

# Probiotics for the Treatment of Atopic Dermatitis in Children: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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**Objective:** Atopic dermatitis (AD) is a prevalent, burdensome, and psychologically important pediatric concern. Probiotics have been suggested as a treatment for AD. Some reports have explored this topic; however, the utility of probiotics for AD remains to be firmly established.

**Methods:** To assess the effects of probiotics on AD in children, the PubMed/Medline, Cochrane Library Scopus, and OVID databases were searched for reports published in the English language.

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Huang R, Ning H, Shen M, Li J, Zhang J and Chen X (2017) Probiotics for the Treatment of Atopic Dermatitis in Children: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front. Cell. Infect. Microbiol. 7:392. doi: 10.3389/fcimb.2017.00392 **Results:** Thirteen studies were identified. Significantly higher SCORAD values favoring probiotics over controls were observed (mean difference [MD], -3.07; 95% confidence interval [CI], -6.12 to -0.03; P < 0.001). The reported efficacy of probiotics in children < 1 year old was -1.03 (95%Cl, -7.05 to 4.99) and that in children 1–18 years old was -4.50 (95%Cl, -7.45 to -1.54; P < 0.001). Subgroup analyses showed that in Europe, SCORAD revealed no effect of probiotics, whereas significantly lower SCORAD values were reported in Asia (MD, -5.39; 95%Cl, -8.91 to -1.87). *Lactobacillus rhamnosus* GG (MD, 3.29; 95%Cl, -0.30 to 6.88; P = 0.07) and *Lactobacillus plantarum* (MD, -0.70; 95%Cl, -2.30 to 0.90; P = 0.39) showed no significant effect on SCORAD values in children with AD. However, *Lactobacillus fermentum* (MD, -11.42; 95%Cl, -13.81 to -9.04), *Lactobacillus salivarius* (MD, -7.21; 95%Cl, -9.63 to -4.78), and a mixture of different strains (MD, -3.52; 95%Cl, -5.61 to -1.44) showed significant effects on SCORAD values in children with AD.

**Conclusions:** Our meta-analysis indicated that the research to date has not robustly shown that probiotics are beneficial for children with AD. However, caution is needed when generalizing our results, as the populations evaluated were heterogeneous. Randomized controlled trials with larger samples and greater power are necessary to identify the species, dose, and treatment duration of probiotics that are most efficacious for treating AD in children.

Keywords: probiotics, constipation, children, meta-analysis, randomized controlled trial

# INTRODUCTION

Atopic dermatitis (AD), is one of the most common chronic inflammatory skin disorders among infants and children. AD is characterized by itching and recurrent eczematous lesions, and its incidence has increased worldwide over the past several decades. The current prevalence rate is 10-20% in infants and children (Weidinger and Novak, 2016). As the leading non-fatal medical skin disorder, AD imposes severe psychosocial burdens on pediatric patients and their families (Chamlin and Chren, 2010; Silverberg, 2016; Sidbury and Khorsand, 2017). AD is associated with high risks of allergy, asthma, and mental health issues (Sung et al., 2017). Infants and children with AD are typically treated with topical corticosteroids (TCS), antihistamines, and even antibiotics (Totri et al., 2017). However, these medications exert several adverse side effects, and AD symptoms may recur rapidly after treatment is stopped. Furthermore, long-term TCS use may trigger new-onset AD.

Probiotics is becoming increasingly attractive as a treatment option for some illnesses in children (Fuchs-Tarlovsky et al., 2016). Probiotics (live bacteria or yeasts) are not necessarily harmless, but they help to protect hosts from harmful bacteria (Mizock, 2015). When administered in adequate amounts, probiotics may play beneficial roles not only in the gastrointestinal tract but also in the gut-brain-skin axis (Ogden and Bielory, 2005; Dehingia et al., 2015; Huang et al., 2016; Huang and Hu, 2017). Several studies on the benefits of probiotics for pediatric AD patients have appeared over the past decades. In 2000, Pessi et al. reported that oral probiotics alleviated the clinical symptoms of gastrointestinal inflammation and AD (Pessi et al., 2000). Kirjavainen et al. (2003) reported lower Bacteroides counts in the fecal microflora of children with atopic eczema than in healthy infants and suggested that probiotics can be used to treat AD in children (Kirjavainen et al., 2003); however, some reports vielded contrasting results (Licari et al., 2015). For instance, Gruber et al. found that Lactobacillus rhamnosus strain GG (LGG) exerted no therapeutic effects in infants with mild-to-moderate AD (Gruber et al., 2007). Therefore, we systematically evaluated the effects of probiotics used to treat AD in children.

# **METHODS**

# **Inclusion Criteria**

The inclusion criteria for the meta-analysis were (1) RCTs of children aged  $\leq$ 18 years in whom AD severity was graded by experienced dermatologists using the Severity scoring of atopic dermatitis: the SCORAD index (1993); Yoon et al. (2015) (2) that evaluated the use of any probiotic culture/strain/dose/therapy regimen (including studies on fermented yogurt; all dosage forms including tablets, powders, oil suspensions, and capsules were included). All results are presented as means  $\pm$  standard deviation. However, if multiple reports evaluated the same group of patients, we selected only the most recent complete report. SCORAD, developed by the European Task Force on AD in 1993 (1993), assesses the AD area, clinical features, visual analog scale data, and clinical symptoms, and it is widely used to evaluate AD severity in children (Machura et al., 2008).

# **Exclusion Criteria**

Studies that did not meet the inclusion criteria or that were published in languages other than English were excluded.

### **Search Process**

Two individuals of our team searched the following databases from the times of the earliest records in 2000 to April 12, 2017: PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Embase (https://www.embase.com/login), Cochrane Library (http:// www.cochranelibrary.com/) and Scopus (https://www.elsevier. com/solutions/scopus) (available on the internet); and Ovid, Orbis, and the Web of Science (available at our university library with free downloads). The following search string was used in searching: [(infant OR infants) OR (neonate OR neonates) OR (newborn OR newborns) OR (toddler OR toddlers)] AND (probiotic OR probiotics OR pro-biotics OR probio\*) AND (atopic dermatitis OR atopic eczema) OR (SCORAD) OR (atopic OR atopy) NOT (animals) NOT (adult). The references listed in each report were examined to allow us to retrieve additional information. We only reviewed works in the English language, thus not those in (for example) Korean or Chinese. Furthermore, conference abstracts were excluded, because they lacked detailed data.

# **Data Collection**

The two individuals collected all data independently. The eligibility of studies was confirmed by both reviewers. A tabulation of study author(s), publication date, recruited numbers, probiotic strain(s), dosage, treatment duration, and treatment results was prepared (**Table 1**). If the study data were unclear, we attempted to contact the corresponding author via email to obtain further information.

# **Statistical Analysis**

RevMan 5.3 software (Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark; http://community.cochrane. org/tools/review-production-tools/revman-5/) was accessed to conduct the meta-analysis. SCORAD was commonly used to measure the efficacy of probiotics in children with AD. As the results were continuous data, the mean difference (MD) and 95%CI were calculated for statistical analyses, and either a randomized-effects model or fixed-effects model was used depending on whether heterogeneity was apparent. Subgroup assessment was performed with regard to different geographical status, infants aged <1 year, children aged between 1 and 18 years, different strains, and LGG. The  $c^2$  test was used to identify statistical heterogeneity (Margolis and Mitra, 2017). The I<sup>2</sup> statistic was calculated to identify and quantify inconsistency. When I<sup>2</sup> was  $\geq$  50%, indicating significant heterogeneity, we used a random-effects model for meta-analysis. When  $I^2$  was < 50%indicating no heterogeneity, we employed a fixed-effects model. Publication bias was assessed by constructing funnel plots. A two-tailed P < 0.05 was used to reflect statistical significance. Sensitivity analyses, also termed uncertainty analyses, were used to explore the extent to which our results and conclusions were altered by changes in the data or analysis approach (Alexander et al., 2016). If the conclusions did not change upon application of the sensitivity analysis, those conclusions were considered robust.

