

# Pre-eclampsia-Eclampsia : an unresolved problem for over 2 millennia

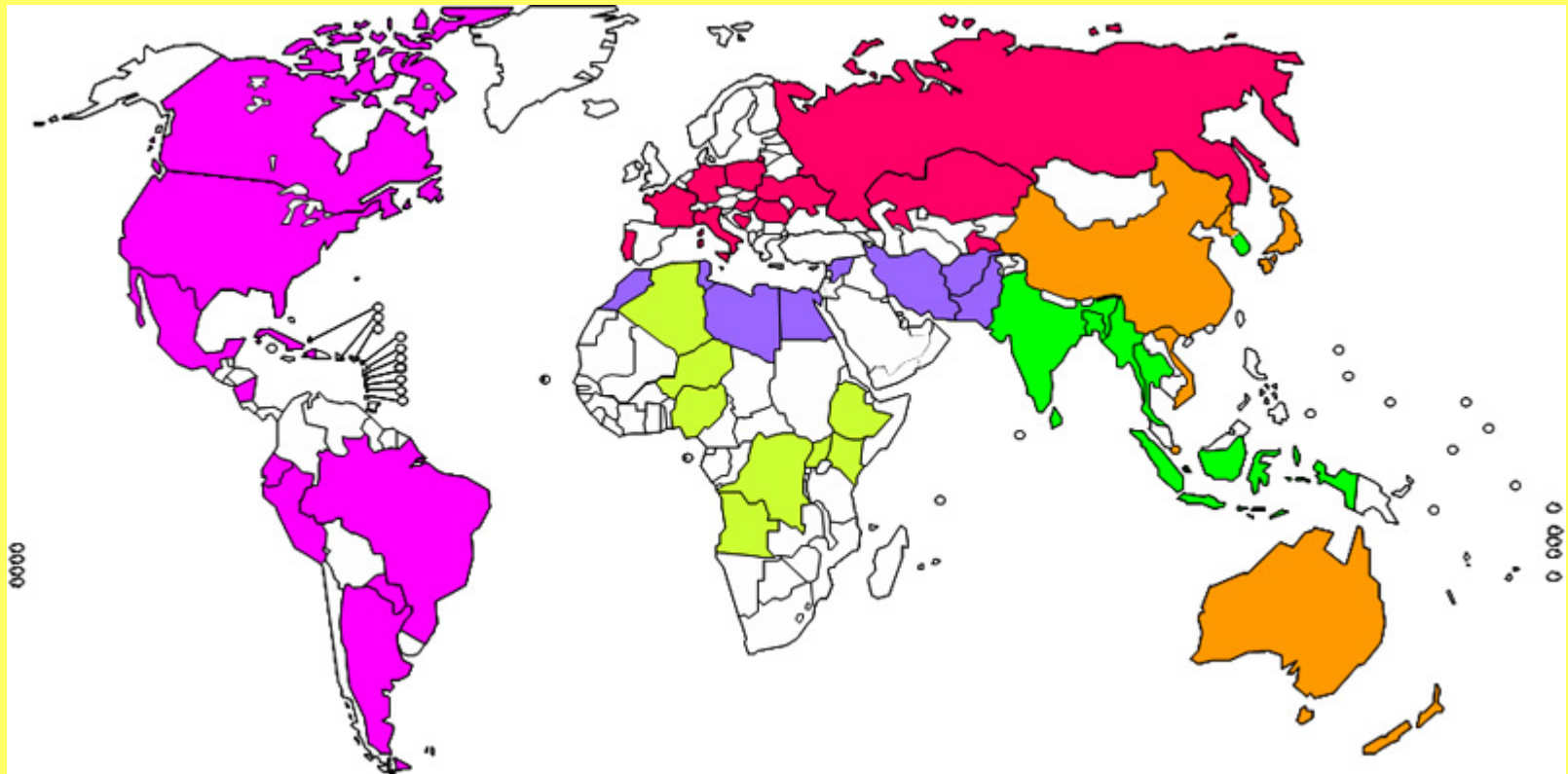
José Villar

Training in Reproductive Health Research  
Geneva, March 2006

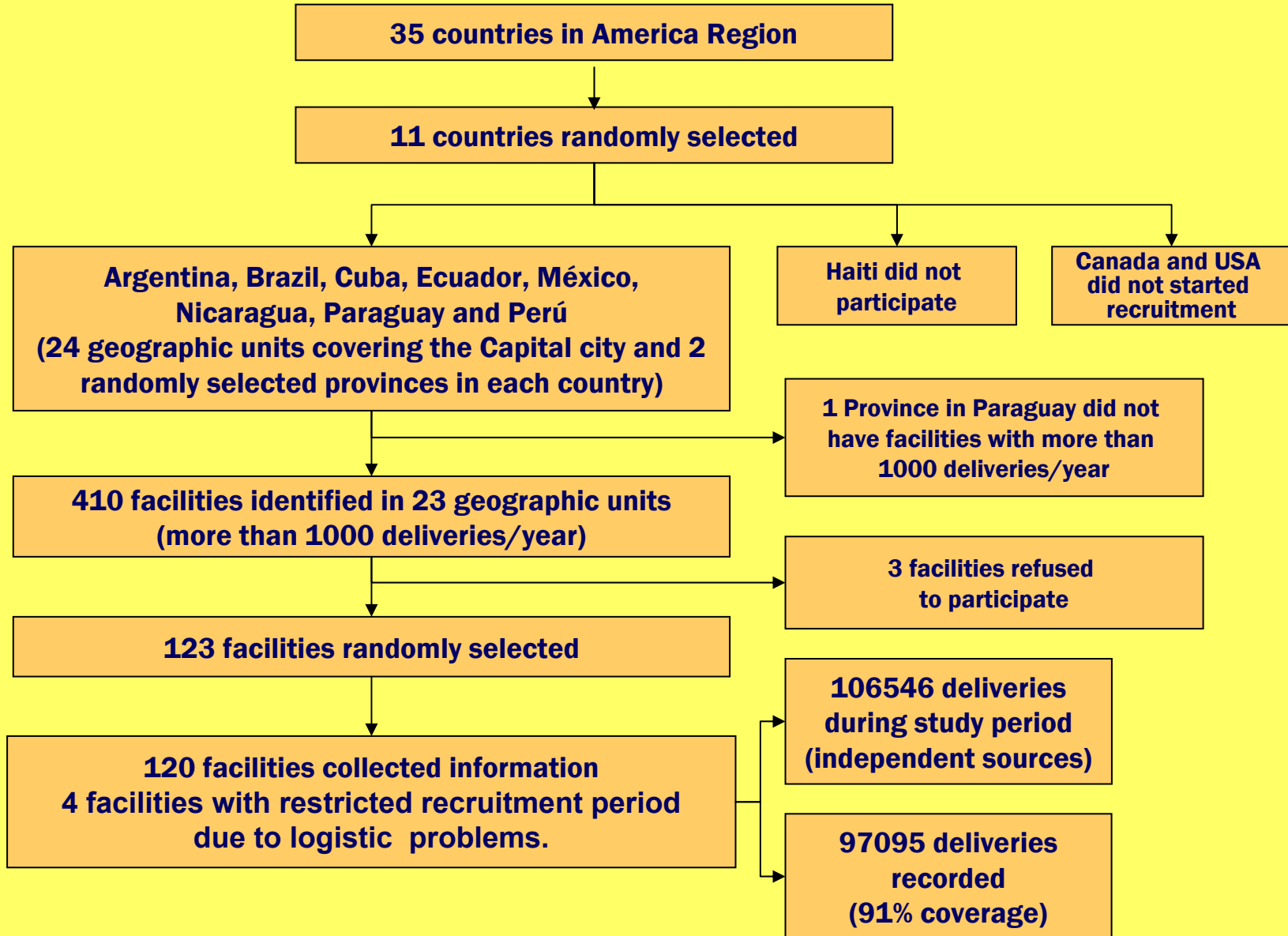
# **Hypertension in pregnancy**

## **The extent of the problem worldwide**

# The 2005 WHO Global Survey



# Latin America: Flow Chart



# Hypertensive disorders of pregnancy

## WHO Global Survey , April 2005

	Africa	Latin America
Number of countries randomly selected	<b>7</b>	<b>8</b>
Number of hospitals randomly selected	<b>119</b>	<b>122</b>
Women surveyed (3 months period)	<b>76,971</b>	<b>97,095</b>
Preeclampsia (%)	<b>2.4</b>	<b>6.2</b>
Eclampsia (%)	<b>0.4</b>	<b>0.3</b>
Hypertension (%) (without proteinuria)	<b>2.6</b>	<b>4.9</b>
Chronic hypertension (%)	<b>0.5</b>	<b>1.4</b>
Any of above conditions (%)	<b>5.9</b>	<b>12.8</b>

