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Lack of evidence for a protective effect of prolonged breastfeeding on childhood eczema: lessons from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two

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Summary

Background Exclusive breastfeeding for at least 4 months is recommended by many governments and allergy organizations to prevent allergic disease.
Objectives To investigate whether exclusive breastfeeding protects against childhood eczema.
Methods Study subjects comprised 51 119 randomly selected 8- to 12-year-old schoolchildren in 21 countries. Information on eczema and breastfeeding was gathered by parental questionnaire. Children were also examined for flexural eczema and underwent skin prick testing. Odds ratios (ORs) were calculated for each study centre and then pooled across populations.
Results There was a small increase in the risk of reported 'eczema ever' in association with 'breastfeeding ever' and breastfeeding < 6 months [pooled adjusted OR 1·11, 95% confidence interval (CI) 1·00–1·22 and OR 1·10, 95% CI 1·02–1·20, respectively]. There was no significant association between reported 'eczema ever' and breastfeeding > 6 months (pooled adjusted OR 1·09, 95% CI 0·94–1·26). Risk estimates were very similar for exclusive breastfeeding < 2 months, 2–4 months and > 4 months and for eczema symptoms in the past 12 months and eczema on skin examination. As for more severe eczema, breastfeeding *per se* conveyed a risk reduction on sleep disturbed eczema (pooled adjusted OR 0·71, 95% CI 0·53–0·96), but this effect was lost where children had been exclusively breastfed for > 4 months (pooled adjusted OR 1·02, 95% CI 0·67–1·54). Allergic sensitization and a history of maternal allergic disease did not modify any of these findings.
Conclusions Although there was a protective effect of ever having been breastfed on more severe disease, we found no evidence that *exclusive* breastfeeding for 4 months or longer protects against eczema. Our results are consistent with findings from a recent systematic review of prospective studies. The U.K. breastfeeding guidelines with regard to eczema should be reviewed. Intervention studies are now required to explore how and when solids should be introduced alongside breastfeeding to aid protection against eczema and other allergic diseases.

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Conflicts of interest
None declared.

Members of the ISAAC Phase Two Study Group are listed in Appendix 1. The views expressed in this publication are those of the authors and are not necessarily those of the NHS, the National Institute for Health Research or the U.K. Department of Health.

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Breastfeeding is still considered by many to be an important strategy to prevent the development of eczema and other allergic diseases, and most European Ministries of Health advocate 4 months of exclusive breastfeeding to aid allergy prevention. The U.K. Department of Health and the World Health Organization even recommend 6 months of exclusive breastfeeding for this purpose. These guidelines were based on earlier observational studies, which suggested an increased risk

for eczema in infants exposed to solid foods during the first few months of life.[1,2] Later, others found the opposite effect, i.e. that delayed introduction of solids was associated with a higher risk in eczema development,[3–7] and a meta-analysis of 21 cohort studies subsequently concluded that there was no convincing evidence for a protective effect of exclusive breastfeeding for at least 3 months on eczema risk. Furthermore, a recent review of the literature on the effect of exclusive breastfeeding for 6 months on infant health, including atopy, has called for a reassessment of the current evidence, partly because the gradual decrease in the proportion of U.K. babies given solids early has coincided with an increase in childhood eczema and food allergy.[8–11] There is also mounting evidence from both animal and human research that the early introduction of potentially allergenic food proteins, such as peanut, might induce tolerance rather than allergy.[12,13]

We therefore studied the effect of breastfeeding on childhood eczema among children who took part in the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. In accordance with the new World Allergy Organization nomenclature we use the term 'eczema' throughout (syn. 'atopic eczema', 'atopic dermatitis').[14]

Materials and methods

The rationale and methods of ISAAC Phase Two have been described elsewhere in detail.[15] In brief and with reference to this paper, ISAAC Phase Two was conducted among 51 119 schoolchildren aged 8–12 years to evaluate the prevalence and risk factors of allergic disease between populations. Study centres were required to make a random selection of at least 10 schools from a complete sampling frame of schools in defined geographical areas, and children ($n \geq 1000$ per centre) attending classes with a majority of 9- to 11-year-olds were invited to participate.

Following written consent, data were collected through parental questionnaires on allergy symptoms identical to those used for children age 6–7 years in ISAAC Phase One.[16] The questions relating to childhood eczema were: 'Has your child ever had an itchy rash which was coming and going for at least 6 months?' (yes/no; 'eczema symptoms ever'), 'Has your child had this itchy rash at any time in the past 12 months?' (yes/no; 'eczema symptoms in the past year'), and 'Has this itchy rash at any time affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?' (yes/no; 'flexural eczema in the past year'). If applicable, parents were additionally asked at what age this itchy rash first occurred (< 2 years/2–4 years/5 years or older). Eczema severity was assessed by asking 'Has this rash cleared completely at any time during the past 12 months?' (yes/no; 'persistent flexural eczema in the past year') and 'In the past 12 months, how often, on average, has your child been kept awake at night by this itchy rash?' ('never in the past 12 months'/'less than one night per week'/'one or more nights per week'). All children with sleep disturbance for one or more nights per week were classified as having 'sleep disturbed flexural eczema in the past year'. Finally, parents were asked whether their child had ever had eczema ('eczema ever').

