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Systematic review and meta-analysis on the use of probiotic supplementation in pregnancy, breastfeeding mother and infancy for the prevention of atopic dermatitis in children

Probiotics in prevention of childhood AD

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Abstract

Probiotic supplementation may decrease the risk of allergic disease, however there are differences between studies such as, the type of probiotic/s, the route and duration of supplementation. Therefore, determining the most effective probiotic strain/s, route of administration and duration of supplementation for clinical recommendation has been difficult. The aim of our systematic review and meta-analysis was to determine firstly whether probiotic supplementation reduces the risk of AD in children and secondly to investigate further as to whether there are any

trends to determine the most effective probiotic strain/s and the method of administration leading to recommendations for clinical practice. An electronic systematic literature search was undertaken between 23rd August and 15th October 2018 using Ovid Medline, Embase, Pubmed, and Cochrane. Risk ratio (RR) and 95% confidence interval (CI) are presented for the studies. PEDro scale and Newcastle-Ottawa scale were used to assess the quality of the included studies. A total of 21 studies met the inclusion criteria. Strain-specific sub-meta-analyses indicated that single strains are not as effective as probiotic mixtures and administration to a combination of pregnant mothers, breastfeeding mothers and infants had a reduced risk in the onset of AD in children. Our systematic review and meta-analysis showed that a mixture probiotic supplementation given to the mother in pregnancy and continuing while breast feeding and also to the infant, in children classified as high-risk for AD and non-high-risk groups is the most efficacious in reducing the risk of incidence of AD in children.

Keywords: probiotics, atopic dermatitis, children

Key points

- Probiotic supplementation when administered to the pregnant mother, breastfeeding mother and infant is effective in reducing the risk of atopic dermatitis (AD) and is preferable over supplementation of just the mother or the infant.
- A mixture of probiotics reduces the risk of AD in children more than single strain probiotics.
- Probiotic supplementation is beneficial in both the high-risk and general population groups.

Abbreviations

AD : Atopic Dermatitis

Th2 : T helper cell type 2

IL-4 : Interleukin-4

IL-5 : Interleukin-5

IL-13 : Interleukin-13

IgE : Immunoglobulin E

Th1 : T helper cell type 1

DC : Dendritic cell

IFN-γ : Interferon- γ

IgA : Immunoglobulin A

TGF-β1: Transforming growth factor-beta 1

TSLP : Thymic Stromal Lymphopoietin

CD4 : Cluster of differentiation 4

CD25 : Cluster of differentiation 25

Foxp3 : Forehead box P3

T reg : Regulatory T

PM : Probiotic supplementation given to pregnant mothers

BM : Probiotic supplementation given to breastfeeding mothers

IF : Probiotic supplementation given directly to the infants

HN001: *Lactobacillus rhamnosus* HN001

HN019: *Bifidbacterium animalis* subsp *lactis* strain HN019

LGG : *Lactobacillus rhamnosus* GG

AD011: *Bifidobacterium lactis* AD011

BGN4 : *Bifidobacterium bifidum* BGN4

AD031: *Lactobacillus acidophilus* AD031

W23 : *Bifidobacterium bifidum* W23

W25 : *Bifidobacterium lactis* W25

W58 : *Lactococcus lactis* W58

BB536: *Bifidobacterium longum* BB536

M-16V: *Bifidobacterium breve* M-16V

CUL08: *Lactobacillus paracasei* CUL08

CUL61: *Lactobacillus salivarius* CUL61

CUL20: *Bifidobacterium bifidum* CUL20

CUL34: *Bifidobacterium animalis* subspecialis *lactis* CUL34

JS : *Propionibacterium freudenreichii* ssp *shermani*i JS

Bb99 : *Bifidobacterium breve* Bb99

LC705: *Lactobacillus rhamnosus* LC705

La-5 : *Lactobacillus acidophilus* La-5

Bb12 : *Bifidobacterium lactis* Bb12

LRh : *Lactobacillus rhamnosus*

BL999 : *Bifidobacterium longum* BL999

ST11 : *Lactobacillus paracasei* ST11

LPR : *Lactobacillus rhamnosus* LPR

F19 : *Lactobacillus paracasei* F19

Introduction

Atopic dermatitis

Atopic dermatitis (AD) is a common and chronic inflammatory skin disease, affecting children globally and more so in Australia, where the prevalence in young children is as high as 30% [(1)]. Around 50% of children with AD will develop other atopic disease, such as food allergy, asthma and allergic rhinitis, known as the atopic march [(2)].

AD Pathophysiology

AD is characterized by abnormalities in the microbial flora of the skin, hyperactive immune response and a defect in epithelial barrier function [(3, 4)]. The pathophysiology of AD has been proposed to arise from two main processes being the adaptive immune system imbalance and the defect of skin barrier. The immunological hypothesis suggests that AD results from a T cell imbalance with the predominating activity being the T helper cell type 2 (Th2) differentiation of naïve CD4+ T cells. This causes an increase in interleukin (IL) production (IL-4, IL-5, IL-13), an increase in immunoglobulin E (IgE) and inhibition of T helper cell type 1 (Th1) differentiation. With regards to skin barrier, the most common genetic polymorphism that leads to barrier dysfunction is filaggrin [(5)].

Potential role of probiotic supplementation in the prevention of AD

Probiotics may be important in modulating microbiota composition, adhesion of potential pathogens, modulation of epithelial cell barrier, Th1/Th2 balance, innate immunity and dendritic cell (DC) maturation [(6)]. It is suggested that probiotics may

improve intestinal barrier integrity resulting in decreased bacteria translocation across the intestinal mucosa and maintain immune tolerance [7].

Probiotic supplementation during pregnancy has shown to produce higher levels of interferon-γ (IFN-γ) in cord blood [8]. Infants may be predisposed to AD when they have impaired IFN-γ activation as this may increase the production of the IL-4 cytokine. In cord blood samples of infants who develop AD, it is shown that there is a production of impaired allergen-induced IFN-γ. This impairment increases apoptosis of IFN-γ producing Th1 cells causing the increase of Th2 cells leading to Th1/Th2 imbalance leading to an increase risk of AD [9].

Probiotic supplementation given to breastfeeding mothers may increase the levels of IgA and transforming growth factor-beta 1 (TGF-β1) in the breast milk [8, 10]. Higher levels of IgA antibodies in breastmilk and colostrum may prevent antigens entering the infant's intestinal surface thereby possibly reducing the risk of allergic disease [11]. TGFβ is present in human breast milk. It plays an important role in immune regulation. IgA and TGFβ regulate mucosal immunity which protects against allergic disease [12]. Additionally, direct supplementation to the infant can also be beneficial. Food antigens can induce immune-inflammatory and allergic responses that may lead to impairment of gut barrier function, leading to abnormal absorption of food, microbes and antigens. Infant supplementation of probiotics may improve barrier defences and intensify colonization of the gut microbiota. Probiotics reduce permeability of the intestine and alter redistribution and expression of tight-junction proteins, hence reducing the absorption harmful molecules from the intestine [13].

Studies have found that oral probiotic administration can regulate skin inflammation and repair processes [14]. In a novel mouse model study, probiotic administration may have prevented the development of AD by suppressing production of inflammatory cytokines, thymic stromal lymphopoietin (TSLP) and IL-4 by a mechanism that may involve CD4(+)CD25(+)Foxp3(+) T reg (Regulatory T) cells in the skin [15]. TSLP is an epithelial-derived cytokine that is expressed by skin, lung and gut epithelial cells. Various cytokines, trauma and allergens are able to activate

TSLP production. TSLP induces Th2 adaptive immune response contributing to Th2 inflammation that can be seen in AD [16].