Villar et al, 2005

# SCREENING

# **WHO systematic review of screening for pre-eclampsia**

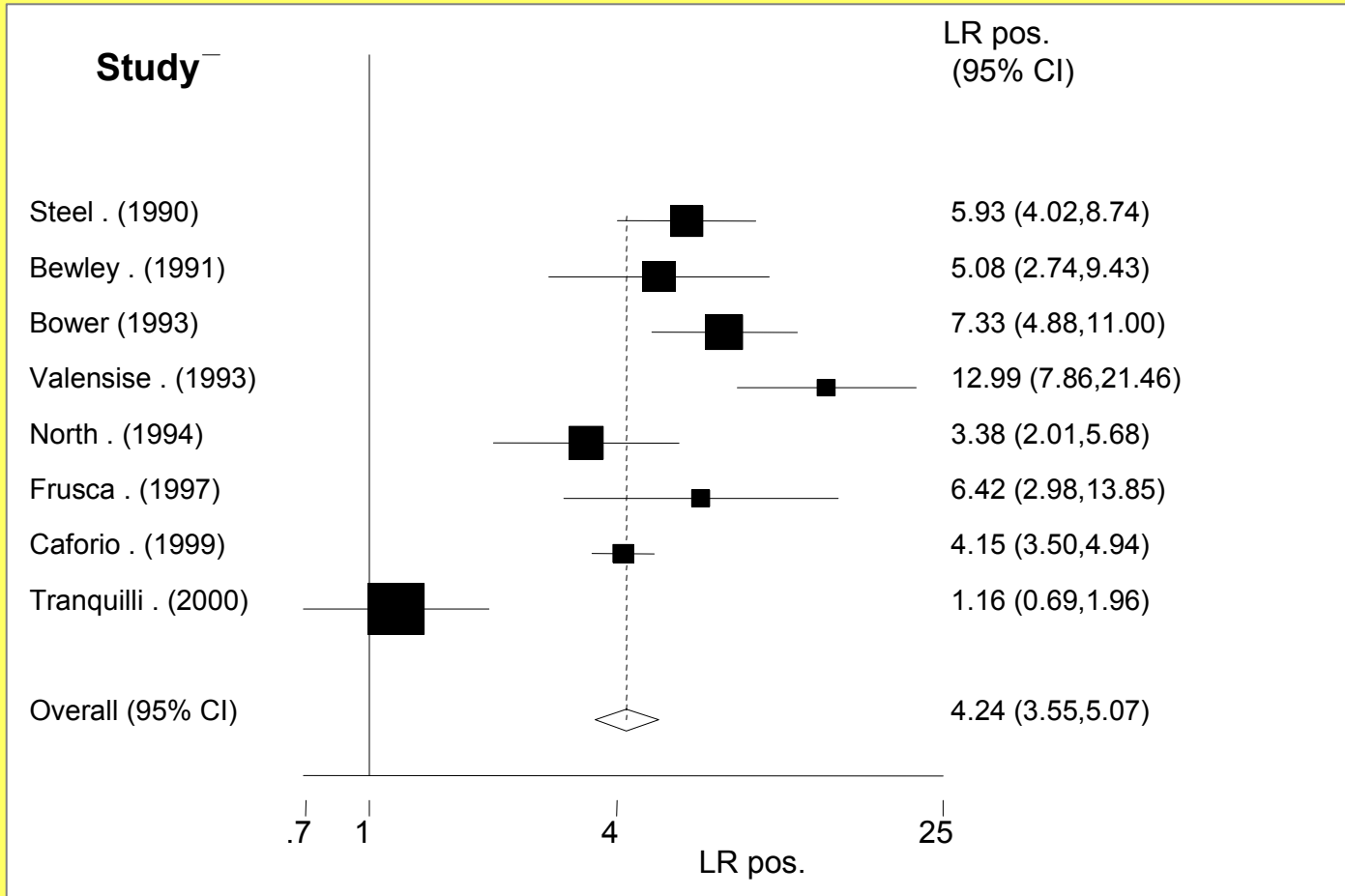
**(Conde-Agudelo A, Villar J, Lindheimer MD  
Obstet and Gynecol 2004;104:1367-1391)**

- **We considered all cohort or cross-sectional studies of tests to predict preeclampsia**
- **7,191 relevant articles → 87 studies included**



# WHO systematic review of screening for preeclampsia

## Abnormal wave form ratio in low-risk women



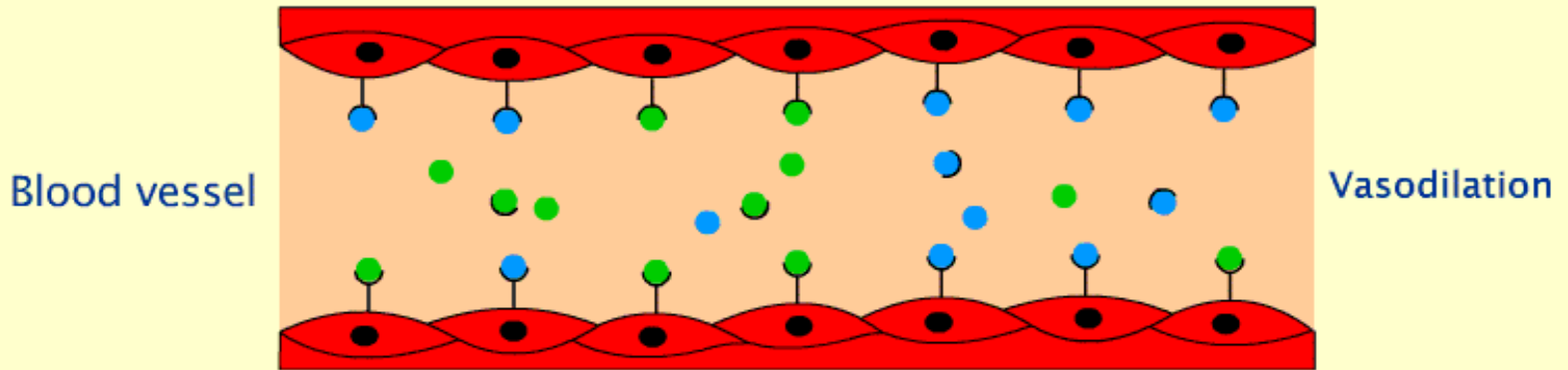
Conde-Agudelo A ,Villar J, Lindheimer M, Obstet and Gynecol 2004

