

Breastfeeding and introduction of complementary foods during infancy in relation to the risk of asthma and atopic diseases up to 10 years

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Summary

Background It has been hypothesized that changes in diet during early life may have contributed to the increase in childhood asthma and atopy. The long-term effect of the timing and content of infant feeding on the incidence of asthma and atopic diseases in children is unclear.

Objective To investigate the associations between duration of breastfeeding and the timing of introduction of complementary foods during the first 6 months and parental-reported asthma, wheeze and atopic eczema up to 10 years of age.

Methods Infant feeding practices (breastfeeding and introduction of complementary foods) of 1924 singleton children participating in the Study of Eczema and Asthma To Observe the Influence of Nutrition (SEATON) birth cohort were prospectively collected up to 6 months with outcomes (wheeze, atopic eczema and asthma) being assessed at 1, 2, 5 and 10 years. Data were analysed using generalized estimating equations and discrete hazards models with adjustment for confounders.

Results By 6 months, 59% and 35% of mothers had stopped exclusive and total breastfeeding, respectively. Although formula feeding was adversely associated with wheeze in the past 12 months (adjusted OR for no formula feeding: 0.70, 95% CI 0.50–0.97), and the introduction of biscuits/bread after 5 months of age adversely associated with atopic eczema (adjusted OR 1.34, 95% CI 1.06–1.69), these results lost their statistical significance after adjustment for multiple testing. Stratification of the results by the presence of eczema by 6 months of age and family atopic history did not substantially differ from the results of the whole study population.

Conclusion and Clinical Relevance Our results suggest that the nature of infant feeding during the first 6 months seems not to substantially influence the long-term risk of asthma and atopic diseases in children, nor in children at high risk of atopic disease because of a family history of atopic disease.

Keywords asthma, breastfeeding, children, complementary foods, eczema, formula feeding, wheeze

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Introduction

Whilst it is universally acknowledged that breastfeeding is the optimal feeding option for infants and their mothers, debate continues as to the role of breastfeeding and the timing of introduction of complementary foods as a preventative strategy for childhood asthma and atopic diseases. The recommendation of expert

bodies is that children should be exclusively breastfed for 4–6 months and that complementary foods should be introduced between 4–6 months [1–4]. The benefits of exclusive breastfeeding for at least 4 months include a reduction in wheezing episodes (up to age 4 years) and atopic dermatitis (AD), particularly in children at high risk of atopic disease by virtue of a family history of atopic disease [1, 2]. These recommendations

acknowledge that the longer term effects of breastfeeding on the likelihood of childhood asthma are unclear, citing studies reporting adverse associations between breastfeeding and an increased risk of childhood asthma [1–4]. The expert panels also highlight the need for further research on the long-term effects of infant feeding on the development of childhood asthma and atopic diseases.

Studies conducted since the publication of the expert panel recommendations have been conflicting. While some studies [5–10] have reported a decreased risk of asthma and atopic diseases with exclusive breastfeeding for at least the first 3–4 months, others [11, 12] have observed no association. For timing of introduction of complementary foods, studies have either demonstrated no association between the early (< 4 months) introduction and asthma/atopic disease [13, 14], or found that late introduction (> 4–6 months) of complementary foods may increase the risk of asthma and/or atopic outcomes in children [15–22]. A recent Cochrane Review of the literature concluded that exclusive breastfeeding for 6 months (vs. 3 to 4 months, with continued mixed breastfeeding thereafter) has no long-term impact on atopic disease [23]. Reverse causality has been suggested as a possible explanation for the reported associations, whereby parental knowledge that their child is at high risk of atopic disease influences breastfeeding behaviour and/or decision on when to introduce complementary foods [24]. The issue of reverse causality has been addressed in recent studies by either excluding high-risk children [5, 9, 10, 14–18] or by performing analyses stratified by atopic risk by virtue of family atopic history or early atopic manifestations in the child [6, 13, 18–22].

We have recently completed the 10-year follow-up of the Study of Eczema and Asthma To Observe the Influence of Nutrition (SEATON) birth cohort that was established to prospectively investigate the associations between early life dietary exposures and childhood asthma and atopic diseases. The study included the prospective collection of data on breast/formula feeding and the timing of introduction of complementary foods. The recommendation at the time was that complementary foods be introduced at 3 months. This 10-year follow-up enabled us to investigate the associations between infant feeding during the first 6 months and the longitudinal development of asthma and atopic diseases up to the age of 10 years. We were also interested to see whether early atopic manifestations and family history of atopy modified the associations between the timing of infant feeding and the asthma and atopic outcomes. Recognizing that the term 'complementary food' is varying used in the literature, we use it in this article to indicate the addition of other foods, including water, to the child's diet alongside breastfeeding.

Methods

Subjects and assessment of outcomes

Details of the SEATON birth cohort have been described elsewhere [25, 26]. Briefly, 2000 healthy pregnant women attending an antenatal clinic, at median 12 weeks gestation, were recruited in 1997/8. An interviewer administered questionnaire collected data on demographics and potential confounding factors. In addition to ascertaining whether the pregnant woman and her partner had histories of asthma, eczema and hayfever, the atopic status of recruited women was ascertained by skin prick testing using ALK lancets and solutions, (ALK, Reading Berkshire, UK) testing for house dust mite (*Dermatophagoides pteronyssinus*), timothy grass pollen, cat fur and saline. A positive skin prick test was defined as a mean wheal diameter of ≥ 3 mm than the negative control [25, 26]. There was no selection for asthma or atopic disease. The ensuing cohort of 1924 live singleton births was followed up at 6 months, 1, 2, 5 and 10 years using postal questionnaires (with a single reminder) to ascertain the presence of respiratory and atopic symptoms, which were reported by the parents of the children. The questions were those used in the International Study of Asthma and Allergies in Childhood (ISAAC) [27], specifically 'wheeze ever', 'wheeze in the last 12 months', 'wheeze in the absence of colds', and 'doctor diagnosis of'; 'asthma', 'eczema' and 'hayfever', with supplementary questions enquiring about the presence of these conditions in the previous 12 months. The follow-up questionnaires did not enquire about food allergies. The study was approved by the North of Scotland Research Ethics Committee. Written parental consent was obtained, and children gave verbal assent.

Dietary assessment

Infant feeding data (breastfeeding, formula feeding, and introduction of complementary foods) were collected prospectively. All mothers of study children were visited on the post-natal ward by the study nurses who provided each mother with a card *pro forma* upon which to record the dates in the ensuing 6 months when formula feeding was introduced, breastfeeding stopped and the dates of introduction of complementary foods (fruit juice, cows' milk/milk products, rice/cereal, vegetables, fruits, biscuits/bread, meat, fish and eggs). The nurses asked mothers to complete the card as the listed foods were introduced and to return it with the 6-month follow-up questionnaire. In total 83% ($n = 1590$) of mothers returned completed dietary cards, approximately 10% of questionnaires were returned after 6 months.

Statistical analysis

The outcomes of interest in this study were parental reports of asthma, wheeze and atopic eczema in the study children at ages 1, 2, 5 and 10 years. The exposures of interest were ever breastfeeding (if the child was ever given breast milk), duration of exclusive breastfeeding (breastfeeding but no formula or complementary feeds), total breastfeeding (duration of any breastfeeding), formula feeding and the timing of introduction of fruit juice, rice/cereals, fruits, vegetables, milk products, biscuits & bread, meat, fish and egg. Generalized estimating equations (GEE) with an exchangeable correlation structure was used to investigate the associations between the exposures and childhood wheeze, to account for the longitudinal repeated measurements of the outcomes. Discrete-time hazards model was used to analyse new incident asthma and atopic eczema.