For breastfeeding parents were asked 'Was your child ever breastfed?' and, if yes, for how long (< 6 months/6–12 months/> 1 year), categorized as 'never breastfed', 'breastfed for < 6 months' or 'breastfed for > 6 months'.[17] In addition, parents were asked 'How long was your child breast fed *without* adding other foods or juices?' (< 2 months/2–4 months/5–6 months/> 6 months). Time of exclusive breastfeeding was categorized as 'never breastfed', 'breastfed for < 2 months', 'breastfed for 2–4 months' or 'breastfed for > 4 months', as exclusive breastfeeding for at least 4 months is recommended in most European countries.

Children were physically examined for flexural eczema in the following five body areas: (i) around the eyes; (ii) the neck; (iii) in front of the elbows; (iv) behind the knees; and (v) in front of the ankles. Participants were categorized as having flexural eczema if they had a typical erythematous rash with surface change (e.g. fine scaling, vesicles, oozing, crusting or lichenification) in any of the above flexural areas.[18] All fieldworkers were first trained and then formally tested in the recognition of flexural eczema, using a manual and photographic images specifically developed for this purpose.[13,16] Children also received skin prick testing for the following six common aeroallergens: *Dermatophagoides pteronyssinus*, *D. farinae*, cat hair, *Alternaria tenuis*, mixed tree and grass pollen and histamine (10 mg mL^{-1}) and normal saline control solutions (all ALK, Hørsholm, Denmark). Study centres were allowed to add allergens of local relevance. Additional allergens were tested in 15 centres and included: cockroach, dog, horse, olive, *Parietaria officinalis*, mixed weeds, local tree mix, mixed moulds and *Cladosporium*. All study children had not received any antihistamines for at least 5 days prior to testing. A drop of each allergen and both control solutions were placed on the volar aspect of the left forearm and pierced vertically using 1-mm ALK lancets. Reactions were recorded after 15 min and were considered positive if the mean weal diameter was at least 3 mm greater than the saline control.[13] Atopy was defined as having at least one positive skin prick test to any of the allergens tested.

Following local data entry, the data were sent to the ISAAC Phase Two Coordinating Centre at the University of Ulm (Germany) for consistency checks and statistical analysis. Crude odds ratios (ORs) for breastfeeding (exposure) and the childhood eczema outcomes 'flexural eczema in the past year' (1-year period prevalence), flexural eczema on skin examination (point prevalence) and reported 'eczema ever' were calculated with corresponding 95% confidence intervals (CIs). If centres had studied stratified subsamples (i.e. approximately 100 children with and 100 children without wheeze in the past year[13]), prevalence rates and ORs were calculated applying appropriate sampling weights.[19,20] Combined OR estimates across study centres were calculated using random effects meta-analysis models.[21] Using World Bank criteria, two

strata were defined for the analyses relating to gross national per capita income (GNI). Centres in countries classified by the World Bank in 2001 as 'high income countries' (GNI ≥ US$ 9200) were combined as 'affluent country' centres, and the remaining centres were grouped together as 'nonaffluent country' centres.[22] As confounders we considered age, sex, current bedroom sharing as an indicator of crowding and living conditions and thus a surrogate marker of socioeconomic status, a history of maternal allergic disease ('Has the child's mother ever had any of the following diseases: asthma, hay fever or eczema?') as well as maternal education. The latter was, however, not associated with breastfeeding and eczema and was therefore not included in the final model. In addition, we explored the effect of eczema severity (sleep disturbance and eczema persistence) and skin sensitization status (at least one positive skin prick test) on eczema risk estimates in stratified analyses. As crude and adjusted risk estimates were similar, we present only adjusted ORs (adj ORs), but univariate estimates can be requested from the corresponding author. The statistical analyses were performed at the ISAAC Phase Two Coordinating Centre in Ulm, Germany, using SAS statistical software version 9.1 (SAS Institute, Cary, NC, U.S.A.). As not all study centres performed physical examination for flexural eczema, we performed a sensitivity analysis to explore the effect of inclusion of only centres with data on all eczema outcomes on risk estimates. All study centres obtained local ethics committee approval. We followed the STROBE guidelines on reporting of epidemiological studies throughout.[23]

Results

Overall, 51 119 schoolchildren aged 8–12 years from 27 centres in 21 affluent and nonaffluent countries took part. Further participant characteristics, including information on age, sex and allergic sensitization as well as breastfeeding-related variables are shown in Table 1 for each study centre.

