

*It takes two and much  
more for successful  
pregnancy*

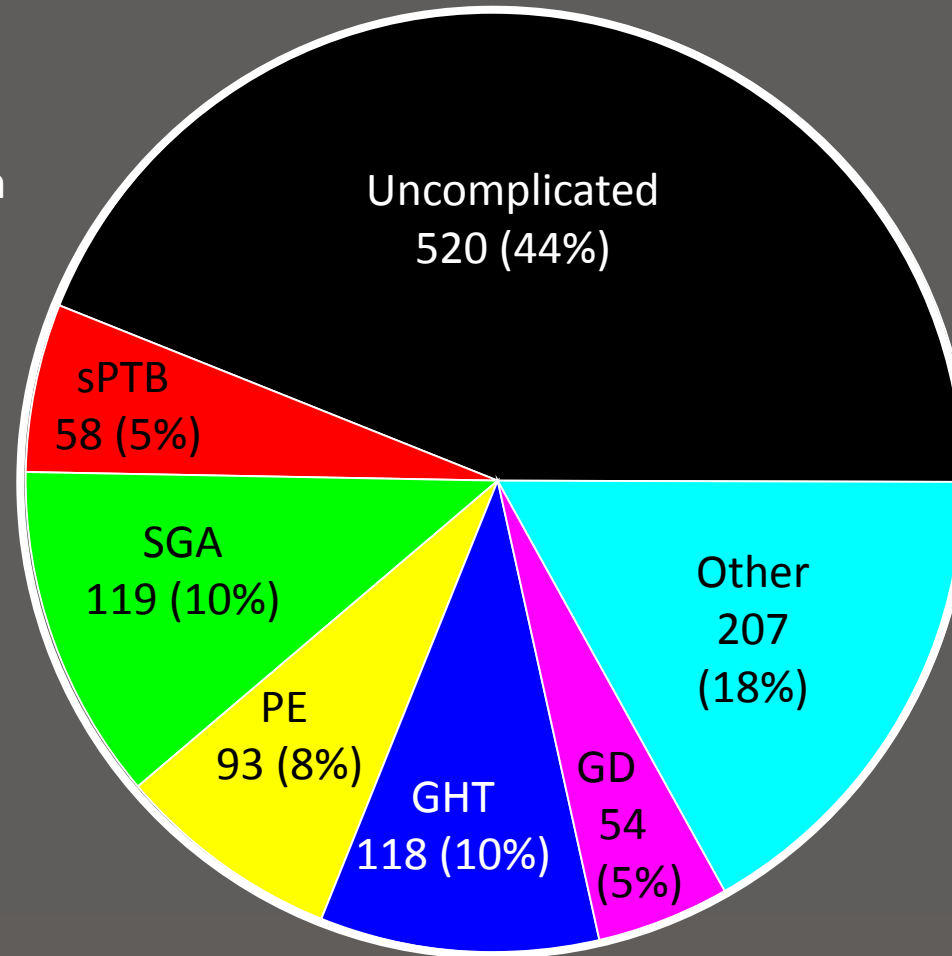
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*Research Centre for Reproductive Health  
Robinson Institute*



# SCOPE Adelaide Outcomes

International cohort  
Adelaide 1380  
nulliparous women  
1169 >20 weeks  
~ 90% partners



# Health Impact of IUGR

Risks to Mother	Risks to Baby
<p><b>Pregnancy-related problems:</b></p> <ul style="list-style-type: none"><li>hypertension</li><li>preeclampsia</li><li>placental abruption</li><li>spontaneous preterm birth</li></ul> <p><b>Lifelong health risks:</b></p> <ul style="list-style-type: none"><li>Premature death from all causes</li></ul>	<ul style="list-style-type: none"><li>5-10 times more likely to die</li><li>50% chance of being born premature</li><li>40-50% admitted to neonatal intensive care</li></ul> <p><b>Lifelong health risks:</b></p> <ul style="list-style-type: none"><li>16-35% risk of minor learning difficulties</li><li>5% risk moderate- severe handicap</li><li>type 2 diabetes ↑ 6 fold</li><li>coronary heart disease ↑ 2-4 fold</li><li>lower the birthweight the higher the adult blood pressure</li></ul>





From Swedish Medical Birth Registry 1973-80  
 573,437 mother child pairs with 10,365 mothers and 22,810 fathers having died before the study

**TABLE 3.** Associations of Birth Weight With All-Cause and Cause-Specific Mortality

	Crude HR (95% CI) for a 1-SD Increase in Birth Weight*	Gestational Age- Adjusted† HR (95% CI) for a 1-SD Increase in Birth Weight
<b>Mothers</b>		
All causes	0.82 (0.80 to 0.83)	0.84 (0.82 to 0.86)
CVD	0.70 (0.67 to 0.73)	0.75 (0.70 to 0.80)
CHD	0.66 (0.61 to 0.71)	0.72 (0.65 to 0.80)
Stroke	0.72 (0.67 to 0.77)	0.75 (0.68 to 0.83)
Alcohol-related	0.63 (0.59 to 0.68)	0.54 (0.49 to 0.60)
All cancer	0.94 (0.92 to 0.97)	0.96 (0.93 to 0.99)
Lung cancer	0.70 (0.65 to 0.76)	0.68 (0.61 to 0.74)
<b>Fathers</b>		
All causes	0.92 (0.91 to 0.93)	0.92 (0.90 to 0.93)
CVD	0.92 (0.90 to 0.94)	0.92 (0.90 to 0.95)
CHD	0.92 (0.89 to 0.94)	0.91 (0.88 to 0.95)
Stroke	0.97 (0.92 to 1.03)	0.98 (0.92 to 1.05)
Alcohol-related	0.85 (0.81 to 0.89)	0.83 (0.78 to 0.87)
All cancer	0.97 (0.95 to 1.00)	0.98 (0.95 to 1.01)
Lung cancer	0.88 (0.83 to 0.94)	0.86 (0.80 to 0.93)