In the models, the duration of breastfeeding and the timing of introduction of the complementary foods were dichotomised about the median time for the study population. Those who were still breastfeeding and those who had not introduced complementary foods by 6 months were included in the upper media category. Unadjusted and adjusted models were performed: the unadjusted models included follow-up time as a covariate, while the adjusted models in addition adjusted for potential confounding covariates. The confounders were selected based on (i) conceptual evidence (maternal smoking during pregnancy, maternal atopy (≥ 1 positive skin prick test, 3 mm cut-off), birth order, child's gender, maternal age at recruitment and maternal socio-economic status at recruitment [quintiles Scottish Index of Multiple Deprivation (SIMD)] [28]; and (ii) statistical tests (birth crown-heel length, i.e. achieved $P < 0.25$ in univariate analyses of the outcomes up to the age of 10 years). Other variables (birth weight, gestational age at birth, use of antibiotics by 1 year, maternal social class (registrar general classification, maternal age at leaving full-time education and maternal highest educational qualification)) were also tested in relation to the end-points but only included in the adjusted models if they achieved the set $P < 0.25$. Breastfeeding (ever breastfed) was included in

the models for formula feeding and other complementary foods. Reverse causality was evaluated by including interaction terms between the infant feeding variables and the presence of eczema by 6 months and family atopic history (maternal and/or paternal and/or sibling history of asthma, eczema or hayfever). Owing to markedly different interactions being observed, the analyses were further stratified by the presence of eczema by 6 months and family history of atopy (i.e. maternal or paternal or sibling atopy). In all analyses, statistical significance was taken as $P < 0.05$. Correction for multiple tests was done by using the Bonferroni adjustments. All analyses were performed using Stata 11 (Stata Statistical Software: Release 11; StataCorp LP, College Station, TX, USA).

Results

Descriptive results

Of the 1924 singleton births recruited for the study, 76% ($n = 1511$), 71% ($n = 1373$), 65% ($n = 1252$) and 49% ($n = 934$) completed the 1, 2, 5 and 10-year follow-up, respectively. The period prevalence of wheeze outcomes and new incidence of atopic eczema and asthma during follow-up are shown in Table 1. During the follow-up visits, mothers who smoked during pregnancy and those with older children were less likely to participate in the study (Table 2). There were no differences in participating in the follow-up visits regarding maternal atopy and the child's gender. The mean maternal age, maternal socio-economic status (SIMD), the child's birth weight and crown-heel length, infant feeding during first 6 months, and the prevalence of doctor-diagnosed atopic eczema did not differ according to follow-up visits (Table 2).

For those who had introduced complementary foods ($n = 1126$) and stopped breastfeeding ($n = 672$) by 6 months, the median (interquartile range) duration was 3.75 (3.00–4.00) months and 2.25 (0.75–4.25) months, respectively. The women ($n = 1252$) who reported that they were still breastfeeding at 6 months were included in the upper median category of age at introduction of complementary foods for analysis. The median age of starting formula feeding was 0.50 (0.00–2.00) months.

Table 1. Period prevalence of wheeze and new incidence of atopic eczema and asthma during follow-up

	Year 1 <i>N</i> = 1511 <i>n</i> (%)	Year 2 <i>N</i> = 1373 <i>n</i> (%)	Year 5 <i>N</i> = 1252 <i>n</i> (%)	Year 10 <i>N</i> = 934 <i>n</i> (%)
Wheeze during the last 12 months	233 (15.4)	210 (15.3)	162 (12.9)	110 (11.8)
Wheeze without cold during the last 12 months	88 (5.8)	77 (5.6)	84 (6.7)	75 (8.0)
New doctor-diagnosed eczema during the last 12 months	218 (14.4)	116 (8.4)	116 (9.2)	34 (3.6)
New doctor-diagnosed asthma during the last 12 months	43 (2.8)	42 (3.1)	73 (5.8)	37 (4.0)

Table 2. Characteristics of the subjects by year of attendance to visits during the study

Covariates	Attendance at each year of study				
	Recruitment <i>N</i> = 1924	Year 1 <i>n</i> = 1551	Year 2 <i>n</i> = 1373	Year 5 <i>n</i> = 1252	Year 10 <i>n</i> = 934
Maternal smoking during pregnancy, <i>n</i> (%)					
No	1357 (71)	1146 (76)	1054 (77)	964 (77)	744 (80)
Yes	566 (29)	365 (24)	319 (23)	288 (23)	190 (20)
Missing	1 (0)				
Maternal atopy, <i>n</i> (%) [*]					
No	1134 (59)	904 (60)	817 (60)	753 (60)	572 (61)
Yes	789 (41)	607 (40)	556 (40)	499 (40)	362 (39)
Missing	1 (0)				
Birth order, <i>n</i> (%)					
0	943 (49)	742 (49)	674 (49)	613 (49)	451 (48)
1	671 (35)	544 (36)	494 (36)	453 (36)	338 (36)
> 1	310 (16)	225 (15)	205 (15)	186 (15)	145 (16)
Maternal age at recruitment, mean (SD) years	28.9 (5.6)	29.6 (5.3)	29.8 (5.1)	29.9 (5.1)	30 (4.8)
Gender of child, <i>n</i> (%)					
Male	–	757 (50)	696 (51)	630 (50)	448 (48)
Female		754 (50)	677 (49)	622 (50)	486 (52)
Maternal SIMD at recruitment, mean (SD)	13.2 (12.2)	11.6 (10.5)	11.4 (10.4)	11.3 (10.2)	10.8 (9.9)
Birth weight, mean (SD)	–	3468.3 (556.2)	3474.6 (547.6)	3460.2 (555.2)	3466.6 (549.8)
Crown-heel length, mean (SD) cm	–	50.0 (2.5)	50.0 (2.5)	49.9 (2.5)	50.0 (2.5)
Child ever breastfed, <i>n</i> (%)					
No	–	393 (27)	356 (27)	302 (26)	212 (24)
Yes		1065 (73)	952 (73)	874 (74)	667 (76)
Child ever formula fed, <i>n</i> (%)					
No	–	270 (19)	243 (19)	222 (20)	178 (21)
Yes		1148 (81)	1028 (81)	917 (80)	673 (79)
Exclusive breastfeeding, <i>n</i> (%)					
Lower median < 3.75	–	544 (51)	480 (50)	441 (51)	334 (80)
Upper median ≥ 3.75		521 (49)	472 (50)	432 (49)	332 (50)
Total breastfeeding, <i>n</i> (%)					
Lower median < 2.25	–	327 (31)	289 (31)	257 (30)	182 (28)
Upper median ≥ 2.25		719 (69)	645 (69)	601 (70)	471 (72)
Doctor-diagnosed atopic eczema by 6 months of age, <i>n</i> (%)					
No	–	1274 (14)	1147 (14)	1029 (14)	770 (16)
Yes		216 (86)	194 (86)	174 (86)	131 (84)

^{*}Maternal atopy: positive skin prick test and/or history of asthma.

The median age at introduction of other complementary foods ranged from 3.75 (3.25–4.00) months for rice/cereals to 6.00 (5.00–6.25) months for biscuit/bread (Table 3).

