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［研究論文］

A Systematic Review and Meta-analysis of the Effects of Probiotics on Children with Atopic Dermatitis

小児のアトピー性皮膚炎におけるプロバイオティクスの維持・改善効果についてのメタアナリシス

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Abstract: Atopic dermatitis (AD) is a chronic allergy characterized by excessive itching, which has one of the highest morbidities of any dermatological allergy. Recently, the relationship between probiotics and AD has been discussed among physicians. In order to determine the effects of probiotics on AD children, we conducted a meta-analysis based on the changes in SCORAD index. Although the main result suggested that the probiotics group had similar result as the control group, the result from sub-group analysis, divided by age and country region, suggested that AD symptoms in the children (< 6 months) group became worse with the intervention of probiotics. From these results, we conclude that it is difficult to determine whether probiotics are an effective intervention for children with AD.

アトピー性皮膚炎 (Atopic dermatitis; AD) はプロバイオティクスの効果が期待される慢性的アレルギー疾患である。本研究では小児 AD におけるプロバイオティクスの効果を明らかにするため、AD にプロバイオティクスで介入した RCT の SCORAD の変化量をもとにメタアナリシスを行った。結果、対照群とは差がない可能性を示したが、年齢と国を考慮したサブグループ解析では生後 6 ヶ月以内の群は AD を悪化させた。以上より、プロバイオティクスは小児 AD の維持・改善効果があるとは一概に言えないと結論づけた。

Keywords: infant, Atopic dermatitis, probiotics, Meta-analysis
小児、アトピー性皮膚炎、プロバイオティクス、メタアナリシス

1 Introduction

Atopic dermatitis (AD) is one of the most pervasive chronic allergic diseases with itching and redness (Kay et al., 1994). One of the features of this disease is that its prevalence in children is higher than that of adults. It is known that up to 10-20% of children and 1-3% of adults have AD in Europe (Leung and Bieber, 2003). Although many causes have been speculated for AD, including genetic factors, environmental factors, nutrition, and intestinal microbiota, the mechanism of this disease is still unclear. As a genetic factor, it has been reported that the genetic mutation of filaggrin may cause the underlying symptoms of AD, while reducing the barrier function of the skin (Hoffjan and Stemmler, 2015). Filaggrin is an essential protein for skin barrier function, in particular, the formation of a horny layer. When the skin barrier become weak due to have a mutation on a gene coding filaggrin, the environment is also important factor for inducing stimulation.

Dysbiosis, a microbial imbalance on our body, is said to be one of the causes of AD. Intestinal microbiota are bacteria that live inside animal intestinal tracts, and support the host's digestive function, and provide nutrition by producing secondary metabolites, as well as maintaining the homeostasis of the host's intestinal tract (Holmes et al., 2012). Additionally, it became clear that there are relationships between intestinal microbiota and some diseases, including AD (Björkstén et al., 1999; 2001; Kalliomäki et al., 2001). Microbiota is used as probiotics for improving our health. The most notable definition of probiotics is, "a live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance," defined by Fuller (Fuller, 1989). Another notable definition states, "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host" as defined by FAO/WHO (FAO/WHO, 2001). Two words that are also related to probiotics, and are widely known are prebiotics and synbiotics (Schrezenmeir and de Vrese, 2001). One definition

of prebiotics states, “a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon” (Gibson and Roberfroid, 1995). Synbiotics is known as the mixture of probiotics and prebiotics.

Many different techniques are used to obtain knowledge from research; however, the quality of the research is dependent upon the study design. In the epidemiology field, two types of observational study are mainly used, case-control study and cohort study. Case-control study involves comparing the control and experimental group retrospectively. On the other hand, cohort study involves following the specific group prospectively. In addition to these designs, there is other kind of study known as intervention study. This study has two methods, nonrandomized and randomized control trials (RCT). A randomized control trial produces more quality data considering its lack of subject bias.