# Summary of the review

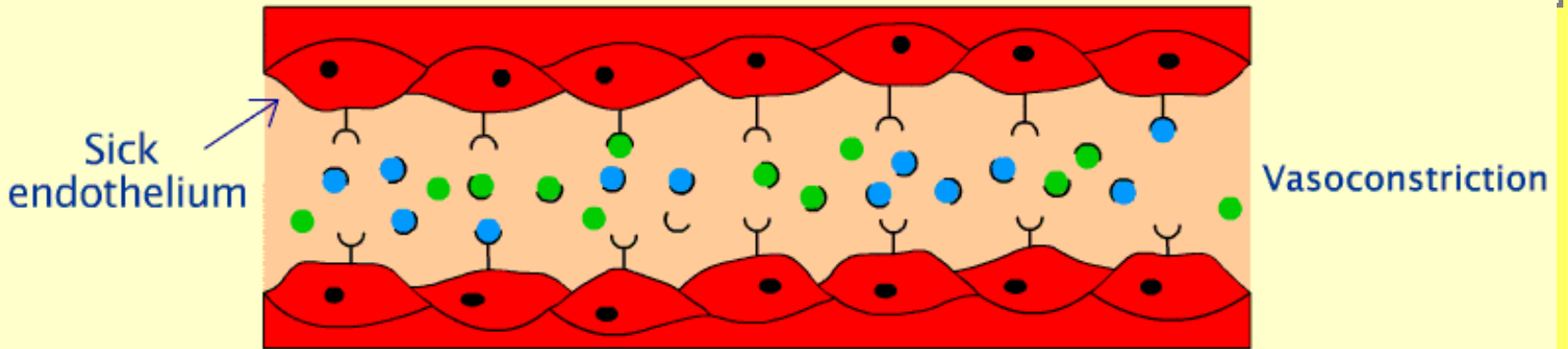
- There is no clinically useful screening test to predict preeclampsia
- Promising :
  - Combinations of tests: e.g., plasminogen activator inhibitor [PAI-1/PAI-2] ratio
  - + leptin
  - + placental growth factor [PIGF])

Reduced first trimester of PIGF and increases in its soluble inhibitor, fms-like tyrosine kinase (sFlt-1)

## Normal Pregnancy



## Preeclampsia



Y FLT-1

● VEGF

● PIGF

∪ sFLT-1

**sFlt-1: Total citations identified : n = 173**

**Citations excluded n = 154**

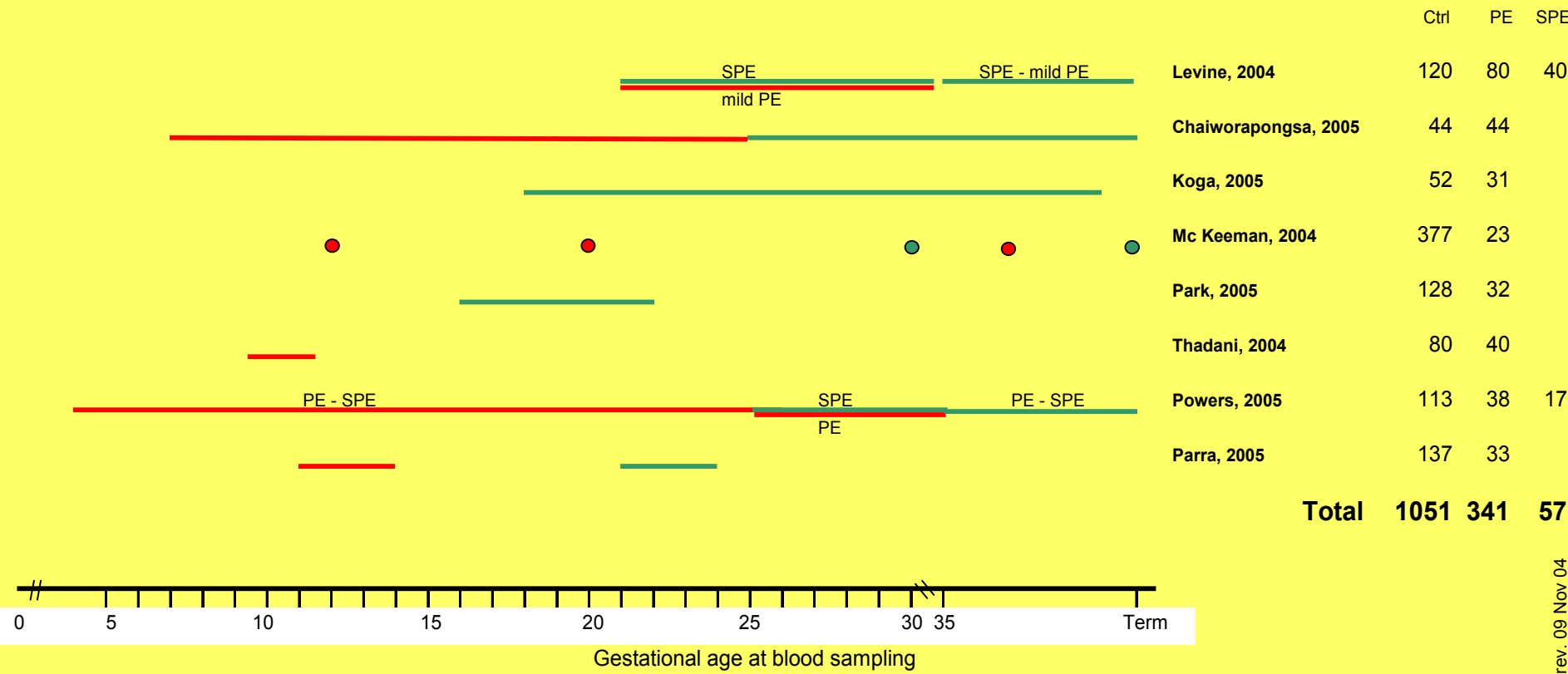
**Primary articles regarding sFlt-1 and pre-eclampsia n = 19**

**11 Articles excluded :**

Lack of original data, reviews ,  
letters, commentaries , sFlt-1 levels  
in cord blood, placental samples ,  
samples at PE diagnosis or delivery  
duplicate data .

**Primary articles included in systematic review: n = 8**

# Circulatory Angiogenic factors and Preeclampsia: sFlt-1



References:

- sFlt-1 significantly increased in women who later developed preeclampsia (PE)
- sFlt-1 did not increase or it did but the difference with the controls was statistically non significant

# PREVENTION

# Prevention of pre-eclampsia: Nutrition

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- Systematic reviews of R.C.T.s
  - increase protein or energy intake
  - restrict protein or energy for obese women
  - supplementing iron, folate, Mg, Zn, fish oil
  - restricting salt intake

**unlikely to be beneficial**
- Promising: Vitamin E and C ( one trial completed ,2 ongoing )
- Calcium: WHO trial completed (N = 8,325 women)

