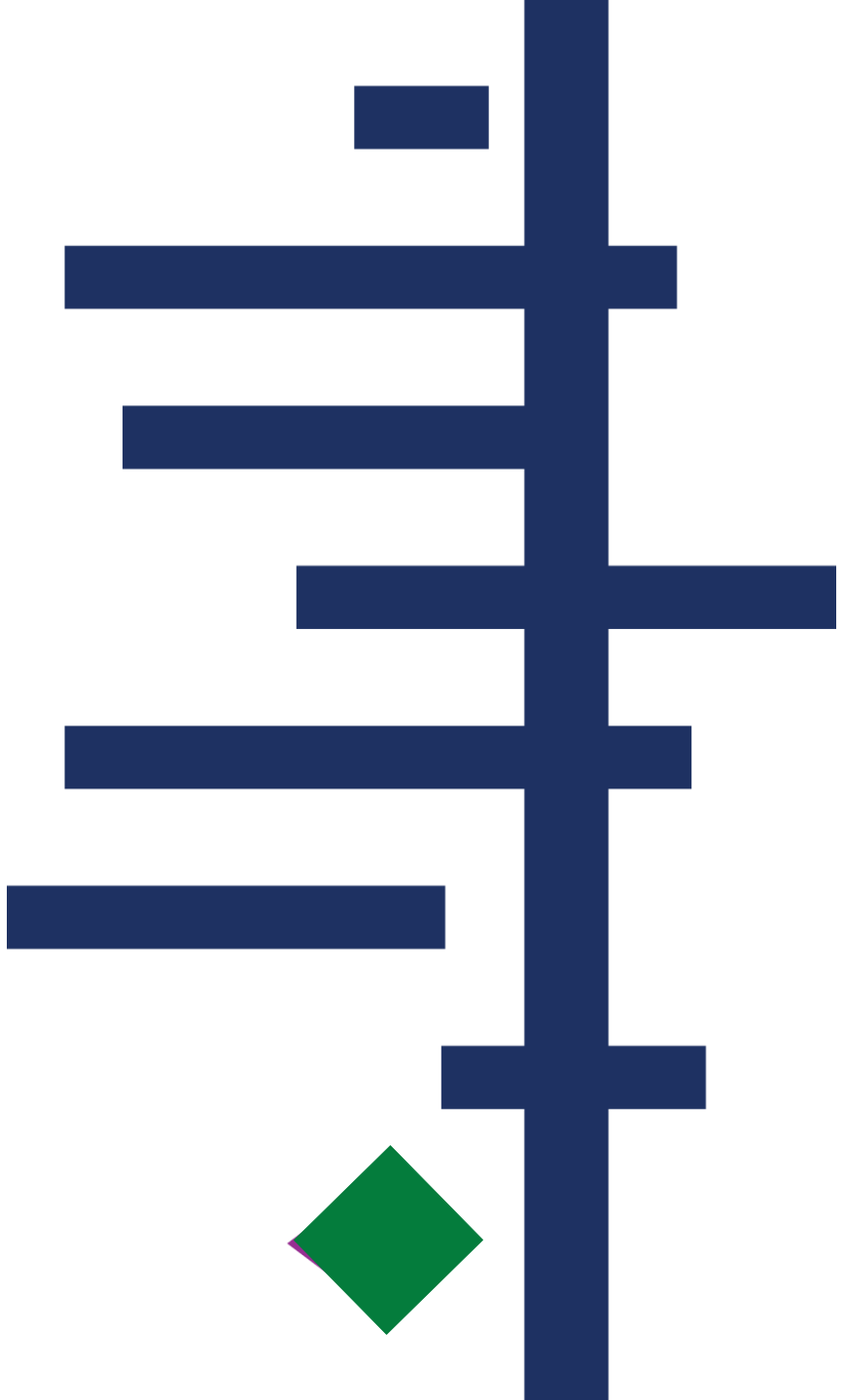
Cochrane Malaysia

Reading & Understanding a Cochrane Review

Prof.Dr.Sumanth Kumbargere Nagraj

Clinical Editor, Cochrane Oral Health

Trusted evidence.
Informed decisions.
Better health.



Cochrane Malaysia

Levels of Evidence

(Therapeutic and Preventive)

Level 1	**1a) systematic review of randomised trials**
	1b) individual randomised trial
Level 2	**2a) systematic review of cohort studies**
	2b) individual cohort (and low quality RCT)
	2c) outcomes research
Level 3	**3a) systematic review of case-control studies**
	3b) individual case-control study
Level 4	**case series (and poor quality cohort and case - control studies)**
Level 5	**expert opinion**

Bias +

Cochrane Malaysia

Why Systematic Reviews (SR)?

- **Use all available evidence.** Summarise all available evidence in one place
- **Different outcomes.** Studies designed to answer the same question may have conflicting outcomes
- **Help sort out apparently conflicting evidence.** Where studies give different and sometimes conflicting results, SR can help explain the differences and point to the true effect
- **Uncommon outcomes.** Outcomes measured may be too uncommon to measure with primary research
- **Average effect.** Able to estimate an average across all the studies

Types of Questions answered by a Cochrane Review

Intervention Reviews

What is the effect of an intervention in a particular population?

Diagnostic accuracy Reviews

What is the accuracy of a clinical sign or a test in detecting a particular problem when used in a particular setting?

