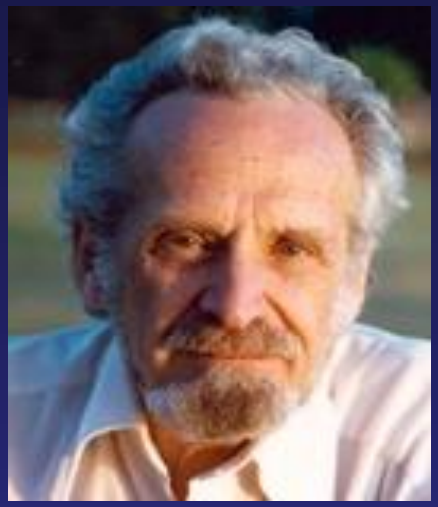
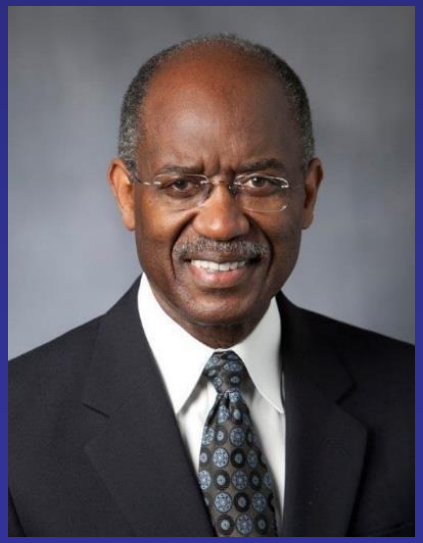
My Epidemiology Mentors at UNC



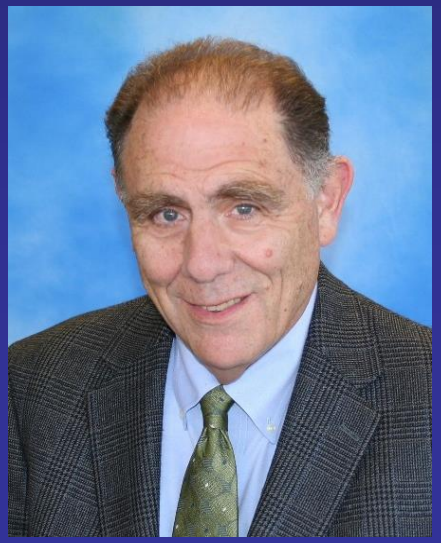
Al Tyroler: My MSPH mentor
Broad lens on the environment and chronic disease

John Cassel
Social change & Health

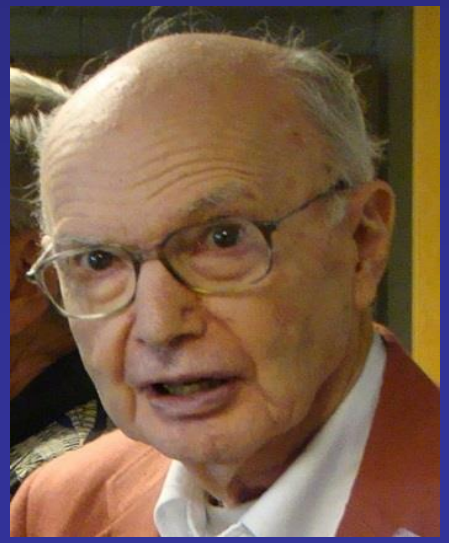
Sherman James
Psychological lens on hypertension



Ed Wagner
Primary mentor



Bert Kaplan
Who Found ME!



Facing Obesity & Co-morbidity in Mothers & Offspring: *A Life Course Approach*

Michele R. Forman, Ph.D.
Distinguished Professor and
Head Department of Nutrition Science
Purdue University

From Semi-nomad to Curious Nutrition Epidemiologist

Great Depression of 1929 on hypertension in adulthood

Infant feeding (IF) research in the deserts of the world:

Arizona, Israel/ Egypt, Tunisia,

Now: Lebanon

RCTs:

Vitamin A

Polyp prevention trial (adults)

National Children's IF and Growth

Nurses' Health Study

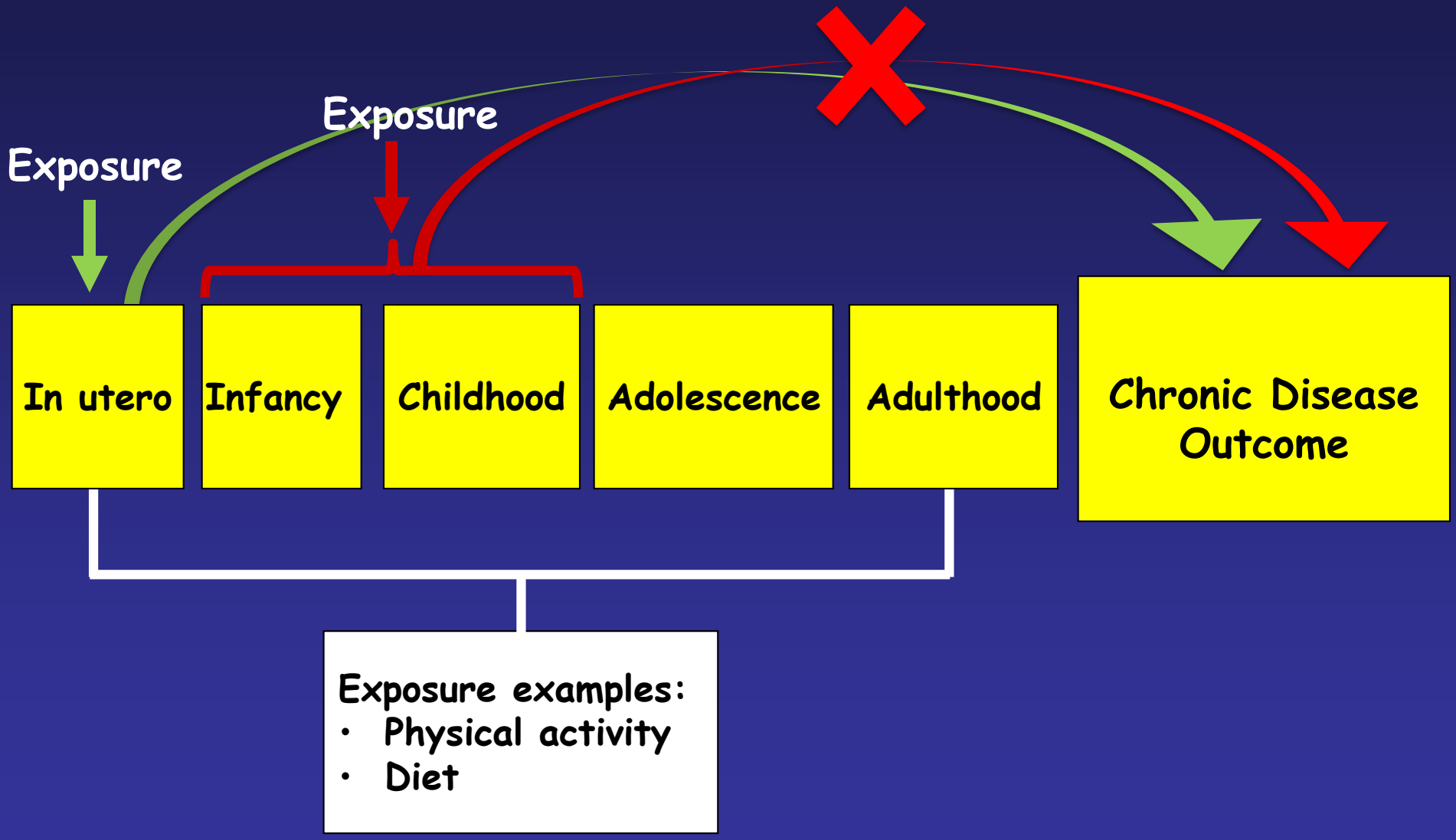
Early life exposures, epigenome & chronic disease risk