Several studies have found that early exposure of antibiotics may be associated with the development of allergic disease. Current experiments indicate that a hygienic living environment and early life antibiotic exposure decrease microbial stimulation and is followed by a reduced Th1 immune response. Concurrently, antibiotic exposure disrupts intestinal microflora thus resulting in a Th2 immune response. The intestinal microflora disruption reduces the T reg immune response thus leading to Th2 response upregulation, and allergic disease development [17].

Currently, there are conflicting results on the use of probiotic supplementation in preventing childhood AD. The contradictory evidence is possibly due to studies using different strains of probiotics, varying routes of delivery and the administration time. A systematic review and meta-analysis is important to conclude if and what strain/s of probiotics are preventative on the onset of AD and consequently the atopic march.

Interest in the area of probiotic supplementation and its potential role in the prevention of AD has increased especially over the past five years where many studies have been undertaken in this area. Since 2012 there have been four systematic reviews, with the latest review published in 2018 [18-21]. These reviews have also completed meta-analysis however whilst probiotics have shown to decrease the risk of developing AD, there has been no definite answer on the best method of supplementation and the specific strain/s needed to enhance this outcome. The aim of this study was to categorise the types of probiotics and methods of administration to determine if there were any conclusions that can be made to aid clinicians with their advice on this topic.

The aim of this systematic review and meta-analysis is to determine whether probiotic supplementation to the pregnant mother and/or breastfeeding mother and/or infant or a combination of the three reduces the risk of AD in children and to decide which probiotic strain/s is most effective as well as the administration method of the probiotic supplementation.

Method

This systematic review was conducted by using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and a priori protocol was established before undertaking a comprehensive literature search.

Eligibility criteria

Participants/population

Pregnant and/or breastfeeding mothers and/or children (0-18 years of age) with eczema and/or atopic eczema and/or atopic dermatitis. Studies in the adult population (>18 years old) with eczema and/or atopic eczema and/or atopic dermatitis were excluded.

Intervention

The intervention was probiotic supplementation given to breastfeeding mothers and/or pregnant mothers and/or directly given to the infants. Studies about prebiotics and/or symbiotic supplementation were excluded.

Outcome measures

The primary outcome that was measured was the prevalence of AD in children (0-18 years of age).

Study design

Randomized controlled trial (RCT), non-randomized controlled trial (NRCT), clinical trials or cohort studies were deemed to be eligible to be included in this review.

Search strategy

A comprehensive electronic bibliography search was undertaken between 23rd August and 15th October 2018. A gray literature search was not performed. Electronic databases used were; Ovid Medline, Embase, Pubmed, and Cochrane.

The Boolean search terms that that were used are listed below, the following terms were combined using the AND command:

- *(eczema OR atopic dermatitis)*

- *probiotic agent*
- *(neonates OR infants OR children OR adolescents)*

Only English language articles published in the last ten years (2008 to October 2018) were included.

Data extraction

The search results were imported to the reference management software (EndNoteTM X8.2). The duplicates were removed then the potential relevant articles were identified by screening the title and abstracts. Hand-searching of the reference lists was also performed in order to find any additional relevant articles. The articles that met the inclusion criteria were selected for full-text analysis. The data from the selected articles was extracted and summarized to compare the results. Data was extracted by two authors to ensure accuracy.

Data analysis and reporting

The data of the articles were extracted and summarized using a summary table that consisted of study design, subject characteristics (e.g. high risk or non-high risk of allergic diseases, history of illness, birth delivery mode), the inclusion criteria, type and dosage of probiotic supplementation, method and duration of probiotic supplementation and key findings.

An overall estimate was generated from all included studies to understand the effect of probiotic supplementation on the risk of AD. The included studies were differentiated into groups according to the method of supplementation. This sub-meta-analysis was generated to observe the most effective method of supplementation. This resulted in five groups:

(1) probiotic given to pregnant mother, breastfeeding mother and infant (PM, BM, IF);
(2) probiotic given to pregnant mother and to infant (PM, IF);
(3) probiotic given to pregnant mother and breastfeeding mother (PM, BM) (note this included a study where the infant received the probiotic if it was not breast fed [22];
(4) probiotics were only given to the pregnant mother (PM);
(5) probiotics were only given to the infant (IF) and this includes a study of preterm infants [23].

Subgroups of probiotic strains were generated in order to determine the most beneficial probiotic strain/s. The probiotic strains were separated into five subgroups (Figure 4). Each study had different reasons on the selection of the probiotic strains supplemented, such as the capacity to suppress the Th2 response, the ability to alleviate allergic symptoms of atopic disease, widely commercially available and used in other studies. The probiotic strains were grouped when there was more than one study observing the same strain. There were four estimates (from two studies) supplementing *Lactobacillus rhamnosus* HN001, three estimates (from one study) supplementing *Bifidobacterium animalis* subsp *lactis* HN019, three estimates (from three studies) supplementing Lactobacillus rhamnosus GG and two estimates (from one study) supplementing *Lactobacillus paracasei* F19. Mixtures of probiotic were accounted as one group as there was lack of studies observing the same specific mixture of probiotics. A sub-meta-analysis was generated to observe the difference between the high-risk and non-high-risk population on the risk of developing AD.

For each study, the total number of children and the number with AD were extracted for the probiotic and control group. The data extracted and double-checked by NA and EK. The risk ratio (RR) and 95% confidence interval (CI) were calculated from the extracted data. This data was imported into Stata version 15.1 and the admetan command was used to create forest plots.

Quality assessment

The study quality was evaluated using quality assessment tools dependent on the study design. The PEDro assessment tool was used to assess RCT or clinical trial studies and the Newcastle-Ottawa Scale (NOS) for cohort studies.

Results

Literature search

An initial literature search was undertaken using four electronic databases and yielded a total of 1,090 potentially relevant articles. Manual hand-searching of the reference lists yielded an additional eight articles. Preliminary screening by removing duplicates resulted in a total 779 potentially relevant articles. Additionally, 735 articles were excluded because they were systematic reviews, meta-analysis, letters, reviews, did not observe preventive effect of probiotic or the intervention did not use probiotics and articles published prior to 2008. Secondary screening based on full text of the remaining articles resulted in 21 articles that were found to be appropriate to be included in this systematic review [10, 22-41]. A flowchart of study screening and selection process is presented in Figure 1 using PRISMA flowchart [42].

Characteristics of the included studies

The study characteristics of the included studies are described in Table 1. From the total of twenty-one studies included in this review, there were eighteen RCTs [10, 22, 24, 26-28, 30-41], one open trial study [29] and two cohort studies [23, 25]. The primary outcome that was measured was the prevalence of AD in children (0-18 years of age). Clinical diagnosis of AD was made by trained research staff or health professionals and determined based upon one of the following tools; The UK Working Party's Diagnostic Criteria for Atopic Dermatitis, repeated parental report of eczema diagnosis, the Guidelines of the Japanese Dermatological Association on Eczema (2005), Basic Clinical Scoring System (BCSS), Hanifin and Rajka diagnostic criteria, questionnaires, clinical assessments and medical records. Twelve studies observed 'high risk' infants [10, 22, 26, 30-34, 36, 39-41] where they had either or both parent/s and/or siblings with a history of treated AD, allergic rhinitis, food allergy and asthma. Only five studies measured the presence of the probiotic supplemented in the child's feces using the fecal DNA sample collection and followed by quantitative real-time Polymerase Chain Reaction (PCR), denaturing gradient gel electrophoresis analysis and random amplified polymorphic DNA [29, 32, 33, 40, 41].

