WHO Randomized controlled trial of calcium supplementation for the prevention of pre-eclampsia among low calcium intake women

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on behalf of the WHO Calcium Supplementation Trial Group

Introduction

- **Epidemiological studies show that preeclampsia is increased with low calcium intake**

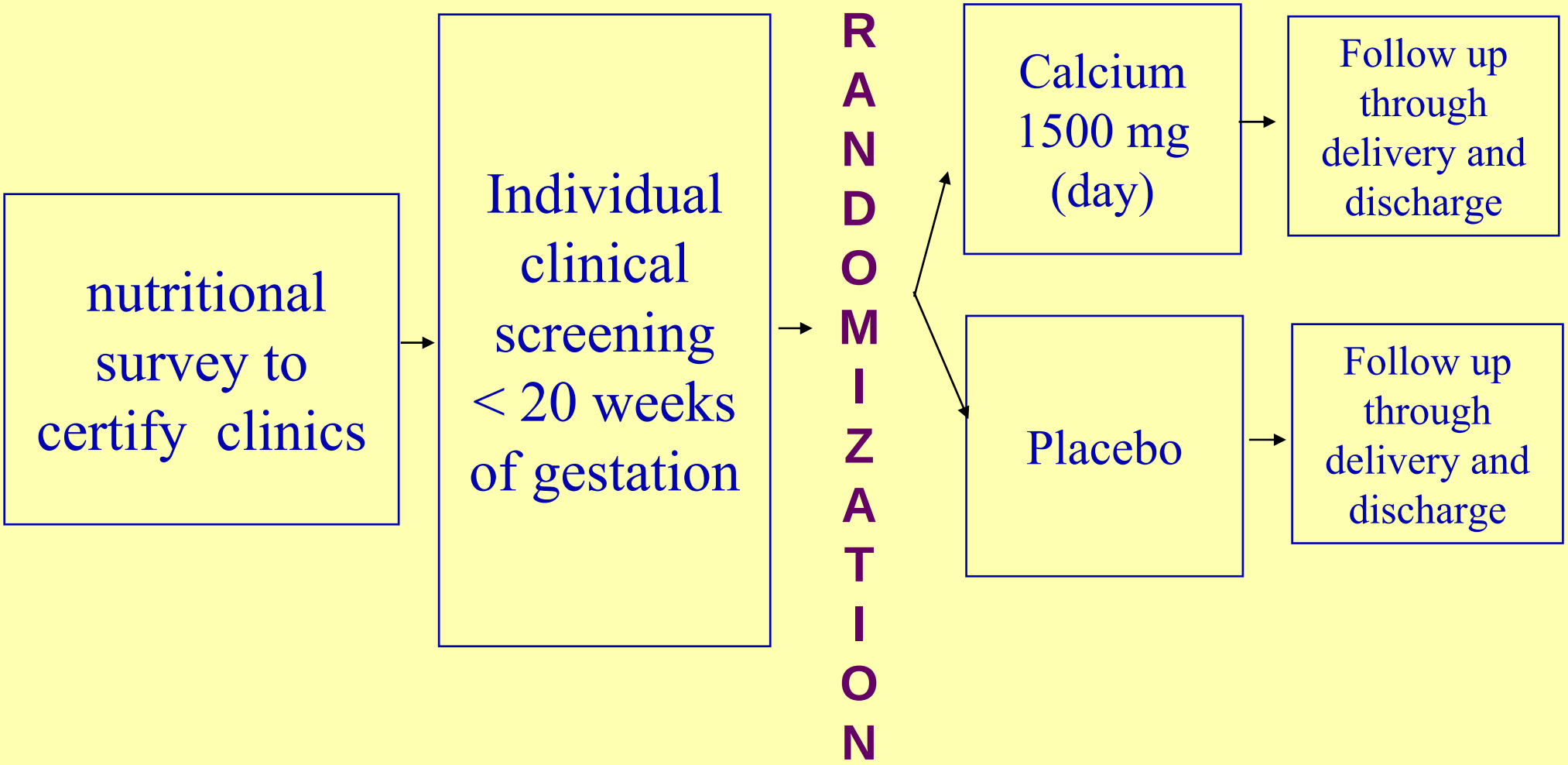
- **Systematic reviews of clinical trials suggest that calcium supplementation prevents preeclampsia in women with low calcium intake *(Carroli et al 1994, Bucher et al 1996, Atallah et al 2003)***

