Clinical study summary:
The GINI study publications

The effect of hydrolysed cows’ milk formula for allergy prevention: the German Infant Nutritional Intervention (GINI) study

Objective:
To assess the preventative effect of differently hydrolysed formulas compared with cows’ milk formula (CMF) on allergy in high-risk infants.

Methods:
Between 1995 and 1998, 2252 infants with a hereditary risk for atopy (allergy - patient reported, physician diagnosed) were enrolled in the GINI Study. This was a prospective, double-blind intervention study with infants randomly assigned at birth to one of four formulas: standard cows’ milk formula (CMF), partially hydrolysed whey formula (pHF-W),* extensively hydrolysed whey formula (eHF-W), and extensively hydrolysed casein formula (eHF-C).

Inclusion criteria:
Parents with a healthy newborn and at least one family member (mother, father, or biologic sibling of the newborn) with an allergic disease according to the study questionnaire were invited to participate.

Protocol:
In this study, mothers were encouraged to exclusively breastfeed for at least 4 months and preferably 6 months. No dietary restrictions during lactation were recommended. If mothers chose to introduce formula, a study formula was provided until the child was 6 months of age. Infants were assessed for symptoms of all allergic manifestations (AM).

Results:
Incidences of allergic manifestations were recorded. These were further analysed into subsets of allergies e.g. atopic dermatitis (AD), urticaria, asthma, allergic rhinitis and food allergy.

Results were presented as adjusted relative risk (RR) with a confidence interval of 95%. RR is used to compare the risk between 2 groups.

A RR of 1 means that there is no difference between the 2 groups. If the RR is >1 it means the risk is higher than the other group. If RR <1 it means that the risk is lower than the other group.

The results of this study were reported as both intention to treat (ITT) and per protocol (PP) analyses. For the purpose of this review we will be focusing on the per protocol results as the study clearly showed the need for compliance with the study protocol.

* SMA H.A Infant Milk
Results: Year 1

Primary outcomes:

Endpoints measured at the end of the first year were AD, urticaria and gastrointestinal symptoms of food allergy.

This analysis shows the RR of a physician’s diagnosis of AM with CMF compared with the study formulas.

13% 119 out of the 945 infants who were given any study formula and whose parents were compliant with the study protocol had some AM during the first year.

When compared with standard cows’ milk formula, those infants fed eHF-C had significantly less AM (p=0.036). Although there was also a reduction in AM in both pHF-W and eHF-W compared to cows’ milk, the results did not reach significant levels (p= 0.114 and p=0.677 respectively).

AD = atopic dermatitis
AM = allergic manifestation
CMF = cows’ milk formula
eHF-C = extensively hydrolysed casein formula
eHF-W = extensively hydrolysed whey formula
pHF-W = partially hydrolysed whey formula (SMA H.A Infant Milk)
RR = relative risk
Relative risk of atopic dermatitis:

When AD was analysed separately, both eHF-C and pHF-W significantly reduced the risk of AD. When AD was analysed separately, both eHF-C and pHF-W significantly reduced the risk of AD.2

**Adjusted relative risk of atopic dermatitis**

<table>
<thead>
<tr>
<th></th>
<th>eHF-C</th>
<th>pHF-W</th>
<th>eHF-W</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0.33</strong></td>
<td></td>
<td></td>
<td><strong>0.49</strong></td>
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<tr>
<td><strong>0.49</strong></td>
<td></td>
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<td><strong>0.81</strong></td>
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</table>

- **67% reduction**
- **51% reduction**

**Points to note:**

- AM was reduced by use of hydrolysed formulas compared to standard cows’ milk (significantly by eHF-C)
- AD was prevented by both eHF-C and pHF-W but not eHF-W
- Effects were stronger in the study groups that were fully compliant with the protocol
- A large number of infants were included in the study and the drop out rate was low
Results: Year 6

Primary outcomes:

Endpoints measured at the end of year 6 were the same as year 1, plus hayfever/allergic rhinitis. This was not previously included as it is difficult to diagnose before 4 years of age.

Information on all AM was collected by questionnaires where parents were asked to recollect whether a physician had diagnosed an AM since their last follow-up (3 years). Parents were also asked specifically if diagnosis had been made in the last 2 years (aged 5 years and 6 years).

The loss to follow up in this study was less than 10%.

The analysis shows the RR of a physician’s diagnosis of AM with CMF compared with the study formulas.

