# Early Life Exposures and Breast Cancer Risk

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# Objective

To identify early exposures related to risk for breast cancer

by window of susceptibility

*Following the yellow brick road of risk factors*

# What am I going to tell you?

In utero

- Birthweight ~ pubertal stage
- Maternal energy balance in pregnancy ~ daughter's age at menarche

Infancy

- Age of greatest weight gain ~ pubertal status

& age varies by maternal preeclampsia

- Age of greatest weight gain ~ age at menarche

Childhood/youth

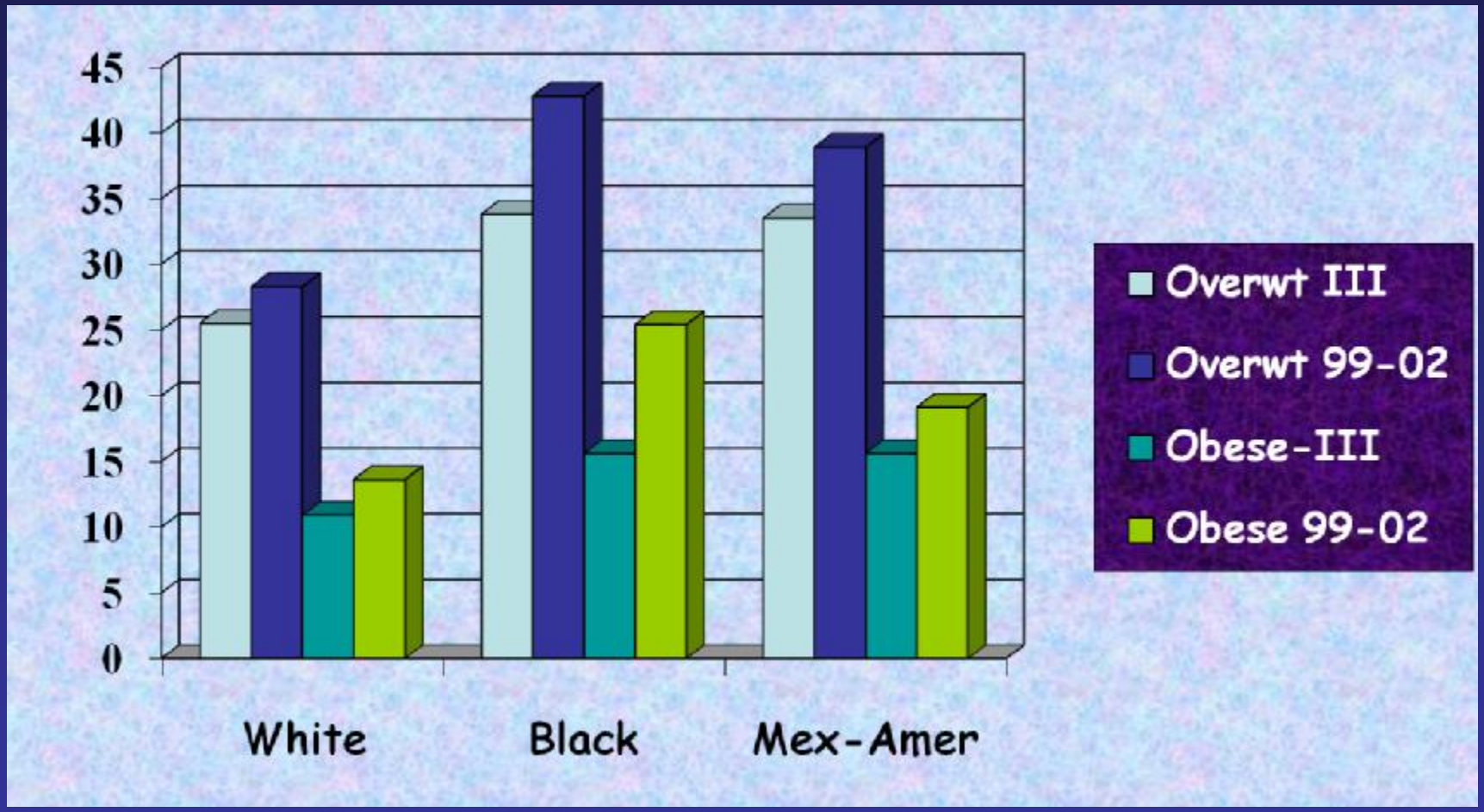
- Body size and family conflict ~ earlier menarche in Mexican American girls.

# What do we know?

# Breast Cancer Risk Factors

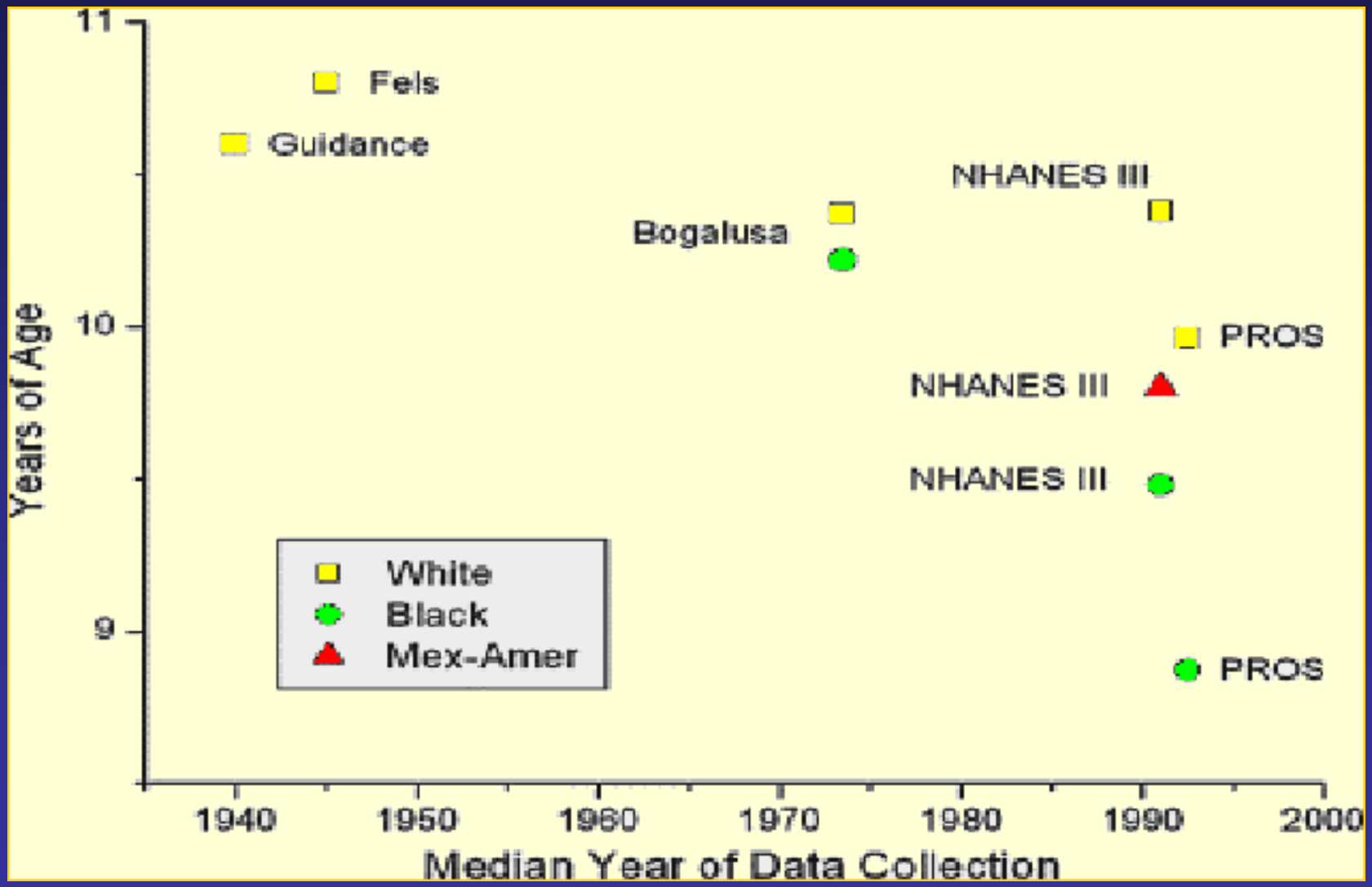
- High birthweight ~ premenopausal breast cancer
- Body mass index by menopausal status
- Height ~ premenopausal breast cancer
- Age at menarche, first and last birth
- Age at menopause
- Physical activity in youth and adult years
- Postmenopausal exogenous hormone preparations

