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Article type : Letter to the Editor

Full breastfeeding and allergies from infancy until adolescence in the GINIplus cohort

Dear editor,

Breastfeeding has major benefits on infant health outcomes and their physical and mental development, but the effect on allergic disease risk remains controversial (1-3). We used the large GINIplus cohort (4) to study short and long term effects of full breastfeeding during the first 4 months compared to formula or mixed feeding on the occurrence of eczema, allergic rhinitis and asthma from birth up to age of 15 years.

The GINIplus birth-cohort (4) is composed of an intervention (I) and non-intervention (NI) group. A total of 5.991 healthy full term newborns were recruited between September 1995 and July 1998 and followed for 15 years by parental self-administered questionnaires. The I-cohort (n=2252) includes only infants with a positive allergy history in at least one first degree relative, while the NI-cohort (n=3739) included 35% infants with positive and 65% with negative family history of allergy.

Participant in the double blind intervention trial were randomized at birth to one of three hydrolyzed formulas [partially hydrolyzed whey (pHF-W); extensively hydrolyzed whey (eHF-W); extensively hydrolyzed casein (eHF-C)] or a formula based on intact cow's milk (CMF) (5). Mothers were encouraged to breastfeed for at least 4 months and were advised to feed the randomized formula as only substitute to breast milk during the strict intervention period of 16 weeks if necessary. Compliance with the milk feeding recommendations was followed by weekly diaries. Full breastfeeding was defined if "breast milk only" was given as milk feeding for each of the first 16 weeks. Of the 2252 recruited infants in the I-cohort at least one yearly questionnaire was available

from 2038. Of those 867 (42.5%) infants were fully breastfed for 16 weeks, 949 had received their randomized study formula, most of them (85%) in addition to breast milk, and 222 were noncompliant to milk feeding.

No feeding recommendations were given to the NI-cohort. In the 1-year questionnaire the type of milk feeding was reported in monthly intervals (N=2754). If the answer "breast milk only" was given for the first 4 months the child was defined as "fully breastfed", which applied to 457 (50.7%) of 902 infants with familial allergy risk and to 865 (46.7%) of 1852 without risk. The remaining infants, labelled as "not fully breastfed", were supplemented with CMF or partially hydrolyzed formulas or both from different manufacturers.

As outcomes we considered doctor diagnoses of eczema, asthma and allergic rhinitis/hay fever reported by the parents in the questionnaires at 1, 2, 3, 4, 6, 10 and 15 years of age of the participant (6). Any positive reply during the lifetime of the child indicating a "yes response" was used to determine cumulative incidence. A positive reply and/or treatment in the last 12 months were used to determine prevalence. The response to yearly questionnaires is given in table S.

Cumulative incidence was estimated by the life table method and analyzed by generalized estimation equations. The results are presented as relative risks (RR) for the specified contrasts: Full breastfeeding in comparison to randomized formula feeding for the intervention infants and to non-full breastfeeding for the non-intervention infants. To determine associations between feeding groups regarding year and period prevalences logistic regression analyses were performed and odds ratios (OR) are reported.

All models were adjusted for a fixed set of risk factors and confounders: family history of the modelled outcome (eczema, asthma and allergic rhinitis, respectively), heredity of family allergy, sex, study region, parental education and older siblings. Results of the adjusted models are given as adjusted OR or RR (aOR, aRR). The introduction of solid feeding was not known in 10% of children in the I-cohort and was considered as confounder in additional models. P values less than 0.05 were considered statistically significant and estimates of OR and RR are given with 95% confidence

intervals (95% CI). Statistical analyses were done using the statistical software SAS for Windows, Release 9.3 (SAS Institute, Cary; NC).

In the I-cohort differences between full breastfeeding and supplementation with study formulas were noted for eczema (Figure a): The cumulative incidence until 15 years was lower in the fully breastfed group compared to the CMF group (adjusted risk ratio aRR=0.73; 95%-CI=[0.55-0.97]) and higher compared to the hydrolyzed formula groups (significant for eHF-C: aRR=1.66; 95%-CI=[1.17-2.35]) (Table 1).

The year- and period prevalences for eczema (Figure b and Table 2) confirmed a risk reducing effect of full breastfeeding compared to CMF supplementation at 2 and 3 years, which however attenuated after longer follow-up. When the fully breastfed group was compared to the hydrolyzed formula groups, the year and period prevalences for eczema were higher in fully breastfed than in the pHF-W supplemented group at 3 years and in the eHF-C group at 2 to 10 years of age.