Quality assessment of the included studies

Of the nineteen articles that were assessed using the PEDro scale fourteen articles were considered as excellent quality studies, four studies were good quality, and one study fair quality. The two cohort studies included were assessed using the Newcastle-Ottawa Scale. Both cohort studies did not have an independent blind assessment or record linkage for the outcome assessment and also the follow-up rate was less than 80% with no description for the reason for loss of follow-up. These two studies were considered to be poor quality.

Probiotics in the prevention of atopic dermatitis onset in children

Collective data from 31,252 children (10,175 in the probiotic group and 21,077 in the control group) were analyzed. From twenty-one articles included in this review, there were seventeen original studies (two had one follow-up study and one had two follow-up studies). There was a total of twenty-four probiotic stains used in the seventeen studies, and were administered as either a single or mixture of probiotic strain/s. The duration and method of supplementation, as well as the follow-up time were heterogenous. The overall RR and CI indicate there was a 23% reduction in risk of developing AD for the probiotic group when compared to the control group (RR 0.77; 95% CI 0.70-0.86). Heterogeneity among studies was moderate (I^2 = 58.5%), and for this reason, the random-effects model was used. (Figure 2)

Subgroup analysis according to the method of probiotic supplementation

Probiotic/s given to pregnant mother, breastfeeding mother and infant (PM, BM, IF)

There were ten estimates from three studies (Figure 3) [10, 30, 31, 40, 41]. The study undertaken by Kim JY, et al. was reported three times as this research was observed at three different time points (3, 6 and 12 months of infant's age). The probiotic supplementation was administered to pregnant mothers, breastfeeding mothers and infants.

Three RCT studies by Wickens K, et al. administered *Lactobacillus rhamnosus* HN001 and *Bifidobacterium animalis* subsp *lactis* HN019 in a high-risk population in New Zealand. These strains were not administered as a mixture, but as a single strain and each of them was compared to placebo (Table 1). This study observed three different follow-up time points (2, 4, and 6 years of age). These three studies are presented by six estimates in Figure 3. The estimate shows that the probiotic group had a decreased risk of AD. However, only two estimates, which were the *Lactobacillus rhamnosus* HN001 at two years of age (RR 0.54; 95% CI 0.34-0.85) and *Bifidobacterium animalis* subsp *lactis* HN019 at four years of age (RR 0.69; 95% CI 0.48-0.98) indicate a more positive result. It appears that the effects of these probiotic strains waned as the children became older and were no longer taking the probiotics.

Kopp MV, et al. observed the administration of *Lactobacillus rhamnosus* GG (Table 1). The risk ratio indicated that the probiotic group had an increased risk of developing AD (RR 1.03; 95% CI 0.53-1.98) by two years of age (Figure 3). Kim JY, et al. supplemented a mixture of *Bifidobacterium lactis* AD011, *Bifidobacterium bifidum* BGN4 and *Lactobacillus acidophilus* AD031 (Table 1). This study had three time points of follow-up at three (RR 0.53; 95% CI 0.26-1.12), six (RR 0.49; 95% CI 0.23-1.05) and twelve months (RR 0.45; 95% CI 0.20-1.04) of age. The three estimates indicated that the probiotic group was at reduced a risk of developing AD, although we cannot be confident that the group risk is different due to the confidence interval (Figure 3).

The overall estimate of these studies indicates that for children in the probiotic group, their risk of having a diagnosis of AD at follow up was 25% less (95% CI 0.65-0.87) than those in the control group (Figure 3).

Probiotic/s given to pregnant mother and to infant (PM, IF)

There were nine estimates from five studies [24, 25, 27, 29, 32, 33]. The study by Niers L, et al. had two follow-up time points and were presented by two estimates. Enomoto T, et al. study had three estimates as they observed the outcomes at three time points. Davies G, et al. undertook a five-year follow-up study from the Allen SJ, et al. trial. All were RCT studies, except Enomoto T, et al. with an open trial study and Bertelsen RJ, et al. a cohort study.

The study by Niers L, et al. supplemented a mixture of *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W25 and *Lactococcus lactis* W58 (Table 1). The probiotic mixture reduced the risk of developing AD at the one (RR 0.74; 95% CI 0.51-1.07) and two years of age follow-up (RR 0.79; 95% CI 0.57-1.08), although this is a weak assertion (Figure 3).

Enomoto T, et al. administered probiotic mixture of *Bifidobacerium longum* BB536 and *Bifidobacterium breve* M-16V (Table 1). It was found that the probiotic mixture decreased the risk of AD at four (RR 0.86; 95% CI 0.30-2.48), ten (RR 0.31; 95% CI

0.41-0.67) and eighteen months of age follow-up (RR 0.37; 95% CI 0.16-0.88) time periods with strong support to this assertion (Figure 3).

Kuitunen M, et al., Allen SJ, et al., and Davies G, et al. study had the same duration of supplementation, although administered different probiotic strains. Allen SJ, et al. and Davies G, et al. supplemented a mixture of *Lactobacillus paracasei* CUL08, *Lactobacillus salivarius* CUL61, *Bifidobacterium bifidum* CUL20 and *Bifidobacteirum animalis* subsp *lactis* CUL34 (Table 1). At the two years of age follow-up, the Allen SJ, et al. study found that probiotics had no protective effect against the risk of developing AD (RR 1.05; 95% CI 0.81-1.37). In Davies G, et al. study, the probiotic group had a weak decreased risk of developing AD at the five years of age follow-up (RR 0.96; 95% CI 0.72-1.27) (Figure 3).

Kuitunen M, et al. supplemented a probiotic mixture of *Lactobacillus rhamnosus* GG, *Propionibacterium freudenreichii ssp shermanii* JS, *Bifidobacterium breve* Bb99 and *Lactobacillus rhamnosus* LC705. It was found that this mixture of probiotics had a protective effect against the risk of developing AD at the five years of age follow-up (RR 0.91; 95% CI 0.78-1.06) (Table 1, Figure 3).

Bertelsen RJ, et al. administered a probiotic mixture of either a mixture *Lactobacillus acidophilus* La-5, *Bifidobacterium lactis* Bb12 and *Lactobacillus rhamnosus* or a mixture of *Lactobacillus acidophilus* La-5 and *Bifidobacterium lactis*. It was found that the probiotic mixture had a strong protective effect against the risk of AD at the eighteen months of age follow-up (RR 0.92; 95% CI 0.86-0.99) (Table 1, Figure 3).

When combining results of all studies supplementing probiotics to the pregnant mother and infant, the overall estimate showed there was a reduced risk of 13% (95% CI 0.76-0.98) in the probiotic group of developing AD at follow up when compared to those in the control group (Figure 3).

Probiotic/s given to pregnant mother and breastfeeding mother (PM, BM)

There were eight estimates from five studies [22, 28, 34, 35, 39]. The study by Rautava S, et al. had two estimates as they observed two mixtures of probiotics and compared

each of them to placebo. Ou CY, et al. had three estimates because they observed the outcomes at three different time points. Although these five studies had the same method of probiotic supplementation delivery, the duration of supplementation time was different. All of the studies performed randomized controlled trials.