# Increasing percentage of girls (9-15 y) who are overweight & obese over time

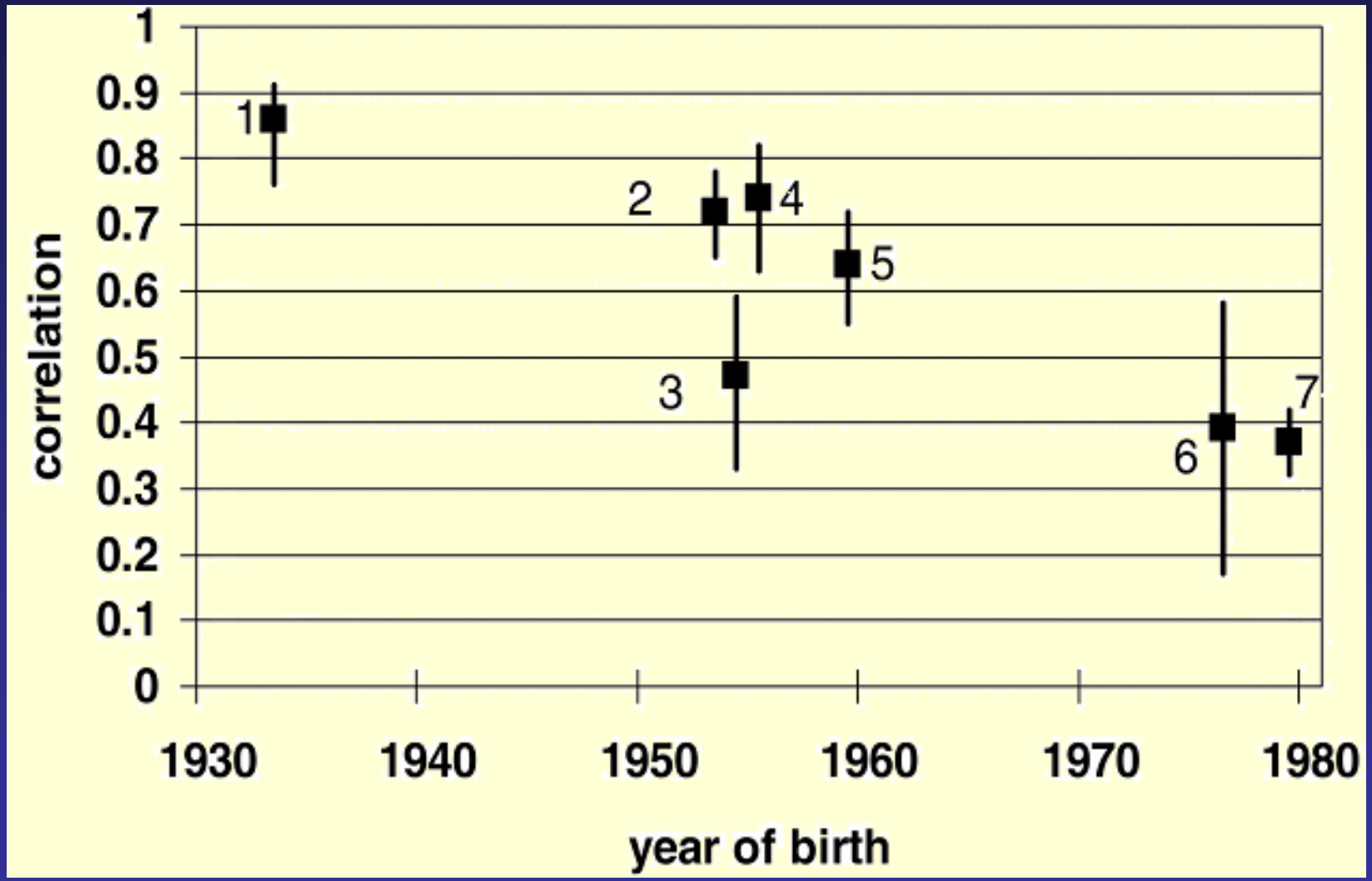



(NHANES III (1988-91) & 1999-2002)