Developmental Origin of Disease: Life Course Research

In utero and early life exposures influence growth, development and risk of disease across the life course

David Barker 1998

Timing Matters: Windows of Susceptibility



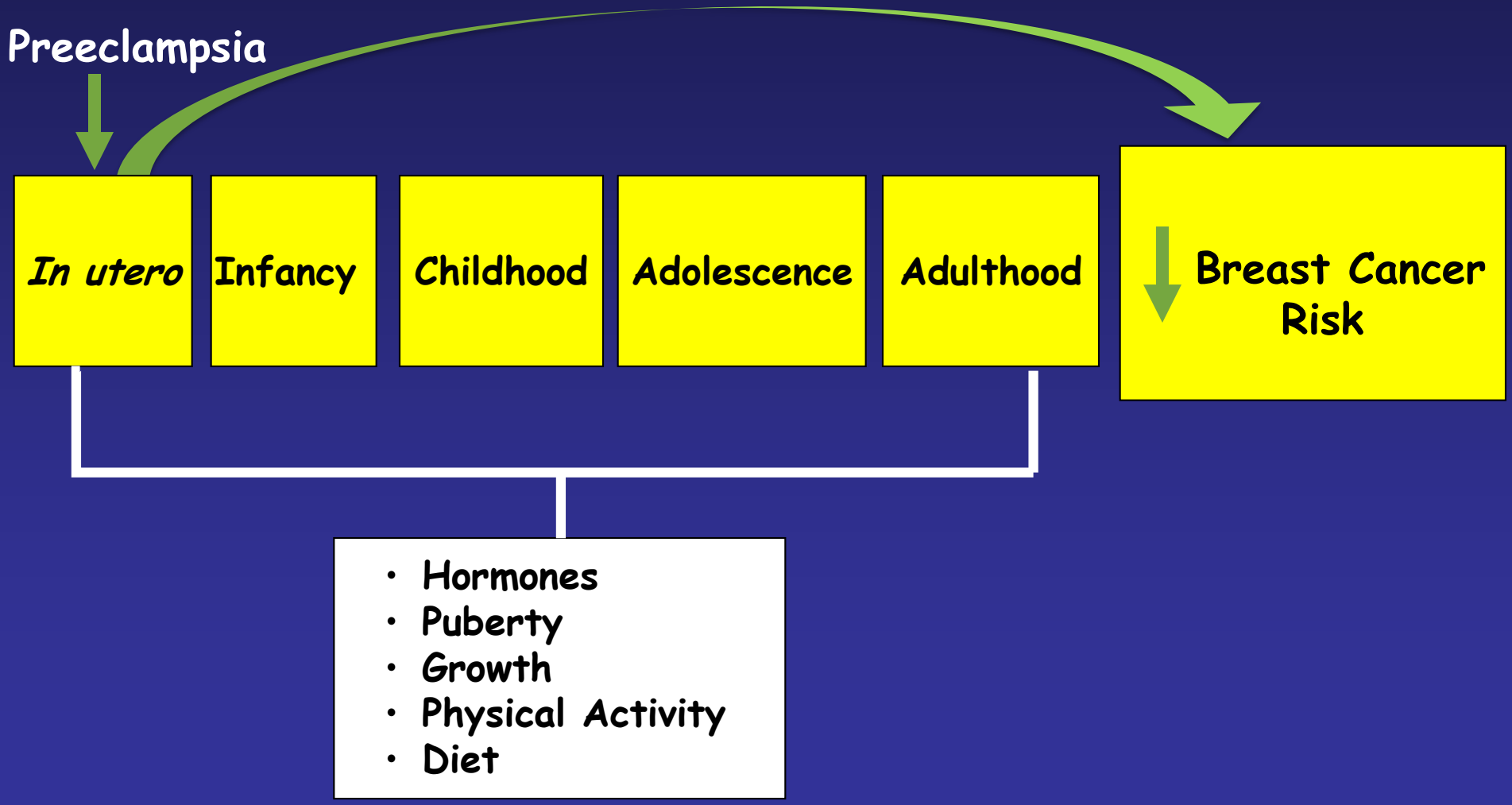
Overview

Part I — Life course of preeclampsia

Part II — The obesogenic environment *in utero* and in early childhood

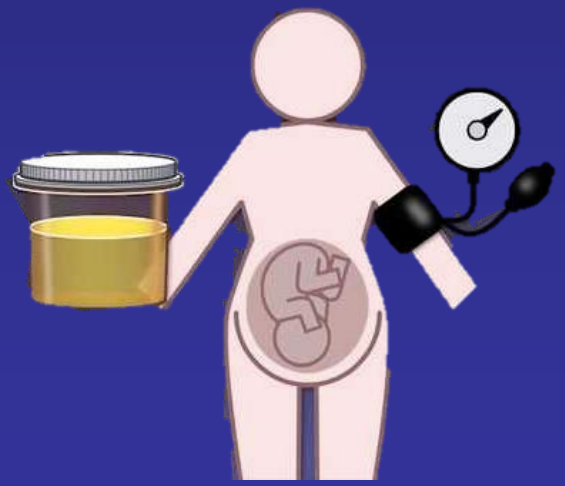
Part III — Growth in infancy: new assessment approaches

