Impaired fetal growth

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Public Health importance

Impaired fetal growth is:

- prevalent in developing countries
- is associated with short and long term negative outcome in fetuses, infants and children
- may be associated with development of disease in adult life

Today's approach

- Pathophysiology of impaired fetal growth
- Assessment of impaired fetal growth
- Prevalence in different countries
- Consequences for health
- Interventions to prevent impaired fetal growth
- Further research

Characteristics of the fetus with IUGR

- Asymmetry in the dimensions of head and abdomen
- Reduced amniotic fluid
- Small placenta

Pathophysiology of impaired fetal growth

Placental insufficiency:

- Reduced transfer of nutrients
- Fetal hypoperfusion

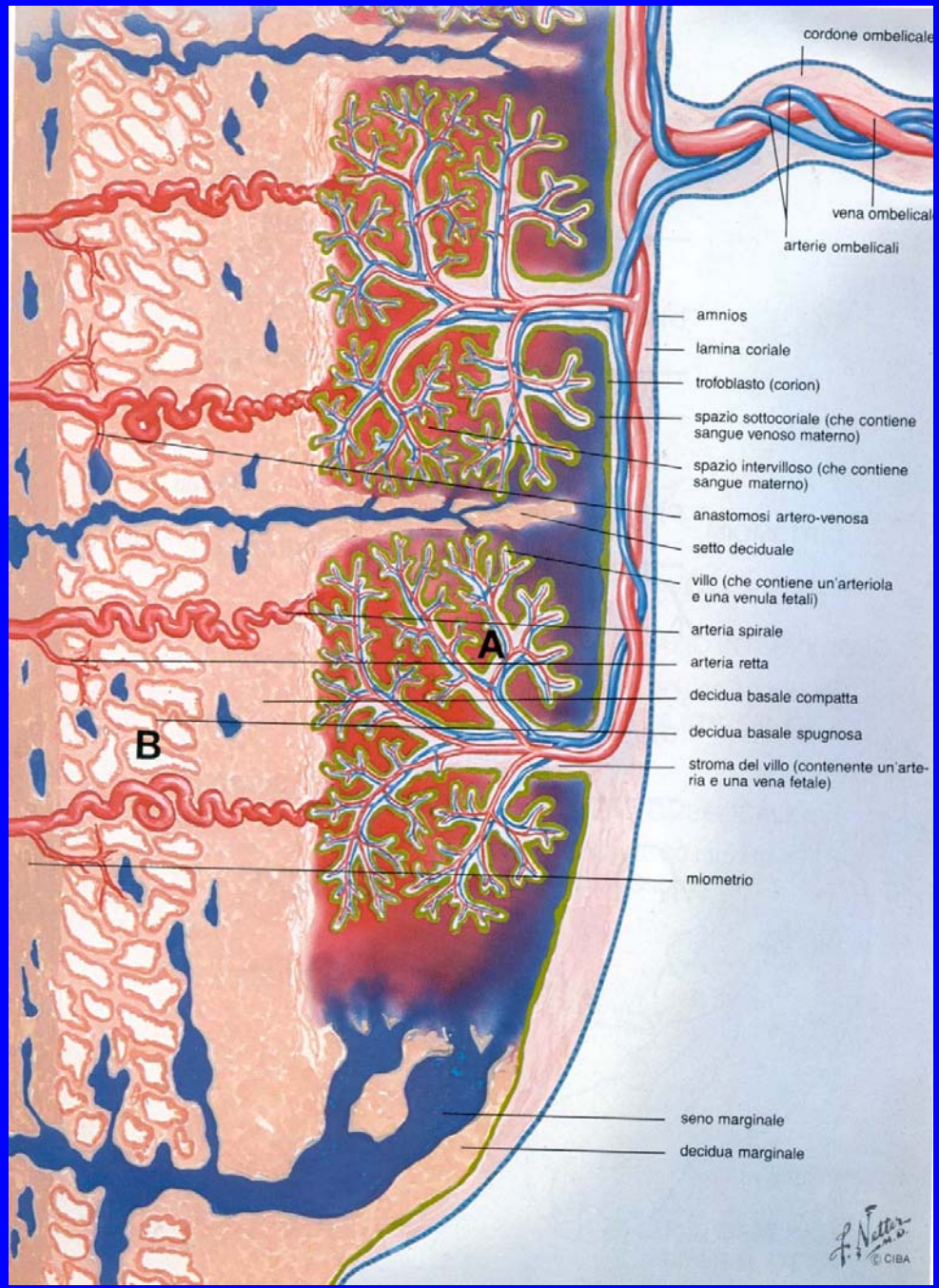
Reduced transfer of nutrients

- Abnormalities of the placenta lead to increased resistance of blood flow in the placenta
- Increased resistance determines a reduction of flow through the placenta
- the fetus reacts to a condition of limited supply of nutrients and oxygen by vascular redistribution that spares vital organs (brain, myocardium, adrenal glands).

