EBM Journal reading

母親於懷孕期間服用益生菌是否能減少小兒異位性皮膚炎的發生率?

Presented by R3林敬凡

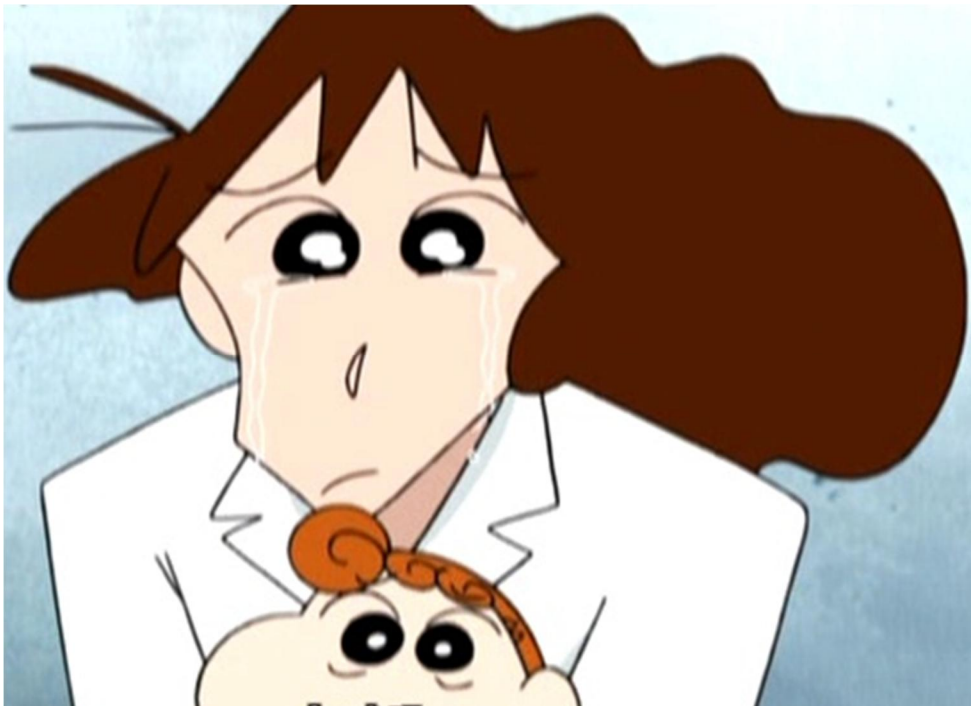
指導醫師-顏宏融 醫師

2012/05/21

Scenario

- R：媽媽，妹妹目前有異位性皮膚炎症狀，我們先用些中藥幫助她。
- 媽媽：醫生~我好擔心現在肚裡的小孩也依樣會有異位性皮膚炎。

聽說益生菌能減少異位性皮膚炎發生率？



Background knowledge

- 異位性皮膚炎
  - 在新生兒或幼兒期便會發生皮膚變化
  - 50 % 的患者在一歲前便會有皮膚的症狀
  - 80 % 的患者會逐漸合併有氣喘、過敏性鼻炎、結膜炎等其他過敏症狀
  - 家族其他成員也常有類似過敏的疾病
- 根據衛生署國民健康局，嬰幼兒異位性皮膚炎盛行率從1995年的1 %，攀升到2004年的6.7 %
- 全台目前約有300萬人受異位性皮膚炎之苦

- 皮膚搔癢
- 皮膚炎的典型型態與分布(嬰幼兒的臉部與身體伸側)
- 慢性或反覆性皮膚炎
- 以過敏性體質的個人或家族史(包含過敏性氣喘，過敏性鼻炎，和異位性皮膚炎)
- 治療與處理：

