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Meta-analysis

Impact of maternal supplementation with probiotics during pregnancy on atopic eczema in childhood – a meta-analysis

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Abstract

In the present study, we sought to conduct a literature review of randomised, double-blind, placebo-controlled trials, which assessed the impact of probiotics intake during pregnancy on the development of eczema in children. A meta-analysis was conducted for comparison of the development of atopic eczema in children whose mothers took probiotics during pregnancy *v.* placebo. Study selection, quality appraisal and data extraction were performed independently and in duplicate. The studies were rated according to their size in order to calculate the influence of individual studies on the meta-analysis. A total of seven randomised, double-blind, placebo-controlled trials, published between 2001 and 2009, were selected from the PubMed and Ovid databases for the meta-analysis. The meta-analysis was performed with statistical software Stata/SE11.0. The completed meta-analysis of the seven studies shows a significant risk reduction for atopic eczema in children aged 2–7 years by the administration of probiotics during pregnancy (reduction 5·7 %; $P=0·022$). However, this effect was only significant for lactobacilli (reduction 10·6 %; $P=0·045$), but not for a mixture of various bacterial strains as probiotics (difference 3·06 %, $P=0·204$). In conclusion, the meta-analysis shows that the administration of lactobacilli during pregnancy prevents atopic eczema in children aged from 2 to 7 years. However, a mixture of various bacterial strains does not affect the development of atopic eczema, independent of whether they contain lactobacilli or not.

Key words: **Atopic dermatitis: Prevention: Probiotics: Meta-analysis: Pregnancy**

Atopic dermatitis belongs to the category of atopic diseases and has a prevalence of 10–20 %, one of the most frequent primary manifestation of atopy in children (10–20 %). Atopy is a chronic or chronically recurrent inflammatory skin disease, with concomitant severe pruritus. Children, whose both parents suffer from atopic eczema, have a risk of 60–80 % of developing the disease themselves. Polygenic inheritance is assumed, in which genomic imprinting and various environmental factors also seem to play a role[(1)].

The prevalence of atopic diseases, and especially atopic eczema, has increased over the past years[(2)]. There are various hypotheses explaining the increasing prevalence of the allergies. One of these hypotheses is the 'linoleic acid hypothesis'. It claims that a possible explanation lies in the choice of dietary fats as well as the modified composition of the dietary fats in food[(3)]. A further hypothesis is the 'hygiene hypothesis', which argues that the missing infections at a critical time point in the development of the immune system increase the risks for later allergic diseases[(4)]. Various other hypotheses also try to explain the increasing prevalence. However, the cause remains unknown.

Therapy consists of expositional prophylaxis and the administration of glucocorticoids, calcineurin inhibitors and cyclosporine A. Additionally, specific immunotherapy can be performed[(5)]. Furthermore, in order to avoid atopic diseases, it is recommended to breastfeed 6 months after delivery, avoid passive smoking and protect the child from house dust mites[(2)].

Probiotics are preparations that contain living microorganisms, i.e. lactic acid bacteria and yeasts. They may be

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contained within food or as pharmaceuticals. When ingested in sufficient quantities orally, probiotics may have a health-promoting influence in obstruction, diarrhoea, chronic inflammatory bowel syndrome and other diseases[6–8].

Some clinical trials confirm that the administration of probiotics already during pregnancy and within the first months of life may reduce the risk for atopic dermatitis[9,10], whereas other studies[11] could not show this effect. The gastrointestinal tract of healthy fetuses is sterile. Only during delivery and in the time following, the mother's bacteria colonise the intestine of the fetus and develop into a complex microflora. If probiotics, for example, the *Lactobacillus rhamnosus* strain GG, are taken during pregnancy, they form part of the mother's gut flora and are thus also transferred to the child. In contrast to the mother, where *L. rhamnosus* strain GG only remains for a short time after the discontinuation of intake, they remain detectable in the child's stool for another 6 months after delivery and the discontinuation of intake[12].