#### TABLE 1 | Characteristics of included RCTs for meta-analysis.

Study, year (country)	n	Age	Genus, species, and strain, duration	Dose	Outcome summary
Viljanen et al., 2005; Finland	220	1.4–11.9 months	Lactobacillus rhamnosus strain GG (LGG); 4 weeks	$5 \times 10^9$ cfu or mixture twice daily capsules	Positive effect of probiotics was seen only in IgE-sensitized infants
Weston et al., 2005; Austria	56	6–18 months	LF; 8-week	2 × 10 <sup>10</sup> CFU/g /d	Positive effect of probiotics was seen only in food-sensitized children
Folster-Holst et al., 2006; Germany	54	1–55 months	Lactobacillus rhamnosus strain GG(LGG); 8-week	10 × 10 <sup>9</sup> CFU	No significant difference between synbiotics and placebo
Gruber et al., 2007; Germany	102	3–12 months	Lactobacillus rhamnosus strain GG(LGG); 8-week	$>5 \times 10^9$ CFU, twice daily orally	No significant difference between synbiotics and placebo
Niers et al., 2009; Netherland	98	1–24 months	B. bifidobacterium infantis, LC. lactis W58; 24-week	$3 \times 10^9$ CFU, once daily	No difference was observed among two groups
Wu et al., 2012; Taiwan	60	2–14 years	Lactobacillus (LS), 8-week	$5 \times 10^{10}$ CFU, twice daily	SCORAD decrease significantly in probiotic group compared to placebo group
Gerasimov et al., 2010; Ukraine	90	1–3 years	Mixture (LA t BL)/synbiotics; 8-week	$5 \times 10^{10}$ CFU, twice daily	SCORAD decrease significantly in probiotic group compared to placebo group
Woo et al., 2010; Korea	75	2–10 years	Lactobacillus (LS2)/synbiotics; 12-week	$2 \times 10^{10}$ CFU, twice daily	SCORAD decrease significantly in probiotic group compared to placebo group
Shafiei et al., 2011; Iran	41	1–36 months	Seven strain probiotics plus prebiotic mixture; 2 months	$1 \times 10^9$ CFU, once daily	No significant difference between probiotics and placebo
Gore et al., 2012; UK	133	3–6 months	Lactobacillus (LP) or Bifidobacterium (BL); 12-week	1 ×10 <sup>10</sup> CFU	No significant difference between probiotics and placebo
Han et al., 2012; Korea	83	1–13 years	Lactobacillus (LP2); 12-week	$5 \times 10^{10}$ CFU, twice daily	SCORAD decrease significantly in probiotic group compared to placebo
Yesilova et al., 2012; Turkey	39	1-12 years	Mixture (BB2, LA, LC, LS2); 8-week	$4 \times 10^{10}$ CFU, daily	SCORAD decrease significantly in probiotic group compared to placebo
Wang and Wang, 2015; Taiwan	220	1–28 years	Lactobacillus paracasei(LP), Lactobacillus fermentum(LF), Mixture; 3 months	LP,LF(2 $\times$ 10 <sup>10</sup> CFU,qd); Mixture(4 $\times$ 10 <sup>10</sup> CFU,qd)	SCORAD decrease significantly in probiotic group compared to placebo

In meta-analyses, sensitivity analyses are conducted by excluding studies one-by-one to identify those studies that materially affect the results (Copas and Shi, 2000). The risk of bias in each RCT was explored using the "risk of risk" tool in Revman software. The PRISMA statement published in 2009 aimed to improve the reporting of systematic reviews and meta-analyses. PRISMA defines an evidence-based minimum set of items to employ, and we followed this guideline (http://www.prisma-statement.org/). PRISMA features both a checklist and a flow diagram. We used the checklist to ensure that our study structure was appropriate and the flow diagram to map the numbers of records identified, included, and excluded, as well as the reasons for exclusion (Zhang et al., 2017). Publication bias was checked by drawing funnel plots, which are commonly used in systematic reviews and meta-analyses. Publication bias is considered absent if the study results are distributed in close proximity to the averages.

# RESULTS

### **Included Studies**

The PRISMA flow diagram (**Figure 1**) shows how we selected the relevant reports. We initially screened 392 articles, excluded those that did not meet our inclusion criteria, and finally retained 26 articles. As some reports did not report data as means  $\pm$  SD,



we contacted the corresponding authors by email. Unfortunately, we sent 13 emails and didn't receive any data suitable for inclusion in the meta-analysis. Ultimately, 13 studies involving 1,070 children fulfilled our selection criteria (**Table 1**).

# **Quality Assessment**

**Figure 2A** shows the risk of bias within all enrolled RCTs, as adjudged by the two reviewers. **Figure 2B** presents the individual risks of bias, again as perceived by the reviewers. Both figures show that the risks of bias were rather low, because all were

RCTs that adhered to high standards. Four studies divided children into probiotic intervention and control groups; two studies created three groups (probiotics, a placebo, and another intervention). Twelve studies were of double-blind design. All 13 studies reported baseline data including socioeconomic status and mean age; these did not differ significantly among the groups.

# Probiotics and Children with AD

Data from 1,070 children (intervention group, 553; control group, 517) were assessed. The outcome of a random-effects



meta-analysis model involving all 13 trials is shown in **Figure 3**. Significant differences in SCORAD values favoring probiotics over the control were observed overall (MD, -3.07; 95%CI, -6.12 to -0.03; P < 0.00001). However, a high degree of heterogeneity was observed across these 14 trials ( $I^2 = 87\%$ ).

# Subgroup Analysis of Probiotics Efficacy by Age

All 13 trials involved children aged 0–18 years. We categorized the children into two groups: infants <1 year old and children 1–18 years old. Accordingly, five trials were included in the <1 year subgroup, and nine trials were included in the 1–18 years subgroup (**Figure 4**). The efficacy of probiotics in the former subgroup was -1.03 (95%CI, -7.05 to 4.99) and that in the latter subgroup was -4.50 (95%CI, -7.45 to -1.54; P < 0.001). However, a high degree of heterogeneity was observed among the <1 year subgroup (I<sup>2</sup> = 94%).

#### **Subgroup Assessment by Continent**

Subgroup assessment by continent showed different effects. In Europe, probiotics showed no effect on SCORAD, whereas significantly lower SCORAD values were reported in Asia (MD, -5.39; 95%CI, -8.91 to -1.87). In Australia, the MD was -11.20

(95%CI, -13.76 to -8.64). However, there was heterogeneity among these trials (**Figure 5**).

# Subgroup Assessment of Different Cultured Organisms

MD scoring compared to control and placebo interventions was performed by cultured organism group. *LGG* (MD, 3.29; 95%CI, -0.30 to 6.88; *P* = 0.07) and *LP* (MD, -0.70; 95%CI, -2.30 to 0.90; *P* = 0.39) showed no significant effects on SCORAD values in children. However, *LF* (MD, -11.42; 95%CI, -13.81 to -9.04), *LS* (MD, -7.21; 95%CI, -9.63 to -4.78), and a mixture of different strains (MD, -3.52; 95%CI, -5.61 to -1.44) showed significant effects on SCORAD values in children (**Figure 6**).

# **Publication Bias**

We used RevMan software to draw funnel plots (Figure 7), wherein each dot represents data from a single RCT. A randomeffects model was used to this end. The funnel plots were somewhat asymmetrical, thus indicating potential publication bias, perhaps attributable in part to the fact that we included only English-language publications and excluded conference abstracts. However, studies with positive outcomes are more

		Expe	eriment	al	C	ontrol			Mean Difference	Mean Difference	Risk of Bias
-	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	ABCDEFG
	2004 Viljanen	12.1	16.8	80	9.8	13.2	74	7.8%	2.30 [-2.45, 7.05]		??
	2005 Weston	22.6	4.92	28	33.8	4.85	28	9.0%	-11.20 [-13.76, -8.64]		$\bullet$ ? $\bullet$ $\bullet$ $\bullet$ $\bullet$ ?
	2006 Folster	35.3	15.2	26	31.6	14.5	27	5.8%	3.70 [-4.30, 11.70]		??
	2007 Gruber	22.5	14.6	54	17.9	13.6	48	7.3%	4.60 [-0.87, 10.07]	<u>+</u>	2 ? ? ? • • ?
	2009 Niers	20.4	10.9	50	21	10.5	48	8.1%	-0.60 [-4.84, 3.64]		? ? • • • ? ? ?
	2010 Gerasimov	27.9	9.9	43	32.4	7.7	47	8.4%	-4.50 [-8.19, -0.81]		• ? • • • ? ?
	2010 Shafiei	41.9	15.4	43	39.9	11.6	18	6.3%	2.00 [-5.06, 9.06]		• ? • • • ? ?
	2010 Woo	28.8	5.4	41	35.8	5.85	34	9.0%	-7.00 [-9.57, -4.43]		?? • • • ? ?
	2011 Gore	12.5	5.33	45	11.8	3.48	47	9.2%	0.70 [-1.15, 2.55]		2 2 2 2 3 3 3 3 3 2 3 2 3 3 3 3 3 3 3 3
	2011 Wu KG	27.4	12.7	27	36.3	14.9	27	6.1%	-8.90 [-16.28, -1.52]	<u> </u>	• ? • • • ? ?
	2012 Yavuz	12.4	7.2	20	15.3	6.1	20	8.1%	-2.90 [-7.04, 1.24]		??
	2012 Youngshin	20.6	9.2	45	23.2	8.2	46	8.5%	-2.60 [-6.18, 0.98]		• ? • • • ? ?
	2015 Wang IJ	25.76	19.23	51	40.1	15.58	53	6.5%	-14.34 [-21.08, -7.60]		•?•••??
	Total (95% CI)			553			517	100.0%	-3.07 [-6.12, -0.03]	•	
	Heterogeneity: Tau <sup>2</sup> =	25.20; 0	) 2012 - 95	5.65, df	= 12 (P	< 0.000	01); I <sup>z</sup>	= 87%			•
	Test for overall effect:	Z=1.98	(P = 0.0	)5)					F	-20 -10 0 10 20	
				-					F	avours (experimental) - Favours (control)	
	Risk of bias legend										
	(A) Random sequenc	e denera	ation (se	electior	i bias)						
	(B) Allocation conceal	Iment (se	election	bias)	,						
	(C) Blinding of particip	oants an	d perso	nnel (p	erforma	nce bia	S)				
	(D) Blinding of outcom	ne asses	ssment	(detect	ion bias	;)	<i>'</i>				
	(E) Incomplete outcon	ne data (	attrition	bias)		,					
	(F) Selective reporting	ı (reportir	na bias)	)							
	(G) Other bias	1-1-10	J								
IGURE 3	MD scoring with p	robiotic	s treat	ment	compa	ared to	conti	rol and j	olacebo interventior	ns. 95%Cl, 95% confidence interval.	

