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Breastfeeding, Asthma and Allergy: A Tale of Two Cities

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Running Title: A Tale of Two Cities

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ABSTRACT

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The effect of breastfeeding duration on subsequent asthma and allergy remains the subject of much controversy. The objective of this analysis was to investigate whether differences in study design or disease-related exposure modification were the cause of the differences in study findings. The data from two cohorts, the Childhood Asthma Prevention Study (CAPS) from Australia and the Barn Allergi Miljo Stockholm (BAMSE) cohort from Sweden, which had reported different findings on the association between breastfeeding and asthma, were combined. For this analysis the definitions for breastfeeding, asthma, allergy and were harmonized. Subjects were included if they had at least one parent with wheeze or asthma and had a gestational age of more than 36 weeks (combined n =882). The risk of disease-related exposure modification was assessed using survival analysis. Breastfeeding reduced the risk of asthma at 4/5 and 8 years of age in children with a family history of asthma. The effect was stronger in the Swedish cohort. Breastfeeding had no effect on the prevalence of sensitization to inhaled allergens in this cohort with a family history of asthma but was a risk factor for sensitization to cow's milk, peanuts and eggs in the CAPS cohort at 4/5 years and in the combined cohort at 8 years. There was no evidence to support the existence of disease-related exposure modification in either cohort. In conclusion,these findings point to the importance of harmonization of features of study design, including subject selection criteria and variable

definitions, in resolving epidemiological controversies such as those surrounding the impact of breastfeeding on asthma and allergic sensitization.

Keywords: breast feeding, birth cohort, prevention, asthma, atopy, sensitization, children, reverse causation

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INTRODUCTION

Asthma is the most common chronic illness that affects children, with a particularly high prevalence in developed countries (1). Simple, inexpensive interventions during early childhood, such as promotion of breastfeeding, may have an important role if they are shown to be effective in preventing this disease.

Numerous studies have assessed the effect of breastfeeding on the risk of asthma, eczema or allergic sensitisation. During the first few years of life breastfeeding is generally considered to be protective for wheeze and asthma (2-4). However, the findings in relation to later childhood are varied. Many studies have found no relation between breastfeeding and asthma and allergy (5-7), others have found a protective effect (8-11) and still others have found breastfeeding to be a risk factor (12-13). It is generally believed by researchers in this area that the diversity of results is due to differences in design of the studies. It has also been argued that apparent adverse associations may be attributable to a form of bias known as reverse causation or disease-related exposure modification (14). Despite improvements in study methodology over the last decade there remain important design differences, for example; differing definitions for breastfeeding, a lack of consensus for the diagnosis of 'asthma', potential for recall bias due to the assessment of breastfeeding practice several years after infancy, and large losses to follow up leading to possible selection bias. In addition, there may be other, unrecognized and unmeasured confounders such as environmental factors or cultural differences that explain some of the observed heterogeneity.

The heterogeneity among the existing data is typified by two studies conducted on opposite sides of the world, which have recently reported their findings. The Childhood Asthma Prevention Study (CAPS) birth cohort was recruited in Sydney, Australia, to include

children whose parent/s or sibling had wheeze or asthma prior to the child's birth. The infants were enrolled in a randomized controlled trial testing dietary and house dust mite avoidance interventions in the first five years of life. In this cohort, duration of breastfeeding was not associated with asthma at age 5 years. However, breastfeeding for 6 months or more was associated with an increased prevalence of sensitisation to inhaled and ingested allergens at age five years (15). In contrast, the Barn Allergi Miljö Stockholm Epidemiologi (BAMSE) general population birth cohort study conducted in Stockholm, Sweden, found a longer duration of breastfeeding was protective against the development of asthma and allergen sensitization at 4 and 8 years of age (16-17). There are important differences in the selection criteria for these study populations and some differences in the definition of exposures or outcomes. It is unclear to what extent these divergent findings are attributable to either methodological differences or, alternatively, real environmental or lifestyle differences that alter the impact of breastfeeding.

The current study aimed to test the hypothesis that there are not true differences between the CAPS and BAMSE populations in the impact of breastfeeding on the risk of asthma and allergic sensitization and that the observed differences are explained by selection criteria for the cohorts and definitions for exposures and outcomes.