Breastfeeding and eczema risk

There was a small positive association between having ever been breastfed ('breastfed ever') and the life-time risk for reported eczema ('eczema ever') across all study centres (pooled adj OR 1·11, 95% CI 1·00–1·22; heterogeneity test $P = 0·01$, $I^2 = 0·45$; Table 2). This was mainly attributable to positive associations found in a number of affluent country centres [Munich (Germany) adj OR 1·53, 95% CI 1·15–2·03; Rome (Italy) adj OR 1·49, 95% CI 1·02–2·19; Utrecht (Netherlands) adj OR 1·21, 95% CI 1·03–1·42; West Sussex (U.K.) adj OR 1·64, 95% CI 1·10–2·44; Fig. 1]. Correspondingly, the pooled risk estimates for all affluent country centres remained positive (pooled adj OR 1·16, 95% CI 1·05–1·28; Table 1 and Fig. 1). Interestingly, these positive associations became weaker and nonsignificant when children whose eczema started under 2 years of age (45·3% of children) were excluded from the analysis to see whether age at eczema onset influenced the risk estimate [pooled adj OR (affluent country centres) 1·10, 95% CI 1·00–1·21; pooled adj OR (all study centres) 1·06, 95% CI 0·97–1·17; heterogeneity test $P = 0·06$, $I^2 = 0·33$]. The pooled adj OR for nonaffluent country settings was 0·95 (95% CI 0·78–1·17). All individual nonaffluent centre risk estimates were nonsignificant apart from Beijing (China) with an adj OR of 0·84 (95% CI 0·73–0·96; Fig. 1).

Further analysis of 'breastfeeding ever' showed no significant associations overall [pooled adj OR 0·98, 95% CI 0·81–1·18; heterogeneity test $P = 0·78$, $I^2 = 0$ for flexural eczema on skin examination (Table 2) and pooled adj OR 1·06, 95% CI 0·96–1·17; heterogeneity test $P = 0·81$, $I^2 = 0$ for flexural eczema in the past year (Table 3)]. West Sussex was the only centre where the positive association seen for 'eczema ever' remained for flexural eczema on skin examination (adj OR 2·54, 95% CI 1·05–6·14; Fig. 2). However, the association once again became weaker and nonsignificant when children with eczema onset at < 2 years were excluded (adj OR 1·82, 95% CI 0·68–4·85).

The picture was very similar when the length of breastfeeding was taken into account. The overall risk estimate across all study centres for reported 'eczema ever' was 1·10 (95% CI 1·02–1·20; heterogeneity test $P = 0·78$, $I^2 = 0$) for children breastfed for < 6 months (Table 2). This positive association was due to the increased risk in affluent country centres (pooled adj OR 1·13, 95% CI 1·02–1·24), to which West Sussex, as before, made a particular contribution (adj OR 1·56, 95% CI 1·00–2·43). There was no overall association between breastfeeding for < 6 months and 'eczema ever' in nonaffluent countries (pooled adj OR 1·04, 95% CI 0·90–1·21). As for those breastfed for > 6 months, there was no significant effect on life-time eczema risk in either affluent (pooled adj OR 1·16, 95% CI 0·98–1·37) or nonaffluent countries (pooled adj OR 0·92, 95% CI 0·72–1·18), with no overall association [pooled adj OR (all centres) 1·09, 95% CI 0·94–1·26; heterogeneity test $P < 0·001$, $I^2 = 0·60$; Table 2]. The associations between the other eczema outcomes ('flexural eczema in the past year' and 'flexural eczema on skin examination') and length of breastfeeding were all nonsignificant (Tables 2 and 3).

Length of exclusive breastfeeding and eczema risk

The picture did not change when the length of exclusive breastfeeding was taken into account. Overall, there was a positive association between 'exclusive breastfeeding for < 2 months' and 'exclusive breastfeeding for 2–4 months' and 'eczema ever' risk (pooled adj OR 1·17, 95% CI 1·07–1·29; heterogeneity test $P = 0·98$, $I^2 = 0$ and pooled adj OR 1·13, 95% CI 1·02–1·26; heterogeneity test $P = 0·18$, $I^2 = 0·22$, respectively; Table 2). There was no overall significant association for children exclusively breastfed for > 4 months and 'eczema ever' (pooled adj OR 1·05, 95% CI 0·89–1·24; heterogeneity test $P < 0·001$, $I^2 = 0·62$; Table 2). Equally, there were no significant associations between exclusive breastfeeding (< 2 months, 2–4 months and > 4 months) and symptoms of 'flexural eczema on skin examination' and 'flexural eczema in the past year' (Tables 2 and 3). These risk estimates did not change apprecia-

Table 1 Sample characteristics and prevalence of eczema and breastfeeding parameters