The relation of potentially confounding maternal and infant factors to breastfeeding is presented in Table 4. The differences in exclusive and total breastfeeding between the categories of the background characteristics were small, but mothers who smoked during pregnancy, those aged ≤ 25 years, those of higher SIMD (more social deprivation), and those with babies of lighter weight at birth and shorter birth crown-heel length seemed less likely to have ever breastfed and had a shorter duration of total breastfeeding.

Associations between breastfeeding and age at introduction of complementary foods and the risk of asthma, wheeze and eczema in the first 10 years of life

Results of unadjusted models. Before adjustment for potential confounding variables, total breastfeeding ≥ 2.25 months and no formula feeding were associated with a reduced risk of wheeze in the last 12 months and wheeze in the absence of a cold in the first 10 years of life. In addition, introduction of juice ≥ 4.50 months was associated with a lower likelihood of wheeze in the absence of a cold (Table 5). Neither breastfeeding nor the timing of introduction of any complementary foods was associated with atopic eczema (Table 6). For asthma, ever breastfeeding,

Table 3. Median duration of breastfeeding and age at introduction of complementary foods

Foods	N = 1924* n (%) [†]	Median (months)	Interquartile range (months)
Exclusive breastfeeding [‡]	1126 (59)	3.75	3.00–4.00
Total breastfeeding [‡]	672 (35)	2.25	0.75–4.25
Formula feeding	1247 (65)	0.50	0.00–2.00
Fruit juice	1023 (53)	4.50	3.50–4.00
Rice/cereal	1563 (81)	3.75	3.25–4.00
Fruits	1514 (79)	4.00	3.75–4.50
Vegetables	1501 (78)	4.00	3.75–4.50
Milk products	887 (46)	5.75	4.75–6.25
Biscuits and bread	997 (52)	6.00	5.00–6.25
Meat	1029 (53)	5.00	4.25–6.00
Fish	710 (37)	5.35	4.50–6.00
Egg	751 (39)	5.00	4.00–6.00

*1924 of the 2000 original cohort were singleton births. Twins (n = 76) were excluded from the analysis.

[†]Calculations based on those who had stopped breastfeeding or introduced the complementary foods at the age of 6 months when data collection was completed.

[‡]The median duration of exclusive breastfeeding was longer than that of total breastfeeding, because the calculation of total breastfeeding was based only on those who had stopped breastfeeding (35%) at 6 months of age when the data collection was completed. The calculation of exclusive breastfeeding on the other hand was based on larger subject series (59%).

exclusive breastfeeding, total breastfeeding ≥ 2.25 months, absence of formula feeding, introduction of juice ≥ 4.50 months, and introduction of eggs ≥ 5.00 months were associated with lower likelihood of asthma (Table 6).

Results of the adjusted models. After adjustment for the potential confounding variables, most of the associations lost their statistical significance: only formula feeding was associated with an increased risk of wheezing in the past 12 months (Table 5); introduction of biscuits/bread ≥ 6.00 months was associated with eczema (Table 6). These results became non-statistically significant after Bonferroni correction for multiple tests.

Results of stratified analysis by presence of eczema by 6 months and family atopic history. Stratification of analyses by the presence or absence of eczema at 6 months and family atopic history revealed that exclusive breastfeeding ≥ 3.75 months was associated with increased risk of wheeze in the past 12 months in children with eczema by 6 months (Table S1), but associated with increased risk of atopic eczema in children without eczema by 6 months (Table S2). Introduction of biscuits/bread ≥ 6.00 months was in addition associated with increased risk of atopic eczema in children without eczema by 6 months (Table S2). Introduction of eggs ≥ 5.00 months was associated with a decreased risk of

asthma in children with eczema by 6 months (Table S2). In children with family history of atopy, formula feeding was associated with an increased risk of both wheezing in the past 12 months and wheeze without cold in the past 12 months (Table S1). Conversely, no formula feeding was associated with a reduced risk of atopic eczema and asthma in children without a family history of atopy (Table S2). Introduction of biscuits/bread ≥ 6.00 months was in addition associated with increased risk of atopic eczema in children without family history of atopy (Table S2). These results became statistically non-significant after correction for multiple tests.

Discussion

The findings from this longitudinal birth cohort study indicate that if mothers of newborn children are advised to breast feed and to introduce complementary foods at 3 months, the duration of breastfeeding and the timing of introduction of complementary foods during infancy are not major influences on the occurrence of asthma and atopic diseases up to the age of 10 years of life. In addition to not observing an association with breastfeeding in all children (i.e., regardless of the atopic risk of the child), we also did not observe any convincing association between breastfeeding and wheeze/asthma during the first 10 years of life, over and above what would be expected for the multiple tests of association conducted, in children with early manifestation of atopic eczema, and in children with a family history of atopic disease.

The general consensus of expert review panels [1–4] is that exclusive breastfeeding for at least 4–6 months may confer protection against the risk of eczema and viral-associated wheeze, particularly in children at high familial atopic risk. However, more recent systematic reviews [29–31] concluded that breastfeeding does not protect against the development of atopic dermatitis nor wheeze after the age of 5 years [23]. Generally, the role of breastfeeding in the development of asthma is unclear, particularly in the long-term (> 6 years) [1, 29, 30]. In recent studies, the role of breastfeeding as a preventative strategy for childhood asthma and atopic diseases is conflicting. For instance, two studies with up to 8 years follow-up reported a decreased risk of asthma with exclusive [9] and total [6] breastfeeding > 4 months. Another study with 8 years follow-up found an inverse association between total breastfeeding ≥ 6 months and wheeze up to 3 years but not later [10]. A Japanese study also reported protection against asthma at the age of 3 years with total breastfeeding ≥ 6 months [7]. Other studies have reported no association between breastfeeding and the risk of asthma and atopic diseases [11, 12]. Recently, a Finnish study found that total breastfeeding, rather than its exclusivity, may protect against the development of

Table 4. Median (interquartile range (IQR)) duration of breastfeeding by background characteristics of subjects