# Decline in the mean or median ages of entry into breast stage 2 (onset of puberty) for US studies

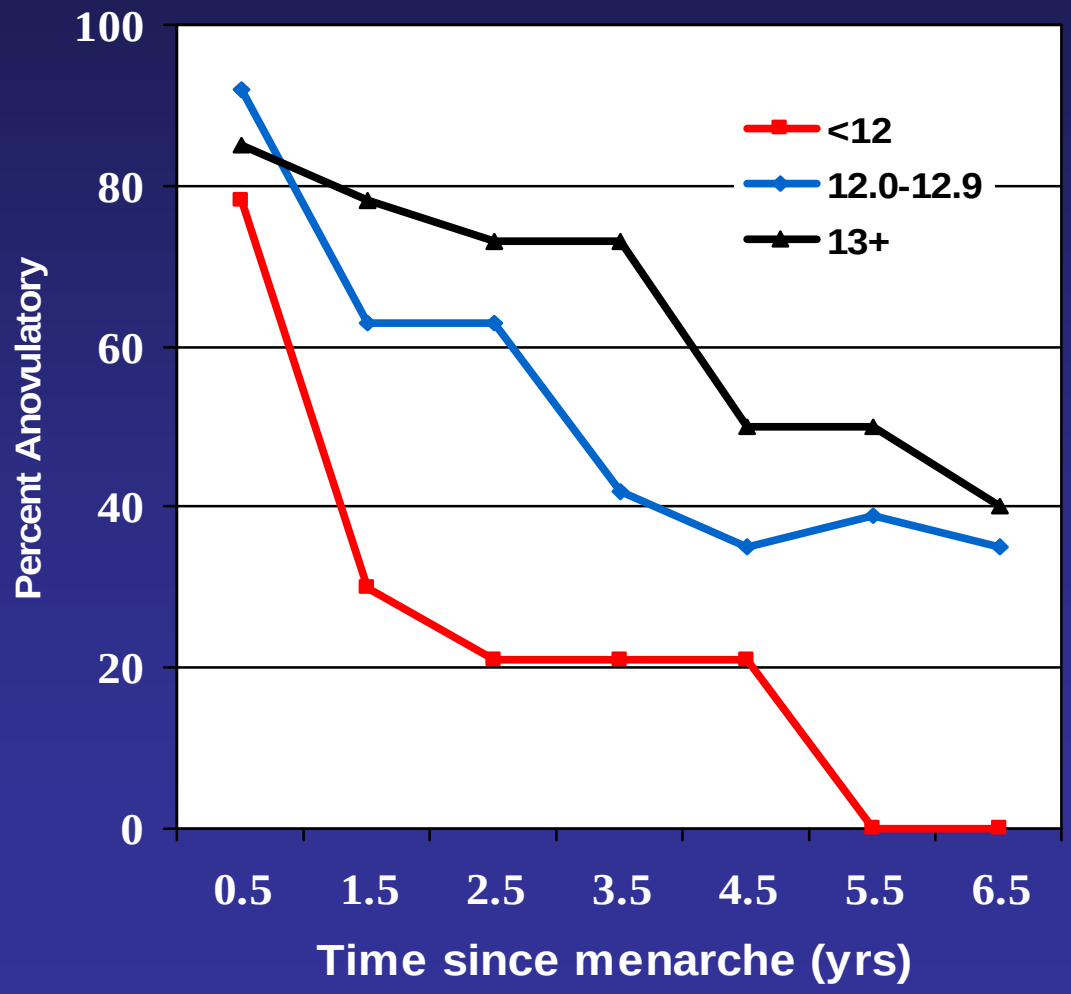


# Lower correlation between age of onset of puberty & age of menarcheover time




Studies: 1-Reynolds; 2- Bielicki; 3-Largo; 4-Taranger; 5-Marshall; 6-de Ridder; 7-NGHS

# Percent anovulatory menstrual cycles increases with later age at menarche: Finnish schoolgirls




- Menarche marks onset of exposure to cyclic hormones
- Menarche indicates "intensity" of hormonal exposure during adolescence

Adapted from Apter & Vihko, J Clin Endocrinol Metab, 1983

# Are hormone levels in adulthood associated with age at menarche ?

- Apter, Vihko and colleagues would say yes:
  - Using recorded age at menarche
    - Early menarche (<12 y) associated with higher estradiol levels in adolescence
    - Early menarche associated with higher follicular but not luteal phase estradiol levels in women 20-31 yr
    - Few women in the later study

*Acta Endocrinol 1983;107:413; J Steroid Biochem 1983;20:231; Int J Cancer 1989;44:783*

# Are hormone levels in adulthood associated with age at menarche ?

- Among 106 Caucasian and 39 Shanghai Chinese women ages 33-38 y, Bernstein would say maybe No?
  - Using self reported age at menarche
  - No evidence of effect of age at menarche on estrogen (estrone, estradiol or urinary estrogens) in follicular or luteal (Chinese) phase

*Bernstein et al Cancer Causes Control 1991;2,221*

# What do we know?

Secular trends:

* Increasing rate of obesity
* Earlier age at onset of puberty
* Earlier age at menarche

But reaching full maturity at same age, so extending the duration of puberty

Ethnic variation in trends, in cyclic fluctuation of hormone levels, & risk of premenopausal breast cancer

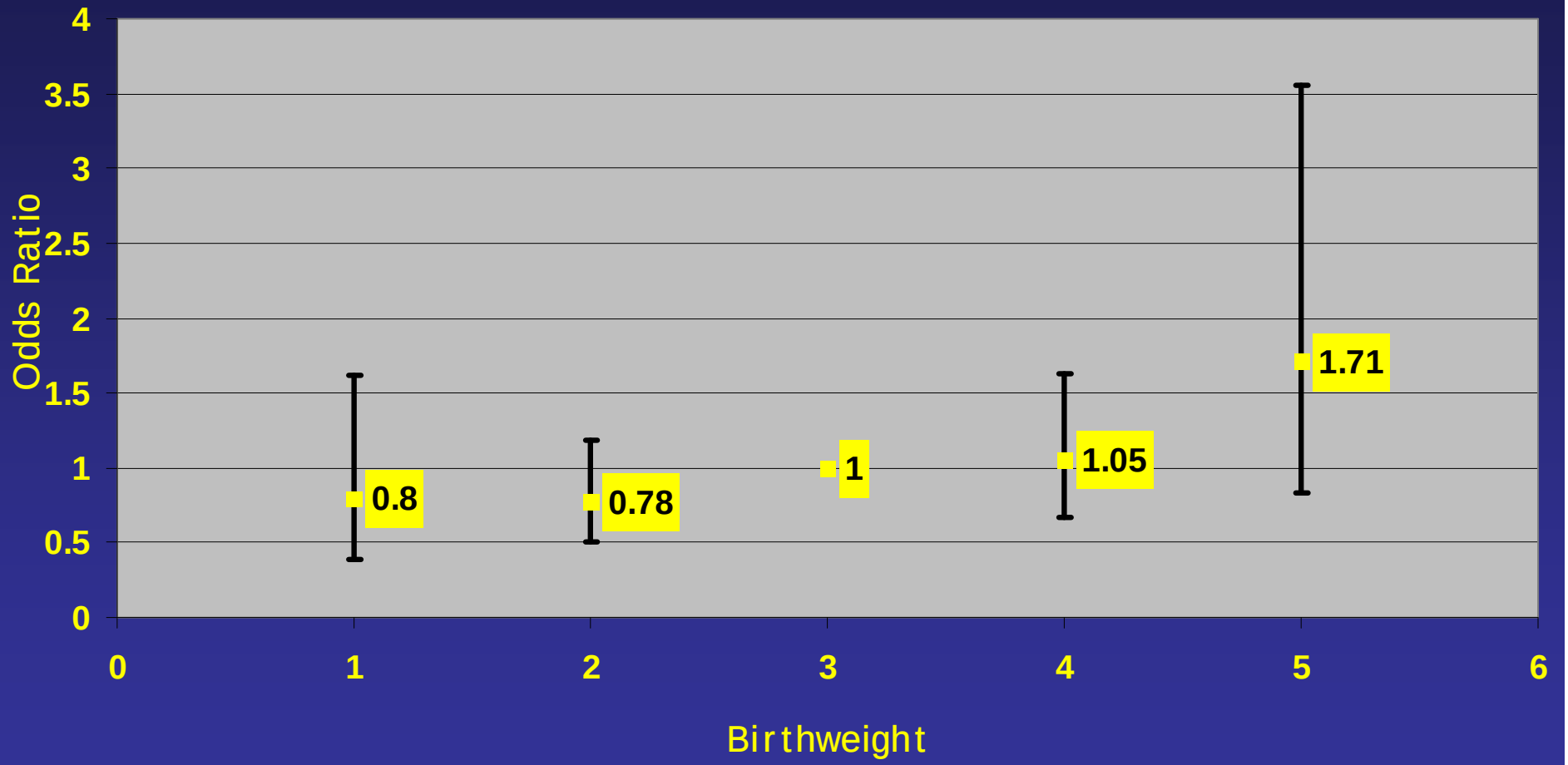
African-Americans > Mexican-Americans > non-Hispanic whites

# Early life exposures: In utero

High birthweight ~ early breast development in girls aged 8-11 years.