The safety of the intake of probiotics during pregnancy has been well tested, especially for lactobacilli and bifidobacteria. It is considered to be well tolerated and has a low risk of side effects[13,14].

In the present study, we sought to conduct a systematic review of randomised trials involving the use of probiotics given during pregnancy and the incidence of atopic eczema in children.

Materials and methods

The present study is based on a systematic database research for randomised, controlled studies on probiotic administration during pregnancy and the risk of atopic eczema within the first years of life.

The following databases were searched starting from the respective start of the database up to and including 23 June 2009. The search terms were 'pregnancy and probiotics':

(1) PubMed
(2) Ovid
   (a) EBM Reviews – Cochrane Central Register of Controlled Trials
   (b) EBM Reviews – Cochrane Database of Systematic Reviews
   (c) EBM Reviews – Cochrane Methodology Register
   (d) EMBASE 1980 until 23 June 2009
   (e) Ovid Medline(r) 1950 until 23 June 2009

Subsequently, the references in the publications were searched for additional, potentially important, publications (Fig. 1). Only publications with ethics approval were included.

Data collection was performed by two independent reviewers while adhering to a data collection sheet. The analyses were then compared and possible discrepancies were solved with the help of a third reviewer (Table 1).

On the basis of the data collection sheets as well as the original articles, quality assessment was made (Table 2). This was done according to the 'CRD's guidance for undertaking reviews in health care' written by the Centre for Reviews and Dissemination. Data that were not found in the original publications could not be considered in the evaluation. An overview of the individual study results is provided in Table 3.

The available data were compared with the statistical software Stata/SE 11.0 (StataCorp LP, College Station, TX, USA). It calculated the risk ratio for each study endpoint as well as the respective 95% CI. In addition, the studies were rated according to their size in order to calculate the influence of individual studies on the meta-analysis. With heterogeneity testing, the comparability of the data that were analysed was assessed.

Results

A total of seven systematic randomised, double-blind and placebo-controlled studies observing 2843 children whose mothers took probiotics or placebo during pregnancy and

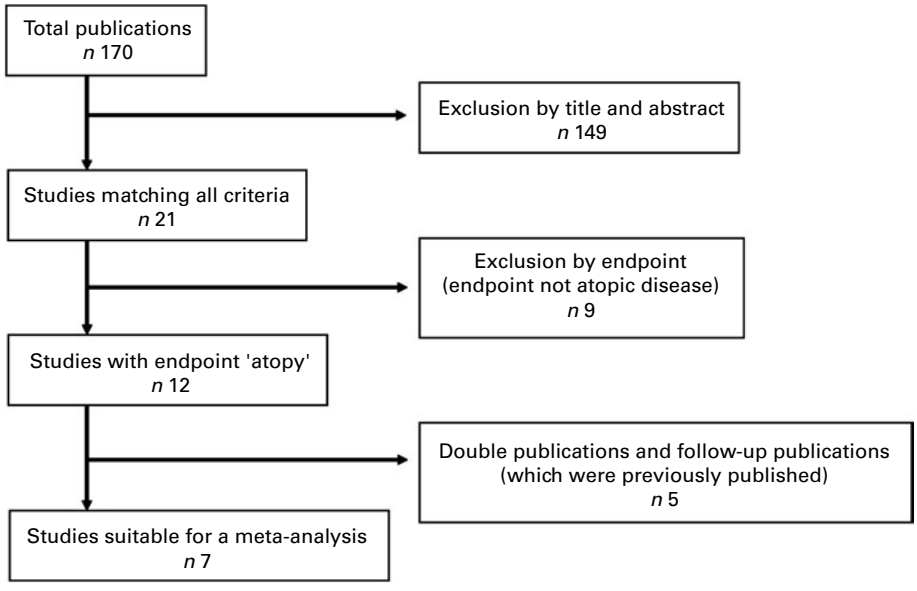

Fig. 1. Study selection.

