The role of meta-analysis in the evaluation of the effects of early nutrition on neurodevelopment

Hania Szajewska
The Medical University of Warsaw
Department of Paediatrics
hania@ipgate.pl

Outline

- Hierarchy of evidence to assess the effectiveness of intervention
- Systematic review *vs* meta-analysis
- Criticism of a meta-analysis
- Problems and limitations of a meta-analysis

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- Hierarchy of evidence to assess the effectiveness of intervention
- Systematic review *vs* meta-analysis
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- Problems and limitations of a meta-analysis

  - In a context of studies on early nutrition and the effects on neurodevelopment
  - Conclusions are applicable to systematic reviews and meta-analyses in general

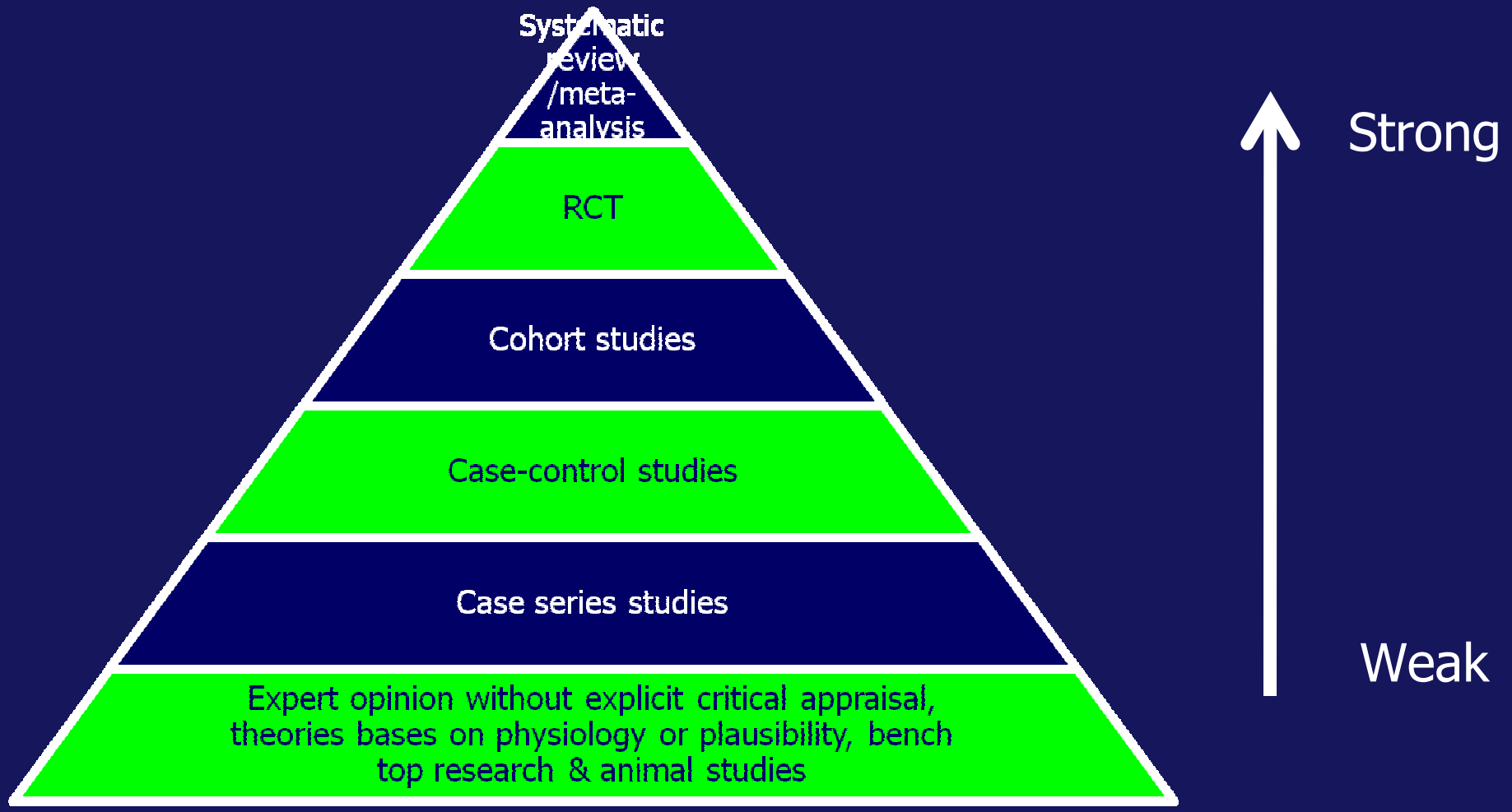
Nutrients *vs* neurodevelopment

- Examples of nutrients relevant for brain structure and function
  - N-3 LCPUFA
  - Iron
  - Zinc
  - B-vitamins

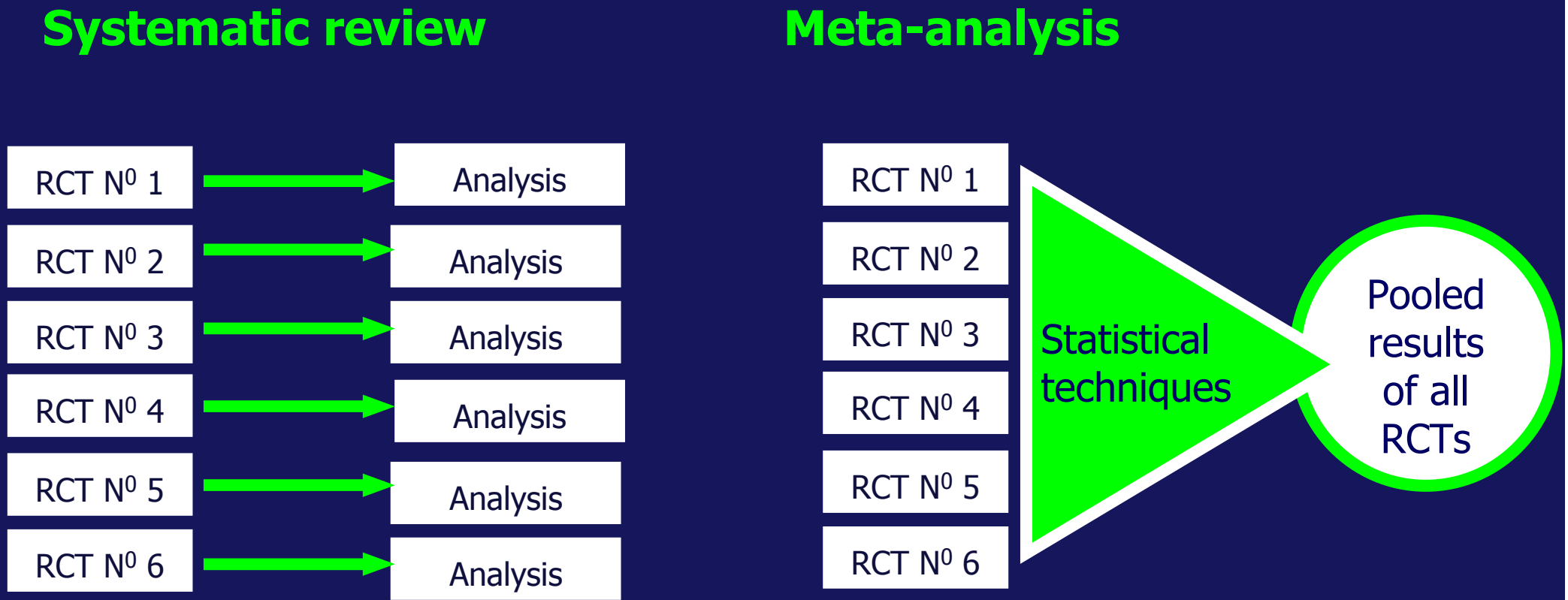
- Lack of clarity and no consensus on their role in mental and motor development of children

Hierarchy of evidence

for questions about the effectiveness of an intervention



Systematic review *vs* meta-analysis



Meta-analysis

Why to perform a MA?