Wickens K, et al. RCT supplemented *Lactobacillus rhamnosus* HN001 and found that the subjects in the probiotic group had a reduced risk of developing AD, however, we cannot be confident that the risk between the probiotic and placebo groups is different (RR 0.85; 95% CI 0.57-1.26) (Table 1, Figure 3). Simpson MR, et al. and Dotterud CK, et al. supplemented a mixture of *Lactobacillus rhamnosus* GG, *Bifidobacterium lactis* Bb-12 and *Lactobacillus acidophilus* La-5 (Table 1). Simpson MR, et al. found that the probiotic mixture reduced the risk of developing AD at six years of age follow-up (RR 0.62; 95% CI 0.40-0.95). Dotterud CK, et al. found that the subjects in the probiotic group had a decreased risk of developing AD at the two years of age follow-up (RR 0.61; 95% CI 0.41-0.91) (Figure 3).

Rautava S, et al. administered a mixture of *Bifidobacterium longum* BL999 and *Lactobacillus rhamnosus* LPR and in the second arm, a mixture of *Bifidobacterium longum* BL999 and *Lactobacillus paracasei* ST11 (Table 1). At the two years of age follow-up, the children of mothers who received either of the probiotic arm were found to have a decreased risk of developing AD when compared to the placebo group (RR 0.41; 95% CI 0.27-0.60, RR 0.40; 95% CI 0.27-0.60) (Figure 3). Ou CY, et al. administered *Lactobacillus rhamnosus* GG, there was no reduction in risk of developing AD at six (RR 1.41; 95% CI 0.83-2.39), eighteen (RR 1.41; 95% CI 0.71-2.79) and thirty-six months of age follow-up (RR 0.98; 95% CI 0.54-1.80) (Table 1, Figure 3).

When combining results of all studies supplementing probiotics to the pregnant mother and breastfeeding mother, the overall RR and CI indicate that children whose mothers were given probiotic supplementation during pregnancy and breastfeeding had a 28% (95% CI 0.52-1.00) less risk of developing AD at follow up compared to those in the control group (Figure 3).

Probiotic/s only given to pregnant mother (PM)

There was one RCT study[26] that administered *Lactobacillus rhamnosus* GG supplementation (Table 1). The overall estimate indicates that for children in the probiotic group, their risk of having a diagnosis of developing AD at one year of age follow up was not less than those in the control group (RR 0.88; 95% CI 0.63-1.22) (Figure 3).

Probiotic/s were only given to the infant (IF)

Four estimates were extracted from four studies in this group [23, 36-38]. All the studies had the same method of administering probiotic supplementation to the infant, however each had a different duration of supplementation. All studies were RCT except Damm JA, et al. cohort study.

Damm JA, et al. administered a mixture of *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis* subsp *lactis* Bb-12 (Table 1). This study found that probiotics were not protective against the risk of developing AD (RR 1.22; 95% CI 0.82-1.83) (Figure 3). Soh SE, et al. administered a mixture of *Lactobacillus rhamnosus* LPR and *Bifidobacterium longum* BL999 (Table 1). It was observed that at the one year of age follow-up, there was a weak association in a reduced risk of developing AD (RR 0.88; 95% CI 0.56-1.39) (Figure 3). West CE, et al. conducted an initial and follow-up study administering *Lactobacillus paracasei* F19 (Table 1). At the thirteen months of age (RR 0.49; 95% CI 0.24-1.02) and eight to nine years of age follow-up (RR 0.66; 95% CI 0.27-1.58), the probiotic was found to reduce the risk of developing AD (Figure 3). However, as time progressed the effect of the probiotics waned.

When combining results of all studies supplementing probiotics to the infant, the overall estimate indicates there was no significant effect when comparing children in reducing the onset of AD when comparing the probiotic and control groups (RR 0.85; 95% CI 0.58-1.25) (Figure 3).

Subgroup analysis according to the probiotic strain supplemented

There were four estimates (from two original studies) where *Lactobacillus rhamnosus* HN001 was administered. The overall estimate of these studies indicates that children in the *Lactobacillus rhamnosus* HN001 group had a reduced risk of developing AD at follow up was 25% less (95% CI 0.62-0.92) than those in the control group. Three estimates (from one trial) administered *Bifidobacterium animalis* subsp *lactis* HN019 to the pregnant mother, breastfeeding mother and infant. The sub-meta-analysis showed that there was no significant effect when comparing children in the *Bifidobacterium animalis* subsp *lactis* HN019 group to those in the control group (RR 0.82; 95% CI 0.67-1.01). *Lactobacillus rhamnosus* GG was administered to mothers and/or infants in three studies. The overall estimate showed that children in the probiotic group had a 4% higher risk of developing AD when compared to the control group (95% CI 0.83-1.30). One study administered *Lactobacillus paracasei* F19 to infants, these children had a 45% less (95% CI 0.32-0.97) risk of developing AD than those in the control group. There were eighteen estimates from eleven original studies where a mixture of probiotics was administered to mothers and/or infant. The overall estimate of these studies indicates that children in the probiotic group had a reduced risk of 28% (95% CI 0.62-0.83) of developing AD when compared to the control group. (Figure 4)

Subgroup analysis according to the population

Twenty one estimates (from ten original studies) supplemented either a single or mixture of probiotic strain/s to a high-risk population with different follow-up times. The overall estimate of these studies showed that the children in the probiotic group had a reduced risk of 24% (CI 0.67-0.87) of developing AD when compared to those in the control group. Seven original studies administered a single or mixture of probiotic strains to a general population with different follow-up times. The overall estimate shows that non-high-risk children in the probiotic group had a 21% less (95% CI 0.65-0.95) risk of developing AD at follow up when compared to those in the control group. (Figure 5)

Discussion

This systematic review and meta-analysis included a total of twenty-one articles, which included seventeen original studies. There were eighteen randomized controlled trials, one open trial and two cohort trials observing probiotic supplementation to pregnant mother and/or breastfeeding mother and/or infant. Similar to previous meta-analysis, data from the included studies found that probiotic supplementation reduced the risk of developing AD in children.

We elected to analyse deeper to determine whether there were any trends towards the type and method of administration to aid clinical advice on this topic. Sub-meta-analysis on the method of probiotic supplementation showed that probiotic administration to a combination of pregnant mother, breastfeeding mother and infant had the most influence on reducing the risk of developing AD in children. It was found that probiotic supplementation was more effective in the high-risk population but was effective in normal population as well. Strain-specific sub-meta-analyses indicated that *Bifidobacterium animalis* subsp *lactis* HN019 (RR 0.82; 95% CI 0.67-1.01) and *Lactobacillus rhamnosus* GG (RR 1.04; 95% CI 0.83-1.30) as a single strain had no effect in reducing the incidence of AD. Single strain of *Lactobacillus rhamnosus* HN001 (RR 0.75; 95% CI 0.62-0.92), single strain of *Lactobacillus paracasei* F19 (RR 0.55; 95% CI 0.32-0.97) and mixtures of probiotics (RR 0.72; 95% CI 0.62-0.83) reduced the risk of developing AD in children. However, single strain of *Lactobacillus rhamnosus* HN001 and *Lactobacillus paracasei* F19 had wider confidence intervals compared to the mixtures of probiotics. Hence, our review concludes that single strains of *Lactobacillus rhamnosus* HN001, *Lactobacillus paracasei* F19, *Bifidobacterium animalis* subsp *lactis* and *Lactobacillus rhamnosus* GG are not as effective as probiotic mixtures.