Table 1. Major contents of the studies on probiotics

Author (year)	Primary objective	Secondary objective	*n*	Male (%)	Comparable groups	Probiotic (colony-forming units)	Placebo	Intake from/until	Results
Kuitunen *et al.* (2009)[15]	Allergy, atopic eczema	Eczema, allergic rhinitis, asthma, food allergy and IgE sensitisation	891	49·5	Yes	*Lactobacillus* GG (5×10^9), *L. rhamnosus* LC705 (5×10^9), *Bifidobacterium breve* Bb99 (2×10^9) and *Propionibacterium freudenreichii* ssp. Shermanii (2×10^9)	Same appearance, taste, smell and intake	36th week of gestation until 6 months after birth	No allergy prevention and less asthma in children with caesarean sections
Wickens *et al.* (2008)[16]	Eczema and atopic eczema	Characteristics of eczemas and detection of bacteria in stool	446	51·9	Yes	Group 1: *L. rhamnosus* HN001 (6×10^9) Group 2: *B. animalis* ssp. lactis HN019 (9×10^9)	Same appearance, taste, smell and intake	25th week of pregnancy until 2 years after birth	Eczemas were reduced by the intake of *L. rhamnosus*
Hurree *et al.* (2008)[17]	Allergic diseases	Cytokine concentration of breast milk	140	NS	Yes	*L. rhamnosus* GG and *Bifidobacterium I actis* Bb12 (1×10^{10})	NS	First trimester until the end of exclusive lactation	Allergy risk can be reduced
Kopp *et al.* (2008)[18]	Atopic dermatitis	Bronchitis and allergies	94	44·7	Yes	*Lactobacillus* GG (5×10^9)	Same appearance, taste, smell, intake and packing	4–6 weeks before birth until 3 months after birth	No differences in atopic dermatitis and reactions to inhalative allergens, recurrent bronchitis in the *Lactobacillus* GG group
Abrahamsson *et al.* (2007)[9]	Allergic diseases	–	188	52	Yes	*L. reuteri* (1×10^8)	Same appearance, taste, smell and intake	36th week of pregnancy until 12 months after birth	Less IgE-associated eczema and less asthma
Kukkonen *et al.* (2007)[19]	Allergic diseases, IgE sensitisation	Eczema	925	49·5	Yes	*Lactobacillus* GG (5×10^9), *L. rhamnosus* (5×10^9), *Bifidobacterium breve* (2×10^8), *Propionibacterium freudenreichii* ssp. Shermanii (2×10^9)	Same appearance, taste, smell and intake	2–4 weeks before birth and until 6 months after birth	Less eczema and same prevalence of allergies
Kalliomäki *et al.* (2007)[10], Kalliomäki (2001, 2003)	Atopic eczema	Allergic rhinitis and asthma	159	50·5	Yes	*Lactobacillus* GG (1×10^{10})	Same appearance, taste, smell and intake	2–4 weeks before birth until 6 months after birth	Less eczemas and a little more asthma

Table 2. Summary of quality criteria

Study	Kuitunen *et al.* (2009)[15]	Wickens *et al.* (2008)[16]	Hurree *et al.* (2008)[17]	Kopp *et al.* (2008)[18]	Abrahamsson *et al.* (2007)[9]	Kukkonen *et al.* (2007)[19]	Kalliomäki *et al.* (2007)[10], Kalliomäki (2001, 2003)
Randomised	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Randomisation method described in detail	No	Yes	No	No	No	Yes	Yes
Double-blinded	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Placebo controlled	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Identical appearance of verum and placebo	Yes	Yes	NS	Yes	Yes	Yes	Yes
Analysis blinded	Yes	Yes	NS	NS	NS	NS	Yes
Inclusion and exclusion criteria listed	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Comparability of the groups present	Yes	Yes	Yes	Yes	Yes	Yes	Yes
All drop-outs described	Yes	Yes	No	Yes	Yes	Yes	No

