



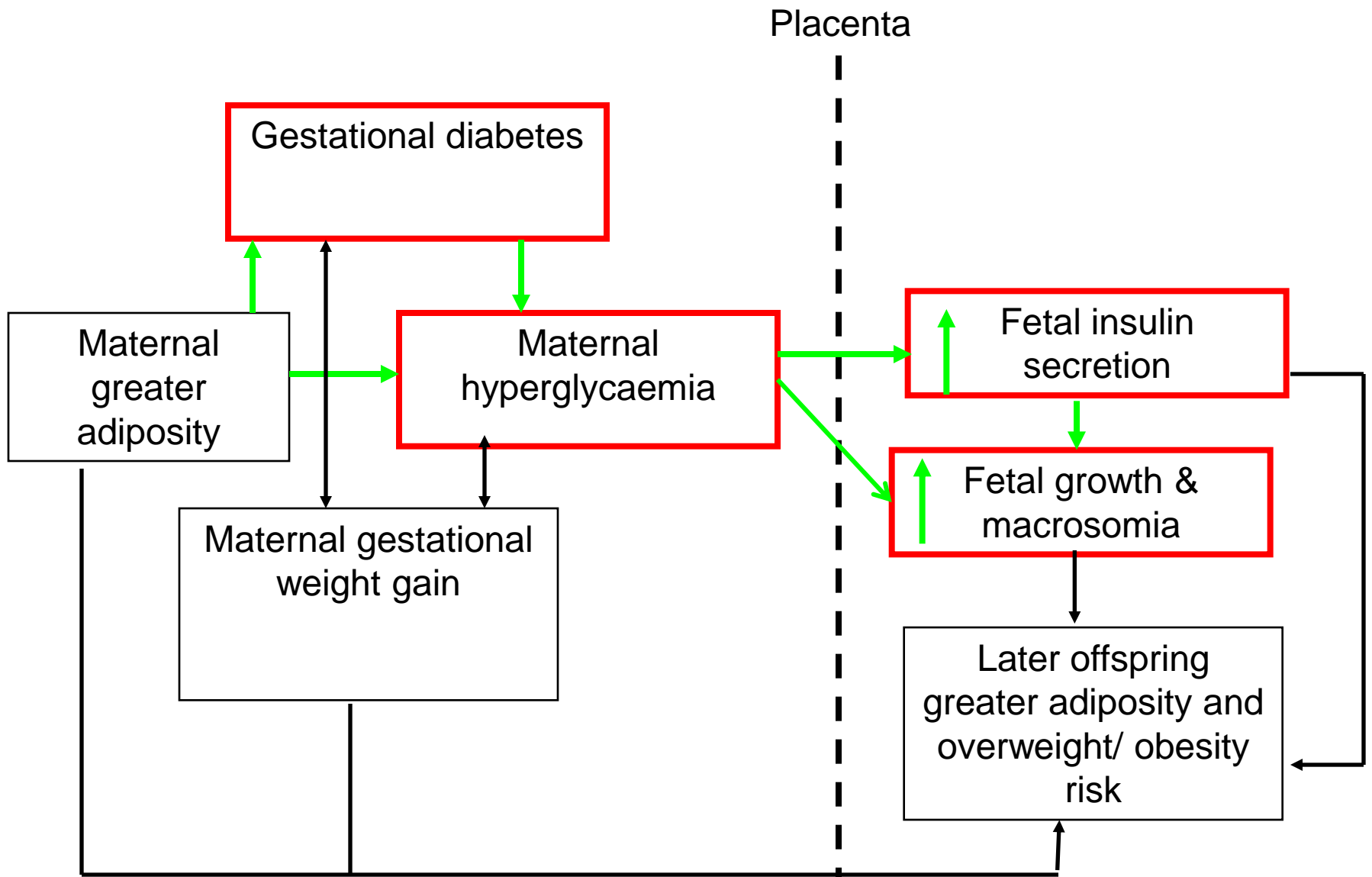
Developmental overnutrition - an old hypothesis with new relevance?