\*Standard deviation of birth weight = 0.53 kg.  
 †Gestational age was controlled for in 15 groups: 22–26, 27–28, 29–30, 31–32, 33–34, 35, 36, 37, 38, 39, 40, 41, 42, 43, and 44–45 wk.  
 HR, hazard ratio.



# Health Impact of Preeclampsia

## Risks to Mother

### Pregnancy-related problems:

severe hypertension  
kidney or liver failure  
pulmonary edema  
seizures, stroke  
placental abruption, hemorrhage, death

### Lifelong health risks:

hypertension 40-50%    diabetes ↑ 2.4-4 fold  
coronary heart disease ↑ 2-2.5 fold  
Stroke  
premature death ↑ 1.5 fold

## Risks to Baby

3 to 10 times more likely to die  
30% chance of being born premature  
40-50% admitted to neonatal intensive care  
20-25% fetal growth restriction

### Lifelong health risks:

2.5% moderate-severe handicap  
Stroke ↑ 3.2 fold  
Hypertension ↑ 1.5 fold

### Lifelong risks if IUGR:

Type 2 diabetes, cardiovascular disease  
hypertension...



# Health Impact of Preterm Birth

Risks to Mother	Risks to Baby
<p><b>Pregnancy-related problems:</b></p> <ul style="list-style-type: none"><li>infection</li><li>septicemia</li><li>placental abruption</li></ul> <p><b>Lifelong health risks:</b></p> <ul style="list-style-type: none"><li>Premature death</li><li>Coronary Heart Disease</li><li>Cancer</li></ul>	<ul style="list-style-type: none"><li>10 to 20 times more likely to die</li><li>70% admitted to neonatal intensive care</li><li>13-20% fetal growth restriction</li></ul> <p><b>Lifelong health risks:</b></p> <ul style="list-style-type: none"><li>2.5% moderate-severe handicap</li></ul>





From Swedish Medical Birth Registry 1973-80 573,437 mother child pairs with 10,365 mothers and 22,810 fathers having died before the study

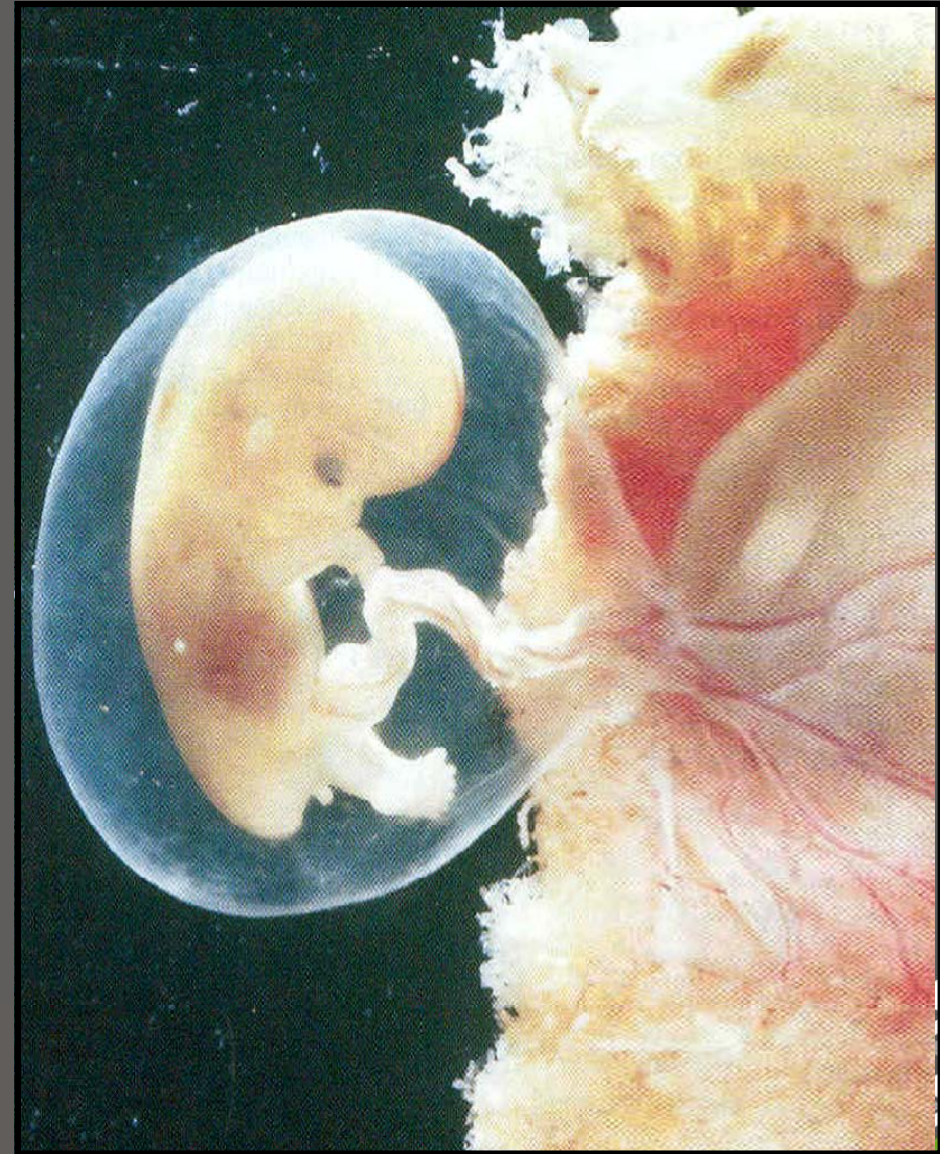
**TABLE 4.** Associations of Gestational Age With All-Cause and Cause-Specific Mortality

