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Early Life Growth Patterns and Later Life Metabolic Consequences

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NHS Foundation Trust

Outline

- Poor growth and the SGA child
- Epidemiological Evidence
  - Small Size at Birth
  - Postnatal Growth Patterns
  - Intergenerational Effects
- Mechanisms
- So can we do anything about this!

Growth Patterns and Later Life Disease Risk

- Poor growth and the SGA child

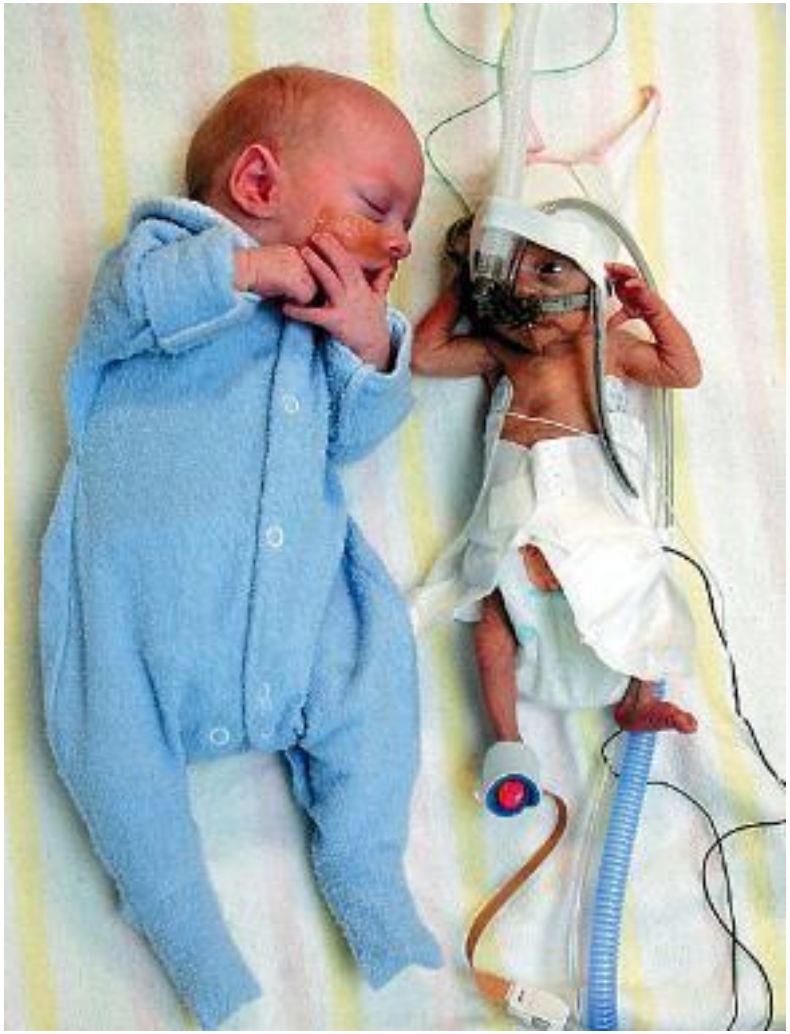
AGA vs SGA

- Appropriate for gestational age (AGA)
  - Birth weight and length within 2 SD of mean for gestational age (GA)
- SGA
  - Birth weight and/or length at least 2 SD below mean for GA
  - Other definitions
    - Birth weight <2500 g, GA ≥37 wk
    - Birth weight and/or length <3rd, <5th, or <10th percentile for GA

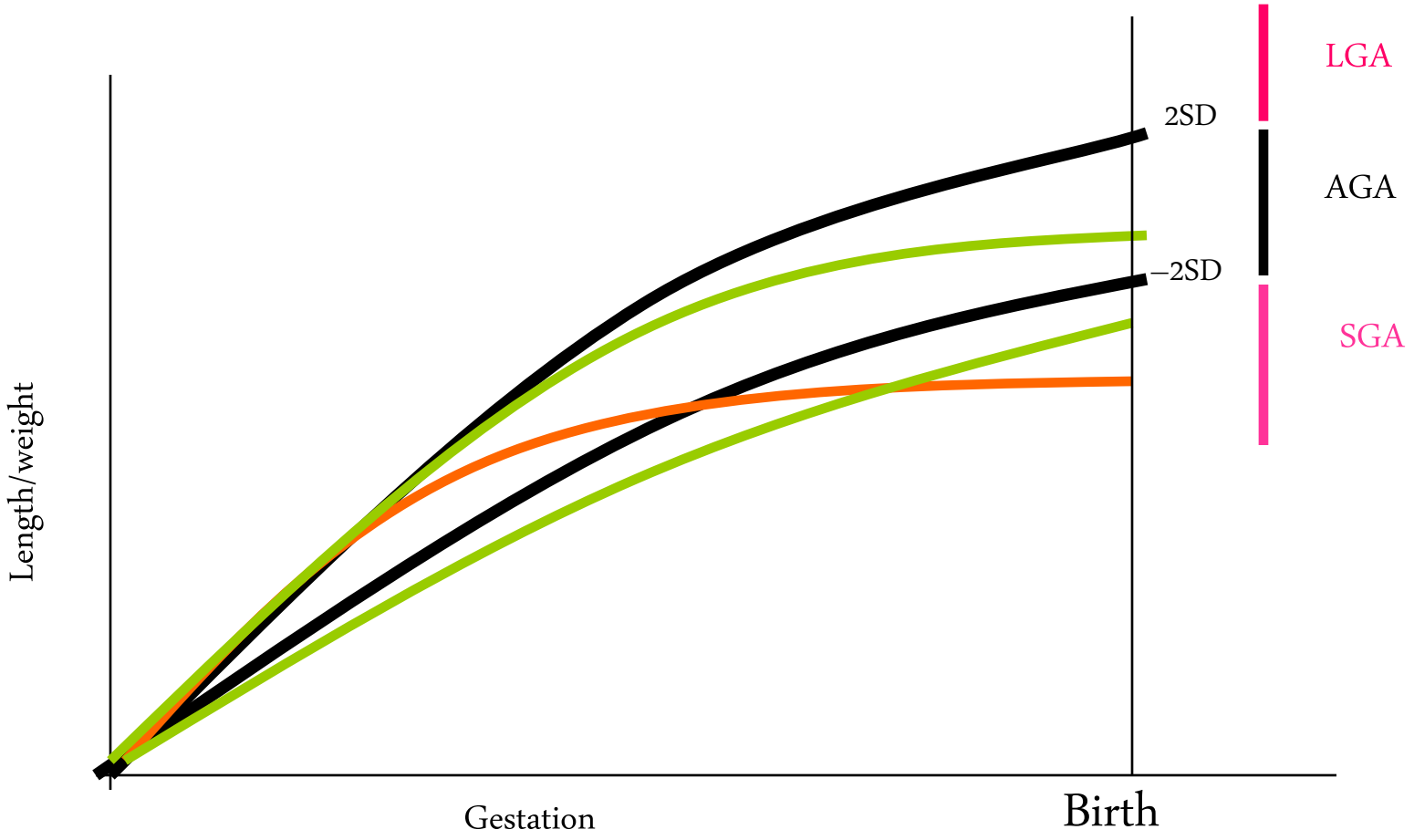
Albertsson-Wikland K, Karlberg J. *Acta Paediatr Suppl*. 1994:399:64.
Miller HC, Hassanein K. *Pediatrics*. 1971;48:511.

Does it matter if you are born small?

- Increased neonatal morbidity and mortality
- Impaired intellectual development and long-term psychological deficits
- More likely to have unskilled or semi-skilled employment as adult
- Associated with the metabolic syndrome
  - Hypertension
  - Hyperlipidemia
  - Type 2 diabetes mellitus



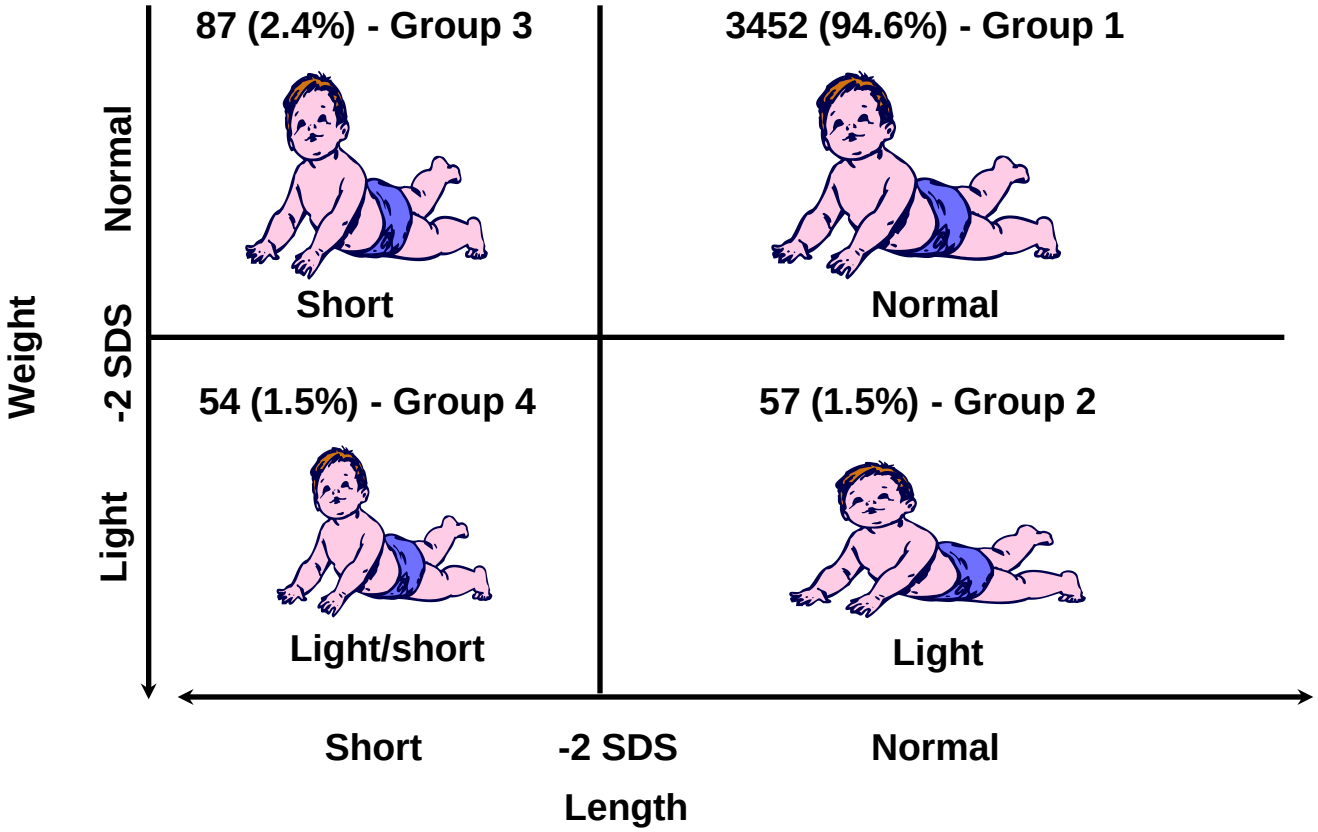
Definition of SGA/IUGR



SGA, small for gestational age
AGA, appropiate for gestational age
LGA, large for gestational age

