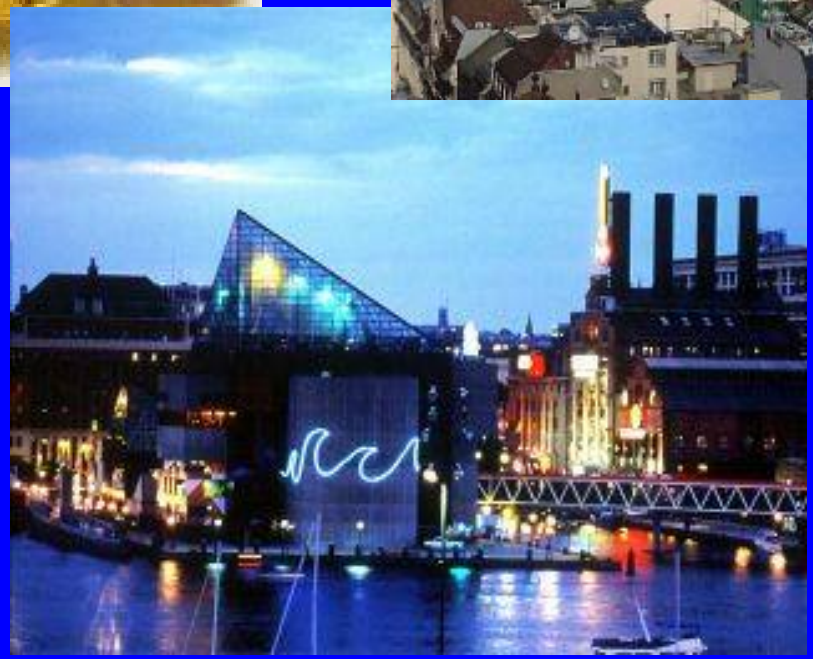

NUTRITIONAL INTERVENTIONS DURING PREGNANCY FOR THE PREVENTION OF MATERNAL MORBIDITY, MORTALITY AND PRETERM DELIVERY

OVERVIEW OF RANDOMISED CONTROLLED TRIALS

José Villar, Mario Merialdi, A Metin Gülmezoglu, Edgardo Abalos, Guillermo Carroli, Regina Kulier, Mercedes de Onis

Overview

Nutritional Interventions during Pregnancy for the Prevention or Treatment of Maternal Morbidity and Preterm Delivery: An Overview of Randomized Controlled Trials[1,2]

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Overview

Nutritional Interventions during Pregnancy for the Prevention or Treatment of Impaired Fetal Growth: An Overview of Randomized Controlled Trials[1,2]

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Background

- It is often thought that mortality and morbidity associated with pregnancy complications and preterm delivery can be reduced only by emergency obstetric care and newborn intensive care.
- Is maternal nutrition playing a role?
- Are nutritional preventive interventions effective?
- Medical vs. public health approach.

How to test effectiveness of interventions?

- Randomized clinical trials are the best evidence of effectiveness
- Experiment: two similar groups, one is given the intervention, the other the placebo
- Analysis of results: we count the number of negative outcomes in the two groups, we calculate the incidence rates and we compare them calculating the relative risk

Analysis of the results. Was the intervention effective?

- Incidence rate for the development of the disease are calculated among the subjects in the treatment and control group
- If the incidence rate of the disease is greater among the persons in the control group than among the ones in the treatment group, we have evidence that the intervention decreased the risk of disease

What is an incidence rate?

- Number of cases of a disease occurring in one of the study groups

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- Number of persons in the study group

Incidence rates of pre-eclampsia

- Incidence rate = cases/number of subjects
- Incidence rate in calcium group 119/4250 = 0.028
- Incidence rate in placebo group 170/4250 = 0.040
- The incidence rate is greater in the placebo than in the calcium group
- We have evidence that calcium supplementation is effective in reducing the risk of pre-eclampsia

How strong is the treatment effect?

- The relative risk measures the strength of the treatment effect
- Incidence rate in the treatment group / incidence rate in the control group
- In our example 0.028 /0.040 =0.7

How to interpret relative risk?

- If relative risk is = 1 there is no evidence of an effect of the treatment (the incidence rate in the treatment group is the same as in the control group)
- If relative risk is < 1 the treatment is beneficial (decreases the risk of disease)
- If relative risk is > 1, the treatment is associated with an increased risk of disease

Systematic reviews

- Used to summarize the available evidence from different clinical trials
- Clinical trials are included or excluded from the analysis on the basis of objective criteria (to avoid bias)
- Results are summarized as pooled relative risks

Systematic reviews of trials reporting the following outcomes

- Pre-eclampsia, hypertension, anaemia, haemorrhage, obstructed labour, duration of labour, caesarean section
- Maternal mortality
- Preterm delivery (<37 completed weeks)

Included in the analyses

- 15 systematic reviews
- 69 randomised trials included in the systematic reviews
- 14 randomised trials not included in systematic reviews: fish oil (4) zinc (5), vitamin A-beta carotene (4), vitamins E and C (1).

Pre-eclampsia

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Nutritional advice	1 (4)	136	0.89 (0.42 - 1.88)
Balanced protein/energy	3 (13)	516	1.20 (0.77 - 1.89)
Isocaloric balanced protein	1 (3)	782	1.00 (0.57 - 1.75)
Energy/ protein restriction	2 (3)	284	1.13 (0.59 - 2.18)
Salt restriction	2 (2)	603	1.11 (0.46 - 2.66)

Pre-eclampsia

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Calcium (low risk)	6 (6)	6307	0.79 (0.65 – 0.94)
Calcium (high risk)	5 (5)	587	0.21 (0.11 – 0.39)
Calcium (adequate intake)	4 (4)	5022	0.86 (0.71 - 1.05)
Calcium (low intake)	6 (6)	1842	0.32 (0.21 – 0.49)

Pre-eclampsia

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Magnesium	**2 (7)**	**474**	**0.87 (0.57 - 1.32)**
Fish Oil*	**2 (2)**	**5021**	**0.70 (0.55 - 0.90)**
Vitamins C and E	**1 (-)**	**283**	**0.46 (0.24 - 0.91)**

* New trials have been published after the last update of the Cochrane review

New fish oil trials: pre-eclampsia

		Total women	RR 95%CI
Salvig 1996	Fish oil vs. no treatment	397	0.16* (0.01 - 4.02)
Onwude 1995	Fish oil vs. placebo	232	0.88 (0.46 - 1.65)
Olsen 2000 (EARL-PIH trial)	Fish oil vs. olive oil in women with previous PIH	321	0.72 (0.35 - 1.49)