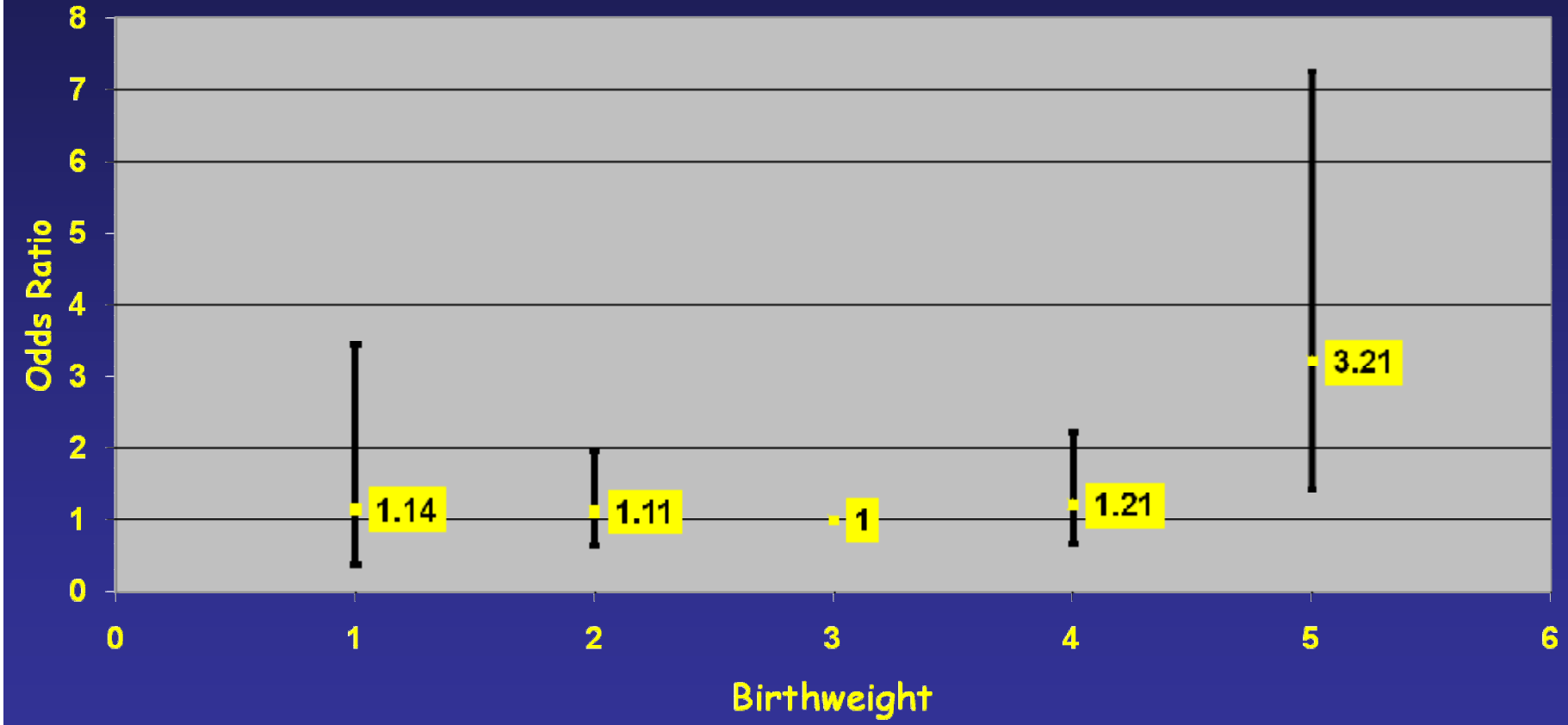
NHANES III

# Adjusted OR (95% CI) for Tanner Stage B2 by birthweight NHANES III 1988-1994 (Olivo-Marston S, Forman MR; 2010)




1 = < 2.5 kg; 2= 2.5 -2.9; 3= 3.0-3.5; 4=3.5-3.9; 5= 4.0+ kg

# Adjusted OR (95% CI) for Tanner Stage B3,4,5 by birthweight NHANES 1988-1994 (Olivo-Marston S, Forman MR; 2010)




1 = < 2.5 kg; 2= 2.5 -2.9; 3= 3.0-3.5; 4=3.5-3.9; 5= 4.0+ kg

# Early life exposures: In utero

Physical activity in pregnancy delays age at menarche.

And Gestational weight gain increases risk of early menarche

MOTHERS of the Nurses' Health Study

# Maternal Cohort Study: Design

- Maternal reporting of prenatal, infant, and early childhood exposures of nurse daughters by questionnaire
  - Baby books and birth certificates
- Maternal data linked to prospective cohort study of nurse daughters (NHSII)
- Bi-annual follow-up of the nurse cohort
- Sample: Nurses from NHS II who were free of cancer in 2000 and reported their mothers were alive in 1996
- N = 26,512 Nurse Daughters in NHSII

# Delay in Daughter's Age at Menarche (months) by Maternal Physical Activity during pregnancy

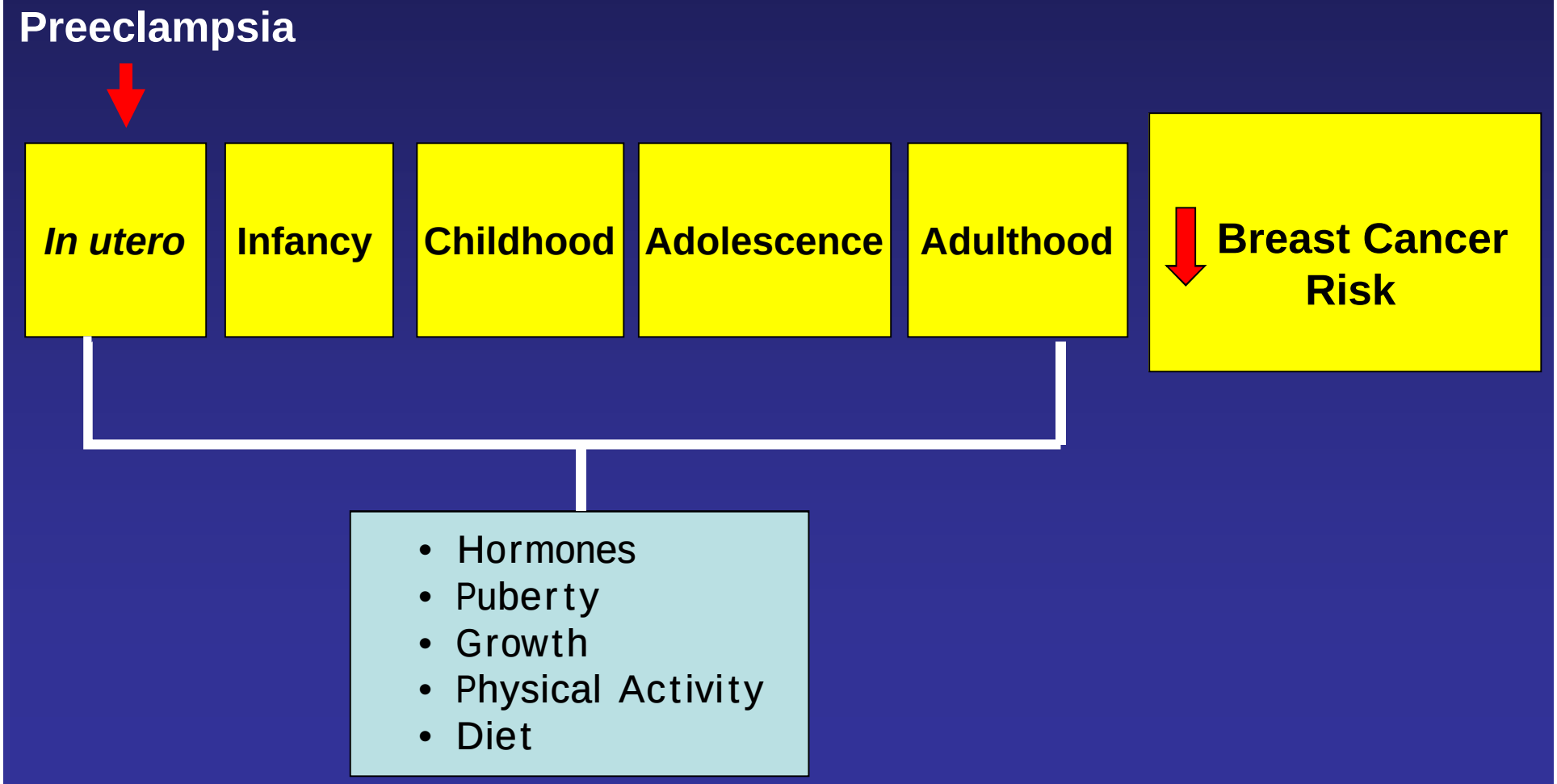
| Home & Leisure Activity | Mean Difference (95% CI) |
|---|---|
| Inactive | 1.00 |
| Mostly Inactive | 0.7 (-1.2, 2.6) |
| Active | 1.0 (-0.9, 3.0) |
| Mostly Active | 1.3 (-0.7, 3.3) |
| Highly Active | 3.0 (0.3, 5.7) |
| *P for trend* | *0.01* |