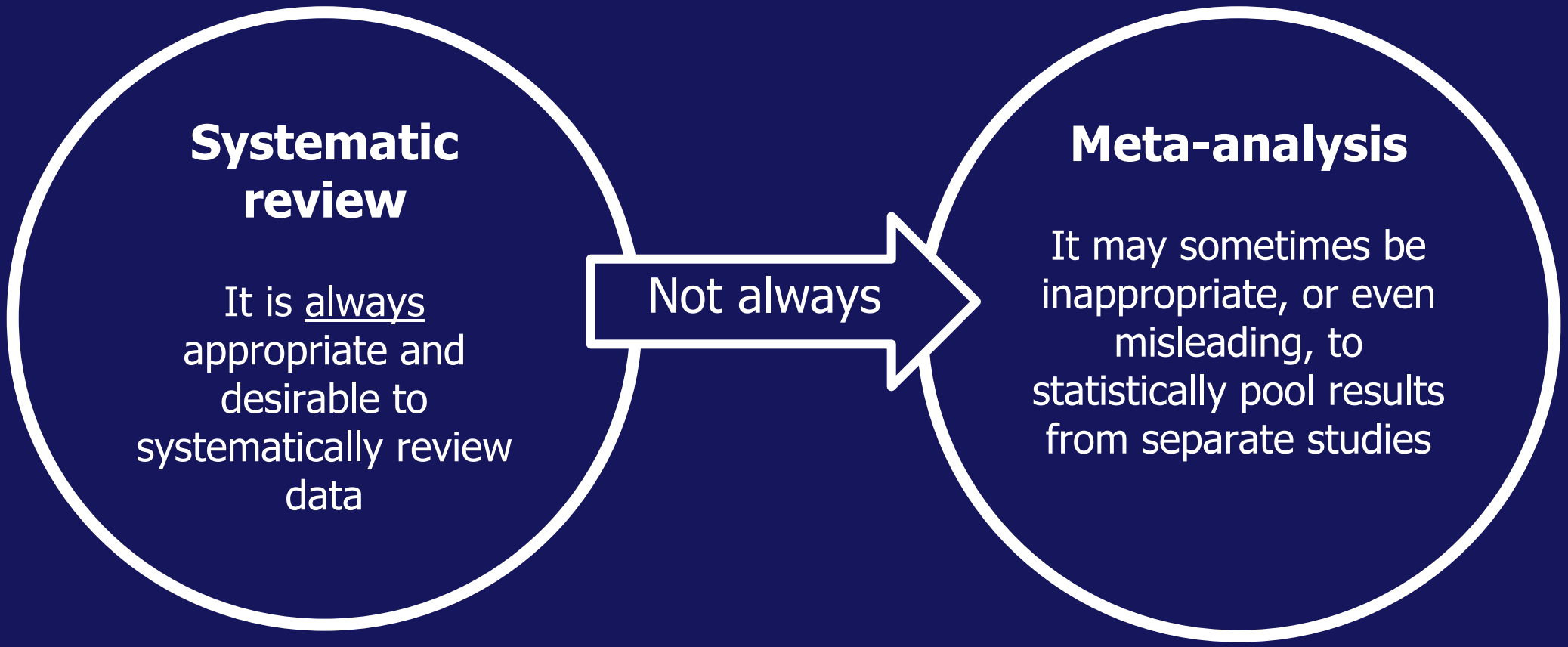
- To increase power
  - The chance to reliably detect a clinically important difference if one actuallly exist
- To improve precision in estimating effects
  - Narrow the confidence interval around the effects

When to pool the results?

- If the studies are considered sufficiently homogenous in terms of the question and methods

Egger, Smith, Altman (ed.).
Systematic review in health care. Meta-analysis in context. BMJ Books 2000.

Take home message



Early nutrition and mental & motor development

Published systematic reviews & meta-analyses

Intervention	Reference	Population	Conclusion
Breastfeeding	US AHRQ	Term infants	NS
	US AHRQ	Preterms	No definitive conclusion
	Dutch Report	Term infants	Probable evidence
LCPUFA	Simmer 2008	Preterms	NS
	Smithers 2008	Preterms	Findings varied according to whether BSDI-I or BSDI-II were used
	Simmer 2008	Term infants	NS
Iron	Sachdev 2005	Infants & toddlers	Modest effect
	Martins 2009	<3 y	No convincing evidence
Multiple micronutrients	Eilander 2010	0-18 y	Fluid intelligence NS Crystallized intelligence NS Other cognitive domains NS