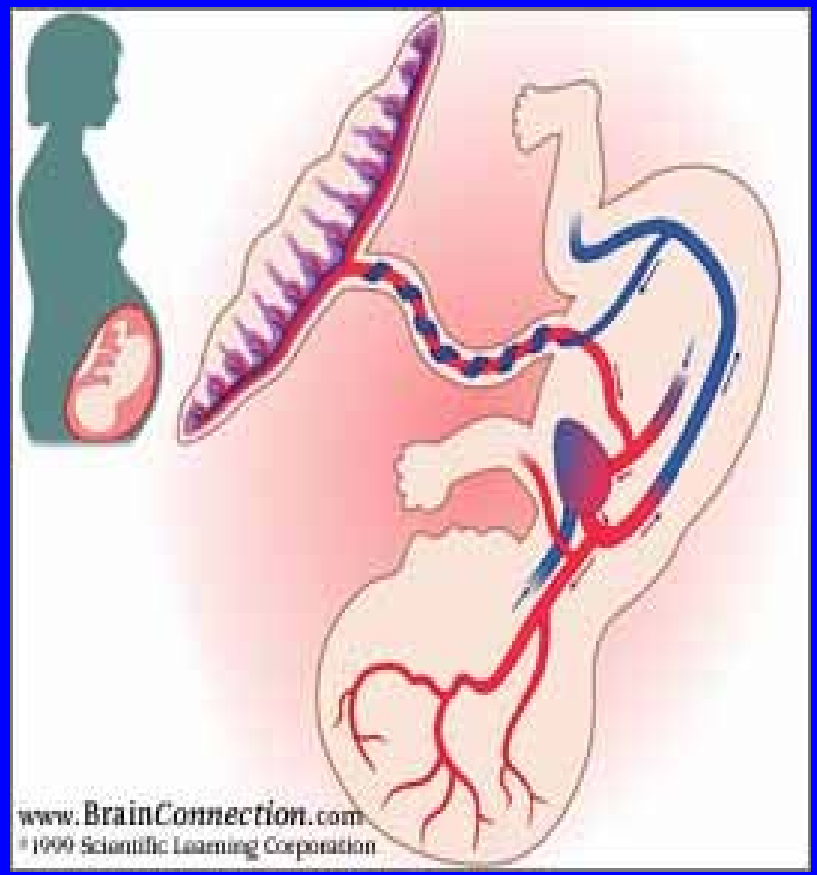
Fetal hypoperfusion

Poiseuille's law (1797-1869)

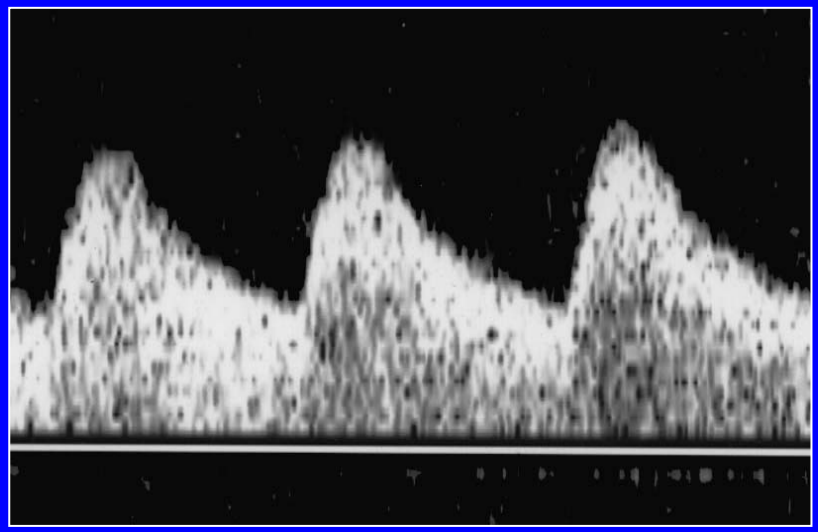
- When blood passes from a large vessel to a bed of small vessels it encounters a resistance which is inversely proportional to the sum of the diameters of the small vessels.