Ref. Villar J et al. J. Nutrition 2003;133:15-205

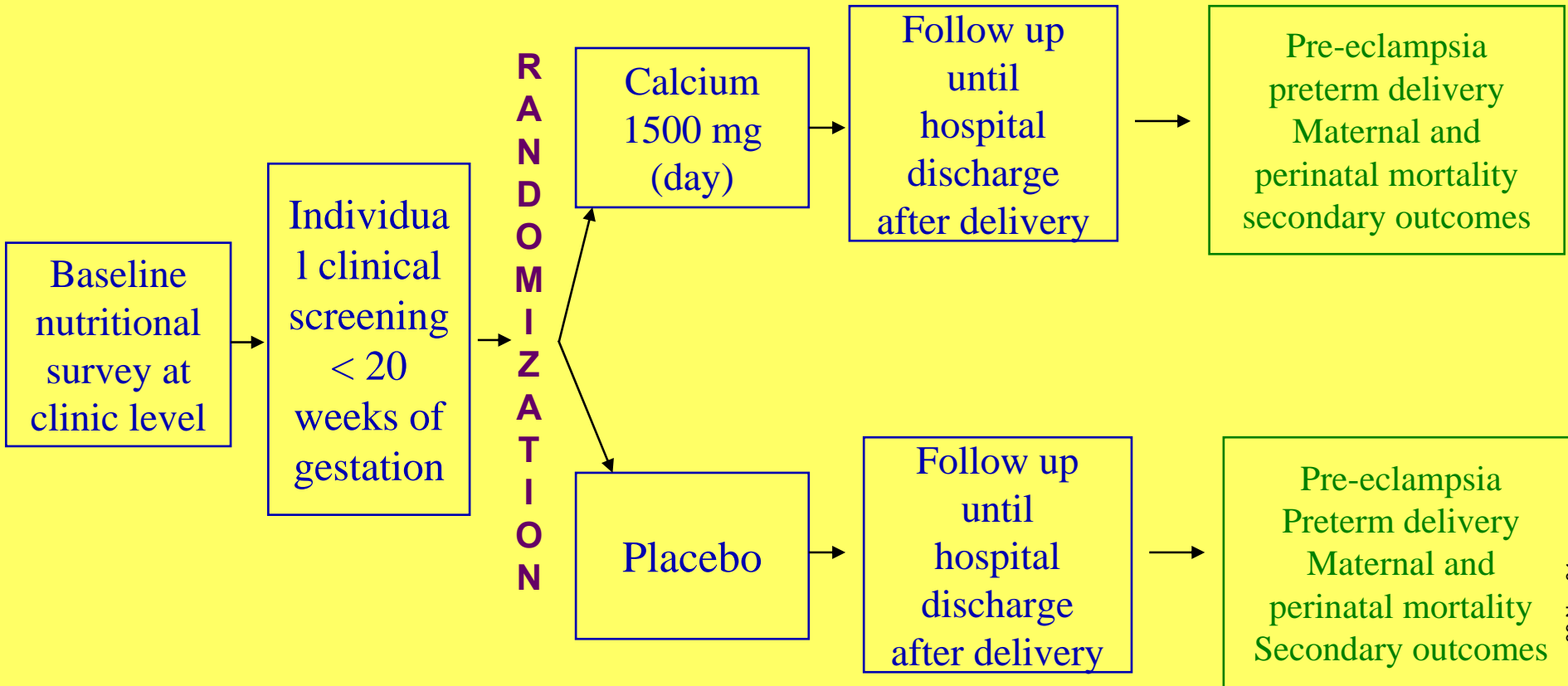
# **WHO Randomized controlled trial of calcium supplementation for the prevention of preeclampsia among low calcium intake women**

**Villar J, Abdel-Aleem H, Merialdi M, Mathai M, Ali M, Zavaleta N, Purwar M, Hofmeyr GJ, Ngoc NTN, Campódonico L , Landoulsi S, Carroli G and Lindheimer MD**

**on behalf of the WHO Calcium Supplementation for the Prevention of Preeclampsia Trial Group ( AJOG , 2006 )**



# Study design and patient flow



# Trial Profile

14362 women screened

8788 eligible women

8325 women randomized

4157 Women Calcium Group

4168 Women Placebo Group

4 Not pregnant / 2 only  
trial admission form

5 Not pregnant / 2 only  
trial admission form

143 Lost to follow  
up - no delivery  
information (3.4%)

155 Lost to follow  
up - no delivery  
information  
(3.7%)

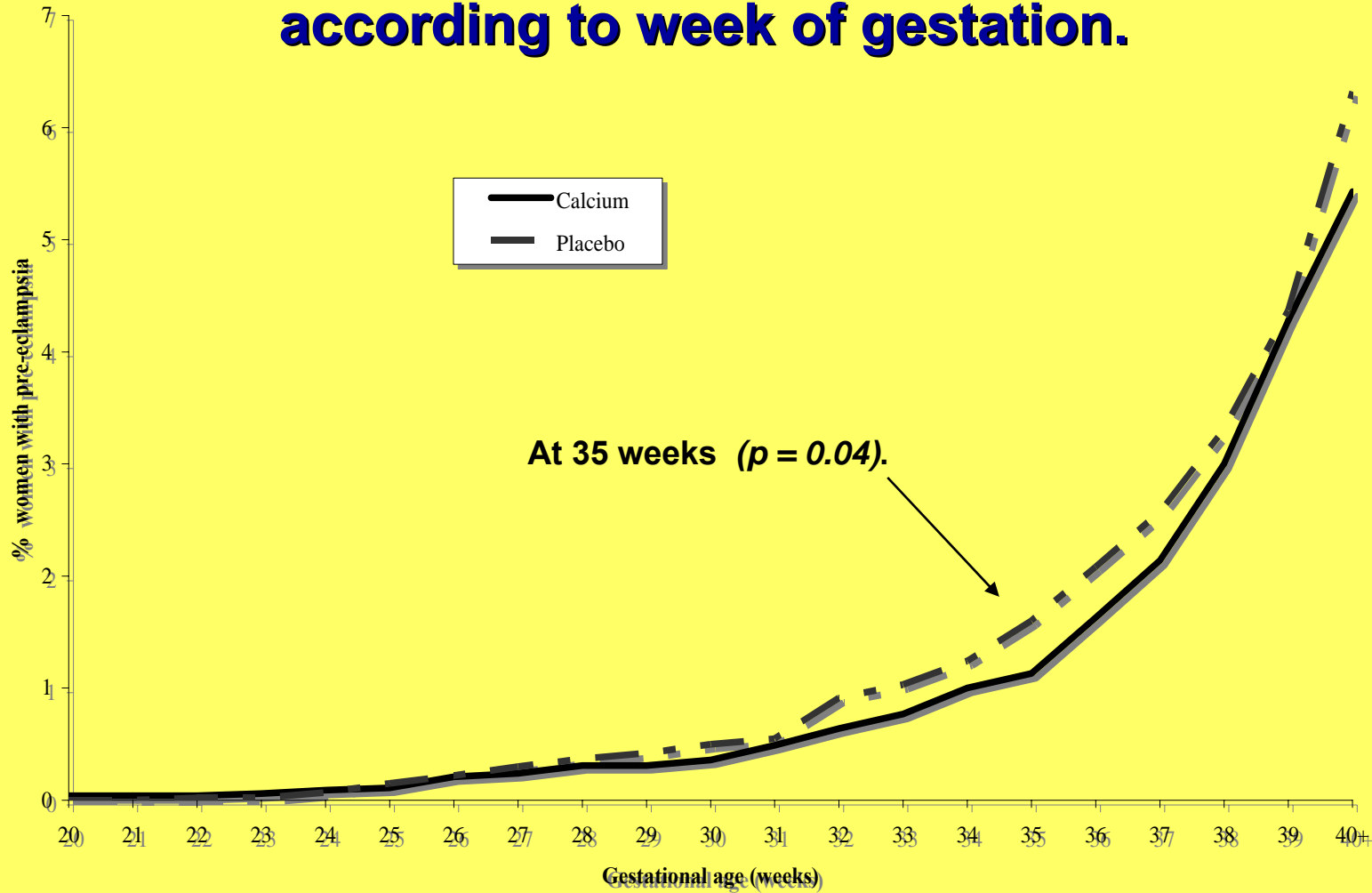
4008 available for  
analysis of  
preterm delivery

4151 available for analysis  
of preeclampsia (at least 1  
ANC visit)