SGA/IUGR

Birth weight and length of 3650 healthy full-term children



Albertsson-Wikland K, et al. Acta Paediatr, 1994; 83(Suppl 399); 64-70

2014 UK – 698,000 Live Births

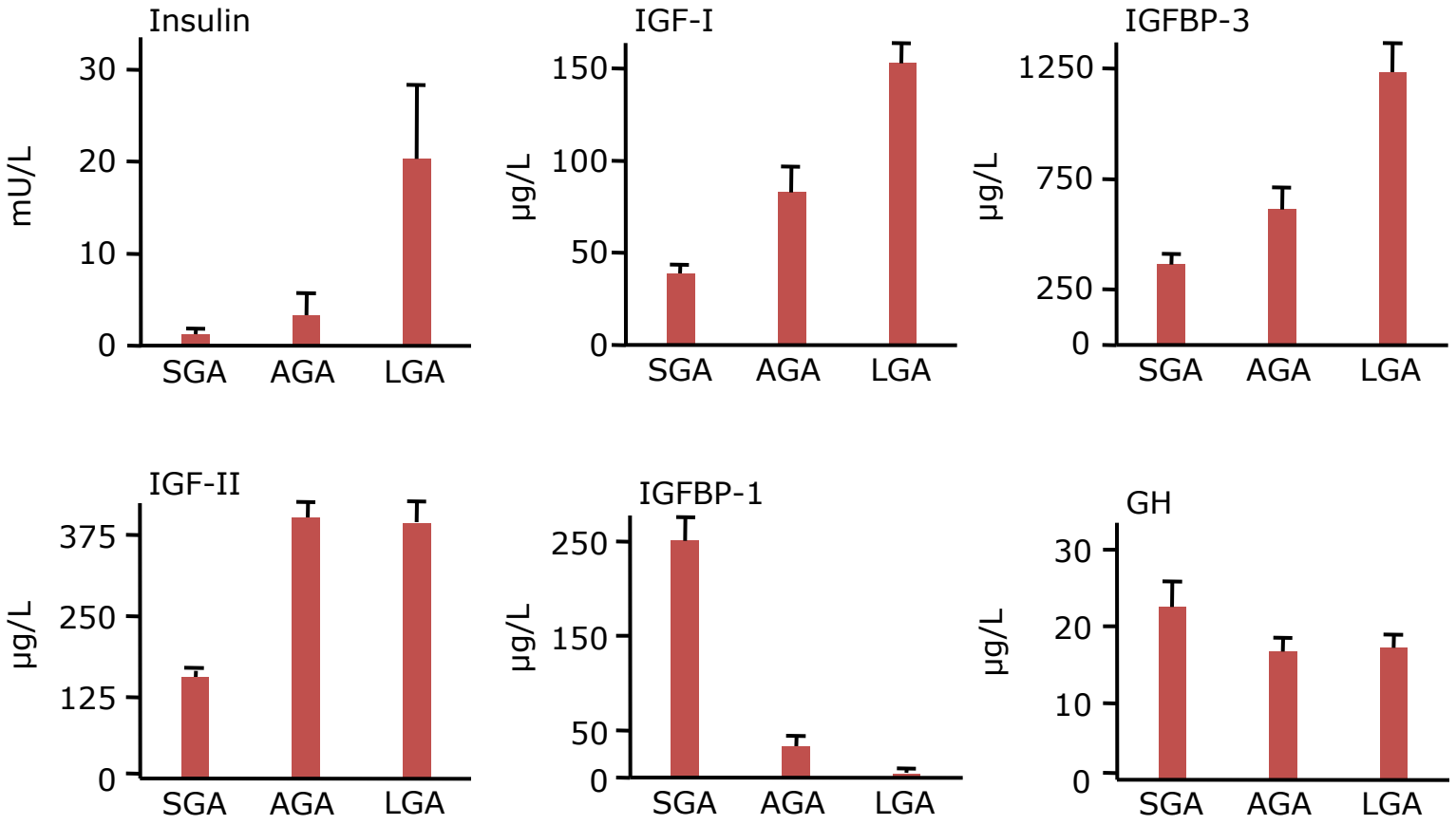
SGA at birth 37,700 infants

Low Birth Weight and Prematurity

- Low birth weight (59% are SGA)
  - Low: <2500 g
  - Very low: <1500 g
  - Extremely low: <1000 g
- Prematurity
  - Preterm: 32/33–36 weeks (12% are SGA)
  - Very preterm: <32/33 weeks (15% are SGA)

Hediger ML et al. *Arch Pediatr Adolesc Med.* 1998;152:1225.
Ventura SJ et al. *Natl Vital Stat Rep*. 2001;49:1.

Hormonal regulation of size at birth



de Zegher 1997a

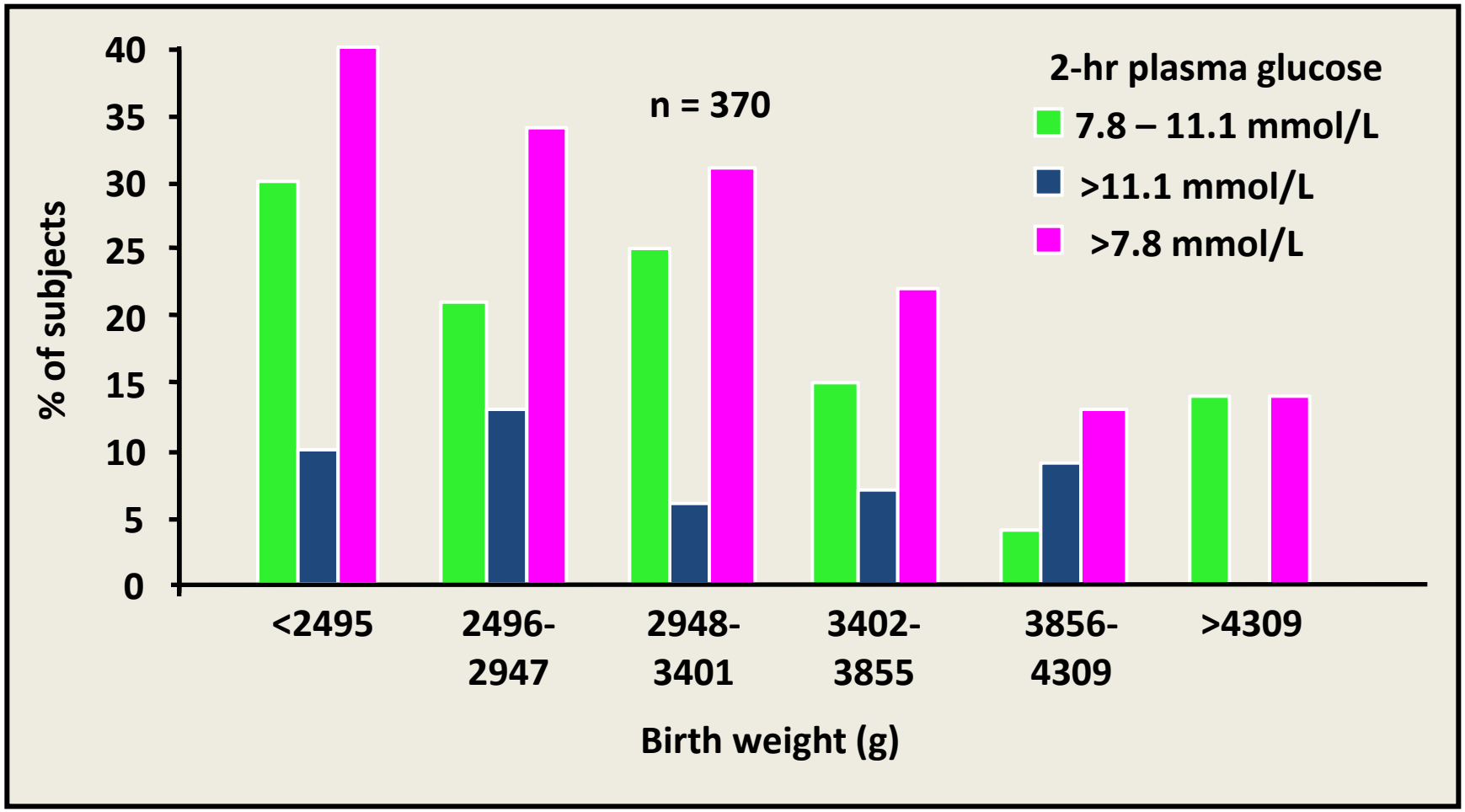
Growth Patterns and Later Life Disease Risk