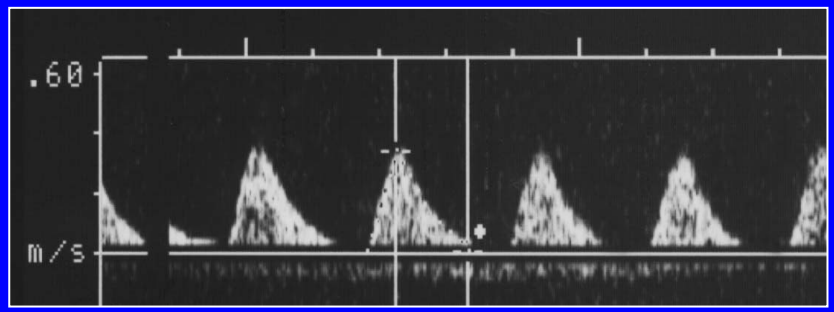


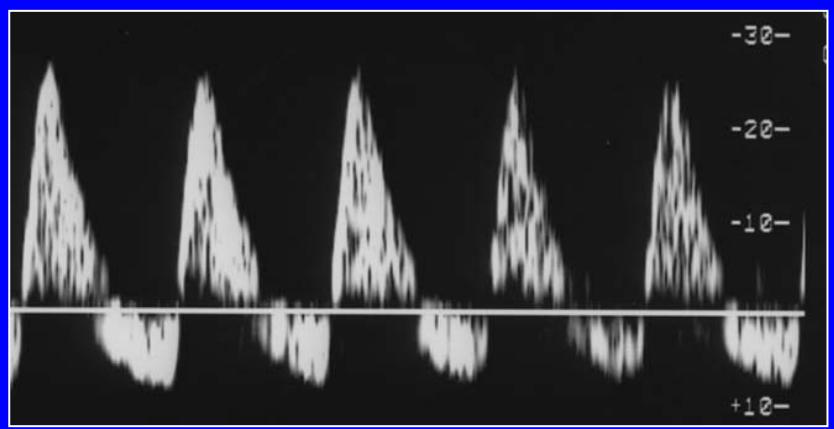
- When the number of capillaries in the placenta is reduced, fetal blood will encounter more resistance in passing from the arterial to the venous capillaries.



- To compensate for the increase in resistance in the capillary bed the fetus will produce a vasoconstriction in the arteries of the splanchnic, pulmonary and peripheral circulation in order to increase the perfusion pressure in the aorta and umbilical arteries







- Mechanisms of compensation work until a certain point when it becomes impossible to overcome the the increased resistance in the umbilical circulation. Doppler sonography shows that flow in the umbilical arteries during diastole becomes absent or it is reversed.

Consequences of IUGR

- Higher perinatal morbidity and mortality
- Higher infant mortality and childhood morbidity
- Poor cognitive development and neurologic impairment
- Increased risk in adulthood of cardiovascular disease, high blood pressure, obstructive lung disease, diabetes, high cholesterol and renal damage.

Assessment of fetal growth

- Retrospective assessment using anthropometric measures of size at birth (birth weight)
- Prospective assessment by serial clinical evaluations (uterine height, ultrasound measurements of fetal anatomical parameters)