When all non-fully breastfed infants independent from their randomized formulas were pooled and compared as one group to the fully breastfed infants no differences were observed between the groups regarding cumulative incidence of eczema (15 years cumulative incidence aRR=1.04; 95%-CI=[0.86-1.24]).

For the NI-cohort there were no major differences in the occurrence of eczema between fully breastfed and other infants neither in those with and those without familial allergy risk (Figure c & d, Table 1 & 2).

For neither group of the GINIplus cohort an association between full breastfeeding and occurrence of asthma until 15 years was found (Table 1 & 2). A risk reducing effect of full breastfeeding on allergic rhinitis in comparison to CMF was observed at age 5-6 years in the I-cohort and also in children without familial risk of the NI-cohort up to 10 years of age (Table 2).

If solid feeding was supplemented as confounder nearly identical results were revealed.

The GINIplus birth cohort with the randomized double blind intervention trial gave us the unique opportunity to investigate the effect of full breastfeeding for 4 months on development of allergies compared to supplementation with different formulas in high-risk children and to compare to the not fully breastfed children stratified by familial risk in the non-intervention-cohort.

We found that full breastfeeding for 4 months reduced the risk for early eczema compared to supplementary feeding a cow's milk formula in high-risk children. This beneficial effect attenuated after the age of 3 years indicating a preventive effect on transient early onset eczema.

A recent meta-analysis (2) reported a protective effect of exclusive breastfeeding on eczema only until 2 years of age. The promotion of breastfeeding intervention trial (PROBIT) from Belarus, where maternity hospitals were randomized to a breastfeeding promotion or no intervention, observed a significant reduction of eczema in infants from the intervention sites at 1 year (7) but not at 6.5 years of follow up (8). For the GINI I-cohort the beneficial effect of full breastfeeding when compared to supplementary feeding a cow's milk formula on 1-year eczema based on physical examination (9) and on parental reported physician's diagnosis in the first 3 years in a slightly modified analysis population (10) was already shown.

In addition, in these analyses we observed that full breastfeeding was associated with an increased risk for early eczema if compared with supplementary feeding of individual hydrolyzed formulas.

This differential effects of the whole protein and hydrolyzed formulas neutralized when all non-fully breastfed infants of the intervention-cohort were pooled together and compared as one group to the fully breastfed group. This may explain that no effect of full breastfeeding on early eczema was found in children of the non-intervention-cohort, who were supplemented with a large variety of cow's milk formulas or hydrolyzed formulas or both regardless of allergy risk. The number of different products per infant varied from 1 to 4 during the first 4 months and 49.5% of infant with familial risk received hydrolyzed formulas.

The differential effect of supplementation with cow's milk and individual hydrolyzed formulas on eczema (6) in our intervention-cohort may explain in part the controversial findings of exclusive breastfeeding compared to formula supplementation in non-randomized cohorts since the proportion of infants receiving non-hydrolyzed and hydrolyzed formulas differed over time and between countries.

In neither group of our cohort we observed an association between full breastfeeding and asthma development from 3 to 15 years of age. Several meta-analyses (1, 2, 11) suggested that breastfeeding is protective against the development of asthma, but for cohort studies and studies of higher methodological quality weaker effects were consistently reported. Moreover in a sub-analysis (2) no significant association between exclusive breastfeeding for longer than 3–4 months and asthma at 5–18 years was found, similarly as in the 6.5 year follow-up of PROBIT (8).

The published effects of breastfeeding on allergic rhinitis are heterogeneous: While a meta-analysis (2) suggested a protective effect of breastfeeding until 5 years of age, supported by the 10 years follow up results from the FAIR-cohort (3), no effect was found in the IoW-cohort (3) until 18 years or in PROBIT (8). We observed protective effects of full breastfeeding at 5-6 years compared to the cow's milk supplemented group of the I-cohort and up to 10 years of age in non-risk children of the NI-cohort. Due to these inconsistent findings our findings should be interpreted with caution.

To assess the effect of full breastfeeding on later childhood allergies is always problematic, since neither breastfeeding itself nor the duration of exclusive or total breastfeeding can be randomized. Mothers who fully breastfeed their infants for 4 months or longer differ to mothers who do not breastfeed or supplement with formula during the first 4 months with respect to the following: higher prevalence of eczema in the family, higher parental education, fewer smoking habits, less pets at home, more from the study region Munich, more older than 30 years of age at child's birth and less introduction of solids in the first 4 months (4, 5, 10). Therefore multiple models were used, but to avoid multicollinearity a fix small set of risk factors and confounders was chosen to adjust for the differences between the breast- and non-breastfeeding groups and between participants of the intervention and non-intervention-cohort. Nevertheless our findings are in agreement with the results from the PROBIT study (7, 8), where the intervention produced two randomized cohorts with different exposure to breastfeeding.