	Centre	Number of participants	Age (years), mean (SD)	Female, %	Eczema ever, n (%)	Flexural eczema in past year, n (%)	Flexural eczema on examination, n (%)	Atopy (at least one positive SPT), %	Breastfed ever, n (%)	Breastfed > 6 months, %	Exclusive breastfeeding > 4 months, %
Affluent countries[a]											
China	Hong Kong	3011	10·2 (0·5)	46·7	557 (18·5)	87 (2·9)	46 (3·5)	45·3[b]	792 (26·4)	13·5	9·9
France	Créteil	1371	9·9 (0·8)	51·1	360 (27·6)	170 (12·9)	101 (6·6)	–	827 (62·4)	16·9	–
Germany	Dresden	3014	9·7 (0·6)	48·0	505 (17·1)	420 (14·1)	144 (5·9)	25·7	2500 (85·6)	26·3	12·0
	Munich	3263	9·5 (0·6)	50·9	499 (15·6)	297 (9·2)	102 (4·1)	22·3	2445 (79·5)	34·0	20·7
Greece	Athens	985	9·8 (0·4)	53·9	169 (17·2)	73 (7·4)	13 (1·3)	14·4[b]	769 (78·7)	22·7	16·5
	Thessaloniki	1018	9·7 (0·5)	50·2	101 (9·9)	52 (5·1)	14 (1·4)	26·8[b]	747 (74·6)	19·8	12·1
Iceland	Reykjavik	939	10·4 (0·5)	55·0	330 (36·4)	205 (22·2)	56 (8·8)	23·5	884 (96·5)	62·8	37·1
Italy	Rome	1348	10·0 (0·4)	47·6	216 (16·4)	88 (6·7)	22 (1·6)	28·9[b]	1022 (76·4)	32·7	30·4
Netherlands	Utrecht	3527	9·5 (1·2)	51·0	1026 (29·4)	446 (12·8)	71 (5·6)	30·9[b]	2343 (66·7)	–	–
New Zealand	Hawkes Bay	1320	10·9 (0·5)	50·4	406 (30·9)	182 (13·8)	106 (8·2)	34·5	1138 (86·9)	55·8	33·0
Norway	Tromso	3679	9·9 (0·7)	49·8	1436 (41·0)	738 (20·8)	71 (10·5)	32·7	3457 (94·9)	66·5	35·7
Spain	Almeria	1126	10·2 (0·8)	47·8	256 (23·4)	109 (10·0)	20 (1·9)	43·0[b]	799 (71·7)	20·3	18·1
	Cartagena	1402	9·5 (0·6)	51·0	384 (28·3)	97 (7·1)	11 (0·9)	23·8[b]	1004 (71·7)	22·7	18·2
	Madrid	964	9·4 (0·7)	52·2	298 (32·3)	124 (13·1)	21 (3·2)	34·5[b]	760 (77·9)	27·2	25·1
	Valencia	1348	9·5 (0·7)	49·8	401(30·7)	114 (8·7)	42 (3·7)	14·3[b]	905 (67·1)	18·7	14·6
U.K.	West Sussex	1056	10·4 (0·5)	50·9	284 (27·2)	152 (14·6)	65 (6·7)	17·5	628 (77·0)	40·0	11·7
Nonaffluent countries[a]											
Albania	Tirana	1040	9·9 (0·6)	50·7	19 (1·8)	60 (5·8)	24 (2·4)	14·7[b]	915 (92·4)	69·4	47·6
Brazil	Uruguaiana	1971	9·6 (0·8)	50·0	104 (5·3)	227 (11·5)	–	13·3	1694 (86·5)	54·0	35·4
China	Beijing	4214	10·4 (0·5)	49·5	1343 (31·9)	71 (1·7)	10 (1·0)	23·9[b]	2013(48·7)	30·8	15·1
	Guangzhou	3510	9·8 (0·5)	50·2	452 (12·9)	46 (1·3)	8 (0·7)	32·0[b]	2638 (75·2)	56·8	30·2
Ecuador	Pichincha	894	10·0 (1·6)	45·6	–	16 (1·8)	40 (4·5)	19·7[b]	894 (100)	91·7	–
Georgia	Tbilisi	941	10·4 (0·6)	50·1	11 (1·2)	57 (6·2)	25 (14·0)	33·0[b]	718 (72·7)	31·1	22·3
Ghana	Kintampo	1354	10·3 (0·6)	46·8	–	47 (3·5)	5 (0·4)	1·7	1325 (97·9)	97·7	71·3
India	Mumbai	1657	9·9 (0·8)	54·0	75 (4·6)	72 (4·4)	18 (1·1)	6·4	1607 (97·6)	86·8	83·9
Latvia	Riga	905	10·7 (0·6)	52·3	93 (10·4)	85 (9·5)	32 (6·4)	19·3	813 (90·2)	37·9	14·3
West Bank	Ramallah	2312	9·8 (1·4)	46·4	123 (5·5)	170 (7·5)	6 (2·8)	10·3	268 (91·7)	69·4	49·1
Turkey	Ankara	2950	9·1 (0·5)	50·6	62 (2·2)	155 (5·4)	39 (1·4)	24·6[b]	2758 (94·2)	64·5	51·0

[a]Distinction between 'affluent' and 'nonaffluent' based on World Bank criteria: gross national per capita income ≥ or < US$ 9200. [b]Allergens of local relevance added to panel. SPT, skin prick test.

