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

OVERVIEW OF RANDOMISED CONTROLLED TRIALS

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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 intervention 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)

Calcium trial: Preeclampsia and related complications according to treatment group

Condition	Calcium (4151)	Placebo (4161)	RR (95% CI)
Preeclampsia	4.12	4.47	0.92 (0.75 – 1.13)
Severe preeclampsia	0.84	1.13	0.75 (0.48 – 1.15)
Early onset preeclampsia (< 32 weeks)	0.46	0.53	0.86 (0.47 – 1.60)
Eclampsia	0.41	0.60	0.68 (0.37 – 1.26)
Placental abruption	0.41	0.53	0.77 (0.41 – 1.46)
Gestational hypertension	10.65	11.03	0.96 (0.85 – 1.09)
Severe gestational hypertension (≥ 160 and/or 110 mmhg)	1.03	1.42	0.73 (0.49 – 1.08)
Gestational proteinuria (no hypertension)	4.84	4.66	1.04 (0.86 – 1.26)
Severe preeclamptic complications*	2.75	3.51	0.78 (0.61 – 1.00)

Any of the following: Severe preeclampsia, early onset preeclampsia, eclampsia, placental abruption, HELLP syndrome, or severe gestational hypertension.

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

Calcium trial: Incidence of neonatal outcomes according to treatment group

Condition	Calcium (4008)	Placebo (4006)	RR (95% CI)
Preterm delivery (< 37 weeks)	9.60	10.28	0.93 (0.82-1.06)
Spontaneous preterm delivery	6.96	7.16	0.97 (0.83-1.14)
Medically indicated preterm delivery	2.64	3.12	0.85 (0.66-1.09)
Early preterm delivery (<32 weeks)	2.57	2.99	0.86 (0.66-1.11)
Low birth weight	13.03	13.31	0.98 (0.87-1.10)
NICU ≥ 7 days*	2.88	3.10	0.92 (0.72-1.19)

*N (3953, 3956)

Perinatal and maternal mortality rates and maternal admission to ICU according to treatment group

	Calcium (4181)	Placebo (4197)	RR (95% CI)
Stillbirth (x 1000 births)	25.11	26.92	0.93 (0.72-1.21)
Neonatal mortality (x 1000 live births)*	9.36	13.40	0.70 (0.46-1.06)
Perinatal mortality (x 1000 births)	33.96	39.55	0.86 (0.69-1.07)
Maternal admission to ICU	2.79	3.31	0.84 (0.66-1.07)
Maternal mortality (x 100.000 women)**	24.09	144.20	0.17 (0.02-1.39)

*N (3953, 3965)