METHODS

Study Design

This study is an historical cohort study using data from both the BAMSE study in Sweden and the CAPS study in Australia.

CAPS

CAPS is a randomized, parallel-group controlled trial designed to test the effectiveness of interventions to reduce house dust mite levels and to increase omega-3 fatty acid levels by supplementation, for the primary prevention of asthma. The results of the randomized controlled trial(15) and further details of the study have been published elsewhere (18). In brief, pregnant women, whose unborn children were at high risk of having asthma because one or more parents or siblings had asthma or wheezing, were identified at the antenatal clinics of six Sydney hospitals. Six hundred and sixteen eligible women were enrolled between September 1997 and December 1999.

Data on the age of the child's mother and father, their educational level, and asthma status, and smoking by mother during pregnancy were recorded perinatally. Gestational age, birth weight and sex of the child were obtained from hospital records after birth. Smoking by any person inside the house was recorded biannually up to 8 years.

Breastfeeding status was recorded by research nurses visiting the home at 1,3,6,9 and 12 months. They recorded the age of the child when breastfeeding ceased, the age when breast milk substitutes were regularly given and whether the child had been given solids at 3, 6, 9 or 12 months.

Asthma outcomes were assessed by questionnaires at 5 yrs and 8 yrs administered to a parent or carer by an independent research nurse who was blind to the feeding practices. Skin prick

tests (SPT) to inhaled and ingested allergens were performed at 5 yrs (n=395) and 8 yrs (n=321), using a method that has been described previously (19).

The study was approved by the Human Research Ethics Committees of the University of Sydney, the Children's Hospital at Westmead and Western and South Western Sydney Area Health Services.

Of the 616 subjects initially enrolled, 'ever' breastfed status could be defined for 601 and 'breastfeeding duration' could be defined for 523. A total of 516 subjects had records for breastfeeding and clinical and skin prick test outcomes at 5 yrs and 450 at 8 yrs.

BAMSE

BAMSE is a general population birth cohort study which recruited newborns in a predefined area of Stockholm between February 1994 and November 1996. In total, 4089 newborn infants were included, which comprised 75% of all infants born in that area of Stockholm. Further details of the study are described elsewhere (20).

Data on the age, educational level, and asthma status of the child's mother and father and smoking by mother during pregnancy were recorded when the infants were newborn (median age 2 months). Smoking inside the house was recorded at 1, 4 and 8 yrs.

Duration of any and exclusive breastfeeding as well as age of introduction of solids were recorded by questionnaire completed by a parent or carer when the child was aged 12 months.

Asthma was assessed by questionnaire at 4yrs and 8yrs. Blood was drawn at 4 yrs (n= 2614) and 8 yrs (n=2480) and specific IgE antibody levels to inhalant and ingested allergens were measured using the ImmunoCAP System™ (Phadia AB, Uppsala, Sweden).

The study was approved by the Ethics Committee of Karolinska Institutet, Stockholm.

Of the 4089 subjects initially enrolled, 3680 (90%) completed the questionnaire at 4 yrs and 3417 (84%) completed the questionnaire at 8 yrs. For the current study, a subset of the population based BAMSE cohort was used according to the selection criteria below.

Selection criteria

In order to harmonize the study populations from the two cohorts we chose selection criteria for this analysis that could be implemented similarly in both studies. These criteria were : 1) one or both parents had current asthma or wheezing prior to child's birth; 2) no cat at home prior to child's birth (CAPS) or at two months of age (BAMSE); 3) singleton pregnancy; 4) gestational age ≥ 36 wks.

Definitions of Exposure Variables and Outcomes

Common definitions were developed for breastfeeding, asthma and sensitization using the data available from both studies.

Fully breastfed ≥ 3 months. Infants who had not been given a breast-milk substitute or solids before 3 months.

Breastfeeding duration. This is defined as the total duration of 'any' breastfeeding, regardless of whether solids and breast-milk substitutes had commenced. This duration was classified as: < 1 month, ≥ 1 month &< 4 months; ≥ 4 months &<7 months; ≥ 7 months &<10 months; ≥ 10 months &<13 months; and ≥ 13 months.