Observational Reviews

Prognostic studies

May look at interventions with rare outcomes

Interventions that cannot be tested by RCT

Risk of a particular exposure on an outcome or disease

Cochrane Malaysia

Total reviews (27 July 2022) : 8872

Review Type	
Intervention	8549
Diagnostic	175
Overview	63
Methodology	41
Qualitative	17
Rapid	11
Prognosis	10

Show 1 more

Cochrane Malaysia

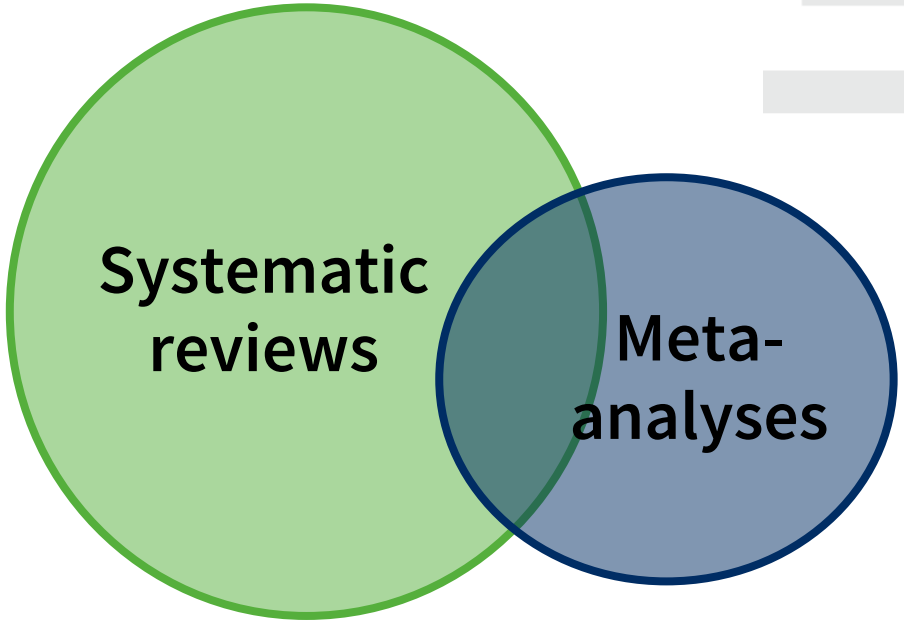
Meta-analysis = systematic review (?)

Meta-analysis is a statistical tool

It combines the results from two or more studies

It estimates an ‘average’ or ‘common’ effect

It is an ***optional part*** of a systematic review



Source: Julian Higgins

Cochrane Malaysia

Meta-analysis is done when….

- More than one study has estimated an outcome
- There are no differences in the study characteristics that are likely to substantially affect the outcome
- The outcome has been measured in similar ways
- The data are available (beware when only some data are available)

Cochrane Malaysia

Meta-analysis would not be done when there is….

Heterogeneity or inconsistency (Included studies differed too widely)

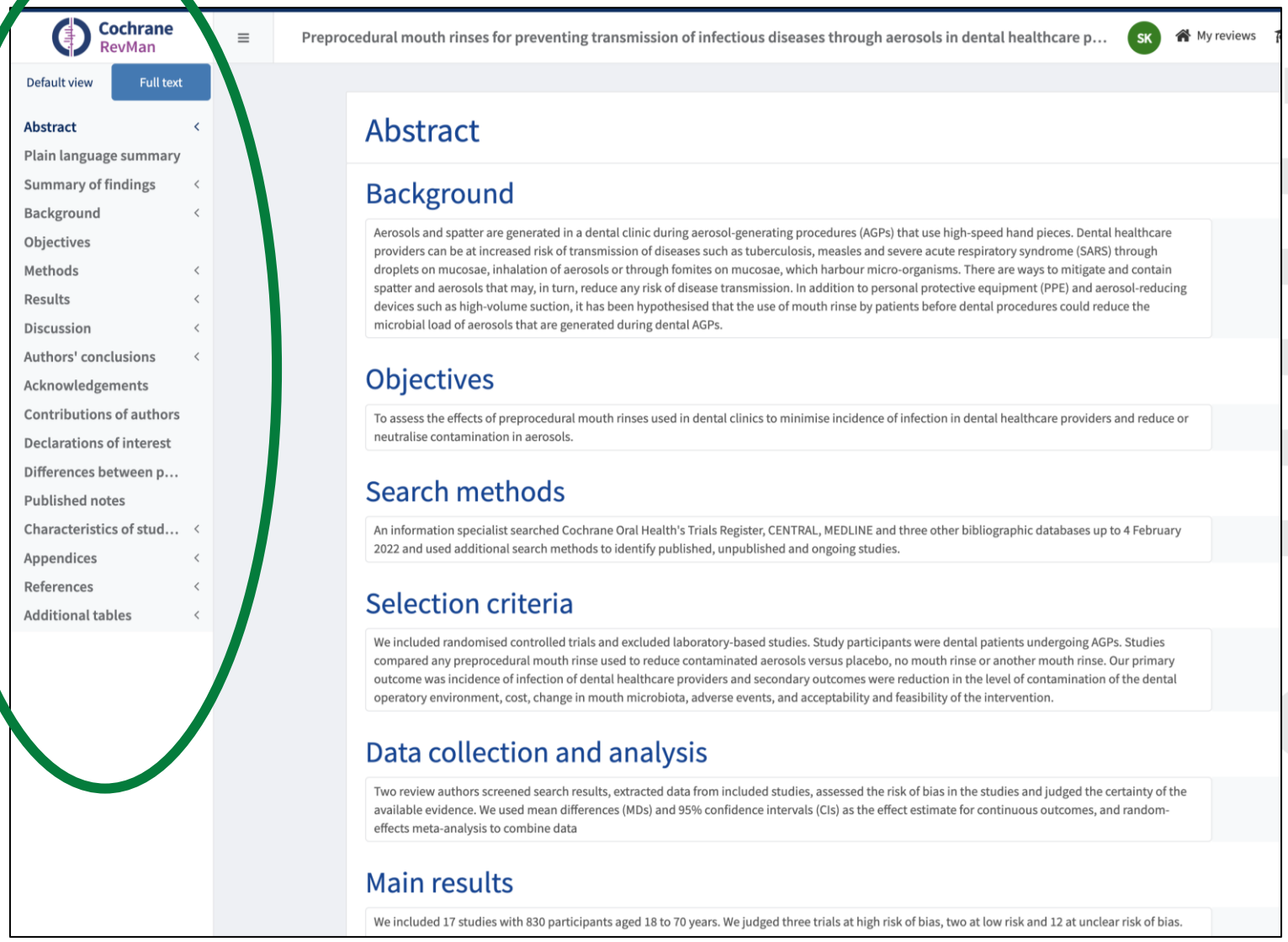
- The patients were not similar enough
- The interventions were not similar enough
- The outcomes were measured very differently and are not likely to be measuring the same thing
- Statistically the studies too different