Study of subplicities       Sub Total Mean       Sub Total Vergin       Tot, Randolit 35-12       TV, Randolit 35-12 <th randoli<="" th="" tv,=""><th>Study of Subgroup</th><th>Expe</th><th>eriment</th><th>al Totol</th><th>( Moon</th><th>ontrol</th><th>Total</th><th>Wojaht</th><th>Mean Difference</th><th>Mean Difference</th><th>Risk of Bias</th></th>	<th>Study of Subgroup</th> <th>Expe</th> <th>eriment</th> <th>al Totol</th> <th>( Moon</th> <th>ontrol</th> <th>Total</th> <th>Wojaht</th> <th>Mean Difference</th> <th>Mean Difference</th> <th>Risk of Bias</th>	Study of Subgroup	Expe	eriment	al Totol	( Moon	ontrol	Total	Wojaht	Mean Difference	Mean Difference	Risk of Bias
$\begin{array}{c} 2004 \ \text{Wigaten} & 12.1 \ 16.8 \ 80 \ 9.8 \ 13.2 \ 74 \ 7.8\% \ 2.30 \ [245, 7.05] \\ 2005 \ \text{Weston} & 22.6 \ 4.92 \ 2.8 \ 33.8 \ 4.85 \ 2.8 \ 9.0\% \ -11.20 \ [13.6, 8.64] \\ 2007 \ \text{Gruber} & 22.5 \ 14.6 \ 54 \ 17.9 \ 13.6 \ 4.8 \ 7.3\% \ 4.80 \ [14.06, 7.10.07] \\ 2008 \ \text{Misr} & 20.4 \ 10.9 \ 50 \ 2.1 \ 10.5 \ 4.8 \ 8.1\% \ -0.60 \ [14.6, 8.64] \\ 2017 \ \text{Gruber} & 22.5 \ 14.6 \ 54 \ 17.9 \ 13.6 \ 4.8 \ 7.9\% \ 0.70 \ [14.7, 8.64] \\ 2010 \ \text{Grav} & 12.5 \ 53.3 \ 45 \ 11.8 \ 3.48 \ 47 \ 9.2\% \ 0.70 \ [14.7, 52.55] \\ \text{Subtatal (95\% CI)} & 257 \ 245 \ 41.4\% \ -1.03 \ [17.0] \ -1.52 \ 5.55 \ 3.0 \ 16.1 \ 14.5 \ 27 \ 5.8\% \ 3.70 \ [14.30, 11.70] \\ 2010 \ \text{Graving} & 27.9 \ 9.9 \ 43 \ 32.4 \ 7.7 \ 47 \ 8.4\% \ -1.60 \ [16.8, 9.0, 9.8] \\ 2010 \ \text{Graving} & 27.9 \ 9.9 \ 43 \ 32.4 \ 7.7 \ 47 \ 8.4\% \ -4.50 \ [16.8, 9.0, 9.8] \\ 2010 \ \text{Graving} & 27.9 \ 9.9 \ 43 \ 32.4 \ 7.7 \ 47 \ 8.4\% \ -4.50 \ [16.8, 9.0, 9.8] \\ 2010 \ \text{Graving} & 27.9 \ 9.9 \ 43 \ 32.4 \ 7.7 \ 47 \ 8.4\% \ -4.50 \ [16.8, 9.0, 9.8] \\ 2010 \ \text{Graving} & 27.9 \ 9.9 \ 43 \ 32.4 \ 7.7 \ 47 \ 8.4\% \ -50.9 \ 50.9 \ 7.00 \ [16.2, 815.2] \\ 2010 \ \text{Graving} & 27.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2.9 \ 2$	231<1 vears	wear	30	TULAI	mean	30	TULAI	weight	IV, Kanuoni, 95% C		ADCDEFU	
$ \begin{array}{c} 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 \\ 2 = 0 $	2004 Vilianen	121	16.8	80	98	13.2	74	7.8%	2 30 1-2 45 7 05		??	
$\begin{array}{c} 2007 \ Gruber \\ 2105 \ 14.6 \ 54 \ 17.9 \ 13.8 \ 48 \ 7.3\% \ 4.60 \ [0.87, 10.07] \\ 2009 \ Nies \\ 204 \ 10.9 \ 50 \ 21 \ 10.5 \ 48 \ 8.1\% \ -0.60 \ [4.84, 3.64] \\ 2011 \ Gore \ 12.5 \ 5.3 \ 45 \ 11.8 \ 349 \ 47 \ 9.2\% \ 0.70 \ [1.15, 2.55] \\ 2010 \ Nies \ 20.4 \ 10.9 \ 50 \ 21 \ 10.5 \ 48 \ 8.1\% \ -0.60 \ [4.84, 3.64] \\ 2011 \ Gore \ 12.5 \ 5.3 \ 45 \ 11.8 \ 349 \ 47 \ 9.2\% \ 0.70 \ [1.15, 2.55] \\ 2010 \ Nies \ 23.2 \ 1.8 \ 25.2 \ 27 \ 9.3\% \ 0.70 \ [1.15, 2.55] \\ 2010 \ Statist \ 43 \ 31.5 \ 25 \ 41.4\% \ -0.80 \ [4.43, 11.70] \\ 2.22 \ 1.8 \ 9ars \ 2.25 \ 14.3\% \ 1.8 \ 3.49 \ 47 \ 9.2\% \ 0.70 \ [1.15, 2.55] \\ 2010 \ Statist \ 27 \ 5.8\% \ 3.70 \ [1.43, 1.50] \\ 2010 \ Statist \ 41.9 \ 15.4 \ 43 \ 39.9 \ 11.6 \ 18 \ 5.3\% \ 2.00 \ [5.06, 9.0] \\ 2010 \ Statist \ 41.9 \ 15.4 \ 43 \ 39.9 \ 11.6 \ 18 \ 5.3\% \ 2.00 \ [5.06, 9.0] \\ 2010 \ Statist \ 41.9 \ 15.4 \ 43 \ 39.9 \ 11.6 \ 18 \ 5.3\% \ 2.00 \ [5.06, 9.0] \\ 2010 \ Statist \ 41.9 \ 15.4 \ 43 \ 39.9 \ 11.6 \ 18 \ 5.3\% \ 2.00 \ [5.06, 9.0] \\ 2010 \ Voo \ 28.8 \ 5.4 \ 41 \ 36.8 \ 5.85 \ 34 \ 9.0\% \ -7.00 \ [9.57, -4.43] \\ 2012 \ Yang \ L \ 2.74 \ 12.7 \ 27 \ 36.3 \ 14.9 \ 27 \ 5.8\% \ -2.60 \ [6.16, 0.98] \\ 2010 \ Voag \ 2.8 \ 5.4 \ 41 \ 36.8 \ 5.85 \ 34 \ 9.0\% \ -7.00 \ [9.57, -4.43] \\ 2012 \ Yang \ L \ 2.74 \ 12.7 \ 27 \ 36.3 \ 14.9 \ 27 \ 5.8\% \ -2.60 \ [6.16, 0.98] \\ 201 \ Vang \ L \ 2.75 \ 14.91 \ 15.5 \ 53 \ 5.5\% \ -2.60 \ [6.16, 0.98] \ 201 \ Vang \ L \ 2.75 \ 1.52 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ 2.2 \ $	2004 Viljanen 2005 Weston	22.6	4 92	28	33.8	4 85	28	9.0% 9.0%	-11 20 [-13 76 -8 64]	<u> </u>		
$\begin{array}{c} 2000 \text{ Nies} & 214 & 103 & 50 & 216 & 103 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 40 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 133 & 13$	2003 Weston 2007 Gruher	22.0	1/1.6	5/	17.0	13.6	18	7.3%	A 60 L0 87 10 07	└ <u> </u>	2222442	
Labor holds $126, 103, 30, 12, 103, 30, 12, 103, 40, 47, 92, 0, 071, 115, 253, 257, 245, 41.4, -1.03 [7.05, 4.99] Subtotal (95% C) 257, 245, 41.4, -1.03 [7.05, 4.99] Heterogeneity, Tau2 = 43.11; Ch2 = 66.90, df = 4 (P < 0.00001); P = 94% Test for overall effect Z = 0.34 (P = 0.74) 2.3.2 1.8 years 2006 Folster 35.3, 15.2, 26, 31.6, 14.5, 27, 5.8%, 3.70 [-4.30, 11.70] 2010 Shafiei 41.9, 15.4, 43, 39.9, 11.6, 18, 6.3%, 2.00 [-5.06, 9.06] 2010 Woo 28.8, 54, 41, 358, 5.85, 34, 9.0%, -7.00 [-9.57, 4.43] 2010 Woo 28.8, 54, 41, 358, 5.85, 34, 9.0%, -7.00 [-9.57, 4.43] 2010 Woo 28.8, 54, 41, 358, 5.85, 34, 9.0%, -7.00 [-9.57, 4.43] 2010 Woo 28.8, 54, 41, 358, 5.85, 34, 9.0%, -7.00 [-9.57, 4.43] 2012 Yavuz 12.4, 7.2, 20, 15.3, 6.1, 20, 8.1%, -2.90 [F.16.8, 1.52] 2012 Yavuz 12.4, 7.2, 20, 15.3, 6.1, 20, 8.1%, -2.90 [F.16.8, 1.52] 2015 Wang JL 25.76, 19.23, 51, 40.1, 15.58, 53, 6.5%, -14.34 [-21.69, -7.60] 2015 Wang JL 25.76, 19.23, 51, 40.1, 15.58, 53, 6.5%, -14.34 [-21.69, -7.60] 2015 Wang JL 25.76, 19.23, 51, 40.1, 15.58, 53, 6.5%, -14.34 [-21.69, -7.60] 40 Participants and personnel (performance bias) East for subgroup differences: Chi2 = 1.03, df = 1 (P = 0.31), P = 2.6% Risk of bias legend (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of outcome assessment (detection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (beformance bias) (D) Blinding of outcome assessment (detection bias) (C) Blinding of participants and personnel (beformance bias) (D) Blinding of outcome assessment (detection bias) (C) Blinding of outcome assessment (detection bias) (F) Selective reporting (reporting bias) ($	2007 Oraber 2009 Niere	22.5	10.0	50	21	10.5	40	2.370 2.1%	4.00-00-00-00-00-00-00-00-00-00-00-00-00-	<b>_</b>	2244422	