	Crude HR (95% CI) Comparing <37 Wk vs. ≥37 Wk Gestational Age	Birth Weight- Adjusted* HR (95% CI) Comparing <37 Wk vs. ≥37 Wk Gestational Age
<b>Mothers</b>		
All causes	1.72 (1.60 to 1.85)	1.23 (1.14 to 1.34)
CVD	2.45 (2.06 to 2.91)	1.32 (1.09 to 1.61)
CHD	3.14 (2.38 to 4.15)	1.66 (1.20 to 2.29)
Stroke	2.02 (1.50 to 2.71)	1.07 (0.77 to 1.49)
Alcohol-related	2.08 (1.51 to 2.89)	0.87 (0.61 to 1.24)
All cancer	1.30 (1.16 to 1.46)	1.19 (1.04 to 1.35)
Lung cancer	1.76 (1.29 to 2.42)	1.04 (0.73 to 1.48)
<b>Fathers</b>		
All causes	1.18 (1.12 to 1.25)	1.03 (0.96 to 1.10)
CVD	1.18 (1.06 to 1.31)	1.03 (0.91 to 1.16)
CHD	1.13 (0.99 to 1.29)	0.99 (0.85 to 1.15)
Stroke	1.19 (0.91 to 1.56)	1.06 (0.79 to 1.44)
Alcohol-related	1.19 (0.96 to 1.46)	0.91 (0.73 to 1.15)
All cancer	1.09 (0.97 to 1.23)	1.00 (0.87 to 1.14)
Lung cancer	1.20 (0.91 to 1.57)	0.93 (0.69 to 1.25)

\*Birth weight was controlled for 6 groups: lowest decile, 2nd and 3rd deciles, 4th and 5th deciles, 6th and 7th deciles, 8th and 9th deciles, and 10th decile.



# Human conceptus at 8 & 10 weeks gestation





# Strategy

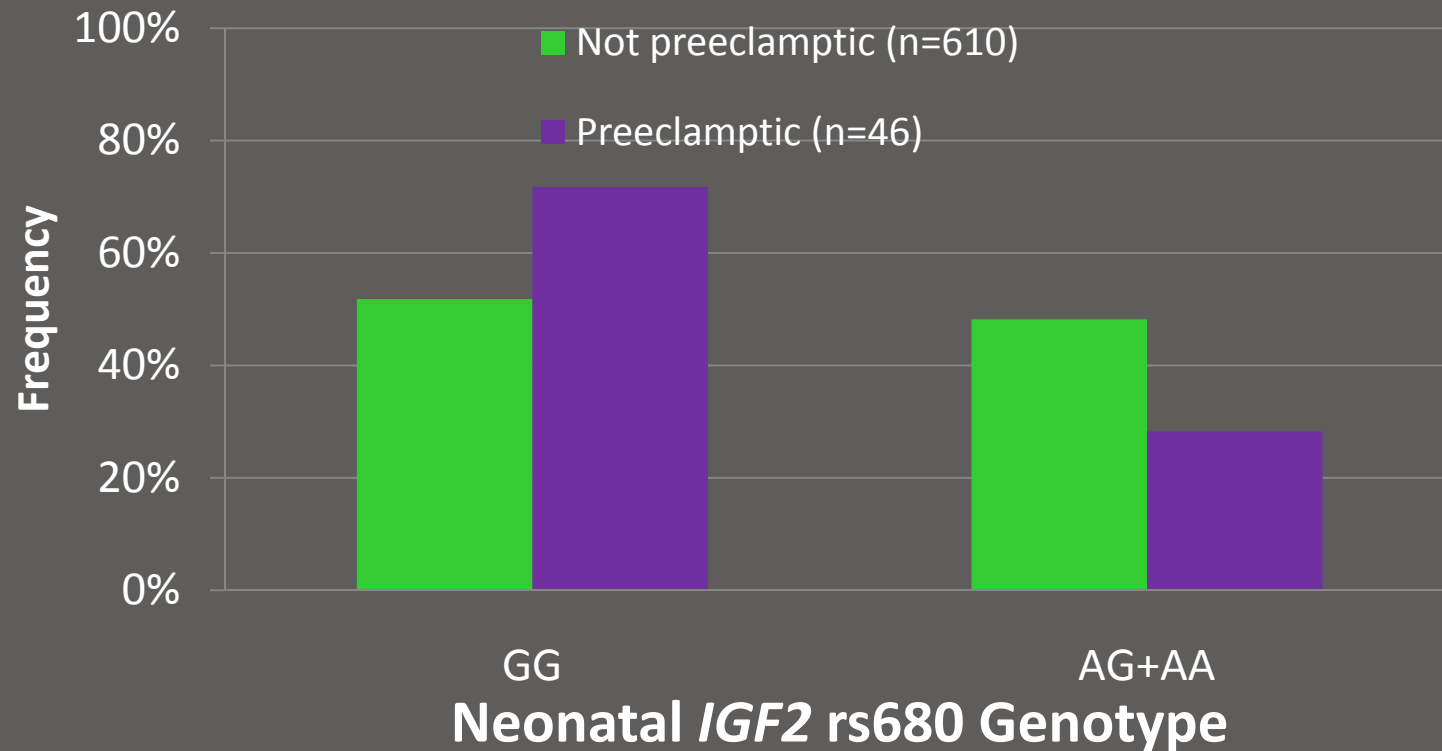
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- 100 SNPs in 79 genes
- Placental invasion, differentiation & function
- IGF/INS related genes
- Proteolytic enzymes
- Extracellular matrix proteins
- Angiogenesis
- Renin angiotensin system
- One carbon metabolism
- DNA synthesis & repair
- Detoxification enzymes
- Cytokines - Immune response
  