- Epidemiological Evidence

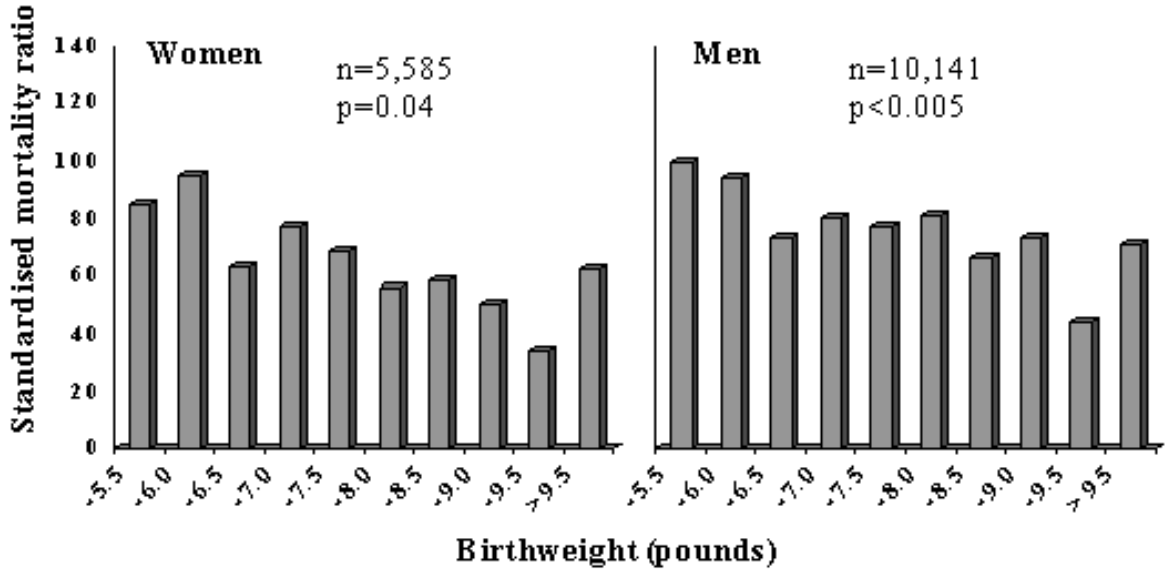
Growth Patterns and Later Life Disease Risk

- Epidemiological Evidence
  - Small Size at Birth

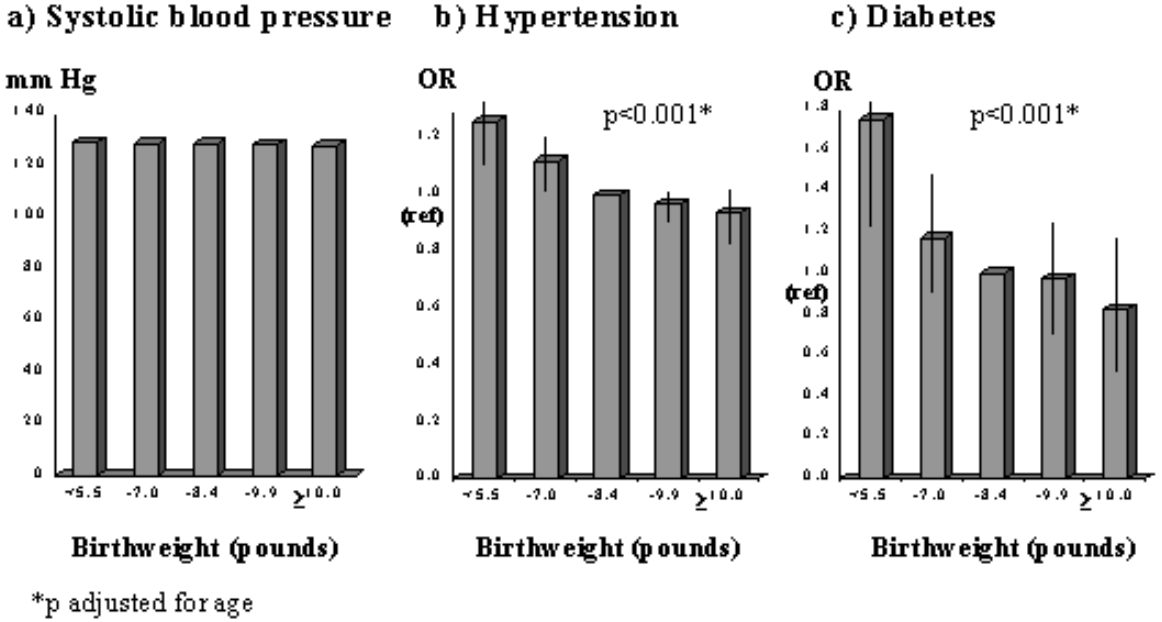
Relation Between Birth Weight and Glucose Tolerance at Age 64 Years



Hales CN et al. *BMJ.* 1991;303:1019.

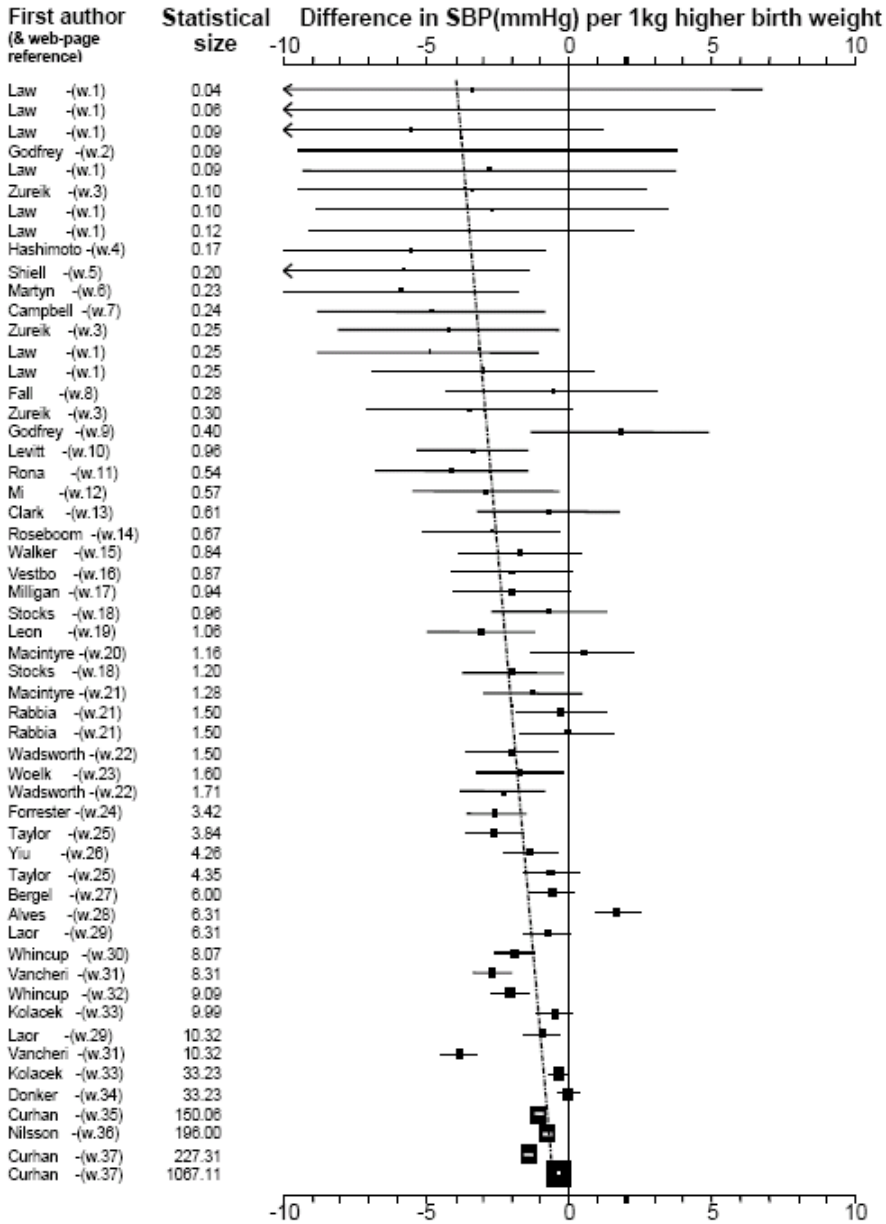


Osmond et al BMJ 1993



Curhan et al Circulation 1996

Figure 1



Huxley et al
Lancet 2002

Growth Patterns and Later Life Disease Risk

- Epidemiological Evidence
  - Small Size at Birth
  - Postnatal Growth Patterns

Postnatal Weight Gain in SGA infants

Table I. Fifteen studies reporting on the association between infancy weight gain (up to age 2 y) and later obesity risk.