Furthermore, systematic review is one of the highest quality research methods used to collect and examine research data. Systematic review is different from the review at the point that evaluation is conducted systematically. This systematic review is an essential process of evidence-based medicine, and the method for integrating this data and evaluating the result is called meta-analysis. (Sacks et al., 1987). Meta-analysis makes is possible to reduce the problem of subject size and the obstacle of bias among clinical trials. Summarizing the results of clinical trials related to AD children and probiotics is important toward understanding the effect of probiotics and their mechanisms; in particular, the medical science, bacteriology, and molecular biology. Recently, Kim reported a meta-analysis for the relationship between AD and the effect of probiotics (Kim et al., 2014). This report conducted a comprehensive study, from infant to adult, and considered the AD severity and patient age. As a result, it was reported that probiotics were effective for moderate to severe AD in patients of all ages. However, as the interaction with the host intestinal environment was

not considered, we focused on the children and home country in order to put the diversity of host intestinal microbiota into consideration. The children's profiles have less diversity than the adults' profiles (Kostic et al., 2013). The purpose of this systematic review and meta-analysis was to determine the effects of probiotics on AD children.

2 Methods

PubMed and Cochrane Library were searched in June of 2015 with the following keywords: "Dermatitis, Atopic"[Mesh] OR atopic dermatitis AND "Probiotics"[Mesh], OR "Lactobacillus"[Mesh], OR "Bifidobacteriales Infections"[Mesh], OR "Lactococcus"[Mesh], OR "Saccharomyces"[Mesh], OR "Streptococcus thermophilus"[Mesh], OR "Bacillus Subtilis"[Mesh], OR "Enterococcus faecalis"[Mesh], OR "Clostridium"[Mesh]. The type of article was filtered to include only Randomized control trials. After a systematic search, we conducted a manual search. Included were (1) articles of the RCT type, (2) patients of age (< 10 years) with AD, (3) cases with intervention conducted by using probiotics, (4) articles written in English. Excluded were (1) cases in which intervention was conducted by using prebiotics or synbiotics, (2) cases in which the main target was an allergy such as food allergy. WHO's definition of probiotics was used for this study, and if indigestible sugar or fibers were included as part of the intervention, we regarded it as prebiotics. Before conducting a meta-analysis, we checked the article qualities using CONSORT (Moher et al., 2010) to compare the quality of the RCTs. The 9 studies that met these requirements included crossover trials. When the quality of an article is checked, CONSORT does not accept crossover trials, however, we used CONSORT because the checklist for crossover trials was not yet published.

The primary outcome was the change of SCORAD index (Stalder et al., 1993) from baseline to post-treatment. SCORAD index is the major index for evaluating AD symptoms. A small index size indicates that

the symptom is mild, and a large index size indicates that the symptom is severe. In order to combine the results from these RCTs, the standard deviation (S.D.) of each study was calculated and incorporated. The requirement of this research was written the average and S.D. or standard error (S.E.) of SCORAD from baseline to after treatment in both group control and intervention. Data syntheses were based upon, either the fixed or the random effect model, according to the extent of heterogeneity (p-value of Cochrane Q-test < 0.05). All of the statistical analyses were performed by R 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/index.html). A two sided p-value < 0.05 was set as the significant level.

3 Results

Sixty-four trials were identified in total from PubMed and Cochrane Library, and nine RCTs were included in the meta-analysis (Figure 1, Supplementary List 1: http://tinyurl.com/znrpexg). We excluded 2 studies that were not written in English, 4 studies that were not original papers and 27 studies that differed from our purpose. Finally, 24 studies were separated into 3 groups, infant and mother, child, and adult. Thirteen studies categorized into the child group included 2 studies focused on infants. It is known that the profile of intestinal microbiota differs between neonates and infants, so we excluded these 2 studies from the child group. Additionally, the outcome of 2 studies did not employ the SCORAD index. Although we performed a hand search for references from these 9 articles, no articles satisfied the requirement (Supplementary List 2: http://tinyurl.com/hmgmjm5).

The summary of these 9 studies is shown in table 1. The maximum and minimum intervention terms were 6 months and 6 weeks, respectively. There were two types of interventions, powder and capsule. When prescribed the powder, the amount and type of liquid were limited. Thirteen