- Epigenetics



# Fetal Insulin-like growth factor II (IGF2) rs680 vs PE

Relative risk of 2.2 for PE if the baby is *IGF2* rs680 GG

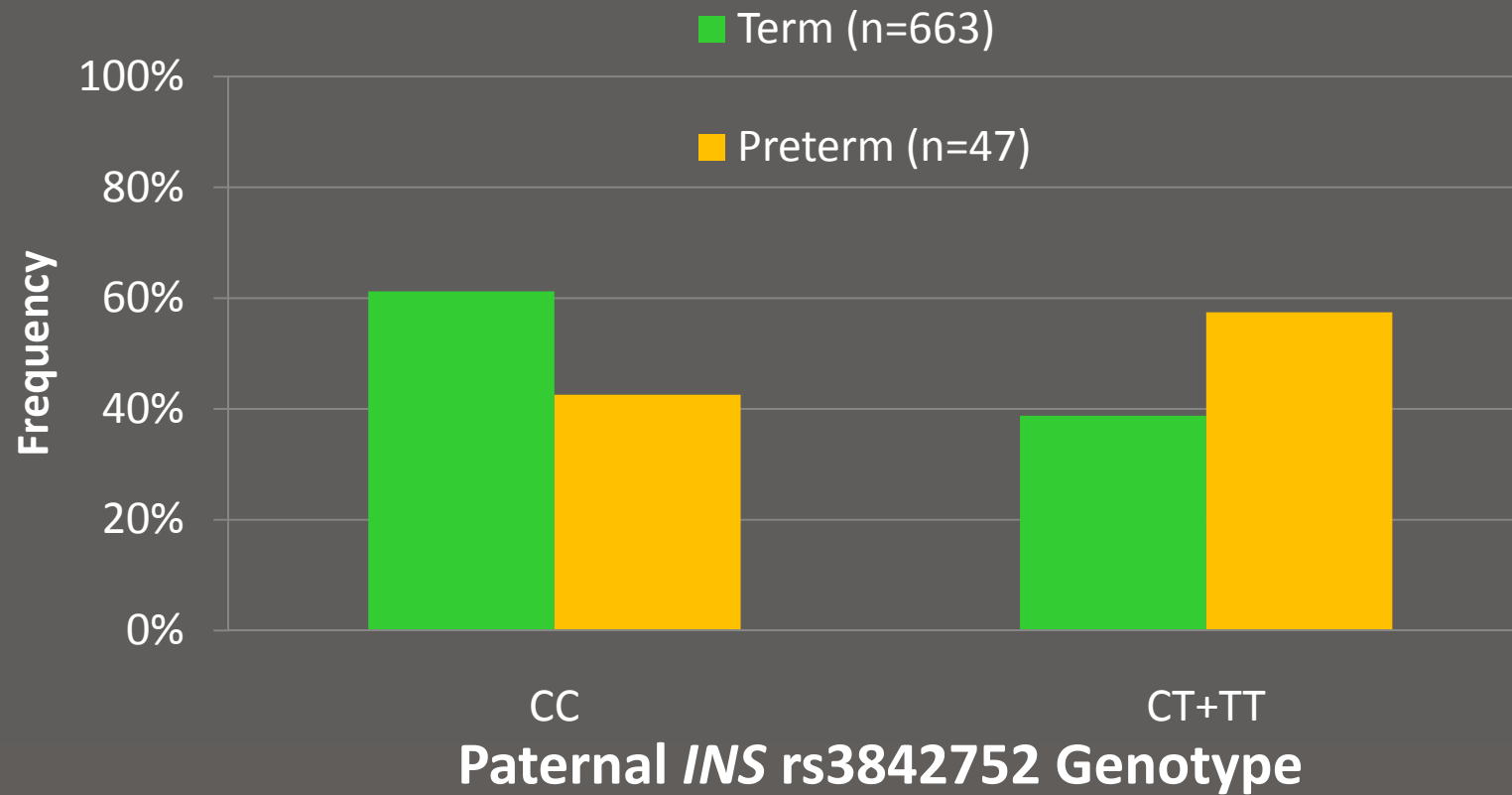


GG: ↓ IGF-II  
↑ BMI



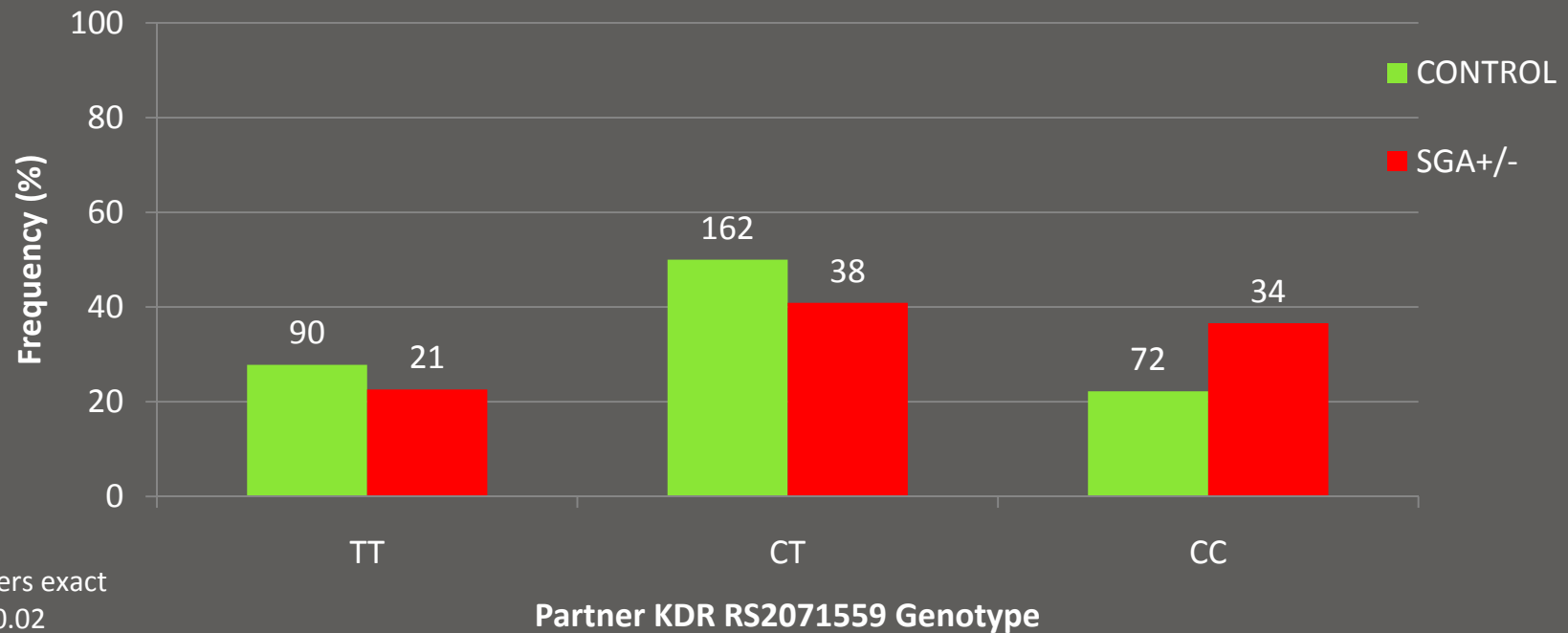
# Paternal Insulin (*INS*) rs3842752 vs PTB

Relative risk of 2 for PTB if the father is *INS* rs3842752 CT or TT



# Paternal KDR RS2071559 vs SGA

Paternal KDR RS2071559 Vs SGA with or without PE



Fishers exact  
P = 0.02  
LR = 7.4



# Genes associated with pregnancy complications

	Maternal	Paternal	Baby
Preeclampsia	7 genes	9 genes	9 genes
SGA	6 genes	6 genes	9 genes
PTB	5 genes	10 genes	6 genes

Some overlap between trio members and pregnancy complications



# Maternal risk factors for adverse outcomes

- Chronic disease
- Poor nutrition
- Elevated BMI ← - - - - -
- Age
- Family history ←
- Ethnicity ←
- Smoking (McCowan *et al.* 2008)
- Alcohol
- Caffeine
- Illicit drugs
- Low folate
- Low Vitamin D??
- Short period of sexual cohabitation (Kho *et al.* 2009)