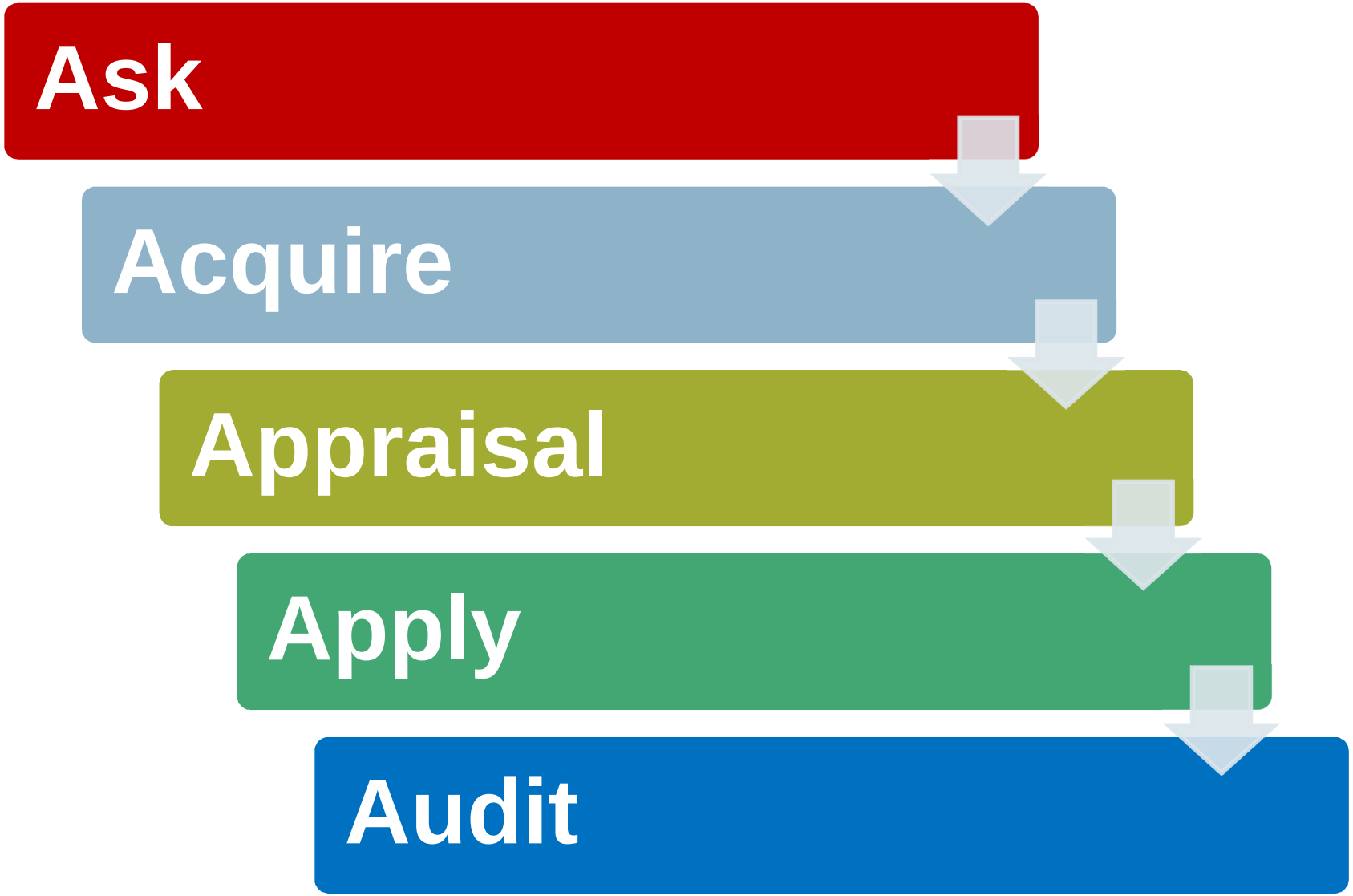
✓ 皮膚清潔與保養

✓ 藥物使用

✓ 環境保護(避免接觸過敏原，減少刺激)

Background knowledge

- 益生菌Probiotics
  - 可以和人體共生而對人體產生益處的細菌
  - 於1965年首次由Lilly與Stillwell提出
  - Probiotics是從希臘字衍生，字義是”for life”為生活
- WHO報告益生菌的好處：恢復健康腸道菌叢、激發黏膜免疫力和改善腸胃不適，包括與使用抗生素、腸道感染和旅行者腹瀉，及改善泌尿生殖道菌叢等。
- 其中被廣為使用的Lactobacillus主要功能為促進腸道蠕動並改善消化情形。此外，Bacillus spp., Bifidobacterium spp., 和 Propionibacterium spp.等之效用也被證實。


Ask
Acquire
Appraisal
Apply
Audit

ASK

母親於懷孕期間服用益生菌是否能減少小兒異位性皮膚炎的發生率?

