ALLERGY PREVENTION BY EARLY NUTRITION: 15 YEARS OF FOLLOW UP IN THE GINI STUDY

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## POTENTIAL CONFLICT OF INTEREST

<table>
<thead>
<tr>
<th>Type of affiliation / financial interest</th>
<th>Name of commercial company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of grants/research supports:</td>
<td>Euroimmum, Immundiagnostik, Inova, Mead Johnson, Menarini, Nestle-Nutrition, R-Biopharm, Schär, ThermoFisher</td>
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<tr>
<td>Receipt of honoraria or consultation fees:</td>
<td>Abbvie, Danone, Janssen, Merck, MSD; Nestle Nutrition, Vifor, Boehringer Ingelheim, Menarini</td>
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<td>Participation in a company sponsored speaker’s bureau</td>
<td>Abbvie, Danone, Euroimmun, Hipp, Immundiagnostik, MSD, Schär, ThermoFischer, Nestle-Nutrition</td>
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RISK FACTORS FOR ALLERGY

- Genetic factors
- Disturbed immune response, barrier dysfunction
- Environmental factors, early feeding

Allergy
**STRONG GENETIC INFLUENCE ON ALLERGY RISK BUT: DIFFERENT GENES FOR DIFFERENT MANIFESTATIONS**

<table>
<thead>
<tr>
<th>Parental allergy</th>
<th>Risk for any allergy in offspring</th>
<th>Risk for eczema in offspring until age 4 yrs</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td>20-30 %</td>
<td>16 %</td>
</tr>
<tr>
<td>1 with allergic disease</td>
<td>30- 40 %</td>
<td>28 %</td>
</tr>
<tr>
<td>2 with allergic disease</td>
<td>50 - 80 %</td>
<td>45 %</td>
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Kiellman, JACI 1999, Exl et al Nutrition 2001
Roduit et al JACI 2012
GINIplus COHORT

5991 Healthy term neonates born 1995-1998

- Pos. family history of allergy
- Neg. family history of allergy

Intervention group: n=2252
breastmilk +/- 4 study formulae
Avoidance of allergenic foods in the first 12 months

Non-Intervention group: n=3739
breastmilk +/- free formula
PREVALENCE OF ALLERGIC DISEASES FROM 1-15 YEARS IN THE GINIPLUS BIRTH COHORT
ALLERGIC COMORBIDITY IN THE GINIPLUS BIRTH COHORT AT 15 YEARS OF AGE.
5991 Healthy term neonates born 1995-1998

Pos. family history of allergy

Non-Intervention group: n=3739 breastmilk +/- free formula

Intervention group: n=2252 breastmilk +/- 4 study formulae
Avoidance of allergenic foods in the first 12 months
FEEDING RECOMMENDATIONS IN THE INTERVENTION GROUP

- Breastfeeding for at least 4, better 6 months.
- Feeding the randomized study formula as only supplement for breastfeeding during intervention period of 4 months
FEEDING RECOMMENDATIONS IN THE INTERVENTION GROUP

- Breastfeeding for at least 4, better 6 months.
- Feeding the randomized study formula as only supplement for breastfeeding during intervention period of 4 months.
- No complementary feeding within the first 4 months.
- Thereafter, only one new solid food per week.
- No potentially allergenic foods as whole cow’s milk and dairy products, hens’s egg, fish, nuts, and citrus during the first year of life.
GINI: DATA COLLECTION UP TO AGE 6 YEARS

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Months</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

- weekly feeding protocols: •X•X•X•X•X•X
- Interviews: •X•X•X•X•X•X
- Questionnaires: •X•X•X•X•X•X
- Blood: •X•X•X•X•X•X
- Physical examination: •X•X•X•X•X•X•X•X
- Spirometry: •X

**Weekly diaries** for the first 24 weeks, thereafter monthly diaries, to record type of milk (breastmilk, formula), time of weaning, time of first introduction of solid food, kind of solid food (48 items, classified into 8 food groups: vegetables, cereals, fruits, meat, dairy products, egg, fish, and others e.g. soy, nuts, cacao etc).
SOLID FOODS IN WEEK 24 IN 165 UNSELECTED GINI-INFANTS (ACCORDING TO DIARIES)
SOLID FOODS IN WEEK 52 IN 170 UNSELECTED GINI-INFANTS ACCORDING TO THE DIARIES

- meat
- cereals
- apple
- banana
- pears
- other fruits
- carrots
- potatoes
- vegetable
- egg
- dairies
- fish
- nuts
- soy
- citrus fruit
- chocolate

Bartels, thesis
Adjusted cumulative incidence of physician diagnosed atopic eczema in 2124 infants fully breast-fed in the first 4 months with positive & negative family history of atopy

\[ \text{HR} \, 1.9 \ (95\% \ CI \ 1.5-2.4) \]

Adj. cumulative incidence of physician diagnosed atopic eczema in formula-fed infants with pos. & neg. family history for atopy
NI = non-intervention: formula freely chosen by mother

HR 2.1 (95% CI 1.6-2.7)

German Infant Nutritional Intervention study

Objective of the study (1994!)