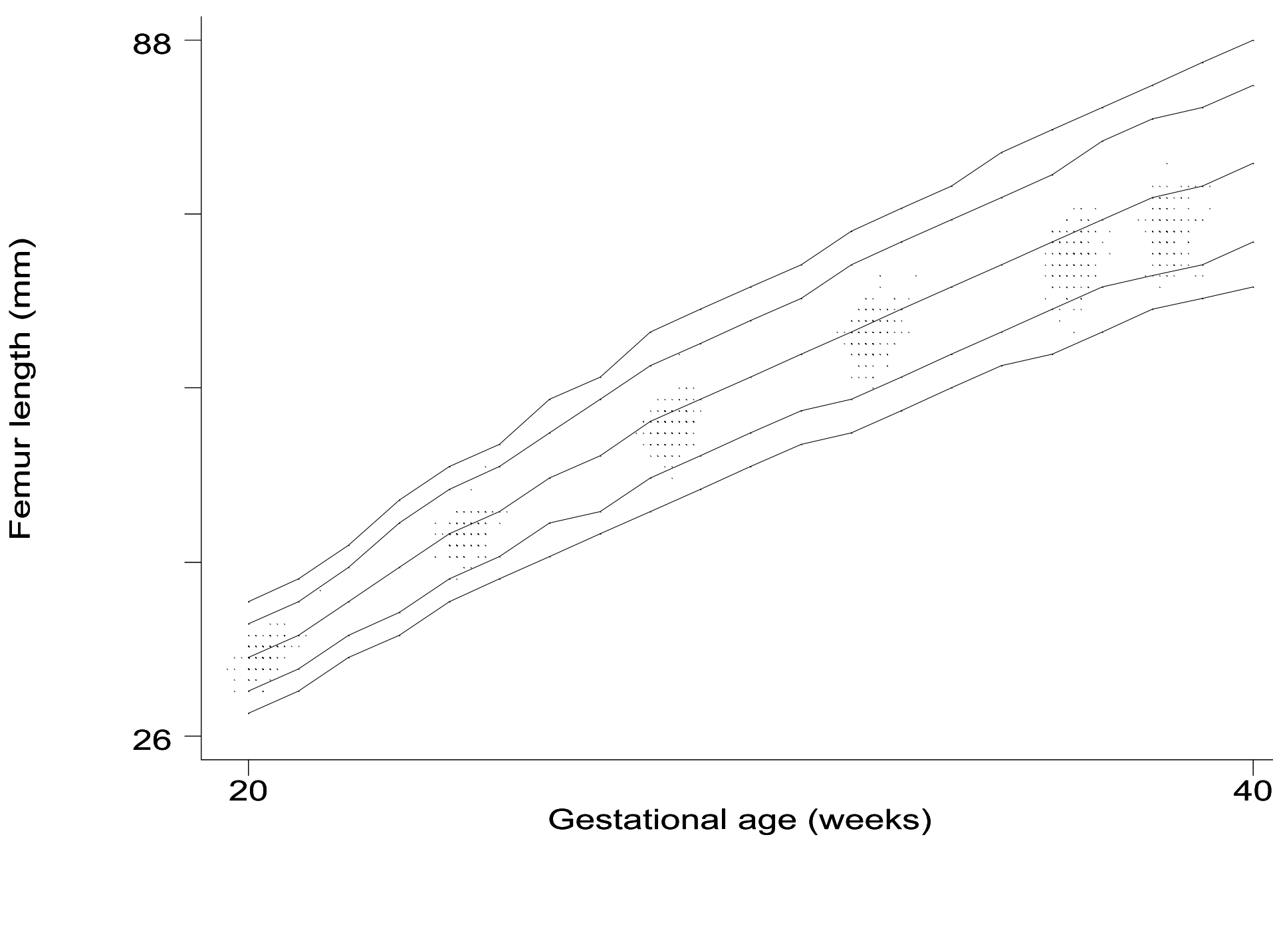
Reference data based on birth weight

The method is relatively easy to implement but has limitations:

- the cross sectional approach (data collected at birth from infants of different ages) may not reflect the longitudinal growth of fetuses of the same ages
- inaccuracies of estimation of gestational age at delivery affect interpretation
- pathological processes that could affect the size of infants born early in gestation

Ultrasound measurements

- Large coefficient of variation associated with estimations of fetal weight
- Margin of error in measuring individual anatomical parameters is contained
- Allow for both cross sectional and longitudinal assessment (Individualized Growth Assessment)


88
26
Femur length (mm)
20
40
Gestational age (weeks)

Classification of fetal growth based on birth weight

- Low birth weight: < 2500 grams (does not differentiate between infants born small at term or infants small because they are preterm)
- Small for gestational age: birth weight below the the 10th percentile for a given gestational age (may erroneously categorize some normal growth newborns as growth impaired).

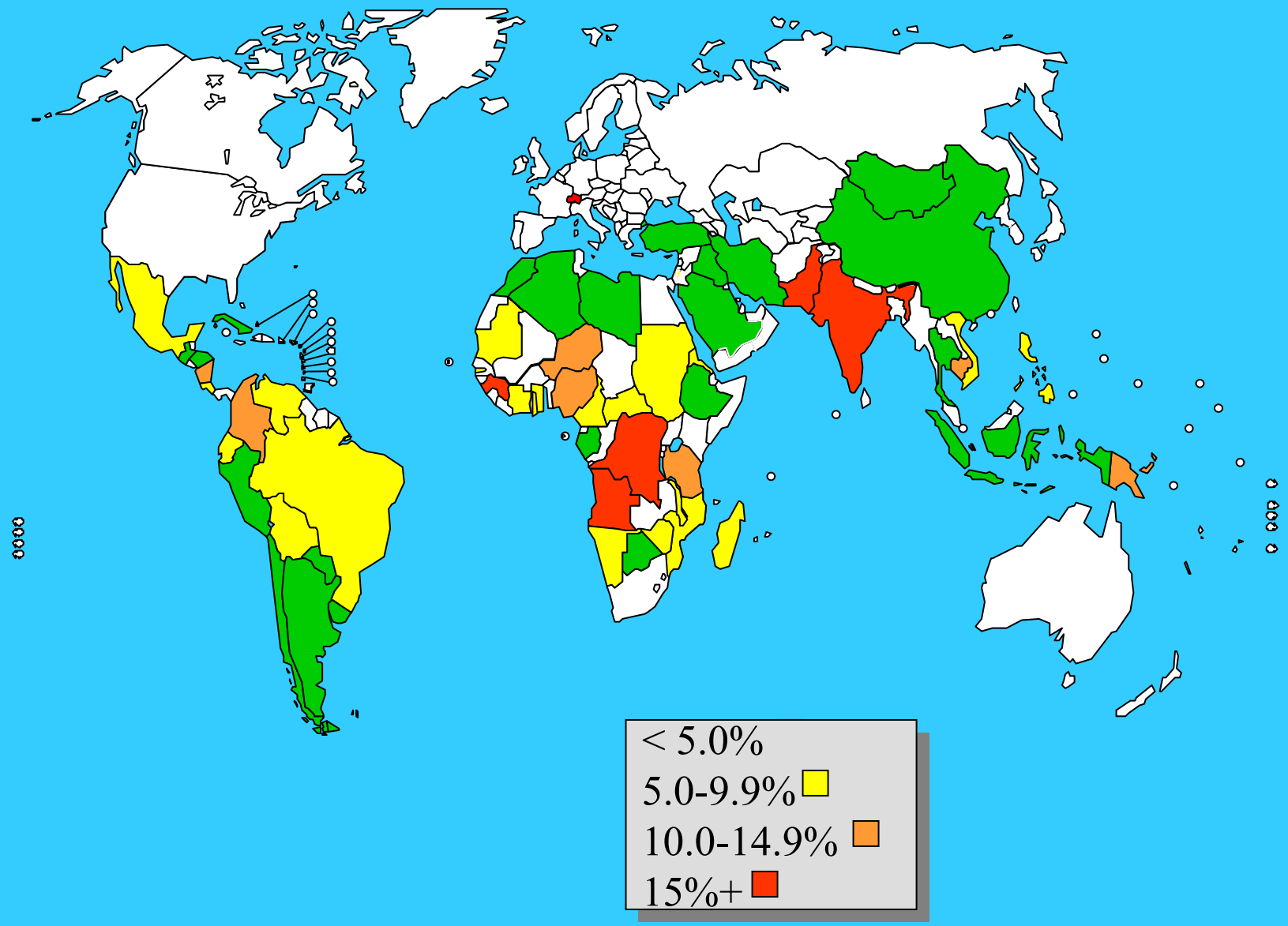
Internationally recommended cut-off levels for triggering public health action