Even adjustment for the potential confounders does not eliminate the phenomenon of reverse causality. Particular early eczema occurring in the first months of life may influence the mother's decision regarding full breastfeeding versus formula supplementation. In our intervention-cohort we can assume that the effects of reverse causality are not different between the four randomized formula groups. When we suppose that early skin symptoms would lead to longer duration of full breastfeeding then the beneficial effect of breastfeeding in comparison to cow's milk formula would be underestimated whereas the differences to the hydrolyzed formula groups would likely decrease.

In the NI-groups a recall bias cannot be excluded, because the kind of milk feeding in the first 4 months was first reported by questionnaire at the age of 12 months. This might have diminished the effects in the NI-cohort.

Despite these limitations, the large GINIplus cohort is a unique opportunity to evaluate the long-term impact of different early milkfeeding pattern on allergy development.

For recommendations it should be considered that full beastfeeding is beneficial in comparison to completely or partially feeding a cow's milk formula.

In summary, in the non-intervention-cohort full breastfeeding showed no effect on eczema and asthma, regardless of familial risk, whereas a risk reduction for allergic rhinitis was observed in children without risk. Full breastfeeding compared to the randomized formulas revealed no or minor effects on later asthma and allergic rhinitis, but decreased the risk for early eczema compared to cow's milk formula supplementation whereas eczema risk increased compared to an extensively hydrolyzed casein formula.

Our results indicate that full breastfeeding compared to cow's milk formula supplementation may reduce the risk for early eczema in high-risk children.

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Additional Supporting Information

Table S. Number of participants during follow-up for fully breastfed infants (FB) and formula fed infants in the intervention-cohort and for fully breastfed (FB) and non-fully breastfed (non-FB) infants with familial allergy risk (FH+) and without risk (FH-) in the non-intervention-cohort.

Table 1. Cumulative incidence of allergies from birth to 15 years of age for fully breastfed infants in comparison to formula fed infants in the intervention-cohort and in comparison to non-fully breastfed infants with familial allergy risk (FH+) and without risk (FH-) in the non-intervention-cohort. Relative risk[#] (RR) and adjusted* RR (aRR) with 95% CI from log-binomial models.

			Eczema 1st to 3rd year	Eczema 1st to15th year	Asthma 3rd to15th year	Allergic rhinitis/ hay fever 4th to 15th year
Intervention	CMF	RR	0.72 (0.55 - 0.94)	0.80 (0.61 - 1.05)	0.94 (0.60 - 1.47)	0.95 (0.71 - 1.27)
		aRR	**0.68 (0.52 - 0.89)**	**0.73 (0.55 - 0.97)**	1.05 (0.67 - 1.66)	0.94 (0.70 - 1.26)
	pHF-W	RR	1.36 (0.97 - 1.92)	1.28 (0.96 - 1.73)	0.73 (0.47 - 1.11)	0.91 (0.68 - 1.23)
		aRR	1.29 (0.92 - 1.83)	1.26 (0.93 - 1.70)	0.87 (0.56 - 1.34)	0.93 (0.69 - 1.26)
	eHF-W	RR	0.99 (0.73 - 1.34)	1.04 (0.78 - 1.40)	0.93 (0.58 - 1.48)	1.00 (0.74 - 1.35)
		aRR	0.98 (0.72 - 1.34)	1.06 (0.78 - 1.43)	1.02 (0.64 - 1.64)	1.02 (0.75 - 1.37)
	eHF-C	RR	1.67 (1.12 - 2.47)	1.70 (1.21 - 2.39)	1.00 (0.61 - 1.63)	1.05 (0.77 - 1.43)
		aRR	**1.61 (1.08 - 2.38)**	**1.66 (1.17 - 2.35)**	1.14 (0.69 - 1.87)	1.07 (0.78 - 1.46)
	Non-compliant	RR	0.93 (0.67 - 1.29)	0.79 (0.57 - 1.08)	0.97 (0.55 - 1.71)	0.75 (0.54 - 1.06)
		aRR	0.91 (0.65 - 1.28)	0.77 (0.56 - 1.07)	1.08 (0.60 - 1.93)	0.75 (0.53 - 1.06)
Non-inter-vention FH+	non-FB	RR	0.94 (0.71 - 1.24)	0.91 (0.70 - 1.18)	0.77 (0.47 - 1.24)	1.03 (0.77 - 1.39)
		aRR	0.88 (0.66 - 1.17)	0.86 (0.65 - 1.12)	0.92 (0.56 - 1.49)	1.09 (0.81 - 1.47)