Covariates*	N = 1924 n (%)	Ever breastfed %	Exclusive breastfeeding Median (IQR) month	Total breastfeeding Median (IQR) month
Maternal smoking during pregnancy				
No	1357 (70.5)	74.9	3.75 (3.25–4.00)	2.50 (0.75–4.50)
Yes	566 (29.4)	60.0	3.50 (3.00–4.00)	1.83 (0.50–3.75)
Maternal atopy†				
No	1134 (58.9)	71.8	3.75 (3.13–4.00)	2.25 (0.75–4.50)
Yes	789 (41.0)	69.8	3.75 (3.00–4.00)	2.13 (0.75–4.00)
Birth order				
0	943 (49.0)	74.8	3.75 (3.25–4.00)	2.00 (0.63–4.00)
1	671 (34.9)	66.5	3.75 (3.00–4.00)	2.25 (0.75–4.25)
> 1	310 (16.1)	69.1	3.75 (3.00–4.00)	4.00 (1.50–5.75)
Gender of child				
Male	945 (49.1)	70.6	3.75 (3.00–4.00)	2.25 (0.75–4.50)
Female	933 (48.5)	71.4	3.75 (3.25–4.00)	2.25 (0.75–4.00)
Maternal age at booking, years				
≤ 25	469 (24.4)	53.0	3.50 (3.00–4.00)	1.25 (0.50–3.00)
26–30	674 (35.0)	71.8	3.75 (3.13–4.00)	2.25 (0.75–4.00)
31–34	485 (25.2)	76.7	3.75 (3.25–4.00)	2.50 (0.75–5.00)
Maternal SIMD at recruitment				
1 st fifth (least deprived)	835 (43.4)	74.3	3.75 (3.25–4.00)	2.50 (0.75–4.50)
2 nd fifth	515 (26.8)	76.1	3.75 (3.13–4.00)	2.25 (0.75–4.63)
3 rd fifth	183 (9.5)	70.6	3.75 (3.00–4.00)	2.00 (0.50–3.75)
4 th fifth	236 (12.3)	60.1	3.50 (3.00–4.00)	1.50 (0.50–3.75)
5 th fifth (most deprived)	155 (8.0)	41.9	3.50 (3.00–4.00)	2.00 (1.00–3.88)
Birth weight				
1 st quarter (lightest)	344 (22.7)	62.2	4.00 (3.25–4.00)	1.88 (0.75–4.00)
2 nd quarter	386 (25.4)	68.7	3.75 (3.25–4.00)	1.75 (0.69–4.00)
3 rd quarter	379 (25.0)	74.1	3.75 (3.25–4.00)	3.00 (0.50–5.00)
4 th quarter (heaviest)	410 (27.0)	74.6	3.50 (3.00–4.00)	3.00 (1.00–4.50)
Crown-heel length				
1 st quarter (shortest)	456 (23.7)	64.1	4.00 (3.25–4.00)	1.88 (0.75–3.50)
2 nd quarter	619 (32.2)	68.8	3.75 (3.25–4.00)	1.88 (0.75–4.00)
3 rd quarter	302 (15.7)	73.5	3.75 (3.25–4.00)	3–50 (2.00–5.00)
4 th quarter (longest)	440 (22.9)	75.1	3.50 (3.00–4.00)	2.50 (0.75–5.00)
Eczema by 6 months of age				
No	1394 (72.4)	71.1	3.75 (3.35–4.00)	2.50 (0.75–4.25)
Yes	234 (12.2)	69.9	3.75 (3.00–4.00)	1.50 (0.63–4.00)

*Totals may not add up to 1924 because of missing data.

†Maternal atopy: positive skin prick test and/or history of asthma.

asthma, in particular, non-atopic asthma, by the age of 5 years [21]. These previous findings were based on the general population, and the studies examining the modification of the effect of breastfeeding by atopic risk by virtue of parental atopy [6, 7, 21, 22] or early atopic manifestations [5, 9, 10, 21, 22] did not see such modifications according to atopic risk.

The timing of introduction of complementary foods has not been associated with the risk of asthma or atopic diseases in some recent studies [13, 14]. Conversely, there is some evidence that late introduction (roughly > 6 months) of fish [15, 19–22], egg [16, 20–22], cereals [19–22], potatoes [20], milk products [17], and 'other' [17] or 'any' [18] food products may increase the risk of development of asthma [19] and

other atopic diseases [15–18, 20–22], although 'late introduction' was variously defined in these studies. Apart from two studies [18, 22] which found that the associations were modified by early atopic manifestation and parental atopic history, there was no evidence of reverse causality reported in the other studies [15–17, 19–21] found it in the whole study population. Also, apart from one cohort study that examined 5-year-old children [19–22], other studies involved younger children between the ages of 1 and 3 years, hence any long-term effect of timing of complementary foods on atopic outcomes remains unclear.

In this study, the timing of introduction of complementary foods was not associated with asthma or other atopic outcomes, suggesting that the timing of

Table 5. Associations between breastfeeding, introduction of foods and the risk of wheeze up to the age of 10 years

Duration of breastfeeding and age at introduction of complementary foods, months	Wheeze in the past 12 months OR (95% CI)*		Wheeze without cold in the past 12 months OR (95% CI)*	
	Unadjusted [†]	Adjusted [‡]	Unadjusted [†]	Adjusted [‡]
Child ever breastfed				
No	1	1	1	1
Yes	0.85 (0.68–1.06)	0.99 (0.78–1.26)	0.87 (0.63–1.22)	1.02 (0.72–1.45)
P-value	0.150	0.920	0.420	0.901
Exclusive BF				
No BF	1	1	1	1
Lower median < 3.75	0.84 (0.65–1.08)	0.91 (0.70–1.19)	0.90 (0.61–1.30)	0.97 (0.66–1.44)
Upper median ≥ 3.75	0.86 (0.67–1.11)	1.09 (0.82–1.43)	0.85 (0.58–1.25)	1.09 (0.73–1.65)
P-value	0.353	0.420	0.703	0.822
Total BF				
No BF	1	1	1	1
Lower median < 2.25	1.06 (0.81–1.41)	1.11 (0.84–1.49)	1.25 (0.84–1.87)	1.30 (0.86–1.96)
Upper median ≥ 2.25	0.74 (0.58–0.94)	0.90 (0.69–1.17)	0.70 (0.48–1.01)	0.86 (0.58–1.28)
P-value	0.007	0.297	0.009	0.114
Formula feeding				
Yes	1	1	1	1
No	0.62 (0.46–0.84)	0.70 (0.50–0.97)	0.55 (0.34–0.90)	0.70 (0.42–1.15)
P-value	0.002	0.033	0.016	0.160
Time of starting formula feeding				
Lower median < 0.5	1	1	1	1
Upper median ≥ 0.5	0.80 (0.64–1.00)	0.77 (0.56–1.07)	0.75 (0.54–1.05)	0.75 (0.47–2.00)
No formula feeding	0.55 (0.40–0.76)	0.58 (0.38–0.87)	0.48 (0.29–0.80)	0.57 (0.31–1.04)
P-value	0.001	0.029	0.013	0.187
Introduction of juice				
Lower median < 4.50	1	1	1	1
Upper median ≥ 4.50	0.89 (0.71–1.11)	1.11 (0.86–1.41)	0.71 (0.52–0.98)	0.91 (0.63–1.29)
P-value	0.287	0.426	0.040	0.583
Introduction of rice/cereal				
Lower median < 3.75	1	1	1	1
Upper median ≥ 3.75	0.91 (0.74–1.12)	1.05 (0.84–1.31)	0.94 (0.68–1.28)	1.09 (0.79–1.51)
P-value	0.393	0.688	0.688	0.587
Introduction of fruits				
Lower median < 4.00	1	1	1	1
Upper median ≥ 4.00	1.09 (0.88–1.34)	1.10 (0.89–1.37)	1.13 (0.83–1.53)	1.15 (0.84–1.58)
P-value	0.422	0.376	0.440	0.374
Introduction of vegetables				
Lower median < 4.00	1	1	1	1
Upper median ≥ 4.00	0.95 (0.77–1.17)	0.99 (0.79–1.22)	0.97 (0.71–1.33)	1.05 (0.76–1.44)
P-value	0.612	0.894	0.852	0.786
Introduction of milk prod.				
Lower median < 5.75	1	1	1	1
Upper median ≥ 5.75	1.11 (0.88–1.41)	1.13 (0.88–1.44)	0.98 (0.70–1.39)	0.97 (0.68–1.39)
P-value	0.371	0.341	0.922	0.888
Introduction of biscuits/bread				
Lower median < 6.00	1	1	1	1
Upper median ≥ 6.00	1.00 (0.80–1.25)	1.00 (0.79–1.26)	0.95 (0.68–1.32)	0.90 (0.64–1.27)
P-value	0.980	0.999	0.764	0.551
Introduction of meat				
Lower median < 5.00	1	1	1	1
Upper median ≥ 5.00	0.92 (0.75–1.14)	0.92 (0.74–1.15)	1.13 (0.81–1.56)	1.18 (0.84–1.64)
P-value	0.471	0.473	0.472	0.341