- IUGR > 20%
- LBW > 15%

Estimates of impaired fetal growth in developing countries

Indicator	Source	%	Estimated total number of newborns affected per year
IUGR-LBW (<2500 g; >= 37 wks)	LBW rates from WHO data bank (1992) and regression model (Villar, 1994)	11	13,699,000
LBW < 2500 g all gestaional ages	LBW rates from who data bank (1982)	16.4	20,423,000
IUGR < 10 percentile all gestational ages	WHO collaborative study on maternal anthropometry and pregnancy outcomes (1995)	23.8	29,639,000

Global estimates of IUGR-LBW in developing countries (1985-1995)



IUGR-LBW

- Estimates should be viewed as conservative
- 75% of all affected newborns are born in Asia
- Rates are 6 times larger than in developed countries
- we need to improve:

  - quality and availability of birth weight data

  - valid assessment of gestational age

Interventions to prevent or treat impaired fetal growth

- Most interventions aimed to prevent or treat impaired fetal growth do not show significant effects on short term perinatal outcomes

Care and advice during pregnancy

Intervention	# trials	Participants (E+C)	Outcome	OR (95% CI)
Continuity of caregivers	2	908+907	Term - LBW	0.94 (0.65, 1.36)
Social support for women at risk	8	3564 + 3477	Term - LBW	0.97 (0.84, 1.13)
Own case-notes	2	276 +276	Term - LBW	0.67 (0.35, 1.30)
Stop smoking	5	2950 + 2771	Term - LBW	0.80 (0.65, 0.98)
Nutritional advice	1	265 + 250	SGA	1.00 (0.48, 2.08)

Antimalarial chemoprophylaxis

Intervention	# trials	Participants (E+C)	Outcome	Mean difference (95% CI)
All parities	5	1453 + 1616	MBW	23g (-13, 59)
Multigravida	2	342 + 362	MBW	65g (4, 125)
Primigravida	4	295 + 340	MBW	112g (41, 183)

Nutritional interventions

Intervention	# trials	Participants (E+C)	Outcome	RR (95% CI)
Balanced protein energy	6	2147+2123	SGA	0.68 (0.57, 0.80)
Isocaloric balanced protein	1	391 + 391	SGA	1.35 (1.12, 1.61)
High protein	1	249 +256	SGA	1.58 (1.03, 2.51)
Salt restriction	1	110 + 132	SGA	1.50 (0.73, 3.07)
Salt restriction	1	184 + 177	LBW	0.84 (0.42, 1.67)