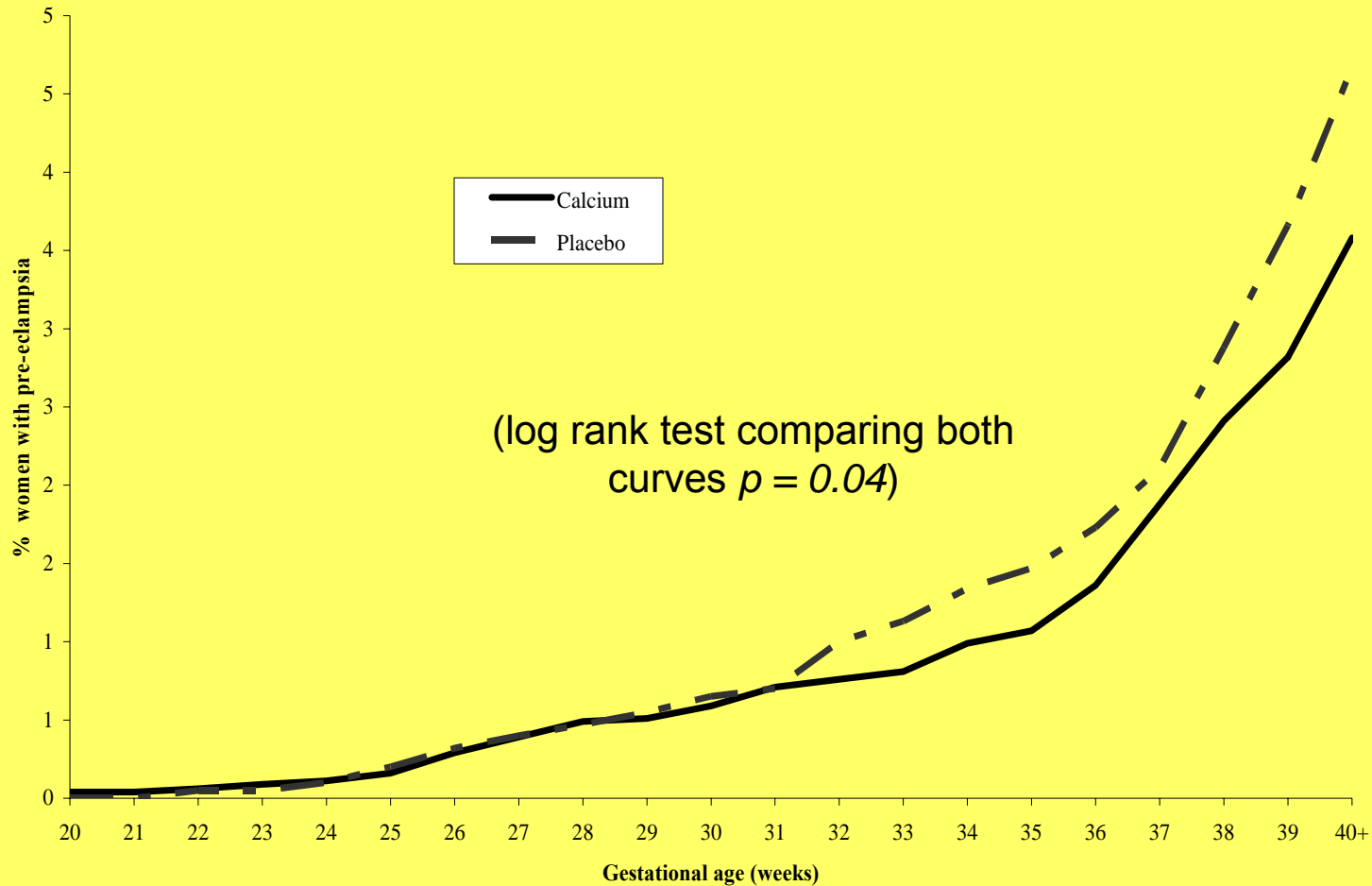
4006 available for  
analysis of  
preterm delivery

4161 available for analysis  
of preeclampsia (at least 1  
ANC visit)

# Cumulative risk for women in the calcium and placebo groups for pre-eclampsia-eclampsia according to week of gestation.



# Cumulative risk for women in the calcium and placebo groups for severe preeclamptic complications according to week of gestation.



# Preterm delivery according to treatment and maternal age

	Calcium n/N	Placebo n/N	Risk Ratio	95% Confidence Interval
<b>Total population</b>				
Preterm delivery (<37 ws)	398/4038	436/4042	0.91	0.79 - 1.05
<b>Early preterm delivery (&lt;32 ws)</b>	<b>106/4038</b>	<b>130/4042</b>	<b>0.82</b>	<b>0.71 - 0.93</b>
<b>Women ≤20 years</b>				
Preterm delivery (<37 ws)	148/1400	180/1404	0.82	0.67 - 1.01
<b>Early preterm delivery (&lt;32 ws)</b>	<b>34/1400</b>	<b>53/1404</b>	<b>0.64</b>	<b>0.42 - 0.98</b>
<b>Women &gt;20 years</b>				
Preterm delivery (<37 ws)	250/2638	256/2638	0.97	0.83 - 1.15
Early preterm delivery (<32 ws)	72/2638	77/2638	0.93	0.68 - 1.28

All risk ratios and 95% Confidence Intervals are adjusted by centre effect.

The denominators include multiple births.

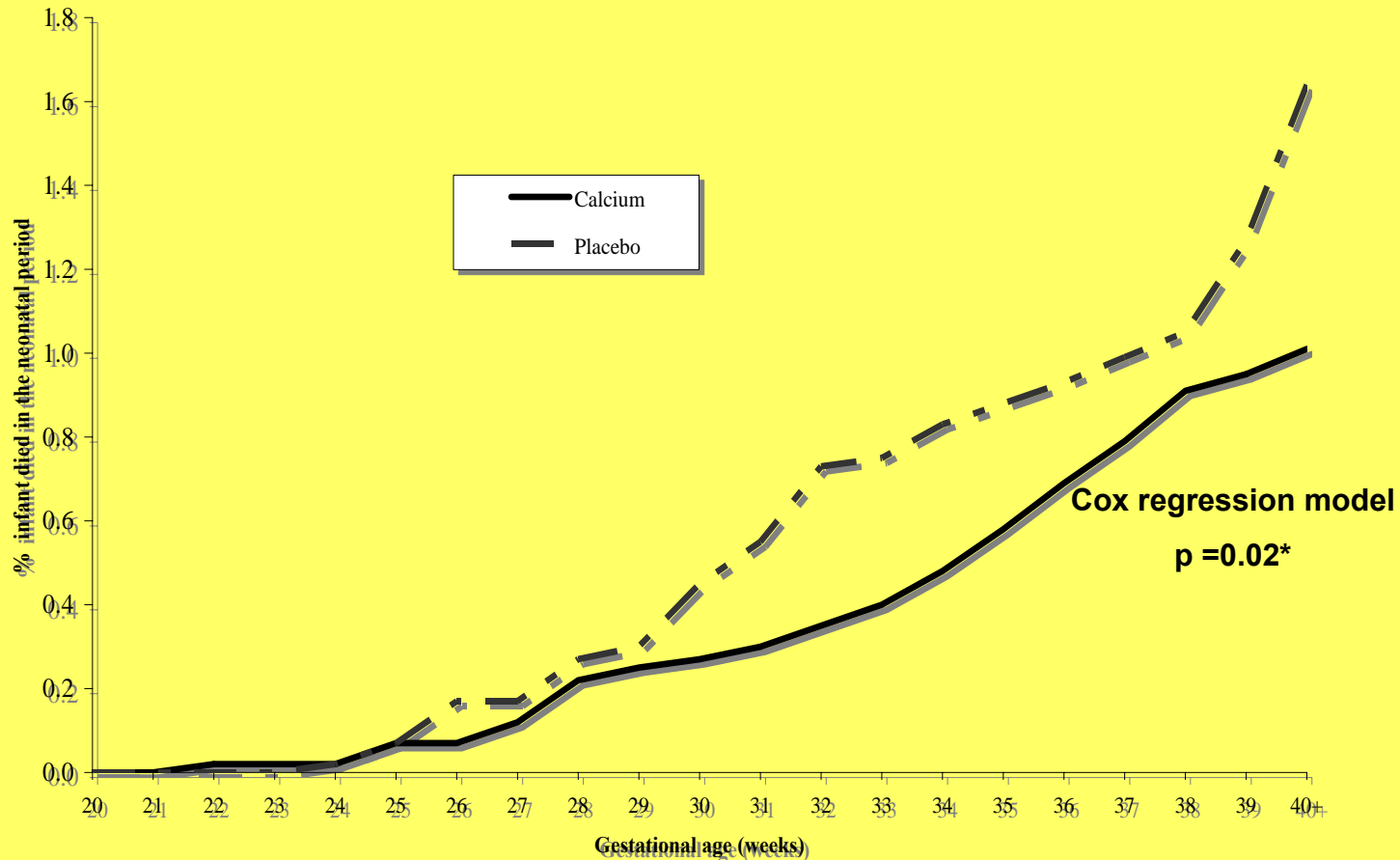
# Severe morbidity and mortality according to treatment group

	Calcium n/N	Placebo n/N	Risk Ratio	95% Confidence Interval
<b>Maternal admission to intensive care any special care unit</b>	116/4151	138/4161	0.85	0.75 - 0.95
<b>Maternal admission <math>\geq</math> 2 days</b>	31/4151	37/4161	0.83	0.57-1.21
<b>Maternal death</b>	1/4151	6/4161	0.17	0.03 - 0.76
<b>Severe maternal morbidity and mortality index (*)</b>	167/4151	209/4161	0.80	0.70 - 0.91
<b>Stillbirth</b>	105/4181	113/4197	0.93	0.74 - 1.17
<b>Neonatal mortality</b>	37/3953	53/3956	0.70	0.56 - 0.88

(\*) At least one of the following: Admission to Intensive Care or any special care unit, eclampsia, severe preeclampsia, placental abruption, HELLP, renal failure or death.