159 out of the 795 infants who were given any study formula and whose parents were compliant with the study protocol had some AM from 4-6 years

Prevalence of physician diagnosed allergic manifestation during years 4-6, per protocol analysis

<table>
<thead>
<tr>
<th>AM Type</th>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td>All allergic</td>
<td>20%</td>
</tr>
<tr>
<td>dermatitis</td>
<td>11%</td>
</tr>
<tr>
<td>Hayfever</td>
<td>7%</td>
</tr>
<tr>
<td>Asthma</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

AD = atopic dermatitis  
AM = allergic manifestation  
CMF = cows’ milk formula  
eHF-W = extensively hydrolysed whey formula  
eHF-C = extensively hydrolysed casein formula  
pHF-W = partially hydrolysed whey formula (SMA H.A Infant Milk)  
RR = relative risk
Relative risk of atopic dermatitis:

For those babies with a family history of allergy, a significant reduction in risk of developing AD was found for those fed hydrolysed formula versus CMF.

For the first time, eHF-W reached significance on relative risk of AD. However, this was not repeated at any other timepoints during the study.

Points to note:

- The preventative effect of pHF-W and eHF-C on AD is now confirmed to have a lasting effect up to 6 years
- For the first time, eHF-W reached significance on RR of AD. However, this was not repeated at any other timepoints during the study
- This analysis was based on parental recollection of physician’s diagnosis rather than clinical diagnosis in the study centre. However, in past analyses in the previous studies, both analyses were performed and were consistent between all groups
Results: Year 10

Primary outcomes:

Endpoints measured at the end of year 10 were consistent with year 6.

The analysis shows the RR of a physician’s diagnosis of AM with CMF compared with the study formulas.

Prevalence of physician diagnosed allergic manifestations measured during years 7-10 per protocol analysis

Relative risk of atopic dermatitis:

PHF-W and eHF-C significantly reduced the risk of AM, whereas eHF-W did not significantly affect AM.

PHF-W and eHF-C significantly reduced the risk of AD, whereas eHF-W did not.

Relative risk of atopic dermatitis 0-10 years

<table>
<thead>
<tr>
<th>Formula</th>
<th>Relative Risk</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>eHF-C</td>
<td>0.58</td>
<td>▼ 42% reduction</td>
</tr>
<tr>
<td>pHF-W</td>
<td>0.67</td>
<td>▼ 33% reduction</td>
</tr>
<tr>
<td>eHF-W</td>
<td>0.77</td>
<td></td>
</tr>
</tbody>
</table>

AD = atopic dermatitis  
AM = allergic manifestation  
CMF = cows’ milk formula  
eHF-C = extensively hydrolysed casein formula  
eHF-W = extensively hydrolysed whey formula  
pHF-W = partially hydrolysed whey formula (SMA HA Infant Milk)  
RR = relative risk
Points to note:

- Feeding with pHF-W and eHF-C in the first 4 months of life to supplement breastfeeding has a preventative effect on the cumulative incidence of AD in children with a family history of allergy lasting until 10 years of age.
- This is heavily influenced by observations in the first 6 years.
- No effect was seen on AD in the eHF-W (with the exception of 6 year data which is unexplainable).
- There is no evidence of a rebound effect, although there is insufficient evidence at this time to suggest on-going preventative effects between the 7-10 year period.
- The GINI study states that only hydrolysates with proved efficacy should be recommended for prevention of AD in infants with a family history of allergy.

References:

IMPORTANT NOTICE: Breastfeeding is best for babies. You should always seek the advice of a doctor, midwife, health visitor, public health nurse, dietitian or pharmacist on the need for and proper method of use of infant milks and on all matters of infant feeding. Good maternal nutrition is important for the preparation and maintenance of breastfeeding. Introducing partial bottle-feeding may have a negative effect on breastfeeding and reversing a decision not to breastfeed is difficult. Social and financial implications should be considered when selecting a method of infant feeding. Infant milk should always be prepared and used as directed. Inappropriate foods or feeding methods, or improper use of infant formula, may present a health hazard.

IMPORTANT
SMA H.A. Infant Milk should NOT be used if a baby has already been diagnosed with allergy to cows’ milk proteins or is suspected of already having an allergy to cows’ milk protein. SMA H.A. Infant Milk should be used as the first formula feed, before babies have been exposed to intact cows’ milk proteins.