Table 2 Association between duration of breastfeeding, weaning, and 'eczema ever' and flexural eczema on skin examination

	Eczema ever			Flexural eczema on skin examination		
	Affluent, adjusted OR (95% CI)	Nonaffluent, adjusted OR (95% CI)	All centres, adjusted OR (95% CI)	Affluent, adjusted OR (95% CI)	Nonaffluent, adjusted OR (95% CI)	All centres, adjusted OR (95% CI)
Breastfeeding						
No	1	1	1	1	1	1
Yes	**1·16 (1·05–1·28)***	0·95 (0·78–1·17)	1·11 (1·00–1·22)	1·02 (0·83–1·24)	0·73 (0·42–1·26)	0·98 (0·81–1·18)
Duration of breastfeeding						
Not breastfed	1	1	1	1	1	1
< 6 months	**1·13 (1·02–1·24)***	1·04 (0·90–1·21)	**1·10 (1·02–1·20)***	1·08 (0·86–1·37)	0·64 (0·34–1·20)	1·02 (0·81–1·27)
6 months or longer	1·16 (0·98–1·37)	0·92 (0·72–1·18)	1·09 (0·94–1·26)	1·14 (0·87–1·49)	0·71 (0·39–1·32)	1·06 (0·83–1·35)
Exclusive breastfeeding						
Not breastfed	1	1	1	1	1	1
< 2 months	**1·19 (1·06–1·33)***	1·15 (0·97–1·35)	**1·17 (1·07–1·29)***	1·13 (0·86–1·48)	0·65 (0·32–1·33)	1·05 (0·82–1·36)
2–4 months	**1·18 (1·04–1·33)***	1·02 (0·85–1·22)	**1·13 (1·02–1·26)***	1·16 (0·90–1·49)	0·86 (0·44–1·65)	1·13 (0·89–1·44)
> 4 months	1·12 (0·93–1·34)	0·88 (0·63–1·22)	1·05 (0·89–1·24)	1·11 (0·82–1·50)	0·59 (0·26–1·36)	1·03 (0·78–1·37)

Results are presented as adjusted odds ratio (OR) with 95% confidence interval (CI) pooled separately for affluent vs. nonaffluent country study centres and across all study centres. ORs are adjusted for age, sex, bedroom sharing and maternal history of allergic disease. Statistically significant risk estimates are in bold (*P < 0·05).

bly when only children with eczema onset after 2 years of age were taken into account.

Breastfeeding and eczema severity

We also explored the impact of breastfeeding on severe eczema (symptoms of 'persistent flexural eczema in the past year' and 'sleep disturbed flexural eczema in the past year'). While there were no overall associations seen between disease persistence and breastfeeding exposures (yes/no, duration of breastfeeding, and length of exclusive breastfeeding; Table 3), there was a significant protective effect in affluent country centres for 'breastfed ever' on symptoms of 'sleep disturbed flexural eczema in the past year' (pooled adj OR 0·69, 95% CI 0·49–0·98) and across all study centres (pooled adj OR 0·71, 95% CI 0·53–0·96; heterogeneity test P = 0·62, I^2 = 0). However, risk estimates became nonsignificant when length of breastfeeding was taken into account, both in separate analyses for high and low income countries as well as in pooled analysis across all study centres [pooled adj OR (all study centres) 0·70, 95% CI 0·48–1·01; heterogeneity test P = 0·75, I^2 = 0 and 0·85, 95% CI 0·58–1·25; heterogeneity test P = 0·64, I^2 = 0 for breastfed for < 6 months and > 6 months, respectively; Table 3]. There were nonsignificant negative associations for children exclusively breastfed up to 4 months and 'sleep disturbed flexural eczema in the past year' in high income countries [pooled adj OR (< 2 months) 0·69, 95% CI 0·39–1·21) and pooled adj OR (2–4 months) 0·68, 95% CI 0·43–1·05], and this effect was further attenuated in children who were exclusively breastfed for longer [pooled adj OR (> 4 months) 0·90, 95% CI 0·51–1·57]. When risk estimates were pooled across all study centres, all adj ORs were nonsignificant (Table 3). In particular, exclusive breastfeeding for > 4 months was not associated with symptoms of 'sleep disturbed flexural eczema in the past year' (pooled adj OR 1·02, 95% CI 0·67–1·54; heterogeneity test P = 0·53, I^2 = 0).

The role of allergic sensitization, parental atopy, maternal education, and sensitivity analysis

The above risk estimates did not change when children's sensitization status (at least one positive skin prick test) and maternal education were taken into account. Equally, stratification by parental atopy (personal history of eczema, asthma or hay fever) had no significant impact on the association between breastfeeding and any of the eczema outcomes. In addition, inclusion only of study centres where we had data on all eczema outcomes (skin examinations were not performed in Uruguaiana) did not appreciably change any of the above risk estimates.

