-13.34)	0.113

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†Adjusted for infant eczema that occurred during breastfeeding, family history of allergic disease, maternal smoking during pregnancy, preterm delivery (<38weeks), number of siblings, maternal country of birth, SES via SEIFA and age of introduction of egg.

TABLE 5: Relationship between type of formula and cow's milk allergy among 2725 infants who underwent skin prick testing to cow's milk

Type of formula	**N**	**% Cow's milk allergy (n)**	**OR (95% CI)**	**P value**	**aOR (95% CI)†**	**P value**
Cow's milk	1084	0.74(8)	1.00		1.00	
Partially hydrolysed	242	1.65(4)	2.26(0.68-7.57)	0.186	3.05(0.76-12.22)	0.116
Soy	26	3.85(1)	5.38(0.65-44.66)	0.119	1.48(0.11-19.11)	0.766

†Adjusted for infant eczema that occurred during breastfeeding, infant eczema that occurred before formula feeding, family history of allergic disease, maternal smoking during pregnancy, preterm delivery (<38weeks), parent reported reaction to cow's milk formula, and age of introduction of egg.

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Supplementary Table: Sensitivity analysis of the relationship between duration of exclusive breastfeeding and infant food allergy stratified by low risk versus high risk.

	Low risk infants		High risk infants	
Completed months of exclusive breastfeeding	**Original analysis aOR†**	**Sensitivity analysis* aOR†**	**Original analysis aOR†**	**Sensitivity analysis* aOR†**
0	1.00	1.00	1.00	1.00
1	1.09	1.15	0.74	0.72
2	1.17	1.05	1.09	1.21
3	1.10	1.49	1.11	1.10
4	1.52	1.32	0.77	0.84
5	1.10	1.18	1.38	1.33
6	0.59	0.64	1.07	1.05

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†Adjusted for infant eczema that occurred during breastfeeding, family history of allergic disease, maternal smoking during pregnancy, preterm delivery (<38weeks), number of siblings, maternal country of birth, SES via SEIFA and age of introduction of egg.

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* For the sensitivity analysis, infants with a SPT wheal size at or above the 95% positive predictive value for positive oral food challenge (Peters et al J Allergy Clin Immunol 2013), and those with a parent-reported history of reaction, were classified as food allergic. Those with no parent-reported reaction history and SPT wheal size less than the 95% PPV were classified as tolerant. Using this definition, of the 161 who failed to attend oral challenge clinics, 46% were classified as food allergic and the remainder (54%) as tolerant.

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