High Risk of Bias. (Poor internal validity). The included studies are not believable, so it is meaningless to combine them. 'Garbage in Garbage out'

Not all studies are available. When only some of the data are available the result again would be misleading. Publication bias is the main threat to systematic reviews

Cochrane Malaysia

Structure of a Cochrane Review



Cochrane Malaysia

Plain Language Summary
Abstract
Background
Objectives
Selection Criteria for studies
Search strategy
Methods of the review
Results of the search
Description of studies
Risk of Bias
Effect of the Intervention
Summary of analyses
Conclusions
Potential conflict of interest
Acknowledgements
Characteristics of included studies
Characteristics of excluded studies
References

Text explaining author's rationale for conducting the review

Details on where and how the authors looked studies, inclusion and exclusion criteria, analysis methods

How many studies did they find, how was each study conducted, were there any bias found in the studies

Forest plots

Summary of Findings Table

How are the Results Expressed

Dichotomous outcome

- Risk ratio (Relative risk)
- Odds ratio
- Risk difference

Continuous outcome

- Mean difference (Mean in Experimental Group – Mean in Control Group)

Precision

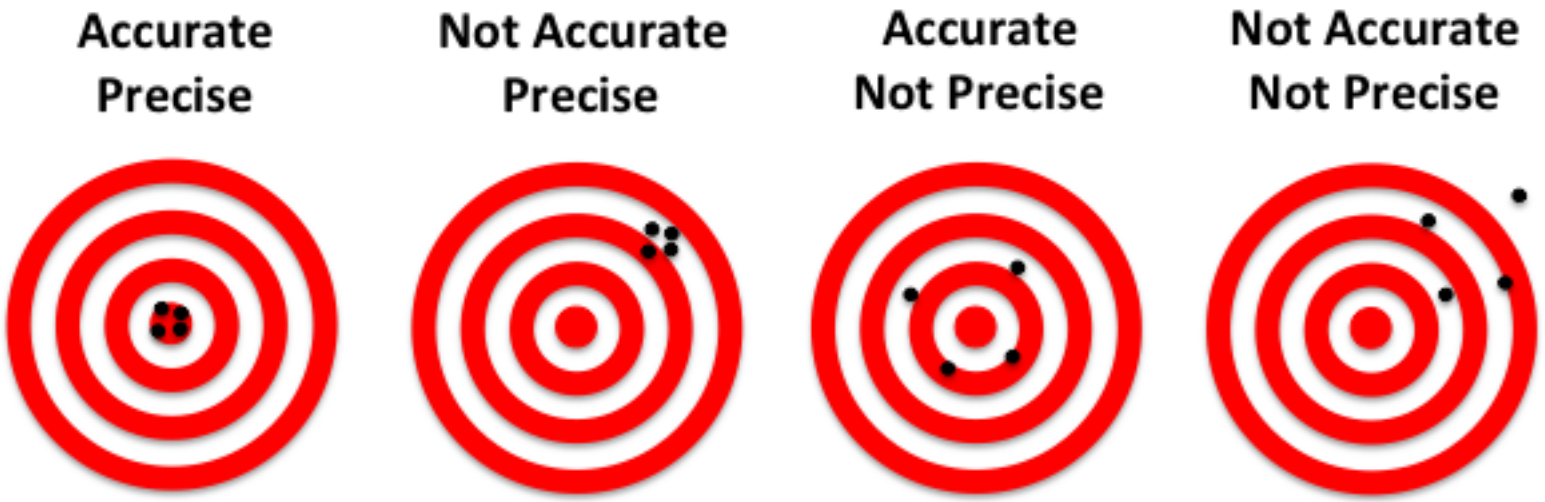
- 95% confidence interval

Certainty of evidence

- GRADE

Cochrane Malaysia

Precision



Cochrane Malaysia

Displaying results graphically

forest plots

'forest of lines'

Cochrane Malaysia

The Cochrane Logo

Crowley P. Prophylactic corticosteroids for preterm birth (Cochrane Review)

Cochrane Malaysia

Let’s read a forest plot

Cochrane Malaysia

Cochrane Library

Trusted evidence.
Informed decisions.
Better health.