* Expt. = 0/266 Placebo = 1/131

Effectiveness of nutritional interventions: pre-eclampsia

	Practice	Research
Nutritional advice	**Not recommended**	**Not needed**
Balanced protein/energy	**Not recommended**	**Not needed**
Isocaloric balanced protein	**Not recommended**	**Not needed**
Energy/protein restriction	**Not recommended**	**Not needed**
Salt restriction	**Not recommended**	**Not needed**

Effectiveness of nutritional interventions: pre-eclampsia

	Practice	Research
Calcium	**Not recommended**	**Possibly beneficial** for women at high risk and with low baseline intake.
Folate	**Not recommended**	**Not needed**
Iron and folate	**Not recommended**	**Not needed**
Magnesium	**Not recommended**	**Not needed**
Fish oil	**Not recommended**	**Needed?** data from low quality studies and heterogeneous results in new trials

Effectiveness of nutritional interventions: pre-eclampsia

	Practice	Research
Zinc	**Not recommended**	**Not needed**
Vitamins C and E	**Not recommended**	RCT in preparation (data from one RCT in high risk, non deficient women RR= 0.46 0.24-0.91)
Vitamin A	**No data**	**Not needed**
Multinutrients	**Data not available yet**	**RCT completed**

Anaemia or haemorrhage

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Iron	**12 (20)**	**1802**	**0.18 (0.13 – 0.24)**
Folate	**6 (21)**	**3114**	**0.72 (0.66 – 0.80)**
Iron and folate	**6 (8)**	**1135**	**0.22 (0.15 - 0.33)**
Magnesium	**2 (7)**	**942**	**0.38 (0.16 – 0.90)**
Vitamin A	**3 (5)**	**813**	**0.91 (0.80 – 1.04)**

Rate of severe postpartum anaemia

WHO ANC trial 2001 - Argentina

	New ANC Model % Women	Standard ANC Model % Women
Women supplemented	85.5	20.6
Severe post partum anaemia	8.8	13.3

Effectiveness of nutritional interventions: anaemia or haemorrhage

	Practice	Research
Iron and folate	**Recommended** Very effective intervention	**Need to complete a systematic review of daily vs. weekly supplementation**
Magnesium	**Not recommended**	**Any future trial should include antepartum hemorrhage as primary outcome**
Zinc	**Not recommended**	**Not needed**
Vitamin A	**Not recommended**	**Not needed**

Obstructed labour/caesarean section

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Salt restriction	1 (2)	361	0.75 (0.44 – 1.27)
Iron (routine vs. selective)	1 (1)	4052	1.33 (1.03 – 1.70)
Iron (anemia treatment)	1 (2)	100	1.25 (0.36 - 4.38)
Iron and folic acid	2 (8)	104	0.19 (0.02 – 1.45)
Folate	2 (21)	237	0.57 (0.26 – 1.24)
Zinc	3 (7)	1747	0.71 (0.52 – 0.97)

Effectiveness of nutritional interventions: Obstructed labour/caesarean section/duration of labour

	Practice	Research
Balanced protein/ energy	**Not recommended**	**Not needed**
Calcium	**Not recommended**	**Not needed**
Iron and folate	**Not recommended**	**Not needed**
Magnesium	**Not recommended**	**Not needed**
Zinc	**Not recommended**	**Any future randomized trial should include rate of caesarean section and/or duration of labour as an outcome**

Vitamin A and maternal mortality in Nepal (West et al, 1999)

Cause	Placebo (N=7241)	Vitamin A (N= 7747)	Beta carotene (N=7201)
Obstetric	1.00	0.88 (0.42-1.81)	0.56 (0.24-1.31)
Infection	1.00	0.94 (0.42-2.05)	0.60 (0.24-1.51)
Injury	1.00	0	0.20 (0.02-2.32)
Miscellaneous	1.00	0.14 (0.03-0.76)	0.38 (0.13-1.21)
Overall	1.00	0.60 (0.37-0.97)	0.51 (0.30-0.86)

Preterm delivery

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Nutritional advice	**1 (4)**	**547**	**0.45 (0.22 - 0.92)**
Balanced protein/energy	**5 (13)**	**2436**	**0.83 (0.65 - 1.06)**
Isocaloric balanced protein	**1 (3)**	**782**	**1.05 (0.69 - 1.70)**
Energy/protein restriction	**1 (3)**	**182**	**0.50 (0.09 - 2.66)**
High protein	**1 (2)**	**505**	**1.14 (0.83 - 1.56)**
Salt restriction	**1 (2)**	**242**	**1.08 (0.46 - 2.56)**

Preterm delivery

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Calcium	**9 (11)**	**6671**	**0.95 (0.82 - 1.10)**
Iron	**1 (20)**	**2694**	**1.40 (0.94 - 2.09)**
Folate	**4 (21)**	**1425**	**1.03 (0.71 - 1.49)**
Magnesium	**5 (7)**	**2275**	**0.73 (0.57 - 0.94)**
Fish oil*	**2 (3)**	**5017**	**0.83 (0.75 - 0.92)**
Zinc*	**5 (7)**	**2539**	**0.74 (0.56 - 0.98)**

* New trials have been published after the last update of the Cochrane review

New fish oil trials: preterm delivery

		Total Women	RR 95%CI
Bulstra-Ramakes 1994	Fish oil vs. placebo	**63**	**0.77 (0.35 - 1.70)**
Onwude 1995	Fish oil vs. placebo	**232**	**0.16 (0.66 - 2.05)**
Olsen 2000 (EARL-PD trial)	Fish oil vs. olive oil in women with previous PTD	**228**	**0.64 (0.41- 0.99)**

New zinc trials: preterm delivery

	INTERVENTION	Total Women	RR 95%CI
Caulfield 1999	Zinc (15 mg/day) plus iron plus folate vs. iron plus folate	1016	0.92 (0.56- 1.51)
Osendarp 2000	Zinc (30 mg/day) vs. placebo	410	1.11 (0.72 -1.72)
Merialdi 2001	Zinc (25 mg/day) plus iron plus folate vs. iron plus folate	217	1.54 (0.57 - 4.18)

Effectiveness of nutritional interventions: preterm delivery

	Practice	Research
Nutritional advice	**Not recommended**	**Promising intervention**
Balanced protein/energy	**Not recommended**	**Not needed**
Isocaloric balanced protein	**Not recommended**	**Not needed**
Energy/protein restriction	**Not recommended**	**Not needed**