Part I: Life course of Preeclampsia

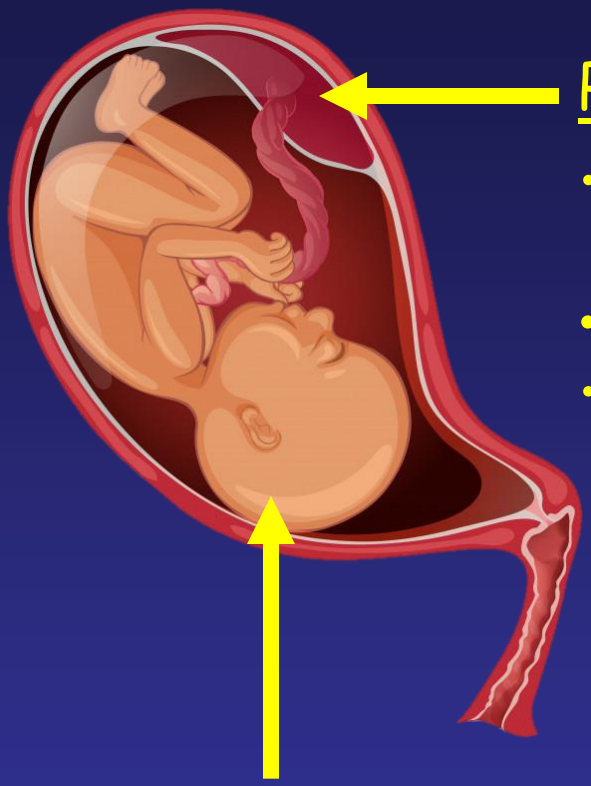


Introduction to Preeclampsia

- 3 to 8% of pregnant women
- Repeaters
- Classical Clinical Diagnosis
  - DBP ≥ 90mm Hg
  - Proteinuria > 0.3 mg/l
- Severity varies by DBP, proteinuria, onset



Preeclampsia: A Placental Disease

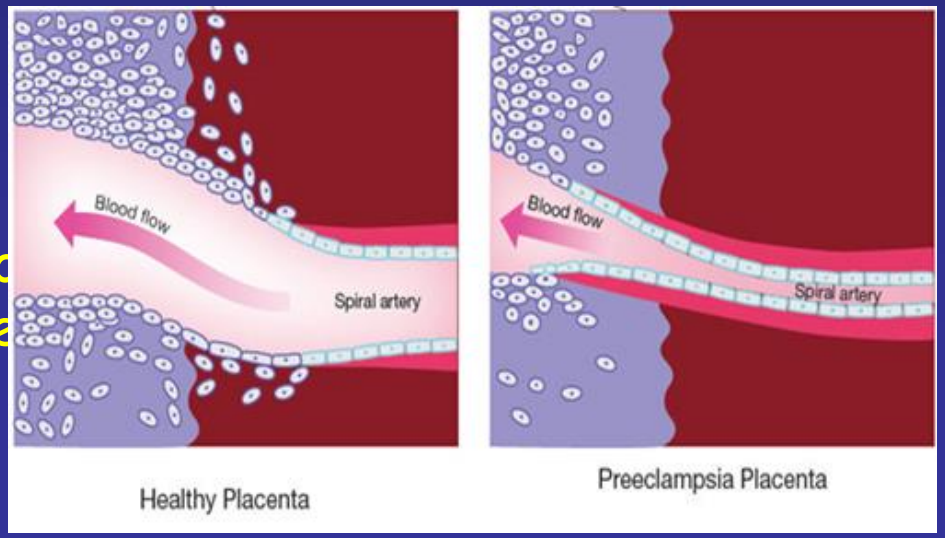


Placenta:

- "Shallow" penetration of the spiral arteries → ischemia and uteroplacetal perfusion
- Arrest at an early immature state
- Deficiency of aromatization of androgens to estrogens:
  - ↑ Androgens & Progesterone
  - ↓ Estrogens & IGF-1

Offspring:

- Blood shunt to brain & heart c
- Small Gestational Age & Prete
  Gestational Age



Cerdiera AS 2017; Mol BWJ 2016

Breast Cancer Risk in the Mother or Daughter By Pre-eclampsia Status

Prior Research*

Maternal Risk:
70% lower to 40% higher

Daughter's Risk:
10-60% lower

Norwegian Data**

Maternal Risk:
14% lower
(OR = 0.86; 95% CI: 0.78-0.94)

Stratified by Offspring Sex

*Forman MR Cancer Invest 2005

**Vatten LJ, Forman MR: BrJCa 2007

Breast Cancer Risk by Pre-eclampsia Status and Sex of the Offspring

Offspring sex	Preeclampsia status	Breast cancer	
		N	RR (95% CI)
Sons	Preeclampsia	246	0.79 (0.60-0.90)
	Normotensive	4468	1.00 (ref)
Daughters	Preeclampsia	252	0.94 (0.86-1.06)
	Normotensive	4194	1.00 (ref)

Vatten LJ, Forman MR: Br J Cancer 2007

Preeclampsia reduces the risk of breast cancer in mothers and daughters.

Stavanger Puberty Study

Who?

case

When?

- At birth. 1993-1995
- First follow up 10.5 y.
- Second follow up 13 y.

Nested case-control
study in 3 birth cohorts

How?