(continued)

Table 5. (continued)

Duration of breastfeeding and age at introduction of complementary foods, months	Wheeze in the past 12 months OR (95% CI)*		Wheeze without cold in the past 12 months OR (95% CI)*	
	Unadjusted [†]	Adjusted [‡]	Unadjusted [†]	Adjusted [‡]
Introduction of fish				
Lower median < 5.25	1	1	1	1
Upper median ≥ 5.25	0.95 (0.74–1.21)	0.92 (0.72–1.19)	0.94 (0.65–1.36)	0.91 (0.63–1.33)
<i>P</i> -value	0.653	0.546	0.749	0.643
Introduction of eggs				
Lower median < 5.00	1	1	1	1
Upper median ≥ 5.00	0.95 (0.75–1.20)	1.00 (0.78–1.27)	0.90 (0.64–1.27)	0.89 (0.63–1.27)
<i>P</i> -value	0.678	0.997	0.555	0.529

*Analysed using binomial generalized estimating equations with exchangeable correlation structure.

[†]Included time as a covariate.

[‡]Adjusted for time, maternal smoking during pregnancy, maternal atopy, birth order, child's gender, maternal age at booking, maternal SIMD at recruitment and crown-heel length; breastfeeding ever included in models for formula feeding and introduction of complementary foods.

introduction of complementary foods during infancy does not have a long-term impact on childhood asthma and atopic outcomes. Although the introduction of biscuits/bread ≥ 6 months was associated with an increased risk of atopic eczema, and the introduction of eggs ≥ 5 months was inversely associated with asthma in children with eczema by 6 months, these findings were likely to have been a consequence of conducting multiple tests of association. As this is one of the first studies with a long-term (up to 10 years) follow-up of the longitudinal development of childhood asthma and atopic diseases, further studies are required to corroborate our findings and further clarify whether the timing of infant feeding has any long-term effects on childhood atopic ailments.

This study has a number of strengths including: the longitudinal study design with repeated data collection, and follow-up until the age of 10 years. At the time of cohort recruitment the advice to mothers was to introduce complementary foods at 3 months, enabling us to investigate introduction of complementary foods earlier than currently recommended. Although some interesting significant associations were seen before confounder adjustments, these associations were largely lost after adjustment for maternal socio-demographic and infant factors (birth anthropometry). This probably suggests that in this population these factors themselves may be important determinants of infant feeding. The data on infant feeding were prospectively collected, minimizing the probability of recall bias; however, since we did not have information on infant feeding beyond the age of 6 months, our data may be unable to capture the true variation in the overall timing of infant feeding but are still relevant to the current recommendations. The outcome data were assessed with a standardized instrument and based on doctor-confirmed diagnosis, and the assessment of asthma up to

the age of 10 years enabled us to measure clinically established asthma which is less likely to be confused with viral-associated wheeze. Although we collected data on skin prick test atopic sensitization and lung function, these were only available from a small sub-sample of the whole study population and were not included in this analysis because of insufficient power. Although this study has a reasonable sample size with a moderate attrition rate, we are unable to exclude the possibility that our results are a consequence of a Type II error. This study did not enquire as to the presence of food allergy and thus cannot comment on the possible association between food allergy and breastfeeding and introduction of complementary foods. We did not enquire as to the brand of formula feed. In addition, some of the complementary food groups overlapped somewhat in their constituent food components, e.g. biscuits contain milk, eggs and cereal, limiting the ability of this study to demonstrate associations with individual food groups e.g. milk, eggs and cereals.

Ethical considerations in relation to breastfeeding and its other benefits make it unfeasible to evaluate the role of breastfeeding in a randomized trial setting. Therefore, the best evidence at present to evaluate the putative role of breastfeeding in the development of asthma and atopic diseases must come from such observational epidemiological studies, despite their potential for bias. The available evidence, in sum, does not seem to support the immunological proposal that the gut mucosal barrier of the infant has limited capacity to mount adequate defence against environmental signals, such as solid foods, early in life [31–33]. The biological mechanisms surrounding this hypothesis, however, are currently not known [33], hence protracts the uncertainty surrounding the immunological consequences of early introduction of solid foods to the infant with regards to the development of atopic diseases. Currently, some clinical trials are

Table 6. Associations between breastfeeding, introduction of foods and the risk of eczema and asthma up to the age of 10 years

Duration of breastfeeding and age at introduction of complementary foods, months	Doctor-diagnosed eczema in the past 12 months OR (95% CI)*		Doctor-diagnosed asthma in the past 12 months OR (95% CI)*	
	Unadjusted	Adjusted†	Unadjusted	Adjusted†
Child ever breastfed				
No	1	1	1	1
Yes	0.95 (0.76–1.20)	1.06 (0.83–1.35)	0.67 (0.50–0.90)	0.81 (0.59–1.13)
P-value	0.678	0.632	0.009	0.216
Exclusive BF				
No BF	1	1	1	1
Lower median < 3.75	0.90 (0.69–1.16)	0.93 (0.71–1.21)	0.69 (0.49–0.97)	0.77 (0.52–1.11)
Upper median ≥ 3.75	1.01 (0.79–1.31)	1.25 (0.95–1.64)	0.65 (0.46–0.92)	0.87 (0.60–1.28)
P-value	0.538	0.049	0.031	0.366
Total BF				
No BF	1	1	1	1
Lower median < 2.25	1.10 (0.82–1.46)	1.12 (0.84–1.51)	0.85 (0.59–1.25)	0.90 (0.61–1.35)
Upper median ≥ 2.25	0.90 (0.71–1.15)	1.04 (0.81–1.35)	0.58 (0.42–0.81)	0.76 (0.53–1.09)
P-value	0.289	0.735	0.003	0.305
Formula feeding				
Yes	1	1	1	1
No	0.77 (0.59–1.00)	0.83 (0.63–1.10)	0.51 (0.34–0.78)	0.65 (0.41–1.03)
P-value	0.046	0.202	0.002	0.070
Time of starting formula feeding				
Lower median < 0.5	1	1	1	1
Upper median ≥ 0.5	0.97 (0.78–1.22)	0.93 (0.68–1.29)	0.70 (0.51–0.94)	0.72 (0.47–1.12)
No formula feeding	0.75 (0.56–1.00)	0.79 (0.54–1.15)	0.43 (0.28–0.67)	0.52 (0.30–0.90)
P-value	0.114	0.404	0.001	0.068
Introduction of juice				
Lower median < 4.50	1	1	1	1
Upper median ≥ 4.50	0.89 (0.71–1.10)	0.97 (0.77–1.23)	0.63 (0.48–0.85)	0.83 (0.60–1.16)
P-value	0.282	0.812	0.002	0.276
Introduction of rice/cereal				
Lower median < 3.75	1	1	1	1
Upper median ≥ 3.75	1.04 (0.85–1.27)	1.21 (0.97–1.50)	0.77 (0.58–1.02)	0.95 (0.70–1.29)
P-value	0.690	0.085	0.071	0.760
Introduction of fruits				
Lower median < 4.00	1	1	1	1
Upper median ≥ 4.00	1.07 (0.87–1.30)	1.10 (0.90–1.36)	1.05 (0.79–1.38)	1.08 (0.80–1.45)
P-value	0.537	0.355	0.755	0.633
Introduction of vegetables				
Lower median < 4.00	1	1	1	1
Upper median ≥ 4.00	0.95 (0.78–1.16)	0.99 (0.80–1.22)	0.91 (0.69–1.21)	0.98 (0.73–1.32)
P-value	0.602	0.941	0.523	0.883
Introduction of milk prod.				
Lower median < 5.75	1	1	1	1
Upper median ≥ 5.75	1.15 (0.92–1.43)	1.16 (0.92–1.46)	0.99 (0.73–1.34)	0.91 (0.66–1.25)
P-value	0.228	0.210	0.944	0.560
Introduction of biscuits/bread				
Lower median < 6.00	1	1	1	1
Upper median ≥ 6.00	1.21 (0.97–1.51)	1.34 (1.06–1.69)	0.89 (0.66–1.19)	0.96 (0.69–1.32)
P-value	0.093	0.016	0.425	0.779
Introduction of meat				
Lower median < 5.00	1	1	1	1
Upper median ≥ 5.00	1.00 (0.81–1.23)	1.03 (0.83–1.28)	0.91 (0.68–1.21)	0.98 (0.72–1.32)
P-value	0.986	0.774	0.518	0.891