Effectiveness of nutritional interventions: preterm delivery

	Practice	Research
High protein	**Not recommended**	**Not needed**
Salt restriction	**Not recommended**	**Not needed**
Calcium	**Not recommended**	**Stratified analysis in the new trial by risk level and age (teenagers)**
Iron	**Not recommended**	**Not needed**
Folate	**Not recommended**	**Not needed**

Effectiveness of nutritional interventions: preterm delivery

	Practice	Research
Iron and folate	**Not recommended**	**Not needed**
Magnesium	**Not recommended**	**Needed Promising intervention**
Fish oil	**Not recommended**	**Needed Promising intervention**
Zinc	**Not recommended**	**Needed Promising intervention**

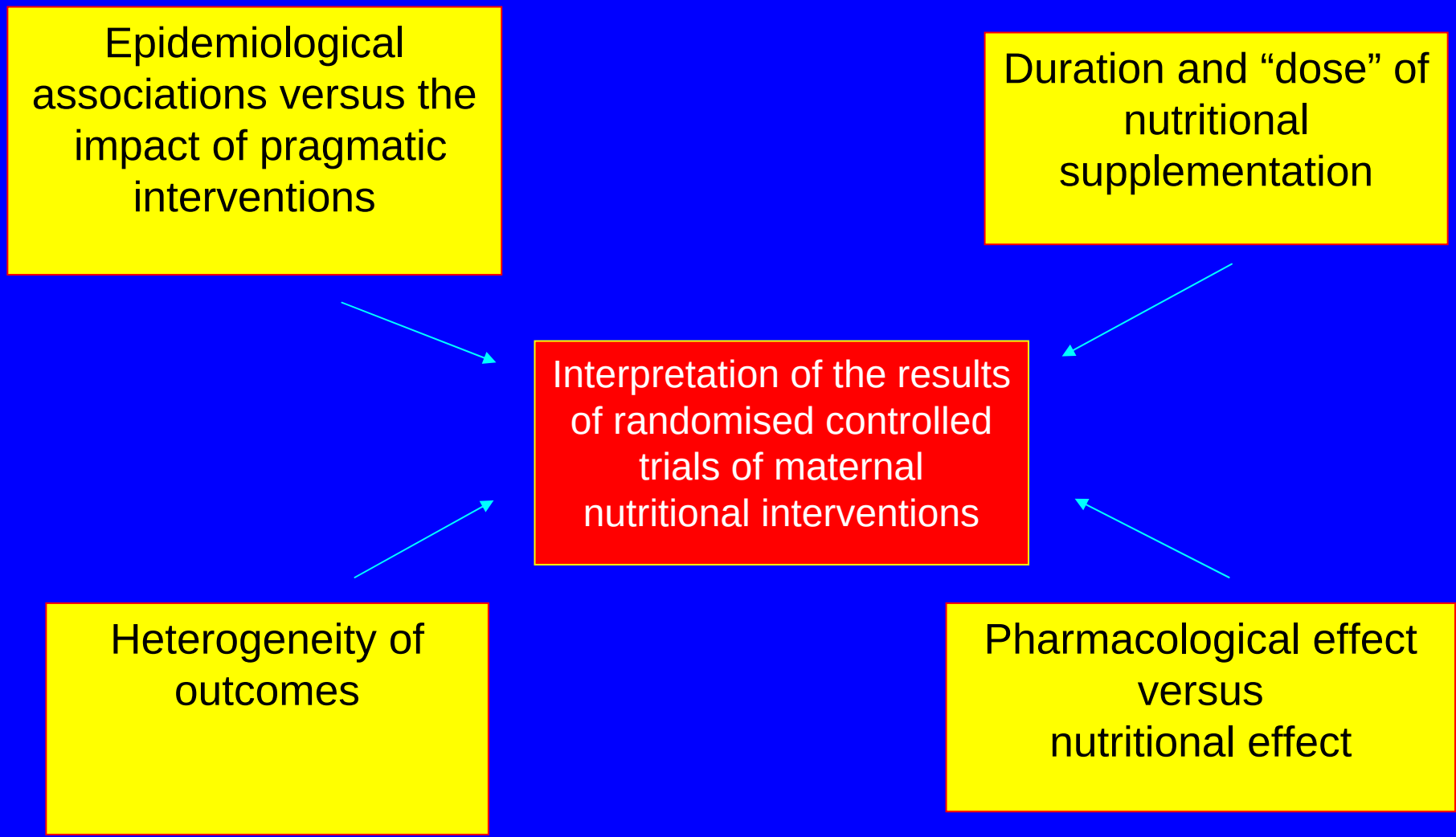
Summary

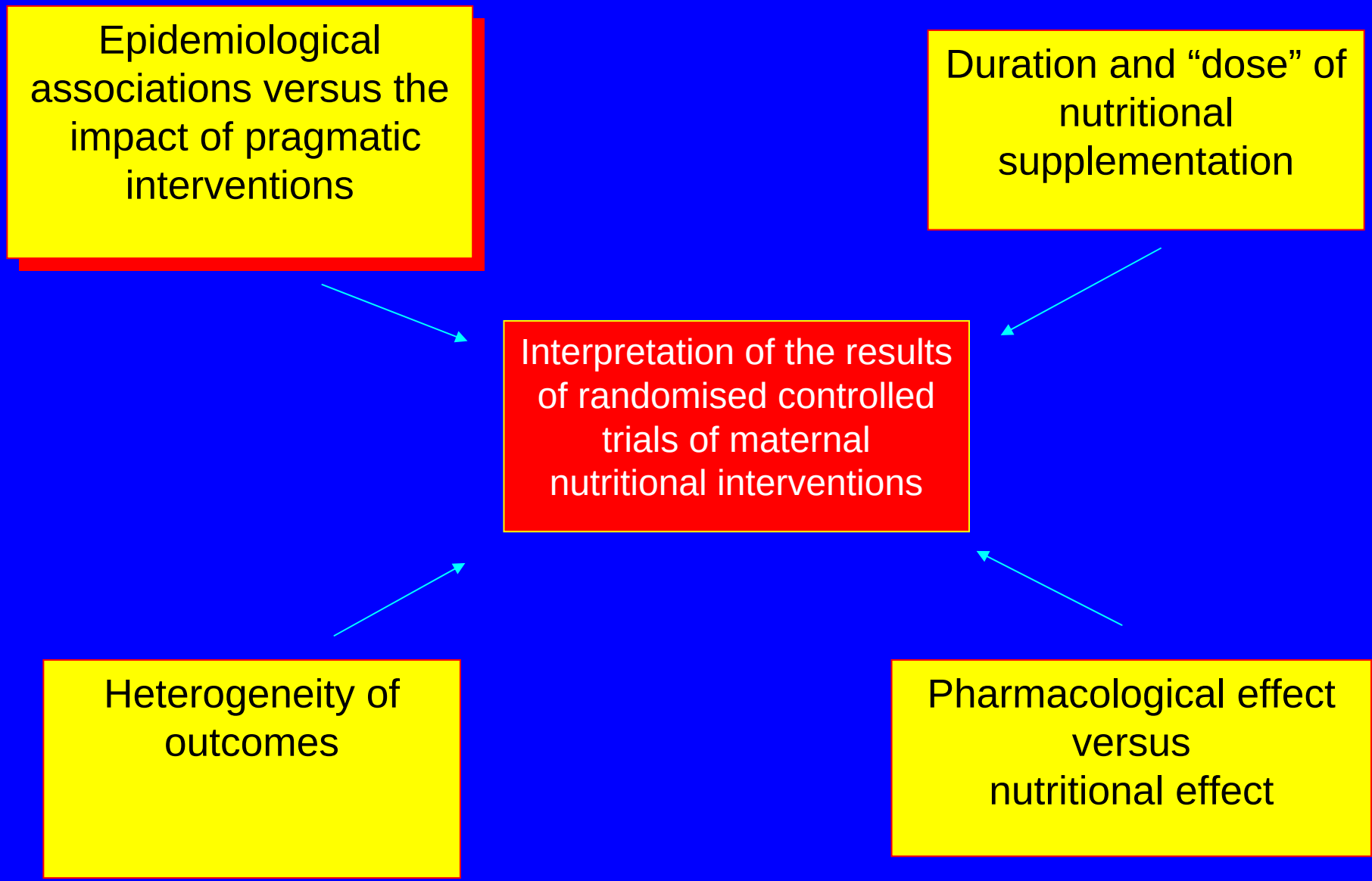
- Limited evidence supports the implementation of large scale nutritional interventions (multivitamins, mineral and protein energy supplementation) to prevent hypertensive disorders of pregnancy, obstructed labor, hemorrhage, infection and preterm delivery

Promising intervention

- Beta carotene for maternal mortality
- Calcium for pre-eclampsia (high risk, low intake women)
- Antioxidants for preeclampsia
- Magnesium and fish oil for preterm delivery
- Iron and folate are recommended to prevent and treat anemia

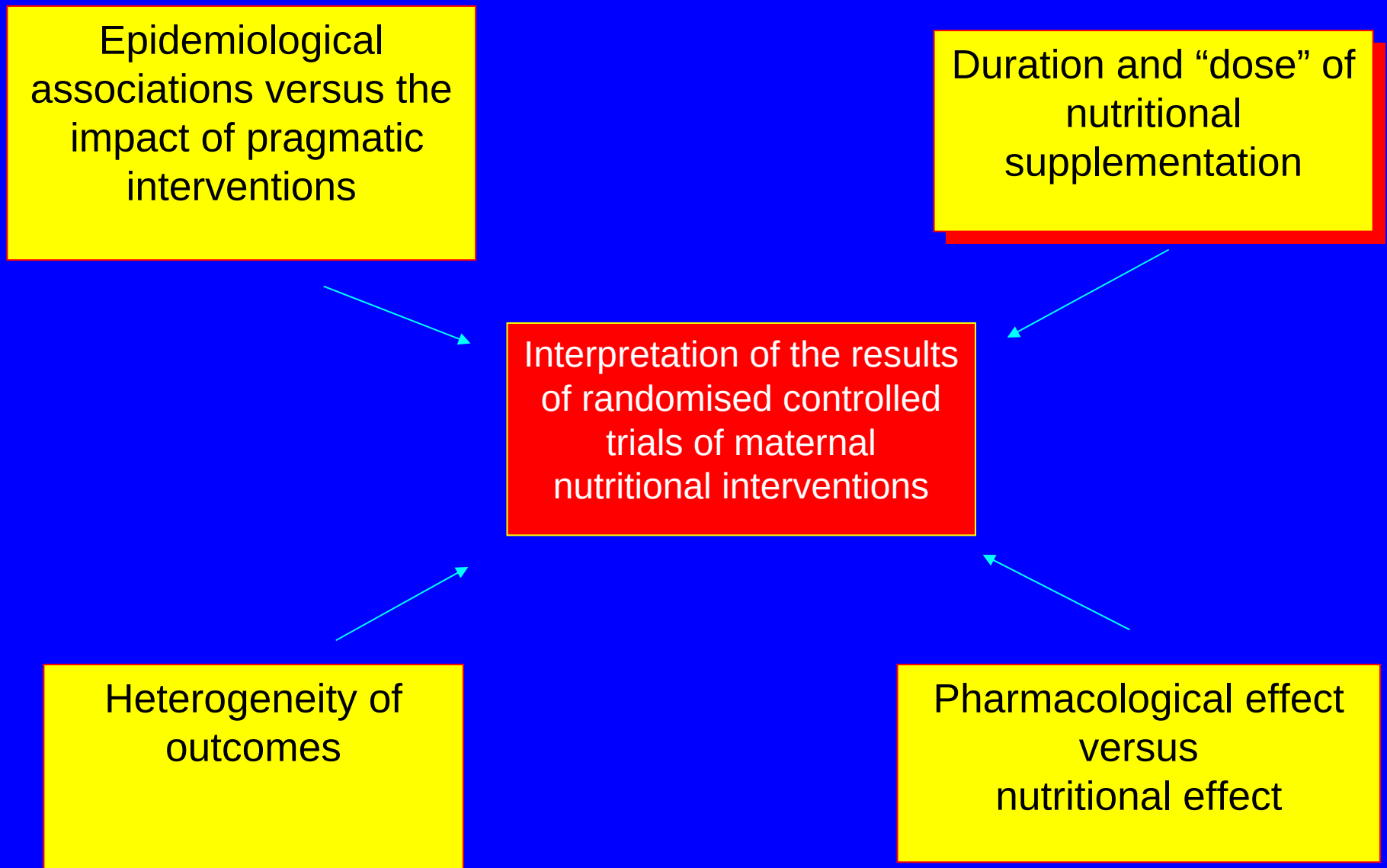
Conceptual framework for the interpretation of results