Table 3. Mentioned frequencies, OR, CI and *P* values in the studies

Study	Endpoint	Prevalence in probiotics group (%)	Prevalence in placebo group (%)	OR	95 % CI	*P*
Kuitunen *et al.* (2009)[15]	Atopic eczema	24·0	25·1	0·94	0·70, 1·28	0·711
Wickens *et al.* (2008)[16]						
Lactobacillus rhamnosus	Atopic eczema	9·9	18·5	0·51	0·27, 0·97	0·04
Bifidobacterium animalis	Atopic eczema	12·8	18·5	0·69	0·38, 1·24	0·04
Hurree *et al.* (2008)[17]	Atopic eczema	9·7	17·6			0·131
Kopp *et al.* (2008)[18]	Atopic eczema	28	27·3	0·96	0·38, 2·33	0·93
Abrahamsson *et al.* (2007)[9]	Atopic eczema	17	28			
Kukkonen *et al.* (2007)[19]	Atopic eczema	12·4	17·7	0·66	0·46, 0·95	0·025
Kalliomäki *et al.* (2007)[10]	Atopic eczema (after 2 years)	23	46	0·51	0·32, 0·84	0·008
Kalliomäki *et al.* (2001)[23]	Atopic eczema (after 4 years)	26·4	46·3	0·57 (RR)	0·33, 0·97	
Kalliomäki *et al.* (2003)[24]	Atopic eczema (after 7 years)	42·6	66·1	0·58	0·35, 0·94	0·027

RR, risk ratio.

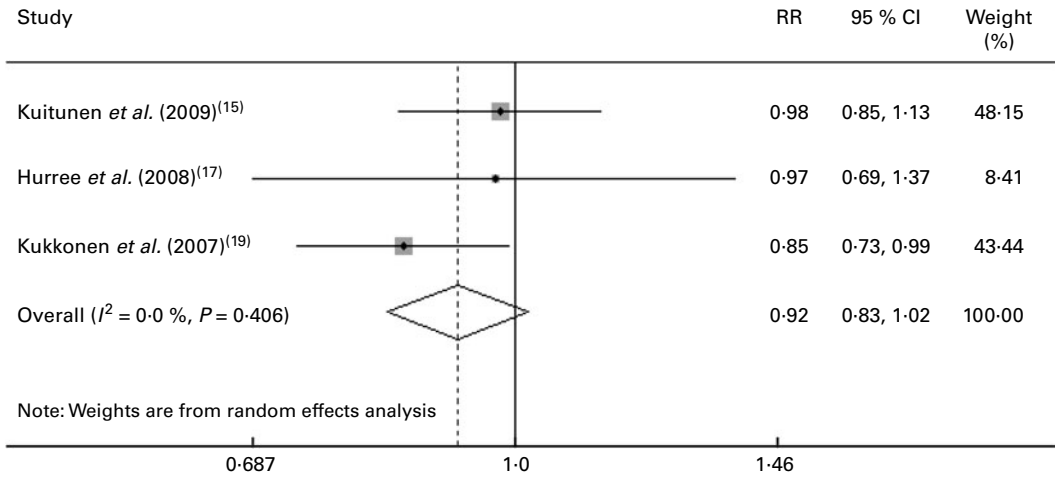

Fig. 2. Endpoint analysis of studies that used mixed probiotics and the development of atopic eczema. RR, risk ratio.

lactation were included in the meta-analysis. All studies that were included used atopic eczema as an endpoint.

Of those studies, four only used lactobacilli as probiotics, three used a mixture of various bacterial strains (including lactobacilli) and one included bifidobacteria.

On the basis of the selected studies, two meta-analyses were performed. It was observed that one study used lactobacilli and the other studies used a mixture of bacterial strains.

The meta-analysis on those studies that used a mixture of various bacterial strains shows no significant association between the intake during pregnancy and lactation and the development of atopic eczema in the children (P=0·204). The study by Kuitunen *et al.*[15] showed the strongest contribution to the meta-analysis (Fig. 2).

The meta-analysis on the studies that used only lactobacilli as probiotics shows a significant correlation between the administration of the probiotics during pregnancy and lactation and the development of atopic eczema (P=0·045, Fig. 3). All the studies that are included contribute equally to the meta-analysis.