(Colbert L, Graubard BI, Michels K, Willett WC, Forman MR CEBP 2008)

# In utero exposures

- Maternal physical activity and weight gain---energy balance—influences age at menarche
- Birthweight ~ pubertal status

# Life Course: Hypotheses Related to Early Exposures & Cancer Risk or Protection



# Adjusted OR for breast cancer in the mother or daughter by pre-eclampsia (yes/no) (Forman MR Cancer Invest 2005)

| Maternal risk | OR |
|---|---|
| Polednak (1983) | 0.3* |
| Thompson (1989) | 0.7* |
| Troisi (1998) | 0.8 |
| Vatten (2002) | 0.8 |
| Innes (2000) | 0.9 |
| Paltiel (2003) | 1.4* |
| **Daughter's risk** | |
| Ekbom (1997) | 0.4* |
| Sanderson (1998) | 0.8 |
| Innes (2000) | 0.9 |

* 95% CI excludes one

## Adjusted RR of Maternal Breast Cancer in Pre-eclamptics & Normotensives: Norway

| Pregnancy | Br. Cancer | R.R. (95% CI) |
|---|---|---|
| Pre-eclampsia | 503 | 0.86 (0.78-0.94) |
| Normotensive | 1081 | 1.00 (ref) |

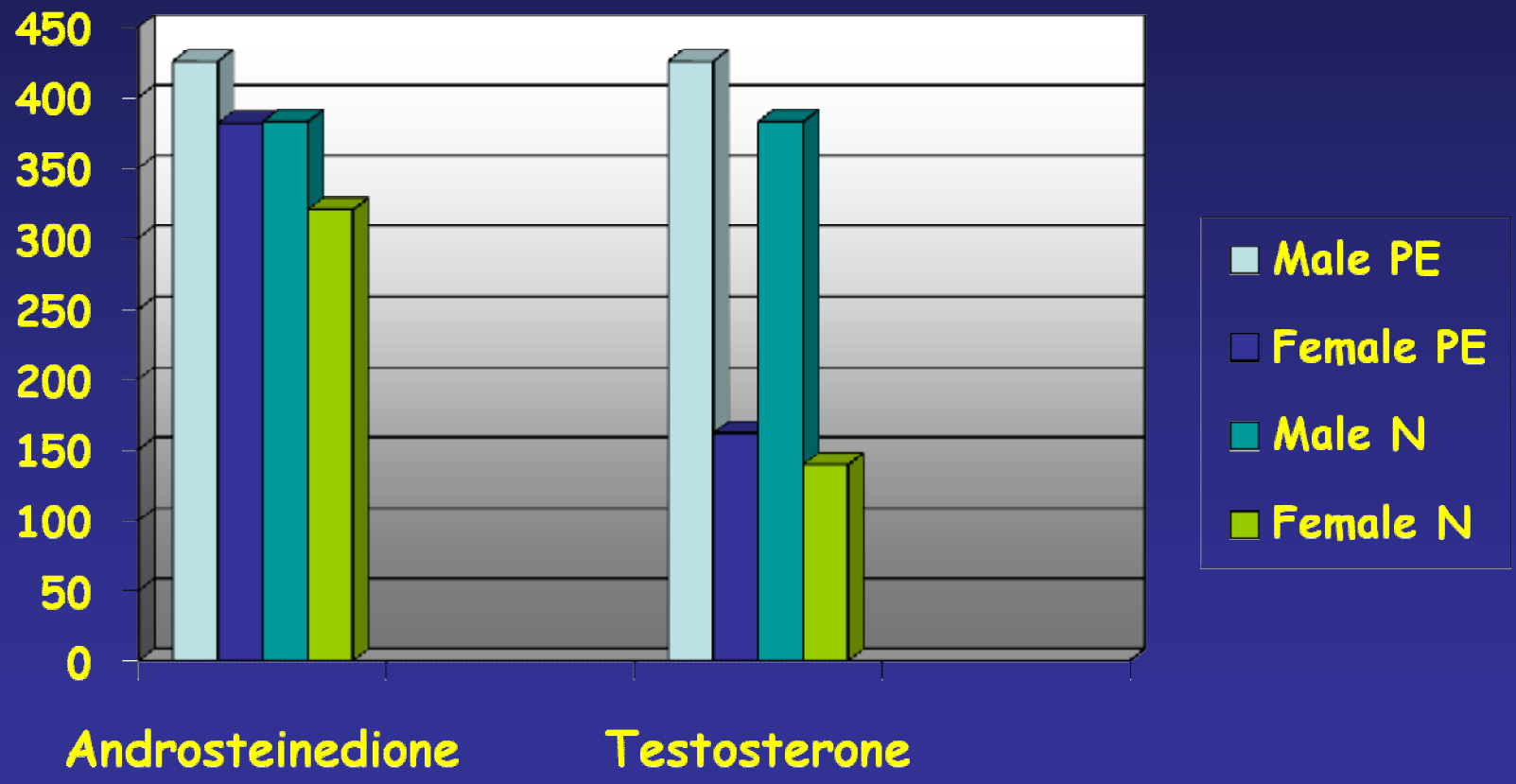
(Vatten LJ, Forman MR: Br J Cancer 2007)

# Adjusted RR of Maternal Breast Cancer in Pre-eclampsia: Norway

| Pregnancy | Br. Cancer | RR (95% CI) |
|---|---|---|
| Sons | | |
| Pre-eclampsia | 246 | 0.79 (0.60-0.90) |
| Normotensive | 4468 | 1.00 (ref) |
| Daughters | | |
| Pre-eclampsia | 252 | 0.94 (0.86-1.06) |
| Normotensive | 4194 | 1.00 (ref) |

(Vatten LJ, Forman MR: Br J Cancer 2007)

# Mean* maternal androstenedione & testosterone levels by gender of the offspring in 86 PE and 86 Normotensive women before delivery




*Means are adjusted for maternal age and gestational age of the neonate.

(Troisi: BrJCa 2007)

# Pre-eclampsia

3 to 5 % of pregnant women

Familial clustering: 5-fold risk in first degree relatives

Offspring: - SGA, Preterm, LGA

Clinical Diagnosis:

- DBP $\geq$ 90mm Hg
- Proteinuria > 0.3 mg/l
- Severity varies by DBP, proteinuria, onset

# Stavanger Study

12,804 births from January 1993 to December 1995

307 cases of pre-eclampsia

2 sets of controls Normotensives (NT) per PE case

Design: Nested case-control study

Follow parents and daughters of the nested case-control study population at ages 10.8 y & 12.8 y.