$\begin{array}{c} 11 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ 120 \ $	2003 Nicia 2011 Gore	12.5	5 3 3	45	11.8	3 // 8	40	0.1% 0.7%	0 70 [-1 15 2 55]		2222422	
$ \begin{array}{c} \text{Link of } 1 \text{ for } 1 \text{ fo } 1 \text{ fo } 1 \text{ for } 1 \text{ for } 1 \text{ for } 1 \text{ for } 1 $	Subtotal (95% CI)	12.0	0.00	257	11.0	3.40	245	41.4%	-1.03[.7.05, 4.99]			
The stepson in the sequence generation (selection bias) (A) Head of participants and personnel (performance bias) (B) Allocation concealment (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of outcome assessment (detection bias) (B) Allocation concealment (selection bias) (C) Blinding of outcome assessment (detection bias) (C) Blinding of outcome assessment (detection bias) (C) Blinding of outcome assessment (detection bias) (C) Selective reporting (reporting bias) (C) Steptive reporting	Heteroneneity: Tau² =	43.1110	Chi² = 6£	201 H 00 A	= A (P -	< N NNN	245 11): IZ =	91%	- 105 [-1105, 4155]			
2.32 1-18 years 2006 Folster 35.3 15.2 26 31.6 14.5 27 5.8% $3.70 [+3.0, 11.70]$ 2010 Gerasimov 27.9 9.9 43 32.4 7.7 47 8.4% $-4.50 [+8.19, -0.81]$ 2010 Shafinei 41.9 15.4 43 39.9 11.6 18 6.3% 2.00 [-5.06, 9.06] 2010 Woo 28.8 5.4 41 35.8 5.85 34 9.0% $-7.00 [-9.57, -4.43]$ 2011 Wu KG 27.4 12.7 27 36.3 14.9 27 6.1% $-8.90 [-16.28, -1.52]$ 2012 Yavuz 12.4 7.2 20 15.3 6.1 20 8.1% $-2.90 [-7.04, 1.24]$ 2012 Yavuz 12.4 7.2 20 15.3 6.1 20 8.1% $-2.90 [-7.04, 1.24]$ 2012 Youngshin 20.6 9.2 45 23.2 8.2 46 8.5% $-2.60 [-6.18, 0.98]$ 2015 Wang L 25.76 19.23 51 40.1 15.86 53 6.5% $-14.34 [-21.08, -7.60]$ Subtata (95% CI) 296 272 58.6% $-4.50 [-6.18, 0.98]$ Test for overall effect Z = 1.98 (P = 0.003); P = 68% Test for overall effect Z = 1.98 (P = 0.05) Test for subgroup differences: Chi <sup>P</sup> = 1.03, df = 1 (P = 0.31), P = 2.6% Risk of bias legand (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias (G) Other bias	Test for overall effect:	Z=0.34	(P = 0.7	74)	- 4 ()	.0.0001		5470				
2.3.2 1-18 years 2006 Folster 35.3 15.2 26 31.6 14.5 27 5.8% $3.70 [4.30, 11.70]$ 2010 Gerasimov 27.9 9.9 43 32.4 7.7 47 8.4% $-4.50 [61.9, 0.81]$ 2010 Woo 28.8 5.4 41 35.8 5.85 34 9.0% $-7.00 [9.57, -4.43]$ 2011 Wu KG 27.4 12.7 27 36.3 14.9 27 6.1% $-8.90 [16.28, -1.52]$ 2012 Yavuz 12.4 7.2 20 15.3 6.1 20 8.1% $-2.90 [-7.04, 1.24]$ 2012 Yavuz 12.4 7.2 20 15.3 6.1 20 8.1% $-2.90 [-7.04, 1.24]$ 2012 Youngshin 20.6 9.2 45 23.2 8.2 46 8.5% $-2.60 [-6.18, 0.98]$ 2015 Wang J 25.76 19.23 51 40.1 15.8 53 6.5% $-14.34 [-21.08, -7.60]$ Subtatal (95% CI) 296 272 58.6% $-4.50 [-7.45, -1.54]$ Heterogeneity. Tau <sup>2</sup> = 11.13; Ch <sup>2</sup> = 21.85, df = 7 (P = 0.003); P = 68% Test for overall effect Z = 1.98 (P = 0.05) Test for subgroup differences: Ch <sup>2</sup> = 1.03, df = 1 (P = 0.31), P = 2.6% Risk of bias legend (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias												
$ \begin{array}{c} 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.00 \ \ 0.0\$	1.3.2 1-18 years	25.2	15.2	26	21.6	14.5	27	E 000	2 70 1 4 20 11 70		2288882	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1000 FUISIEI 2010 Corocimou	30.3 37.0	10.2	40	31.0 33.4	14.0	47	U.070 0.400	3.70[-4.30, 11.70]		A 2 A A A 2 2	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	2010 Gerasiniuv 2010 Chofioi	27.9 44.0	9.9 15.4	40	02.4 00.0	11.6	47	0.470 6.300	20016060006		A 2 A A A 2 2	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	2010 Shaher 2010 Woo	41.3 20.0	10.4	40	39.9 36.0	5.05	10	0.3%	2.00[-0.00, 9.00]		2244422	
$\begin{array}{c} \text{var} (1 + \sqrt{12}, 2 + 1$	2010 9900	20.0 27 /	0.4 10.7	41	0.00 0.00	1/0	04 07	9.070 6.100	-7.00[9.07,-4.45]		A 2 A A A 2 2	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	2011 000 NO	27.4 10.4	7.2	27	16.0	14.5 G 1	27	0.170	-0.30[-10.20,-1.32]	<b>_</b> _	2244442	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	2012 Tayuz 2012 Vounachin	20.6	0.2	45	10.0	0.1	20 46	0.170	2.20 [-7.04, 1.24] 00 0 0 0 0 1 0 0 0 0			
Subtotal (95% CI) 296 272 58.6% -4.50 [-7.45, -1.54] Heterogeneity: Tau <sup>2</sup> = 11.13; Chi <sup>2</sup> = 21.85, df = 7 (P = 0.003);   <sup>2</sup> = 68% Test for overall effect: Z = 2.98 (P = 0.003) Intel (95% CI) 553 517 100.0% -3.07 [-6.12, -0.03] Heterogeneity: Tau <sup>2</sup> = 25.20; Chi <sup>2</sup> = 95.65, df = 12 (P < 0.00001);   <sup>2</sup> = 87% Test for overall effect: Z = 1.98 (P = 0.05) Test for overall effect: Z = 1.98 (P = 0.05) Test for subgroup differences: Chi <sup>2</sup> = 1.03, df = 1 (P = 0.31),   <sup>2</sup> = 2.6% Risk of bias legend A) Random sequence generation (selection bias) B) Allocation concealment (selection bias) B) Allocation concealment (selection bias) C) Blinding of participants and personnel (performance bias) D) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (attrition bias) F) Selective reporting (reporting bias) G) Other bias	2012 TOURIYSHIN	20.0	3.2	40	20.2	16.60	40 50	0.070	-2.00[-0.10, 0.90]		A 2 A A A 2 2	
Heterogeneity: Tau <sup>2</sup> = 11.13; Chi <sup>2</sup> = 21.85, df = 7 (P = 0.003); I <sup>2</sup> = 68% Test for overall effect: Z = 2.98 (P = 0.003) <b>Total (95% Cl)</b> 553 517 100.0% -3.07 [-6.12, -0.03] Heterogeneity: Tau <sup>2</sup> = 25.20; Chi <sup>2</sup> = 95.65, df = 12 (P < 0.00001); I <sup>2</sup> = 87% Test for overall effect: Z = 1.98 (P = 0.05) Test for subgroup differences: Chi <sup>2</sup> = 1.03, df = 1 (P = 0.31), I <sup>2</sup> = 2.6% <b>Risk of bias legend</b> <b>A</b> ) Random sequence generation (selection bias) <b>B</b> ) Allocation concealment (selection bias) <b>B</b> ) Allocation concealment (selection bias) <b>C</b> ) Blinding of participants and personnel (performance bias) <b>D</b> ) Blinding of outcome assessment (detection bias) <b>(E</b> ) Incomplete outcome data (attrition bias) <b>(F</b> ) Selective reporting (reporting bias) <b>(G</b> ) Other bias	Subtotal (95% Cl)	20.70	19.25	206	40.1	10.00	00 272	0.0% 58.6%	450[745 154]	•		