Zuccotti et al published a systematic review and meta-analyses of 17 studies in 2015 on the supplementation of probiotics for the prevention of atopic disease in infants. This review concluded that developing AD may be reduced by administering probiotics to the pregnant mother and infant. This review did not come to a conclusion on what the most effective probiotic strain/s is. A sub-meta-analysis evaluating the method of probiotic supplementation was not undertaken [21].

An additional systematic review and meta-analysis undertaken by Li L, et al. in 2018 included 28 studies on this topic. This review showed that probiotic supplementation was beneficial in reducing the risk of developing AD for both the general and high-risk population. They found mixtures of probiotics including *Lactobacillus*, *Bifidobacterium* and *Propionibacterium* strains reduced the risk of developing AD from gestation and continuing through the first 6 months of infant's life. However, this review did not perform sub-meta-analyses on the method of supplementation, population and probiotic strains supplemented [18].

A systematic review and meta-analysis undertaken by McFarland LV, et al. in 2018 concluded that probiotic efficacy is affected by the probiotic strain and the disease. And suggested that a meta-analysis observing probiotics should report on the specific strains relevant to the type of disease [43]. Our review supported this and came to a conclusion on what is the most appropriate probiotic strain/s are to prevent the incidence of AD.

The strength of our review is the inclusion of meta-analysis and sub-meta-analyses. This information offers more conclusive evidence on the overall effect of probiotics in reducing the risk of developing AD, as well as determining the method of supplementation and the specific probiotic strain/s.

Due to the heterogeneity of the information supplied in the included articles, there is a need for additional good quality long-term follow up studies to determine the specific probiotic strain/s, method and duration of supplementation.

Study Limitations

This was a thorough systematic review and meta-analysis as it observed the strains, duration, method, dosage and length of treatment of probiotic supplementation in each of the 21 articles. Limitations to this review include; the search being undertaken from August to October 2018, there may have been new studies published since then. Only English language articles were reviewed, thus relevant non-English articles may have been excluded in this review. The subdivision of the

meta-analysis was decided arbitrarily in that it was thought that it would provide the most useful information for treating clinicians. Dividing the studies into different groups may have yielded alternative outcomes.

Conclusion

A mixture of probiotic strains supplemented to a combination of the pregnant mother, breastfeeding mother and infant reduces the risk of developing AD in children. Supplementation in both high-risk and the general population was effective although it was found that probiotic supplementation was more effective in the high-risk population. There is a need for more high-quality and long-term follow-up studies to support the current evidence. These studies should specifically observe specific single or mixture of probiotic strains in individual treatment arms to determine the most effective probiotic/s as well as the specific duration of treatment and the method of supplementation that is in pregnancy, breastfeeding and infancy.

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Figure Legends:

Figure 1 Prisma flow diagram summarizing the identification, screening, eligibility and inclusion of the articles that investigated the probiotic supplementation in prevention of AD

Figure 2 Forest plot showing the overall estimate of all included articles in regards to probiotic supplementation in reducing the risk of onset of AD in children

Figure 3 Forest plot showing the sub-meta-analysis according to the method of supplementation in regards to probiotic supplementation in reducing the risk of onset of AD in children
*Cohort study of infants born preterm.
! The age of children was assessed varied: 7.0 (3.5–8.5) years in control condition and 3.8 (1.5–6.5) years in the probiotic group.

Figure 4 Forest plot showing the sub-meta-analysis according to the probiotic strain supplemented in regards to the probiotic supplementation in reducing the risk of onset of AD in children

Figure 5 Forest plot showing the sub-meta-analysis according to high-risk and non-high-risk population in regards to the probiotic supplementation in reducing the risk of onset of AD in children

Table 1 Summary of characteristics of the included studies

No	References	Location	Study Design	Inclusion Criteria	Time Exposed	Caesarian Delivery	Follow-up Time	Prenatal Exposure	High-risk Population	Eczema Severity Assessment Tool	Faecal Assessment Tool	Probiotic Treatment (Dosage)	Key Findings		
													Incidence of Atopic Dermatitis	Atopic Dermatitis Severity	Probiotic Detection in Faecal Assessment Tool
1	Wickens K, et al. (2008) [41]	New Zealand	db RCT	Mother or father of the infant had a history of treated eczema, asthma, or hay fever	PM: 5 weeks BM: 6 months IF: 2 years	HN001 group: 29.3% HN019 group: 36.1% Placebo group: 31.5%	2 years	Yes	Yes	SCORing Atopic Dermatitis (SCORAD)	PCR primers of fecal DNA samples	*Bifidobacterium animalis subsp lactis* HN019 (9 x 10^9 CFU) or *Lactobacillus rhamnosus* HN001 (6 x 10^9 CFU)	HN001 reduced risk of eczema development significantly at 2 years of age (p=0.01)	The risk of developing SCORAD ≥ 10 significantly reduced by HN001 (p=0.009), *B animalis* subsp *lactis* HN019 had no effect (p=0.97)	The amount of HN019 rose from 3 months (22.6%) to 24 months (53.1%), Number of *L. rhamnosus* HN001 was at the highest (71.5%) at 3 months and decreased (62.3%) at 24 months
2	Wickens K, et al. (2012) [40]	New Zealand	db RCT	Mother or father of the infant had a history of treated eczema, asthma, or hay fever	PM: 5 weeks BM: 6 months IF: 2 years	HN001 group: 29.3% HN019 group: 36.1% Placebo group: 31.5%	4 years	Yes	Yes	SCORing Atopic Dermatitis (SCORAD)	Real-time PCR	*Bifidobacterium animalis subsp lactis* HN019 (9 x 10^9 CFU) or *Lactobacillus rhamnosus* HN001 (6 x 10^9 CFU)	Eczema was significantly less likely to have developed among children in HN001 group if compared to placebo at 4 years (p=0.003), *B. animalis* subsp *lactis* HN019 gave no significant effect on the outcomes	*L. rhamnosus* HN001 insignificantly protect against SCORAD ≥ 10 (p=0.09)	*B. animalis* subsp *lactis* HN019 showed in 8.5% of children in the HN019 group, *L rhamnosus* HN001 showed in 33% of children in HN001 group