# Maternal characteristics and gestation data by severity of PE and in NT controls: Stavanger Study

| | Pre-Eclampsia | | Controls |
|---|---|---|---|
| | Severe (n=67) | Mild (n=191) | (n=609) |
| Maternal age (μ) | 26.4 | 27.2 | 28.3 |
| Nulliparous (%) | 70 | 63 | 36 |
| Maternal smoking (%) | 16 | 19 | 27 |
| Gestational age at birth (days) | 249 | 270 | 280 |
| SGA (%) | 17 | 8 | 3 |

(Vatten LJ, *Obstet Gynecol* 2002;99:85-90)

# Follow-up of the Stavanger Pre-eclampsia Study

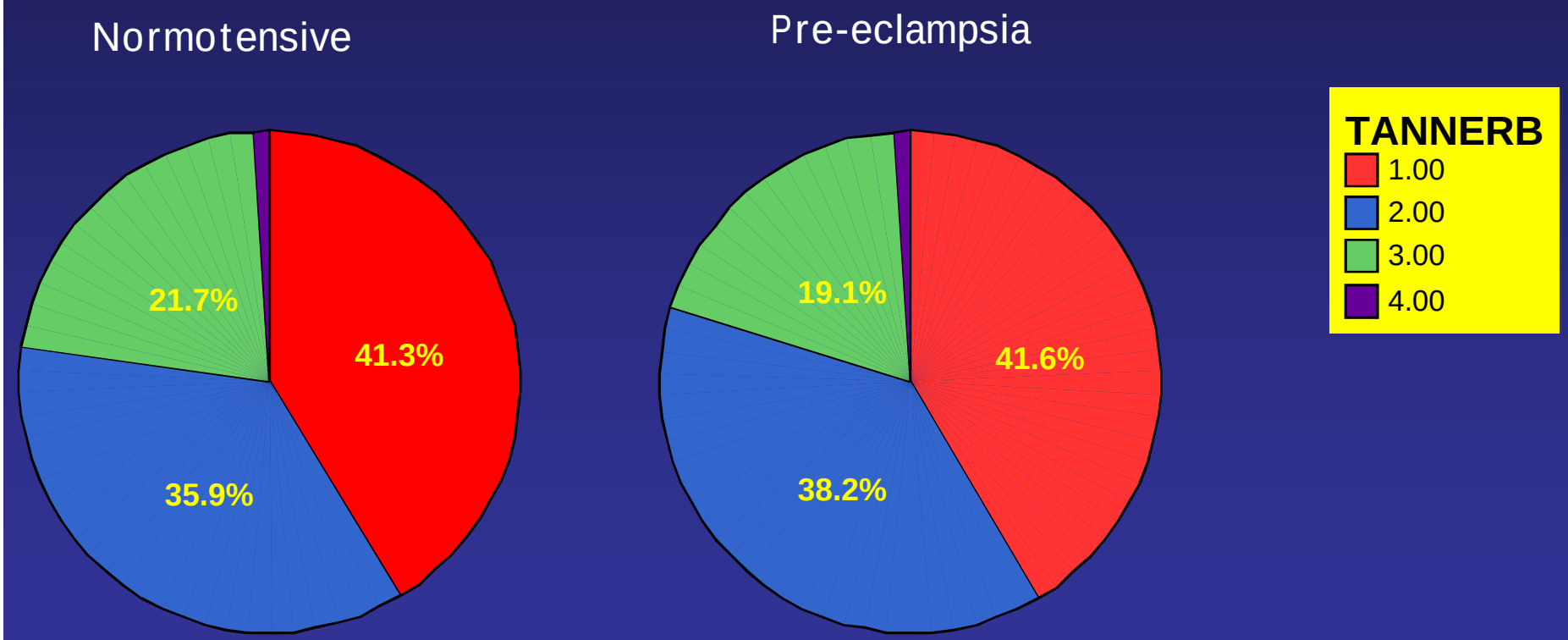
Aims

To compare:

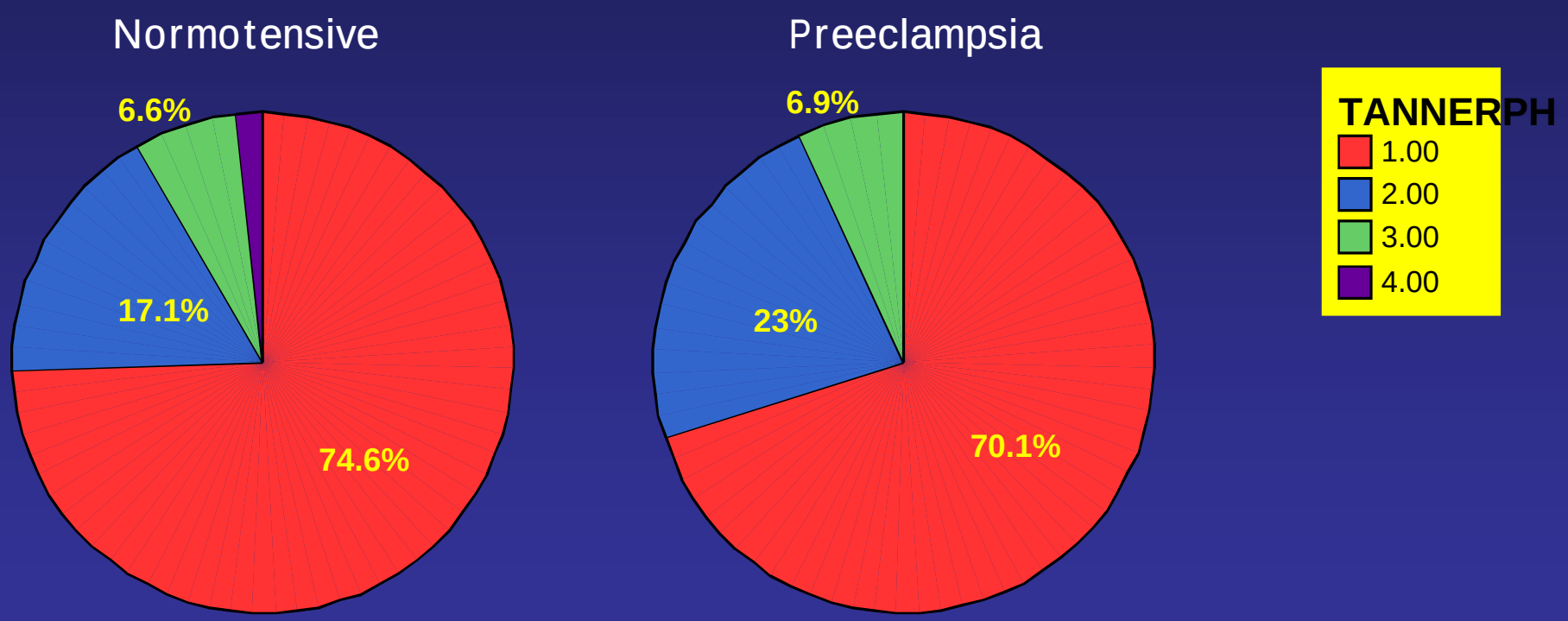
Tanner Stage, anthropometrics, and hormone levels in offspring of the pre-eclampsia group to offspring of normotensives.