Pregnant women

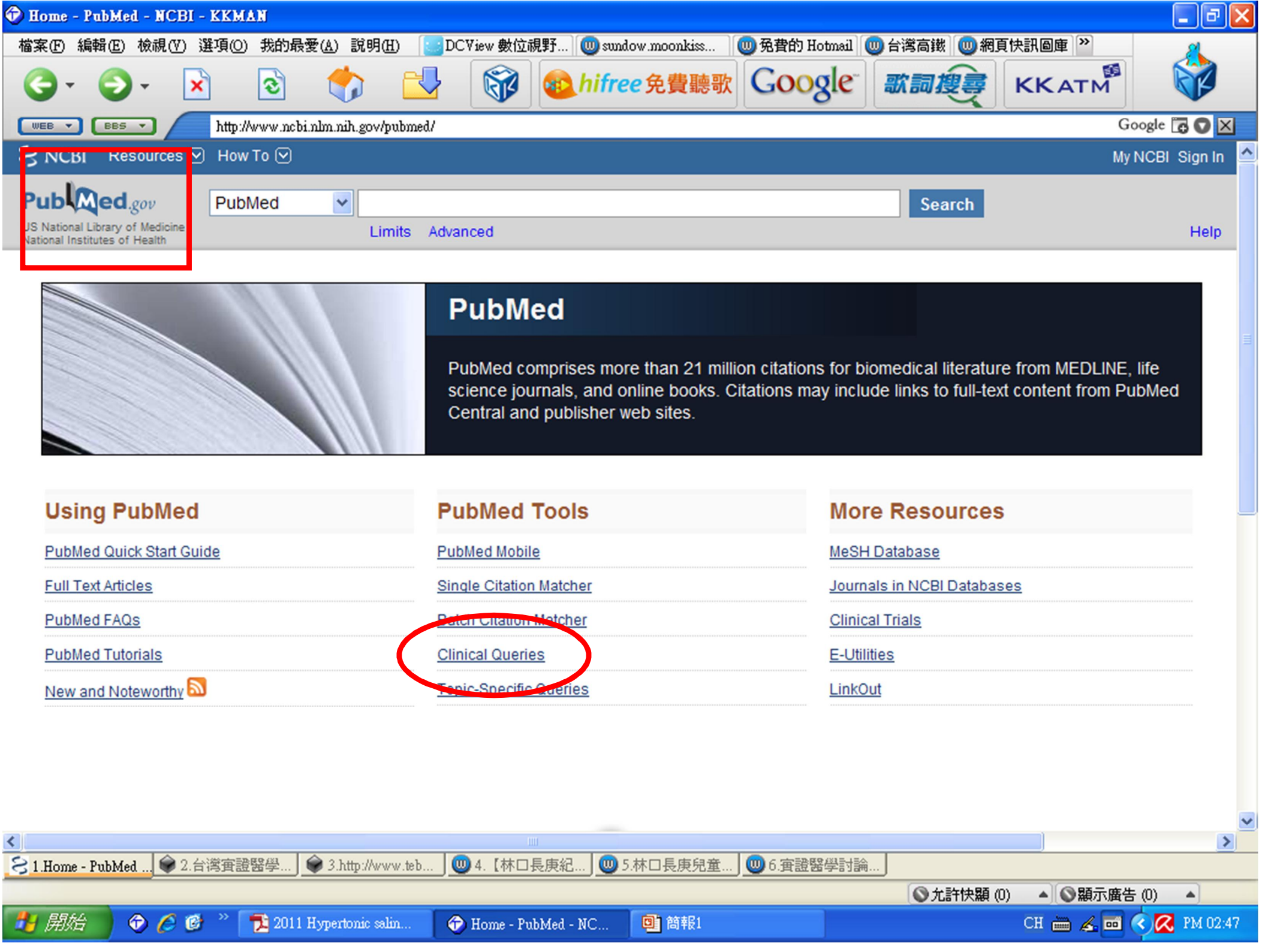
Probiotics

Placebo

Children's incidence of atopic dermatitis

Acquire

- Database : PubMed
- Key word: Probiotics, atopic dermitis, pregnancy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Showing results for ***probiotics, atopic dermatitis, pregnancy***. Your search for *Probiotics, atopic dermitis, pregnancy* retrieved no results.

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1. **Probiotics** Supplementation During **Pregnancy** or Infancy for the Prevention of **Atopic Dermatitis**: A Meta-analysis.
   Pelucchi C, Chatenoud L, Turati F, Galeone C, Moja L, Bach JF, La Vecchia C.
   Epidemiology. 2012 May;23(3):402-14.
   PMID: 22441545 [PubMed - in process]

2. Impact of maternal supplementation with **probiotics** during **pregnancy** on **atopic** eczema in childhood--a meta-analysis.
   Doege K, Grajecki D, Zyriax BC, Detinkina E, Zu Eulenburg C, Buhling KJ.
   Br J Nutr. 2012 Jan;107(1):1-6. Epub 2011 Jul 26.
   PMID: 21787448 [PubMed - indexed for MEDLINE]
   Related citations

3. **Atopic dermatitis** and nutrition.
   Finch J, Munhutu MN, Whitaker-Worth DL.
   Clin Dermatol. 2010 Nov-Dec;28(6):605-14. Review.
   PMID: 21034985 [PubMed - indexed for MEDLINE]
   Related citations

4. **Probiotics** in pregnant women to prevent allergic disease: a randomized, double-blind trial.
   Dotterud CK, Storrø O, Johnsen R, Oien T.
   Br J Dermatol. 2010 Sep;163(3):616-23. doi: 10.1111/j.1365-2133.2010.09889.x. Epub 2010 Jun 9.
   PMID: 20545688 [PubMed - indexed for MEDLINE]
   Related citations

5. What's new in **atopic** eczema? An analysis of systematic reviews published in 2007 and 2008. Part 2. Disease prevention and treatment.

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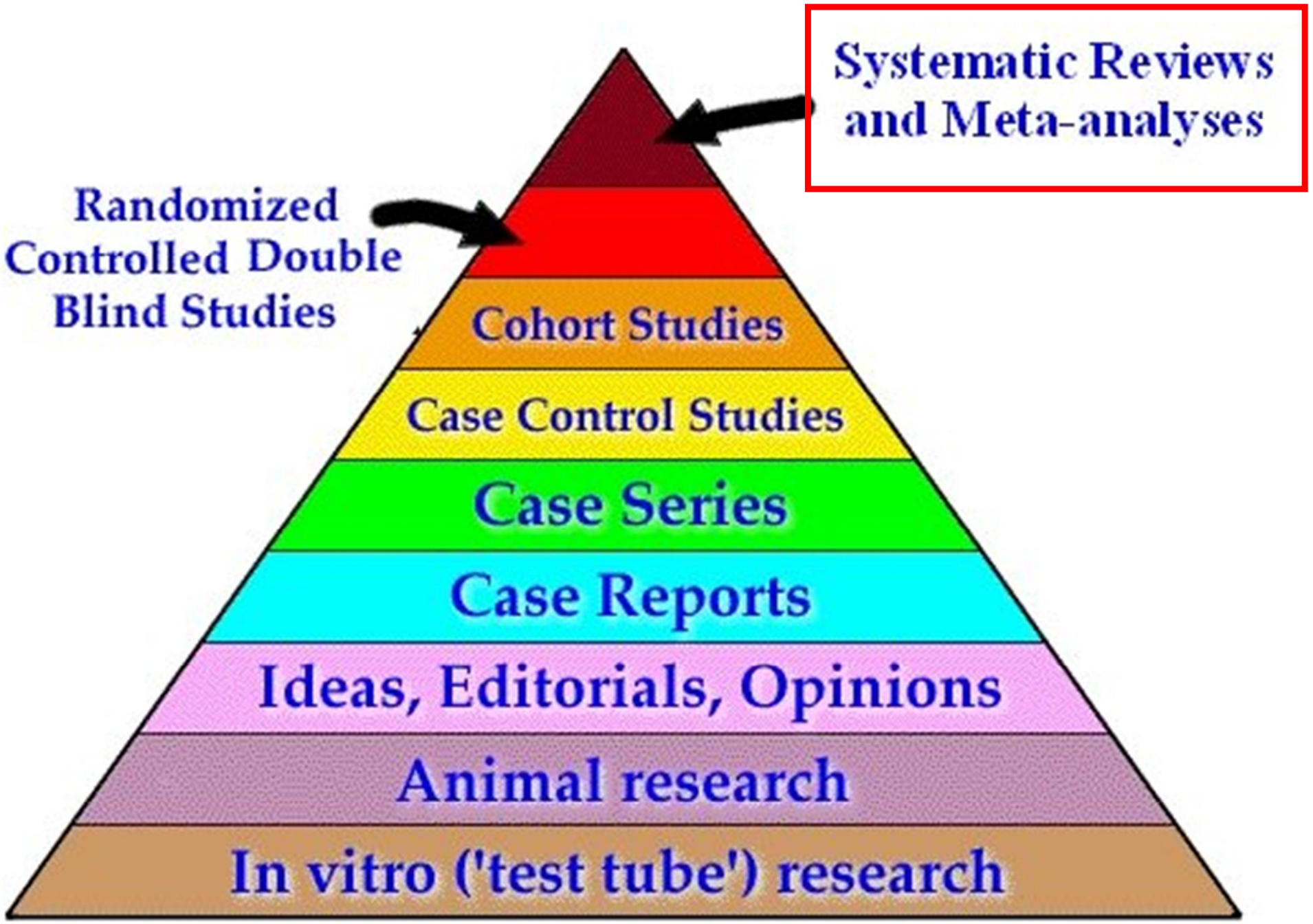
Probiotics Supplementation During Pregnancy or Infancy for the Prevention of Atopic Dermatitis