# Body Mass Index



**BMI 55**  
super  
morbidly  
obese



**BMI 36**  
obese



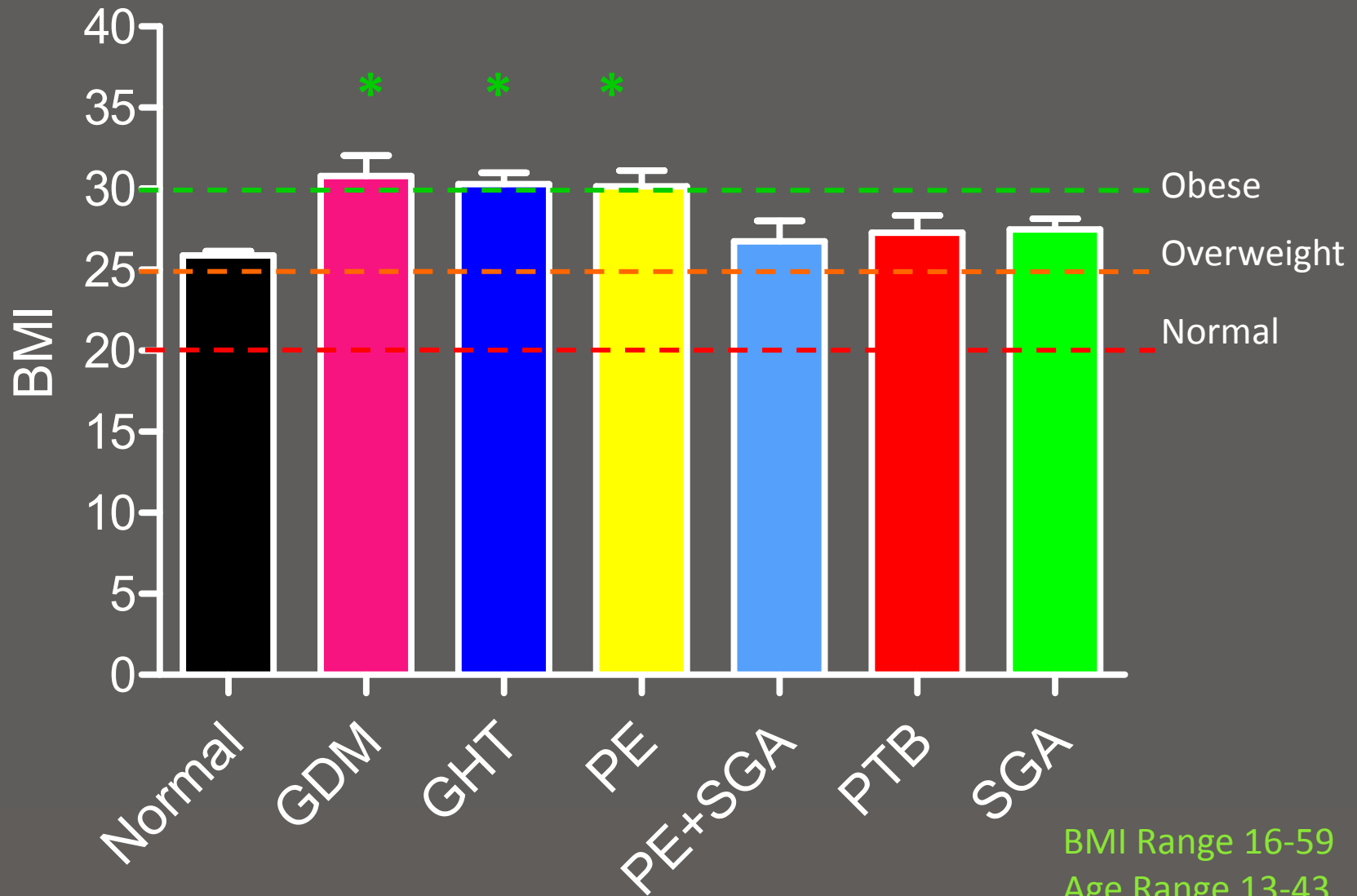
**BMI 23.9**  
ideal



**BMI 18**  
thin



# SCOPE Adelaide Outcomes & Maternal BMI



# Paternity and Pregnancy Complications

- Men who were themselves of low birthweight are 3.5 times more likely to father a growth restricted baby  
(Jaquet *et al.* 2005)
- Men who were born to a PE pregnancy are twice as likely to father a PE pregnancy  
(Esplin *et al.* 2001)
- Some men have fathered PE in more than one woman  
(Dekker & Robillard 2005)
- PE is a disease of primipaternity with greatest risk in first pregnancy and upon changing partner  
(Dekker 2002)



# Paternity

- Obese men???



Photo: Min Kho



# Paternal Characteristics vs SGA



Paternal characteristics	SGA N=209	Non-SGA N=1793
Age (yrs)	31.1 (6.3)	31.0 (6.2)
European	84.2%	86.5%
Socioeconomic index	42.4 (15.9)	43.5 (16.0)
<b>Height</b>	<b>177.9* (6.8)</b>	<b>179.3 (6.9)</b>
Weight	86.2 (15.6)	86.4 (15.2)
BMI	27.2 (4.6)	26.9 (4.3)
Waist circumference	95.0 (12.2)	94.3 (11.3)
Blood pressure	122/76 (12/10)	122/77 (13/10)
<b>Birthweight</b>	<b>3282.3* (535)</b>	<b>3465.8 (588)</b>

Data are mean (sd)



# Paternal Characteristics vs SGA



Paternal characteristics	SGA N=209	Non SGA N=1793	OR (95%CI)	Pat Adj OR (95% CI)*	Pat + Mat Adj OR(95% CI)†
Age ≤ 25	20%	19%	1.1 (0.8-1.6)	0.9 (0.6-1.4)	1.2 (0.7-2.0)
<b>BMI &gt; 30</b>	25%	19%	1.5 (1.04-2.1)	1.6 (1.1-2.3)	<b>1.6 (1.1-2.3)</b>
<b>WC &gt; 102cm</b>	25%	19%	1.4 (1.1-2.0)	1.6 (1.1-2.3)	<b>1.6 (1.1-2.3)</b>
SBP ≥ 140 or DBP ≥ 90	14%	16%	0.9 (0.6-1.3)	0.8 (0.5-1.3)	0.8 (0.5-1.3)