MRC

Centre for Causal
Analyses in Translational
Epidemiology

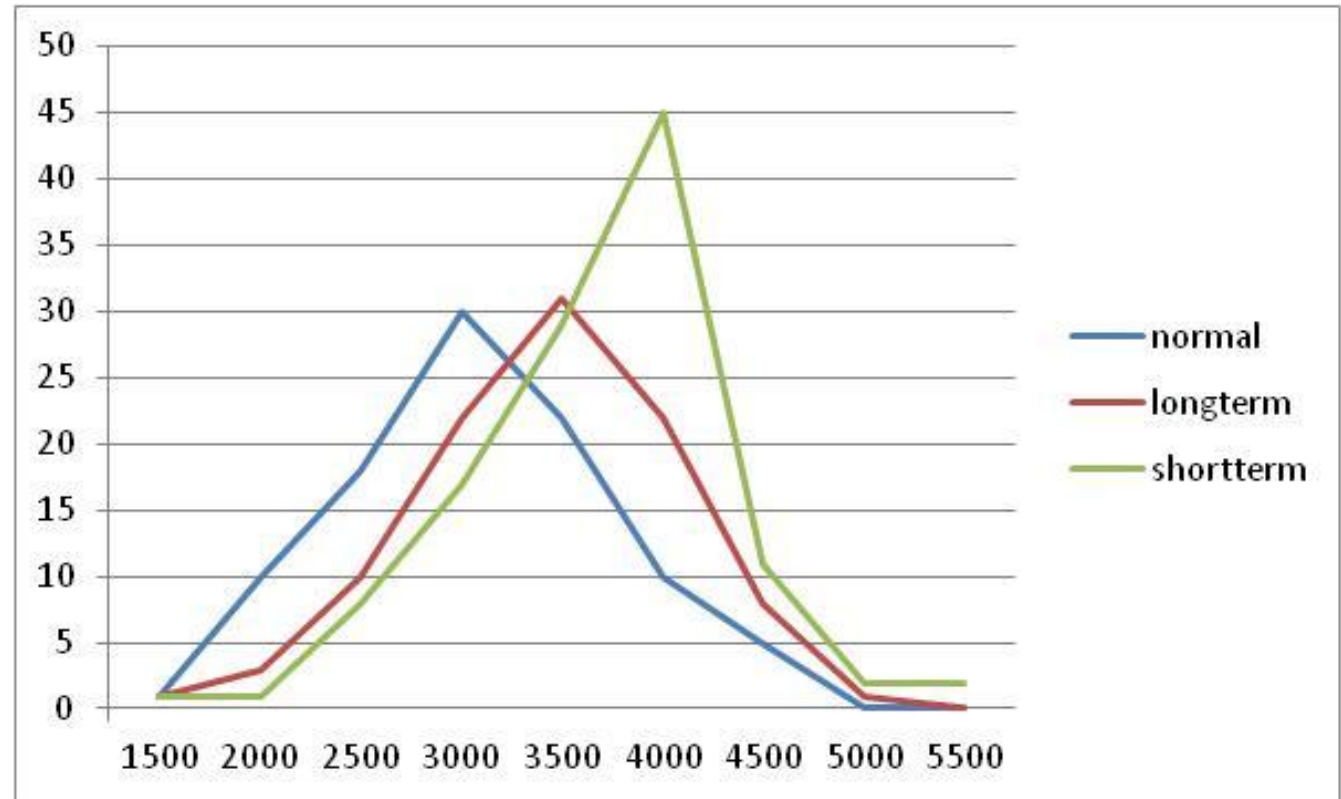
Debbie A Lawlor (d.a.lawlor@bristol.ac.uk)





🌿 Birth weight by diabetes & treatment

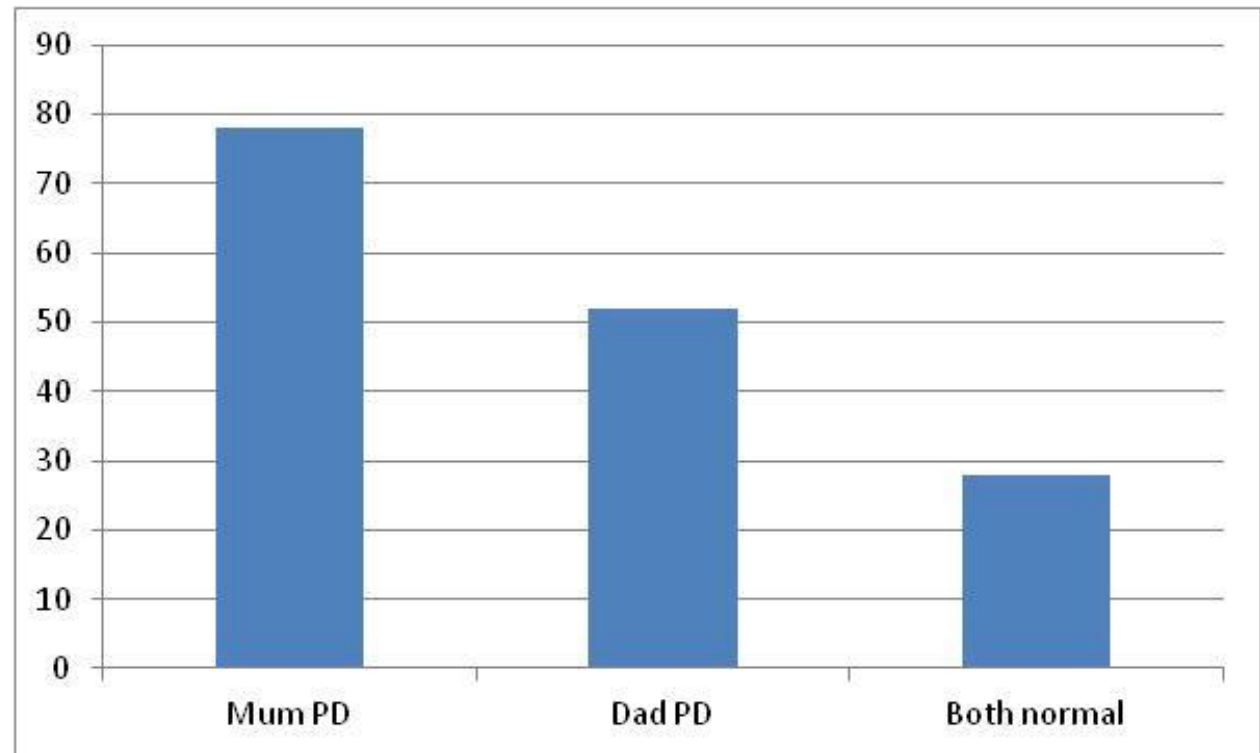
“The maternal blood sugar level may influence weight and length of the infants directly ... but also indirectly , [by] foetal insulin, as foetal insulin may act as a growth stimulating factor.”