- Follow up enrollment by letters

Follow-up Study at Puberty

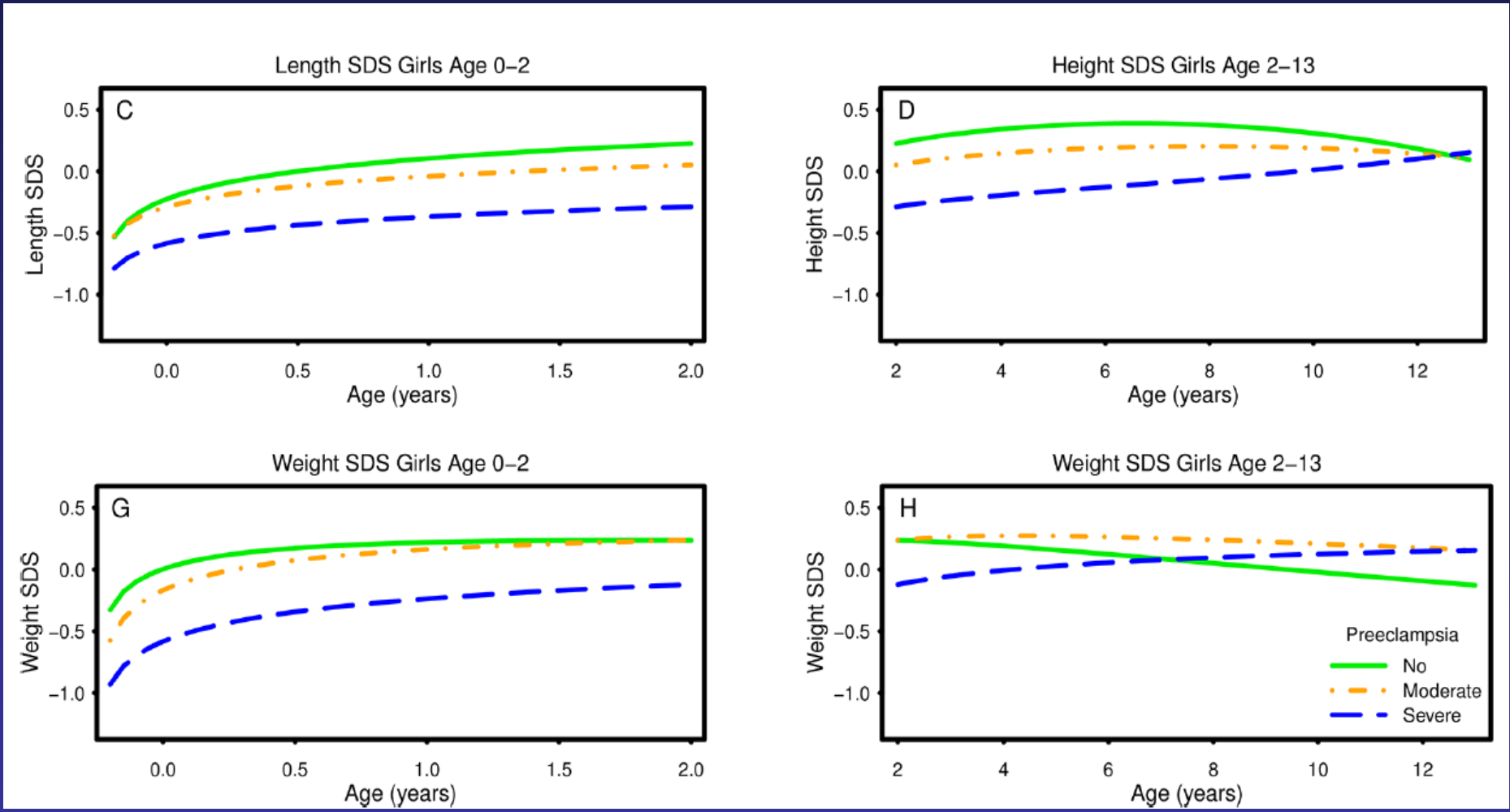
Aims

- To compare the offspring of pre-eclampsia (PE) to offspring of normotensives by
  - Tanner Stage
  - Anthropometrics
  - Hormone levels

Hypotheses

- Offspring of PE will:
  - delay puberty
  - be shorter and heavier
  - have ↓ IGF-1, estrogens and ↑ androgens and leptin

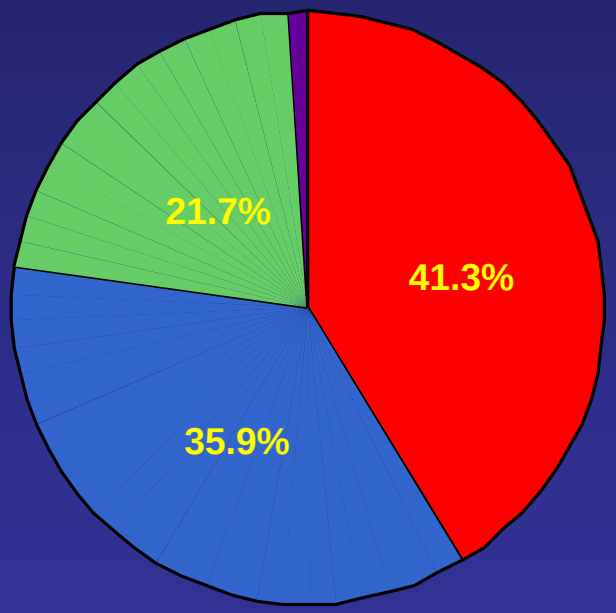
Growth Trajectories from Birth to 13 Y. for Girls by Severity of PE