Test for overall effect: $Z = 2.98$ (P = 0.003) Total (95% Cl) 553 517 100.0% -3.07 [-6.12, -0.03] Heterogeneity: Tau <sup>2</sup> = 25.20; Chi <sup>2</sup> = 95.65, df = 12 (P < 0.00001); I <sup>2</sup> = 87% Test for overall effect: $Z = 1.98$ (P = 0.05) Test for subgroup differences: Chi <sup>2</sup> = 1.03, df = 1 (P = 0.31), I <sup>2</sup> = 2.6% Risk of bias legend (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias	Hotorogonoity: Tou <sup>2</sup> –	11.12-0	`hi≅ – 01	1 95 df	- 7 (P -	- 0 003)	- 12 - 60	206	-130 [-1143, -1134]	•		
Total (95% Cl)553517100.0% $-3.07$ [-6.12, -0.03]Heterogeneity: Tau <sup>2</sup> = 25.20; Chi <sup>2</sup> = 95.65, df = 12 (P < 0.00001); i <sup>2</sup> = 87% Test for overall effect: Z = 1.98 (P = 0.05) Test for subgroup differences: Chi <sup>2</sup> = 1.03, df = 1 (P = 0.31), i <sup>2</sup> = 2.6% Risk of bias legend (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias517100.0% $-3.07$ [-6.12, -0.03] $-20$ $-20$ $-10$ $-20$ $-10$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-10$ $-20$ $-20$ $-10$ $-20$ $-10$ $-20$ $-20$ $-10$ $-20$ $-10$ $-20$ $-20$ $-10$ $-20$ $-10$ $-20$ $-20$ $-10$ $-20$ $-20$ $-20$ $-10$ $-20$ $-20$ $-10$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-10$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-20$ $-2$	Test for overall effect:	Z = 2.98	(P = 0.0)	003) 003)	- (0 -	- 0.003)	,1 = 00					
Total (95% CI)       553       517       100.0%       -3.07 [-6.12, -0.03]         Heterogeneity: Tau <sup>2</sup> = 25.20; Chi <sup>2</sup> = 95.65, df = 12 (P < 0.00001); I <sup>2</sup> = 87%       -20       -10       0       10       20         Test for overall effect: Z = 1.98 (P = 0.05)       Favours [control]       -20       -10       0       10       20         Test for subgroup differences: Chi <sup>2</sup> = 1.03, df = 1 (P = 0.31), I <sup>2</sup> = 2.6%       Favours [experimental]       Favours [control]         Risk of bias legend       (A) Random sequence generation (selection bias)       (B) Allocation concealment (selection bias)       (C) Blinding of participants and personnel (performance bias)       (D) Blinding of outcome assessment (detection bias)         (E) Incomplete outcome data (attrition bias)       (F) Selective reporting (reporting bias)       (G) Other bias				,						•		
Heterogeneity: Tau <sup>2</sup> = 25.20; Chi <sup>2</sup> = 95.65, df = 12 (P < 0.00001); I <sup>2</sup> = 87% Test for overall effect: Z = 1.98 (P = 0.05) Test for subgroup differences: Chi <sup>2</sup> = 1.03, df = 1 (P = 0.31), I <sup>2</sup> = 2.6% Risk of bias legend (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias	Fotal (95% CI)			553			517	100.0%	-3.07 [-6.12, -0.03]	• • • • •		
Test for overall effect: Z = 1.98 (P = 0.05)       Favours [control]         Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), l² = 2.6%       Favours [experimental]         Risk of bias legend       [A] Random sequence generation (selection bias)         (A) Random sequence generation (selection bias)       [B] Allocation concealment (selection bias)         (C) Blinding of participants and personnel (performance bias)       [D] Blinding of outcome assessment (detection bias)         (E) Incomplete outcome data (attrition bias)       [F] Selective reporting (reporting bias)         (G) Other bias       [G] Other bias	Heterogeneity: Tau² =	25.20; C	)hi² = 95	5.65, df	'= 12 (F	' < 0.000	)01); I <sup>z</sup>	= 87%		-20 -10 0 10 20	-	
Test for subgroup differences: Chi <sup>2</sup> = 1.03, df = 1 (P = 0.31), l <sup>2</sup> = 2.6% <u>Risk of bias legend</u> (A) Random sequence generation (selection bias) (B) Allocation concealment (selection bias) (C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias	Fest for overall effect:	Z=1.98	(P = 0.0	05)						Favours (experimental) Favours (control)		
Risk of bias legend A) Random sequence generation (selection bias) B) Allocation concealment (selection bias) C) Blinding of participants and personnel (performance bias) D) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (attrition bias) F) Selective reporting (reporting bias) G) Other bias	Fest for subgroup diff	erences	: Chi <sup>z</sup> =	1.03, d	f=1 (P	= 0.31),	1 <sup>2</sup> = 2.8	6%				
A) Random sequence generation (selection bias) B) Allocation concealment (selection bias) C) Blinding of participants and personnel (performance bias) D) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (attrition bias) F) Selective reporting (reporting bias) G) Other bias	Risk of bias legend											
B) Allocation concealment (selection bias) C) Blinding of participants and personnel (performance bias) D) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (attrition bias) F) Selective reporting (reporting bias) G) Other bias	A) Random sequenc	e gener:	ation (si	electior	n bias)							
(C) Blinding of participants and personnel (performance bias) (D) Blinding of outcome assessment (detection bias) (E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias	(B) Allocation conceal	lment (s	election	bias)								
D) Blinding of outcome assessment (detection bias) E) Incomplete outcome data (attrition bias) F) Selective reporting (reporting bias) G) Other bias	(C) Blinding of particip	pants an	d perso	nnel (p	erforma	ance bia	s)					
(E) Incomplete outcome data (attrition bias) (F) Selective reporting (reporting bias) (G) Other bias	(D) Blinding of outcom	ne asses	ssment	(detect	tion bia:	s)						
(F) Selective reporting (reporting bias) (G) Other bias	(E) Incomplete outcon	ne data i	(attrition	ı bias)								
(G) Other bias	(F) Selective reporting	ı (reportii	ng bias)	)								
	(G) Other bias											