- **Calcium supplementation has been shown to decrease the risk of preterm delivery *(Villar and Repke, 1990)***

Hypothesis

Supplementing nulliparous women with low dietary Ca intake with 1500 mg/day of calcium reduces the risk preeclampsia and preterm delivery

Trial design



Maternal Outcomes

- **Primary Outcome:**
  - **Preeclampsia/Eclampsia**
- **Secondary outcomes:**
  - **Severe preeclampsia**
  - **Eclampsia**
  - **Early onset pre-eclampsia (<32 wks)**
  - **Severe gestational hypertension**
  - **Placental abruption**
  - **HELLP**
- **Severe preeclamptic complication index (at least one of the secondary outcomes)**

Severe maternal morbidity and mortality index

(as in the Cochrane Systematic Review)

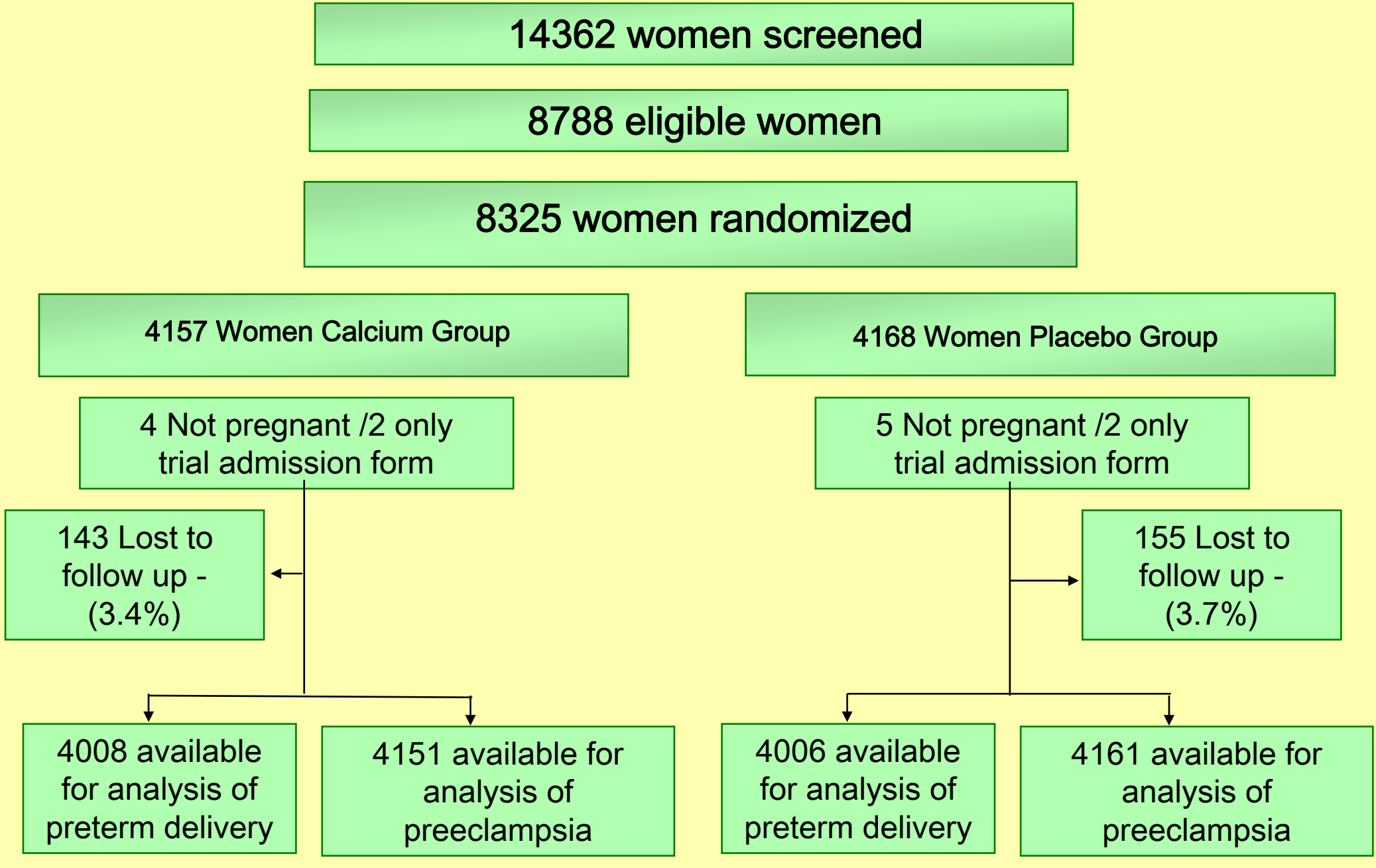
Defined as the presence of at least one of the following:

- Maternal admission to intensive care or any special care unit
- Eclampsia
- Severe pre-eclampsia
- Placental abruption
- HELLP
- Renal failure
- Death

Neonatal Outcomes

- **Primary Outcome:**
  - **Preterm delivery (<37 wks)**
- **Secondary outcomes:**
  - **Early preterm delivery (<32 wks)**
  - **Term-LBW**
  - **Hospitalization**
  - **Fetal death**
  - **Neonatal mortality**

Trial Profile



Baseline characteristics

	Calcium (4151)	Placebo (4161)
Maternal Age (y)	**22.6 (4.4)**	**22.7 (4.4)**
Maternal age <20y (%)	**24.1**	**24.6**
Ever smoked (%)	**5.3**	**5.3**
Years of schooling	**10.1 (3.4)**	**10.0 (3.5)**
Number of pregnancies including present	**1.1 (0.4)**	**1.1 (0.5)**
Maternal weight (kg)	**53.4 (11.1)**	**53.3 (11.3)**
Maternal height (cm)	**156.0 (6.2)**	**155.9 (6.4)**
Body mass index (kg / cm^2)	**21.9 (3.9)**	**21.9 (4.1)**
Gestational age at randomization (wks)	**15.1 (3.5)**	**15.1 (3.5)**
Systolic blood pressure at randomization	**105.0 (10.7)**	**105.1 (10.9)**
Diastolic blood pressure at randomization	**60.8 (9.5)**	**60.8 (9.5)**
A medication taken at randomization (%)	**23.0**	**22.6**
Health complaint at randomization (%)	**13.1**	**13.0**

Treatment compliance

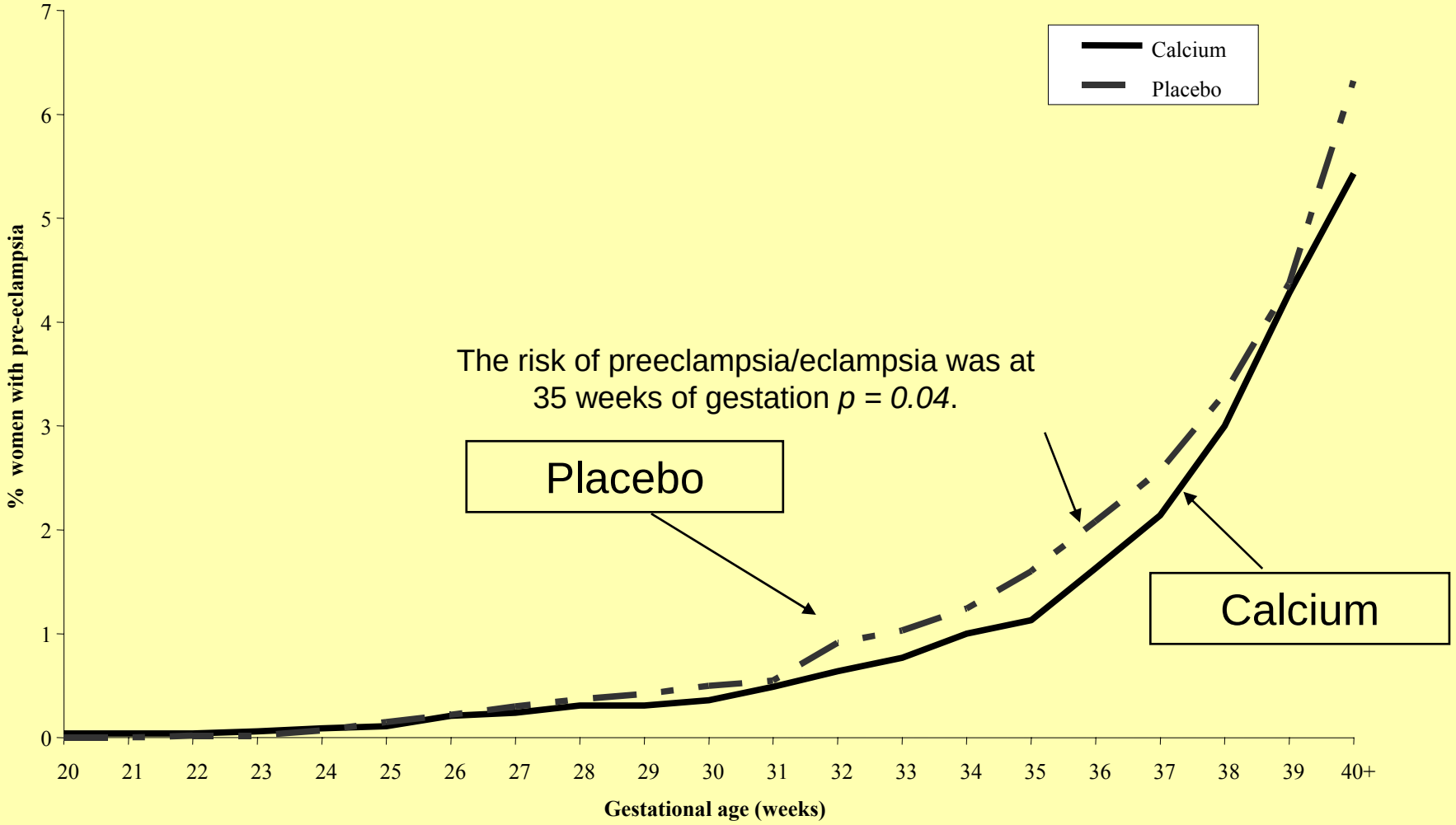
(based on tablet count)