A Meta-analysis

Claudio Pelucchi,[a] *Liliane Chatenoud,*[a] *Federica Turati,*[a,b] *Carlotta Galeone,*[a,b] *Lorenzo Moja,*[a,c] *Jean-François Bach,*[d,e] *and Carlo La Vecchia*[a,b]

- Epidemiology • Volume 23, Number 3, May 2012.
- Meta-Analysis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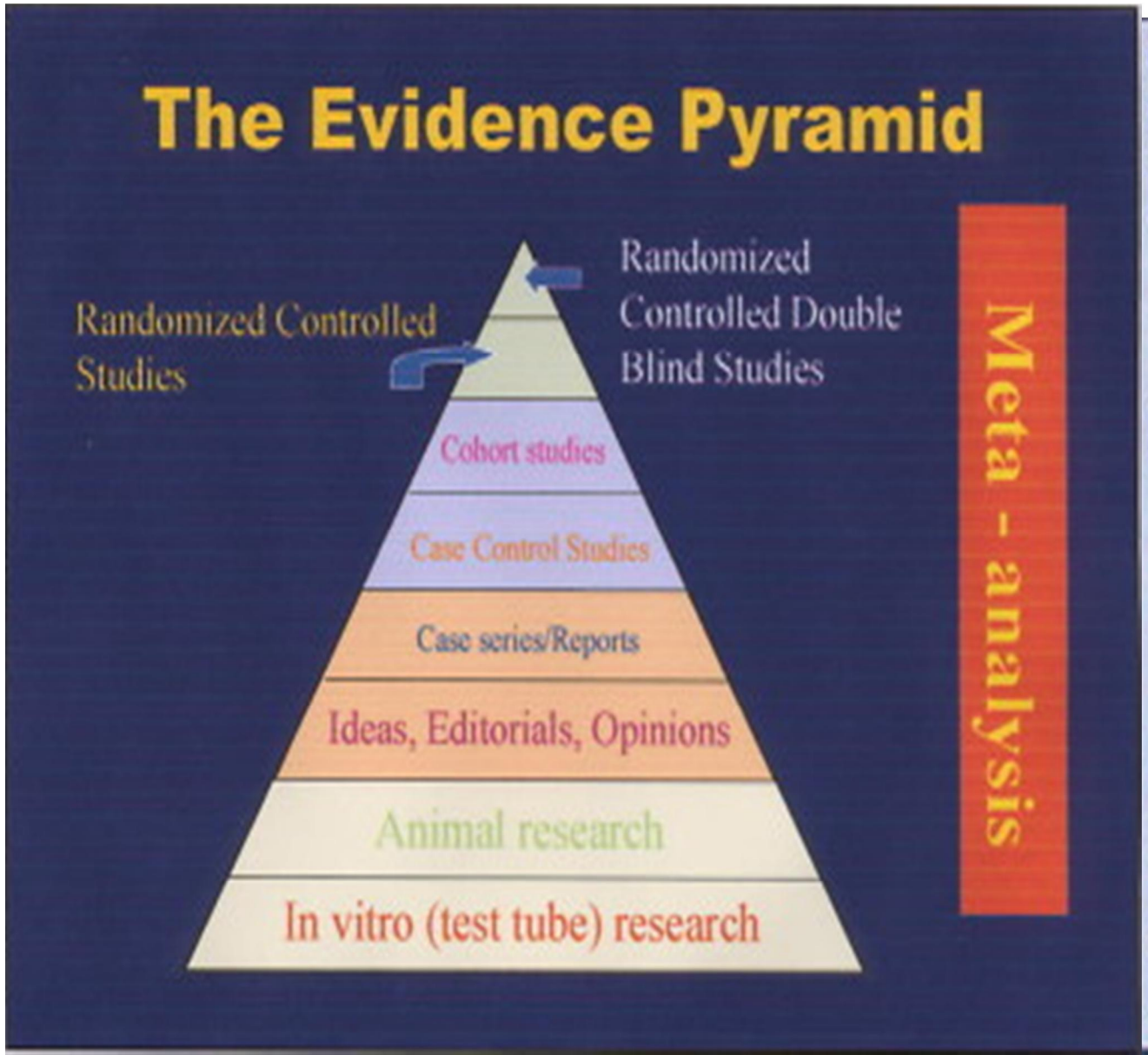
搜尋最有用的資料