Current Asthma. At ages 4 yrs (BAMSE) or 5 yrs (CAPS) *current asthma* was defined as wheeze in the last 12 months and ever having a doctor or hospital's diagnosis for asthma OR wheeze ≥ 4 times in the last 12months (BAMSE), wheeze for longer than a week ≥ 3 times in the last 12 months (CAPS). At 8 yrs of age *current asthma* was defined as wheeze in the last

12 months and ever having a doctor or hospital's diagnosis for asthma OR wheeze ≥ 4 times in the last 12 months (BAMSE and CAPS).

Sensitization to Ingested Allergens was defined as SPT wheals to egg, milk and peanut allergen that were ≥3mm and > negative control at 5 and 8 yrs in CAPS and specific IgE antibody titer to the same allergens ≥ 0.35kU/L at 4 and 8 yrs in BAMSE. There is of at least fair agreement between these two methods of identifying immediate hypersensitivity to inhaled and ingested allergens.(21-22) *Sensitization to Local Inhaled Allergens*. Because the environments of Australia and Sweden are geographically isolated from one another and experience different climates, the relevant inhalant allergens in each region are different. In Australia, sensitization to inhaled allergens was defined as an allergen weal≥ 3mm and > negative control at 5 and 8 yrs to *Dermatophagoides pteronyssinus*(house dust-mite), cockroach, cat, *Alternaria*, rye or grass mix. In Sweden, sensitization to inhaled allergens was defined as IgE antibody levels≥ 0.35kU/L at 4 and 8 yrs to cat, dog, horse, birch, timothy, mugwort, *Dermatophagoides pteronyssinus,* and *Cladosporium herbarum*.

Statistical Analysis

All statistical analyses were performed with SAS version 9.1 (SAS, Inc, Chicago, Ill). Bivariate associations between breastfeeding and asthma, and sensitization were first evaluated using χ^2 tests and by computing crude relative risks (RRs) and 95% confidence intervals (CI).

The data from the two cohorts were combined for analysis. We used multiple logistic regression with stepwise selection to identify relevant confounders. Potential confounders that were tested included maternal asthma, paternal asthma, maternal education, paternal education, smoking in pregnancy, second hand smoke (SHS) at 12months, 4/5years or 8years,

sex of child, birth weight, maternal age, and gestational age. Adjusted relative risks were estimated using log-binomial model that included the main effect and the selected covariates that were associated with P values less than 0.1 in the final logistic model.

The interaction between study (CAPS or BAMSE) and breastfeeding status was also tested and if this was significant ($p<0.1$) the model was fitted separately for CAPS and BAMSE.

Whether the effect of breastfeeding differed between atopic (those with positive specific IgE or skin prick test to one or more allergens) and non-atopic children was tested by including an atopy by breastfeeding interaction term in the regression model. Additionally, a three-way interaction term was included to test whether this interaction differed between CAPS and BAMSE. Stratified analyses were conducted where indicated by significant interactions.

Survival analysis was used to test where early manifestations of illness may have altered breastfeeding practices and hence induced a spurious association between breastfeeding and disease, that is, disease-related exposure modification. If there was no relationship between onset of allergic symptoms and risk of ceasing breastfeeding this would make reverse causation very unlikely as an explanation for any observed association. A Cox proportional hazards regression model with a time varying covariate was used for this purpose. (23-24)The outcome variable was duration of breastfeeding in months. The time of onset of symptoms (wheeze, eczema diagnosis or itchy rash) was modeled as a time varying covariate taking the value of 0 if the symptom was not present during the breastfeeding period and taking the value of 1 if the symptom was present during the breastfeeding period. This model was fitted separately for the CAPS and BAMSE data and adjusted for socio-economic status.

RESULTS

The study population that met the inclusion criteria and had outcome data available consisted of 419 subjects from CAPS at 5 yrs, 362 subjects from CAPS at 8 yrs and 463 subjects from BAMSE at 4 and 8 yrs.