	Calcium (4151) %	Placebo (4161) %
Tablets compliance index (total taken/total provided)	**84.5**	**86.2**

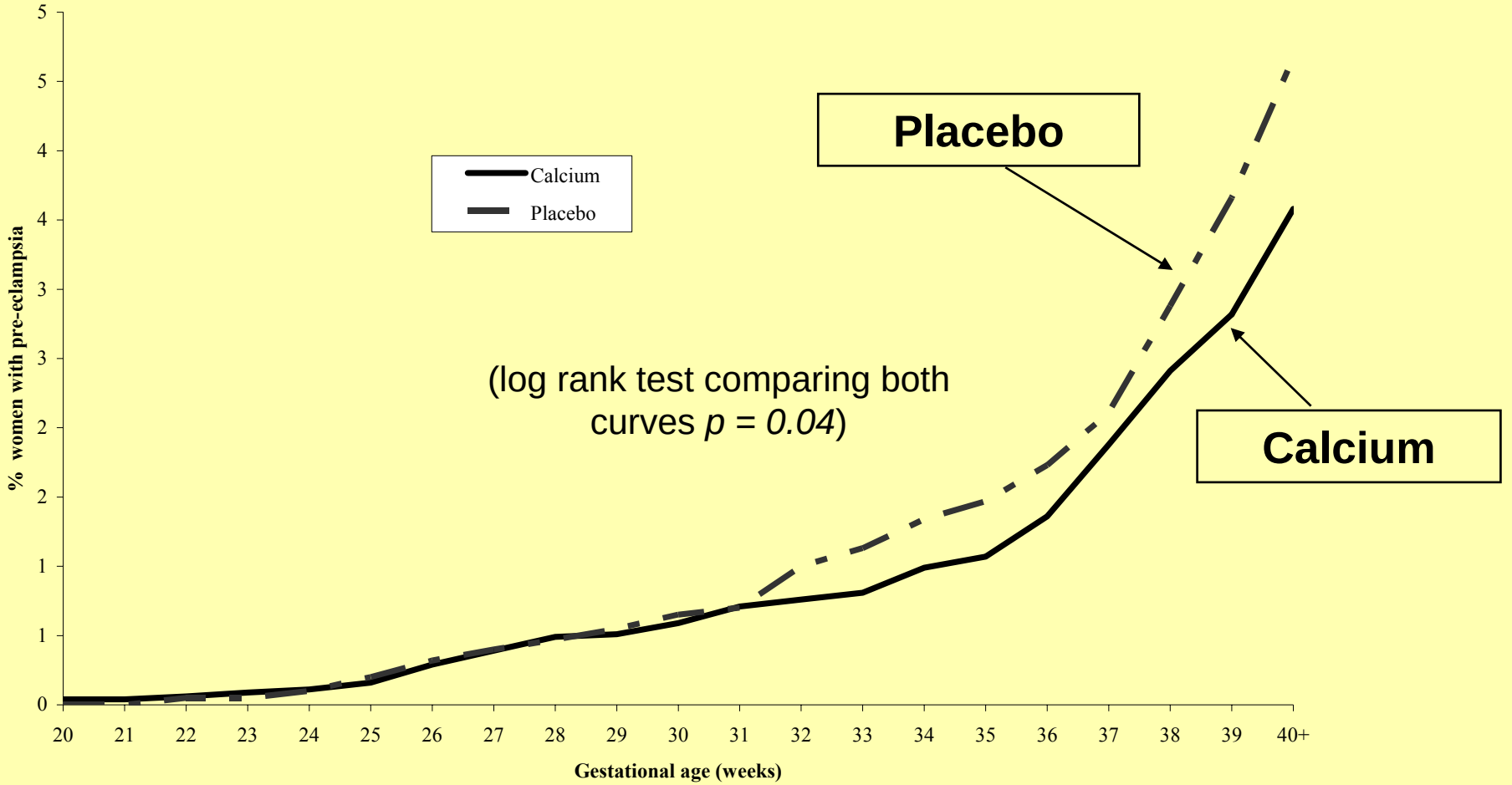
Preeclampsia and complications by to treatment group