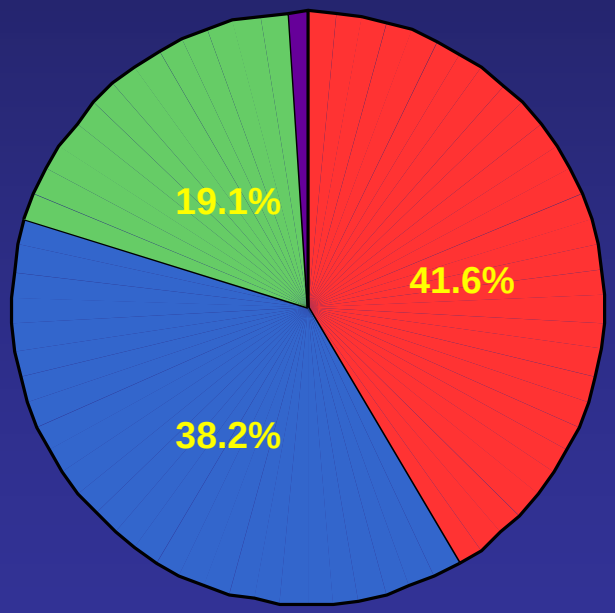
Byberg KK et al Plos One 2017

Breast Development at 10.8 Y.: No difference in Tanner Stage

Normotensives



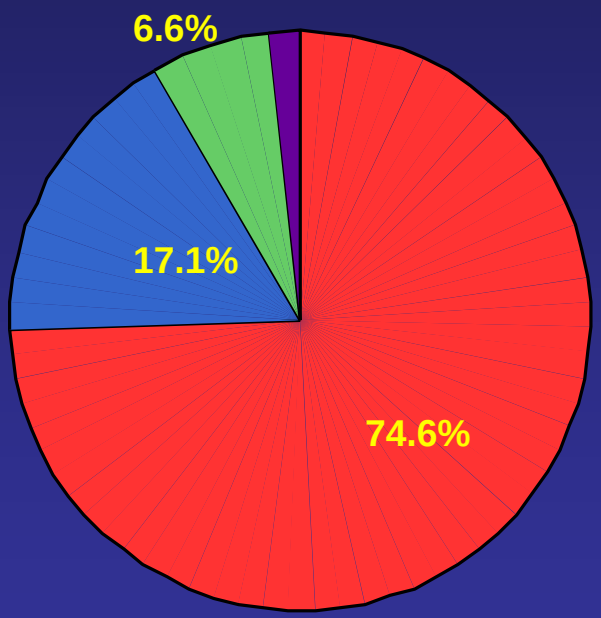
Pre-eclampsia



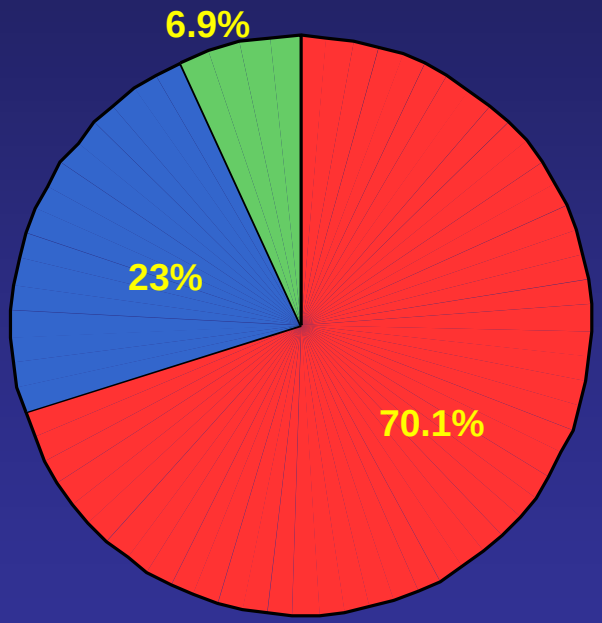
Ogland B, Nilsen ST, Forman MR: *Arch Dis Childhood* 2010

Pubic hair at 10.8 Y.: No difference

Normotensives



Pre-eclampsia



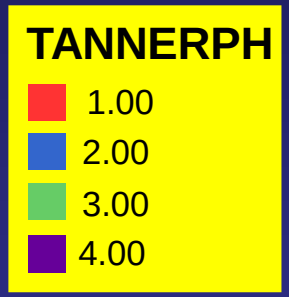


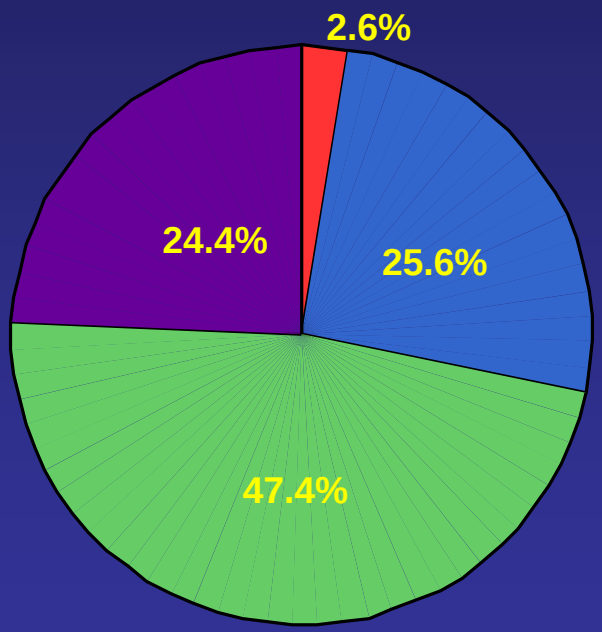
Table 4. Unadjusted and adjusted odds ratios for thelarche at 10.8 years among exclusively breastfed girls				
	Unadjusted[3]	Early life model[4]	Childhood model[5]	Adjusted model[6]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Duration of exclusive breastfeeding				
6 – 9 months	0.82 (0.36 – 1.89)	0.68 (0.28 – 1.66)	-	0.59 (0.19 – 1.82)
> 9 months	1.00	1.00	-	1.00
Age started solids				
3 - 6 months	1.00	1.00	-	1.00
6 - 9 months	0.75 (0.45 – 1.25)	0.58 (0.27 – 1.22)	-	0.57 (0.22 – 1.44)
PE exposure	0.54 (0.27 – 1.07)	**0.47 (0.23 – 0.97)**	-	**0.29 (0.11 – 0.76)**
Per extra weekly dairy consumption event[1]	0.98 (0.96 – 1.00)	-	0.98 (0.95 – 1.01)	0.97 (0.94 – 1.01)
Per extra weekly protein consumption event[2]	0.97 (0.91 – 1.04)	-	1.05 (0.93 – 1.18)	1.04 (0.91 – 1.18)
Maternal BMI (kg/m^2)				
18.5 – 24.99	-	-	1.00	1.00
25 – 29.99	-	-	**6.29 (2.05 – 19.29)**	**5.71 (1.65 – 19.84)**
≥ 30	-	-	1.17 (0.29 – 4.68)	1.12 (0.25 – 4.93)
Height (cm)	-	-	1.04 (0.95 – 1.13)	1.01 (0.91 – 1.11)
Weight (kg)	-	-	**1.11 (1.02 – 1.20)**	**1.15 (1.04 – 1.26)**

Jeremy Schraw Ph.D.