			Infancy weight gain		Obesity risk outcome			
Reference	*n*	Population	Birth to (y)	Reported definition	Age	Reported definition	OR for obesity per 0.67 SD wt gain[b]	Adjusted?[c]
Stettler 2005[a]	653	US	0.3	>+1 SD	20–32 y	BMI >25 kg/m^2	1.26	Yes
Stettler 2002a	5514	Seychelles	1	kg (cont.)	4–17 y	IOTF overweight	1.39	Yes
Stettler 2002b	19 397	US	0.33	100g/month	7 y	BMI >95th	1.54	Yes
Euser 2005	403	Holland, preterms	0.25	SD (cont.)	19 y	BMI (cont.)	1.54	Yes
Mellbin 1976	895	Sweden	1	>90th centile	7 y	Wt-for-ht >120%	1.55	No
Kinra 2005	1335	UK	1.5	SD (cont.)	7 y	BMI (cont.)	1.63	Yes
Monteiro 2003	1041	Brazil	2	>+0.67 SD	14–16 y	BMI >85th	1.66	Yes
Ekelund 2006	248	Sweden	0.5	>+0.67 SD	17 y	IOTF overweight	1.80	Yes
Shapiro 1984	450	US	0.5	>85th centile	9 y	Skinfolds >85th	1.85	No
Eid 1970	224	UK	0.5	>90th centile	8 y	Wt-for-ht >120%	2.08	No
Stettler 2005[a]	653	US	0.022	>+1 SD	20–32 y	BMI >25 kg/m^2	2.37	Yes
Reilly 2005	857	UK	2	>+0.67 SD	7 y	BMI >95th	2.60	Yes
Gunnarsdottir 2003	90	Iceland	1	kg (cont.)	6 y	BMI (cont.)	2.90	No
Stettler 2003	300	African Americans	0.33	>+1SD	20 y	BMI >30 kg/m^2	3.03	Yes
Cameron 2003	193	South Africa	2	>+0.67 SD	9 y	BMI (cont.)	3.23	No
Toschke 2004	4235	Germany	2	>9764 g	5–6.9 y	BMI >85th	4.55	No
Total (unadjusted)	35 835		1.0	>+0.67 SD	10 y		2.76	No
Total (adjusted)	35 835		1.0	>+0.67 SD	10 y		1.84	Yes

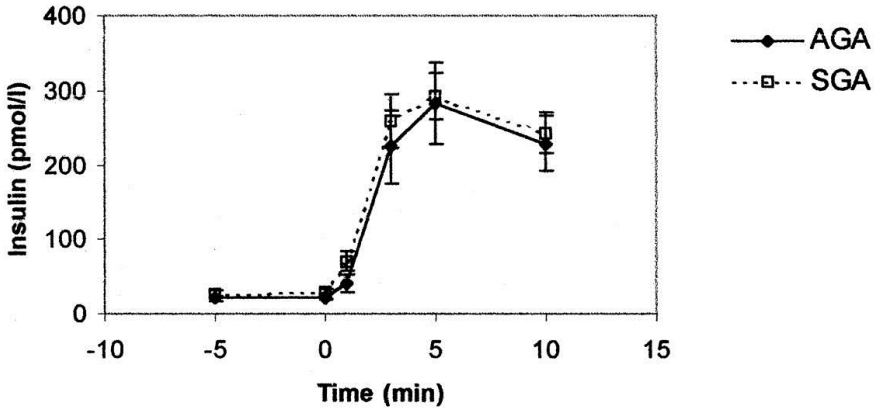
TABLE 4. Blood Pressure in Randomized Formula-Fed Groups at Age 6–8 Years

	Unadjusted Blood Pressure, mm Hg					Adjusted Blood Pressure, mm Hg*		
	Standard (n=83)	Nutrient Enriched (n=70)	Mean Difference	95% CI	*P*	Mean Difference	95% CI	*P*
Diastolic	61.3 (8.2)	64.5 (8.3)	−3.2	−5.8 to −0.5	0.02	−3.5	−6.2 to −0.7	0.01
MAP	76.9 (8.3)	79.5 (7.8)	−2.5	−5.1 to 0.1	0.06	−3.0	−5.6 to −0.3	0.03
Systolic	100.5 (10.2)	102.2 (9.8)	−1.7	−4.9 to 1.5	0.3	−2.0	−5.3 to 1.3	0.2

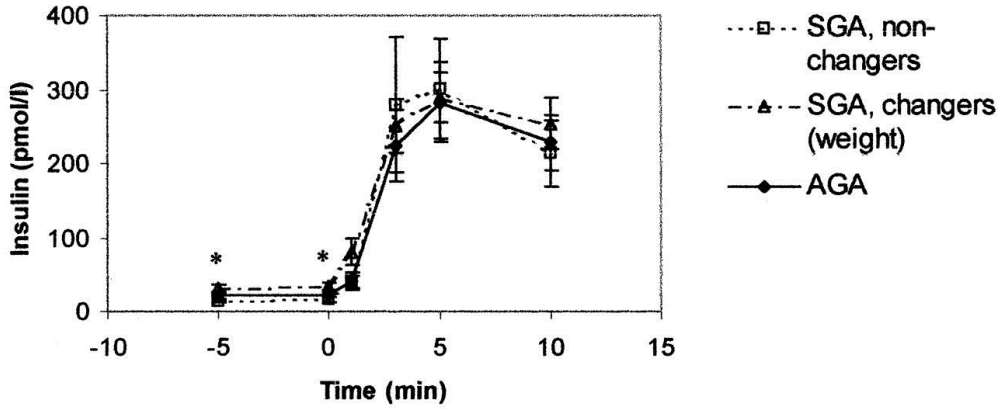
Data are mean (SD) in each formula group.
*Adjusted for age, sex, *z* score for weight and height at 6–8 years, and social class.

Insulin Resistance and Catch-up growth in SGA infants

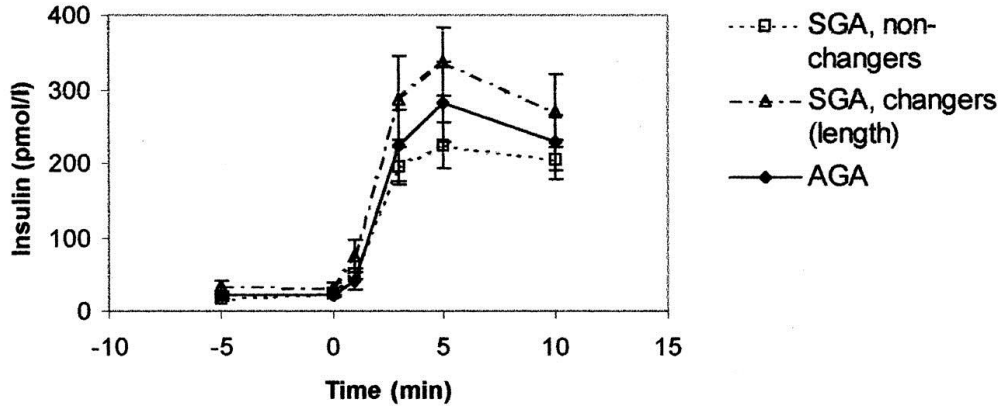
A

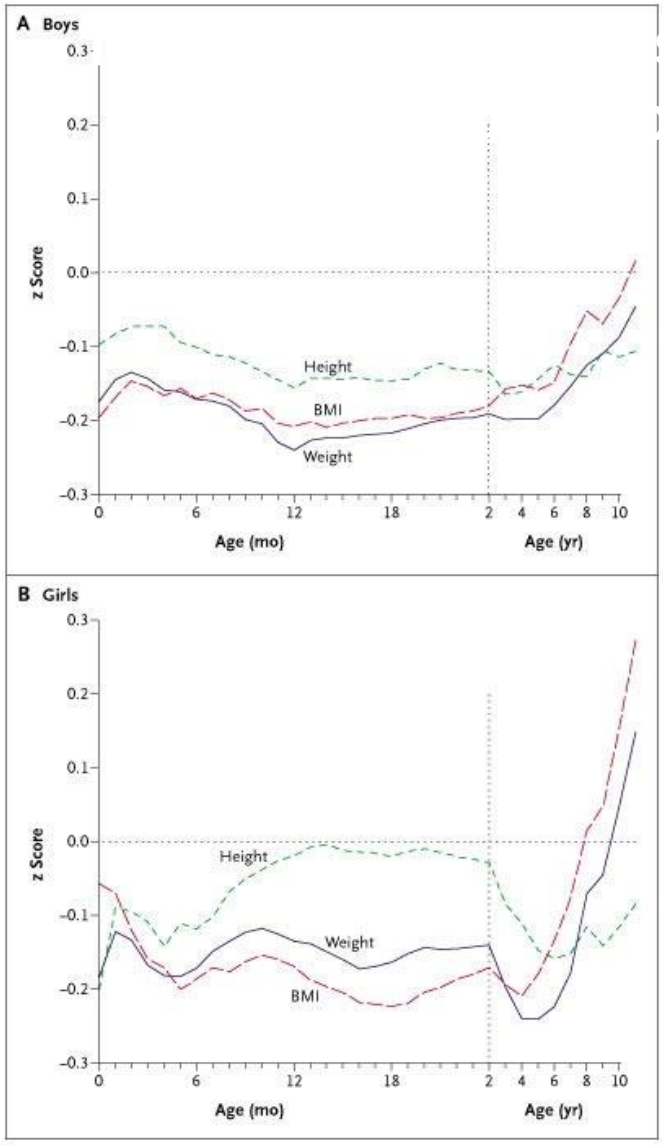


B



C





Early Life Growth Patterns in Adults with Cardiovascular Disease

Barker DJ et al. N Engl J Med 2005;353:1802-1809.

Growth Patterns and Later Life Disease Risk

- Epidemiological Evidence
  - Small Size at Birth
  - Postnatal Growth Patterns
  - Intergenerational Effects