Baseline characteristics of the study population, by cohort source, are shown in Table 1. The subjects in the CAPS study, compared with those in the BAMSE study, were more likely to have parents with higher levels of tertiary education; mothers with asthma; and exposure to smoking during pregnancy, the first year of life and at 4/5 years.

Rates of fully breastfeeding ≥ 3 months were much higher in BAMSE (81.2%) than in CAPS (33.9%). Similarly, duration of any breastfeeding was longer in Sweden (see Table 1). Only 2.2% of infants in BAMSE were breastfed for less than a month compared with 31.3% of infants in CAPS. The median breastfeeding duration in BAMSE was 8.8 months, whereas in CAPS it was 4.0 months. The decision to fully breastfeed for ≥ 3 months in CAPS was associated with higher levels of education for either parent and no SHS exposure during the first year of life. In BAMSE full breastfeeding was associated with a higher birth weight and no smoking by the mother during pregnancy.

Table 2 shows the prevalence of asthma and sensitization in each subgroup used in this study as well as their respective cohorts of origin. At 5 and 8 years the selected subjects from the CAPS cohort had higher rates of wheeze, asthma and sensitization to local inhaled allergens, whereas the selected BAMSE subjects had significantly higher rates of sensitization to ingested allergens. The disease rates in the selected CAPS subjects were similar to those in the full CAPS cohort.(15) This was expected as the selected sub-group represented a large proportion of the original cohort. In contrast, the subjects selected from the BAMSE cohort

had disease rates that were almost double those in the full cohort.(16-17) This is because the whole BAMSE cohort had been taken from the general population whereas the subgroup selected for this analysis consisted of those who had a parental history of asthma, which is a known risk factor for asthma and allergy.

The effect of fully breastfeeding ≥ 3 months on risk of current asthma at 4/5 years of age differed between the CAPS and BAMSE cohorts (p for interaction = 0.06 (see Table 3). In CAPS, fully breastfeeding ≥ 3 months made no difference to the asthma outcome at age 5 years, but in BAMSE fully breastfeeding ≥ 3 months reduced the risk of having asthma at age 4 years (RR 0.48, 95% CI 0.31 to 0.76). The duration of any breastfeeding and its association with asthma at 4/5 years of age did not vary significantly between the two cohorts (p for interaction =0.14) and there was no significant relationship found(see Table 4).

However, the association between fully breastfeeding ≥ 3 months and asthma at age 8 years did not differ between CAPS and BAMSE cohorts (p for interaction > 0.1). Overall, fully breastfeeding ≥ 3 months was associated with a decreased risk of developing asthma (RR 0.69, 95% CI 0.52 to 0.93). The effect of any breastfeeding duration on asthma risk at age 8 years differed between the two studies (p for interaction = 0.03). Table 4 shows duration of any breastfeeding did not have an effect on asthma at age 8 years in CAPS. However, in BAMSE every 3 month increase in breastfeeding duration was associated with a reduced risk of asthma (RR 0.85 per 3 month period, 95% CI 0.72 to 1.01).

Full breastfeeding for more than 3 months was associated with an increased risk of sensitization to ingested allergens (egg, milk and peanut) in the CAPS study at 4/5 years, but not in the BAMSE study (see Table 3). At 8 years the association between full breastfeeding and sensitization to ingested allergens did not differ between the cohorts (p for interaction= 0.59), and the relative risk was 1.81 (95% CI 1.18 to 2.76). Moreover, longer duration of any breastfeeding was associated with an increased risk of sensitization to ingested allergens (egg,

milk and peanut) at 4/5 and 8 years in the combined data (see Table 4). Tables 3 and 4 show that there was no association between breastfeeding duration (any or full) and sensitization to local inhaled allergens at 4/5 yrs or at 8 years.

Survival analysis (Table 5) found that the presence of early allergic symptoms did not influence mothers to breastfeed their children longer than those who did not exhibit these symptoms, therefore there is no evidence of reverse causation in these studies. In fact, in this subset of the BAMSE cohort, the presence of wheeze while still breastfeeding was associated with a 39% increase in the risk of ceasing to fully breastfeed. In other words, in this instance early symptoms reduced, rather than increased, the duration of breastfeeding.