No	Reference	Location	Study Design	Inclusion Criteria	Time Exposure	Caesarian	Follow-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings		
3	Wickens K, et al. (2013) [10]	New Zealand	db RCT	Mother or father of the infant had a history of treated eczema, asthma, or hay fever	PM: 5 weeks BM: 6 months IF: 2 years	HN001 group: 29.3% HN019 group: 36.1% Placebo group: 31.5%	6 years	Yes	Yes	SCORing Atopic Dermatitis (SCORAD)	N/A	*Bifidobacterium animalis subsp lactis* HN019 (9 x 10^9 CFU) or *Lactobacillus rhamnosus* HN001 (6 x 10^9 CFU)	Risk for cumulative prevalence of eczema significantly reduced among children in HN001 group by 6 years of age (p=0.03), no significant effect of HN019 on any outcome	HN001 group had significant reduction of SCORAD ≥ 10 compared to placebo (p=0.04)	N/A
4	Enomoto T, et al. (2014) [29]	Japan	Open trial	None	PM: 1 month IF: 6 months	Probiotic group: 16.4% Placebo group: 5.5%	18 months	Yes	No	N/A	PCR	Mixture of *Bifidobacterium longum* BB536 and *Bifidobacterium breve* M-16V (5 x 10^9 CFU/day)	At 18 months of age, in the probiotic group the prevalence of eczema was significantly lower (p=0.033)	N/A	At 4 months of age bacteroidetes in infants in the probiotic group were significantly higher compared to placebo group
5	Allen SJ, et al. (2014) [24]	Australia	db RCT	Pregnant women with normal singleton and aged 16 years or more	PM: 1 month IF: 6 months	Probiotic group: 29.6% Placebo group: 32.3%	2 years	Yes	No	SCORAD	N/A	Mixture of *Lactobacillus paracasei* CUL08 (1.25 x 10^9 CFU), *Lactobacillus salivarius* CUL61 (6.25 x 10^9 CFU), *Bifidobacterium bifidum* CUL20 (1.25 x 10^9 CFU), *Bifidobacterium*	Atopic eczema was significantly less frequent in probiotic compared to placebo group at 2 years (p=0.024)	At 2 years, median score of severity of eczema in probiotic arm (11.1) and in placebo arm (14.2)	N/A

No	Referenc es	Locat ion	Study Design	Inclusion Criteria	Time Expose	Caesaria n	Follo w-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings		
												animalis subspecialis *lactis* CUL34 (1.25×10^9 CFU)			
6	Niers L, et al. (2009) [33]	Neth erlan ds	db RCT	Mother or father plus an older sibling of the infants had history of allergic disease such as atopic eczema, food allergy, asthma, or allergic rhinitis	PM: 6 weeks IF: 12 months	Probiotic group: 8% Placebo group: 11%	2 years	Yes	Yes	Basic Clinical Scoring System (BCSS) and SCORAD	Denaturin g gradient gel electroph oresis analysis and DNA isolation for quantitati ve PCR	Mixture of *B. bifidum* W23, *Bifidobacterium lactis* W25, *Lc. Lactis* W58 (3×10^9 CFU/day)	In the probiotic group (12%), the prevalence of eczema was significantly lower than in placebo group (29%) (p=0.035) at 3 months of life reported by parents, At 2 years old follow-up, the incidence of eczema between two groups was insignificantly different (p=0.876)	Eczema severity was similar between probiotic and placebo groups	The number of *Lc. Lactis* was significantly higher In the probiotic group compared to placebo group, High number of *Bifidobacterium* spp. can be seen in both groups

No	Reference	Location	Study Design	Inclusion Criteria	Time Exposure	Caesarian	Follow-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings		
7	Kuitunen M, et al. (2009) [32]	Finland	db RCT	Mother or father of the infant had doctor-diagnosed asthma, allergic rhinitis, or atopic eczema	PM: 4 weeks IF: 6 months	Probiotic group: 15.7% Placebo group: 17.7%	5 years	Yes	Yes	N/A	Random amplified polymorphic DNA	Mixture of LGG (5×10^9 CFU), *Propionibacterium freudenreichii* ssp *shermanii* JS (2×10^9 CFU), *Bifidobacterium breve* Bb99 (2×10^8 CFU), *L. rhamnosus* LC705 (5×10^9 CFU) twice daily	No significant differences in frequency of eczema (p=0.231) and IgE-associated eczema (p=0.711) between probiotic and placebo groups	N/A	The prevalence of LGG, *L rhamnosus* LC705 and total bifidobacteria was significantly different between probiotic and placebo groups
8	Wickens K, et al. (2018) [39]	New Zealand	db RCT	Mother or father of the infant had a history of treated eczema, asthma, or hay fever	PM: 6 months BM: 6 months	Probiotic group: 27.7% Placebo group: 25.4	1 year	Yes	Yes	SCORAD	N/A	*Lactobacillus rhamnosus* HN001 (6×10^9 CFU/day)	At 12 months, children in HN001 group had no significant protective effect (p=0.40)	At 12 months, children in HN001 group had no significant protective effect on SCORAD ≥ 10	N/A
9	West CE, et al. (2009) [37]	Sweden	db RCT	Infants with 37-42 week of gestational age, >2500 g , delivered through vaginal, and no allergic	IF: 10 months	N/A	13 months	No	No	N/A	N/A	*Lactobacillus paracasei* F19 (1×10^8 CFU/day)	Children in placebo group (22%) had higher cumulative incidence of eczema compared to children in probiotic group (11%) at 13 months of age	N/A	N/A

No	Referenc es	Locat ion	Study Design	Inclusion Criteria	Time Expose	Caesaria n	Follo w-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings		
				manifesta tion or medicatio n									(p=0.049) In the high-risk infants, development of eczema was higher among infants in placebo group (26%) compared to infants in probiotic group (11%) (p=0.038)		
10	West CE, et al. (2013) [38]	Swed en	db RCT	Infants with 37-42 week of gestation al age, >2500 g , vaginally through vaginal, and no allergic manifesta tion or medicatio n	IF: 10 months	N/A	8-9 years	No	No	N/A	N/A	*Lactobacillus paracasei* F19 (1×10^8 CFU/day)	No significant difference in any allergic disease between the two groups	N/A	N/A

No	References	Location	Study Design	Inclusion Criteria	Time Exposure	Caesarian	Follow-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings		
11	Soh SE, et al. (2009) [36]	Singapore	db RCT	Infants who had first-degree relative with allergic rhinitis, eczema, or asthma and a positive skin prick test (SPT) to dust mites, birth weight above 2 kg, gestational age minimum 35 weeks, and no major congenital malformation or illness	IF: 6 months	Probiotic group: 28% Placebo group: 26%	1 year	No	Yes	SCORAD	N/A	Mixture of *Lactobacillus rhamnosus* LPR (2×10^7 CFU/g) and *Bifidobacterium longum* BL999 (1×10^7 CFU/g)	Incidence of eczema was similar between probiotic (22%) and placebo group (25%) (95% CI=0.44-1.52)	At 12 months the median SCORAD score was 17.10 and 11.60 in probiotic and placebo groups respectively	N/A

No	References	Location	Study Design	Inclusion Criteria	Time Exposure	Caesarian	Follow-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings		
12	Simpson MR, et al. (2015) [35]	Norway	db RCT	None	PM: 4 weeks BM: 3 months	N/A	6 years	Yes	No	N/A	N/A	Mixture of *Lactobacillus rhamnosus* GG (LGG), *L. acidophilus La-5* (5×10^9 CFU) and *Bifidobacterium animalis* subsp. *lactis* Bb-12 (5×10^{10} CFU)	Children in probiotic group had significantly lower cumulative incidence of AD compared to placebo group (p=0.027)	N/A	N/A
13	Rautava S, et al. (2012) [34]	Finland	db RCT	Pregnant women with atopic sensitization and intended to breastfeed for at least 2 months	MP: 2 months MB: 2 months	LPR + BL999: 5% group ST11 + BL999 group: 12% Placebo group: 19%	2 years	Yes	Yes	N/A	N/A	*Bifidobacterium longum BL999 (1 x 109 CFU) + Lactobacillus rhamnosus* LPR (1×10^9 CFU) or *L paracasei* ST11 (1×10^9 CFU) + *B longum* BL999 (1×10^9 CFU)	Consumption of both of the probiotic mixture associated with statistically significant reduction in risk of eczema at the first 24 months of life (p<0.001)	N/A	N/A
14	Ou CY, et al. (2012) [22]	Taiwan	db RCT	Family history of allergic disease, absence of maternal rheumatoid arthritis, infectious disease, or	PM: 4 months IF: 6 months if breastfeeding, BM: 6 months	N/A	36 months	Yes	Yes	Assessed based on total score of area of rash, rash elements severity and flaring duration	N/A	*Lactobacillus rhamnosus* GG (1×10^{10} CFU)	The incidence of eczema had no significant difference between the groups at 36 months (p=0.960)	Incidence of moderate-to-severe eczema between probiotic and placebo group had no difference at 36 months of follow-up (p=0.540)	N/A