NUTRIMENTHE

http://www.nutrimenthe.eu/

The effect of diet on the mental performance of children

Project coordinator: Cristina Campoy

Nutri MENTHE

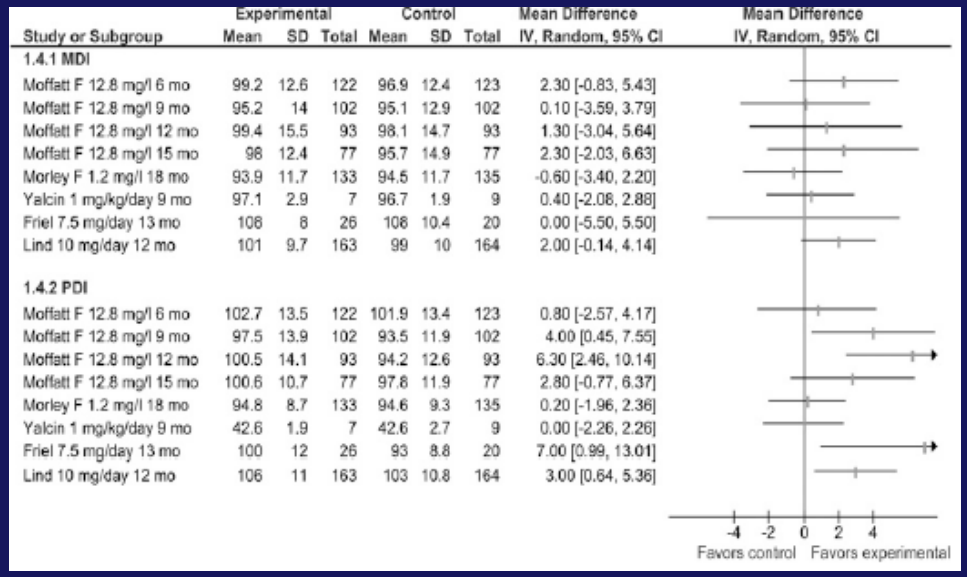
Iron supplementation

Population	Non-anaemic pregnant women Non-anaemic healthy children aged <3 y
Intervention	Iron supplementation
Comparison	Placebo or no intervention
Outcome	Mental performance Psychomotor development
Studies	RCT
Search strategy	Cochrane Library, MEDLINE, EMBASE, reference lists, no language restriction