Outcome	Risk Ratio	95% Interval
Preeclampsia and/or eclampsia	0.91	0.69 - 1.19
Severe preeclampsia and/or eclampsia	0.73	0.49 - 1.07
Early onset preeclampsia or eclampsia	0.77	0.54 - 1.11
Eclampsia only	**0.68**	**0.48- 0.97**
Placental abruption	0.77	0.43 - 1.39
Gestational hypertension (≥140 and/or ≥ 90)	0.96	0.86 - 1.06
Severe gestational hypertension (≥160 and/or ≥ 110)	**0.71**	**0.61 - 0.82**
Severe preeclamptic complications	**0.76**	**0.66 - 0.89**

Risk of pre-eclampsia and/or eclampsia according to week of gestation



Risk of severe preeclamptic complications according to week of gestation



Severe maternal morbidity and mortality

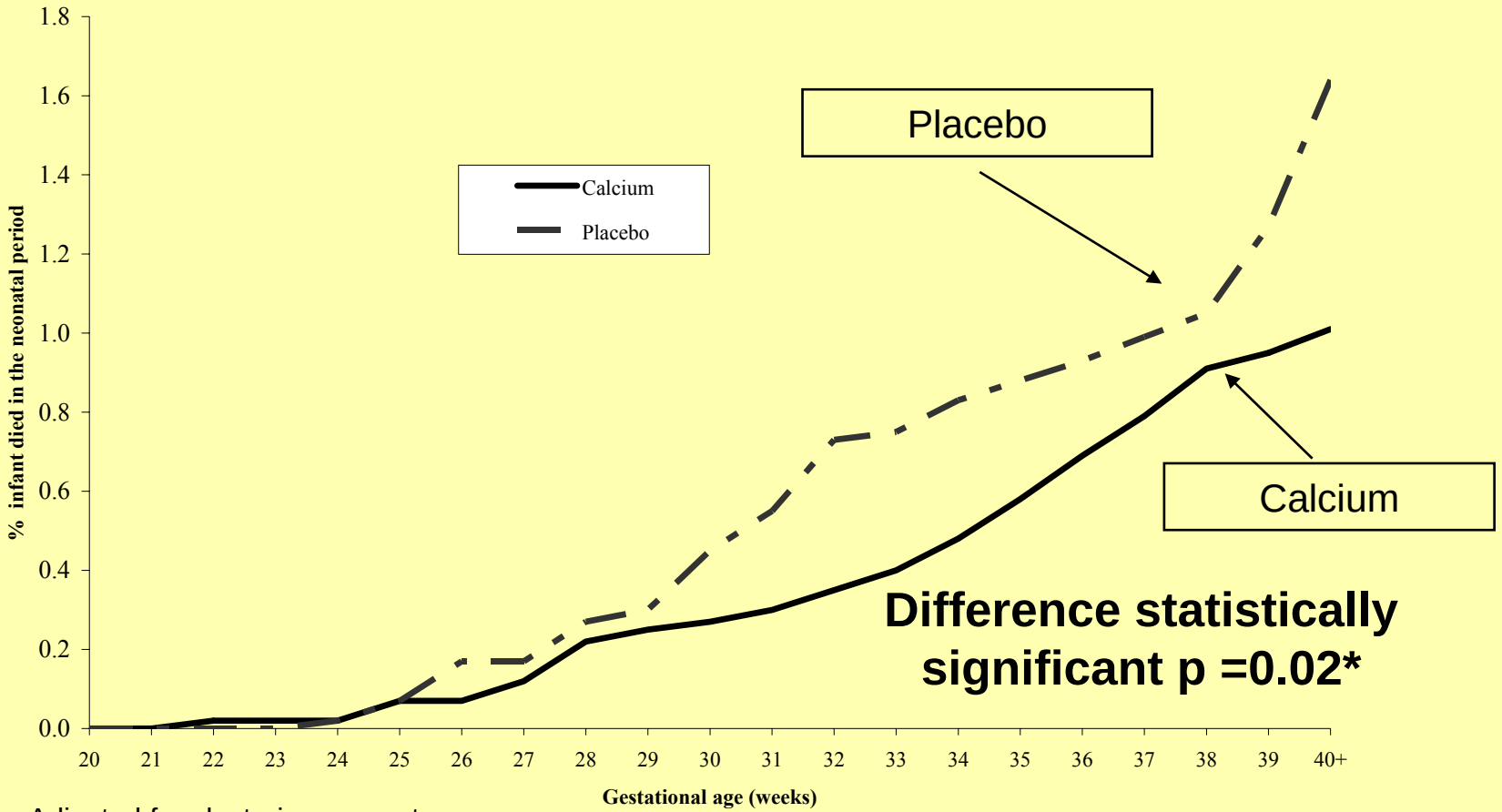
	Risk Ratio	95% CI
Maternal admission to intensive or special care	**0.85**	**0.75 - 0.95**
Maternal admission ≥ 2 days	0.83	0.57-1.21
Maternal death	**0.17**	**0.03 - 0.76**
Severe maternal morbidity and mortality index	**0.80**	**0.70 - 0.91**

Preterm delivery

	Risk Ratio	95% CI
Total population		
Delivery <37 weeks	0.91	0.79 - 1.05
Delivery <32 weeks	**0.82**	**0.71 - 0.93**
Women ≤20 years		
Delivery <37 weeks	**0.82**	**0.67 - 1.01**
Delivery <32 weeks	**0.64**	**0.42 - 0.98**
Women >20 years		
Delivery <37 weeks	0.97	0.83 - 1.15
Delivery <32 weeks	0.93	0.68 - 1.28

Neonatal mortality by treatment group

overall: RR=0.70 (0.56-0.88)



Adjusted for clustering on centre

Discussion 1: Strengths

- **Strict standardization of measurement techniques and blood pressure equipment**
- **Similar and minimal follow-up losses (~3%)**
- **High compliance rate in both arms (~85%)**
- **Treatment and outcome evaluation completely blinded**
- **Consistent effect on severe morbidity and mortality**
- **Populations at nutritional risk of calcium deficiency**
- **Large sample size permitted assessment of severe events**

Discussion 2: Limitations

- **Failure to achieve significant differences in the primary outcomes**
- **Reliance on the secondary outcomes (though they were serious and life-threatening complications).**
- **Mechanisms were hardly explored**

Conclusions

- **We failed to detect a statistically significant reduction in the incidence of pre-eclampsia (~10%)**
- **Calcium supplementation reduced the most serious complications of preeclampsia**
- **Neonatal mortality was significantly lower in the calcium group**
- **Preterm delivery was reduced among women < 20 years**
- **We believe that both perinatal and long term consequences of these outcomes support supplementation in low calcium intake women.**

Thank you for your attention….

…also on behalf of Dr Villar!

Global Program to Conquer Preeclampsia / Eclampsia

From basic science to implementation

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