No	References	Location	Study Design	Inclusion Criteria	Time Exposure	Caesarian	Follow-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings		
				maternal diabetes mellitus, uneventful pregnancy											
15	Kopp MV, et al. (2008) [31]	Germany	db RCT	Uneventful pregnancy, family history of atopic disease with AD, asthma, or allergic rhinitis, absence of underlying chronic disease	PM: 4 to 6 weeks BM: 3 months IF: 3 months	Probiotic group: 18% Placebo group: 18%	2 years	Yes	Yes	SCORAD	N/A	*L. rhamnosus* GG (1×10^{10} CFU)	Cumulative incidence of atopic symptoms between placebo and probiotic group had no significant difference (p=0.53) at 2 years old	Severity of AD between probiotic and placebo group was insignificant (p=0.80)	N/A

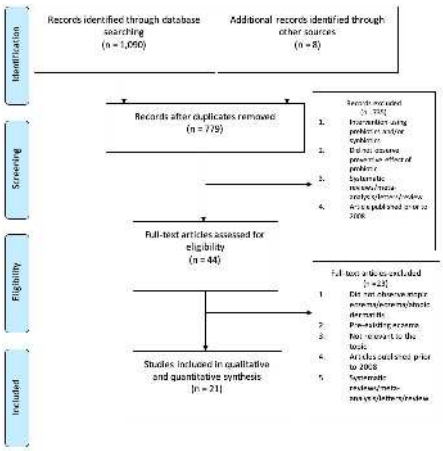
No	References	Location	Study Design	Inclusion Criteria	Time Exposure	Caesarian	Follow-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings		
16	Kim JY, et al. (2009) [30]	Korea	db RCT	Family history of allergic disease	PM: 8 weeks BM: 3 months IF: 3 months	Probiotic group: 15.2% Placebo group: 31.4%	1 year	No	Yes	Six Area Six Sign in Atopic Dermatitis (SASSAD) score	N/A	Mixture of *Bifidobacterium lactis* AD011 (1.6×10^9 CFU), *Bifidobacterium bifidum* BGN4 (1.6×10^9 CFU) and *Lactobacillus acidophilus* AD031 (1.6×10^9 CFU)	Prevalence rate of eczema in 12 months of age in probiotic group (18.2%) was significantly reduced compared to the placebo group (40%) (p=0.048), At 12 months of age, children in probiotic group (36.4%) had significantly lower cumulative incidence of eczema compared to placebo group (62.9%) (p=0.029)	Severity of eczema between two groups had no significant difference	N/A
17	Boyle RJ, et al. (2010) [26]	Finland	db RCT	Mother, father, or sibling(s) of the infants doctor-diagnosed with allergic disease such as eczema, asthma,	PM: 4 weeks	Probiotic group: 27.6% Placebo group: 26.4%	1 year	Yes	Yes	SCORAD	N/A	*Lactobacillus rhamnosus* GG (1.8×10^{10} CFU)	No significant difference in atopic eczema between the two groups (p=0.84)	Eczema severity had no difference in the first 12 months of life (p=0.39)	N/A

No	References	Location	Study Design	Inclusion Criteria	Time Exposure	Caesarian	Follow-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings		
				allergic rhinitis or food allergy											
18	Dotterud CK, et al. (2010) [28]	Norway	db RCT	Planning for breastfeed for 3 months postnatal, understood Norwegian, not at risk of pregnancy complications, in ≤ 36 weeks of pregnancy, like and tolerate fermented milk	PM: 4 weeks BM: 3 months	N/A	2 years	Yes	No	Nottingham Eczema Severity Score (NESS)	N/A	Mixture of *Lactobacillus rhamnosus* GG (5×10^{10} CFU), *B. lactis* Bb-12 (5×10^{10} CFU), and *L. acidophilus* La-5 (5×10^{9} CFU)	Cumulative incidence of AD had significant difference (p=0.022)	Risk of having moderate AD had reduced in the probiotic group (p=0.044)	N/A

No	References	Location	Study Design	Inclusion Criteria	Time Exposure	Caesarian	Follow-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings		
19	Davies G, et al. (2018) [27]	UK	db RCT	Family history of allergy, absence of breastfeeding, smoking household	PM: 4 weeks IF: 6 months	N/A	5 years	Yes	No	N/A	N/A	Mixture of *Lactobacillus salivarius* CUL61, *Lactobacillus paracasei* CUL08, *Bifidobacterium animalis* subsp. *lactis* CUL34, *Bifidobacterium bifidum* CUL20 M: 1 x 10^{10} CFU/day	Children in the probiotic arm (33.3%) had lower eczema compared to children in the probiotic arm (34.8%) but statistically insignificant	N/A	N/A
20	Damm JA, et al. (2017) [23]	Denmark	cohort study	First cohort: children who were born <30 weeks of gestation and hospitalized in the neonatal unit from January 2007 to February 2010 Second cohort: children who were born <30	From third day of life until discharge from hospital	N/A	Follow up in May-July 2015	No	No	N/A	N/A	Mixture of *Bifidobacterium animalis* subsp. *lactis* Bb12 (1 x 10^8 CFU) and *Lactobacillus rhamnosus* GG (1 x 10^9 CFU)	No significant difference on prevalence of AD between non-probiotic cohort (17.1%) and probiotic cohort (20.9%) (p=0.33)	N/A	N/A

No	Referenc es	Locat ion	Study Design	Inclusion Criteria	Time Expose	Caesaria n	Follo w-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings
				weeks of gestation and hospitaliz ed in the neonatal unit from March 2010 to February 2013									

No	References	Location	Study Design	Inclusion Criteria	Time Exposure	Caesarian	Follow-up	Prenatal Exposure	High-risk	Eczema Severity	Faecal Assessm	Probiotic Treatment	Key Findings	
21	Bertelsen RJ, et al. (2014) [25]	Norway	cohort study	Subjects are from Norwegian Mother and Child Cohort Study (MoBa) recruited from 1999-2008	PM: 9 months IF: 1 year	Probiotic and placebo groups: 14%	18 months	Yes	No	N/A	N/A	Biola milk: *Lactobacillus acidophilus* La-5, *Bifidobacterium lactis* Bb12, *Lactobacillus rhamnosus* Biola yogurt: *Lactobacillus acidophilus* La-5, *Bifidobacterium lactis* Bb12, *Lactobacillus rhamnosus* Cultura milk: *L acidophilus* La-5 and *Bifidobacterium lactis* Bb12 at least one of the products	Intake of probiotic in infants and mothers showed slightly reduced risk of current eczema at 18 months of age (95% CI [0.86-1.00))	N/A	N/A