Discussion

Overall, probiotics significantly reduce the risk of the development of atopic eczema (P=0·022). However, the effect can only be ascribed to the results of three of the seven studies.

In a separate analysis of the studies that used lactobacilli and those that used a bacterial strain mixture, only monotherapy resulted in a significant risk reduction for atopic eczema (P=0·045 *v.* P=0·204). Surprisingly, the bacterial load per bacterial strain is comparable in the strain mixture and monotherapy. However, it may be possible that the orally applied bacteria remain in the gut for only a short time due to displacement effects. A possible reason could be a repression of each other, which anticipates the attainment of effective concentrations.

There is some evidence that probiotics maintain the integrity of the intestinal barrier. Some of the effects appear to be mediated through Toll-like receptors, which are also expressed by the enterocytes[20]. But this effect is limited only to some species (*Lactobacillus reuteri* and *Lactobacillus casei*) and not to others (*Lactobacillus planarum*).

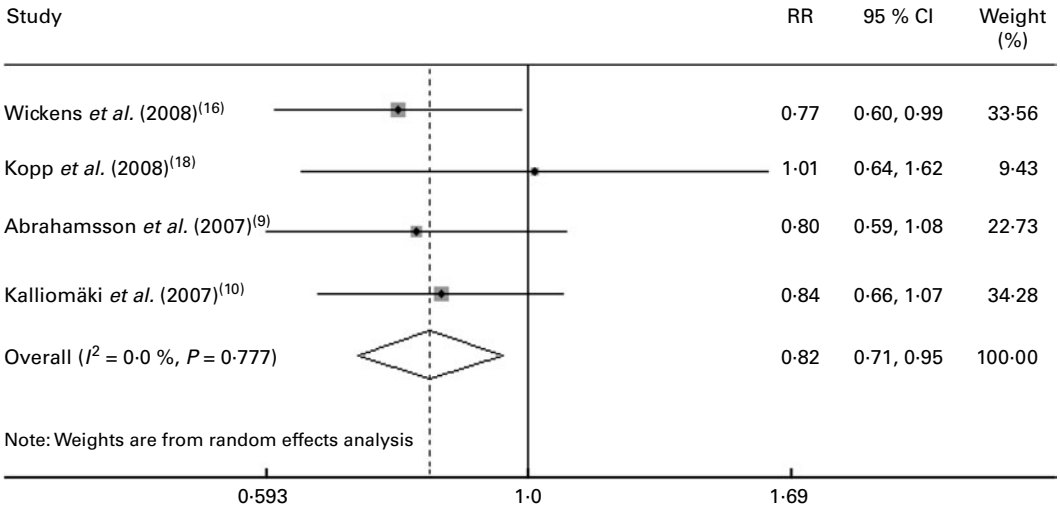

Fig. 3. Endpoint analysis of studies that used lactobacilli and the development of atopic eczema. RR, risk ratio.

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The reason for the different effects might be that those species cannot bind the three grabbing non-integrin molecules that are blocking the antibodies that are responsible for intercellular adhesion molecule. On the basis of available data, the recommendation for the administration of probiotics consisting of lactobacilli during pregnancy and lactation can be made, as it may lead to a reduction in the development of atopic eczema in children at risk. More longitudinal studies observing the clinical and experimental factors as well as the time of the beginning such a therapy are necessary[21].

This effect could not be found in the actual S-3 guidelines from the German Society of Dermatology since two of the publications cited were published after the literature research in March 2008[22].

Due to non-significant results, no recommendation for probiotics consisting of different bacterial strains can be given. No evidence-based studies are currently available on other probiotics.

The severity of atopic eczema was less in the group that received *L. rhamnosus* than in the group that took *Bifidobacterium animalis* spp. lactis[16].

In conclusion, probiotics, especially lactobacilli, reduce when taken as a monotherapy during pregnancy the child's risk of developing atopic eczema. The long-term development of this effect will have to be assessed in further studies, and so do the possibly differing effects of single bacterial strains.

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