DISCUSSION

Our results generally support the hypothesis that, after harmonizing selection criteria by restricting the population to those with a family history of asthma and using common outcome definitions, the effect of breastfeeding on risk of asthma and allergic disease does not differ significantly between the Australian CAPS population and the Swedish BAMSE population. Overall, our study shows that longer duration of breastfeeding has protective effects against asthma and may have adverse effects on the risk of food sensitization. However, the findings are complex and some between study centre differences in the observed associations were found despite this harmonization of methods. These may be attributable to unmeasured confounders such as environmental factors or cultural differences between Sweden and Australia.

The major strength of this current analysis was the use of two birth cohort studies from opposite sides of the world with sufficient data in common to allow us to compare and contrast their findings. Access to individual patient data from these two cohorts has allowed us to undertake a meta-regression using these data, as opposed to the more conventional random effects meta-analysis based only on summary measures. The use of individual data allowed adjustment for confounding at the level of individual subjects and improved the power of the analysis.(25) Although we could apply the same definitions for most of the analysis there were some features of the data that could not be harmonized.

The first is in the definition for asthma at 4/5 years. In both studies we included children with ‘ever diagnosed asthma’ and ‘wheeze in the last year’. However, we also included subjects without a diagnosis of asthma but with frequent wheeze. In BAMSE this

was measured as ‘wheeze more than four times in the last year’ and in CAPS it was measured as ‘wheeze for more than 1week more than three times in the last year’. This difference may have influenced the findings. However, since most (>80%) of those classified as having current asthma in both cohorts were included based on the common component of the definition (‘ever diagnosed asthma’ and ‘wheeze in the last year’), it is unlikely this difference in selection criteria had a substantial effect.

The second difference is that CAPS children were assessed at age 5 yrs and BAMSE children at 4 yrs. This age difference may be enough to explain the fact that longer duration of breastfeeding protected against asthma in BAMSE, but not CAPS at this age. Interestingly, at 8 years when the asthma definition and age were the same for both cohorts the study groups were found to be similar, full breastfeeding was shown to be protective for asthma. This finding is supported by several other studies which measured exclusive breastfeeding for 3 months and asthma in subjects of similar age (5, 17, 26-27).

A third difference between the two cohorts is that CAPS was a randomized controlled trial and BAMSE was an observational cohort study. It is unlikely that the interventions in CAPS will have influenced the findings in this analysis as they did not affect the study outcomes (19, 28) and also, as the interventions were randomized, they are unlikely to be confounded with breastfeeding status. However, the nature of the trial meant that CAPS participants were followed up at frequent intervals throughout the first year of life whereas this did not occur in BAMSE. It is possible that this influenced the measurement of breastfeeding status.

The duration of any breastfeeding did not have an effect on asthma prevalence in either cohort at either age except in BAMSE at 8 years where every 3 month increase in breastfeeding slightly improved the odds of developing asthma.

Until recently, recommendations for infant feeding to decrease the risk of allergy have promoted exclusive breastfeeding for at least 6 months and avoidance of solids until at least 3-6 months (depending on the country).(29) However, recent studies have challenged the validity of these recommendations and in some countries they are being re-evaluated. (29) For example, some studies have found that increased breastfeeding duration is related to an increased sensitization to food allergens in children with a family history of atopy. (30-31) We have previously shown in the CAPS cohort that early introduction of solid foods was associated with a reduced risk of sensitization. (15) The current analysis supports these findings for any breastfeeding and full breastfeeding (except BAMSE at 4 years).

Some studies have attempted to adjust for reverse causality by excluding infants who developed eczema or wheeze before breastfeeding ended or before the age of one year. (16, 30) The rationale for this restriction is that the mothers of these children may have continued to breastfeed these children longer than planned and this would result in a spurious (reverse causal) association between breastfeeding duration and asthma. The main problem with this method is that if there is a true causal association between longer breastfeeding duration and increased risk of symptoms, this will tend to exclude those who manifest this problem. Hence, this exclusion method will tend to bias results towards the null whether the apparent association is directly causal or reverse causal. The limitation of our study population to those with a family history of asthma will have reduced the potential for bias due to reverse causation because all subjects have the same family history. Nevertheless, it is possible that early manifestations of allergic illness might have led to prolonged breastfeeding and hence reverse causation bias. However, the findings of the survival analysis have confirmed that this did not, in fact, occur.