**N (4151, 4161)

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**

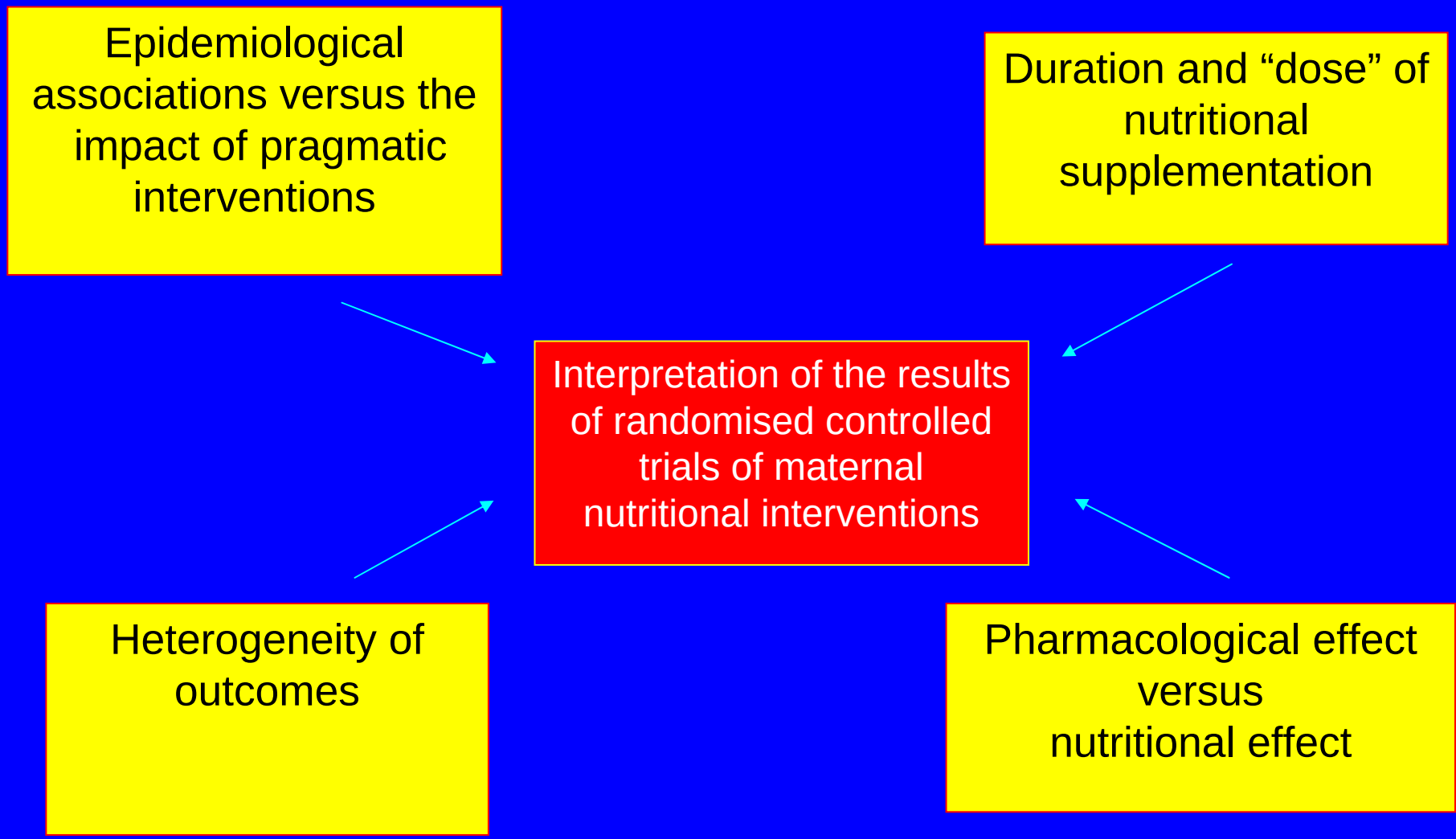
Summary

- 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

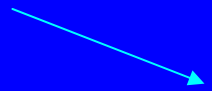
Promising intervention

- 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



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

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

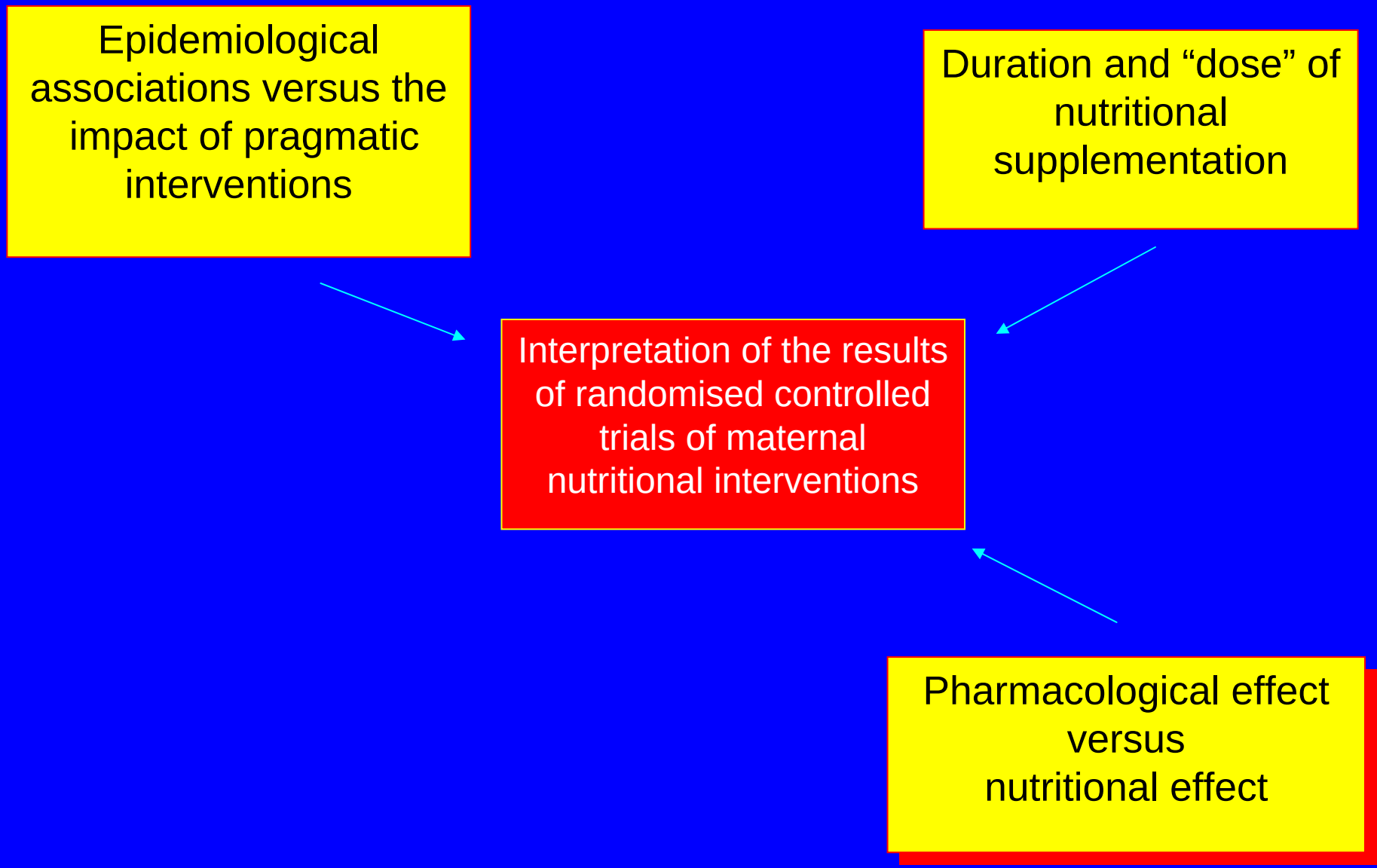
Epidemiological associations versus the impact of pragmatic interventions