(continued)

Table 6. (continued)

Duration of breastfeeding and age at introduction of complementary foods, months	Doctor-diagnosed eczema in the past 12 months OR (95% CI)*		Doctor-diagnosed asthma in the past 12 months OR (95% CI)*	
	Unadjusted	Adjusted [†]	Unadjusted	Adjusted [†]
Introduction of fish				
Lower median < 5.25	1	1	1	1
Upper median ≥ 5.25	0.99 (0.78–1.26)	0.99 (0.77–1.27)	0.80 (0.58–1.11)	0.83 (0.59–1.16)
P-value	0.934	0.952	0.179	0.276
Introduction of eggs				
Lower median < 5.00	1	1	1	1
Upper median ≥ 5.00	0.88 (0.70–1.10)	0.91 (0.72–1.15)	0.70 (0.52–0.94)	0.78 (0.57–1.08)
P-value	0.264	0.412	0.018	0.137

*Analysed using discrete-time hazard model.

[†]Adjusted for maternal smoking during pregnancy, maternal atopy, birth order, child's gender, maternal age at booking, maternal SIMD at recruitment and crown-heel length; breastfeeding ever included in models for formula feeding and introduction of complementary foods.

underway to evaluate the effect of modifying the timing of introduction of complementary on allergic outcomes. The results from those studies may clarify the putative role of the age of introduction of complementary foods in the onset of the diseases.

An implication of the present findings for current recommendations on breastfeeding and timing of introduction of complementary foods as preventative strategies for the development of asthma and atopic diseases in children is that, regardless of the infant's atopic risk, this study does not provide evidence to support continuation of exclusive breastfeeding beyond 3 months up to 4–6 months as a public health strategy to reduce the burden of long-term asthma and atopic disease. Clearly, further study is required to verify our findings, if confirmed current breastfeeding recommendations may require revision so as to advise on the optimal feeding strategy for children with and without high risk for atopy. Furthermore, the results from this study, in line with findings from previous studies, and the lack of adequate mechanisms explaining the effect of timing of introduction of complementary foods on the development of atopic diseases, indicate the need for consideration of further review of the current recommendations of the expert bodies regarding the timing of infant feeding.

Conclusions

The findings from this study suggest that the duration of breastfeeding and the timing of introduction of complementary foods during infancy seem not to play a major role in the long-term (up to 10 years) risk of asthma and atopic disease in children in general, including children at high risk of asthma and atopic disease.

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Author contributions

Conception of the idea for the study (AS, GD, GMcN, LC, ST). Expert advice on dietary aspects and supervised collection of dietary data (GMcN, LC). Collection of the study data (GD, KA, NP). Analysed the data and prepared the initial version of the manuscript (BN, GD, LC). Actively contributed to writing, editing and evaluation of the manuscript (AS, BN, GMcN, GD, KA, LC, ME, ST).

Conflict of interest

The authors declare no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Adjusted associations between breastfeeding, introduction of foods and the risk of wheeze up to

the age of 10 years, stratified by eczema by 6 months and family history of allergy

Table S2. Adjusted associations between breastfeeding, introduction of foods and the risk of atopic eczema and asthma up to the age of 10 years, stratified by eczema by 6 months and family history of allergy

TABLE S1. Adjusted associations between breast feeding, introduction of foods and the risk of wheeze up to the age of 10 years, stratified by eczema by 6 months and family history of allergy

Duration of breast feeding and age at introduction of complementary foods, months	No eczema by the age of 6 months OR (95% CI) ^{a,b}		Eczema by the age of 6 months OR (95% CI) ^{a,b}		No family history of atopy OR (95% CI) ^{a,b}		Family history of atopy OR (95% CI) ^{a,b}	
	Wheeze in the past 12 months	Wheeze without cold in the past 12 months	Wheeze in the past 12 months	Wheeze without cold in the past 12 months	Wheeze in the past 12 months	Wheeze without cold in the past 12 months	Wheeze in the past 12 months	Wheeze without cold in the past 12 months
Child ever breast fed								
No	1	1	1	1	1	1	1	1
Yes	0.89 (0.68-1.15)	1.01 (0.69-1.50)	1.75 (0.94-3.24)	1.24 (0.54-2.82)	1.02 (0.68-1.59)	1.02 (0.50-2.08)	0.97 (0.73-1.28)	1.04 (0.69-1.56)
<i>P</i> -value	0.376	0.947	0.075	0.613	0.920	0.957	0.811	0.850
Exclusive BF								
No BF	1	1	1	1	1	1	1	1
Lower median < 3.75	0.85 (0.63-1.14)	1.05 (0.68-1.61)	1.37 (0.71-2.67)	0.73 (0.28-1.87)	0.83 (0.50-1.39)	1.16 (0.54-2.51)	0.94 (0.68-1.29)	0.95 (0.60-1.51)
Upper median ≥ 3.75	0.94 (0.69-1.27)	0.831	2.56 (1.27-5.13)	2.16 (0.89-5.23)	1.33 (0.79-2.23)	0.80 (0.31-2.04)	1.00 (0.72-1.38)	1.15 (0.72-1.83)
<i>P</i> -value	0.530		0.020	0.027	0.194	0.708	0.893	0.673
Overall BF								
No BF	1	1	1	1	1	1	1	1
Lower median < 2.25	1.09 (0.80-1.49)	1.43 (0.92-2.45)	1.33 (0.63-2.79)	0.91 (0.33-2.51)	1.46 (0.87-2.45)	1.66 (0.77-3.57)	1.01 (0.72-1.43)	1.23 (0.76-1.98)
Upper median ≥ 2.25	0.76 (0.57-1.02)	0.76 (0.49-1.20)	2.12 (1.09-4.13)	1.53 (0.64-3.62)	0.79 (0.48-1.31)	0.52 (0.21-1.28)	0.92 (0.67-1.26)	0.95 (0.60-1.49)
<i>P</i> -value	0.041	0.020	0.069	0.419	0.056	0.038	0.798	0.488
Formula feeding								
Yes	1	1	1	1	1	1	1	1
No	0.74 (0.52-1.07)	0.76 (0.44-1.33)	0.58 (0.27-1.25)	0.44 (0.14-1.34)	0.83 (0.44-1.55)	1.58 (0.60-4.20)	0.64 (0.44-0.94)	0.55 (0.31-1.00)
<i>P</i> -value	0.106	0.338	0.166	0.148	0.552	0.356	0.022	0.048
Time of starting formula feeding								
Lower median < 0.5	1	1	1	1	1	1	1	1
Upper median ≥ 0.5	0.74 (0.51-1.07)	0.69 (0.40-1.18)	1.16 (0.56-2.41)	1.25 (0.48-3.28)	0.66 (0.36-1.23)	0.90 (0.26-3.12)	0.81 (0.55-1.18)	0.71 (0.42-1.19)
No formula feeding	0.59 (0.38-0.94)	0.59 (0.30-1.17)	0.64 (0.25-1.65)	0.51 (0.13-1.92)	0.60 (0.28-1.31)	1.45 (0.37-5.68)	0.55 (0.34-0.88)	0.43 (0.22-0.87)
<i>P</i> -value	0.078	0.268	0.683	0.294	0.345	0.656	0.040	0.065