All risk ratios and 95% Confidence Intervals adjusted by centre effect. Maternal outcomes are also adjusted by maternal body mass index.

# Cumulative risk of neonatal mortality, by treatment group



Adjusted for clustering on centre

# Conclusions

Supplementation with 1.5 gm Ca/day did not reduce the overall incidence of preeclampsia, however it decreased the risk for its more serious complications, including maternal and neonatal morbidity and mortality, as well as preterm delivery among young women.



# ETIOLOGY

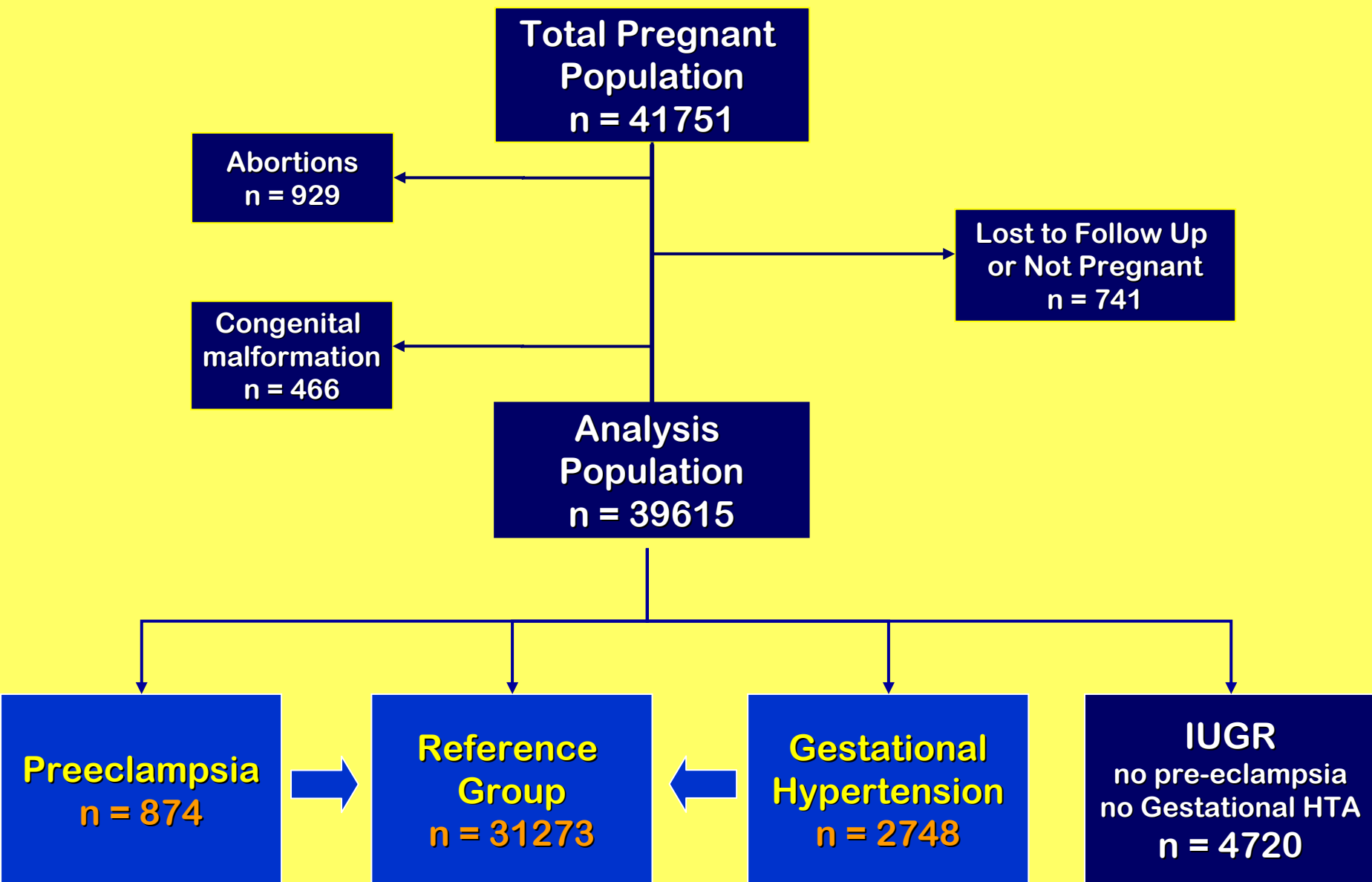
# Are preeclampsia and gestational hypertension different entities ?

- Risk Factors
- Pregnancy outcomes

Villar J et al AJOG 2006 (in press)

Analyses based on data from the WHO Antenatal Care trial :  
Lancet 2001 and et al Obstet & Gynecol 2004

# Preeclampsia versus Gestational Hypertension



# Risk Factors for Preeclampsia and Gestational Hypertension as compared to the Reference Population

	Preeclampsia (n = 874) OR* (95% CI)	Gestational HTA (n = 2748) OR* (95% CI)
Diabetes / Renal / Cardiac	2.4 (1.5 – 3.6) ✓	2.7 (2.1 – 3.5) ✓
Chronic Respiratory conditions	2.7 (1.2 – 6.5) ✓	0.9 (0.4 – 2.1)
Pre-eclampsia last Pregnancy	12.7 (10.0 – 16.2) ✓✓	9.4 (7.8 – 11.2) ✓✓
Spontaneous Abortions (> 2)	1.0 (0.7 – 1.5)	1.0 (0.8 – 1.3)
Urinary Tract Infection	1.4 (1.1 – 1.7) ✓	1.3 (1.2 – 1.5) ✓
Haemorrhage 1 <sup>st</sup> / 2 <sup>nd</sup> trimester	1.0 (0.6 – 1.5)	1.4 (1.1 – 1.7) ✓
Reproductive Tract Surgery	1.0 (0.7 – 1.5)	2.2 (1.8 – 2.6) ✓
Reproductive Tract Infection	0.8 (0.6 – 0.9)	1.3 (1.2 – 1.5) ✓

\* Adjusted OR, compared with reference population (n = 31273)

## Risk Factors for Preeclampsia and Gestational Hypertension as compared to the Reference Population

	Preeclampsia (n = 874) OR* (95% CI)	Gestational HTA (n = 2748) OR* (95% CI)
Maternal Age (< 16 years-old)	1.4 (1.0 – 1.9) ✓	1.3 (1.1 – 1.6) ✓
Primiparous	2.2 (1.9 – 2.5) ✓	1.2 (1.1 – 1.3)
Maternal Age (> 40 years-old)	2.8 (1.7 – 4.5) ✓	3.0 (2.4 – 3.9) ✓
Obesity (BMI > 30)	2.7 (2.3 – 3.2) ✓	2.8 (2.5 – 3.1) ✓
Low BW in Last Pregnancy	1.3 (0.9 – 1.9)	1.4 (1.1 – 1.7) ✓
Previous High Weight Babies	0.9 (0.5 – 1.7)	1.7 (1.3 – 2.2) ✓

\* Adjusted OR, compared with reference population (n = 31273)

# Are they different ?

- **Preeclampsia : Primiparous ; Chronic respiratory conditions ?**
- **Gestational Hypertension : Reproductive pathology, haemorrhage and reproductive infections ?**