To investigate the allergy preventive effect of three different hydrolysed formulas compared with a regular cow’s milk based formula in the first three years of life in children at risk of allergic diseases

The study is supported by the German Federal Ministry for Education, Science, Research and Technology, grant no 01 EE 9401-4
FORMULA USED FOR INTERVENTION

Protein hydrolyzates:

- Partially hydrolyzed whey formula $\text{pHF-W}$
- Extensively hydrolyzed whey formula $\text{eHF-W}$
- Extensively hydrolyzed casein formula $\text{eHF-C}$

compared with

- Regular cow's milk based formula $\text{CMF}$

Blinded formulas of the GINI study,

4 letters for each kind of formula
FEEDING CHARACTERISTICS IN INTERVENTION GROUP: DISTRIBUTION OF STUDY FORMULA AND HUMAN MILK

- CMF n=453
- pHF-W n=455
- eHF-W n=456
- eHF-C n=446

n= 1810

- excl. study formula
- study formula + human milk
- excl. human milk
ADJUSTED CUM. INCIDENCE (PP) OF PHYSICIAN DIAGNOSED ATOPIC ECZEMA UP TO 10 YEARS

RELATIVE RISK OF ECZEMA: CUMULATIVE INCIDENCE, BIRTH TO 10 YEARS

SUMMARY: GINI STUDY UNTIL 10 YEARS OF AGE

After 4 months intervention with hydrolysates in at-risk infants:

- Early onset of effect – first 4-6 months
- Risk reduction for atopic eczema
  - until 6 years by 26%, 36% & 45%
  - until 10 years by 23%, 33% & 42%
- No rebound effect
- No significant effect on respiratory allergy

GINI-COHORT: 15 YEARS FOLLOW UP

RELATIVE RISKS FOR CUMULATIVE INCIDENCE FROM BIRTH TO 15 YEARS (♦) 
ODDS RATIOS FOR PERIOD PREVALENCE BETWEEN 11 AND 15 YEARS (◇) 
FOR THE HYDROLYZED FORMULA COMPARED TO COW’S MILK FORMULA

ASTHMA

In PP: RR and OR adjusted for family history of disease, heredity of family allergy, sex, study region, siblings, and parental education

RELATIVE RISKS FOR CUMULATIVE INCIDENCE FROM BIRTH TO 15 YEARS (◆)
ODDS RATIOS FOR PERIOD PREVALENCE BETWEEN 11 AND 15 YEARS (◊)
FOR THE HYDROLYZED FORMULA COMPARED TO COW’S MILK FORMULA

ALLERGIC RHINITIS/ HAY FEVER

In PP: RR and OR adjusted for family history of disease, heredity of family allergy, sex, study region, siblings, and parental education

RELATIVE RISKS FOR CUMULATIVE INCIDENCE FROM BIRTH TO 15 YEARS (◆)
ODDS RATIOS FOR PERIOD PREVALENCE BETWEEN 11 AND 15 YEARS (◇)
FOR THE HYDROLYZED FORMULA COMPARED TO COW'S MILK FORMULA

ECZEMA

In PP: RR and OR adjusted for family history of disease, heredity of family allergy, sex, study region, siblings, and parental education
RELATIVE RISKS FOR CUMULATIVE INCIDENCE FROM BIRTH TO 15 YEARS (♦)
ODDS RATIOS FOR PERIOD PREVALENCE BETWEEN 11 AND 15 YEARS (◊)
FOR THE HYDROLYZED FORMULA COMPARED TO COW’S MILK FORMULA

ALLERGIC MANIFESTAION

In PP: RR and OR adjusted for family history of disease, heredity of family allergy, sex, study region, siblings, and parental education

CONCLUSIONS: GINI 15 YEARS FOLLOW UP

- The different recommendation regarding **solid food introduction** between the intervention and non-intervention group did **not** influence the risk of eczema.

- In **formula fed infants with high risk for allergies**, **early** intervention (<4 months) using different hydrolyzed formulas compared to normal CM-formula has risk reducing effects on eczema, allergic rhinitis and asthma up to adolescence. No effect was noticed on sensitization.

- The previously reported effect of eHF-C and pHF-W on eczema was sustained.
Thank you for your kind attention!