likely to be published than are those with negative outcomes, thus creating bias.

# **Sensitivity Testing**

FIG

We performed sensitivity analyses to assess the relative influence of each study by excluding the studies one by one, and the results suggested no significant changes in effects with regard to subgroups.

# DISCUSSION

Overall, the data suggested an overall benefit of probiotics supplementation in children with AD, and age-specific subanalyses showed that probiotics effectively reduce SCORAD values in children aged 1–18 years. Geography-specific subanalyses showed that probiotics effectively reduced SCORAD values in Asia, while no effect was observed for Europe. Strain-specific sub-analyses indicated that *Lactobacillus (LS), Lactobacillus fermentum (LF)*, and a probiotic mixture reduced SCORAD values in children with AD, while LGG and Lactobacillus plantarum (LP)showed no effect in children with AD.

Hippocrates (460-370) stated that "All diseases begin in the gut", which is the earliest suggestion that bacteria affect health (Hippocrates, 2002). Metchnikoff, known as the father of probiotics (Gordon, 2016), proposed that colonic bacteria afforded health benefits in aging adults. In recent decades, probiotics that aid in the resolution of pediatric atopic eczema have been investigated. Viljanen et al. explored probiotic effects on pediatric atopic eczema/dermatitis syndrome but found no significant difference between the treatment and control groups (Viljanen et al., 2005). Passeron et al. compared probiotics and prebiotics and found that both significantly improved AD manifestations in children (Passeron et al., 2006). Brouwer et al. evaluated the clinical and immunological effects of Lactobacillus rhamnosus (LR) supplementation in a hydrolyzed formula given to children with AD but found no significant effect (Brouwer et al., 2006). The cited authors suggested that the discrepancies between their results and those of other trials were likely attributable to differences in treatment timing and the strains

FIG

~	Expe	erimenta	al	C	ontrol			Mean Difference	Mean Difference	Risk of Bias
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	IV, Random, 95% Cl	ABCDEFG
2.1.2 europe										
2004 Viljanen	12.1	16.8	80	9.8	13.2	74	7.8%	2.30 [-2.45, 7.05]	T	
2006 Folster	35.3	15.2	26	31.6	14.5	27	5.8%	3.70 [-4.30, 11.70]		
2007 Gruber	22.5	14.6	54	17.9	13.6	48	7.3%	4.60 [-0.87, 10.07]		
2009 Niers	20.4	10.9	50	21	10.5	48	8.1%	-0.60 [-4.84, 3.64]		3366633
2010 Gerasimov	27.9	9.9	43	32.4	7.7	47	8.4%	-4.50 [-8.19, -0.81]		
2011 Gore	12.5	5.33	45	11.8	3.48	47	9.2%	0.70 [-1.15, 2.55]	Ť	3333933
Subtotal (95% CI)			298			291	46.5%	0.43 [-2.01, 2.87]	•	
Heterogeneity: Tau² =	= 4.48; Cł	hi² = 10.6	60, df =	= 5 (P =	0.06); l <sup>a</sup>	= 53%				
Test for overall effect	Z = 0.34	(P = 0.7	73)							
2.1.3 Asia										
2010 Shafiei	41.9	15.4	43	39.9	11.6	18	6.3%	2.00 [-5.06, 9.06]		• ? • • • ? ?
2010 Woo	28.8	5.4	41	35.8	5.85	34	9.0%	-7.00 [-9.57, -4.43]	-	?? • • • ? ?
2011 Wu KG	27.4	12.7	27	36.3	14.9	27	6.1%	-8.90 [-16.28, -1.52]	_ <b></b>	
2012 Yavuz	12.4	7.2	20	15.3	6.1	20	8.1%	-2.90 [-7.04, 1.24]		??
2012 Youngshin	20.6	9.2	45	23.2	8.2	46	8.5%	-2.60 [-6.18, 0.98]		
2015 Wand IJ	25.76	19.23	51	40.1	15.58	53	6.5%	-14.34 [-21.087.60]	<b>_</b> _	
Subtotal (95% CI)			227			198	44.5%	-5.39 [-8.91, -1.87]	•	
Heterogeneity: Tau <sup>2</sup> =	= 12.49: C	Chi <sup>z</sup> = 17	2.07. df	f = 5 (P =	= 0.004)	: <b> </b> ² = 7:	1%	. , ,		
Test for overall effect	Z = 3.00	(P = 0.0	)03)	,						
2.4.4 Austria										
2.1.4 Austria		1.00	20		1.07		0.000	44 00 / 40 70 0 00		
2005 Weston Subtatal (05%, CD	22.6	4.92	28	33.8	4.85	28	9.0%	-11.20[-13.76, -8.64]	▲	
Subtotal (95% CI)			28			20	9.0%	-11.20 [-13.70, -8.04]	•	
Heterogeneity: Not aj	opiicabie									
l est for overall effect	.Z=8.58	i (P < U.U	10001)							
Total (95% CI)			553			517	100.0%	-3.07 [-6.12, -0.03]	•	
Heterogeneity: Tau <sup>2</sup> =	= 25.20; C	Chi <sup>z</sup> = 95	5.65, df	f= 12 (P	< 0.000	001); P	= 87%			_
Test for overall effect	Z=1.98	(P = 0.0	)5)						-20 -10 0 10 20	
Test for subgroup dif	ferences	: Chi²=	41.57,	df = 2 (F	° < 0.00	001), P	= 95.2%		Favours (experimental) Favours (control)	
Risk of bias legend										
(A) Random sequen	ce dener:	ation (se	election	n bias)						
(B) Allocation concea	Iment (s	election	bias)	,						
(C) Blinding of partici	nants an	d persor	nnel (n	erforma	ance bia	is)				
(D) Blinding of outcor	ne asse	ssment	(detect	tion hias	ano one a)	,				
(E) Incomplete outco	me data i	(attrition	hias)	a with writin	~/					
(E) Selective reporting	n (renorti	na hiae)	ana a)							
<ul> <li>A server reholm i</li> </ul>	a (reporti	ng maa)								
(G) Other bigs										

used. Sistek et al. conducted a 12-week trial in the UK and found that a combination of *LR* and *Bifidobacteria lactis* (*BL*) improved AD symptoms in food-sensitive children (Sistek et al., 2006). At roughly the same time, a prospective German study by Folster-Holst et al. yielded insufficient evidence to make the conclusion that *LGG* is an effective treatment for moderate-to-severe AD in infants (Folster-Holst, 2010). Gruber et al. also found that *LGG* had no therapeutic effect in such patients (Gruber et al., 2007). Despite these discouraging findings, Gerasimov et al. reported that *Lactobacillus acidophilus DDS-1* and *Bifidobacterium lactis UABLA-12* afforded significant clinical improvements in children with moderate-to-severe AD (Gerasimov et al., 2010). Similarly, Wu et al. showed that *Lactobacillus salivarius* (*LS*) exerted shortterm beneficial effects in patients with moderate-to-severe AD (Wu et al., 2012). Drago et al. suggested that such effects may be attributable to restoration of the altered intestinal microbiota (Drago et al., 2011). In contrast, Gore et al. found that *LS* exerted no beneficial effects on eczema when given as an adjunct to basic topical treatment (Gore et al., 2012). Several reports have examined the effects of other bacterial strains on AD in children. Supplementation with *LPCJLP 133*, *Lactobacillus paracasei*, and *LF* was reported to be effective. The discrepancies described above may be attributable to differences in the strains used, the study areas, and/or the ethnicities of the subjects. Several groups have performed meta-analyses to evaluate the effectiveness of probiotics on AD. Da Costa Baptista et al. reviewed all published trials and reported that the biological effects observed in most trials suggest that probiotic adjuvant treatments are of benefit for AD (da et al., 2013). The cited review, although comprehensive, did not report total MDs or 95%CIs. Chang performed a