\* Paternal adjustment: age, ethnicity, SEI, birthweight, height, weight, blood pressure, health

† Maternal adjustment: age, ethnicity, BMI, BP, smoking, gravidity, gestation at delivery, family history of preeclampsia

(Kho *et al.* O&G 2009 Submitted)



# Gene-Environment Interactions - Smoking

Genotype	Non-smoker	Smoker
-	-	↓372g
CYP1A1 Aa/aa	-	↓520g
GSST-	-	↓642g
CYP1A1 Aa/aa GSST-	-	↓1250g



# Smoking in SCOPE women

	Non-smoker	Ceased Smoker	Smoker	Odds Ratio (95% CI)	P
<b>SGA</b>	10%	10%	17%	1.76 (1.03-3.02)	0.03
<b>PTB</b>	4%	4%	10%	3.21 (1.42-7.23)	0.006



# Alcohol and Infant Mortality

**TABLE 3.** Association of Alcohol Consumption During Pregnancy With Infant, Neonatal and Postneonatal Mortality Among All Live-born Singletons (n = 79,216)

	Crude HR (95% CI)	Smoking-adjusted HR (95% CI) <sup>a</sup>	Multivariate-adjusted HR (95% CI) <sup>b</sup>
<b>Average alcohol consumption (drinks/week)</b>			
<b>Infant mortality</b>			
0 <sup>c</sup> (n = 43,655)	1.00	1.00	1.00
0.5–1.5 (n = 26,295)	0.94 (0.73–1.21)	0.95 (0.74–1.23)	1.01 (0.78–1.31)
2–3.5 (n = 7602)	0.57 (0.34–0.95)	0.57 (0.34–0.95)	0.63 (0.37–1.05)
4 (n = 1664)	1.79 (0.97–3.30)	1.64 (0.89–3.03)	1.78 (0.96–3.32)
<b>Neonatal mortality</b>			
0 <sup>c</sup> (n = 43,655)	1.00	1.00	1.00
0.5–1.5 (n = 26,295)	1.01 (0.75–1.35)	1.01 (0.75–1.36)	1.09 (0.81–1.46)
2–3.5 (n = 7602)	0.54 (0.29–1.00)	0.54 (0.29–1.00)	0.60 (0.32–1.12)
4+ (n = 1664)	1.12 (0.46–2.74)	1.09 (0.44–2.67)	1.20 (0.49–2.97)
<b>Postneonatal mortality</b>			
0 <sup>c</sup> (n = 43,538)	1.00	1.00	1.00
0.5–1.5 (n = 26,224)	0.76 (0.45–1.28)	0.79 (0.46–1.34)	0.82 (0.48–1.39)
2–3.5 (n = 7591)	0.65 (0.26–1.64)	0.65 (0.26–1.64)	0.68 (0.27–1.71)
4+ (n = 1659)	3.59 (1.53–8.41)	2.86 (1.21–6.77)	2.91 (1.22–6.95)
<b>No. binge episodes</b>			
<b>Infant mortality</b>			
0 <sup>c</sup> (n = 58,618)	1.00	1.00	1.00
1 (n = 12,837)	1.12 (0.82–1.53)	1.11 (0.82–1.52)	1.14 (0.83–1.56)
2 (n = 4611)	0.60 (0.32–1.13)	0.59 (0.31–1.11)	0.61 (0.32–1.16)
3+ (n = 3150)	1.30 (0.77–2.20)	1.25 (0.74–2.12)	1.32 (0.78–2.25)
<b>Neonatal mortality</b>			
0 <sup>c</sup> (n = 58,618)	1.00	1.00	1.00
1 (n = 12,837)	1.22 (0.86–1.74)	1.24 (0.88–1.76)	1.28 (0.90–1.82)
2 (n = 4611)	0.65 (0.32–1.32)	0.66 (0.33–1.35)	0.70 (0.34–1.43)
3+ (n = 3150)	0.82 (0.39–1.76)	0.84 (0.39–1.80)	0.91 (0.42–1.95)
<b>Postneonatal mortality</b>			
0 <sup>c</sup> (n = 58,469)	1.00	1.00	1.00
1 (n = 12,797)	0.84 (0.43–1.65)	0.78 (0.40–1.53)	0.78 (0.40–1.54)
2 (n = 4603)	0.46 (0.11–1.88)	0.40 (0.10–1.65)	0.42 (0.10–1.71)
3+ (n = 3143)	2.67 (1.27–5.60)	2.16 (1.02–4.58)	2.21 (1.04–4.72)

<sup>a</sup>Adjusted for smoking only. An interaction term between infant age, categorized as <28 days vs. ≥28 days, and smoking was included in the analyses of neonatal and postneonatal mortality.

<sup>b</sup>Adjusted for maternal age, marital status, socio-occupational status, parity, time-to-pregnancy and infertility treatment, prepregnancy BMI, and smoking. Interaction terms of age, categorized as <28 days vs. ≥28 days, with BMI and with smoking, were included in the analyses of neonatal and postneonatal mortality.