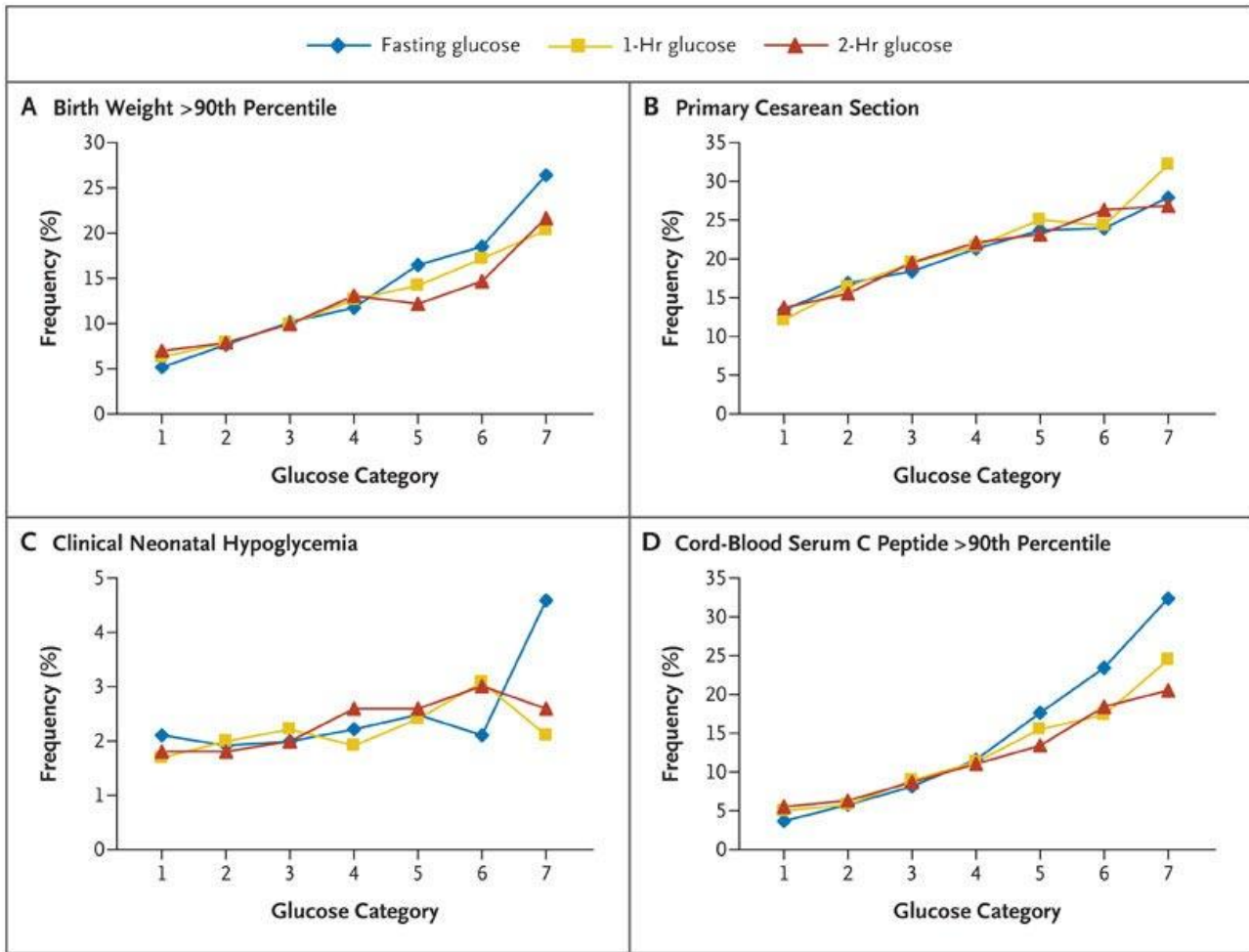
Pedersen J *Acta Endocrinology* 1954

🌟 Large birth weight in infants born **before** mothers & fathers were diagnosed with diabetes

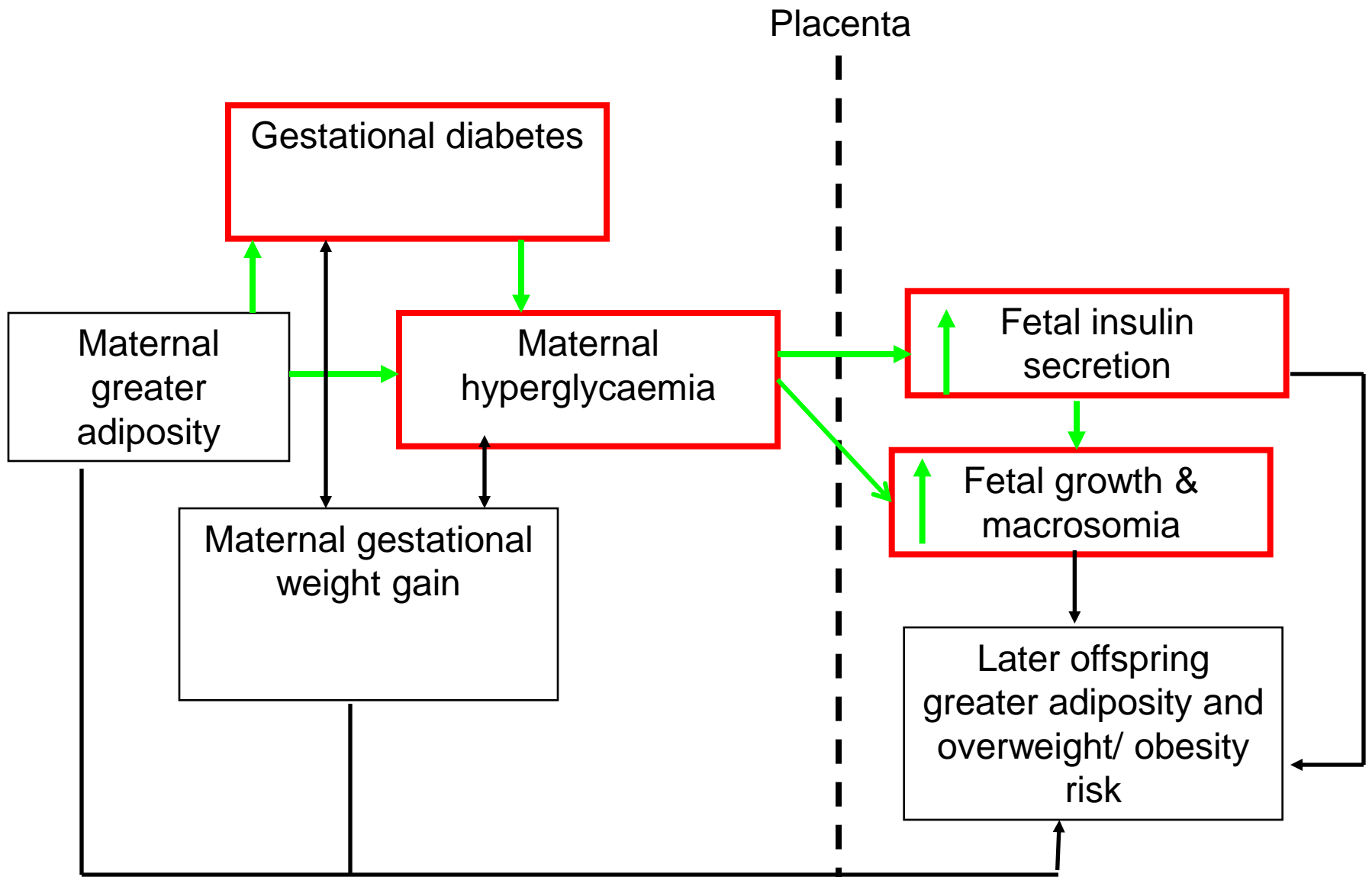
“The evidence suggests that the tendency to produce large babies is partly an inherited characteristic ... and partly an effect of maternal internal environment.”