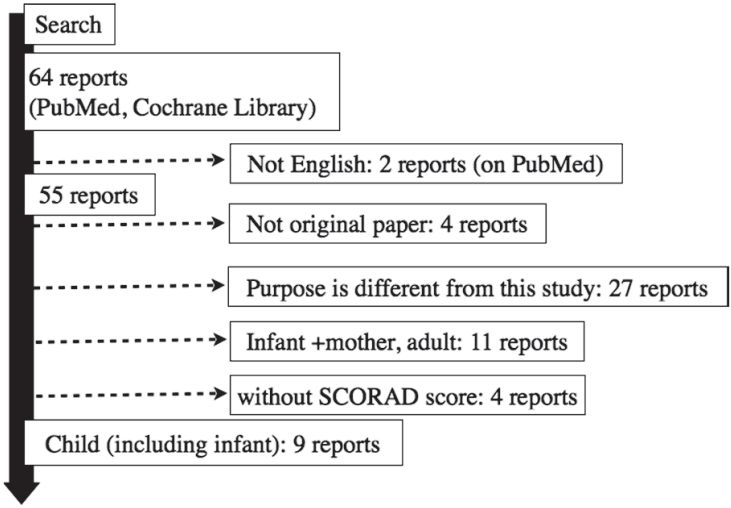

Figure 1 Flow diagram of the process of selecting relevant trials
In total, 64 articles were satisfactory using these keywords.

species of intestinal microbiota were used as probiotics. Probiotics were composed of one specific species of bacteria in 5 studies and 2 species of bacteria in 4 other studies. Bacteria from the *Lactobacillus* genus were used as probiotics in all 9 studies. The most frequently used bacteria in these studies were the *Lactobacillus rhamnosus* strain GG (LGG). The minimum amount of bacteria was 1×10^9 Count-Forming Units (CFU), twice a day, and the maximum amount of bacteria was 2×10^{10} CFU / g once a day. In these studies, allergy existence was also considered as baseline data, along with personal data. As usual, a steroid was used as a main treatment. Although the amount of steroid was limited, steroid uses in these studies were permitted. Within these 9 studies, 4 studies showed improvement of the symptom outcome, and the other 5 studies showed no improvement. In addition, the 4 studies showing the effects of probiotics were focused on children with age > 6 months.

Table 1 Evidence table of review

	Article	Study size	Years	Proviotics	Amount	Intervention term (weeks)	Follow up (weeks)	Outcome A	Outcome B	Outcome C
1	Fölster-Holst *et al* 2006	n = 53	1-55 months	*Lactobacillus rhamnosus* strain GG	5×10^9CFU, twice/day	8	4	○		●
2	Gore *et al* 2011	n = 208	3-6 months	*Lactobacillus paracasei* CNCM I-2116 *Bifidobacterium lactis* CNCM I-3446	1×10^{10}CFU, everyday	12	3 years	○		●
3	Nermes *et al* 2010	n = 39	2.2-13 months	*Lactobacillus rhamnosus* strain GG ATCC 53103	3.4×10^9CFU, everyday	12	-	○	○	●
4	Weston *et al* 2005	n = 56	6-18 months	*Lactobacillus fermentum* VRI-033 PCC	1×10^9CFU, twice/day	8	8	○		◆
5	Rose *et al* 2010	n = 121	6-24 months	*Lactobacillus rhamnosus* strain GG ATCC 53103	1×10^{10}CFU, twice/day	6	6	○		●
6	Larsen *et al* 2011	n = 50	7-24 months	*Lactobacillus acidophilus* NCFM ATCC SD5220 *Bifidobacterium animalis* subsp. *lactis* Bi-07	1×10^{10}CFU, everyday	8	-		○	◆
7	Sistek *et al* 2006	n = 59	1-10 years	*Lactobacillus rhamnosus* *Bifidobacteria lactis*	Total 2×10^{10}CFU/g, everyday	12	4			◆
8	Han *et al* 2012	n = 118	1-13 years	*Lactobacillus plantarum* CJLP133	5×10^9CFU, twice/day	16	2	○		◆
9	Rosenfeldt *et al* 2004	n = 43	1-13 years	*Lactobacillus rhamnosus* 19070-2 *Lactobacillus reuteri* DSM 12246	1×10^{10}CFU, twice/day	8	8	○		●

Outcome A: molecular outcome, B: microbial outcome, C: Symptom outcome. Molecular outcome represented as amount of IgA. Microbial outcome included amount of microbial population. Symptom outcome included SCORAD index.
○: written, ●: ineffective, ◆: effective

After screening, we conducted an evaluation on the quality of RCTs (Table 2). Only 5 studies within the 9 studies estimated the 95% CI within the SCORAD index. Weston's study reported statistic results and baseline data separately; therefore, these two reports were used for evaluation. As a result, no studies significantly lacked the necessary data. For this reason, sub-group analysis was not conducted in this study.