To conclude, longer duration of breastfeeding may protect against asthma in childhood but may also be associated with an increased risk of sensitization to foods in children with a

family history of asthma. These effects do not seem to be explained by reverse causation. Whilst we cannot make a recommendation for or against breastfeeding to reduce the risk of allergy-related disorders we can say that applying the same selection criteria and methods to combined data sets does harmonize the breastfeeding allergy relationships and needs to be attempted using larger sources of data. This will depend on collaboration amongst researchers on an international scale.

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Competing Interests

None

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TABLES

Table 1. Baseline characteristics in selected CAPS and BAMSE subjects[#]. Values are numbers (percentages) unless stated otherwise.

Variable	CAPS (n=419)	BAMSE (n=463)
Male sex	211 (50.4)	240 (51.8)
Mean Birth Weight (kg)	3.49	3.58
Mean Gestational age (weeks)	39.6	40.1
Mean maternal age at delivery (yrs)	28.9	30.0
Maternal Education:	N= 419	N= 459
Incomplete Secondary	149 (35.6)	169 (36.8)
Complete Secondary	68 (16.2)	97 (21.1)
Tertiary	202 (48.2)	193 (42.1)
Paternal Education:	N= 414	N = 445
Incomplete Secondary	150 (36.2)	163 (36.7)
Complete Secondary	79 (19.1)	120 (27.0)
Tertiary	185 (44.7)	162 (36.4)
Maternal Asthma	287 (68.5)	263 (56.8)
Paternal Asthma	203 (48.6)	231 (50.3)
Maternal Smoking during Pregnancy*	104 (24.8)	57 (12.3)
SHS in first year of life*	124 (29.6)	76/452 (16.8)
SHS at 4/5 yrs*	109 (26.0)	79/460 (17.2)
SHS at 8 yrs*	78/398 (19.6)	85/455 (18.7)

Breastfeeding:		
Fully Breastfed ≥ 3 months	135/398 (33.9)	367/452 (81.2)
Duration of Any Breast milk:	N=419	N= 452
< 1 month	131 (31.3)	10 (2.2)
1-3 months	68 (16.2)	32 (7.1)
4-6 months	71 (17.0)	79 (17.5)
7-9 months	41 (9.8)	150 (33.2)
10-12 months	27 (6.4)	114 (25.2)
≥ 13 months	81 (19.3)	67 (14.8)

selected for: current maternal and/or paternal asthma or wheeze, >36 weeks gestation, no cat in first 2 months of life, singleton pregnancy,* more than one cigarette/day, ^ SPT in CAPS/ IgE in BAMSE

Table 2. Asthma and Atopy Outcomes in selected CAPS and BAMSE subjects[#] and whole cohorts. Values are numbers (percentages).

Variable	CAPS[#]	CAPS Whole Cohort	BAMSE[#]	BAMSE Whole Cohort
4/5 yrs*:	**(n=419)**	**(n=516)**	**(n=463)**	**(n=3729)**
Wheeze in last 12 months	139 (33.2)	165 (32)	109 (23.5)	546 (14.6)
Current Asthma	96 (22.9)	109 (21.1)	67/461 (14.5)	285 (7.6)
Sensitization to Ingested Allergens^	24/395 (6.1)	25/488 (5.1)	59/348 (17.0)	332/2616 (12.7)
Sensitization to Local Inhaled Allergens^	151/395 (38.2)	179/488 (36.7)	69/348 (19.8)	382/2616 (14.6)
8yrs:	**(n=361)**	**(n=450)**	**(n=463)**	**(n=3417)**
Wheeze in last 12 months	106 (29.3)	124 (27.6)	91 (19.7)	343 (10)
Current Asthma	87 (24.1)	103 (22.9)	63 (13.6)	223 (6.5)
Sensitization to Ingested Allergens^	18/331 (5.4)	22/414 (5.3)	80/350 (22.9)	416/2461 (16.9)
Sensitization to Local Inhaled Allergens^	144/320 (45.0)	178/414 (44.3)	124/350 (35.0)	615//2461 (25.0)