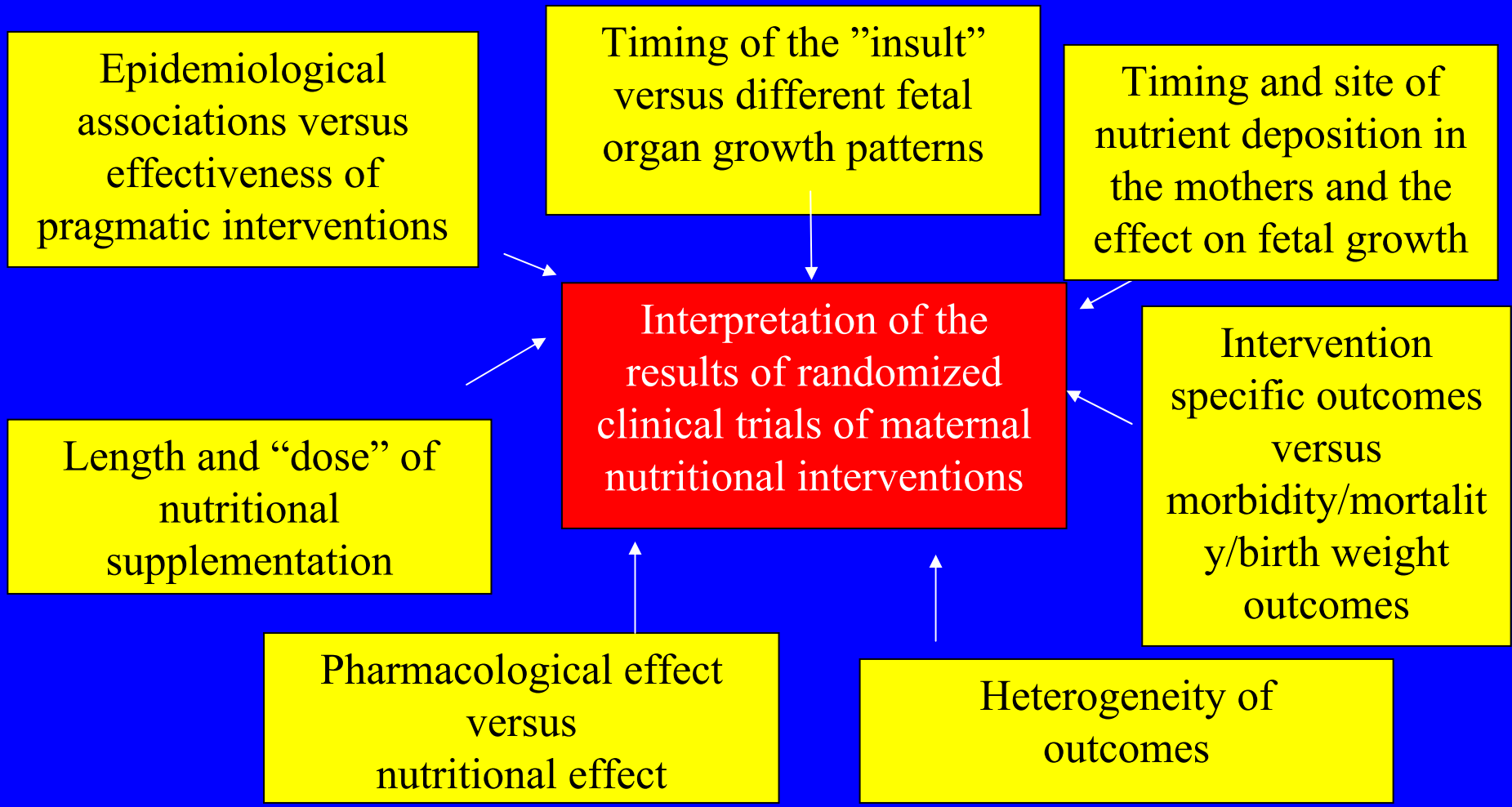
Nutritional interventions

Intervention	# trials	Participants (E+C)	Outcome	RR (95% CI)
Calcium	1	97 +93	SGA	0.72 (0.26, 1.99)
Calcium	7	3230 + 3261	LBW	0.83 (0.71, 0.98)
Folate	5	754 +734	LBW	0.75 (0.50, 1.12)
Iron selective vs. routine	1	50 + 50	SGA	1.60 (0.56, 4.56)

Nutritional interventions

Intervention	# trials	Participants (E+C)	Outcome	RR (95% CI)
Magnesium	3	865 + 876	SGA	0.70 (0.53, 0.93)
Magnesium	4	968 + 986	LBW	0.67 (0.46, 0.96)
Zinc	3	909 + 931	SGA	0.90 (0.64, 1.28)
Zinc	5	750 + 722	LBW	0.77 (0.56, 1.06)
Vitamin D	1	67 + 59	SGA	0.54 (0.26, 1.10)

Factors influencing the results of clinical trials evaluating nutritional interventions during pregnancy



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

Timing of the insult and different fetal organ growth patterns

- Fetal organs show differential growth patterns and contribute differently to total fetal volume at different gestational ages (eg.: relationship between head and abdomen)
- The effect of a nutritional deficiency or nutritional intervention on a the growth of a fetal organ is likely to be related to the timing of he insult during gestation