Intergenerational Effects – Birth Weight

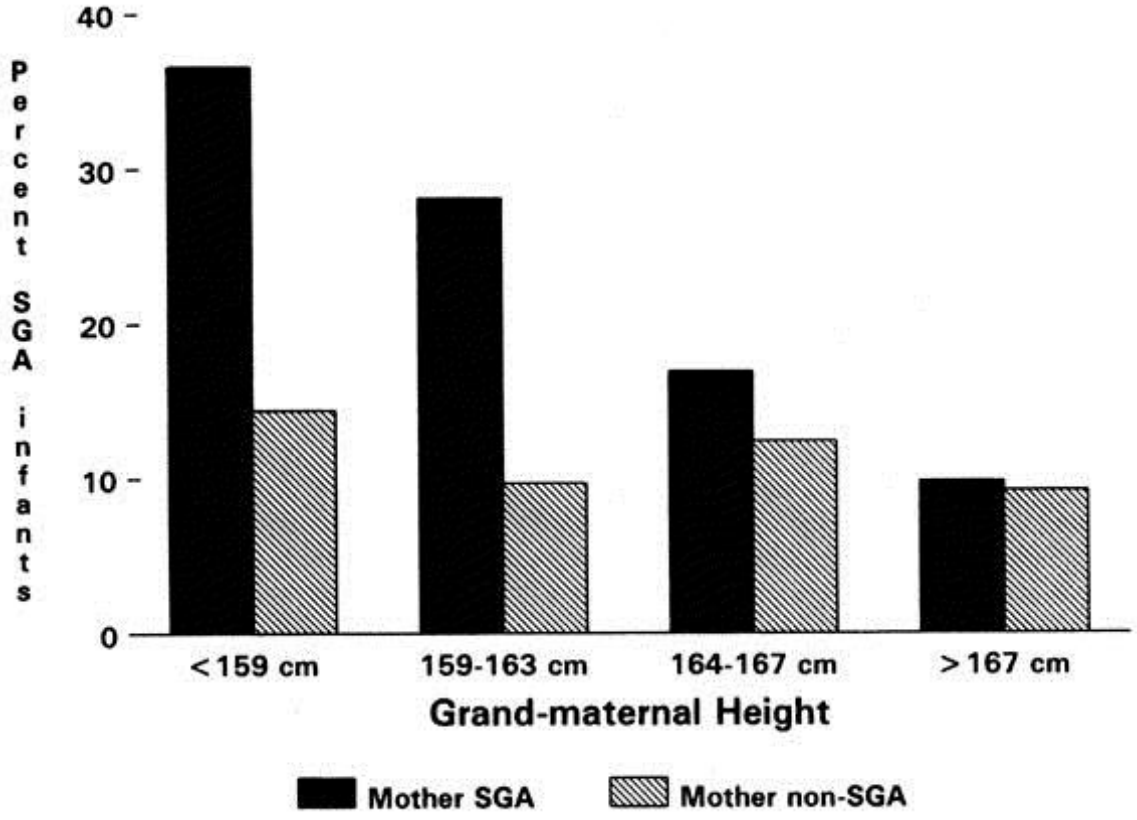
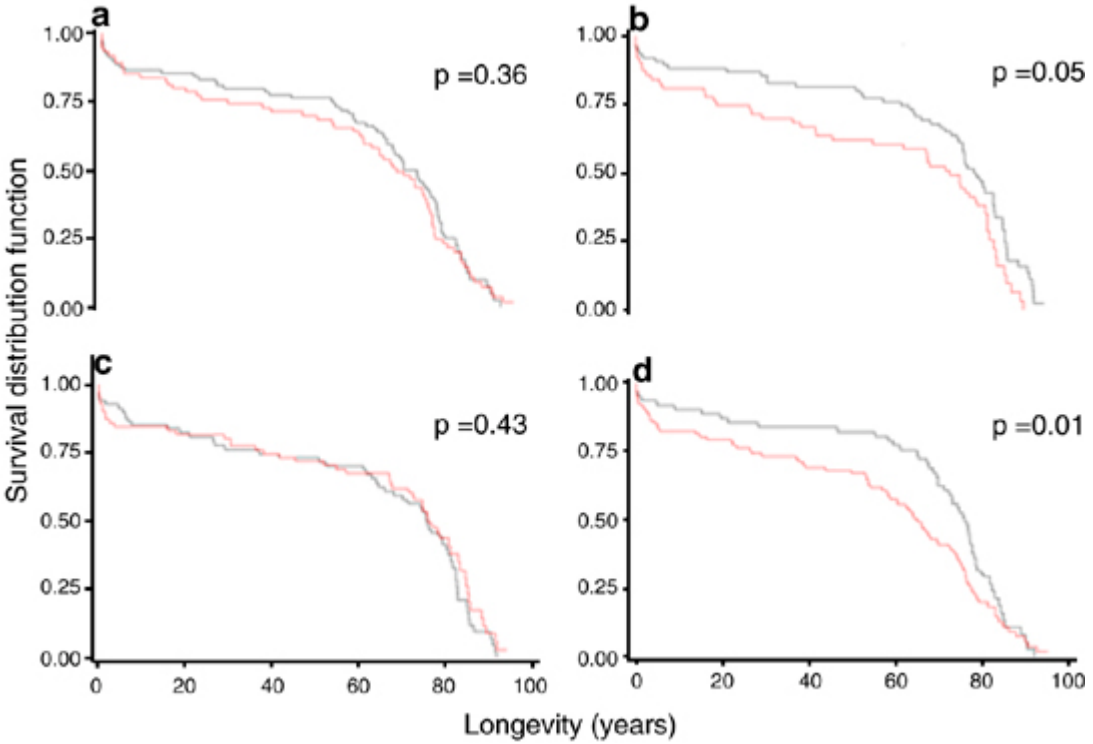
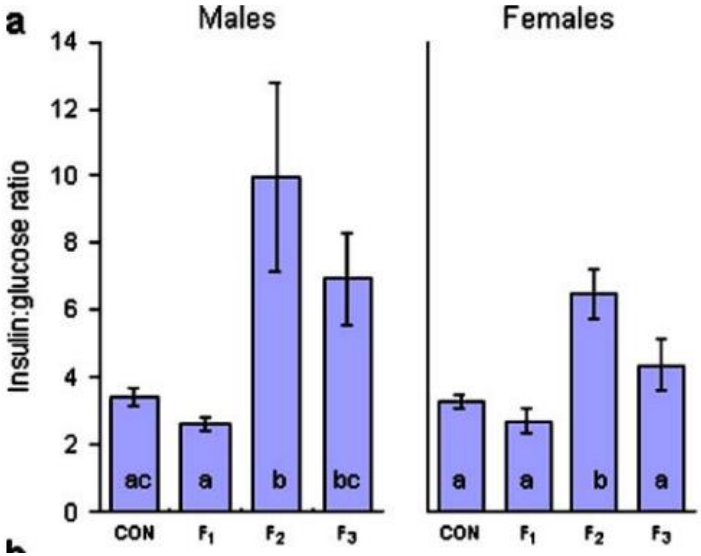


Fig. 1 Percent SGA infants by grandmaternal height and maternal SGA status.

Intergenerational Effects – Longevity



The empirical distribution of longevity. Male and female probands survival when the paternal grandparent experienced at least 1 year of good availability of food in the environment (dashed line), or no year of good availability (solid line), during their SGP that is at 8–10 years of age for the paternal grandmother and at 9–12 years of age for the paternal grandfather. No adjustments. *N*=306. (**a**) Paternal grandmothers availability of food during her SGP and the survival of the male probands. (**b**) Paternal grandmothers availability of food during her SGP and the survival of the female probands. (**c**) Paternal grandfathers availability of food during his SGP and the survival of the female probands. (**d**) Paternal grandfathers availability of food during his SGP and the survival of the male probands.

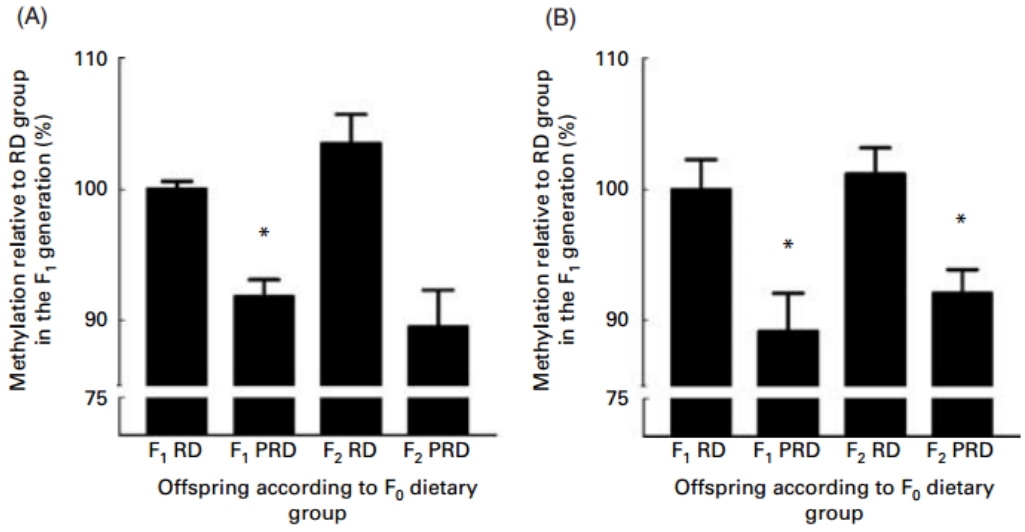


Diabetologia (2006) 49: 1117–1119
DOI 10.1007/s00125-006-0196-5

RESEARCH LETTER

D. C. Benyshek · C. S. Johnston · J. F. Martin

Glucose metabolism is altered in the adequately-nourished grand-offspring (F_3 generation) of rats malnourished during gestation and perinatal life