Epidemiological associations versus the impact of pragmatic interventions
Duration and “dose” of nutritional supplementation
Interpretation of the results of randomised controlled trials of maternal nutritional interventions
Heterogeneity of outcomes
Pharmacological effect versus nutritional effect

Epidemiological association vs. effectiveness of pragmatic interventions

- Results from observational studies or uncontrolled observations are likely to be confounded by the effect of population characteristics
- Women from disadvantaged populations are more at risk for nutritional deficiencies as well as for pregnancy complications
- Intervention groups may be better off and have better outcomes


Epidemiological associations versus the impact of pragmatic interventions
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Heterogeneity of outcomes
Pharmacological effect versus nutritional effect

Length and amount of nutritional supplementation

- It is unrealistic to assume that chronic undernutrition during two or three decades of life will be overcome, in terms of reproductive performance with only a few months of extra nutrient intake

Epidemiological associations versus the impact of pragmatic interventions

Duration and “dose” of nutritional supplementation

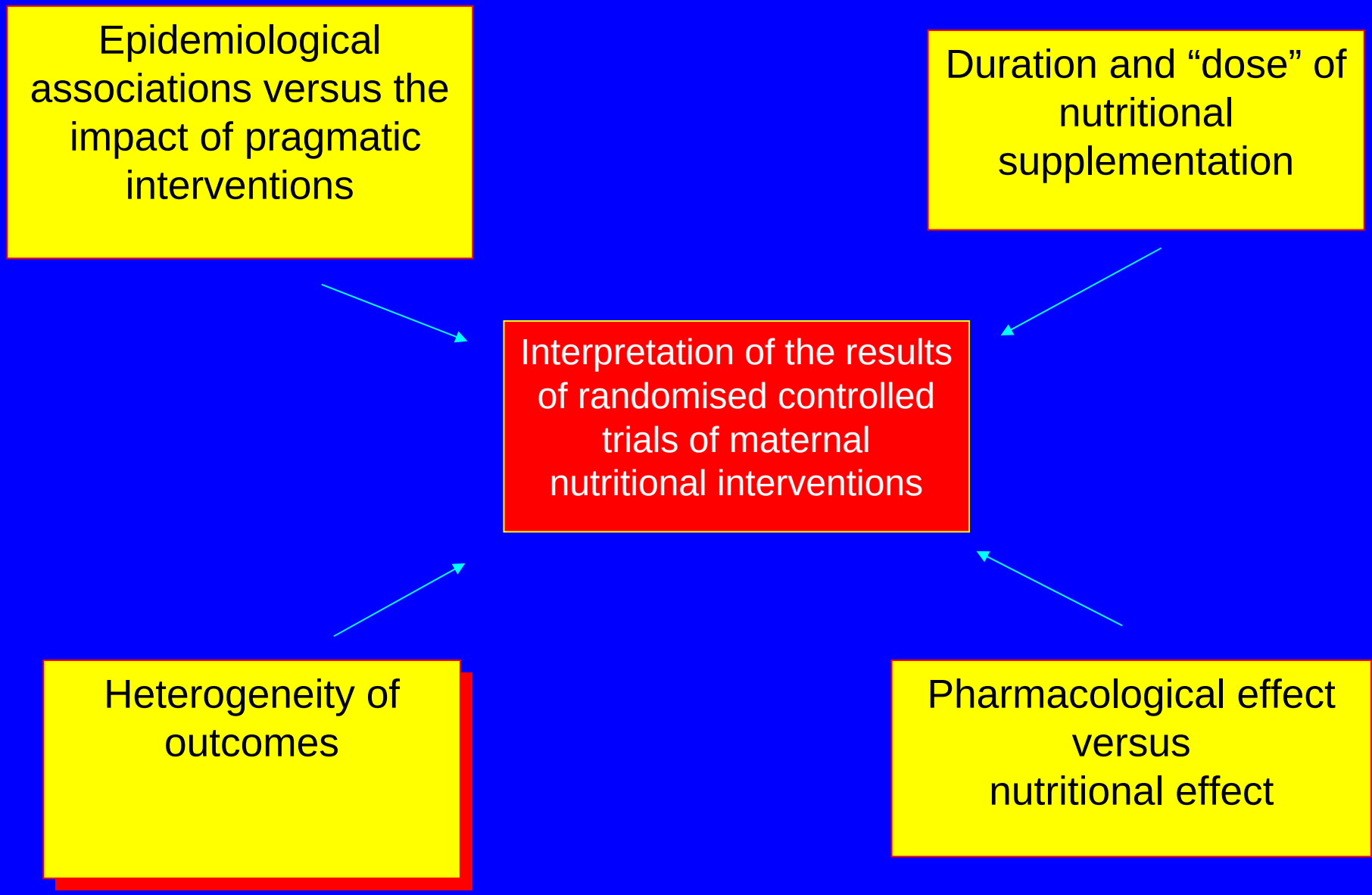
Interpretation of the results of randomised controlled trials of maternal nutritional interventions

Heterogeneity of outcomes

Pharmacological effect versus nutritional effect

Pharmacological vs. Nutritional effect

- Nutrients can be provided to population with dietary deficiency (nutritional effect) or to population with adequate intake (pharmacological effect)
- Calcium supplementation for the prevention of preeclampsia seems to be effective in low calcium intake women but not in adequate calcium intake women.