Szajewska, Ruszczyński, Chmielewska. Am J Clin Nutr 2010

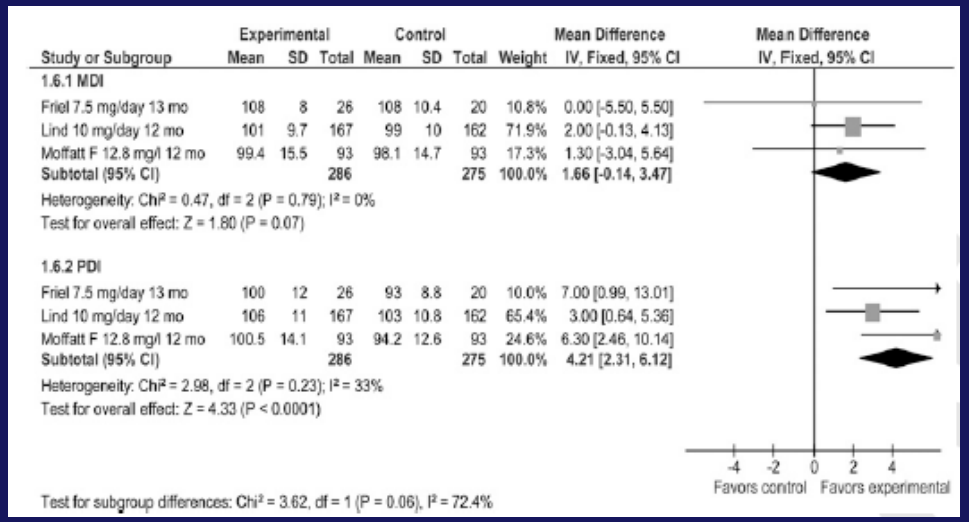
Iron supplementation

MDI & PDI at different ages throughout the first 18 mo



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Random, 95% CI
1.4.1 MDI							
Moffatt F 12.8 mg/l 6 mo	99.2	12.6	122	96.9	12.4	123	2.30 [-0.83, 5.43]
Moffatt F 12.8 mg/l 9 mo	95.2	14	102	95.1	12.9	102	0.10 [-3.59, 3.79]
Moffatt F 12.8 mg/l 12 mo	99.4	15.5	93	98.1	14.7	93	1.30 [-3.04, 5.64]
Moffatt F 12.8 mg/l 15 mo	98	12.4	77	95.7	14.9	77	2.30 [-2.03, 6.63]
Morley F 1.2 mg/l 18 mo	93.9	11.7	133	94.5	11.7	135	-0.60 [-3.40, 2.20]
Yalcin 1 mg/kg/day 9 mo	97.1	2.9	7	96.7	1.9	9	0.40 [-2.08, 2.88]
Friel 7.5 mg/day 13 mo	106	8	26	108	10.4	20	0.00 [-5.50, 5.50]
Lind 10 mg/day 12 mo	101	9.7	163	99	10	164	2.00 [-0.14, 4.14]
1.4.2 PDI							
Moffatt F 12.8 mg/l 6 mo	102.7	13.5	122	101.9	13.4	123	0.80 [-2.57, 4.17]
Moffatt F 12.8 mg/l 9 mo	97.5	13.9	102	93.5	11.9	102	4.00 [0.45, 7.55]
Moffatt F 12.8 mg/l 12 mo	100.5	14.1	93	94.2	12.6	93	6.30 [2.46, 10.14]
Moffatt F 12.8 mg/l 15 mo	100.6	10.7	77	97.8	11.9	77	2.80 [-0.77, 6.37]
Morley F 1.2 mg/l 18 mo	94.8	8.7	133	94.6	9.3	135	0.20 [-1.96, 2.36]
Yalcin 1 mg/kg/day 9 mo	42.6	1.9	7	42.6	2.7	9	0.00 [-2.26, 2.26]
Friel 7.5 mg/day 13 mo	100	12	26	93	8.8	20	7.00 [0.99, 13.01]
Lind 10 mg/day 12 mo	106	11	163	103	10.8	164	3.00 [0.64, 5.36]

MDI & PDI at approximately 12 mo of age



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 MDI								
Friel 7.5 mg/day 13 mo	108	8	26	108	10.4	20	10.8%	0.00 [-5.50, 5.50]
Lind 10 mg/day 12 mo	101	9.7	167	99	10	162	71.9%	2.00 [-0.13, 4.13]
Moffatt F 12.8 mg/l 12 mo	99.4	15.5	93	98.1	14.7	93	17.3%	1.30 [-3.04, 5.64]
Subtotal (95% CI)			**286**			**275**	**100.0%**	**1.66 [-0.14, 3.47]**
Heterogeneity: $Chi^2 = 0.47$, df = 2 (P = 0.79); $I^2 = 0\%$								
Test for overall effect: Z = 1.80 (P = 0.07)								
1.6.2 PDI								
Friel 7.5 mg/day 13 mo	100	12	26	93	8.8	20	10.0%	7.00 [0.99, 13.01]
Lind 10 mg/day 12 mo	106	11	167	103	10.8	162	65.4%	3.00 [0.64, 5.36]
Moffatt F 12.8 mg/l 12 mo	100.5	14.1	93	94.2	12.6	93	24.6%	6.30 [2.46, 10.14]
Subtotal (95% CI)			**286**			**275**	**100.0%**	**4.21 [2.31, 6.12]**
Heterogeneity: $Chi^2 = 2.98$, df = 2 (P = 0.23); $I^2 = 33\%$								
Test for overall effect: Z = 4.33 (P < 0.0001)								
Test for subgroup differences: $Chi^2 = 3.62$, df = 1 (P = 0.06), $I^2 = 72.4\%$								

Limited evidence suggests that iron supplementation in infants may positviely influence children's psychomotor development, whereas it does not seem to alter their mental development or behavior

Szajewska, Ruszczyński, Chmielewska. Am J Clin Nutr 2010

Nutri MENTHE

n-3 LCPUFA

Population	Pregnant and/or lactating women
Intervention	n-3 LCPUFA
Comparison	Placebo or no supplementation
Outcome	Neurodevelopment Visual function
Studies	RCTs
Search strategy	Cochrane Library, MEDLINE, EMBASE, references lists No language restriction
Conclusion	Evidence from RCTs does not demonstrate a clear and consistent benefit of n-3 LCPUFA supplementation during pregnancy and/or lactation on child neurodevelopment and visual acuity.