British Journal of Nutrition (2007), **97**, 435–439
DOI: 10.1017/S0007

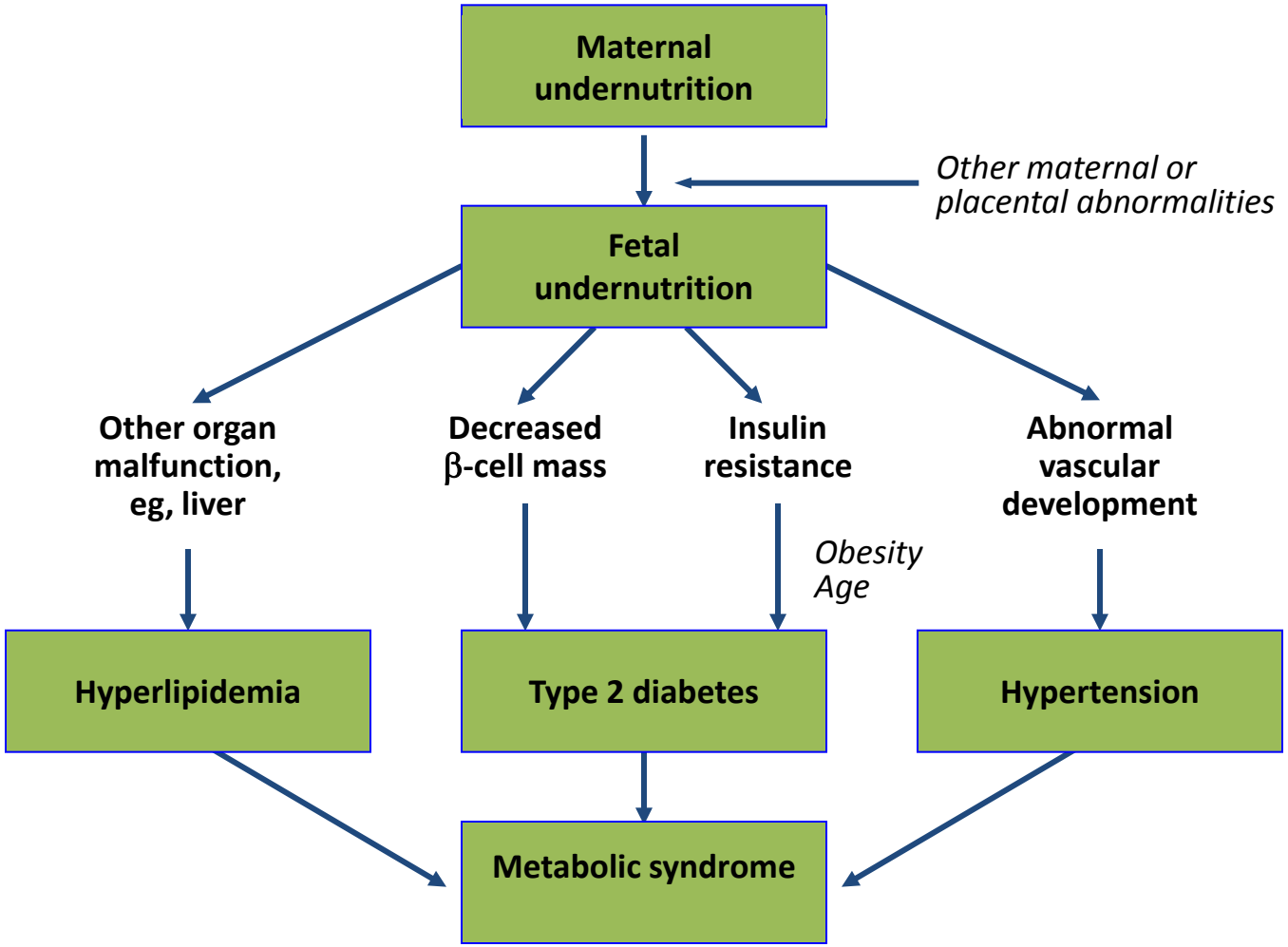
Dietary protein restriction of pregnant rats in the F_0 generation induces altered methylation of hepatic gene promoters in the adult male offspring in the F_1 and F_2 generations

Graham C. Burdge[1]*, Jo Slater-Jefferies[1], Christopher Torrens[1], Emma S. Phillips[2], Mark A. Hanson[1] and Karen A. Lillycrop[2]

Growth Patterns and Later Life Disease Risk

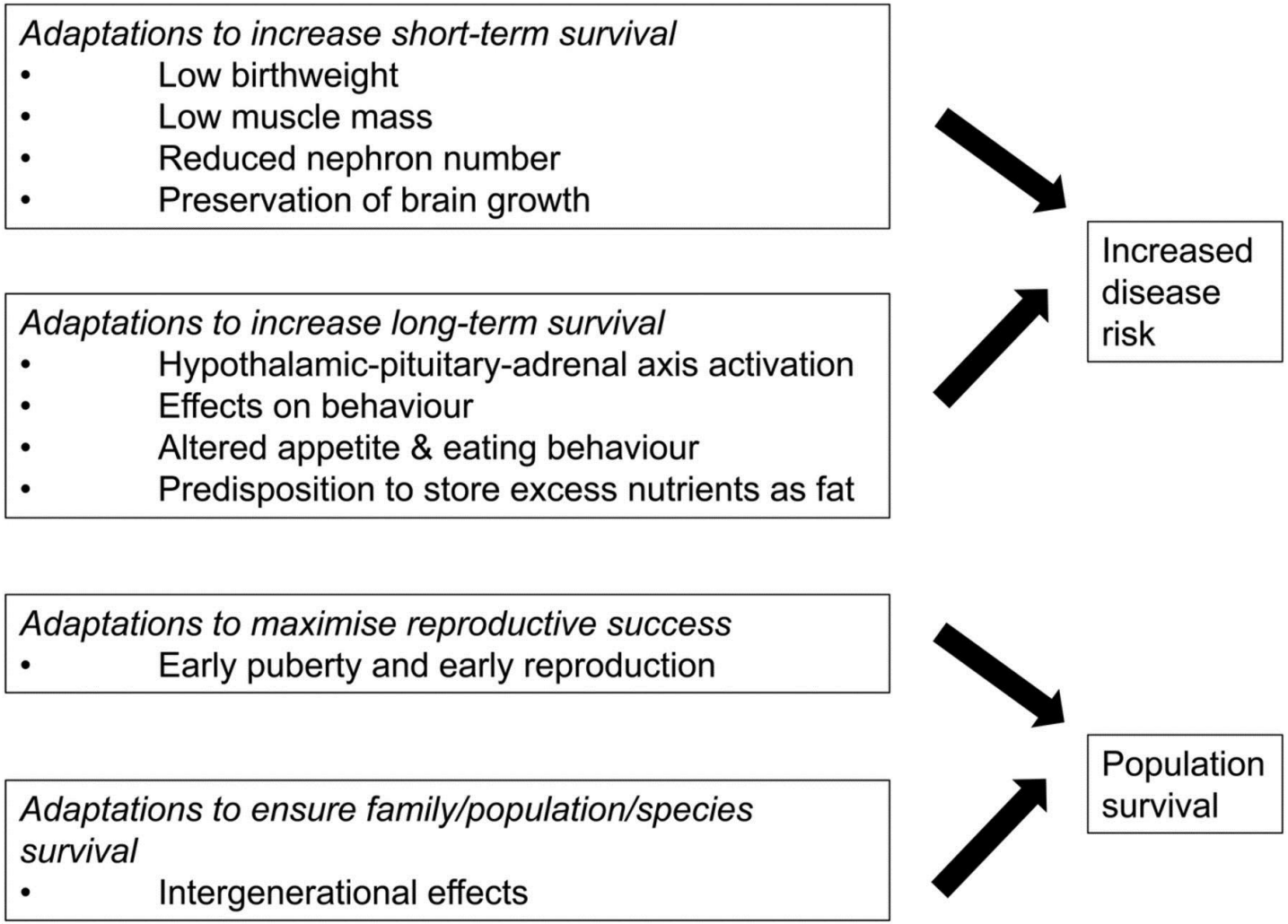
- Mechanisms

Fetal Origins of Metabolic Syndrome



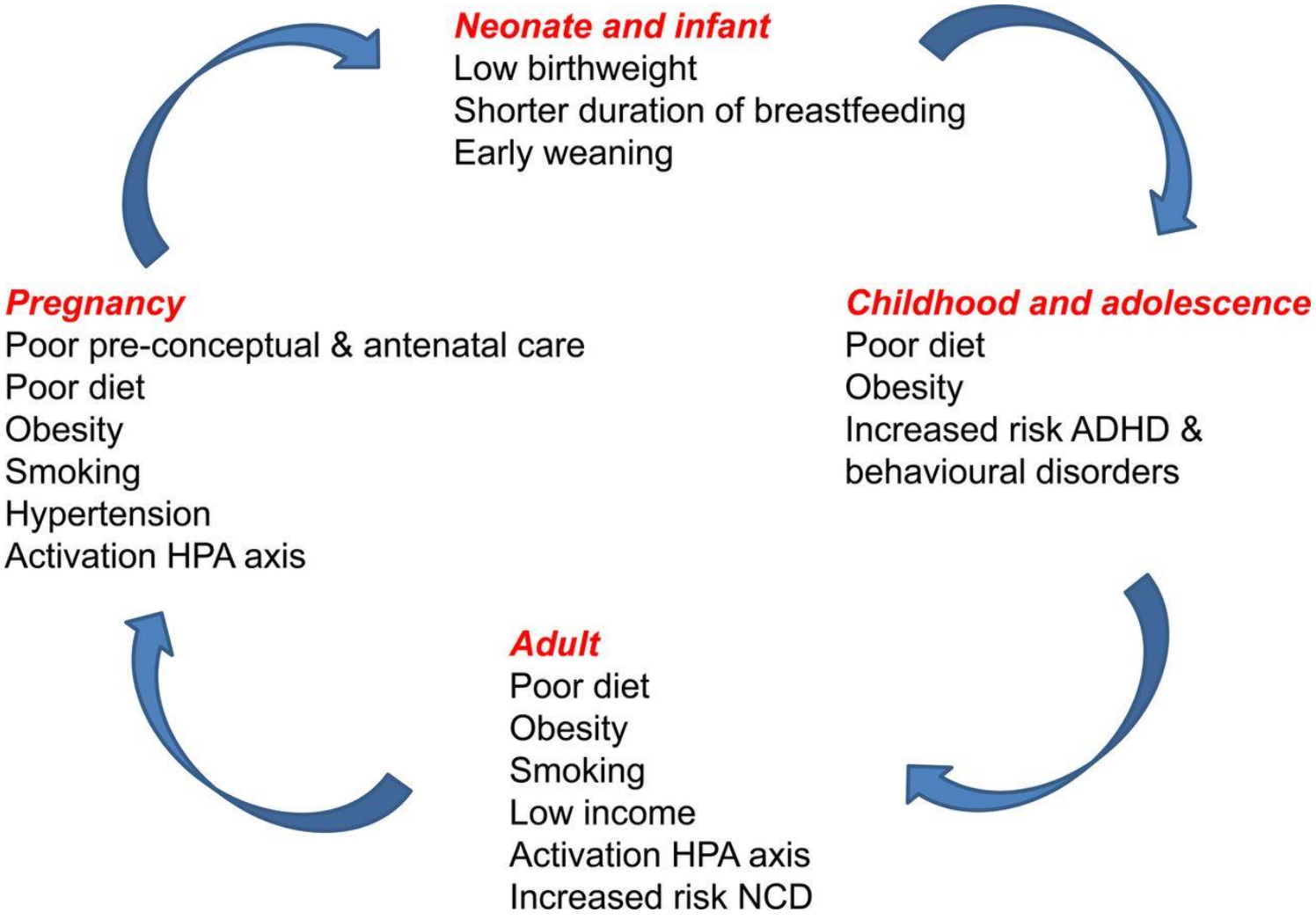
Barker DJP et al. *Diabetologia*. 1993;36:62. Barker DJP. *BMJ.* 1995;311:171.