Grade of Recommendation	Level of Evidence	Therapy
[A]	1a	Systemic review of RCTs
	1b	Single RCT
	1c	'All-or-none'
[B]	2a	Systemic review of cohort studies
	2b	Cohort study or poor RCT
	2c	'Outcomes' research
	3a	Systemic review of case-control studies
	3b	Case-control study
[C]	4	Case series
[D]	5	Expert opinion, physiology, bench research

Appraisal

- Validity
  - 研究方法評析以判斷結果之可信與否
- Importance
  - 結果差異的重要性及對臨床的意義
- Practicability
  - 可否用來照顧我的病人

CASP for meta-analysis

Critical Appraisal Skills Programmer (CASP)

- 1. Did the review ask a clearly-focused question?
- 2. Did the review include the right type of study?
- 3. Did the reviewers try to identify all studies?
- 4. Did the reviewers assess the quality of the included studies?
- 5. If the results of the studies have been combined, was it reasonable to do so?
- 6. How are the results presented and what is it?
- 7. How precise are these results?
- 8. Can the results be applied to the local population?
- 9. Were all important outcomes considered?
- 10. Should policy or practice change as a result of the evidence contained in this review?

Validity

REVIEW ARTICLE

Probiotics Supplementation During Pregnancy or Infancy for the Prevention of Atopic Dermatitis

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Impact Factor: 5.866

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Appraisal

- Did the review ask a clearly-focused question ？ - Yes

Background: The study of probiotics to prevent allergic conditions has yielded conflicting results in children. We undertook a meta-analysis of randomized controlled trials to investigate whether probiotic use during pregnancy and early life decreases the incidence of atopic dermatitis and immunoglobulin E (IgE)-associated atopic dermatitis in infants and young children.

Appraisal

- Did the review include the right type of study？
  - Yes

We conducted a formal systematic review and a meta-analysis of randomized controlled trials to investigate whether probiotic use during pregnancy and early life decreases the incidence of atopic dermatitis and IgE-associated atopic dermatitis in infants and young children. We did not consider asthma as one of the outcomes of this review, because the distinction between asthma and wheezing is difficult in young children, and asthma generally occurs at a later age than atopic dermatitis. Furthermore, there is no evidence that probiotics have an effect in the prevention of asthma.[17]

Appraisal

- Did the reviewers try to identify all studies ？
  - Yes

methods of our investigation.[20] In March 2011, we performed a systematic literature search in the Medline database, Embase, and the Cochrane Library (reviews only) for clinical trials that investigated factors related to infection, including probiotic use, and atopic dermatitis in infants and children. The literature search was updated on 26 October 2011, during the final revision process. Full details on the search strings used are given in eAppendix 1 (http://links.lww.com/EDE/A572). We restricted our search to clinical or randomized controlled trials conducted in humans, and to the papers published in English.

Appraisal

- Did the reviewers assess the quality of the included studies ？ - Yes

Table 2 reports selected quality measures of trials included in the meta-analysis. All trials were double-blinded. The proportion of subjects that completed the follow-up period did not show relevant differences between treatment and placebo groups in any of the trials. Clinical assessment of atopic dermatitis was performed by study-outcome assessors or clinicians in 12 of 14 studies. In the remaining 2 studies, atopic dermatitis was reported by parents, either as complaint in questionnaires/diaries or as diagnosed by a family doctor or other physician.

TABLE 2. Quality Measures of Double-blinded Randomized Controlled Trials Included in the Meta-analysis on Probiotics and Prevention of Atopic Dermatitis

1st Author, Year	% Completed the Study		Outcome Assessment
	Treatment Group(s)	Placebo Group	
Kalliomaki et al, 2001[12]	83.1	82.9	Performed by clinicians/study outcome assessors
Rautava et al,[a] 2002[37]	90.0	93.8	Performed by clinicians/study outcome assessors
Kalliomaki et al,[a] 2003[32]	65.9	68.8	Performed by clinicians/study outcome assessors
Kalliomaki et al,[a] 2007[33]	68.8	75.6	Performed by clinicians/study outcome assessors
Rautava et al, 2006[36]	NA	NA	Performed by clinicians/study outcome assessors
Abrahamsson et al, 2007[28]	81.2	80.9	Performed by clinicians/study outcome assessors
Taylor et al, 2007[39]	77.4	80.2	Performed by clinicians/study outcome assessors
Kukkonen et al, 2007[43]	75.6	75.7	Performed by clinicians/study outcome assessors
Kuitunen et al,[b] 2009[42]	72.9	72.8	Performed by clinicians/study outcome assessors
Huurre et al, 2008[31]	NA	NA	Performed by clinicians/study outcome assessors
Kopp et al, 2008[34]	92.6	86.3	Performed by clinicians/study outcome assessors
Wickens et al, 2008[21]	Group 1: 84.7 Group 2: 88.8	87.7	Performed by clinicians/study outcome assessors
Kim et al, 2009[41]	57.9	63.6	Performed by clinicians/study outcome assessors
Niers et al, 2009[35]	64.1	61.5	Based on diaries and/or diagnosis from family doctor or consulted physician
Soh et al, 2009[38]	97.6	96.0	Performed by clinicians/study outcome assessors
West et al, 2009[40]	94.3	96.7	Based on questionnaires/diaries and/or diagnosis from doctor
Dotterud et al, 2010[30]	65.4	68.6	Performed by clinicians/study outcome assessors
Boyle et al, 2011[29]	87.2	82.4	Performed by clinicians/study outcome assessors

Appraisal

- If the results of the studies have been combined, was it reasonable to do so？

The larger number of randomized controlled trials of probiotics now available allowed us to conclude, using a meta-analytic approach, that probiotics have a moderately beneficial effect on the onset of atopic dermatitis and IgE-associated atopic dermatitis in infants. This conclusion is supported by the low-to-moderate heterogeneity of results among trials, the consistency of findings in several subgroups, and apparent lack of publication bias or other major biases. Further studies could explore whether different probiotic strains have different effects on the incidence of atopic dermatitis, whether the effects of probiotics vary with breastfeeding, and aspects of their biologic mechanisms of effect.