Intro. of juice Lower median < 4.50 Upper median ≥ 4.50 <i>P</i> -value	1 1.03 (0.78-1.34) 0.852	1 0.79 (0.53-1.16) 0.230	1 1.67 (0.87-3.20) 0.125	1 1.59 (0.65-3.87) 0.305	1 1.19 (0.76-1.87) 0.456	1 0.52 (0.24-1.13) 0.098	1 1.05 (0.78-1.40) 0.767	1 0.99 (0.65-1.49) 0.944
Intro. of rice/cereal Lower median < 3.75 Upper median ≥ 3.75 <i>P</i> -value	1 0.97 (0.76-1.24) 0.816	1 0.98 (0.68-1.42) 0.931	1 1.44 (0.86-2.44) 0.169	1 1.73 (0.86-3.46) 0.124	1 1.16 (0.76-1.76) 0.487	1 0.82 (0.40-1.65) 0.572	1 1.01 (0.78-1.31) 0.938	1 1.15 (0.79-1.65) 0.465
Intro of fruits Lower median < 4.00 Upper median ≥ 4.00 <i>P</i> -value	1 1.05 (0.83-1.33) 0.700	1 1.15 (0.81-1.64) 0.424	1 1.29 (0.77-2.13) 0.332	1 1.20 (0.61-2.39) 0.595	1 0.76 (0.50-1.15) 0.186	1 0.68 (0.33-1.40) 0.295	1 1.27 (0.98-1.63) 0.068	1 1.30 (0.91-1.85) 0.145
Intro of vegetables Lower median < 4.00 Upper median ≥ 4.00 <i>P</i> -value	1 0.92 (0.73-1.17) 0.522	1 1.07 (0.75-1.53) 0.692	1 1.28 (0.76-2.14) 0.351	1 0.99 (0.48-2.02) 0.978	1 0.87 (0.58-1.30) 0.490	1 0.75 (0.38-1.51) 0.425	1 1.01 (0.78-1.30) 0.935	1 1.11 (0.77-1.59) 0.978
Intro of milk prod. Lower median < 5.75 Upper median ≥ 5.75 <i>P</i> -value	1 1.13 (0.87-1.48) 0.358	1 1.08 (0.72-1.52) 0.714	1 1.03 (0.56-1.89) 0.930	1 0.62 (0.29-1.32) 0.214	1 1.09 (0.71-1.69) 0.692	1 1.02 (0.51-2.04) 0.966	1 1.12 (0.84-1.51) 0.437	1 0.96 (0.63-1.45) 0.838
Intro of biscuits/bread Lower median < 6.00 Upper median ≥ 6.00 <i>P</i> -value	1 0.98 (0.76-1.27) 0.893	1 0.90 (0.62-1.32) 0.597	1 1.05 (0.58-1.89) 0.874	1 0.78 (0.36-1.67) 0.527	1 1.29 (0.83-2.00) 0.265	1 0.83 (0.41-1.66) 0.591	1 0.94 (0.71-1.23) 0.646	1 0.98 (0.66-1.46) 0.936
Intro of meat Lower median < 5.00 Upper median ≥ 5.00 <i>P</i> -value	1 0.92 (0.72-1.17) 0.490	1 1.30 (0.89-1.90) 0.168	1 0.85 (0.49-1.45) 0.543	1 0.70 (0.34-1.46) 0.345	1 0.96 (0.63-1.45) 0.836	1 1.00 (0.51-1.97) 0.989	1 0.90 (0.69-1.17) 0.646	1 1.19 (0.81-1.74) 0.380
Intro of fish Lower median < 5.25	1	1	1	1	1	1	1	1

Upper median ≥ 5.25 <i>P</i> -value	0.91 (0.68-1.20) 0.500	1.07 (0.69-1.66) 0.759	0.97 (0.54-1.74) 0.906	0.53 (0.25-1.12) 0.095	1.52 (0.92-2.51) 0.099	1.21 (0.55-2.68) 0.639	0.78 (0.58-1.04) 0.096	0.85 (0.55-1.30) 0.448
Intro of eggs Lower median < 5.00 Upper median ≥ 5.00 <i>P</i> -value	1 1.01 (0.77-1.33) 0.923	1 1.03 (0.69-1.53) 0.901	1 0.94 (0.52-1.68) 0.823	1 0.49 (0.23-1.06) 0.070	1 1.00 (0.63-1.58) 0.991	1 0.97 (0.45-2.07) 0.931	1 0.98 (0.74-1.31) 0.928	1 0.90 (0.61-1.35) 0.623

^aAnalyzed using binomial GEE with exchangeable correlation structure.

^bAdjusted for time, maternal smoking during pregnancy, maternal atopy, birth order, child's sex, maternal age at recruitment, maternal SIMD at recruitment, and crown heel length; breast feeding ever included in models for formula feeding and introduction of complementary foods.

TABLE S2. Adjusted associations between breast feeding, introduction of foods and the risk of atopic eczema and asthma up to the age of 10 years, stratified by eczema by 6 months and family history of allergy