Epidemiological associations versus the impact of pragmatic interventions
Duration and “dose” of nutritional supplementation
Interpretation of the results of randomised controlled trials of maternal nutritional interventions
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Heterogeneity of outcomes

- Complications such as haemorrhage, pre-eclampsia, obstructed labour, infection, preterm delivery may include conditions with different aetiologies.
- These outcomes may be too comprehensive to be significantly affected by a single nutritional intervention
- Need to better determine the different aetiologies

Further research

- Extend the duration of nutritional supplementation interventions and follow up
- Identify new outcomes and evaluate their biological and clinical relevance
- Evaluate combinations of interventions
- Develop mechanistic hypotheses
- Better determine the causes of the outcomes studied

SELECTION CRITERIA

- Any systematic review or randomised controlled trial of a nutritional intervention during pregnancy

Investigaciones futuras

- Extender la duración de los suplementos (periconcepcional)
- Identificar nuevos outcomes mas especificos que el bajo peso al nacer
- Evaluar el efecto de combinaciones de intervenciones
- Desarrollar hipótesis sobre los mecanismos
- Seguimiento de los niños

SYSTEMATIC REVIEWS/TRIALS EXCLUDED

- Interventions to stop labour
- Interventions to prolong pregnancy after preterm labour
- Interventions that were not exclusively nutritional (ANC packages, social support)

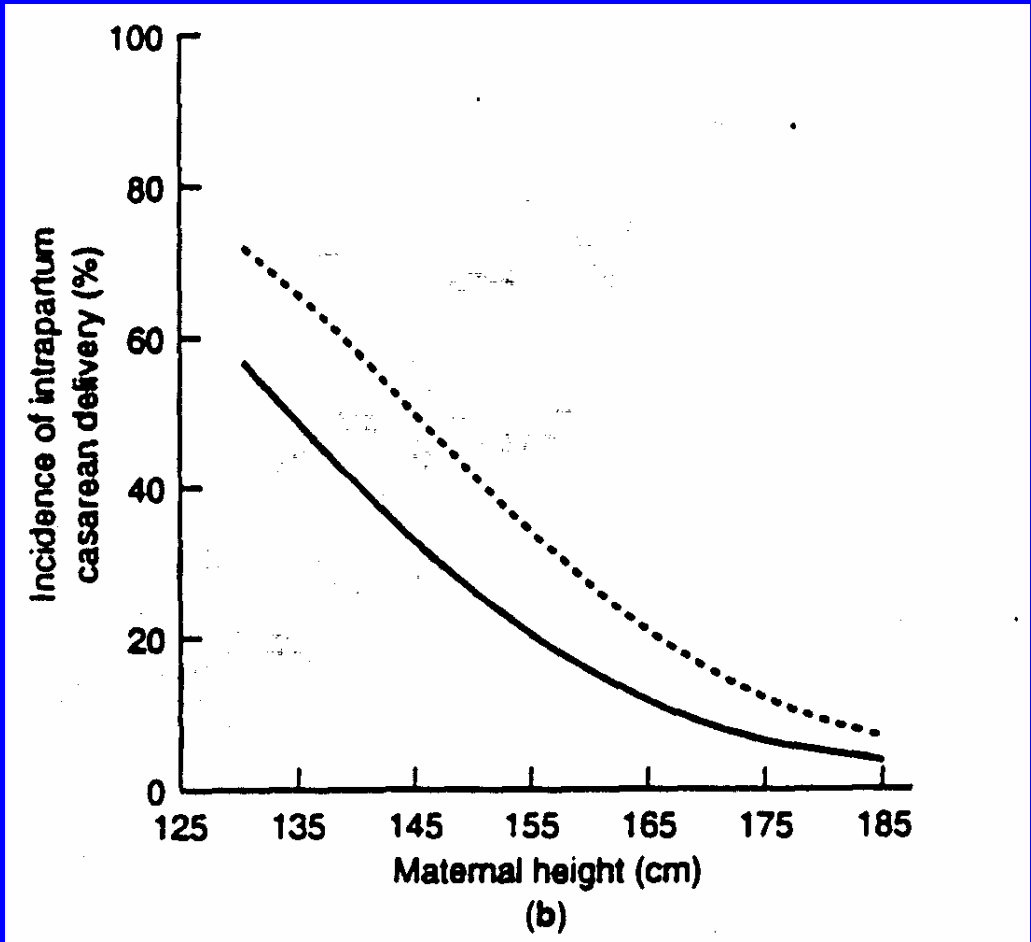
SEARCH STRATEGY

- Cochrane Database of Systematic Reviews up to issue 2, April 2002 (The Cochrane Library)
- For reviews not updated, the Cochrane Controlled Trials Register (CCTR) and Medline were searched up to July 2002.
- Trials identified were considered independently.

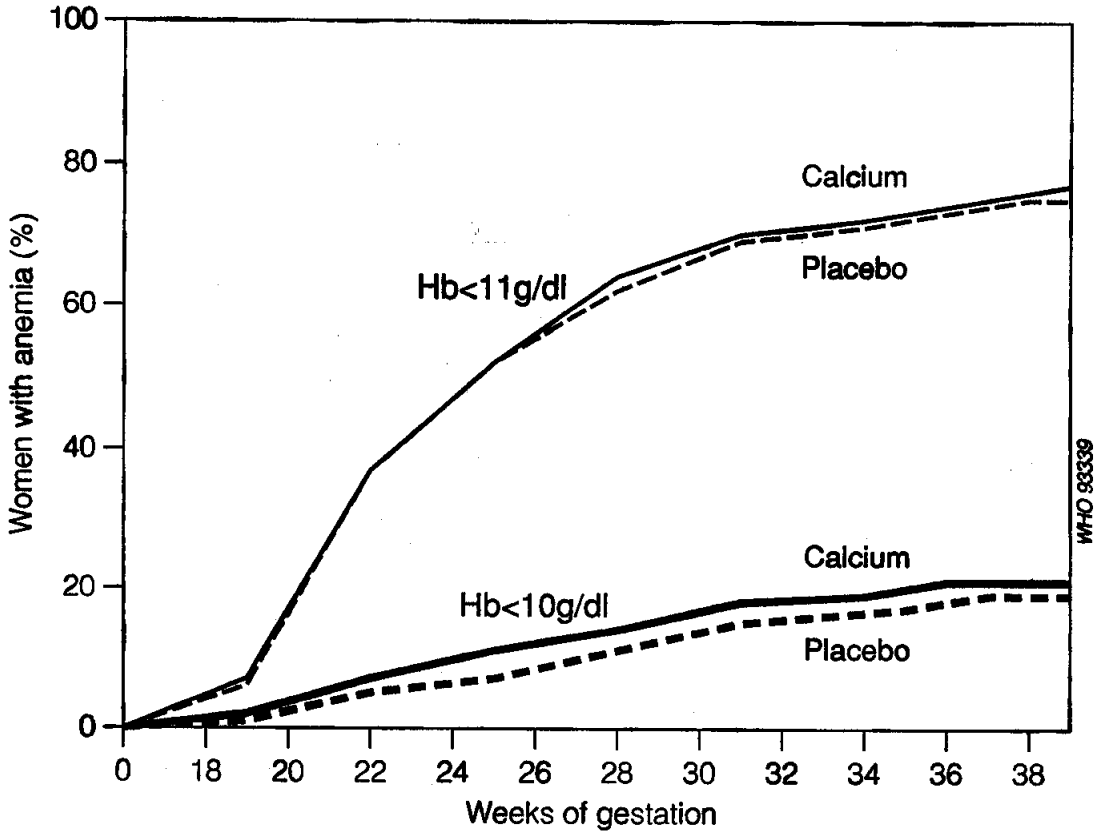
SEARCH STRATEGY

- Database of Abstracts of Reviews of Effectiveness (DARE)
- Electronic search of the CCTR for nutritional interventions which have not been reviewed
- Authors of the systematic reviews and trials