Early life programming and later disease risk – Predictive Adaptive Response



Thomas C Williams, and Amanda J Drake Arch Dis Child
doi:10.1136/archdischild-2014-307958

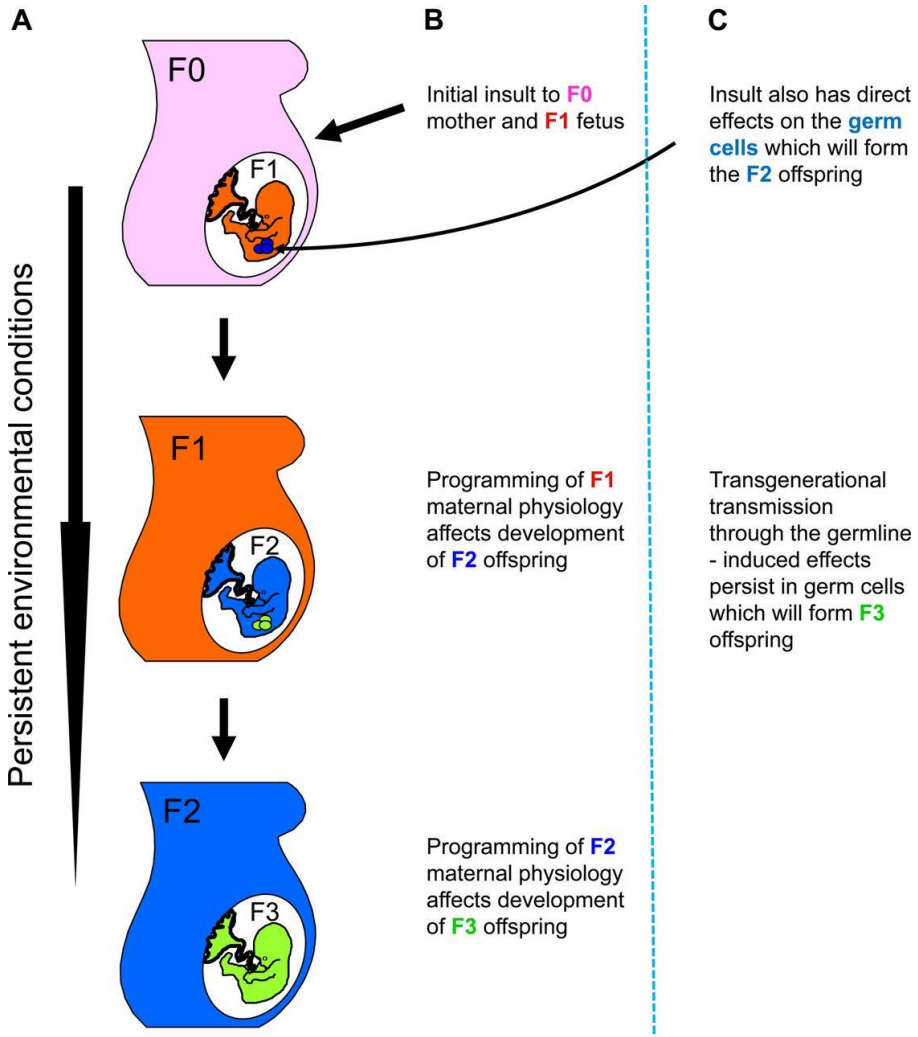
Intergenerational cycle of disease risk.



Thomas C Williams, and Amanda J Drake Arch Dis Child
doi:10.1136/archdischild-2014-307958

ADC

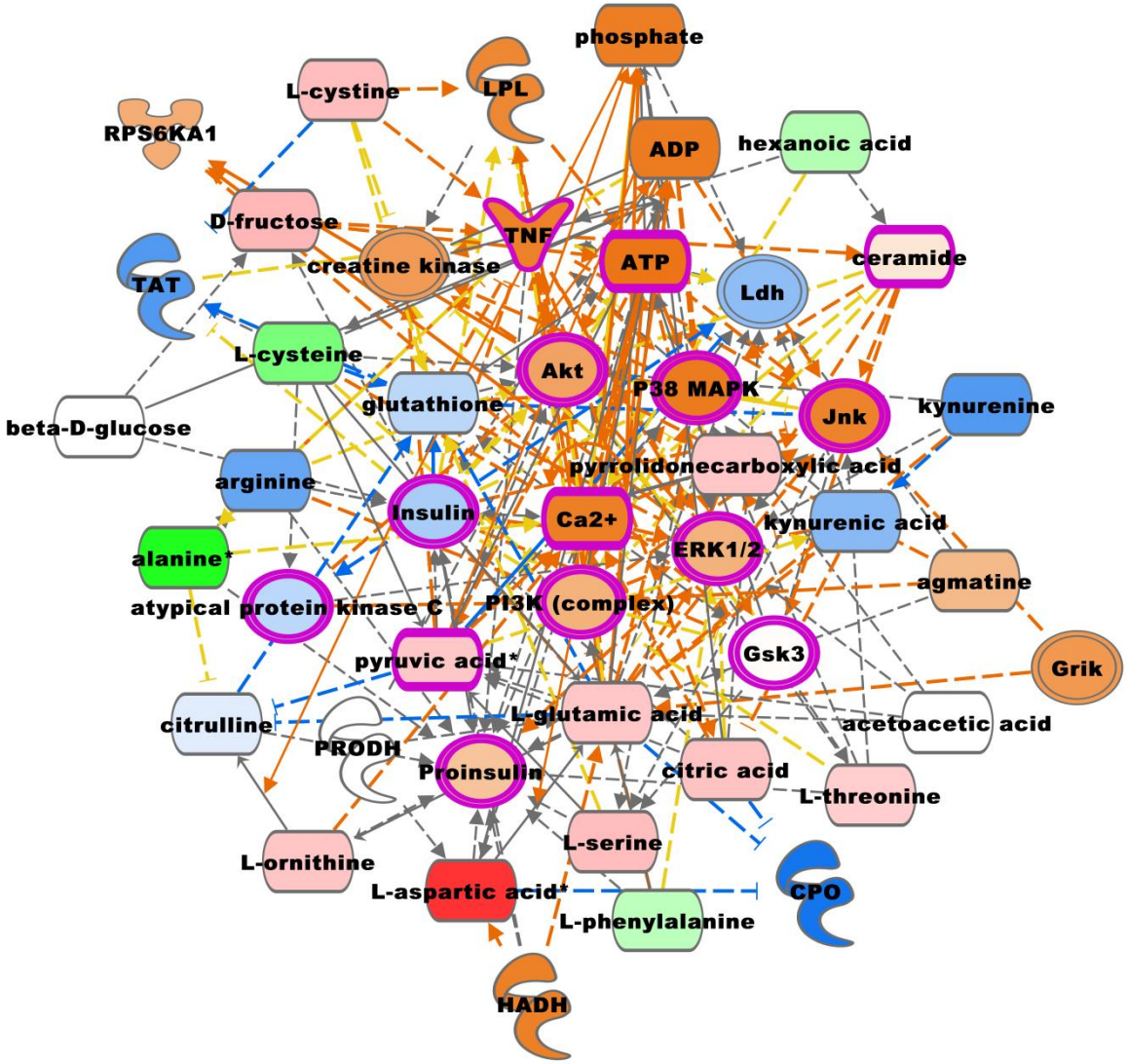
Potential mechanisms accounting for the transgenerational transmission of disease risk.



Thomas C Williams, and Amanda J Drake Arch Dis Child
doi:10.1136/archdischild-2014-307958