Although 9 studies were included for evaluation, only 5 studies were used for meta-analysis (Table 3, Figure 2A) due to the limitation of statistical data. Four studies were not significant enough to mention the results of their SCORAD index. Figure 2 shows the results of meta-analysis based on the changes of SCORAD index. Although heterogeneity was large in

Table 2 CONSORT checklists for evaluating studies' quality

Check list			1	2	3	4	5	6	7	8	9
Title, abstract	Title	1a	Y	n.r.	Y	n.r.	n.r.	n.r.	I	Y	n.r.
	Abstract	1b	Y	Y	Y	Y	n.r.	Y	Y	Y	Y
Introduction	Background	2a	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Objectives	2b	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods	Trial Design	3a	Y	Y	Y	I	Y	I	Y	Y	Y
	Changes to trial design	3b	-	-	-	-	-	-	-	-	-
	Participants	4a	Y	Y	Y	Y	n.r.	Y	Y	Y	Y
	Study settings	4b	n.r.	n.r.	n.r.	Y	Y	n.r.	n.r.	n.r.	n.r.
	Interventions	5	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Outcomes	6a	Y	I	Y	Y	I	I	Y	Y	Y
	Changes to outcomes	6b	-	-	-	-	-	-	-	-	-
	Sample size	7a	Y	n.r.	n.r.	Y	n.r.	Y	Y	Y	Y
	Interim analyses and stopping guidelines	7b	-	-	-	-	-	-	-	-	-
	Randomisation: sequence generation	8a	n.r.	n.r.	n.r.	n.r.	n.r.	Y	n.r.	n.r.	n.r.
	Randomization: type	8b	Y	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	Y	Y
	Randomisation: allocation concealment mechanism	9	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	Y	n.r.	n.r.
	Randomisation: implementation	10	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	Y	n.r.	n.r.
	Blinding	11a	Y	Y	Y	Y	n.r.	Y	Y	Y	Y
	Similarity of interventions	11b	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	Statistical methods	12a	Y	Y	Y	Y	Y	n.r.	Y	Y	Y
	Additional analyses	12b	Y	-	-	-	-	-	-	-	-

Result	Participant Flow	13a	Y	Y	Y	Y	n.r.	Y	Y	Y	Y
	Losses and exclusions	13b	Y	Y	Y	Y	n.r.	Y	Y	Y	Y
	Recruitment	14a	n.r.	n.r.	I	I	n.r.	I	n.r.	I	I
	Reason for stopped trial	14b	n.r.	Y	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	Baseline Data	15	n.r.	Y	Y	Y	n.r.	Y	Y	Y	Y
	Numbers analyzed	16	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Outcomes and estimation	17a	Y	Y	Y	Y	I	Y	I	Y	Y
	Binary outcomes	17b	-	-	I	Y	-	Y	-	-	Y
	Ancillary analyses	18	-	-	-	-	-	-	-	-	-
	Harms	19	n.r.	n.r.	Y	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Discussion	Limitations	20	Y	n.r.	Y	Y	Y	Y	n.r.	n.r.	Y
	Generalizability	21	Y	Y	Y	Y	n.r.	n.r.	n.r.	Y	Y
	Interpretation	22	Y	Y	Y	Y	Y	Y	Y	Y	Y
Other information	Registration	23	Y	Y	n.r.	Y	n.r.	n.r.	Y	n.r.	n.r.
	Protocol	24	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	Funding	25	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y: Written, I: Written partially, n.r.: Not reported, -: Not reported (not necessary)
1-9: Corresponded to the article's number from table 1

Table 3 Studies included in meta-analysis

#	Author (Year)	Age (months)	Probiotics	Country
1	Fölster-Holst *et al* (2006)	1-55	*Lactobacillus rhamnosus* strain GG	Germany
2	Gore *et al* (2012)	3-6	*Lactobacillus*	England
3			*Bifidobacterium*	
4	Larsen *et al* (2011)	7-24	NCFM	Denmark
5			Bifidobacterium animalis subsp. lactis Bi-07	
6	Sistek *et al* (2006)	1-10 (years)	*Lactobacillus rhamnosus* *Bifidobacteria lactis*	New Zealand
7	Han *et al* (2012)	1-13 (years)	*Lactobacillus plantarum* CJLP133	Korea

a randomized effect model, meta-analysis of entire studies did not show a significant decrease in the SCORAD index within the probiotics group as compared to that within the control group (estimator: -0.27, 95% CI: -3.69 to 3.15, $p = 0.88$; Table 4, Figure 2A). This 95% CI was extended across 0; therefore, the effect of probiotics was not observed in this meta-analysis. Additionally, Han's study was the only study showing the effects of probiotics for AD, and there were no commonalities between other studies in terms of probiotics type, intervention term, or patients.