Non-intervention FH-	non-FB	RR	1.12 (0.87 - 1.45)	0.97 (0.77 - 1.23)	0.76 (0.49 - 1.17)	0.80 (0.60 - 1.06)
		aRR	1.14 (0.88 - 1.48)	0.99 (0.78 - 1.26)	0.84 (0.54 - 1.29)	0.81 (0.61 - 1.07)

* adjusted for family history of disease, heredity of family allergy, sex, study region, siblings, parental education

RR of < 1 indicates a decreased relative risk of disease, that is lower incidence in the fully breastfed group than in the compared feeding group, whereas RR >1 indicates higher incidence in fully breastfed group than in the compared formula feeding group

Table 2. Year and period prevalence of allergies for fully breastfed infants in comparison to formula fed infants in the intervention-cohort and in comparison to non-fully breastfed infants with familial allergy risk (FH+) and without risk (FH-) in the non-intervention-cohort. Adjusted* OR (aOR#) with 95% CI from logistic models.

		Eczema					
		1st year	2nd year	3rd year	5 to 6th year	7 to 10th year	11 to 15th year
Intervention	CMF	0.69 (0.46 - 1.04)	**0.58 (0.39 - 0.86)**	**0.66 (0.44 - 0.99)**	0.84 (0.55 - 1.29)	1.10 (0.61 - 1.99)	0.75 (0.42 - 1.35)
	pHF-W	1.33 (0.80 - 2.20)	1.24 (0.76 - 2.04)	**1.88 (1.08 - 3.28)**	1.25 (0.77 - 2.03)	1.19 (0.65 - 2.21)	1.70 (0.78 - 3.69)
	eHF-W	0.94 (0.60 - 1.47)	0.79 (0.52 - 1.22)	0.93 (0.60 - 1.43)	1.60 (0.96 - 2.68)	1.27 (0.69 - 2.33)	0.74 (0.41 - 1.32)
	eHF-C	1.37 (0.80 - 2.34)	**2.29 (1.19 - 4.39)**	**2.82 (1.43 - 5.53)**	1.69 (0.98 - 2.93)	**2.43 (1.09 - 5.45)**	1.69 (0.74 - 3.82)
Non-intervention FH+	Non-BF	0.97 (0.64 - 1.46)	1.04 (0.70 - 1.56)	1.09 (0.72 - 1.66)	1.12 (0.71 - 1.75)	0.70 (0.42 - 1.16)	0.85 (0.48 - 1.53)
Non-intervention FH-	Non-BF	0.95 (0.64 - 1.42)	1.11 (0.76 - 1.60)	1.00 (0.67 - 1.47)	1.01 (0.68 - 1.51)	1.02 (0.60 - 1.72)	0.89 (0.44 - 1.79)

	Asthma			Allergic rhinitis/hay fever		
	5 to 6th year	7 to 10th year	11 to 15th year	5 to 6th year	7 to 10th year	11 to 15th year

Intervention	CMF	1.25	(0.50 - 3.14)	1.21	(0.64 - 2.30)	0.94	(0.52 - 1.68)	**0.61**	**(0.38 - 1.00)**	1.11	(0.72 - 1.73)	0.94	(0.63 - 1.39)
	pHF-W	0.91	(0.40 - 2.11)	0.95	(0.52 - 1.73)	1.01	(0.56 - 1.85)	0.76	(0.45 - 1.29)	1.00	(0.64 - 1.55)	1.20	(0.78 - 1.83)
	eHF-W	0.96	(0.40 - 2.28)	0.87	(0.48 - 1.58)	0.94	(0.51 - 1.74)	1.44	(0.75 - 2.74)	0.98	(0.63 - 1.53)	0.99	(0.66 - 1.48)
	eHF-C	0.57	(0.27 - 1.21)	1.34	(0.67 - 2.65)	1.98	(0.87 - 4.49)	0.92	(0.51 - 1.65)	1.42	(0.86 - 2.34)	1.03	(0.67 - 1.58)
Non-intervention FH+	Non-BF	0.62	(0.24 - 1.63)	0.97	(0.49 - 1.91)	0.82	(0.43 - 1.55)	0.90	(0.51 - 1.59)	1.13	(0.73 - 1.75)	1.10	(0.73 - 1.64)
Non-intervention FH-	Non-BF	0.86	(0.36 - 2.08)	0.51	(0.26 - 1.01)	0.97	(0.57 - 1.67)	0.52	(0.25 - 1.07)	**0.65**	**(0.42 - 0.99)**	0.96	(0.66 - 1.38)