Dziechciarz, Horvath, Szajewska. 2010. Submitted.

Nutri MENTHE

Folic acid

Population	Pregnant women Pregnant women and then their children up to 3 y of age
Intervention	Folic acid
Comparison	Placebo or no supplementation
Outcome	Neurodevelopment Mental/behavioral disorders
Studies	RCTs
Search strategy	Cochrane Library, MEDLINE, EMBASE, references lists No language restriction
Conclusion	The use of multivitamin-containing folic acid supplementation during pregnancy is associated with no benefit to the mental performance of children.

Skórka, Gieruszczak-Białek, Pieścik, Szajewska. 2010. Submitted.

A common criticism of a meta-analysis

- 'Mega-silliness'

  Eysenck HJ. Am Psychol 1978;33:517

- 'Shmeta-analysis'

  Shapiro S. Am J Epidemiol 1994;140:771-8.

- 'Statistical alchemy'

  Feinstein AR. J Clin Epidemiol 1995;48:71-9.

- 'Mixing apples and oranges'

  Sharpe D. Clin Psychol Rev 1997;17:881-901

Mixing apples & oranges

Dangerous or delicious?

Problems and limitations of a meta-analysis

- Failure to identify all relevant studies
- Unpublished data
- Quality of included trials
- Inconclusive systematic reviews
- Opposite conclusions
- Discrepancies between the results of a meta-analysis and a large RCT

Failure to identify all relevant studies

- The core of SR/MA is the identification of every relevant evidence

- What is important
  - Searching one database is never enough
  - At least Medline, Embase, Cochrane Library
  - No restriction on language
  - In order to minimise bias, 2 or more reviewers
  - The set of key words as complete as possible

Unpublished data

To include or not to include?

Controversial issue

Unpublished data
Arguments in favor

- Unpublished studies differ systematically from those that have been published
  - Methodological weaknesses
  - Smaller or no treatment effects revealed in these trials
  - Often, but not always, industry sponsored
- Non-publications can lead to false assumptions regarding the efficacy of the treatment
- Inclusion reduces the risk of publication bias

Cook et al. JAMA 1993;269:2749-53
Dickersin et al. JAMA 2003;290:516-23.
Whittington et al. Lancet 2004;363:1341-5.

Unpublished data
Arguments against

- Challenges
  - Gaining access to the studies
  - Obtaining sufficient information to evaluate the methodological quality
    - Unpublished data may be of lower methodological quality
  - Located trial data may be an unrepresentative sample of data from all unpublished studies
    - Further introduce bias

MacLean et al. J Clin Epidemiol 2003;56:44-51.

Garbage in – garbage out

Egger et al. BMJ Books 2003

Quality of included trials

- Adequate allocation generation
  - Selection bias
- Allocation concealment
  - Selection bias
- Blinding
  - Perfomance bias
- Loss to follow-up
  - Attrition bias

Egger et al. BMJ Books 2003

Iron supplementation

Methodological quality of 8 included RCTs

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?
Friel 2003	?	+	+	-
Lind 2004	+	+	+	+
Moffatt 1994	+	+	+	+
Morley 1999	+	+	+	+
Parson 2007	+	+	+	-
Yalcin 2000	?	?	+	-
Zhou 2006	+	+	+	-

Yes (low risk of bias)
Unclear
No (high risk of bias)

Szajewska, Ruszczyński, Chmielewska. AJCN 2010

N-3 LCPUFA supplementation

Methodological quality of 13 included RCTs

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?
Dunstan 2008	+	+	+	-
Helland 2001	+	?	?	-
Helland 2003	+	?	?	+
Helland 2008	+	?	?	+
Innis 2008	+	+	+	+
Jensen 2005	+	?	+	-
Judge 2007	+	?	+	?
Judge 2007	?	?	?	+
Lauritzen 2004	+	+	+	+
Lauritzen 2005	+	+	+	-
Malcolm 2003	?	?	+	?
Malcolm 2003	?	?	?	?
Tofail 2006	?	?	+	+

Yes (low risk of bias)
Unclear
No (high risk of bias)

Dziechciarz, Horvath, Szajewska. 2010. Submitted.