Duration of breast feeding and age at introduction of complementary foods, months	No eczema by the age of 6 months OR (95% CI) ^{a,b}		Eczema by the age of 6 months OR (95% CI) ^{a,b}		No family history of atopy OR (95% CI) ^{a,b}		Family history of atopy OR (95% CI) ^{a,b}	
	Doctor-diagnosed eczema in the past 12 months	Doctor-diagnosed asthma in the past 12 months	Doctor-diagnosed eczema in the past 12 months	Doctor-diagnosed asthma in the past 12 months	Doctor-diagnosed eczema in the past 12 months	Doctor-diagnosed asthma in the past 12 months	Doctor-diagnosed eczema in the past 12 months	Doctor-diagnosed asthma in the past 12 months
Child ever breast fed								
No	1	1	1	1	1	1	1	1
Yes	1.22 (0.91-1.63)	0.73 (0.50-1.06)	0.87 (0.51-1.49)	1.14 (0.53-2.43)	1.13 (0.73-1.74)	0.80 (0.42-1.55)	1.03 (0.77-1.38)	0.78 (0.53-1.14)
P-value	0.190	0.093	0.606	0.741	0.594	0.515	0.850	0.196
Exclusive BF								
No BF	1	1	1	1	1	1	1	1
Lower median < 3.75	1.00 (0.72-1.39)	0.75 (0.49-1.12)	0.96 (0.53-1.72)	0.93 (0.40-2.16)	0.95 (0.58-1.54)	0.77 (0.37-1.59)	0.92 (0.67-1.28)	0.75 (0.49-1.15)
Upper median ≥ 3.75	1.53 (1.10-2.12)	0.70 (0.45-1.10)	0.75 (0.40-1.42)	1.48 (0.62-3.53)	1.46 (0.87-2.46)	0.86 (0.39-1.90)	1.16 (0.83-1.61)	0.81 (0.52-1.25)
P-value	0.006	0.235	0.612	0.437	0.175	0.781	0.289	0.193
Overall BF								
No BF	1	1	1	1	1	1	1	1
Lower median < 2.25	1.25 (0.87-1.79)	0.81 (0.51-1.28)	0.95 (0.50-1.81)	1.20 (0.48-3.01)	1.43 (0.84-2.45)	1.25 (0.59-2.66)	1.00 (0.70-1.43)	0.77 (0.49-1.23)
Upper median ≥ 2.25	1.23 (0.90-1.68)	0.67 (0.45-1.02)	0.83 (0.46-1.50)	1.20 (0.53-2.74)	1.03 (0.64-1.66)	0.58 (0.27-1.23)	1.05 (0.76-1.44)	0.77 (0.51-1.17)
P-value	0.360	0.171	0.805	0.898	0.335	0.119	0.940	0.417
Formula feeding								
Yes	1	1	1	1	1	1	1	1
No	0.81 (0.58-1.14)	0.62 (0.36-1.08)	1.00 (0.53-1.87)	0.82 (0.34-1.98)	0.55 (0.30-1.02)	0.63 (0.23-1.75)	0.94 (0.68-1.31)	0.61 (0.36-1.03)
P-value	0.229	0.092	0.996	0.663	0.060	0.378	0.726	0.064
Time of starting formula feeding								
Lower median < 0.5	1	1	0.76 (0.38-1.52)	1	1	1	1	1
Upper median ≥ 0.5	1.07 (0.72-1.57)	0.75 (0.45-1.26)	0.84 (0.38-1.85)	0.72 (0.29-1.78)	0.56 (0.32-1.00)	0.37 (0.16-0.87)	1.18 (0.80-1.76)	0.94 (0.56-1.58)
No formula feeding	0.85 (0.54-1.34)	0.51 (0.26-0.99)	0.742	0.63 (0.22-1.87)	0.36 (0.17-0.76)	0.31 (0.10-0.98)	1.07 (0.68-1.68)	0.59 (0.30-1.13)

<i>P</i> -value	0.432	0.141		0.684	0.026	0.043	0.659	0.185
Intro. of juice Lower median < 4.50 Upper median ≥ 4.50 <i>P</i> -value	1 0.96 (0.73-1.27) 0.790	1 0.83 (0.57-1.21) 0.328	1 0.91 (0.52-1.60) 0.755	1 0.95 (0.44-2.06) 0.904	1 0.86 (0.56-1.31) 0.477	1 0.92 (0.47-1.80) 0.809	1 0.97 (0.72-1.30) 0.828	1 0.75 (0.51-1.10) 0.139
Intro. of rice/cereal Lower median < 3.75 Upper median ≥ 3.75 <i>P</i> -value	1 1.23 (0.95-1.58) 0.116	1 0.87 (0.61-1.24) 0.426	1 1.09 (0.67-1.77) 0.723	1 1.09 (0.58-2.08) 0.787	1 1.04 (0.69-1.57) 0.837	1 0.91 (0.49-1.72) 0.780	1 1.29 (1.00-1.66) 0.051	1 0.94 (0.66-1.34) 0.727
Intro of fruits Lower median < 4.00 Upper median ≥ 4.00 <i>P</i> -value	1 1.19 (0.93-1.52) 0.170	1 1.09 (0.78-1.54) 0.615	1 0.91 (0.56-1.45) 0.684	1 1.12 (0.60-2.10) 0.724	1 1.03 (0.69-1.55) 0.874	1 0.76 (0.40-1.43) 0.393	1 1.10 (0.86-1.41) 0.456	1 1.14 (0.81-1.61) 0.446
Intro of vegetables Lower median < 4.00 Upper median ≥ 4.00 <i>P</i> -value	1 1.09 (0.85-1.39) 0.510	1 1.00 (0.71-1.41) 0.998	1 0.94 (0.58-1.51) 0.792	1 0.97 (0.51-1.84) 0.927	1 0.75 (0.50-1.13) 0.176	1 0.99 (0.53-1.82) 0.964	1 1.04 (0.81-1.34) 0.759	1 0.91 (0.65-1.29) 0.600
Intro of milk prod. Lower median < 5.75 Upper median ≥ 5.75 <i>P</i> -value	1 1.14 (0.87-1.51) 0.338	1 0.81 (0.56-1.17) 0.263	1 1.53 (0.90-2.59) 0.119	1 1.55 (0.73-3.12) 0.254	1 0.88 (0.59-1.34) 0.558	1 0.73 (0.39-1.36) 0.318	1 1.27 (0.96-1.69) 0.099	1 0.94 (0.64-1.38) 0.753
Intro of biscuits/bread Lower median < 6.00 Upper median ≥ 6.00 <i>P</i> -value	1 1.51 (1.14-2.01) 0.005	1 1.12 (0.77-1.64) 0.541	1 0.65 (0.38-1.11) 0.112	1 0.55 (0.28-1.10) 0.093	1 1.58 (1.01-2.46) 0.045	1 1.73 (0.86-3.50) 0.126	1 1.25 (0.94-1.66) 0.120	1 0.81 (0.56-1.16) 0.249
Intro of meat Lower median < 5.00 Upper median ≥ 5.00 <i>P</i> -value	1 1.14 (0.88-1.47) 0.329	1 1.10 (0.77-1.57) 0.606	1 0.73 (0.45-1.17) 0.192	1 0.70 (0.36-1.33) 0.270	1 0.89 (0.60-1.32) 0.561	1 0.96 (0.51-1.80) 0.893	1 1.05 (0.80-1.36) 0.738	1 0.94 (0.66-1.34) 0.736

Intro of fish								
Lower median < 5.25	1	1	1	1	1	1	1	1
Upper median ≥ 5.25	1.17 (0.86-1.58)	0.96 (0.64-1.44)	0.65 (0.38-1.11)	0.58 (0.29-1.15)	0.81 (0.52-1.25)	1.65 (0.74-3.64)	1.05 (0.78-1.42)	0.69 (0.47-1.02)
<i>P</i> -value	0.321	0.828	0.114	0.121	0.339	0.217	0.745	0.063
Intro of eggs								
Lower median < 5.00	1	1	1	1	1	1	1	1
Upper median ≥ 5.00	0.88 (0.67-1.16)	0.92 (0.63-1.34)	0.86 (0.51-1.47)	0.48 (0.24-0.95)	0.76 (0.49-1.16)	0.56 (0.29-1.08)	0.95 (0.71-1.26)	0.86 (0.59-1.26)
<i>P</i> -value	0.365	0.651	0.583	0.035	0.204	0.085	0.720	0.448

^aAnalyzed using discrete-time hazard model.

^bAdjusted for maternal smoking during pregnancy, maternal atopy, birth order, child's sex, maternal age at recruitment, maternal SIMD at recruitment, and crown heel length; breast feeding ever included in models for formula feeding and introduction of complementary foods.