	Exp	eriment	al	(	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	IV, Fixed, 95% Cl
2.4.1 LGG									
2004 Viljanen	12.1	16.8	80	9.8	13.2	74	4.2%	2.30 [-2.45, 7.05]	
2007 Gruber	22.5	14.6	54	17.9	13.6	48	3.2%	4.60 [-0.87, 10.07]	
Subtotal (95% Cl)			134			122	7.4%	3.29 [-0.30, 6.88]	-
Heterogeneity: Chi <sup>2</sup> =	= 0.39, df	= 1 (P =	0.53);	I² = 0%					
Test for overall effect	t: Z = 1.80	) (P = 0.1	07)						
2.4.2 LF									
2005 Weston	22.6	4.92	28	33.8	4.85	28	14.6%	-11.20 [-13.76, -8.64]	
2015 Wang IJ	27.23	18.1	51	40.1	15.58	53	2.3%	-12.87 [-19.37, -6.37]	
Subtotal (95% CI)			79			81	16.9%	-11.42 [-13.81, -9.04]	◆
Heterogeneity: Chi <sup>2</sup> =	= 0.22, df	= 1 (P =	0.64);	<sup>2</sup> = 0%					
Test for overall effect	t: Z = 9.40	) (P < 0.1	00001)						
2431P									
2011 Gore	12.5	5 2 2	45	11.0	3.40	17	78 1 %	0 70 [-1 15 2 55]	<b>_</b>
2011 Core 2012 Youngshin	20.6	0.00 Q 2	45	23.2	9.40	46	7.5%	-7 60 [ 6 18 0 98]	
2012 Toungshin 2016 Wong Ll	20.0	0.2 21 72	4J 61	40.1	16 60	40 62	1 006	-14 62 [-21 01 -7 22]	
Subtotal (95% Cl)	23.40	21.75	141	40.1	15.50	146	37.3%	-14.02 [-21.31, -7.33]	•
Unteregonaity: Chi2-	- 17 20 -	IF = 2 /D	- 0.00	10\+ IZ	000	140	51.57	-0.10[-2.50, 0.50]	•
Test for overall effect	t: Z = 0.86	6 (P = 0.3	39)		00.0				
2.4.4 LS									
2010 Woo	28.8	5.4	41	35.8	5.85	34	14.5%	-7.00 [-9.57, -4.43]	
2011 Wu KG	27.4	12.7	27	36.3	14.9	27	1.8%	-8.90 [-16.28, -1.52]	
			68			61	16.3%	-7.21 [-9.63, -4.78]	•
Subtotal (95% CI)			00						•
<b>Subtotal (95% CI)</b> Heterogeneity: Chi <sup>z</sup> =	= 0.23, df	= 1 (P =	0.63);	I² = 0%					
Subtotal (95% CI) Heterogeneity: Chi² = Test for overall effect	= 0.23, df t: Z = 5.82	= 1 (P = 2 (P < 0.1	: 0.63); 00001)	I² = 0%				. , , ,	
Subtotal (95% CI) Heterogeneity: Chi <sup>z</sup> - Test for overall effect 2.4.5 mixture	= 0.23, df t: Z = 5.82	= 1 (P = 2 (P < 0.1	0.63); 00001)	I² = 0%				. , .	
Subtotal (95% CI) Heterogeneity: Chi <sup>≆</sup> : Test for overall effect 2.4.5 mixture 2009 Niers	= 0.23, df t: Z = 5.82 20.4	= 1 (P = ? (P < 0.) 10.9	0.63); 00001) 50	I² = 0% 21	10.5	48	5.3%	-0.60 [-4.84, 3.64]	
Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> : Test for overall effect 2.4.5 mixture 2009 Niers 2010 Gerasimov	= 0.23, df t: Z = 5.82 20.4 27.9	= 1 (P = ? (P < 0.1 10.9 9.9	0.63); 00001) 50 43	I² = 0% 21 32.4	10.5 7.7	48 47	5.3% 7.0%	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81]	
Subtotal (95% CI) Heterogeneity: Chi² : Test for overall effect 2.4.5 mixture 2009 Niers 2010 Gerasimov 2010 Shafiei	= 0.23, df t: Z = 5.82 20.4 27.9 41.9	= 1 (P = 2 (P < 0.) 10.9 9.9 15.4	0.63); 00001) 50 43 43	I <sup>2</sup> = 0% 21 32.4 39.9	10.5 7.7 11.6	48 47 18	5.3% 7.0% 1.9%	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81] 2.00 [-5.06, 9.06]	
Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> : Test for overall effect 2.4.5 mixture 2009 Niers 2010 Gerasimov 2010 Shafiei 2012 Yavuz	= 0.23, df t: Z = 5.82 20.4 27.9 41.9 12.4	= 1 (P = 2 (P < 0.1 10.9 9.9 15.4 7.2	50 00001) 50 43 43 20	² = 0% 21 32.4 39.9 15.3	10.5 7.7 11.6 6.1	48 47 18 20	5.3% 7.0% 1.9% 5.6%	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81] 2.00 [-5.06, 9.06] -2.90 [-7.04, 1.24]	
Subtotal (95% CI) Heterogeneity: Chi² = Test for overall effect 2009 Niers 2010 Gerasimov 2010 Shafiei 2012 Yavuz 2015 Wang IJ	= 0.23, df t: Z = 5.82 20.4 27.9 41.9 12.4 25.76	= 1 (P = 2 (P < 0.1 10.9 9.9 15.4 7.2 19.23	50 50 50 50 43 43 20 51	² = 0% 21 32.4 39.9 15.3 40.1	10.5 7.7 11.6 6.1 15.58	48 47 18 20 53	5.3% 7.0% 1.9% 5.6% 2.1%	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81] 2.00 [-5.06, 9.06] -2.90 [-7.04, 1.24] -14.34 [-21.08, -7.60]	
Subtotal (95% CI) Heterogeneity: Chi¤ = Test for overall effect 2.4.5 mixture 2009 Niers 2010 Gerasimov 2010 Shafiei 2012 Yavuz 2015 Wang IJ Subtotal (95% CI)	= 0.23, df : Z = 5.82 20.4 27.9 41.9 12.4 25.76	= 1 (P = 2 (P < 0.1 10.9 9.9 15.4 7.2 19.23	50 50 50 43 43 20 51 207	² = 0% 21 32.4 39.9 15.3 40.1	10.5 7.7 11.6 6.1 15.58	48 47 18 20 53 <b>186</b>	5.3% 7.0% 1.9% 5.6% 2.1% <b>22.0%</b>	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81] 2.00 [-5.06, 9.06] -2.90 [-7.04, 1.24] -14.34 [-21.08, -7.60] - <b>3.52 [-5.61, -1.44]</b>	
Subtotal (95% CI) Heterogeneity: Chi¤ = Test for overall effect 2.4.5 mixture 2009 Niers 2010 Gerasimov 2010 Shafiei 2012 Yavuz 2015 Wang IJ Subtotal (95% CI) Heterogeneity: Chi¤ =	= 0.23, df t Z = 5.82 20.4 27.9 41.9 12.4 25.76 = 14.42, c	= 1 (P = 2 (P < 0.1 10.9 9.9 15.4 7.2 19.23 If = 4 (P	50 50 50 43 43 20 51 207 = 0.000	² = 0% 21 32.4 39.9 15.3 40.1 3);  ² = 7	10.5 7.7 11.6 6.1 15.58 72%	48 47 18 20 53 <b>186</b>	5.3% 7.0% 1.9% 5.6% 2.1% <b>22.0%</b>	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81] 2.00 [-5.06, 9.06] -2.90 [-7.04, 1.24] -14.34 [-21.08, -7.60] - <b>3.52 [-5.61, -1.44</b> ]	
Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect 2.009 Niers 2010 Gerasimov 2010 Shafiei 2012 Yavuz 2015 Wang IJ Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect	= 0.23, df t Z = 5.82 20.4 27.9 41.9 12.4 25.76 = 14.42, c t Z = 3.31	= 1 (P = 2 (P < 0.1 10.9 9.9 15.4 7.2 19.23 If = 4 (P (P = 0.1	50 50 50 43 43 20 51 207 = 0.000	² = 0% 21 32.4 39.9 15.3 40.1 3);  ² = 7	10.5 7.7 11.6 6.1 15.58 72%	48 47 18 20 53 <b>186</b>	5.3% 7.0% 1.9% 5.6% 2.1% <b>22.0%</b>	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81] 2.00 [-5.06, 9.06] -2.90 [-7.04, 1.24] -14.34 [-21.08, -7.60] - <b>3.52 [-5.61, -1.44]</b>	
Subtotal (95% CI) Heterogeneity: Chi <sup>™</sup> = Test for overall effect 2.4.5 mixture 2009 Niers 2010 Gerasimov 2010 Shafiei 2012 Yavuz 2015 Wang IJ Subtotal (95% CI) Heterogeneity: Chi <sup>™</sup> = Test for overall effect Total (95% CI)	= 0.23, df t Z = 5.82 20.4 27.9 41.9 12.4 25.76 = 14.42, c t Z = 3.31	= 1 (P = 2 (P < 0.1 9.9 15.4 7.2 19.23 If = 4 (P (P = 0.1	50 50 50 43 43 20 51 207 = 0.000 0009) 629	² = 0% 21 32.4 39.9 15.3 40.1 6);  ² = 7	10.5 7.7 11.6 6.1 15.58 72%	48 47 18 20 53 <b>186</b> 596	5.3% 7.0% 1.9% 5.6% 2.1% <b>22.0%</b>	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81] 2.00 [-5.06, 9.06] -2.90 [-7.04, 1.24] -14.34 [-21.08, -7.60] - <b>3.52 [-5.61, -1.44]</b> - <b>3.90 [-4.88, -2.92]</b>	
Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect 2.4.5 mixture 2009 Niers 2010 Gerasimov 2010 Shafiei 2012 Yavuz 2015 Wang IJ Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect Total (95% CI) Heterogeneity: Chi <sup>2</sup> =	= 0.23, df : Z = 5.82 20.4 27.9 12.4 25.76 = 14.42, c : Z = 3.31 = 108.89.	= 1 (P = 2 (P < 0.1 10.9 9.9 15.4 7.2 19.23 If = 4 (P 1 (P = 0.1 df = 13	50 50 50 43 43 20 51 207 = 0.00( 0009) 629 (P < 0.1	<sup>2</sup> = 0% 21 32.4 39.9 15.3 40.1 5);   <sup>2</sup> = 7	10.5 7.7 11.6 6.1 15.58 72%	48 47 18 20 53 <b>186</b> 5 <b>96</b> %	5.3% 7.0% 1.9% 5.6% 2.1% <b>22.0%</b>	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81] 2.00 [-5.06, 9.06] -2.90 [-7.04, 1.24] -14.34 [-21.08, -7.60] - <b>3.52 [-5.61, -1.44]</b> - <b>3.90 [-4.88, -2.92]</b>	
Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect 2.4.5 mixture 2009 Niers 2010 Gerasimov 2010 Shafiei 2012 Yavuz 2015 Wang IJ Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect Total (95% CI) Heterogeneity: Chi <sup>2</sup> =	= 0.23, df : Z = 5.82 20.4 27.9 41.9 12.4 25.76 = 14.42, c : Z = 3.31 = 108.89, : Z = 7.80	= 1 (P = 2 (P < 0.1 10.9 9.9 15.4 7.2 19.23 if = 4 (P 1 (P = 0.1 df = 13 ) (P < 0.1	50 50 50 43 43 20 51 207 = 0.000 00009) 629 (P < 0.1 00001)	<sup>2</sup> = 0% 21 32.4 39.9 15.3 40.1 5);   <sup>2</sup> = 7	10.5 7.7 11.6 6.1 15.58 22%	48 47 18 20 53 <b>186</b> 5 <b>96</b> %	5.3% 7.0% 1.9% 5.6% 2.1% <b>22.0%</b>	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81] 2.00 [-5.06, 9.06] -2.90 [-7.04, 1.24] -14.34 [-21.08, -7.60] - <b>3.52 [-5.61, -1.44]</b> - <b>3.90 [-4.88, -2.92]</b>	
Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect 2.4.5 mixture 2009 Niers 2010 Gerasimov 2010 Shafiei 2012 Yavuz 2015 Wang IJ Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect Total (95% CI) Heterogeneity: Chi <sup>2</sup> = Test for overall effect Test for overall effect	= 0.23, df : Z = 5.82 20.4 27.9 41.9 12.4 25.76 = 14.42, c t Z = 3.31 = 108.89, t Z = 7.80 fferences	= 1 (P = 2 (P < 0.1 10.9 9.9 15.4 7.2 19.23 df = 4 (P (P = 0.1 df = 13 ) (P < 0.1 ; Chi <sup>2</sup> =	50 50 50 43 43 20 51 207 = 0.000 00009) 629 (P < 0.1 00001) 76.35.	<sup>2</sup> = 0% 21 32.4 39.9 15.3 40.1 5);   <sup>2</sup> = 7 00001); df = 4 (	10.5 7.7 11.6 6.1 15.58 22% , I² = 889 P < 0.00	48 47 18 20 53 <b>186</b> 596 %	5.3% 7.0% 1.9% 5.6% 2.1% 22.0% 100.0%	-0.60 [-4.84, 3.64] -4.50 [-8.19, -0.81] 2.00 [-5.06, 9.06] -2.90 [-7.04, 1.24] -14.34 [-21.08, -7.60] - <b>3.52 [-5.61, -1.44]</b> - <b>3.90 [-4.88, -2.92]</b>	