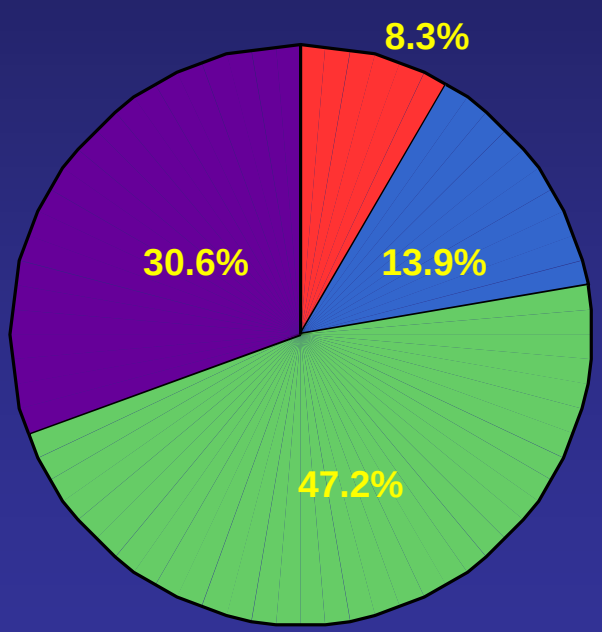
Schraw JM … Forman MR. *Reproductive toxicology 2015* 54:19-25.

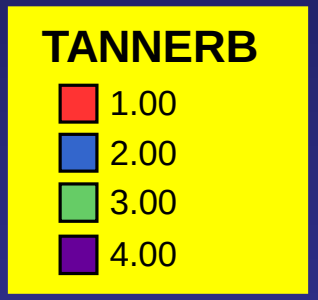
Breast Development at 12.8 Y.: PE Offspring Have Higher % Pre-pubertal

Normotensives



Pre-eclampsia

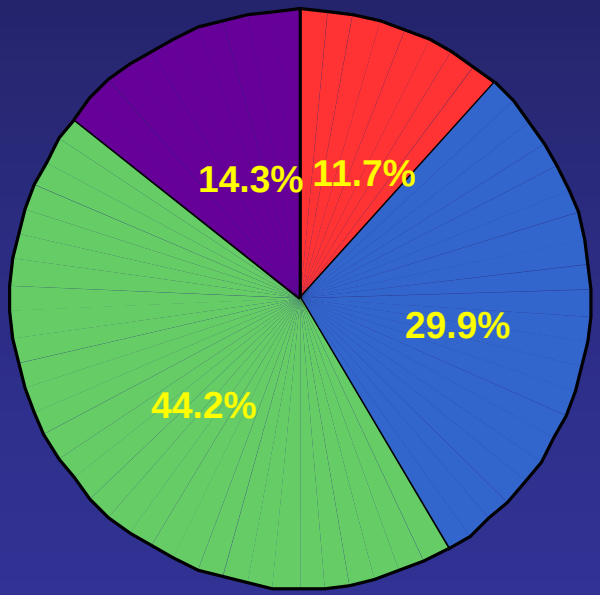




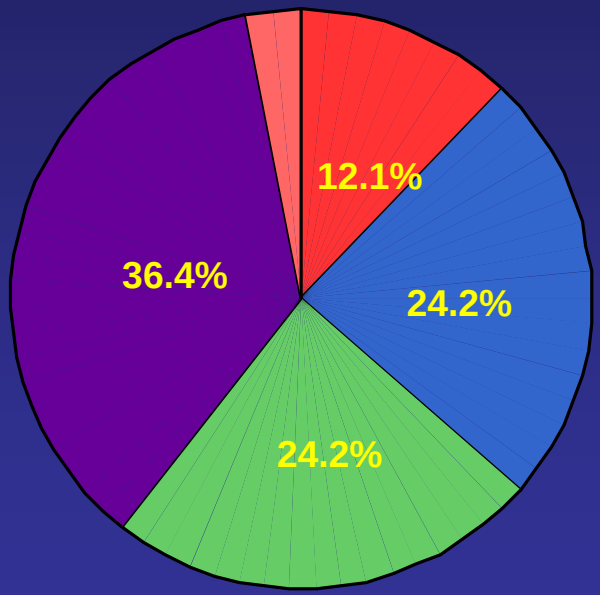
Ogland B, Nilsen ST, Forman MR: Arch Dis Childhood 2010

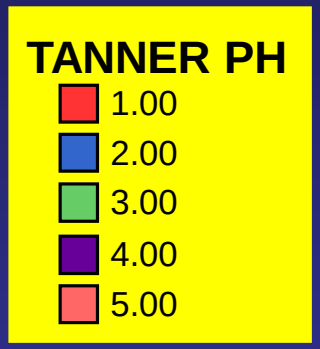
Pubic Hair at 12.8 Y.: More Advanced Tanner Score In PE

Normotensives



Pre-eclampsia





Ogland B, Nilsen ST, Forman MR: Arch Dis Childhood 2010

Maternal Health: CVD and Metabolic Syndrome

TABLE 1

Description of maternal characteristics according to preeclampsia status

Characteristic, n	No PE (n = 383)	Mild PE (n = 73)	Moderate PE (n = 91)	Severe PE (n = 54)	*P* value
Age (y), mean (median, SD)[a]	28.5 (28.2, 4.8)	27.7 (26.8, 4.5)	27.3 (26.9, 4.5)	26.8 (27.0, 4.8)	.01
Weight, mean (median, SD)[b]	69.0 (67.6, 13.1)	76.8 (73.8, 16.4)	74.3 (70.4, 17.8)	70.2 (66.4, 11.6)	.00
BMI (kg/m^2), mean (median, SD)[b]	24.7 (24.0, 4.3)	27.5 (26.5, 5.5)	26.5 (24.6, 6.01)	25.3 (25.0, 4.4)	.00
Waist/hip ratio, mean (median, SD)[b]	0.85 (0.81, 0.68)	0.83 (0.84, 0.06)	0.81 (0.80, 0.07)	0.82 (0.79, 0.09)	.93
Pregnancy length (d), mean (median, SD)	280.6 (281.0, 10.5)	273.1 (275.0, 16.2)	268.3 (271.1, 17.4)	247.7 (253.0, 28.2)	.00
Parity, mean (median, SD)[b]	3.0 (3.0, 0.9)	3.1 (3.0, 0.8)	2.8 (3.0, 0.9)	2.6 (2.5, 0.9)	.00
Diabetes mellitus, n (%)[b]	5 (1.3)	4 (5.5)	7 (7.7)	2 (3.7)	.02
Antihypertensive medication, n (%)[b,c]	8 (2.1)	4 (5.5)	6 (6.6)	0 (0.0)	.04
Education (y), n (%)					
≤9	86 (22.8)	17 (23.3)	15 (16.9)	11 (21.2)	.67
9-12	192 (50.8)	35 (47.9)	46 (51.7)	31 (59.6)	.61
>12	100 (26.5)	21 (28.8)	28 (31.5)	10 (19.5)	.45