Next, we conducted sub-group analysis by age group. These 9 studies were separated by the patients age, which was 6 months (Figure 2B). The heterogeneity of studies that focused on children < 6 months was small ($p = 0.96$). As the result of sub-group analysis, the estimator of SCORAD was 2.01 (95% CI: 0.89 to 3.13, $p < 0.001$; Table 4, Figure 2B) and the effects of probiotics in increasing the index are shown. The heterogeneity of studies that focused on children > 6 months was large ($p < 0.001$). As the result of sub-group analysis, the estimator of SCORAD was -2.04 (95% CI: - 6.06 to 1.99, $p = 0.32$; Table 4, Figure 2 C) and the effects of probiotics in decreasing the index are shown (Figure 2C). 95% CI was extended across 0; therefore, the effects of probiotics were not shown in this sub-group analysis.

As the other sub-group analysis, we focused on the patient's country of origin. In this analysis, we found that the studies conducted in Europe showed a similar result among each trial (Figure 2D). The heterogeneity of the sub-group analysis was not significant ($p = 0.14$). As the result of sub-group analysis, the estimator of SCORAD was 1.53 (95% CI: 0.60 to 2.47, $p < 0.001$; Table 4, Figure 2D) and the effects of probiotics in significantly increasing the index were shown. As the result of these sub-group analyses, the common factor toward showing large heterogeneity came from including Han and Sistek's studies.

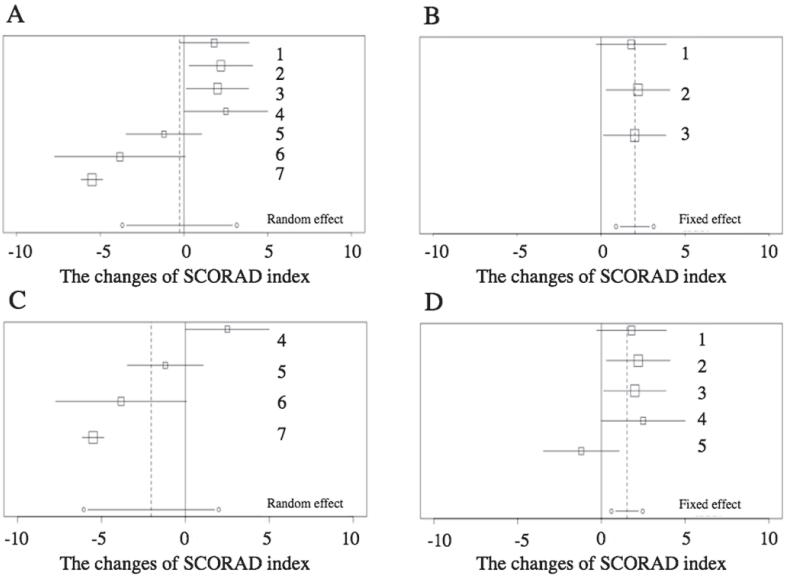

Figure 2 Includes the forest plots and statistics of shifts of SCORAD

A-D: Left side means negative and right side means positive. The horizontal axis shows the estimator of changes of SCORAD index mean and the box size depends on the size of population. Dotted line indicates the estimator of statistical model. A: All, B: < 6months, C: > 6 months, D: Europe.

Table 4 Estimator of changes of SCORAD index mean

	Object	Included trial numbers	F/R[1]	Estimator (P-value)	95% CI (Estimator)	Heterogeneity P-value
A	All	7	R	-0.27 (P = 0.88)	- 3.69 / 3.15	< 0.001
B	< 6 months	3	F	2.01 (P < 0.001)	0.89 / 3.13	0.96
C	> 6 months	4	R	-2.04 (P = 0.32)	- 6.06 / 1.99	< 0.001
D	Europe	5	F	1.5341 (P = 0.001)	0.60 / 2.47	0.14