meta-analysis of studies in which either prebiotics or probiotics were given and reported that synbiotics may be useful to treat AD (Chang et al., 2017). However, the focus was on synbiotics rather than probiotics. Szajewska et al. stressed the need for data on individual probiotic strains rather than on probiotics in general (Szajewska and Mrukowicz, 2003; Szajewska et al., 2015). Ogden et al. suggested probiotics as a complementary approach to the treatment and prevention of pediatric AD (Ogden and Bielory, 2005). They concluded that probiotics should be an active area of investigation, considering the role of gut microbiota in altered immune responses in atopic patients. However, the authors did not perform a meta-analysis to obtain further details about the treatment effects of probiotics. Kim et al. reviewed 25 RCTs on the effects of probiotics in the treatment of AD in patients of all ages. They observed significant differences in SCORAD values favoring probiotics over the control group in children 1–18 years old and in adults, whereas no favorable effects were seen in infants <1 year old (Kim et al., 2014). We found that probiotics were efficacious in children aged 1–18 years (MD, –4.50; 95%CI, –7.45 to –1.54) and showed strong efficacy in Asia but not in Europe; furthermore, *LGG* had no effects on AD whereas *LS*, *LF*, *LP*, and a mixture of strains showed beneficial effects. Our findings are in agreement with those of Lee et al., who concluded that the evidence for probiotics as a useful treatment of AD in children is convincing. However, the cited authors reviewed only trials published before 2008, whereas we included later



trials to afford greater insight. The differences may be because we included only RCTs involving children under the age of 18 years and those that reported MDs. Some RCTs presented values other than MDs, including the study by Kim et al. (2010), and some presented the results as figures, rendering calculations impossible. We contacted the corresponding authors but did not receive useful replies. Thus, we excluded those studies. Third, some of the included studies had small sample sizes, which may affect the reliability and validity of the conclusions. Thus, our overall results are affected by these issues, and the data were highly heterogeneous. These topics require further attention. Also, in the subgroup analyses, children with AD may have different gut microbiota profiles from those of normal children. Thus, probiotics supplementation in children < 1 year old and 1-18 years old may promote a healthier gut microbiota profile, boosting their immune response. People from different areas have different dietary structures and gut bacterial compositions. Dehingia et al. compared gut bacterial diversity between Indian populations and worldwide data (Dehingia et al., 2015). Zhang et al. also suggested that a phylogenetically diverse gut microbiota at the genus level may be commonly shared by distinctive healthy populations, which may explain the diversity of the effects of probiotics across people from different countries (Zhang et al., 2015). The above discussion is of importance to physicians, dermatologists, and other public healthcare workers who deal with diverse ethnic populations.

To the best of our knowledge, there are no previous reports on the effects of different probiotic strains on AD in children. In our meta-analysis, all trials involving *LGG* and one trial involving *LP* showed no effects, while two studies confirmed the beneficial

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(1993). Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology* 186, 23–31. doi: 10.1159/000247298 effects of *LP* on AD (MD, -0.70; 95%CI, -2.30 to 0.90; *P* = 0.39). This discrepancy may be associated with differences in dosages, the timing and duration of intervention, and sample sizes, and further trials are required to clarify this point.

Our meta-analysis had certain limitations. First, we attempted to minimize heterogeneity and publication bias, but significant heterogeneity among trials remained evident. Differences in study samples, study populations, and intervention methods contributed to the heterogeneity. For example, some of the included studies had small sample sizes, compromising the reliability and validity of the conclusions. In addition, the RCTs were performed in various countries, thus, the subjects differed among RCTs in terms of their genetic make-up and microbial exposure, which in turn are associated with varying responses to the same probiotic. Also, we excluded some RCTs from this meta-analysis, and fewer studies included will reduce the confidence associated with the data interpretation and increase heterogeneity and publication bias. Finally, we cannot draw robust conclusions as to which probiotic strain/mixture should be given to children with AD and which population(s) would receive maximum benefit from such treatment.

#### CONCLUSION

Our present work demonstrated that probiotics may have the potential to decrease SCORAD values in children with AD. However, the findings presented here must be generalized with caution because of heterogeneity. The results are a source of optimism with regard to the management of AD in children. More adequately powered RCTs using standardized measurements are necessary to assess which species of probiotics and dosages and what treatment periods are most efficacious for children with AD.

#### AUTHOR CONTRIBUTIONS

RH, MS, and XC proposed the idea of this study and designed the study; RH, HN, MS, and JL conducted data screening and performed quality assessment; RH and MS used RevMan software to assess the data and performed the statistical analysis and gave the explanations of the statistical results. RH drafted the initial manuscript. JL, JZ, and XC critically reviewed and revised the manuscript.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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