Maternal diabetes / glucose and fetal birth size and outcomes – HAPO



The HAPO Study Cooperative Research Group. N Engl J Med 2008;358:1991-2002



“the obesity epidemic could accelerate through successive generations independent of further genetic or environmental factors”.

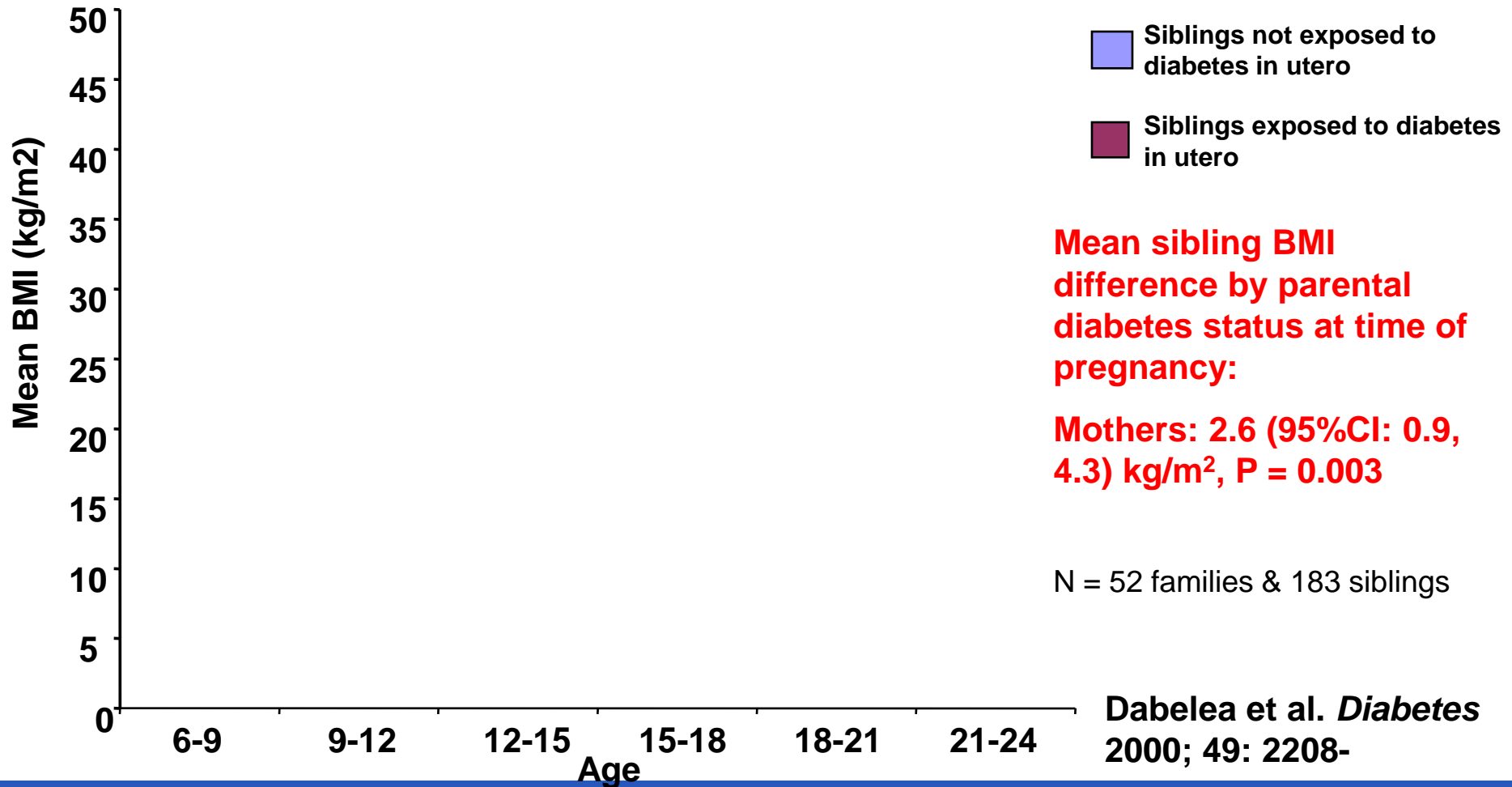
Ebbeling CB, Pawlak DB, Ludwig DS.
Lancet 2002; 360:473-482