[#] selected for: current maternal and/or paternal asthma or wheeze, >36 weeks gestation,no cat in first 2 months of life, singleton pregnancy,* 4 in BAMSE, 5 in CAPS, ^ SPT in CAPS/ IgE in BAMSE

Table 3. Effect of Full Breastfeeding for ≥ 3 months on Asthma at 4/5 yrs and 8 yrs

		Outcome n/N (%)				P value of Interaction*	Adjusted RR (95%CI)	
		CAPS	Crude RR (95% CI)	BAMSE	Crude RR (95% CI)			
Current Asthma								
4/5yrs[#]	< 3 months	57/263(21.7)	1.00	20/85 (23.5)	1.00	0.06	1.00	1.00
	≥ 3 months	30/135 (22.2)	1.03 (0.69 to 1.51)	46/367 (12.5)	0.53 (0.33 to 0.85)		1.06 (0.97 to 1.56)[a] CAPS	0.48 (0.31 to 0.76)[b] BAMSE
8 yrs	< 3 months	57/224 (25.4)	1.00	18/85 (21.2)	1.00	0.22	1.00	
	≥ 3 months	28/118 (23.7)	0.93 (0.63 to 1.38)	48/367 (13.1)	0.62 (0.38 to 1.01)		0.69 (0.52 to 0.93)[c]	
Sensitization to Ingested Allergens								
4/5 yrs[#]	< 3 months	10/248 (4.0)	1.00	13/63 (20.6)	1.00	0.02	1.00	1.00
	≥ 3 months	14/127 (11.0)	2.73 (1.25 to 5.98)	44/279 (15.8)	0.76 (0.44 to 1.33)		2.73 (1.25 to 5.99)[d] CAPS	0.76 (0.44-1.33)[d] BAMSE
8 yrs	< 3 months	11/206 (5.3)	1.00	15/59 (25.4)	1.00	0.59	1.00	
	≥ 3 months	7/106 (6.6)	1.24 (0.49 to 3.1)	62/283 (21.9)	0.86 (0.53 to 1.41)		1.81 (1.18 to 2.76)[d]	
Sensitization to Inhaled Allergens								
4/5 yrs[#]	< 3 months	87/248 (35.1)	1.00	8/63 (12.7)	1.00	0.19	1.00	
	≥ 3 months	55/127 (43.3)	1.23 (0.95 to 1.6)	60/279 (21.5)	1.69 (0.85 to 3.36)		0.9 (0.71 to 1.13)[e]	
8 yrs	< 3 months	88/199 (44.2)	1.00	19/58 (32.8)	1.00	0.52	1.00	
	≥ 3 months	47/103 (45.6)	1.03 (0.79 to 1.34)	103/284 (36.3)	1.11 (0.74 to 1.65)		0.89 (0.73 to 1.08)[f]	

CI: confidence interval; RR: relative risk; *: Study by full BF interaction. If interaction term p ≤ 0.1, then countries are analysed separately, if interaction term p >0.1 then studies are analysed together, [#] age 4 in BAMSE, 5 in CAPS. [a]= adjusted for birth weight. [b]= adjusted for maternal age, gender. [c]= adjusted for gestational age, gender. [d]= no confounders had a significant effect on this relationship. [e]= adjusted for gender, maternal age, SHS at 5 years, gestational age. [f]= adjusted for maternal education, gender, smoking during pregnancy.

Table 4. The Effect of the Duration of Any Breastfeeding on Outcomes at 4/5 yrs and 8 yrs.