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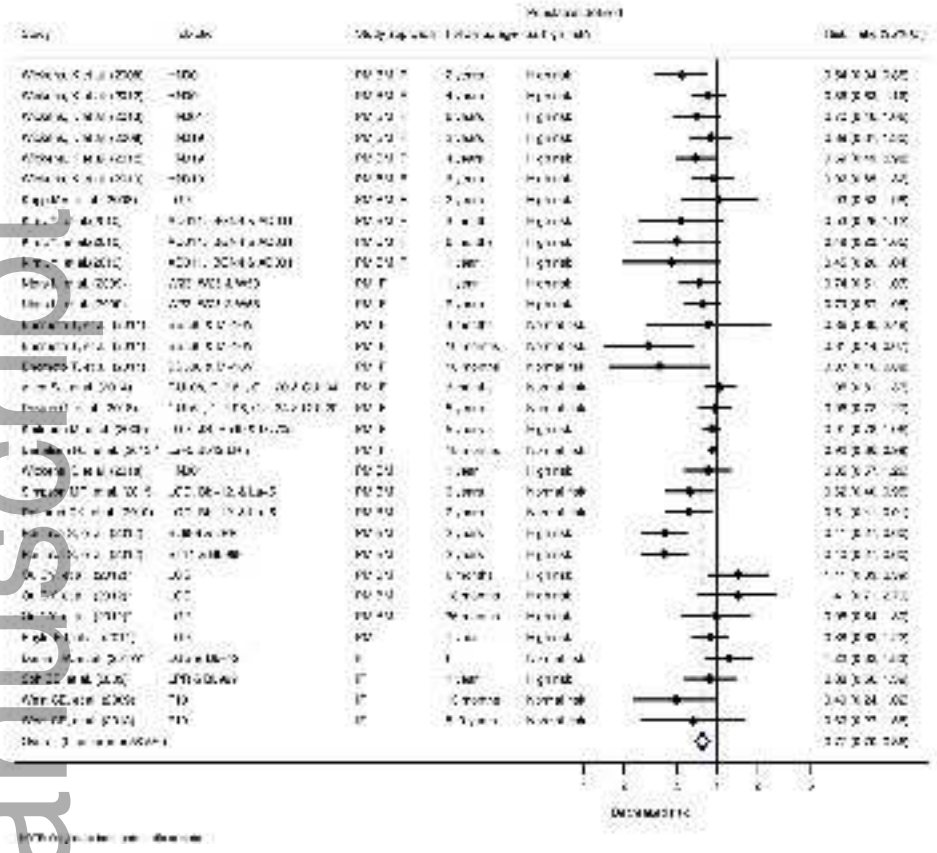

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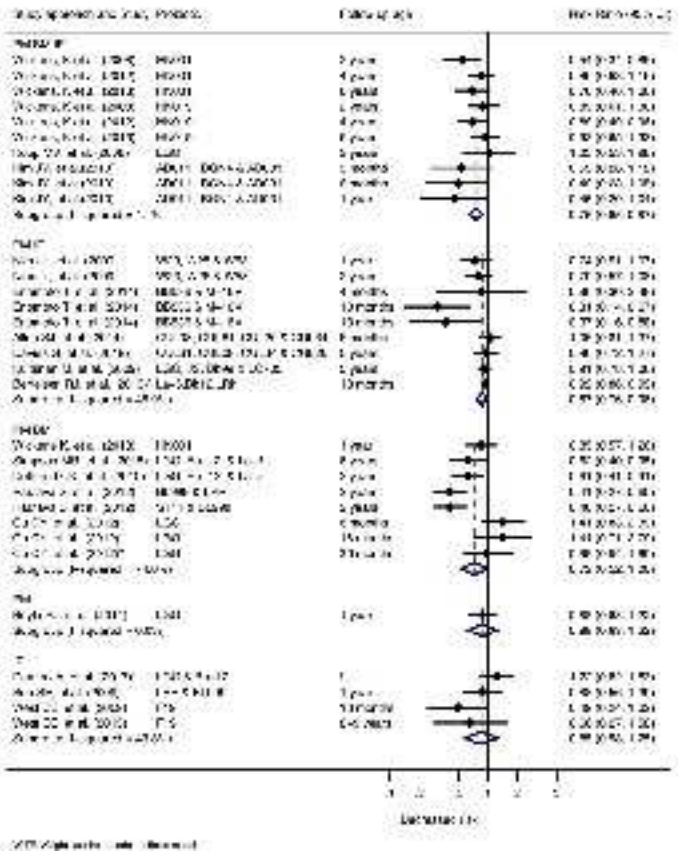

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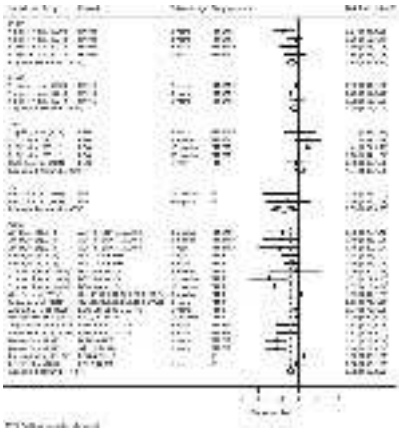

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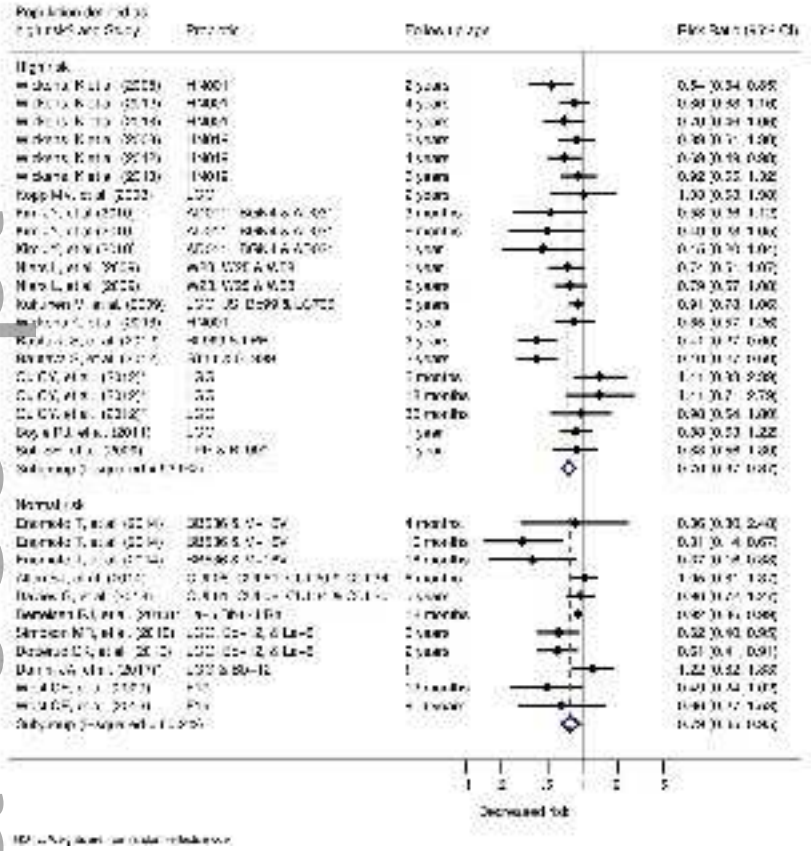

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