Discussion

ISAAC Phase Two represents the worldwide biggest data set with examined eczema and for the first time provides extensive information on the link between breastfeeding and

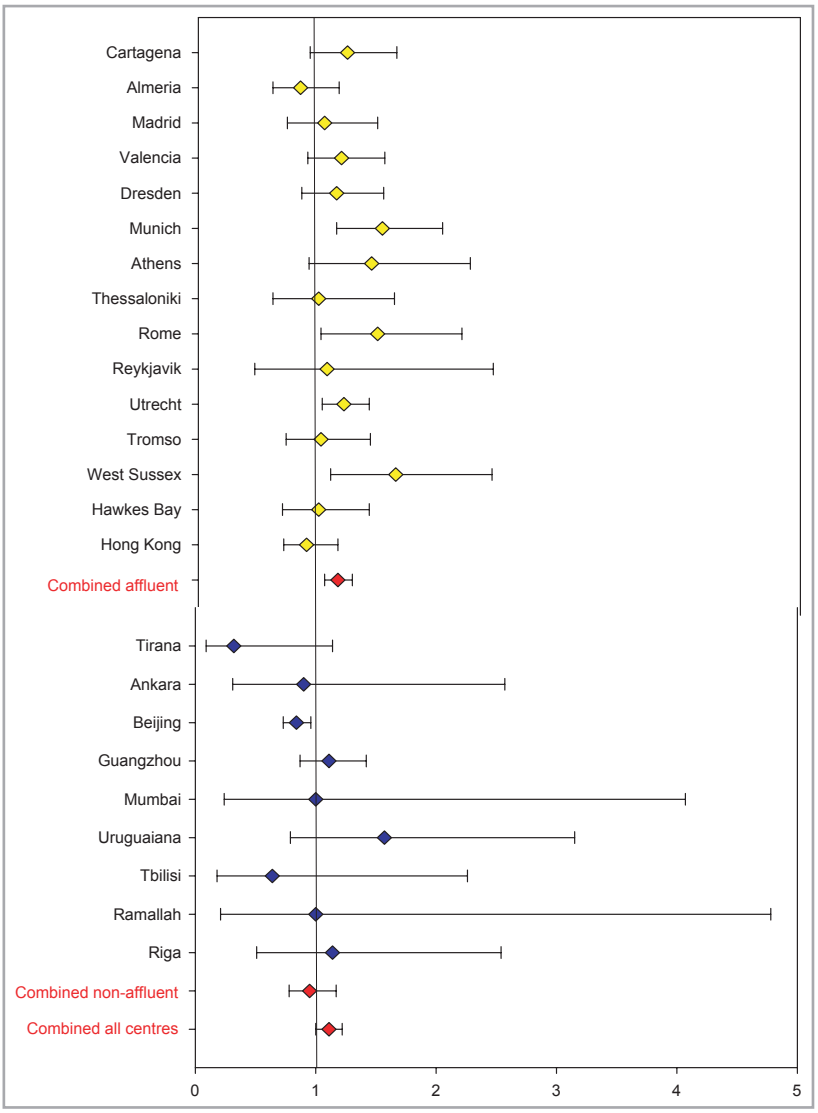

Fig 1. 'Eczema ever' and 'breastfed ever'. Odds ratios adjusted for age, sex, bedroom sharing and maternal history of allergic disease with corresponding 95% confidence intervals.

flexural eczema in both affluent and nonaffluent countries. Overall, we found no protective effect of breastfeeding and delayed weaning on eczema risk. Breastfeeding was positively related to 'eczema ever' in affluent countries, even where breastfeeding was prolonged and weaning delayed. As this association disappeared when children with early-onset eczema were excluded from the analysis, reverse causation is the most likely explanation, i.e. the fact that mothers in high income countries are aware of current breastfeeding recommendations and are therefore more likely to prolong breastfeeding if their baby develops eczema in early infancy. By contrast, breastfeeding *per se* conveyed a small protective effect on severe eczema associated with sleep disturbance in affluent country settings only. However, this effect was lost in children breastfed for 6 months or longer, and there was no association between sleep disturbed flexural eczema and exclusive breastfeeding for > 4 months.

ISAAC Phase Two provides a very large population-based data set and lack of statistical power is therefore not a likely explanation for the absence of a protective effect of breastfeeding and delayed weaning on eczema outcomes. ISAAC Phase Two uses standardized validated methods in all study centres and rigid quality control for ascertaining the physical signs of flexural eczema and determination of skin sensitization. This ensures direct comparability of results between centres and allows statistical pooling of risk estimates across study populations. Very little was known about the association between breastfeeding and allergic disease in nonaffluent countries prior to the ISAAC data presented in this paper.

As with any other cross-sectional study, there are several unavoidable design-related shortcomings. Information on breastfeeding was gathered retrospectively, relying on parental recall. Parents with a child with eczema were probably more

Table 3 Association between breastfeeding, weaning, and symptoms of 'flexural eczema in the past year', 'persistent flexural eczema in the past year' and 'sleep disturbed flexural eczema in the past year'