English English Sign In

Title Abstract Keyword

Browse Advanced

Cochrane Reviews Trials Clinical Answers About Help About Cochrane

Cochrane Database of Systematic Reviews | Review - Intervention

Vitamin D supplementation for term breastfed infants to prevent vitamin D deficiency and improve bone health

May Loong Tan, Steven A Abrams, David A Osborn Authors' declarations of interest

Version published: 11 December 2020

https://doi.org/10.1002/14651858.CD013046.pub2

View PDF
Cite this Review
Request Permissions
Comment on Review
Read comments on this Review(

Print Share

Am score 35

Collapse all Expand all

Abstract

Available in English | Español | Français | 한국어

Background

Vitamin D deficiency is common worldwide, contributing to nutritional rickets and osteomalacia which have a major impact on health, growth, and development of infants, children and adolescents. Vitamin D levels are low in breast milk and exclusively breastfed infants are at risk of vitamin D insufficiency or deficiency.

Cochrane Malaysia

PICO

Participants	Breastfed infants under 6 months old
Intervention	Vitamin D (baby/mother)
Comparison	Placebo/ No treatment Vitamin D to mother Sunlight
Outcomes	Bone mineral density Vitamin D deficiency Rickets Serum Vitamin D levels Growth

Cochrane Malaysia

Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 2: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L

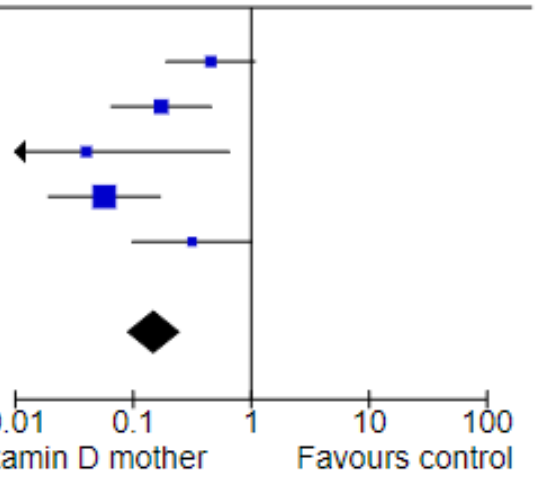
Analysis 2.2

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Total (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			

Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%

Test for overall effect: Z = 7.69 (P < 0.00001)

Test for subgroup differences: Not applicable



Footnotes

(1) < 27.5 nmol/L

Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 2: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L

Cochrane Malaysia

First things first

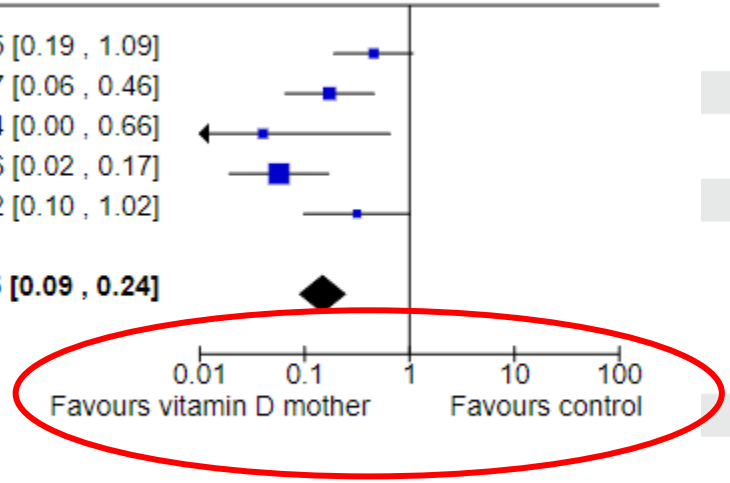
Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 2: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L

Label to tell you what the comparison is and the outcome of interest

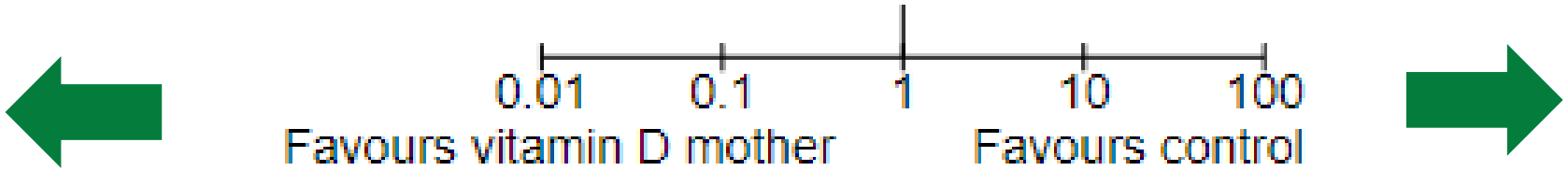
Cochrane Malaysia

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Total (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			

Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 7.69 (P < 0.00001)
Test for subgroup differences: Not applicable