* adjusted for family history of disease, heredity of family allergy, sex, study region, siblings, parental education

aOR of < 1 indicates a decreased risk of disease, that is lower prevalence in the fully breastfed group than in the compared feeding group, whereas RR >1 indicates higher prevalence in fully breastfed group than in the compared formula feeding group

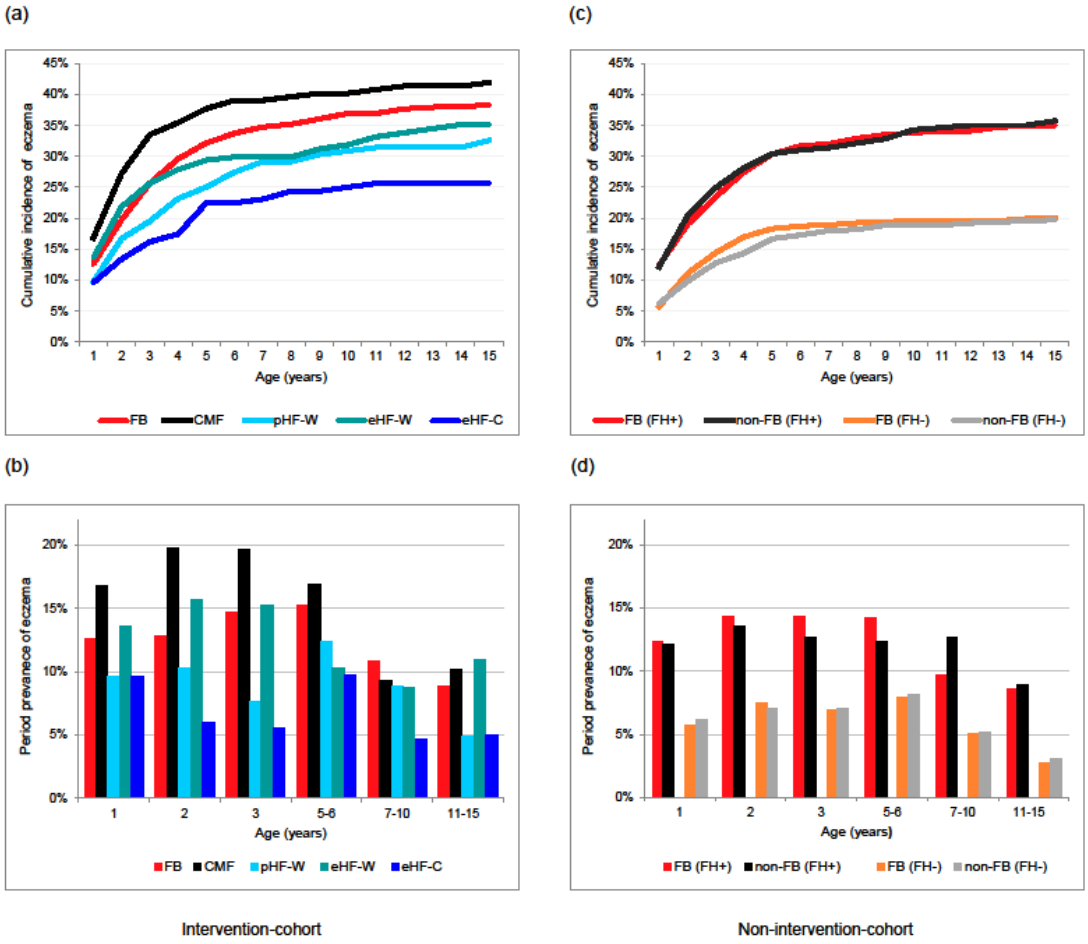

Figure. (a) Cumulative incidence of eczema from birth to 15 years of age and (b) year and period prevalence for the full breastfeeding group (FB) and for the 4 groups supplemented only with their randomized formula in the intervention cohort, (c) cumulative incidence of eczema and (d) year and period prevalence for the full breastfeeding group (FB) and the group supplemented with any formula (non-FB) in the non-intervention-cohort, stratified by infants with familial allergy risk (FH+) and without risk (FH-).