Duration and “dose” of nutritional supplementation

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

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
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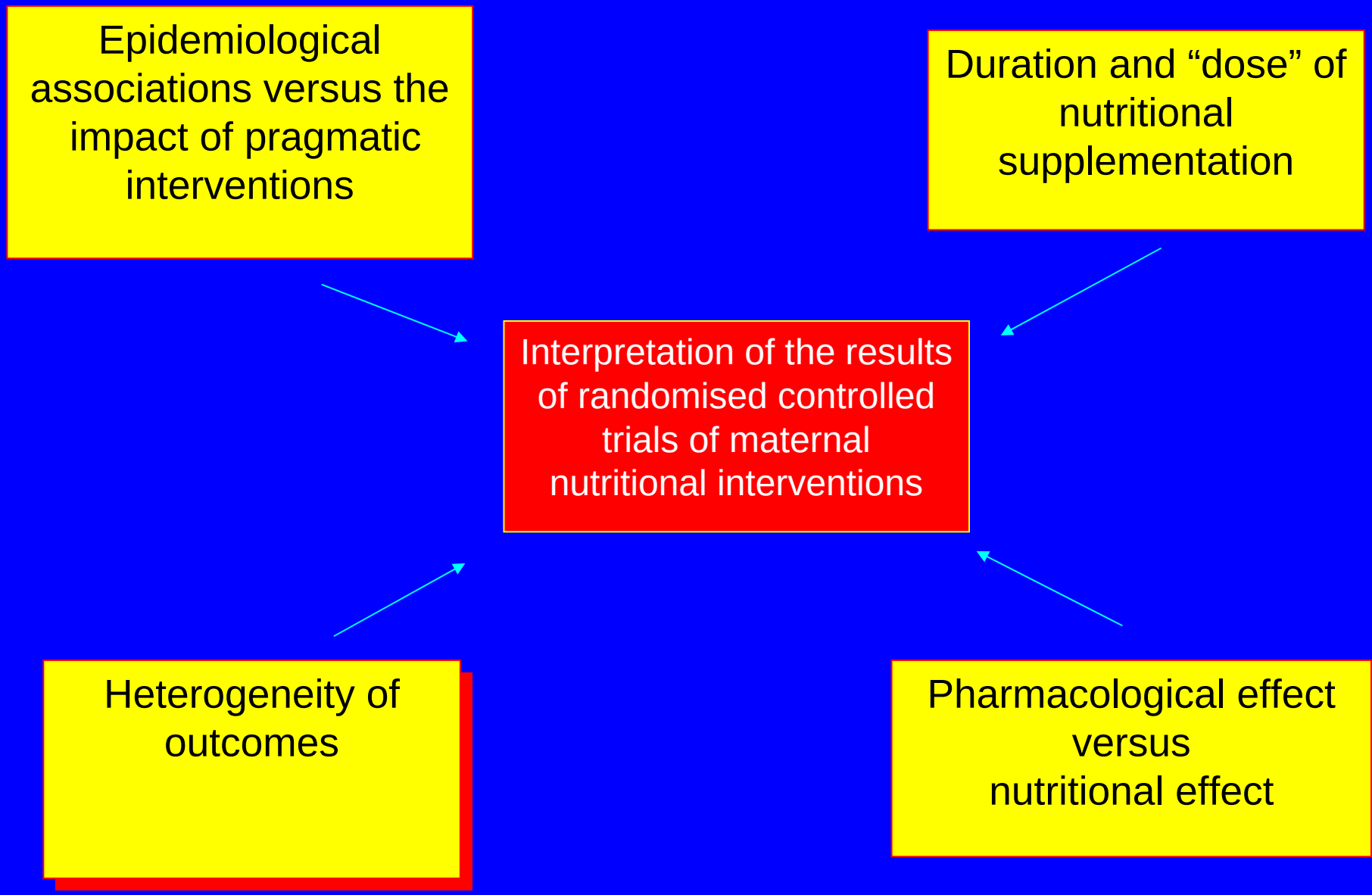
Pharmacological effect versus nutritional effect

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
Heterogeneity of outcomes
Pharmacological effect versus nutritional effect

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