# Perinatal Outcomes for Preeclampsia and Gestational Hypertension as compared to the Reference Population

	Preeclampsia (n = 874) OR (95% CI)	Gestational HTA (n = 2748) OR (95% CI)
<b>NICU Stay 7 or more days</b>		
Crude	6.0 (5.0 – 7.3)	2.1 (1.7 – 2.4)
Adjusted *	1.5 (1.2 – 2.0)	1.2 (1.0 – 1.5)
<b>Neonatal Death</b>		
Crude	4.6 (2.9 – 7.4)	1.4 (0.9 – 2.3)
Adjusted *	0.9 (0.5 – 1.8)	1.8 (1.0 – 3.3)

\* OR adjusted by country, treatment, birth weight and socioeconomic status

# **WHO systematic review of the theories of preeclampsia:**

## **The role of homocysteine**

Mignini, L. et al, Obstet Gynecol 2005;105:411-425



**Total citations identified : n = 101**

**Citations excluded n = 34**

**Primary articles regarding homocysteine and preeclampsia n = 67**

**Articles excluded :**  
Lack of original data  
reviews, letters,  
comments,  
duplicate data

**Primary articles included in systematic review: n = 25**

# Review of the association between hyperhomocysteinemia and preeclampsia

## Follow up Studies

Sorensen 1999

Hogg 2000

Cotter 2001

Hietala 2001

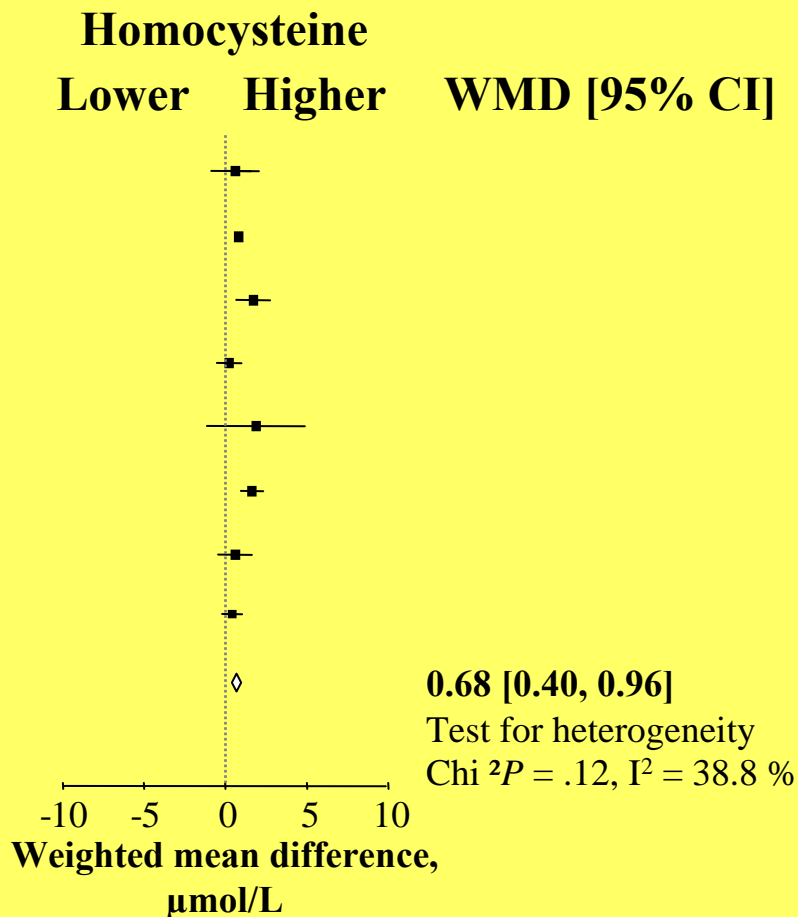
Murakami 2001

Cotter 2003

Zeeman 2003

D'Anna 2004

**Subtotal (fixed effect model,  $P < .001$ )**



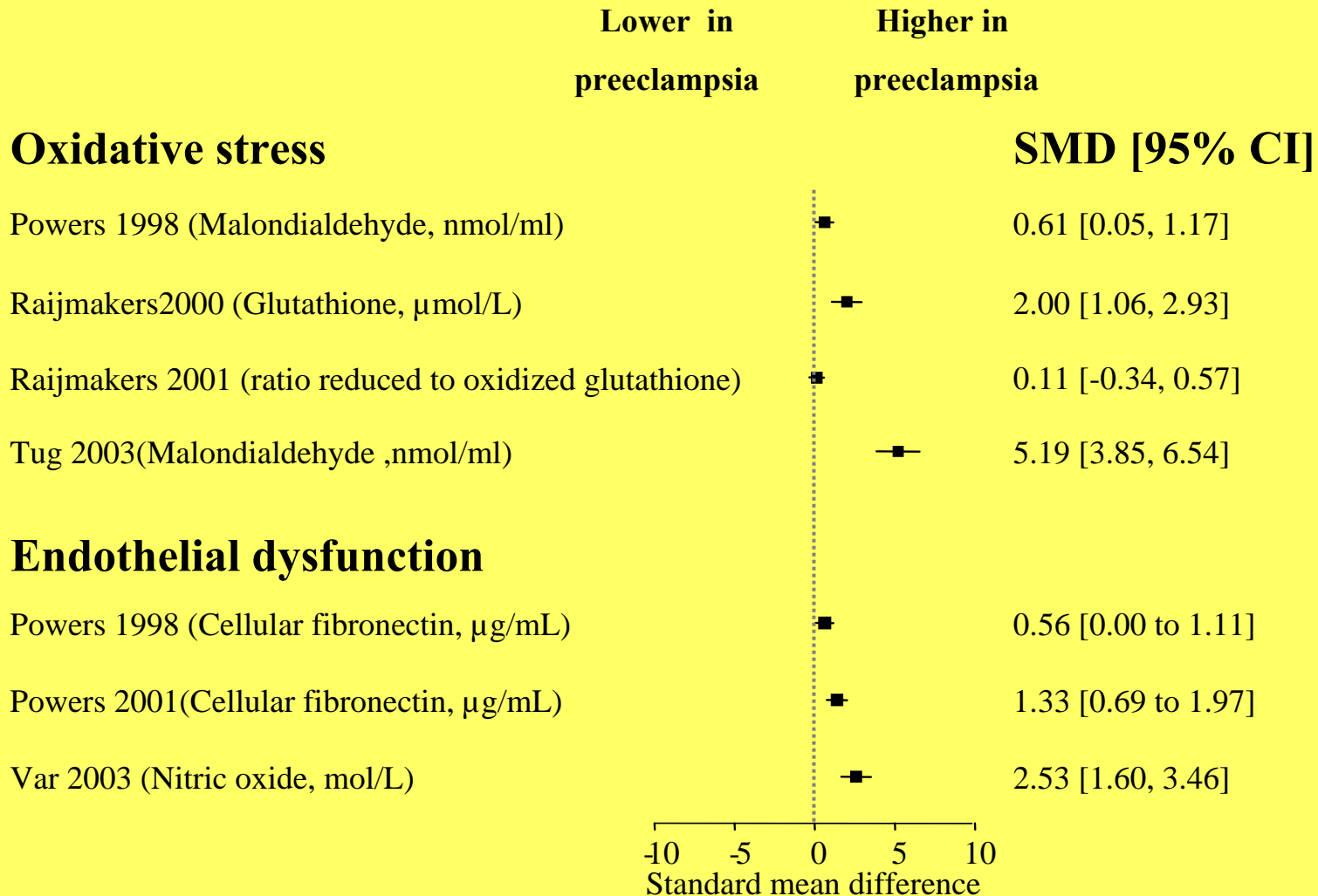
 Temporality

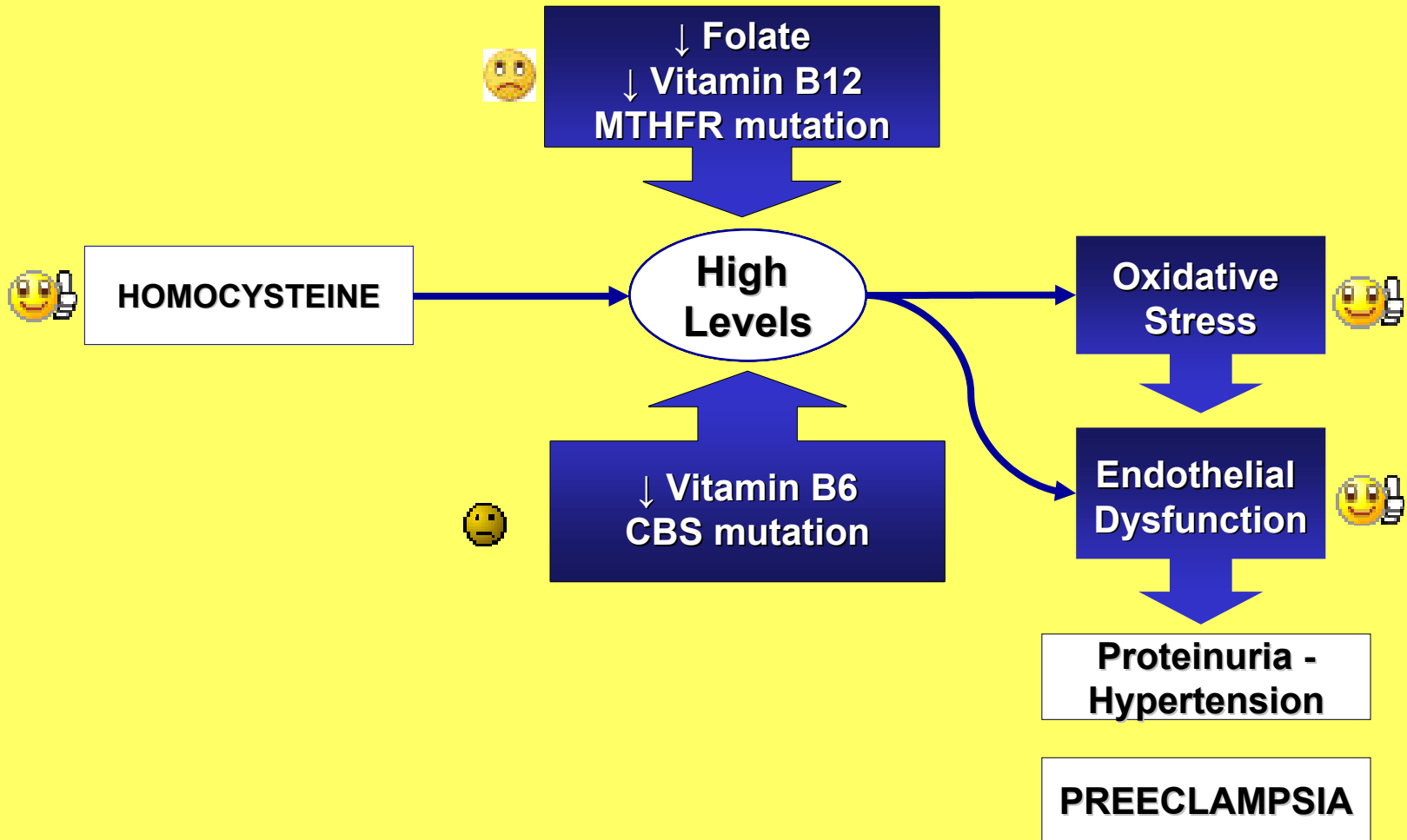
 Consistency ?

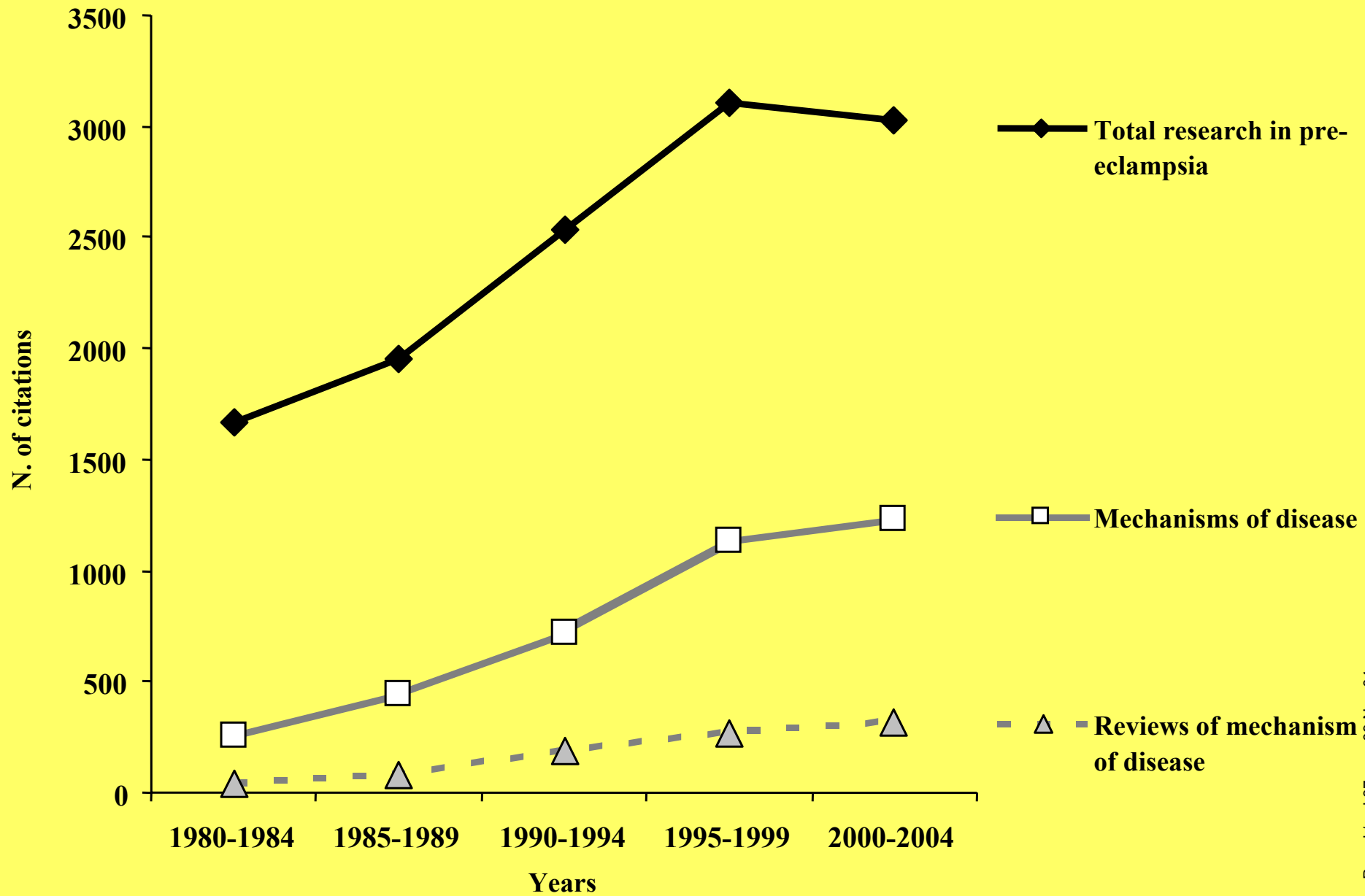
 Strength

# Oxidative stress and endothelial dysfunction among women with and without preeclampsia

## Concentrations







# Mapping the theories of pre-eclampsia:

## The need for systematic reviews of mechanisms of the disease

Mignini, L. Villar, J. Khan ,K. Am. J. Obstet–Gynecol  
(2006)

**First, Do the Trials  
Then, Do No Harm**  
**By David Brown**  
**Sunday, August 4, 2002;**  
**Page B01, The**  
**Washington Post**