Importance

REVIEW ARTICLE

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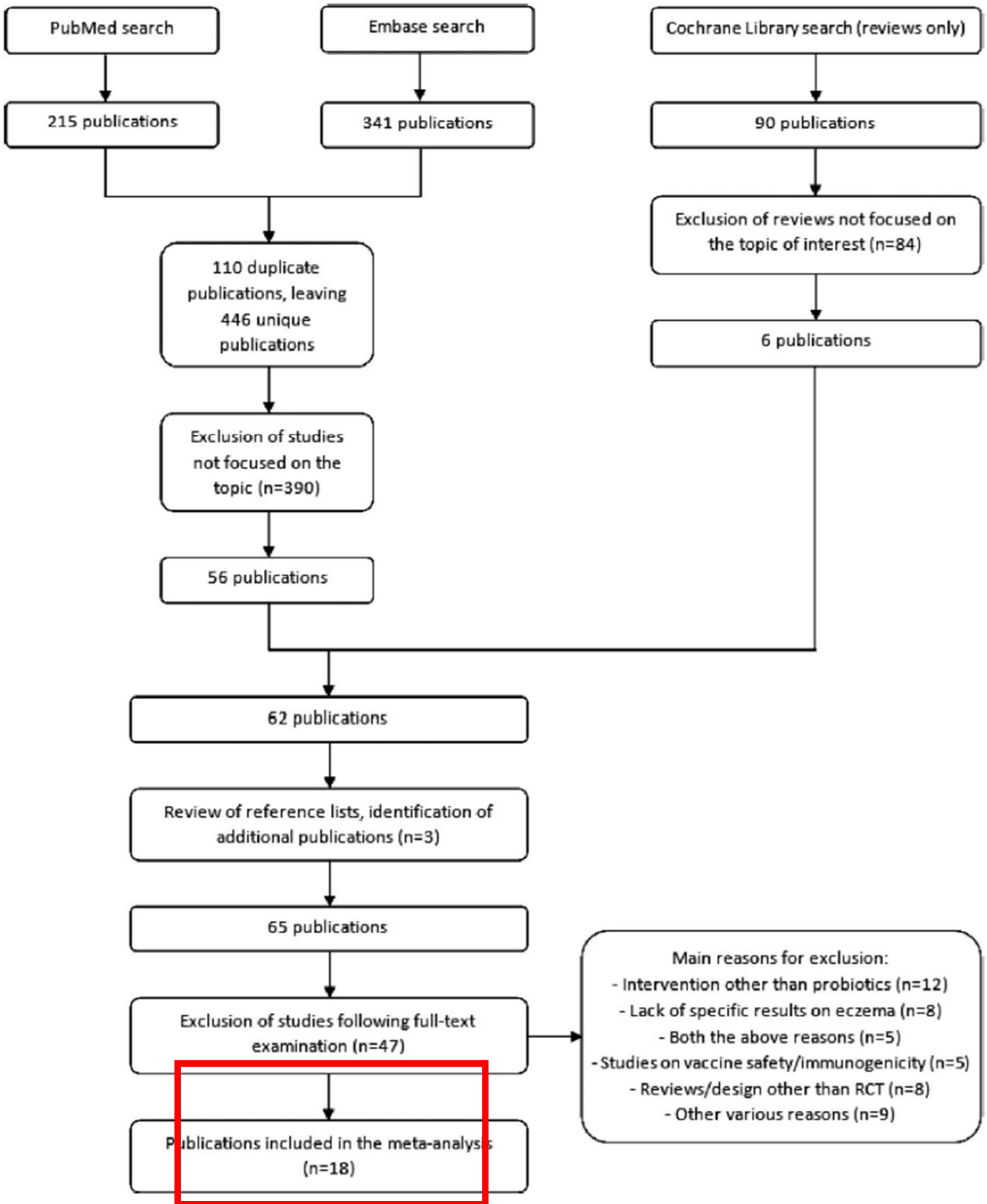

IGURE 1. Flowchart for search and election of publications for the neta-analysis.

TABLE 3. Summary RRs for Probiotics in the Prevention of Atopic Dermatitis, According to Selected Subgroups