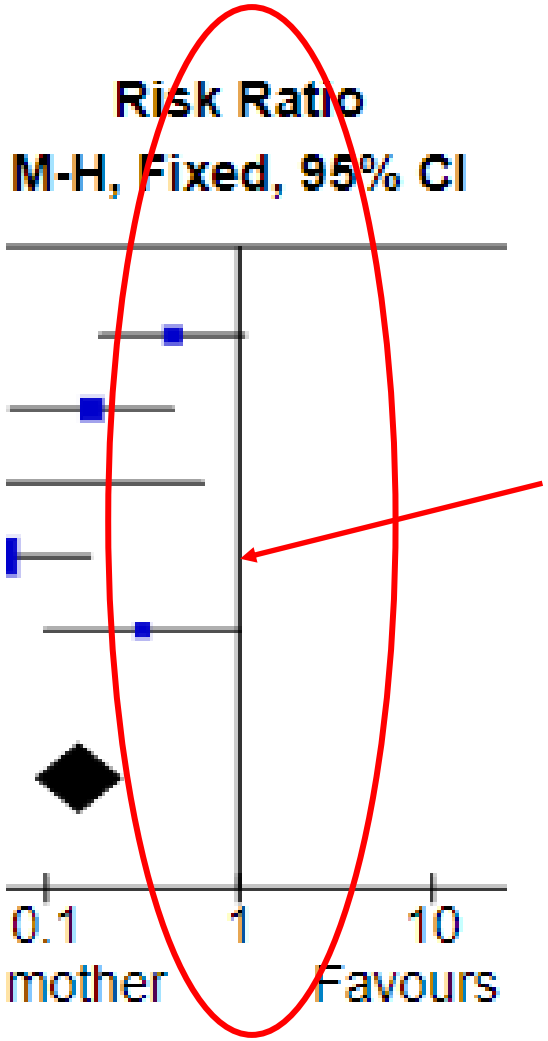
Footnotes
(1) < 27.5 nmol/L



Less than 1 / Reduced risk/ lower score

More than 1 / Increased risk/ higher score

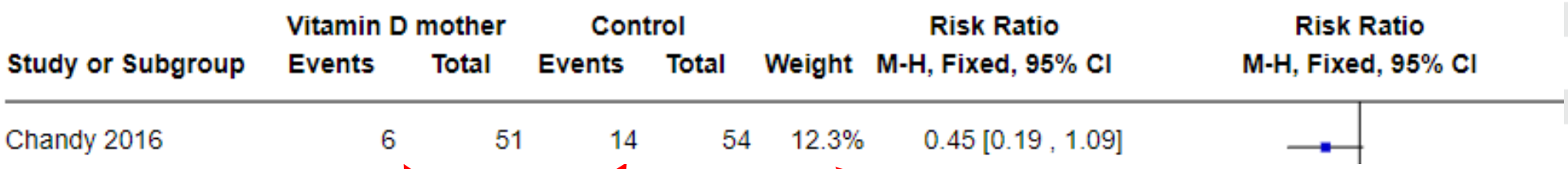
Cochrane Malaysia



The vertical line in the middle is where the treatment and control have the same effect – there is no difference between the two

Line of no effect

Cochrane Malaysia



For each study there is an ID

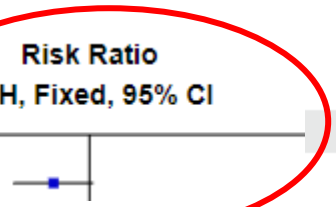
The data for each trial are here, divided into the experimental and control groups

This is the % weight given to this study in the pooled analysis

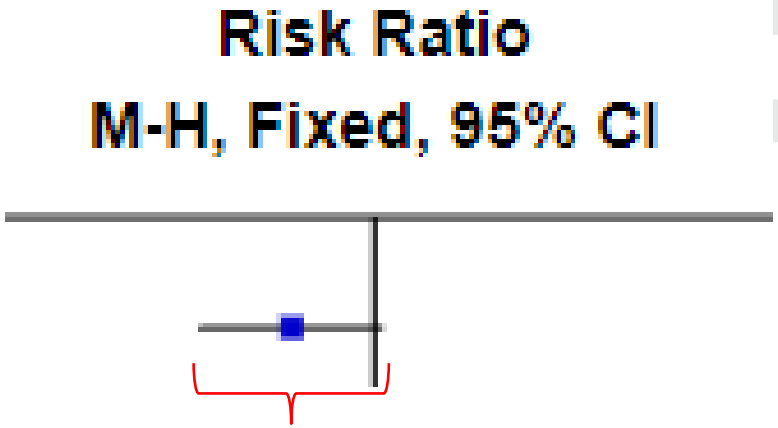
Cochrane Malaysia

The label above the graph tells you what statistic has been used

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]



The data shown in the graph are also given numerically

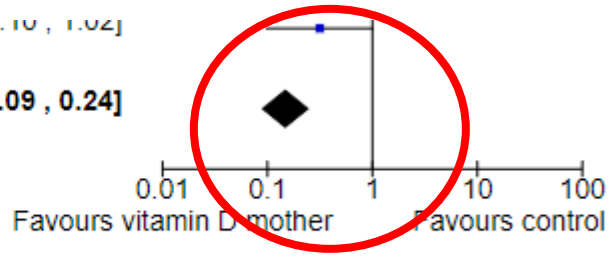


Confidence Interval

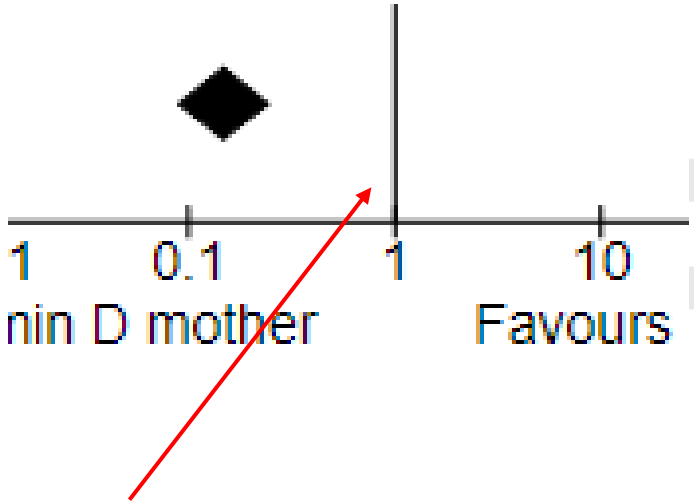
Cochrane Malaysia

Wheeler 2016	4	33	6	26	7.4%	0.32 [0.10 , 1.02]
Total (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			

Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 7.69 (P < 0.00001)
Test for subgroup differences: Not applicable



The pooled analysis is given a diamond shape where the widest bit in the middle is located at the calculated best guess (point estimate), and the horizontal width is the confidence interval



Line of no effect

Cochrane Malaysia

Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 2: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L

Analysis 2.2

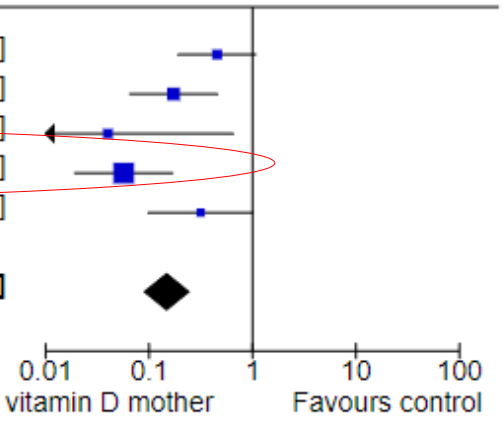
Open in figure viewer

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Total (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			

Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%

Test for overall effect: Z = 7.69 (P < 0.00001)

Test for subgroup differences: Not applicable



Footnotes

(1) < 27.5 nmol/L

Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 2: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L

Larger blue dots indicate a higher weighting
Longer lines indicate a wide confidence interval

Cochrane Malaysia

Let's go back to this forest plot

Analysis 2.2

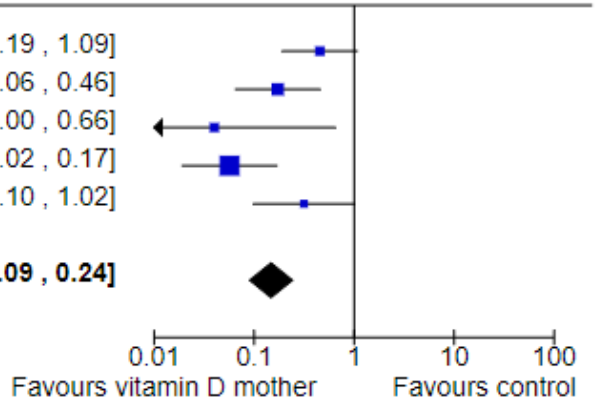
Open in figure viewer

Study or Subgroup	Vitamin D mother Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chandy 2016	6	51	14	54	12.3%	0.45 [0.19 , 1.09]
Naik 2017 (1)	4	53	25	57	21.8%	0.17 [0.06 , 0.46]
Roth 2016	0	49	13	53	11.7%	0.04 [0.00 , 0.66]
Trivedi 2020	3	58	51	56	46.9%	0.06 [0.02 , 0.17]
Wheeler 2016	4	55	6	26	7.4%	0.32 [0.10 , 1.02]
Total (95% CI)		**266**		**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17		109			

Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%

Test for overall effect: Z = 7.69 (P < 0.00001)

Test for subgroup differences: Not applicable



Footnotes

(1) < 27.5 nmol/L

Comparison 2: Vitamin D given to lactating mothers compared to placebo or no treatment, Outcome 2: Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L

RR 0.15, 95% CI 0.09 to 0.24

Cochrane Malaysia

The relative risk of Vitamin D deficiency is reduced from 1 to 0.15 with maternal supplementation of Vitamin D during lactation compared to placebo/control

OR

The risk of Vitamin D deficiency in the baby compared to placebo/control is reduced by 85% with maternal supplementation of Vitamin D during lactation

Cochrane Malaysia

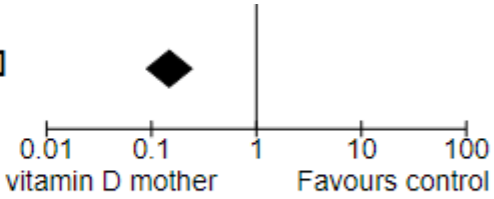
Interpretation of forest plot when ratios are used as effect measures

Type of event	Example	Which side of 1 does the label 'favours intervention' lie?	Which side of 1 does the overall estimate and 95% CI lie?	Interpretation
Bad event	Mortality	Left	Left	Favours intervention
Bad event	Mortality	Left	Right	Favours control
Good event	Early return to work	Right	Left	Favours control
Good event	Early return to work	Right	Right	Favours intervention

Number Needed to Treat -NNT (and Number Needed to Harm - NNH)

Total (95% CI)		**266**	**246**	**100.0%**	**0.15 [0.09 , 0.24]**
Total events:	17	109			