Timing of nutrient deposition in the mother and the effect on fetal growth

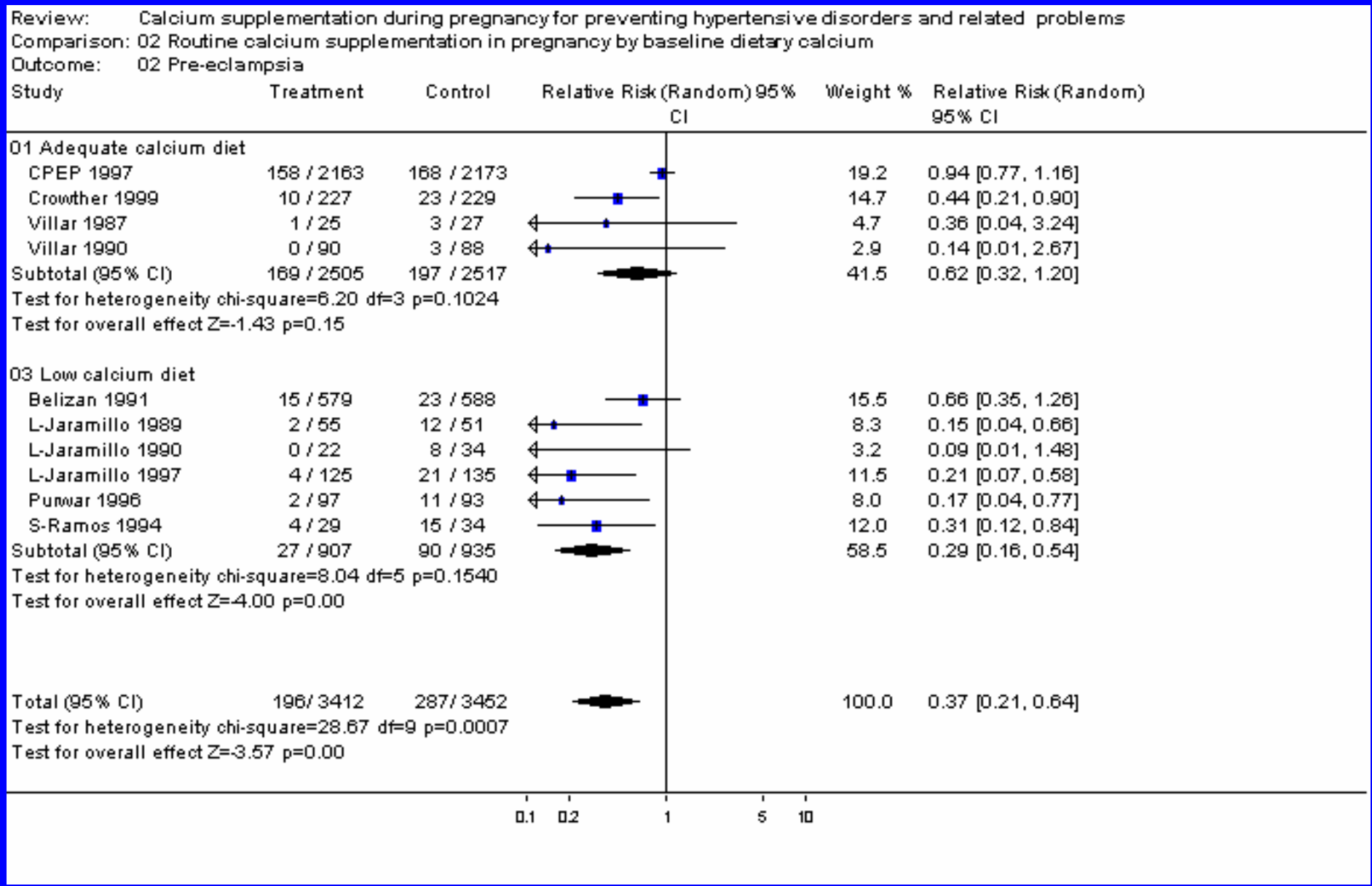
- Differential timing of nutrient deposition and its body location may also influence nutrient transfer to the fetus
- Birth weight is associated more with maternal changes in thigh skinfolds and early gestation fat gain than with other body sites or pregnancy times

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
- Energy supplementation was more effective on birth weight if it was provided for two consecutive pregnancies than during only one pregnancy

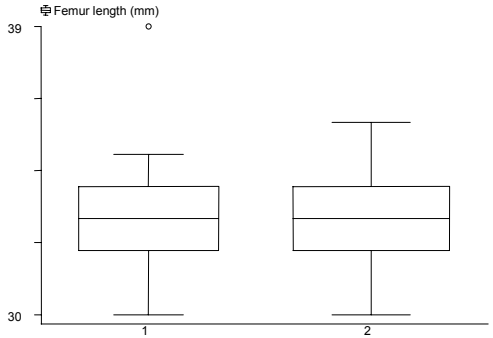
Pharmachological vs. Nutritional effect

- 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.