Alsnes I et al Am J Obstet Gynecol 2014

Maternal Health: CVD and Metabolic Syndrome

TABLE 2

Metabolic and hormonal factors among mothers and offspring approximately 11 years after the delivery, according to PE status at birth[a]

Variable	No PE (n = 383), mean (SD)	Mild PE (n = 73), mean (SD)	Moderate PE (n = 91), mean (SD)	Severe PE (n = 54), mean (SD)	*P* value
Mothers					
Total cholesterol, mmol/L	4.98 (0.05)	5.10 (0.11)	5.11 (0.10)	5.09 (0.13)	.53
HDL cholesterol, mmol/L	1.68 (0.02)	1.57 (0.05)	1.62 (0.04)	1.78 (0.06)	.03
Non-HDL cholesterol, mmol/L	3.30 (0.05)	3.53 (0.12)	3.49 (0.11)	3.31 (0.14)	.16
Glucose, mmol/L	4.81 (0.04)	5.10 (0.10)	5.17 (0.09)	4.82 (0.12)	< .001
Insulin, μU/mL	5.50 (0.26)	7.08 (0.58)	7.51 (0.54)	4.88 (0.72)	.001
HOMA-IR	1.21 (0.072)	1.64 (0.16)	1.81 (0.15)	1.07 (0.20)	< .001
Systolic BP, mm Hg	122.3 (1.33)	131.3 (3.00)	129.7 (2.74)	125.5 (3.57)	< .001
Diastolic BP, mm Hg	74.2 (0.50)	82.6 (1.14)	79.00 (1.04)	79.16 (1.36)	< .001

Alsnes I et al Am J Obstet Gynecol 2014

Summary: Life course of Pre-eclampsia

- PE Female Offspring:
  - Delayed breast development
  - Accelerated pubic hair development
  - Heavier than their peers at 11 y
  - Maternal & child's weight are associated with breast development at 10 years

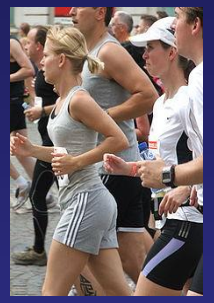
- Mothers 11 years postpartum:
  - Hypertensive
  - Overweight
  - Insulin resistant

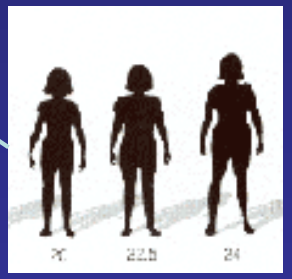
Part II: The Obesogenic Environment *in Utero* and Early Childhood

Risk Factors:
Maternal age
Hypertension
GDM
Preeclampsia
Race/ethnicity
Parity

Physical Activity

Diet





Pre-pregnancy BMI

Weight Gain

Mother's Study Design and Population

Nurses' Health Study II (NHS II)-*Daughters*

- Prospective cohort begun 1989
- 116,430 female nurses
- Reported health behaviors and medical history

Nurses' Mothers' Cohort Study-*Mothers*

- Retrospective cohort begun 2001
- 35,696 mothers of nurses in NHS II
- Mothers reported early life exposures of nurse

Ambidirectional Cohort study

Michels et. al, 2007, *International Journal of Obesity*, 31(7)

In Utero Exposures and Age at Menarche of the Index Daughter

- Physical activity in pregnancy delays age at menarche.
- Gestational weight gain is associated with early menarche.

Delay in Daughter's Age at Menarche by Maternal Physical Activity in Pregnancy

Maternal home & leisure activity during pregnancy	Mean Difference (95% CI)	*P*-for trend
Inactive	1.00 (ref)	
Mostly Inactive	0.7 (-1.2, 2.6)	
Active	1.0 (-0.9, 3.0)	*0.01*
Mostly Active	1.3 (-0.7, 3.3)	
Highly Active	3.0 (0.3, 5.7)	

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

Higher Odds of Early Menarche by Gestational Weight Gain

Gestational Weight Gain (pounds)	Early Menarche <11 years OR (95% CI)
<10	1.31 (1.05-1.42)
10-14	1.08 (0.94-1.25)
15-19	0.97 (0.86-1.10)
20-29	1.00 (ref.)
30-40	1.10 (0.97-1.25)
40+	1.27 (1.06-1.54)

Boynton-Jarrett R, Forman MR, Michels KB: J Women's Health 2011

In Utero and Early Life Exposures and Obesity of the Index Daughter

- Mother's pre-pregnancy BMI predicts daughter's risk of obesity.
- T.V. and physical inactivity among children send a persistent signal for obesity across the life course.

Mothers' Pre-pregnancy BMI Predicts Daughters' Chance For Being Overweight or Obese at Age 18

Maternal pre-pregnancy BMI (kg/m^2)	Overweight daughter OR (95% CI)	Obese daughter OR (95% CI)
21	1.00 (ref)	1.00 (ref)
23	1.40 (1.44-1.56)	1.72 (1.59-1.86)
25	2.09 (1.96-2.24)	2.77 (2.40-3.20)
27	2.73 (2.50-2.99)	4.21 (3.46-5.11)
29	3.34 (2.95-3.79)	5.99 (4.69-7.66)

Stuebe A, Forman MR, Michels KB: Internat J Obesity 2009

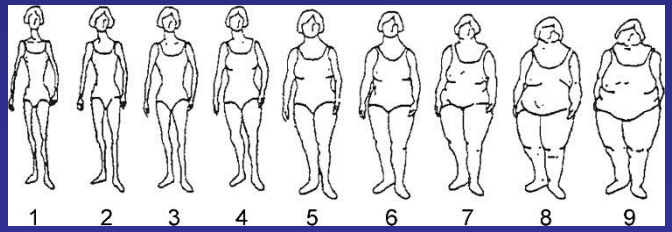
Obesity, TV, Physical Activity Data: Mother's Study

Maternal Reporting of TV viewing and Physical Activity (PA)