	Flexural eczema in the past year			Persistent flexural eczema in the past year			Sleep disturbed flexural eczema in the past year		
	Affluent, adjusted OR (95% CI)	Nonaffluent, adjusted OR (95% CI)	All centres, adjusted OR (95% CI)	Affluent, adjusted OR (95% CI)	Nonaffluent, adjusted OR (95% CI)	All centres, adjusted OR (95% CI)	Affluent, adjusted OR (95% CI)	Nonaffluent, adjusted OR (95% CI)	All centres, adjusted OR (95% CI)
Breastfeeding									
No	1	1	1	1	1	1	1	1	1
Yes	1·08 (0·97–1·20)	0·98 (0·79–1·23)	1·06 (0·96–1·17)	1·13 (0·95–1·34)	0·74 (0·52–1·06)	1·04 (0·89–1·22)	**0·69 (0·49–0·98)***	0·79 (0·42–1·46)	**0·71 (0·53–0·96)***
Duration of breastfeeding									
Not breastfed	1	1	1	1	1	1	1	1	1
< 6 months	1·04 (0·91–1·19)	1·17 (0·91–1·51)	1·07 (0·95–1·20)	**1·28 (1·02–1·59)***	0·92 (0·62–1·38)	1·18 (0·97–1·44)	0·67 (0·44–1·02)	0·81 (0·35–1·87)	0·70 (0·48–1·01)
6 months or longer	1·05 (0·90–1·21)	0·91 (0·71–1·16)	1·01 (0·89–1·14)	1·03 (0·81–1·33)	0·69 (0·47–1·03)	0·92 (0·75–1·14)	0·78 (0·48–1·26)	1·00 (0·53–1·90)	0·85 (0·58–1·25)
Exclusive breastfeeding									
Not breastfed	1	1	1	1	1	1	1	1	1
< 2 months	1·07 (0·91–1·28)	1·03 (0·77–1·38)	1·07 (0·92–1·24)	**1·32 (1·03–1·69)***	0·88 (0·56–1·39)	1·20 (0·97–1·50)	0·69 (0·39–1·21)	0·69 (0·28–1·72)	0·69 (0·43–1·11)
2–4 months	1·05 (0·91–1·20)	1·07 (0·82–1·39)	1·05 (0·93–1·19)	1·17 (0·90–1·53)	0·91 (0·60–1·38)	1·08 (0·88–1·33)	0·68 (0·43–1·05)	0·96 (0·43–2·17)	0·73 (0·50–1·08)
> 4 months	1·05 (0·88–1·25)	0·94 (0·72–1·24)	1·03 (0·89–1·18)	1·12 (0·85–1·47)	0·71 (0·43–1·14)	1·00 (0·79–1·27)	0·90 (0·51–1·57)	1·23 (0·61–2·48)	1·02 (0·67–1·54)

Results are presented as adjusted odds ratio (OR) with 95% confidence interval (CI) pooled separately for affluent vs. nonaffluent country study centres and across all study centres. ORs are adjusted for age, sex, bedroom sharing and maternal history of allergic disease. Statistically significant risk estimates in bold (*$P < 0·05$).