Association of gestational diabetes with offspring adiposity

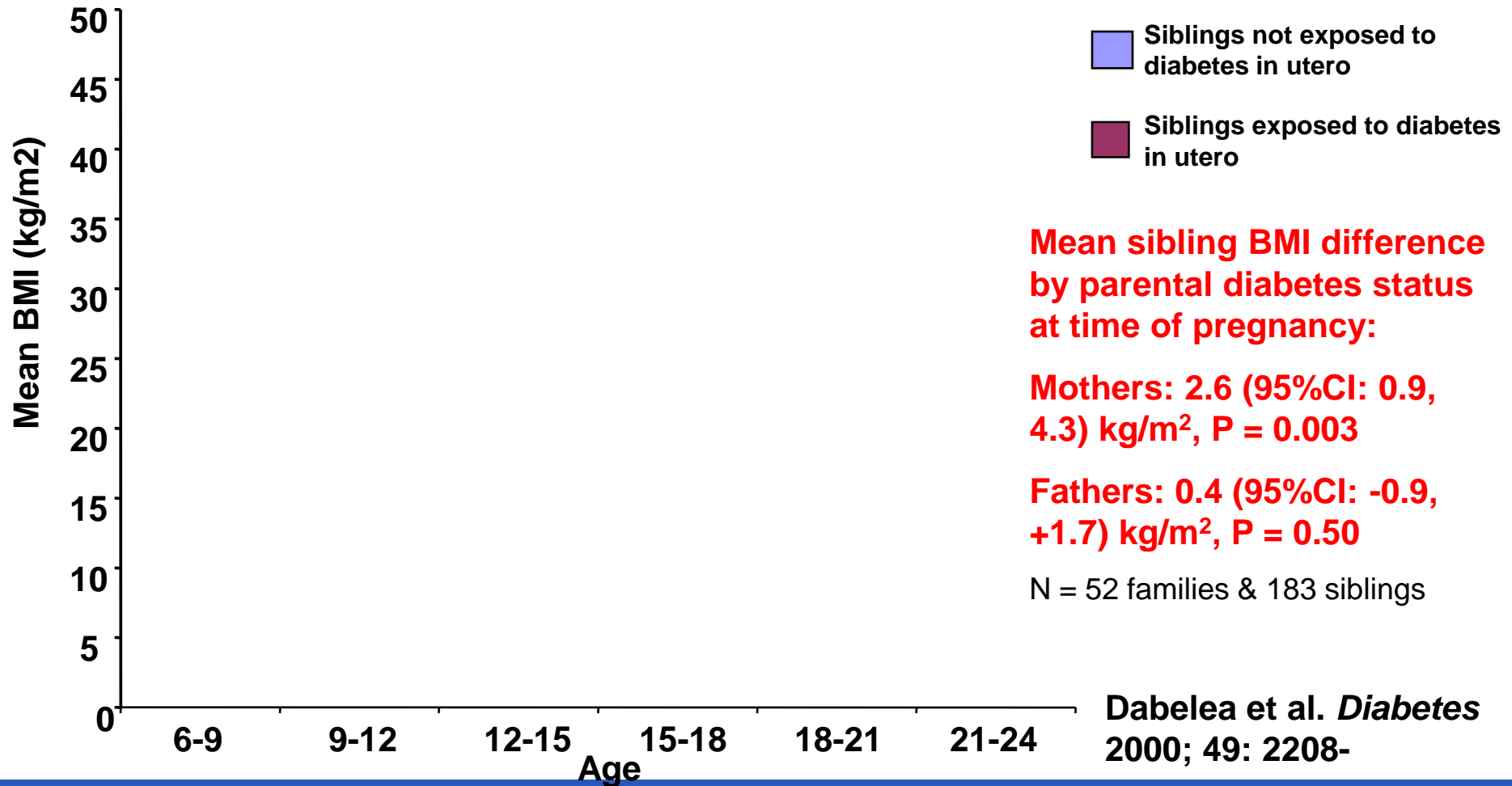
- Evidence from Pima Indians
 - Gestational diabetes associated with increased mean BMI and odds of obesity in offspring at least up to age 20s
 - Sibling and parental comparison study suggests intrauterine effects play some part
- Evidence from non-Pima populations
 - Few studies
 - Inconsistent results