How much loss to follow-up is acceptable?

How much loss to follow-up is acceptable in long-term randomised trials and prospective studies?

Mary S Fewtrell,[1] Kathy Kennedy,[1] Atul Singhal,[1] Richard M Martin,[2] Andy Ness,[3] Mijna Hadders-Algra,[4] Berthold Koletzko,[5] Alan Lucas[1]

Box 2 Suggested minimum reporting requirements for addressing attrition in long-term follow-up studies

1. Provide clear, unambiguous information on the flow of subjects through the study/cohort at each stage. Give explicit information on the attrition rate and the attrition in each group for a randomised trial.
2. Discuss the ability of the follow-up study to detect the hypothesised outcome effect with the sample size attained.
3. Discuss the potential for attrition to have introduced bias. Do baseline and/or measured variables differ in those seen and not seen? Provide baseline characteristics for those seen and not seen at follow-up separately for each intervention group.
4. Discuss whether attrition is likely to have affected the generalisability of the findings to the original study population (which may or may not have been representative of the larger population) and to the general population.
5. Provide an appropriate sensitivity analysis; describe the assumptions on which it is based.*

*In its simplest terms this could estimate how different the result would have to be in subjects not seen at follow-up to negate the difference between groups observed in those who were successfully studied.

Fewtrell at al. Arch Dis Child 2008;93:458-61.

External validity

- Patients
  - Age, sex
- Intervention
  - Dosage, timing, duration
- Setting
  - High-income *vs* low-income countries
- Modalities of outcomes
  - Type or definition of outcomes
  - Length of follow-up

External validity

- Patients
  - Age, sex
- Intervention
  - Dosage, timing, duration
- Setting
  - High-income *vs* low-income countries
- Modalities of outcomes
  - Type or definition of outcomes
  - Length of follow-up

Lack of clear effect of LCPUFA may be due to the dose and/or duration of LCPUFA supplementation

Simmer, Schulzke, Patole 2008
Simmer, Patole, Rao 2008

External validity

- Patients
  - Age, sex
- Intervention
  - Dosage, timing, duration
- Setting
  - High-income *vs* low-income countries
- Modalities of outcomes
  - Type or definition of outcomes
  - Length of follow-up

Iron supplementation – most of the studies performed in industrialised countries. Applicability to low-income settings?