Heterogeneity: Chi² = 11.70, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 7.69 (P < 0.00001)
Test for subgroup differences: Not applicable



$$= \frac{1}{\text{Incidence in Controls}^{*} - \text{Incidence in Cases}^{**}}$$

$$= \frac{1}{17/266 - 109/246}$$

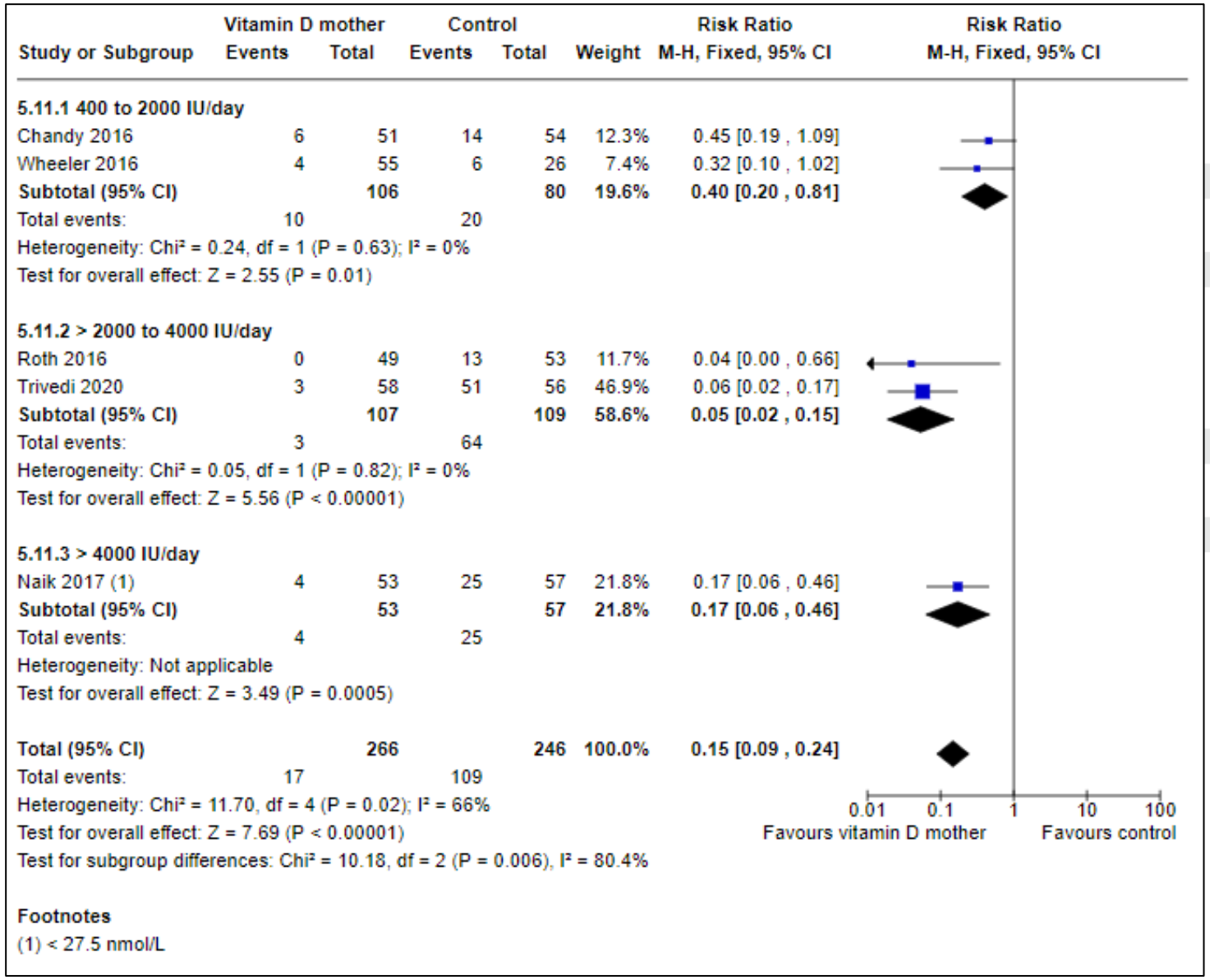
$$= \frac{1}{0.064 - 0.44} \qquad = \frac{1}{-0.377} \qquad = 2.6(3)$$

3 mothers would have to take Vitamin D during lactation to prevent 1 infant Vitamin D deficiency

*Incidence in controls = control event rate (CER)
**Incidence in cases = experimental event rate (EER)

Cochrane Malaysia

Subgroup Analysis: Dose



Cochrane Malaysia

Patient or population: term breastfed infants to prevent vitamin D deficiency and improve bone health

Settings: community

Intervention: vitamin D given to lactating mothers compared to placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with vitaminD given to lactating mothers				
Vitamin D insufficiency: 25-OH vitamin D < 50 nmol/L Follow-up: 6 months	**679 per 1000**	**319 per 1000** (265 to 387)	**RR 0.47** (0.39 to 0.57)	512 (5 studies)	⨁⨁◯◯ **low**[1,2]	Infant risk of vitamin D insufficiency was related to maternal dosage.
Vitamin D deficiency: 25-OH vitamin D < 30 nmol/L Follow-up: 6 months	**443 per 1000**	**66 per 1000** (40 to 106)	**RR 0.15** (0.09 to 0.24)	512 (5 studies)	⨁⨁◯◯ **low**[1,3]	Infant risk of vitamin D deficiency was related to maternal dosage.

Cochrane Malaysia

Author's Conclusion

For breastfed infants, vitamin D supplements may increase vitamin D levels and reduce the incidence of vitamin D insufficiency. There was insufficient information to determine if there was a reduction in vitamin D deficiency or in signs of poor bone health.

For breastfed infants at higher risk of vitamin D deficiency, vitamin D supplementation for the mother **may increase infant vitamin D levels** and **may prevent vitamin D deficiency**. There was not enough information to determine if there are benefits for bone health.