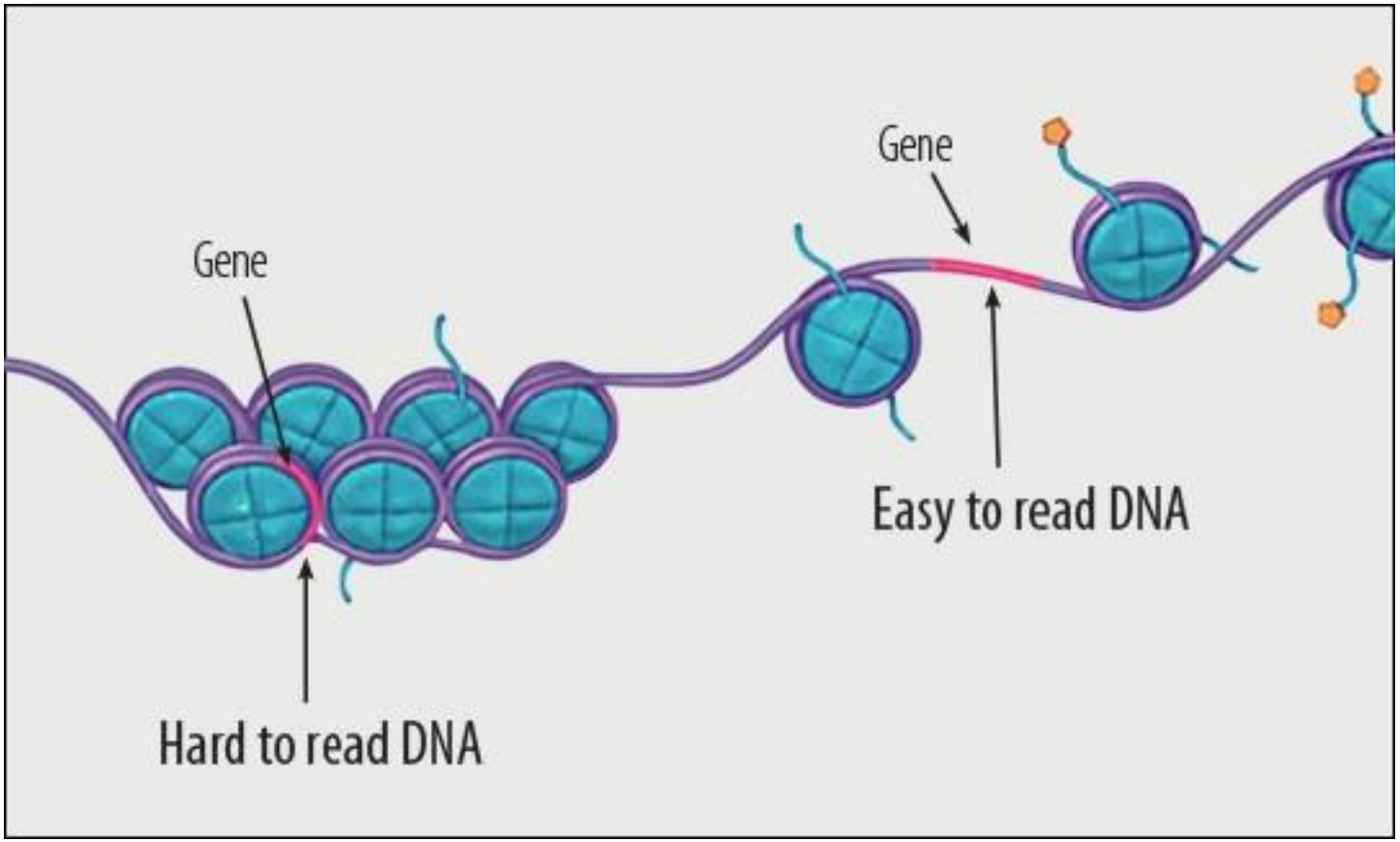
Cellular Metabolic Differences Occur in SGA derived fibroblasts

- Intracellular and Extracellular Metabolome extracted and analysed via GC-MS in 8 SGA and 3 control fibroblast cell lines
- 19 significantly differentially regulated metabolites mostly amino acids and intermediaries involved in carbohydrate metabolism

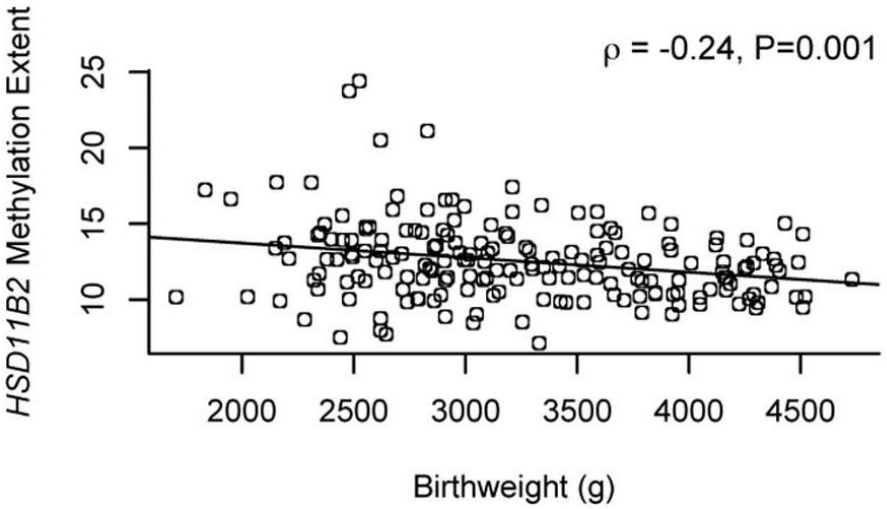


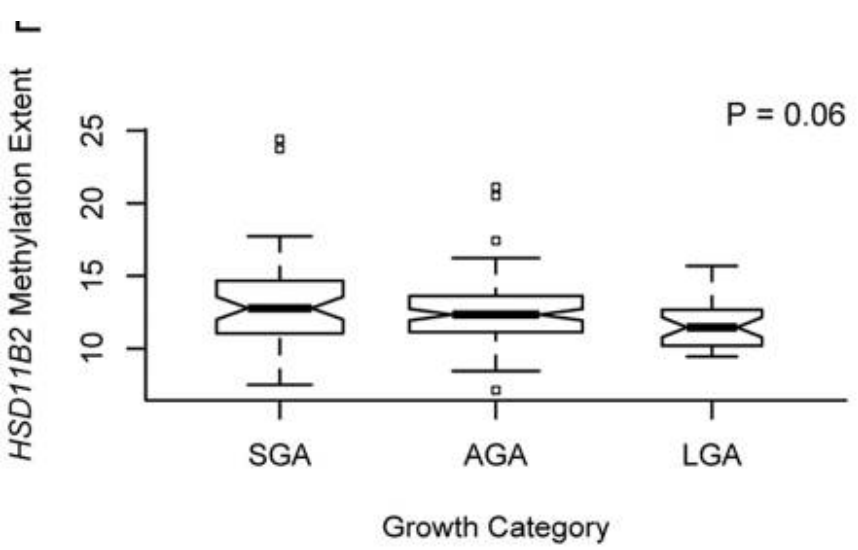
Interaction network of differences in metabolite regulation between control and SGA patient cell lines. Nineteen metabolites were identified as differentially regulated between control and patient cells, these were used to define a network with inferred protein and metabolite interactions (Ingenuity Pathway Analysis Software [IPA]).

Epigenetics



Methylation and Birth Size





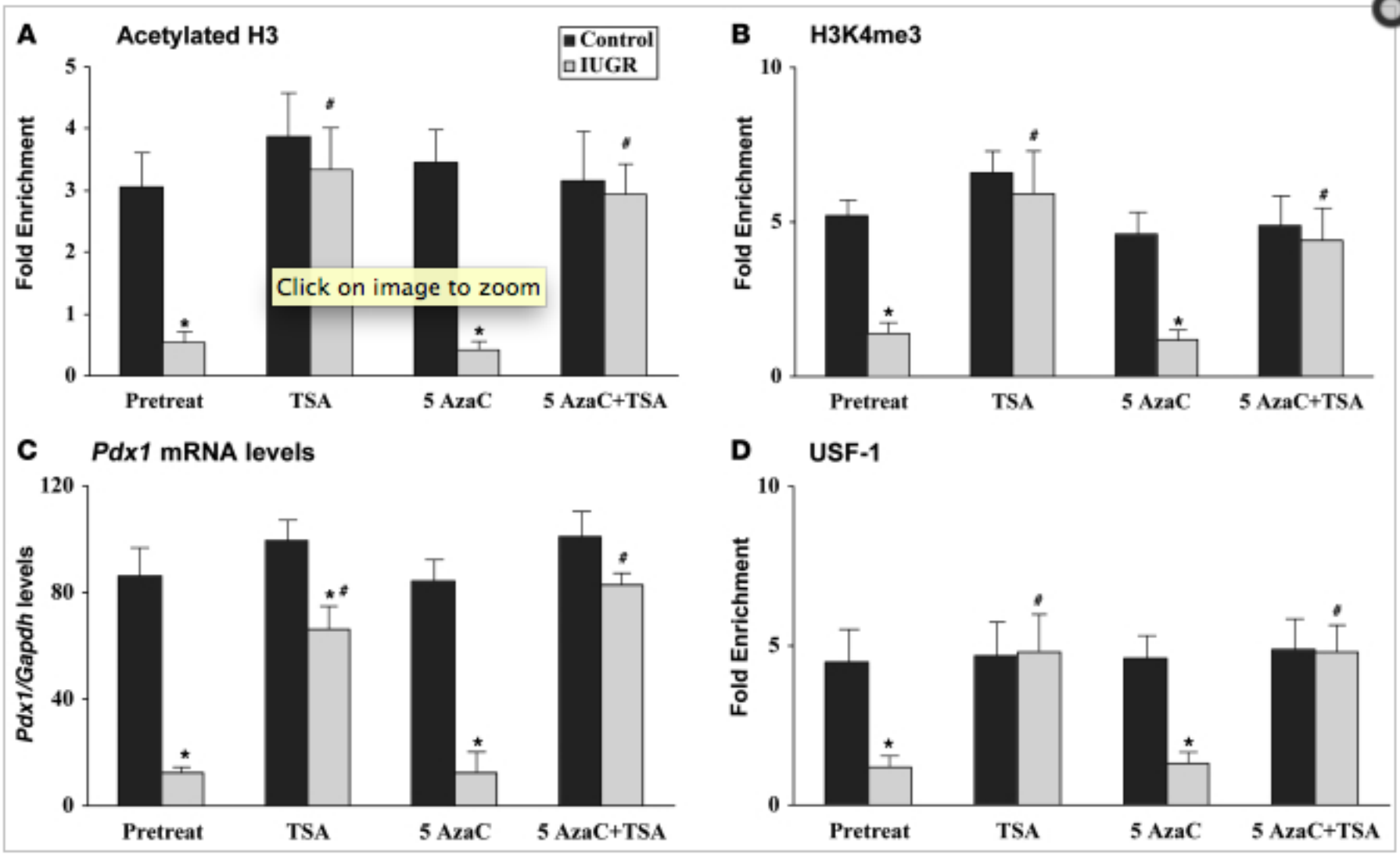
Growth Patterns and Later Life Disease Risk

- So can we do anything about this!

Reprogramming

- IUGR rodent model associated with reduced Pdx1 (transcription factor involved pancreatic beta cell development) associated with postnatal
  - Recruitment of HDAC1 and co-repressor Sin3A
  - Deacetylation of histones H3 and H4
  - Loss of USF-1 binding at Pdx1 promotor

HDAC inhibitor treatment



Conclusions

- Being born small increases risk of cardiovascular disease in adulthood
- Increased postnatal growth is associated with increased disease risk
- This increased risk is passed through generations as far as grandchildren