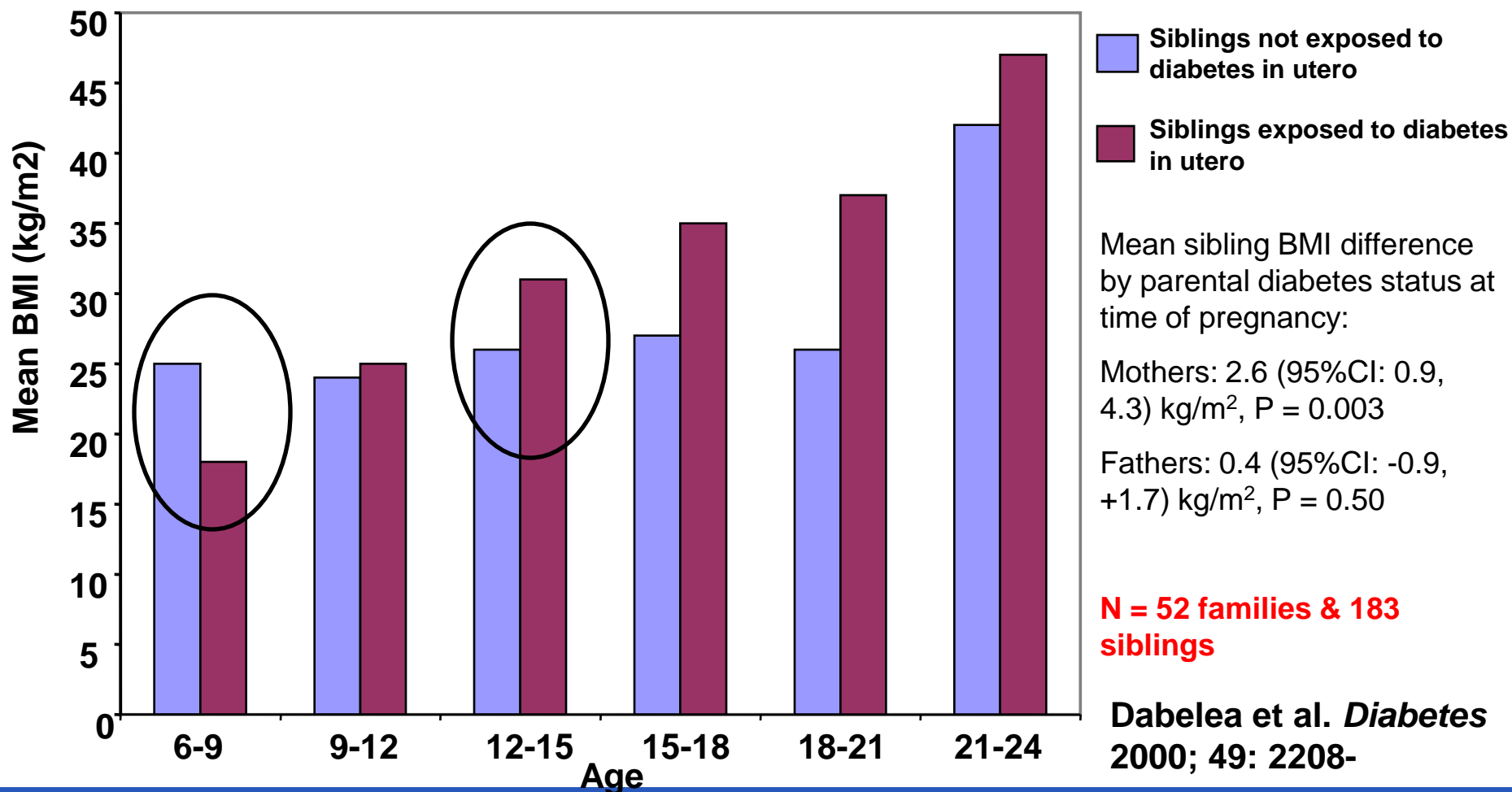
Pima-Indians: mean BMI in siblings by exposure to diabetic intrauterine environment



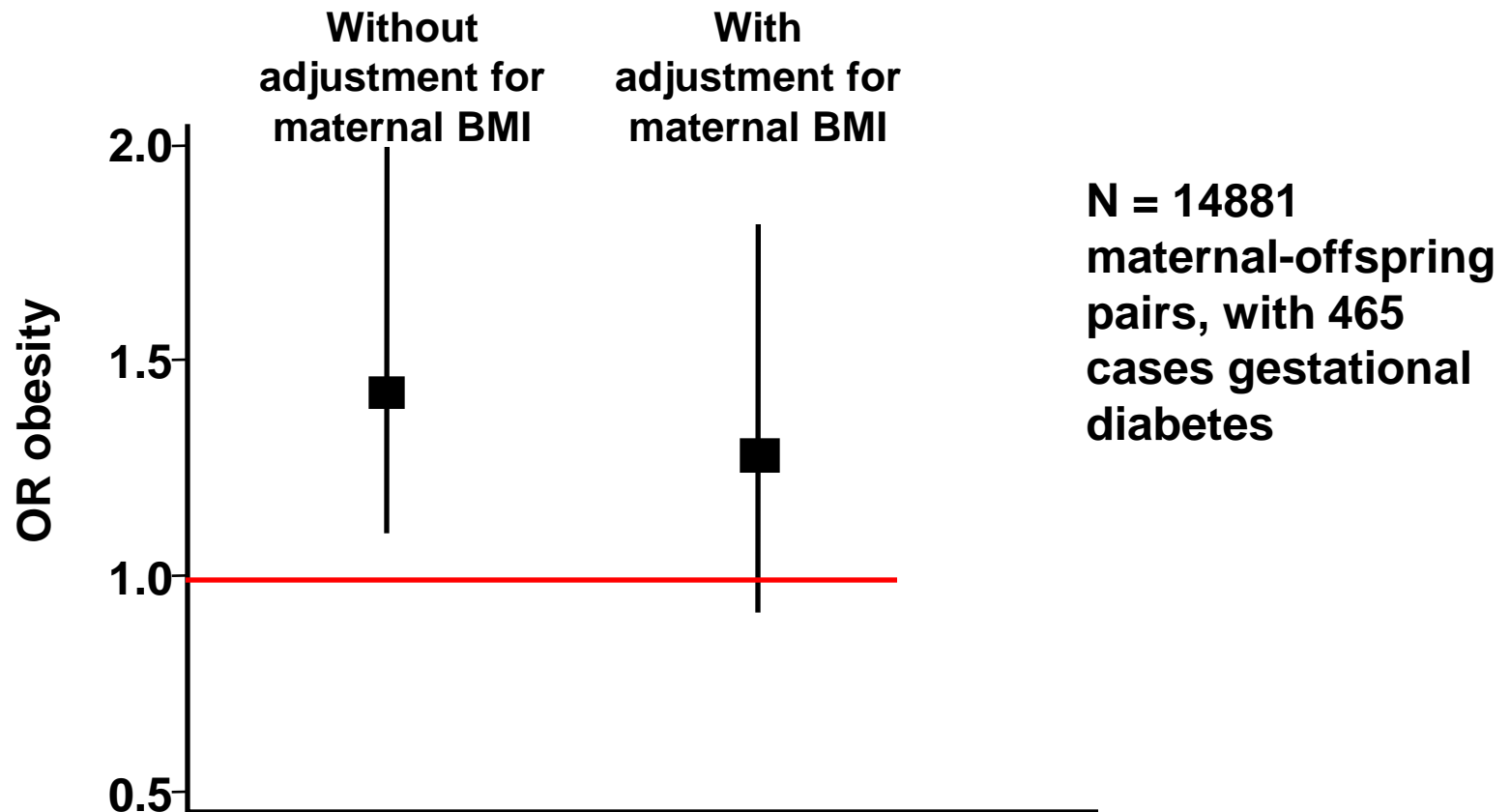
Pima-Indians: mean BMI in siblings by exposure to diabetic intrauterine environment