<sup>c</sup>Reference category.



# Maternal Alcohol and Infant Mortality in 79,216 mothers in the Danish National Birth Cohort 1996-2002

Number of drinks per week	Post-neonatal Mortality OR (95% CI)*
0 (n=43,538)	1.00
0.5-1.5 (n=26,224)	0.82 (0.48-1.39)
2-3.5 (n=7,591)	0.68 (0.27-1.71)
4+ (n=1,659)	2.91 (1.22-6.95)

\*Adjusted for maternal age, marital status, socio-occupational status, parity, time-to-pregnancy and infertility treatment, pre-pregnancy BMI and smoking.  
Strandberg-Larsen *et al.* *Epidemiology* 2009 20:884–891



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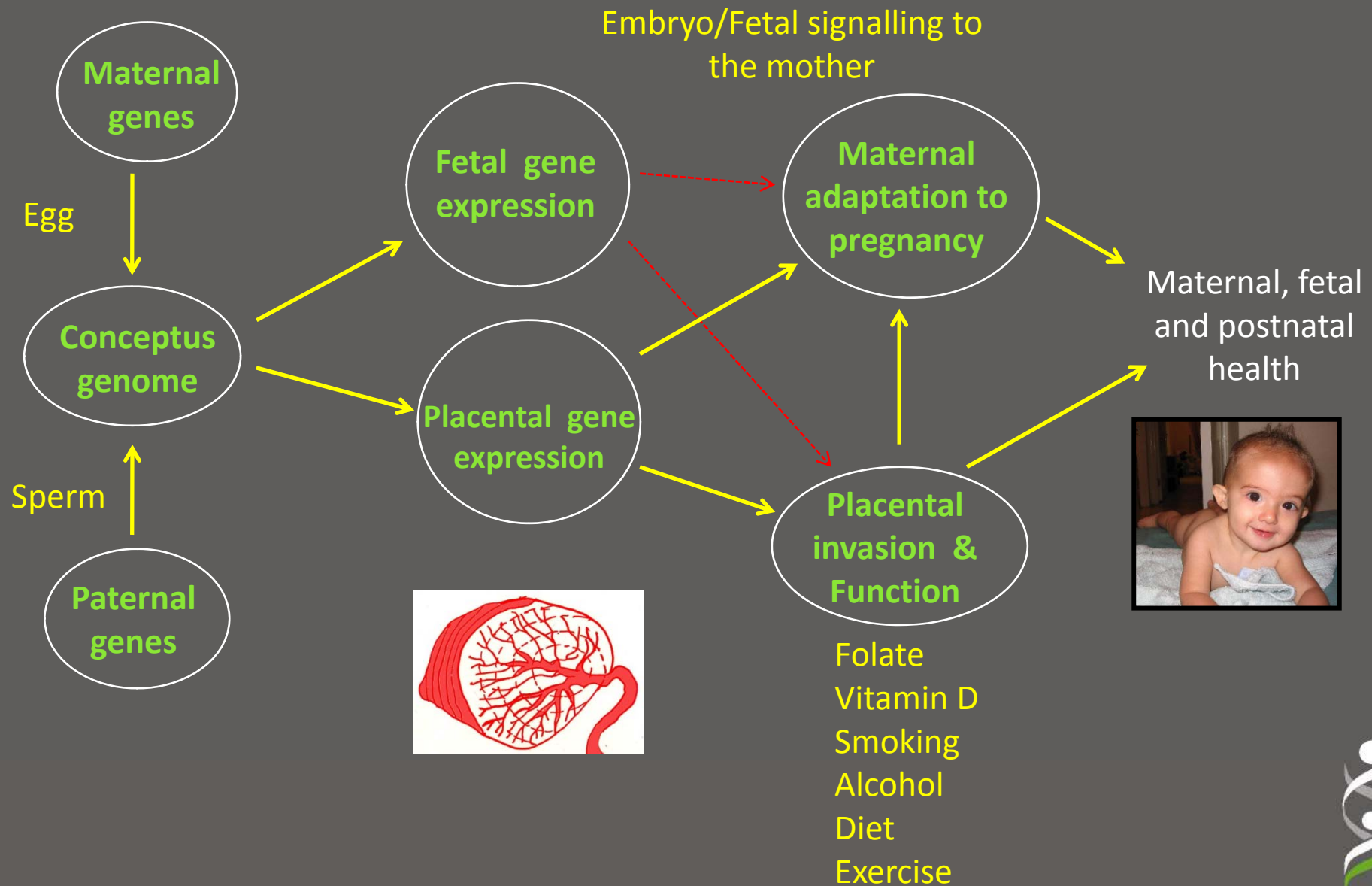
Number of binge episodes	Post-neonatal Mortality OR (95% CI)*
0 (n=58,469)	1.00
1 (n=12,797)	0.78 (0.40-1.54)
2 (n=4,603)	0.42 (0.10-4.72)
3+ (n=3,143)	2.21 (1.04-4.72)

\*Adjusted for maternal age, marital status, socio-occupational status, parity, time-to-pregnancy and infertility treatment, pre-pregnancy BMI and smoking.

Strandberg-Larsen *et al. Epidemiology* 2009 20:884–891



# Genes & environment contribute to poor outcomes



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