Expect that offspring of PE will delay puberty, be shorter height-for-age & larger BMI, and have ↓ IGF-1 and ↑ androgens & leptin.

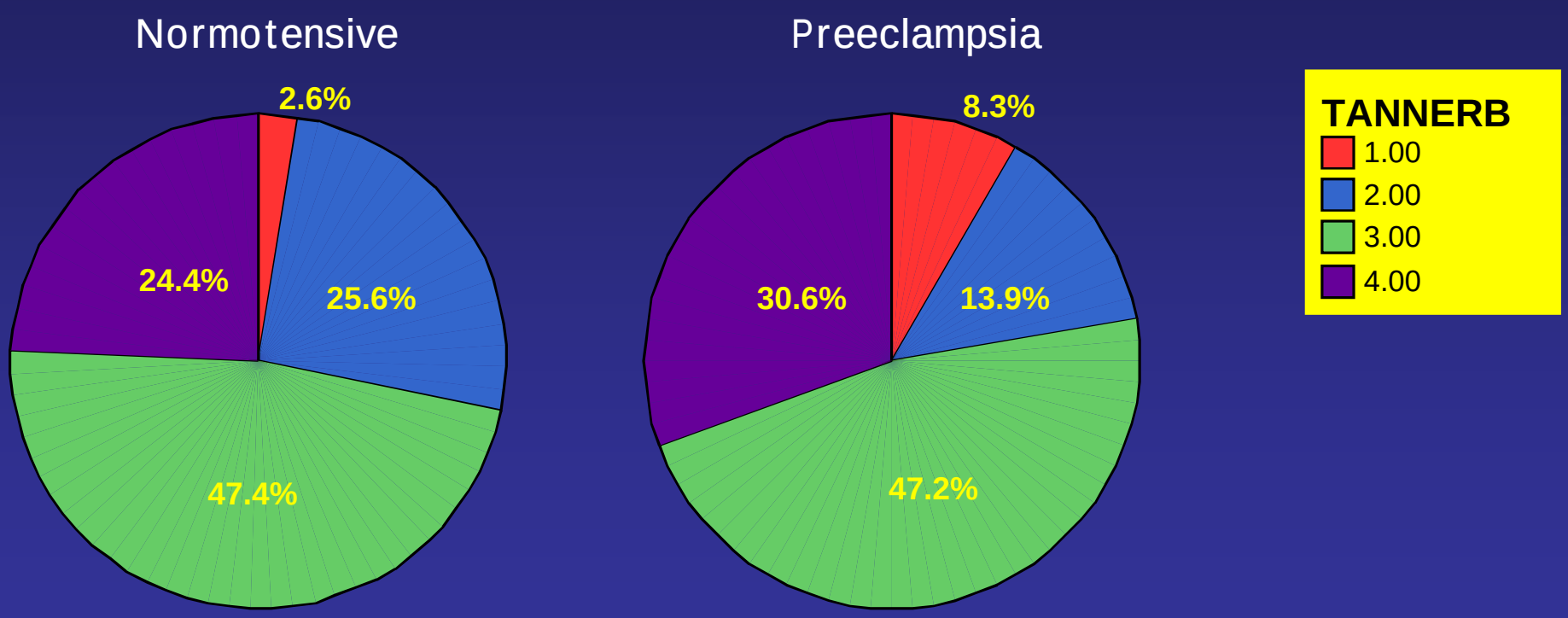
# Breast Development 10.8 years: No difference in Tanner Stage.



# Pubic hair 10.8 years: No difference

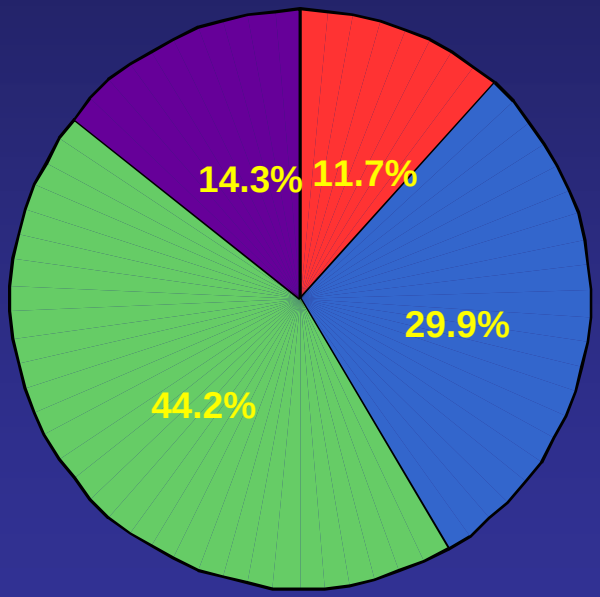


# Breast Development 12.8 years. PE have higher % pre-pubertal

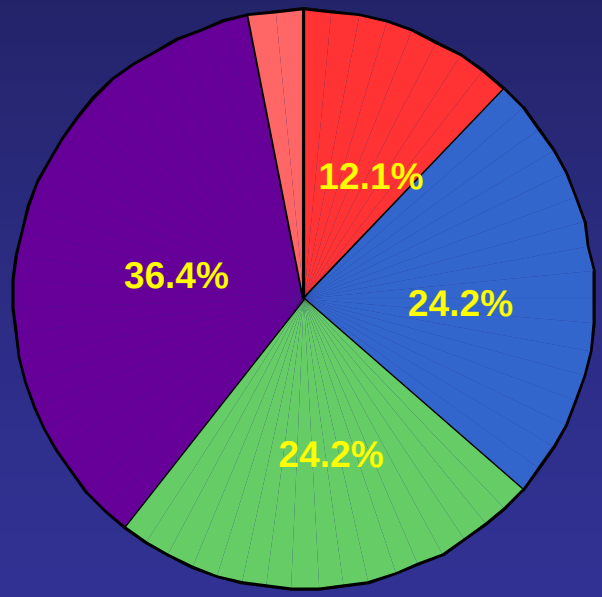


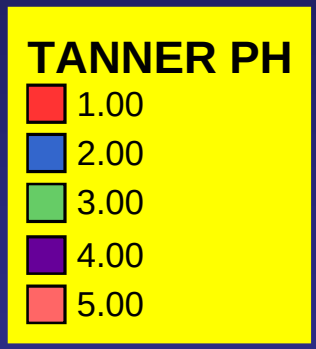
# Pubic hair 12.8 years. More advanced Tanner score in PE.