[1]F: Fixed effect, R: Random effect

4 Discussion

In this study, we conducted meta-analyses including 5 trials that considered the age and country region. Five trials conducted in Europe were gathered as one sub-group. The result of the sub-group analysis showed that the symptoms became worse when the European AD children took probiotics. The heterogeneity of these data was large and 95% CI was extended across 0, even when using a randomized effect model. This result suggests that it is difficult to conclude if the probiotics had an effect on AD children, as this result is consistent with Kim's previous research (Kim et al., 2014). Björkstén reported that the amount of *Enterococcus and Bifidobacterium* was significantly small between one-month-old and one-year-old AD children's intestinal tract (Björkstén et al., 2001), as it is said that probiotics rearrange the profiles of intestinal microbiota and suppress symptoms. Although the method of treatment was discussed, the effect was not shown clearly in the case of AD. There remains causal ambiguity, as many reports and books do not refer to the effect of probiotics for AD, and the effects were dependent on each clinical trial (van der Aa et al., 2010). The reasons for variation in the effects of bacteria on patients were thought to include patient age, gender, race, life style, original profiles of intestinal microbiota, amount of probiotics, kinds of species, and the clinical trial design. The features of intestinal microbiota were dependent on kinds and strains, which served to produce the disparity in data regarding the effect of these microbiota.

LGG, used in many reports, was bacillus and produced lactate. It was reported to give benefits for hosts and resistance to stomach acid and bile acid. Unfortunately, the trials that used LGG had the following 3 results; probiotics had effects, no effects were observed, and unclear, therefore, LGG's effects as probiotics are still unclear. In addition, some trials did not refer to the strain of bacteria, and because the species were different among these trials, it is difficult to discuss the effect of the probiotics.

We conducted sub-analysis according to the patient's age and country,

which were thought to be a cause of heterogeneity. In the case of sub-group analysis including trials with patient age < 6 months, the changes in SCORAD index increased. This suggested that the probiotics did not have the effect of suppressing the AD symptoms, as AD became worse. In the case of sub-group analysis including trials with object age > 6 months, the heterogeneity was small and the changes in SCORAD index did not increase. This suggested that probiotics had the effect of suppressing the AD symptoms, as AD did not become worse. The clinical use of probiotics is defined as intake of bacteria known to benefits us, and the effects of probiotics were thought to depend on the host intestinal environment and immune system. It is known that the host microbial profiles change relative to the host age, and it was reported that aerobic bacteria increased first, followed by anaerobic bacteria that increased through oxygen consumption, as reported by the study focused on the host's growth (Turroni et al., 2012). Smith reported that microbial patterns were almost the same and not dependent on the host animal (Smith, 1965).

Additionally, the result of sub-group analysis considering the patient's country showed that the heterogeneity was small. The changes in SCORAD index increased. When we compared the heterogeneity of meta-analysis including whole trials and sub-analysis by considering the country, the size of heterogeneity decreased. This sub-group segmentation, which considered patient country regions, was different from Kim's research, and suggested that the country regions are a possible factor in changing the size of heterogeneity. When we considered the results of the sub-group analysis, it seems that one of the causes for effects of bacteria on patients was the host intestinal environment. There were already some reports focused on the relationship among the microbial profiles, diet, and country, and the intestinal microbial profiles were divided into three types and the differences were dependent on the diet (Arumugam et al., 2011). It may also be noted that Japanese intestinal microbiota have a potential to digest seaweed such as laver (Hehemann et al., 2010). The country region and race are important factors in understanding the

details of systems related to intestinal microbiota.

There were some similarities within the large heterogeneity. For example, when data was integrated and the heterogeneity was large, studies by Han and Sistek were included for analysis. From this result, it was suggested that these two trials most directly affected the size of heterogeneity. We did not integrate these two trials because there were many discrepancies in the data, because the reliability was low, as the countries in which the trials were performed were Korea and New Zealand. *Lactobacillus plantarum* CJLP133, used in Han's study, was isolated from Kimchi and suggested to control the immune system (Lee et al., 2011). In addition, this strain was also reported to have the effect of suppressing AD in an AD mouse by oral intervention (Won et al., 2011). This strain also demonstrated the effect of curing dermatitis-like AD by inducing house dust and mites on an NC/Nga mouse (Won et al., 2012).

In summary, clinical trials that focused on the effects of probiotics on infant AD were screened systematically. Among these studies, the differences of patient age and country region produced the strongest effects on AD. On the other hand, it is difficult to discuss the effect of probiotics considering the differences in probiotics, as well as the differing dynamics of microbial profiles, which proved to be a major limitation of this study. As the number of trials using the same strain of probiotics increases around the world, it will become easier to analyze and discuss the effect of probiotics. In addition, the effect of host microbial profiles was considered in this study; therefore, it is important to focus on these profiles, as well as changes to the host environment.

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