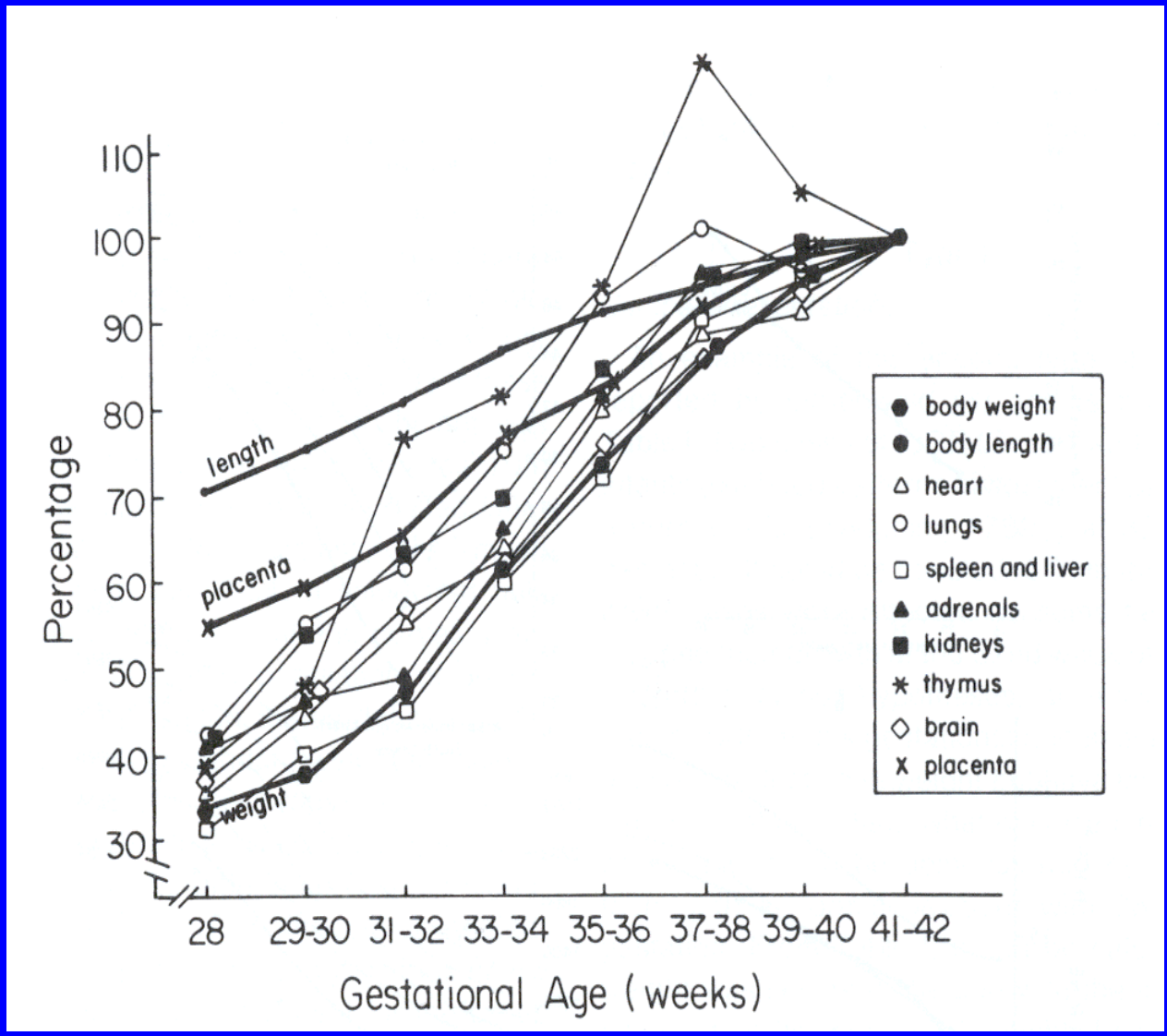
CAESAREAN SECTION AND MATERNAL HEIGHT



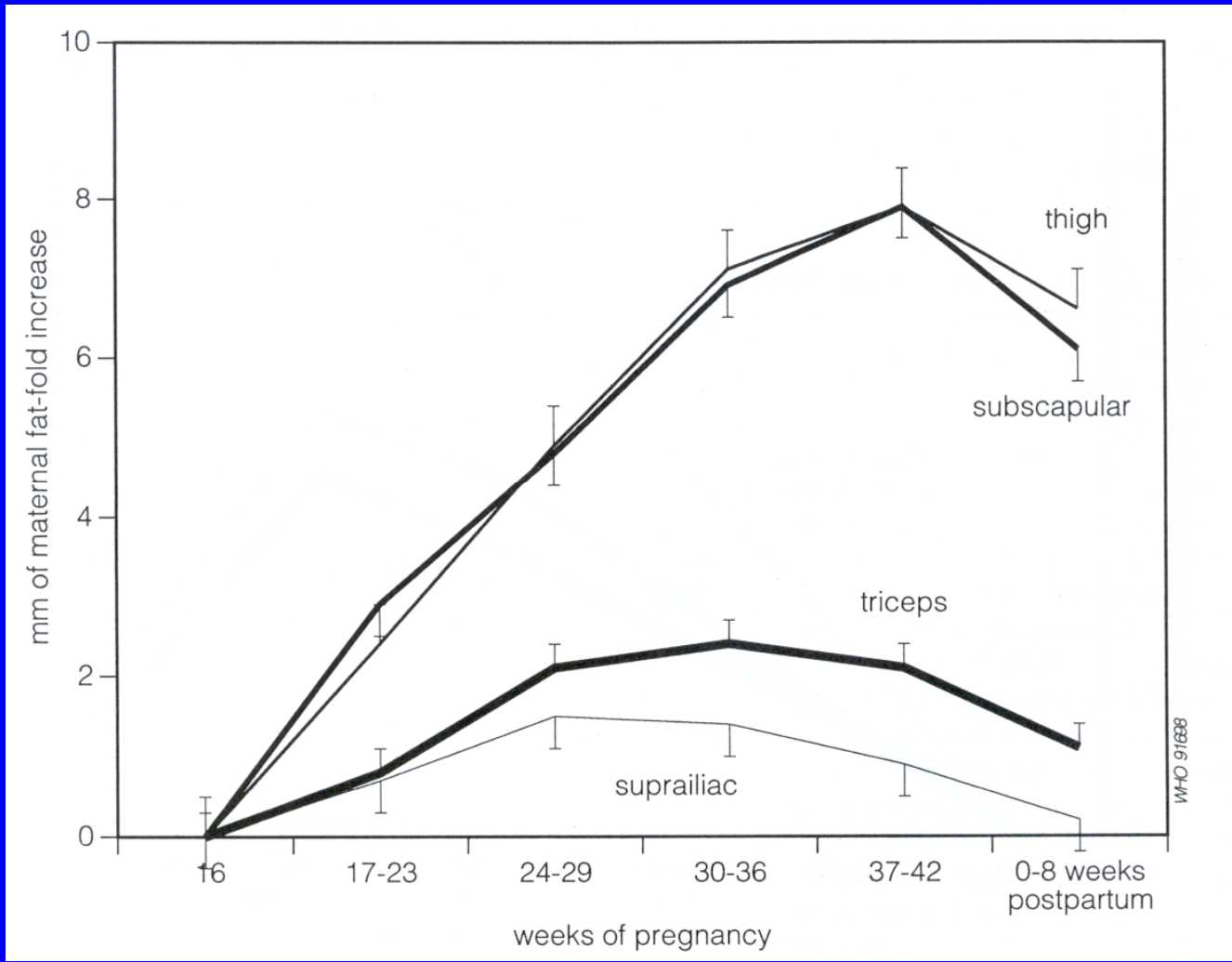
Nulliparous women with (……) or without (_____) perinatal distress .BJOG 2001



Percentage of women in the calcium and placebo groups in whom hemoglobin values were < 10g/dl or < 11g/dl



Percentage of placental and organ weight of the total weight at term by week of gestation



Absolute changes in skin-fold thickness during pregnancy and post partum

Pregnancy and Childbirth Trials in the *Cochrane Library, 2000*

	N = 9014	%
PPH	45	0.5
Pre-eclampsia	156	1.7
IUGR/SGA	111	1.2
Pre-term delivery	1203	13.3

Global Programme to Conquer Preeclampsia / Eclampsia

Department of Reproductive Health and Research,
World Health Organization and the Global Preeclampsia/
Eclampsia Collaboration

2002

NEW FISH OIL TRIALS: HYPERTENSION

	INTERVENTION	Total Women	RR 95%CI
Salvig 1996	Fish oil vs. no treatment	397	1.97 (0.42 - 9.14)
Bulstra-Ramakes 1994	Fish oil vs. placebo	63	1.66 (0.75 - 3.66)
Onwude 1995	Fish oil vs. placebo	232	1.14 (0.78 - 1.67)
Olsen 2000 (EARL-PIH trial)	Fish oil vs. olive oil in women with previous PIH	350	0.99 (0.73 - 1.33)

MATERNAL INFECTION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Zinc	**1 (7)**	**487**	**1.22 (0.79 – 1.90)**

OBSTRUCTED LABOUR/CAESAREAN SECTION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Calcium (low risk)	**4 (6)**	**6080**	**0.94 (0.84 – 1.06)**
Calcium (high risk)	**2 (5)**	**252**	**0.77 (0.43 – 1.37)**
Calcium (adequate intake)	**3 (4)**	**4981**	**0.95 (0.84 - 1.07)**
Calcium (low intake)	**3 (6)**	**1351**	**0.86 (0.64 – 1.18)**

DURATION OF LABOUR

	Trials with outcome reported (trials in systematic review)	Total women	Mean difference (hours) 95%CI
Balanced energy/ protein	**1 (6)**	**345**	**-0.1 (-1.20 – 0.90)**
Magnesium	**1 (7)**	**568**	**0 (0.52 – 0.97)**

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: HYPERTENSION