In populations at higher risk of vitamin D deficiency, vitamin D supplementation of infants may be better than vitamin D supplementation of the mother whilst breastfeeding for preventing vitamin D deficiency. However, the evidence is very uncertain for markers of bone health. High-dose maternal supplementation (≥ 4000 IU per day) achieved similar infant vitamin D levels as infant supplementation with 400 IU per day.

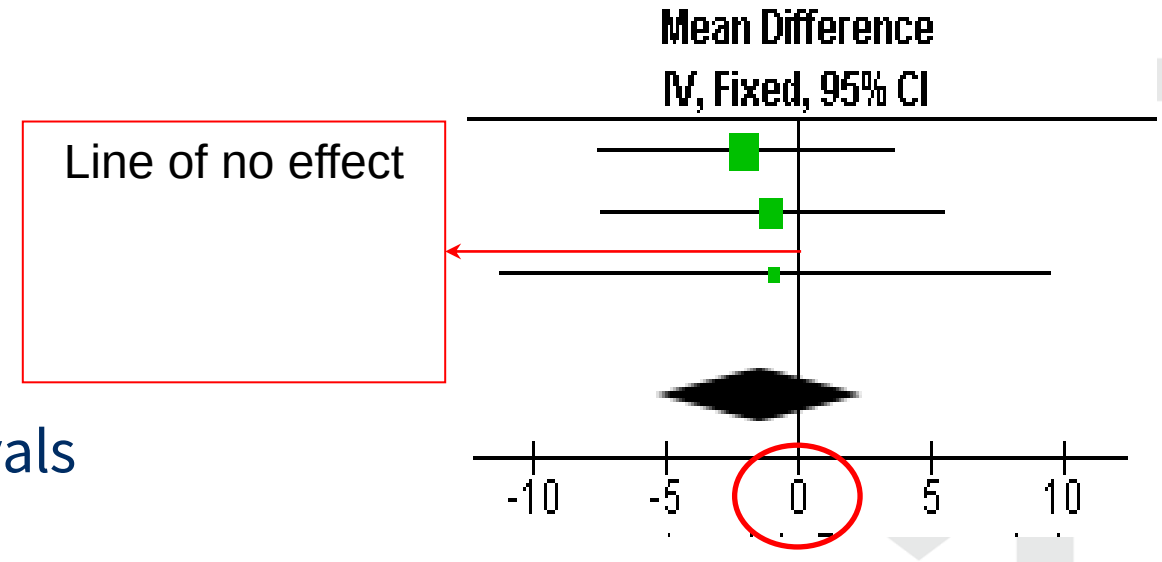
Cochrane Malaysia

Interpretation of forest plot when differences are used as effect measures

Absolute measures

All differences

- 0 indicates no effect
- If 0 is included in the 95% confidence intervals
  - No statistical significance at 5% significance levels
- If 0 is not included in the 95% confidence intervals
  - Statistical significance at 5% significance levels
  - Benefit or harm depends upon the context



Cochrane Malaysia

Interpretation of forest plot when differences are used as effect measures

Type of event	Example	Which side of 0 does the label 'favours intervention' lie?	Which side of 0 does the overall estimate and 95% CI lie?	Interpretation
Bad outcome	Pain score (visual analogue score)	Left	Left	Favours intervention
Bad outcome	Pain (visual analogue score)	Left	Right	Favours control
Good outcome	Quality of life	Right	Left	Favours control
Good outcome	Quality of life	Right	Right	Favours intervention

Cochrane Malaysia

Certainty of Evidence

GRADE Assessment:

1. Risk of bias
2. Imprecision: less number of events
3. Inconsistency: heterogeneity
4. Indirectness: indirect comparisons or interpretations
5. Publication bias: selective publication of studies

Cochrane Malaysia

GRADE

Certainty level	Current definition	Grade
High	We are very confident that the true effect lies close to that of the estimate of the effect	⊕⊕⊕⊕
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	⊕⊕⊕⊖
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	⊕⊕⊖⊖
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	⊕⊖⊖⊖

Cochrane Malaysia

Results Certainty

Cochrane Malaysia

Omega-3 LCPUFA compared with no omega-3 during pregnancy: birth/infant outcomes

Population: pregnant women and their babies

Settings: Angola (1 RCT), Australia (1 RCT), Belgium (1 RCT), Canada (1 RCT), Chile (1 RCT), Croatia (1 RCT), Chile (1 RCT), Denmark (3 RCTs), Egypt (1 RCT), Germany (2 RCTs), India (1 RCT), Iran (3 RCTs), Italy (1 RCT), Mexico (1 RCT), Netherlands (3 RCTs), Norway (1 RCT), Russia (1 RCT), Sweden (1 RCT), Turkey (1 RCT), UK (4 RCTs), USA (8 RCTs)

Intervention: omega 3

Comparison: no omega-3

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Risk with no omega-3	Risk with omega-3				
Preterm birth < 37 weeks	134/1000	119 per 1000 (109 to 130)	RR 0.89 (0.81 to 0.97)	10,304 (26 RCTs)	⊕⊕⊕⊕ HIGH[1]	
Early preterm birth < 34 weeks	46/1000	27 per 1000 (20 to 35)	RR 0.58 (0.44 to 0.77)	5204 (9 RCTs)	⊕⊕⊕⊕ HIGH[2]	

Cochrane Malaysia

THANK YOU

Trusted evidence.
Informed decisions.
Better health.