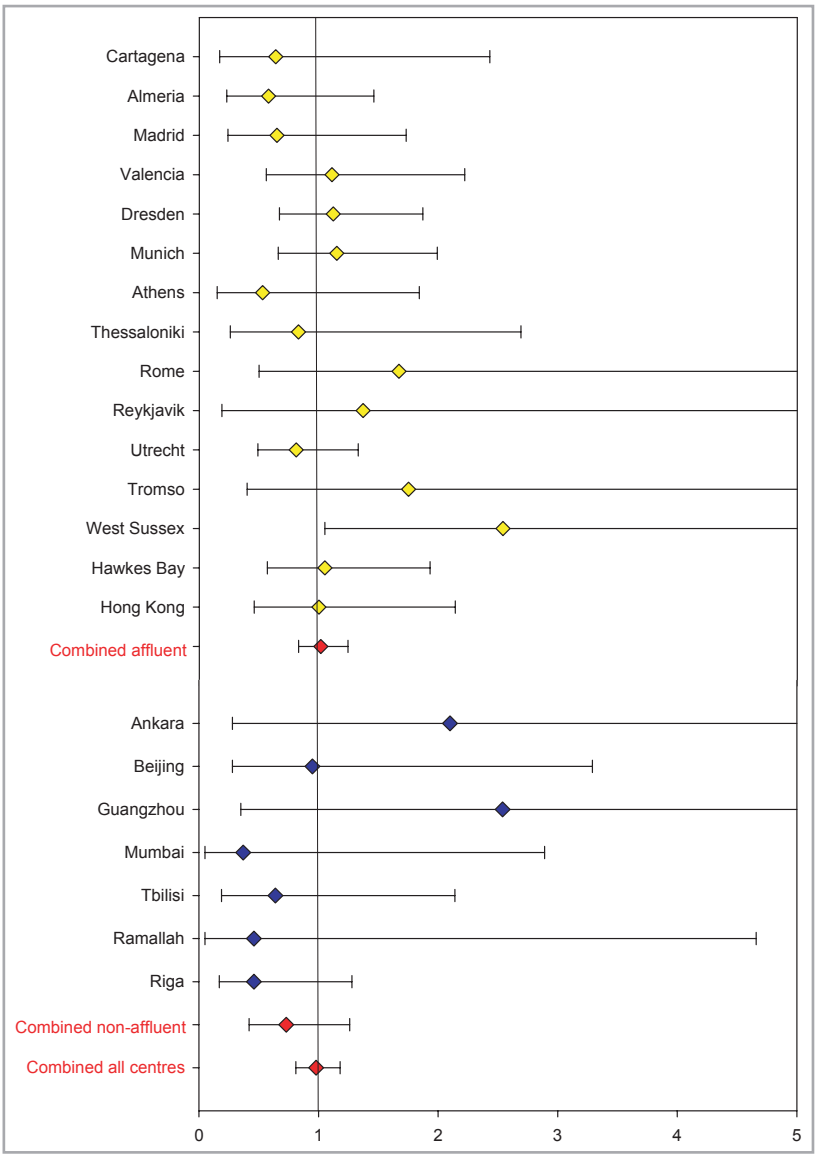

Fig 2. 'Flexural eczema on skin examination' and 'breastfed ever'. Odds ratios adjusted for age, sex, bedroom sharing and maternal history of allergic disease with corresponding 95% confidence intervals.

likely to remember whether and for how long their offspring was breastfed. However, such differential misclassification is likely to bias the results away from the null association and therefore cannot explain the overall lack of an association between breastfeeding and eczema found here. We have no information as to whether individual children's eczema commenced while they were still breastfed and whether this resulted in delayed weaning in some cases. Early-onset eczema may well be one of the reasons why a positive association between breastfeeding and eczema was found in some European settings, but this fact is unlikely to explain the overall lack of an association between breastfeeding and eczema. Having said that, our cross-sectional study design does not allow us to exclude fully the theoretical possibility that breastfeeding might delay eczema onset up to age 2 years. However, we are not aware of any convincing evidence from the substantial body of prospective studies that this might be the case.

Although socioeconomic status is well known to be linked to eczema risk in industrialized countries, the reasons for this link are still not fully understood. ISAAC Phase Two did not collect data on parental income, as it would have been impossible to deduce socioeconomic status for individual study centres and then compare these between countries. We therefore adjusted for bedroom sharing as a proxy for social class instead. Maternal education was also explored as a potential confounder but was not associated with any of the eczema outcomes.

It is widely accepted that breastmilk is the most important and appropriate nutrition in early life.[24] Especially in the context of nonaffluent countries it is also important to keep in

mind that exclusive breastfeeding for at least 3–4 months reduces the risk of gastrointestinal infections compared with mixed or bottle feeding, probably because in such settings contaminated water is often used to make up formula milk.[25] The data presented here do not change this notion.

Based on earlier studies, most European governments and allergy organizations recommend 4 months of *exclusive* breastfeeding to prevent allergies, including eczema. The World Health Organization and U.K. Department of Health even endorse weaning as late as 6 months.[26,27] However, we found no evidence for a protective effect of breastfeeding and delayed weaning on eczema risk in both affluent and nonaffluent countries, in keeping with other more recent studies, suggesting that the current U.K. breastfeeding guidelines with regard to eczema need to be reviewed.[1,28]

An area that warrants more exploration is the potential protective effect of breastfeeding on more severe disease and why this effect was lost for prolonged and exclusive breastfeeding. In this context, it would be important to explore the role of maternal diet and food antigen leakage through breastmilk and how this can impact on the infant's immune system, as maternal dietary changes during pregnancy and lactation with regard to food avoidance might at least in part be responsible for the observed change in study evidence, since the current breastfeeding recommendations were published.[29]

In addition, it appears that delayed food protein introduction in babies prevents tolerance induction, as for instance peanut protein consumption in infancy has been shown to reduce the risk of sensitization in Jewish children in Israel compared with Jewish children in the U.K., who start consuming peanuts much later in life.[13]

We therefore call for studies that look more closely at the relationship between maternal diet and antigen leakage in breastmilk as well the role of gut food protein exposure (timing and dose) on the infant's developing immune system. For instance, an interventional birth cohort study is currently under way in the U.K. to examine the effect of exclusive breastfeeding for 6 months vs. introduction of solid foods from 3 months of age alongside breastfeeding on eczema and other allergies ['Enquiring About Tolerance' (EAT) Study; http://www.eatstudy.co.uk]. More work needs to be done to help us better understand when and how solid foods should be introduced, optimally to confer protection against allergic disease.

What's already known about this topic?

- Earlier studies suggested a protective effect of breastfeeding on childhood eczema, and the U.K. Department of Health recommends exclusive breastfeeding for 6 months.
- However, a recent review of the literature found no evidence for a protective effect of exclusive breastfeeding for at least 3 months on eczema development.
- Little is known about the effect of breastfeeding on eczema in nonaffluent countries.

What does this study add?

- This is the worldwide biggest data set on the association between breastfeeding, time of weaning and examined eczema.
- Based on ISAAC Phase Two data, we found no evidence that *exclusive* breastfeeding for 4 months or longer protects against childhood eczema in both affluent and nonaffluent nations.
- The current U.K. breastfeeding guidelines with regard to eczema should be reviewed.

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Appendix 1. Composition of the ISAAC Phase Two Study Group

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