Pima-Indians: mean BMI in siblings by exposure to diabetic intrauterine environment



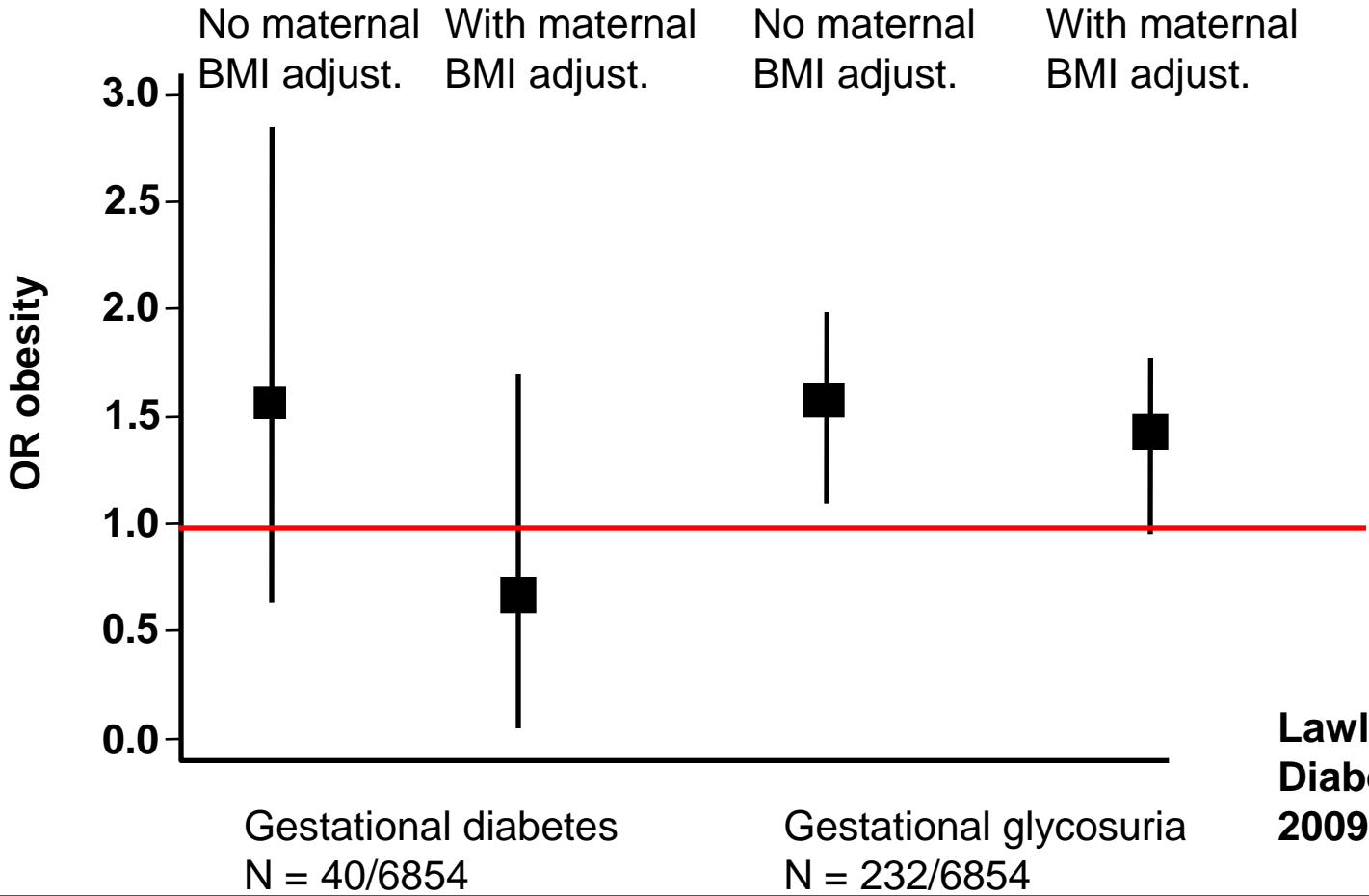
US population: Odds of obesity by maternal gestational diabetes



Gillman et al., *Pediatrics* 2003;111:e221-e226



UK population: odds of offspring obesity by maternal gestational diabetes and glycosuria



Lawlor et al.
Diabetologia
2009



🌟 Mean difference in BMI at age 18 years by maternal pregnancy exposures: sibling study of 280,866 singleton born Swedish men from 248, 293 families

	Within brothers	Between unrelated men	P-value for difference
Maternal diabetes in pregnancy (yes versus no)	0.94 (0.35, 1.52)	0.87 (0.68, 1.07)	0.87