Nurse Self-Reporting Overweight and Obesity

Nurse's life course

Age 3 | Age 5 | Age 10 | Age 18 | Adulthood



Somatotype ≥ 5

Body Mass Index ≥25kg/m^2

Daughters' Television Viewing Increases Odds of Overweight/Obesity

Hours watching TV daily at ages 3-5 years	Somatotype ≥5		BMI ≥25kg/m^2	
	at age 5	at age 10	at age 18	in adulthood
No TV	ref.	ref.	ref.	ref.
0.5	0.96	0.94	0.89	0.92
1	1.07	1.05	0.98	0.96
2	**1.16***	**1.18***	1.06	1.02
3	**1.39***	**1.35***	1.12	1.07
≥4	**1.61***	**1.46***	**1.31***	**1.32***
P-for trend	**<0.001**	**<0.001**	**0.04**	**<0.001**

Tahir MJ, Willett WC, Forman MR Am J Epidemiol 2019

* 95% CI excludes one

Composite Score: Television Viewing & Physical Activity & OR of Overweight/Obesity

Score	Somatotype ≥5		BMI ≥25kg/m^2	
	at age 5[1]	at age 10[1]	at age 18[2]	adulthood[3]
≤2 hrs TV + *highly active or active*	ref.	ref.	ref.	ref.
≥3 hrs TV + *highly active or active*	**1.33***	**1.29***	**1.16***	**1.12***
≤2 hrs TV + *mostly inactive or inactive*	**2.01***	**1.91***	**1.84***	**1.30***
≥3 hrs TV + mostly inactive or inactive	**3.22***	**2.80***	**2.30***	**1.82***
P-for trend	**<0.001**	**<0.001**	**<0.001**	**<0.001**

* 95% CI excludes one

Tahir MJ, Willett WC, Forman MR Am J Epidemiol 2019

Summary: Nurses' Mothers' Cohort

- Maternal physical activity in pregnancy delays menarche among daughters.
- Maternal extremes of gestational weight gain accelerate menarche among daughters.
- Maternal pre-pregnancy BMI is directly associated with obesity risk by age 18 among daughters.
- Daughter's TV viewing and low physical activity send a persistent signal for obesity across the life course.

Part III: Growth in Infancy: New Assessment Approaches

Paper grid

Caliper

Recumbent length

Ruler

Estimation of Recumbent Length and Height from Ulnar Length and Arm Span Among Children Aged 1 month-5.9 Years

Aim

- To determine whether ulnar length can serve as a surrogate for recumbent length and height by 1 of 3 simple and portable tools

THE NATIONAL CHILDREN'S STUDY
HEALTH GROWTH ENVIRONMENT

Design

- Cross-sectional study
- N = 1400+ in 8 centers

Forman MR et al J Nutri 2014;144:1480-7

Demographic Characteristics

Formative Research in Growth	N (%)
Total	1509
Sex	
Boys	779 (51.62)
Age group (month)	
0-12	638 (42.28)
12.01-24	290 (19.22)
24.01-36	191 (12.66)
36.01-72	390 (25.84)
Race/ethnicity	
Hispanic	678 (44.93)
Non-Hispanic White	346 (22.93)
Non-Hispanic Black	356 (23.59)
Chinese American	71 (4.71)

UL Circumference; Ruler; Grid

TABLE 3 Pearson's correlation coefficients between ULC, ULR, ULG, arm span, and recumbent length and height of infants and children by age, sex, and ethnicity[1]

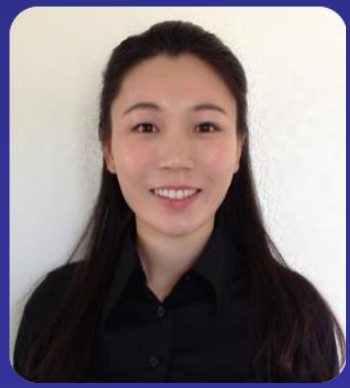
	n	ULC	ULR	ULG	Arm span
Recumbent length	941	0.90*	0.85*	0.86*	0.98*
Age (mo)					
0–11.9	567	0.81*	0.75*	0.65*	0.95*
12–23.9	272	0.77*	0.68*	0.77*	0.95*
24–35.9	102	0.74*	0.71*	0.73*	0.86*
Sex					
Boys	497	0.89*	0.87*	0.85*	0.98*
Girls	444	0.91*	0.84*	0.87*	0.99*
Ethnicity					
NHW	172	0.91*	0.88*	0.86*	0.99*
Hispanic	458	0.87*	0.90*	0.83*	0.98*
NHB	242	0.94*	0.74*	0.89*	0.98*
Other	66	0.97*	0.94*	0.91*	0.99*

UL Circumference; Ruler; Grid

TABLE 4 Regression equations to estimate recumbent length in children aged 0–3 y and height in children aged 2–5.9 y by using ULC, ULR, ULG, or arm span[1]

			Surrogate measures (cm)							Ethnicity			
	n	Intercept	ULC	ULR	ULG	Arm span	Age (mo)	ln (t)	Boy	NHW	NHB	$R^2_{marginal}$	SE
Length (cm)													
Model 1	918	36.83	1.48*	—	—	—	0.51*	5.42*	0.91*	—	—	0.95	2.(
Model 2	864	39.84	—	1.09*	—	—	0.55*	5.90*	1.09*	—	—	0.95	2.1
Model 3	741	38.15	—	—	1.44*	—	0.53*	5.01*	0.99*	—	—	0.92	2.1

The % variation in length explained in the models 1-4 was 95%, 95%, 92%, and 97%.



Yeyi Zhu, Ph.D.

Summary: Paper Grid to Assess Growth

- The use of a grid or ruler to measure recumbent length is accurate

Timing Matters: Windows of Susceptibility

Pregnancy---------Puberty in the index daughter

- Preeclampsia delays breast development but accelerates pubic hair development more than NT daughters at 13 y

Pregnancy----------Menarche

-Physical activity delays menarche

-Extremes of gestational weight gain increase the odds for early menarche

Timing Matters: Windows of Susceptibility

Childhood TV viewing and low physical activity send a persistent signal for risk of obesity across the life course.

Collaborators

Stavanger Study:

Pal Romunstad
Lars Vatten
Bjorn Ogland
Stein Tore Nilsen
Lisa Colbert
Rose Thelus Jean
Yong Q. Dong
Jeremy Schraw
Kristine Byberg
Ingvild Alsnes

National Children's Study:

Yeyi Zhu
Ladia Hernandez
John Himes
Laura Caulfied
Lenore Arab
Donna Dabalea
Kane Dong
Jean Kerver
Daniel Hale
Steven Hirschfeld

Nurses' Mothers' Study:

Walter Willett
Karin Michels
Alison Stuebe
Lisa Colbert
Renee Boynton Jarrett


THANK YOU
Questions?