	Current Asthma n/N (%)		Sensitization to Ingested Allergens n/N (%)		Sensitization to Inhaled Allergens n/N (%)	
	CAPS	**BAMSE**	**CAPS**	**BAMSE**	**CAPS**	**BAMSE**
4/5 yrs[#] Duration of Breastfeeding						
< 1 month	30/131 (22.9)	1/10 (10)	4/120 (3.3)	2/7 (29)	42/120 (35.0)	1/7 (14.3)
≥ 1&< 4 months	14/68 (20.6)	11/32 (34.4)	4/66 (6.1)	5/27 (18.5)	18/66 (27.3)	5/27 (18.5)
≥ 4 &< 7 months	17/71 (23.9)	9/79 (11.4)	3/68 (4.4)	11/55 (20.0)	25/68 (36.8)	7/55 (12.7)
≥7&< 10 months	9/41 (22.0)	20/150 (13.3)	4/39 (10.3)	15/115 (13.0)	21/39 (53.9)	21/115 (18.3)
≥10&<13 months	4/27 (14.8)	17/114 (14.9)	1/27 (3.7)	13/88 (14.8)	10/27 (37.0)	21/88 (23.9)
≥ 13 months	22/81 (27.2)	8/67 (11.9)	8/75 (10.7)	11/50 (22.0)	35/75 (46.7)	13/50 (26.0)
P value of interaction*	0.14		0.26		0.37	
Adj P trend	0.7		0.01		0.58	
RR per Bf duration step	0.97 (0.89-1.05)[a]		1.19 (1.05 – 1.34)[b]		1.01 (0.95 – 1.08)[c]	
8 yrs Duration of Breastfeeding						
< 1 month	24/109 (22.0)	2/10 (20)	5/98 (5.1)	2/6 (33)	43/95 (45.3)	2/6 (33)
≥ 1&< 4 months	18/62 (29.0)	9/32 (28.1)	4/57 (7.0)	8/24 (33.3)	22/56 (39.3)	7/24 (29.2)
≥ 4 &< 7 months	14/58 (24.1)	13/79 (16.5)	1/56 (1.8)	12/57 (21.1)	18/52 (34.6)	22/57 (38.6)
≥ 7&< 10 months	10/32 (31.2)	19/150 (12.7)	1/30 (3.3)	20/117 (17.1)	17/31 (54.8)	36/117 (30.8)
≥ 10&<13 months	5/27 (18.5)	16/114 (14.0)	2/24 (8.3)	19/87 (21.8)	9/21 (42.9)	33/87 (37.9)
≥ 13 months	20/73 (27.4)	7/67 (10.5)	5/66 (7.6)	16/51 (31.4)	35/65 (53.9)	22/51 (43.1)
P value of interaction*	0.03		0.7		0.64	
Adj P trend	0.6	0.07	0.03		0.91	
RR per Bf duration step	1.02 (0.95-1.09)[d]	0.85 (0.72 -1.01)[e]	1.14 (1.01 – 1.29)[f]		1.01 (0.95 – 1.07)[g]	

CI: confidence interval; RR: relative risk; *Study by BF duration interaction. If interaction term p ≤ 0.1, then countries are analysed separately, if interaction term p >0.1 then studies are analysed together. [#] age 4 in BAMSE, 5 in CAPS. [a] = adjusted for gestational age, maternal age, father's education, gender. [b]= adjusted for birth weight. [c]= adjusted for gestational age, SHS at 5years, gender. [d]= adjusted for birth weight, gestational age, gender, maternal and paternal asthma . [e]= adjusted for maternal education, maternal asthma. [f]= adjusted for father's education, SHS at 5 years. [g]= adjusted for smoking during pregnancy, gender.

Table 5. Hazard Ratios (HR) for Survival Analysis.

	Any breastfeeding*			**Full Breastfeeding***		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
CAPS						
Itchy Rash	0.85	0.62-1.17	0.31	0.81	0.55-1.18	0.27
Wheeze	1.13	0.84-1.52	0.41	1.29	0.92-1.80	0.14
Eczema diagnosis	0.96	0.67-1.39	0.84	0.91	0.51-1.65	0.76
BAMSE						
Itchy Rash	0.96	0.72-1.27	0.75	0.87	0.60-1.27	0.46
Wheeze	0.99	0.75-1.31	0.95	1.42	1.01-2.00	0.045
Eczema diagnosis	0.94	0.71-1.23	0.64	0.88	0.64-1.23	0.46

Interpretation: If HR is <1 then early sign of symptom is associated with increased risk of prolonged breastfeeding duration.

If HR>1 then early sign of symptom is associated with an increased risk of breastfeeding cessation.

*Adjusted for mother's education and father's education at the child's birth.