Normotensive




Pre-eclampsia



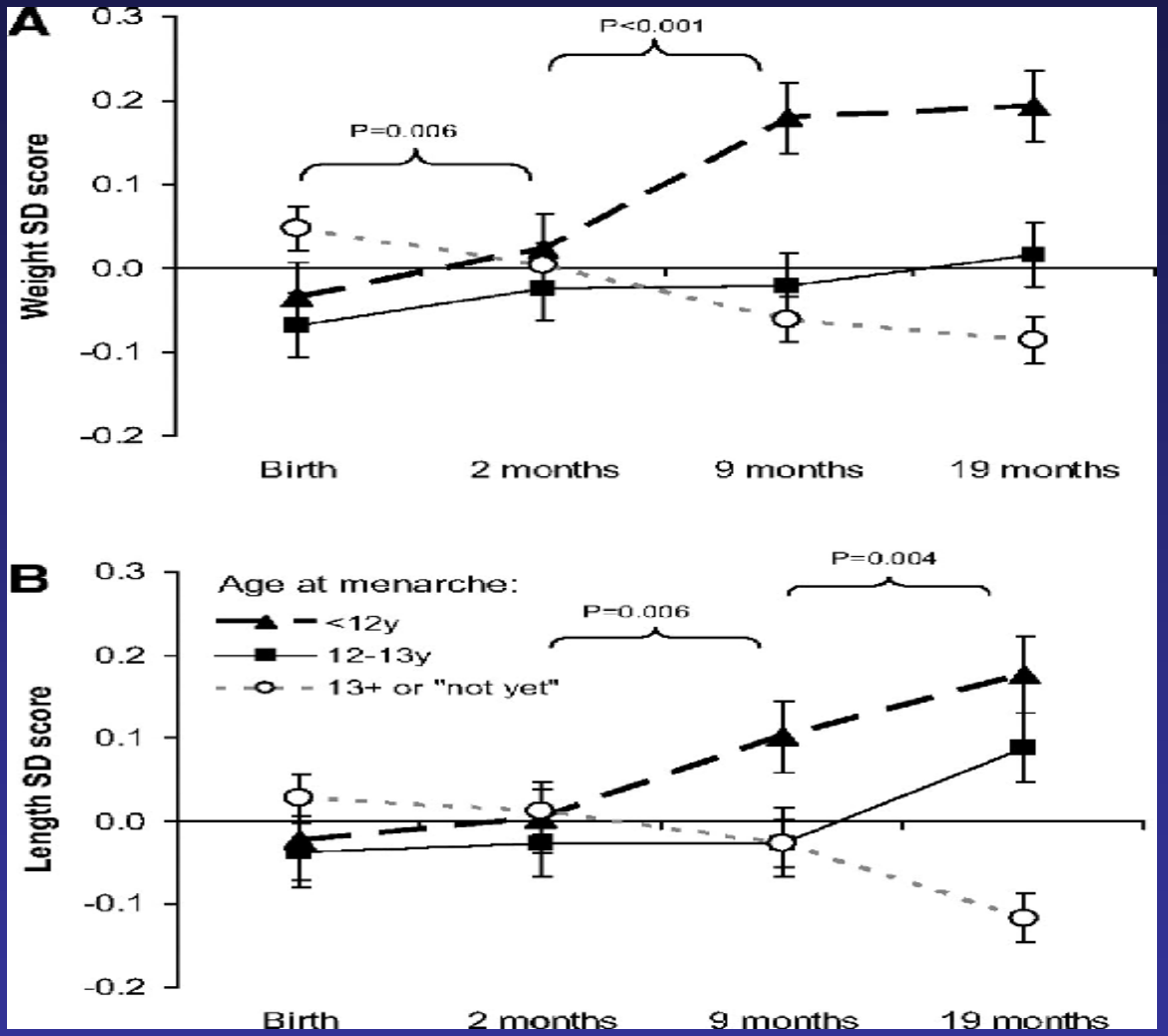



# Odds ratio (OR) for Pathway of Pubertal Development in daughters of Preeclampsia compared to Normotensive pregnancies (Ogeland B, Forman MR, Vatten L: Arch Dis Childhd in press)

| Pathway | Normotensive | Preeclampsia | OR (CI) |
|---|---|---|---|
| Adrenarche (Pubic hair) | 8.1 | 17.9 | 2.14 (1.07-4.30) |
| Symmetrical | 28.8 | 31.6 | 1.00 (Referent) |
| Thelarche (Breast) | 62.9 | 50.4 | 0.52 (0.33-0.83) |

Referent group were classified simultaneously as both pubertal for adrenarche/pubic hair and thelarche/breast development of Tanner stage 2.

# Age at menarche in girls by infancy weight gain (A) & infancy growth rates (B):
## Avon Longitudinal Study of Pregnancy and Childhood




Δ < 12

□ 12-13

○ > 13 y

**Ong, K. K. et al.**

**J Clin Endocrinol Metab**

**2009;94:1527-1532**

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

# Early Life Exposures: Childhood

Body size & family conflict are directly related to risk of early menarche in Mexican American girls.
MATCh


# Mexican American Tobacco Use in Children (PI: Spitz MR)

Longitudinal cohort study

Follow-up (3 years)

- Baseline and final home visits
- Phone calls every six months

Home Visit

- Collect buccal sample
- Survey on PDA to maintain privacy

# OR (95% CI) for Early age at menarche (≤ 11y) among Mexican American Girls (Thelus-Jean R, Wilkinson A, Bondy ML, Spitz MR, Forman MR Submitted)

| BMI For Age | N=522 | N=461 |
|---|---|---|
| *Normal* | 1.00 (REF) | 1.00 (REF) |
| *Overweight* | 2.01 (1..24- 3.25) | 2.15 (1.25-3.71) |
| *Obese* | 1.49 (1.01- 2.21) | 1.06 (0.68-1.67) |
| Height | ----- | 1.02 (0.96-1.01) |
| Age at baseline | ----- | 0.66 (0.51-0.86) |
| Family Conflict | ----- | 1.60 (1.07-2.37) |
| Marriage | ----- | 1.77 (0.94-3.36) |
| Mother's age at menarche | ----- | 0.82 (0.73-0.92) |

# Conclusions In utero Exposures

- High birthweight ~ 70% to 3 fold higher odds of breast development in girls 8-11 years.
- Compared to nurse daughters of inactive mothers, those who had physically active mothers in the index pregnancy delayed menarche by 3 months on average.
- Maternal pre-pregnancy physical activity and weight gain at the extremes are associated with age at menarche in the nurse daughter.

# Conclusions

Stavanger Puberty Study:

- No differences in breast or pubic hair development at 10 years among PE and NT girls.
- Girls of NT pregnancies who experienced the greatest weight gain at 3-6 months had a higher odds of breast development at 10.8 .
- Girls of PE pregnancies who experienced the greatest weight gain at 6-12 months had a higher odds of breast and pubic hair development at 10.8 years.
- Higher percent of PE have pubic hair development but lower percent of PE have breast development at 12 years than NT girls.

# Conclusions

MATCh:

- High BMI and family conflict increase the risk of early menarche.
- The later the maternal age at menarche, the lower the risk of early menarche in Mexican American girls.

# What am I going to tell you?

In utero

- Birthweight ~ pubertal stage
- Maternal energy balance in pregnancy ~ daughter's age at menarche

Infancy

- Age of greatest weight gain ~ pubertal status

& age varies by maternal preeclampsia

- Age of greatest weight gain ~ age at menarche

Childhood/youth

- Body size and family conflict ~ earlier menarche in Mexican American girls.

# Early Life Exposures

In utero exposures plus cumulative adaptive response to environmental exposures— which involve changes in the epigenome, proteome, transcriptome and genome—through the life course

Lead to risk of: early onset of puberty, early age of menarche, obesity, diabetes, and cancer

*(Burdge GC, Lillycrop KA, JacksonAA, Br J Nutr 2009; Burdge GC, Lillcrop KA,, Nutrition, Epigenetics, and Developmental Plasticity: Implications for Understanding Human Disease, Annu Rev Nutr 2010;30:315-339)*

# Collaborators

Stavanger study:
- Pal Romunstad
- Lars Vatten
- Bjorn Ogland
- Stein Tore Nilsen
- Lisa Colbert
- Fred Kadlubar
- J. Carl Barrett

Mothers:
- Walter Willett
- Karin Michels
- Barry Graubard
- Alison Stuebe
- Lisa Colbert
- Renee Boynton-Jarrett
- Janet Rich-Edwards

MDACC:

Stavanger
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- Barry Graubard

Please contact the authors of submitted or unpublished data before use!