Subgroup	No. Studies	RR (95% CI)	I^2	Test for Heterogeneity
Intervention period				
Predelivery only	1	0.77 (0.54–1.10)	—	
Pre- and postdelivery	8	0.76 (0.65–0.89)	31%	
Postdelivery only	4	0.85 (0.61–1.19)	32%	$P = 0.54$
Intervention subject[a]				
Mother only	2	0.70 (0.53–0.91)	0%	
Child only	4	0.85 (0.61–1.19)	32%	
Mother and child	6	0.81 (0.70–0.94)	9%	$P = 0.38$
Duration of intervention				
<9 months	8	0.78 (0.65–0.94)	40%	
≥9 months	5	0.79 (0.65–0.95)	1%	$P = 0.97$
Probiotic dose				
$<1 \times 10^{10}$	6	0.78 (0.65–0.93)	7%	
$\geq 1 \times 10^{10}$	7	0.79 (0.65–0.96)	42%	$P = 0.85$
No. of probiotic types				
1	7	0.82 (0.65–1.03)	50%	
>1	6	0.76 (0.66–0.87)	0%	$P = 0.47$
End of follow-up				
Children <24 months	6	0.79 (0.62–1.00)	25%	
Children ≥24 months	7	0.78 (0.66–0.92)	33%	$P = 0.87$
Geographic area				
Europe	8	0.76 (0.64–0.91)	33%	
Asia/Oceania	5	0.81 (0.66–0.99)	21%	$P = 0.69$
Family history of allergic diseases[b]				
Yes	12	0.80 (0.70–0.91)	24%	
No	2	0.35 (0.06–2.01)	49%	$P = 0.28$
Diagnostic criteria				
Hanifin and Rajka,[44] or similar	6	0.80 (0.61–1.06)	49%	
UK Working Party,[45] or similar	5	0.78 (0.67–0.90)	0%	
Reported by parents[c]	2	0.70 (0.47–1.04)	26%	$P = 0.69$
Conflict of interest				
Apparently no	3	0.74 (0.40–1.35)	61%	
Only probiotic supplied	2	0.81 (0.61–1.07)	0%	
Yes[d]	8	0.79 (0.67–0.92)	31%	$P = 0.86$

Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial

Marko Kalliomäki, Seppo Salminen, Heikki Arvilommi, Pentti Kero, Pertti Koskinen, Erika Isolauri

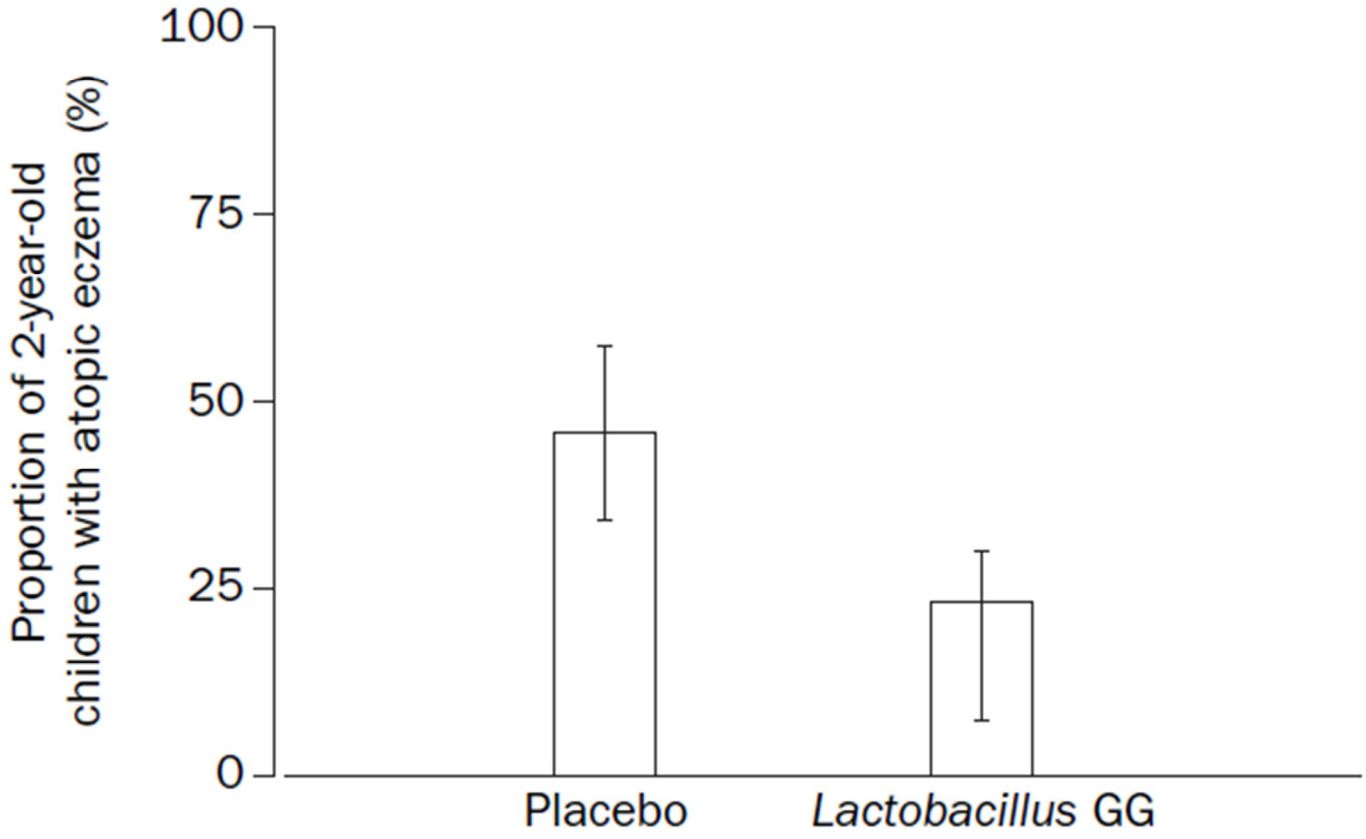

Figure 2: **Treatment effect of *Lactobacillus* GG on atopic disease**

Bars are 95% CI.

Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial

Marko Kalliomäki, Seppo Salminen, Tuija Poussa, Heikki Arvilommi, Erika Isolauri

Perinatal administration of the probiotic *Lactobacillus rhamnosus* strain GG (ATCC 53103), reduces incidence of atopic eczema in at-risk children during the first 2 years of life (infancy). We have therefore assessed persistence of the potential to prevent atopic eczema at 4 years. Atopic disease was diagnosed on the basis of a questionnaire and a clinical examination. 14 of 53 children receiving lactobacillus had developed atopic eczema, compared with 25 of 54 receiving placebo (relative risk 0·57, 95% CI 0·33–0·97). Skin prick test reactivity was the same in both groups: ten of 50 children previously given lactobacillus compared with nine of 50 given placebo tested positive. Our results suggest that the preventive effect of lactobacillus GG on atopic eczema extends beyond infancy.

Lancet 2003; **361:** 1869–71

Result

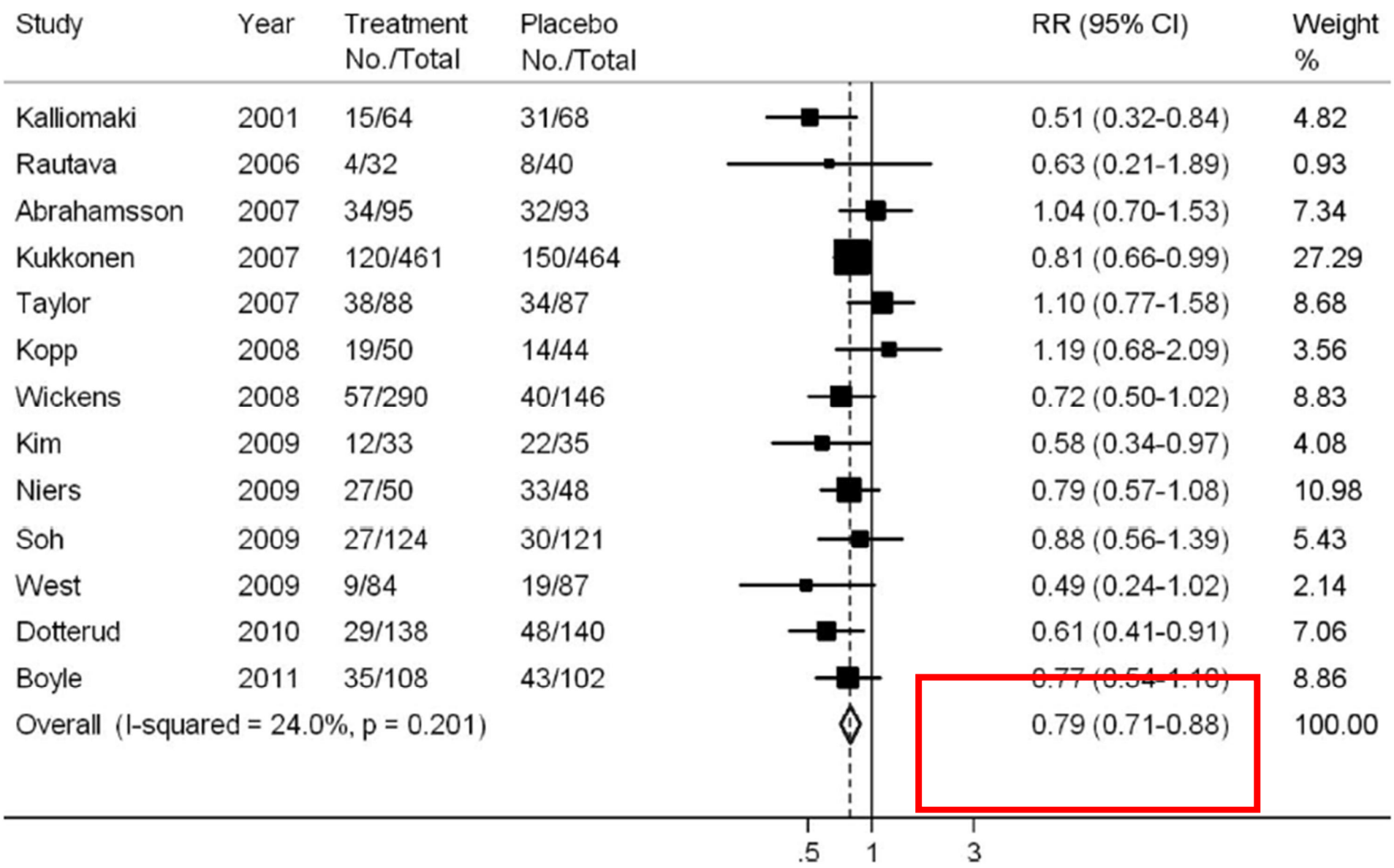

FIGURE 2. Summary RR for probiotics in the prevention of atopic dermatitis.

Appraisal -Importance

- 母親於懷孕期間服用益生菌，可以減少小孩異位性皮膚炎發生率
- RR(95%CI)=0.79(0.71~0.88)
- NNT(95%CI)=5

Practicability

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Apply

- Can the results be applied to the local population? – Yes
- Were all important outcomes considered? – Yes
- Should policy or practice change as a result of the evidence contained in this review? – ?

Apply

	Practical in Practice?	
1	我們的病人是否與研究中差異很大?	否
2	此治療在目前是否可行?	是
3	我們的病人是否可從該項治療中獲益?	部分是
4	我們的病人如何看待此治療的結果?	

Audit

媽媽妳好，就目前的實證醫學研究看來，於懷孕期間服用益生菌，是可以減少大約兩成的小孩異位性皮膚炎發生率

Conclusion

Limitation

- 缺乏異位性皮膚炎嚴重度方面的資料
- 追蹤時間的問題
- 缺乏如何從母體影響到胎兒異位性皮膚炎發生機率的mechanism
- 缺乏其他相關過敏疾病的資料

THANKS FOR YOUR ATTENTION