Szajewska, Ruszczyński, Chmielewska. Am J Clin Nutr 2010

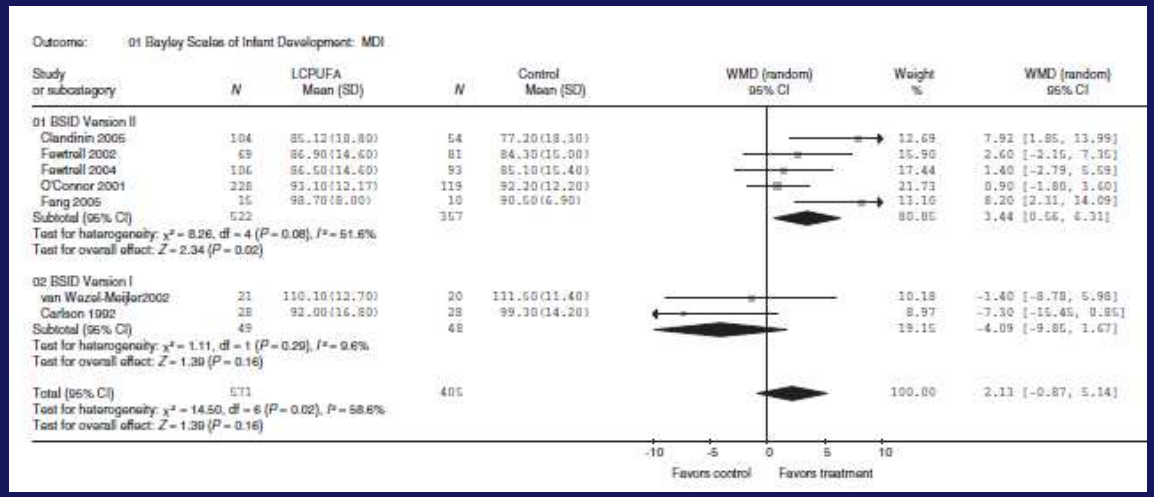
External validity

- Patients
  - Age, sex
- Intervention
  - Dosage, timing, duration
- Setting
  - High-income *vs* low-income countries
- Modalities of outcomes
  - Type or definition of outcomes
  - Length of follow-up

Bayley Scales of Infant Development

- Many of the included trials utilised global tests, such as BSID
  - Designed to detect delayed development
  - Do not measure important cognitive abilities
  - May not be sensitive enough to detect subtle differences between infants
  - May by inappropriate for detecting differences in neurodevelopment

Effect of LCPUFA supplementation of preterm infants on disease risk and neurodevelopment



- The effect of dietary LCPUFA on the MDI varied according to whether version I or version II were used
  - BSID-I compared with BSID-II more likely to report worse mental development

BSID, the Bayley Scales of Infant Development
MDI, mental development index

Smithers et al. AJCN 2008;87:912-20.

Inconclusive systematic review

- ‘No clear evidence’
- ‘Some evidence of a trend’

Inconclusive systematic review

Frustrating!

But….

- Clearly demonstrating the inadequacy of existing evidence is an important objective of systematic reviews
- Should serve as a stimulus for conducting the appropriate and necessary trials

Alderson & Roberts. Br Med J 2000;320:376-7.

Opposite conclusions

- Systematic reviews addressing the same issue and performed at almost the same time have reached opposite conclusions

Table 1: Sources of discordance among meta-analyses
Clinical question
Populations of patients
Interventions
Outcome measures
Settings
Study selection and inclusion
Selection criteria
Application of the selection criteria
Strategies to search the literature
Data extraction
Methods to measure outcomes
End points
Human error (random or systematic)
Assessment of study quality
Methods to assess quality
Interpretations of quality assessments
Methods to incorporate quality assessments in review
Assessment of the ability to combine studies
Statistical methods
Clinical criteria to judge the ability to combine studies
Statistical methods for data synthesis

Jadad et al. Can Med Ass J 1997;156:1411-6.

Discrepancies between the results of a meta-analysis and a large RCT

- No agreement what should be done
- Consider methodological quality of RCT and MA
  - If both are of high quality, the results of the RCT are (probably) more reliable

- It is considered that a deviation in 5 percent of cases would be expected on the basis of chance alone

Bailar C 3rd. NEJM 1997;337:559-61.
Lelorier et al. NEJM 1997;337:536-42.

Systematic review of non-RCT?

Systematic review of RCTs *vs* non-RCTs

- Reasons to consider including non-RCTs
  - To examine the necessity for undertaking RCT by summarizing non-RCTs and providing an explicit evaluation of the weaknesses of available non-RCTs
  - To assess the evidence when RCT design would be unethical
  - To provide evidence regarding long-term and/or rare outcomes

Reeves et al. Cochrane Handbook for Systematic Reviews of Interventions

Systematic review of RCTs *vs* non-RCTs

- If for any reason non-RCTs are included, the results should be always interpreted with caution as potential biases, particularly selection bias, are more likely to occur!

Reeves et al. Cochrane Handbook for Systematic Reviews of Interventions

Key messages

- Systematic reviews with/out a meta-analysis are a well-established means of reviewing existing evidence.
- Every meta-analysis should be proceded by a systematic review. However, not every systematic review should be finalized with a meta-analysis.
- An understanding of the strengths and limitations of the meta-analytical approach is needed.

Final comment…

‘Science is always wrong. It never solves a problem without creating ten more’.

George Bernard Shaw

Thank you
for your attention