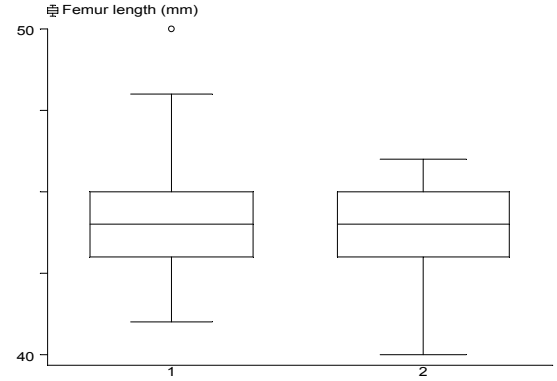

Review: Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems
Comparison: 02 Routine calcium supplementation in pregnancy by baseline dietary calcium
Outcome: 02 Pre-eclampsia
Study
Treatment
Control
Relative Risk (Random) 95% CI
Weight %
Relative Risk (Random) 95% CI
01 Adequate calcium diet
CPEP 1997 158 / 2163 168 / 2173 19.2 0.94 [0.77, 1.16]
Crowther 1999 10 / 227 23 / 229 14.7 0.44 [0.21, 0.90]
Villar 1987 1 / 25 3 / 27 4.7 0.36 [0.04, 3.24]
Villar 1990 0 / 90 3 / 88 2.9 0.14 [0.01, 2.67]
Subtotal (95% CI) 169 / 2505 197 / 2517 41.5 0.62 [0.32, 1.20]
Test for heterogeneity chi-square=6.20 df=3 p=0.1024
Test for overall effect Z=-1.43 p=0.15
03 Low calcium diet
Belizan 1991 15 / 579 23 / 588 15.5 0.66 [0.35, 1.26]
L-Jaramillo 1989 2 / 55 12 / 51 8.3 0.15 [0.04, 0.66]
L-Jaramillo 1990 0 / 22 8 / 34 3.2 0.09 [0.01, 1.48]
L-Jaramillo 1997 4 / 125 21 / 135 11.5 0.21 [0.07, 0.58]
Purwar 1996 2 / 97 11 / 93 8.0 0.17 [0.04, 0.77]
S-Ramos 1994 4 / 29 15 / 34 12.0 0.31 [0.12, 0.84]
Subtotal (95% CI) 27 / 907 90 / 935 58.5 0.29 [0.16, 0.54]
Test for heterogeneity chi-square=8.04 df=5 p=0.1540
Test for overall effect Z=-4.00 p=0.00
Total (95% CI) 196/ 3412 287/ 3452 100.0 0.37 [0.21, 0.64]
Test for heterogeneity chi-square=28.67 df=9 p=0.0007
Test for overall effect Z=-3.57 p=0.00
0.1
0.2
1
5
10

Intervention specific outcomes

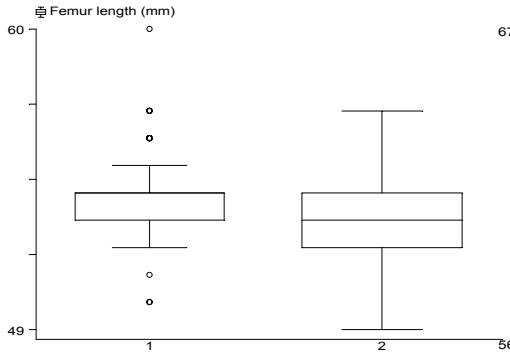
- It is important to identify the most specific outcome in reference to the nutrient being evaluated
- Zinc supplementation did not increased birthweight but had a positive effect on femur length measured by ultrasonography
- “Birth weight may be too crude a marker to to capture the range of all possible uterine exposure and experiences”



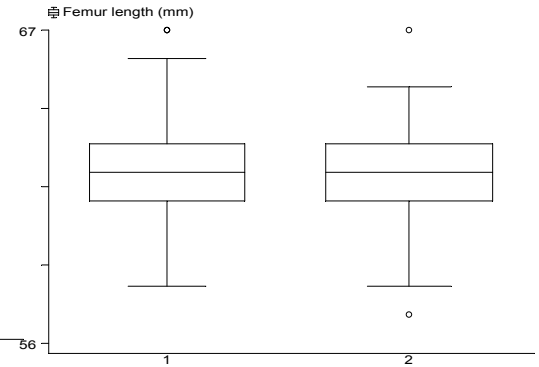
20 weeks



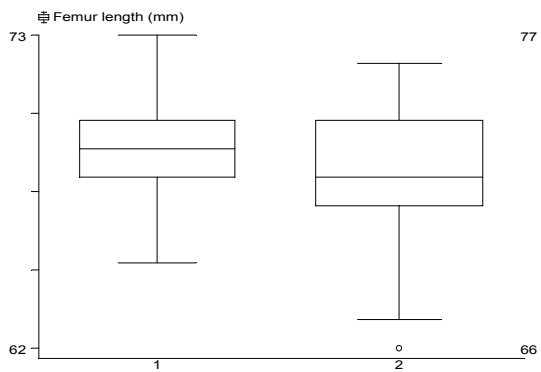
24 weeks



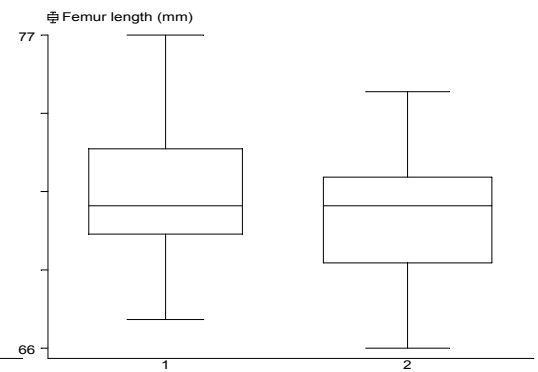
28 weeks



32 weeks



36 weeks



38 weeks

Heterogeneity of outcomes

- Low birth weight and small for gestational age includes conditions with different etiologies.
- These outcomes may be too comprehensive to be significantly affected by a single nutritional intervention

Further research

- Extend the duration of nutritional supplementation interventions
- Identify new outcomes and evaluate their biological and clinical relevance
- Evaluate combinations of interventions
- Develop mechanistic hypotheses
- Identify the determinants of fetal growth (genetics vs. environment)and develop standards of fetal growth for international applications
- Individualized Growth Assessment