Nutrient	Practice	Research
Energy protein restriction	**Not recommended**	**Not needed**
Salt restriction	**Not recommended**	**Not needed**
Calcium	**Not recommended**	**RCT in progress** Possibly beneficial for women at high risk RR=0.45 (0.31-0.66) and with low baseline intake RR= 0.49 (0.38-0.62)
Folate	**Not recommended**	**Not needed**

EFFECTIVENESS OF NUTRITIONAL INTERVENTIONS: HYPERTENSION

	Practice	Research
Iron and folate	Not recommended	Not needed
Fish oil	Not recommended	Not needed
Zinc	Not recommended	Not needed
Vitamins E and C	Not recommended	Not needed (RCT in different populations)
Multinutrients	Data not available yet	RCT completed

OVERVIEW

- Epidemiological associations versus impact of pragmatic interventions
- Timing of the “insult” and different fetal organ growth patterns
- Timing and location of nutrient deposition in the mother and fetal growth

OVERVIEW

- Duration and “dose”of supplementation
- Pharmacological versus nutritional effect
- Intervention specific outcomes versus overall mortality/birth weight outcomes
- Heterogeneity of outcomes and their causes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HYPERTENSION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Energy/protein restriction	3 (3)	384	0.97 (0.75 - 1.26)
Salt restriction	2 (1)	242	0.97 (0.49 - 1.94)

HYPERTENSION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Calcium (low risk)	6 (6)	6307	0.84 (0.76 – 0.92)
Calcium (high risk)	5 (5)	587	0.21 (0.11 – 0.39)
Calcium (adequate intake)	4 (4)	5022	0.86 (0.71 - 1.05)
Calcium (low intake)	6 (6)	1842	0.32 (0.21 – 0.49)

HYPERTENSION

	Trials with outcome reported (trials in systematic review)	Total women	RR 95%CI
Iron and folate	2 (8)	87	1.15 (0.41 – 3.81)
Folate	2 (21)	696	1.26 (0.90 – 1.76)
Fish Oil*	2 (2)	5108	0.96 (0.86 - 1.07)
Zinc*	4 (7)	1962	0.87 (0.65 – 1.15)
Vitamins E and C	1 (-)	283	1.24 (0.62 – 2.48)