Lawlor DA, Lichtenstein P, Långström N. *Circulation* 2011

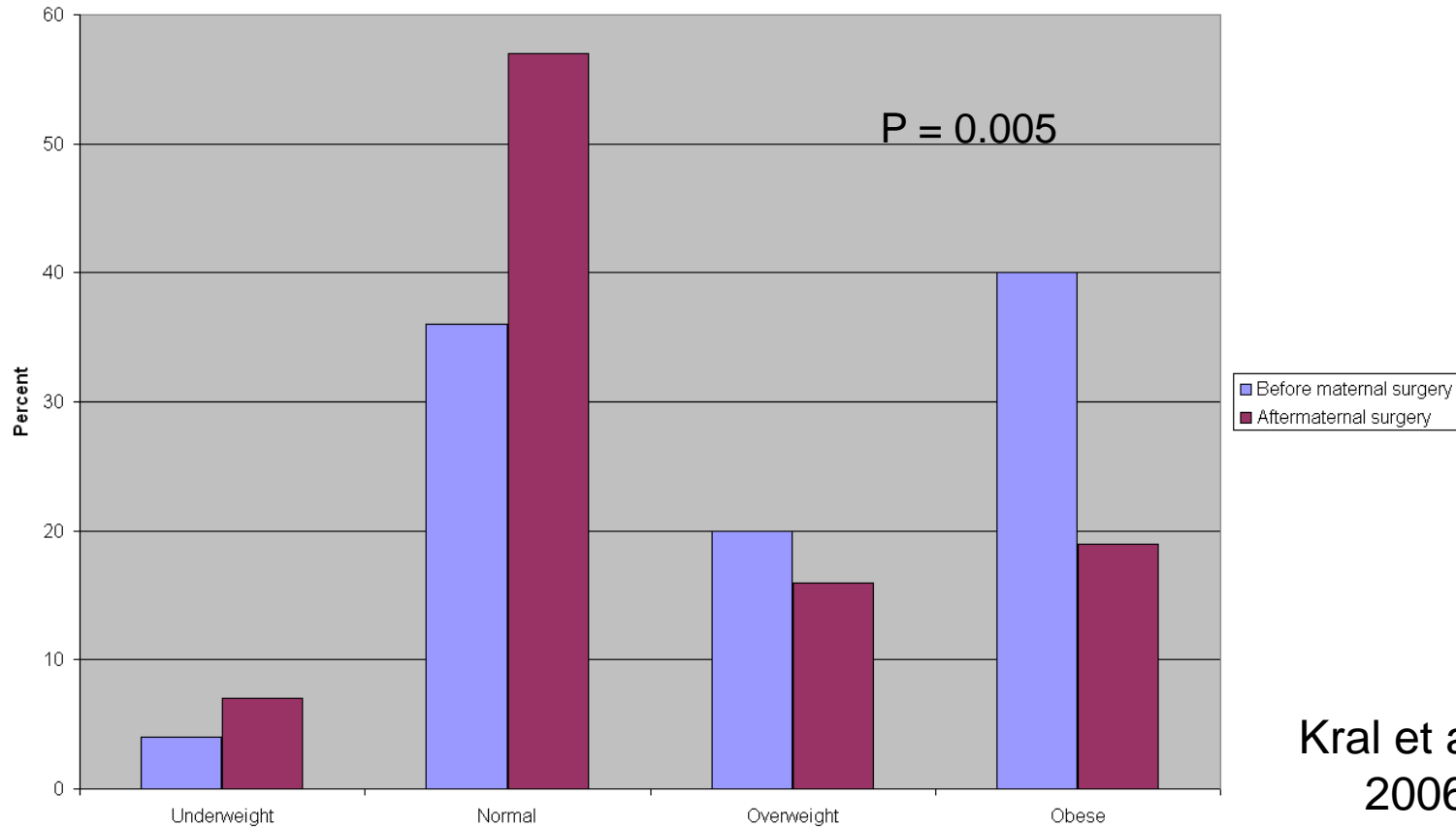


Maternal extreme obesity and later offspring adiposity



Exposure to extreme obese intrauterine environment and offspring obesity

N = 172 children from 133 families. Age offspring 2-18yrs
Offspring weight categories in siblings born before and after maternal bariatric surgery



Kral et al. *Pediatrics*
2006;118:e1644-

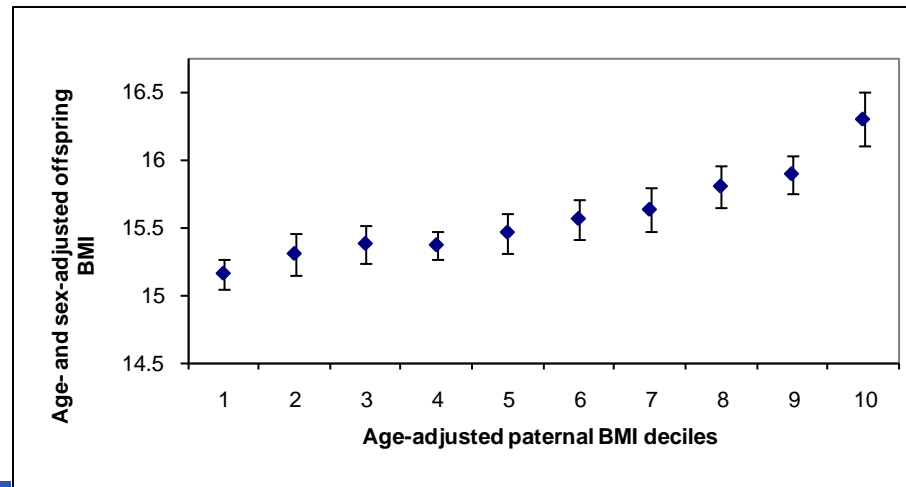
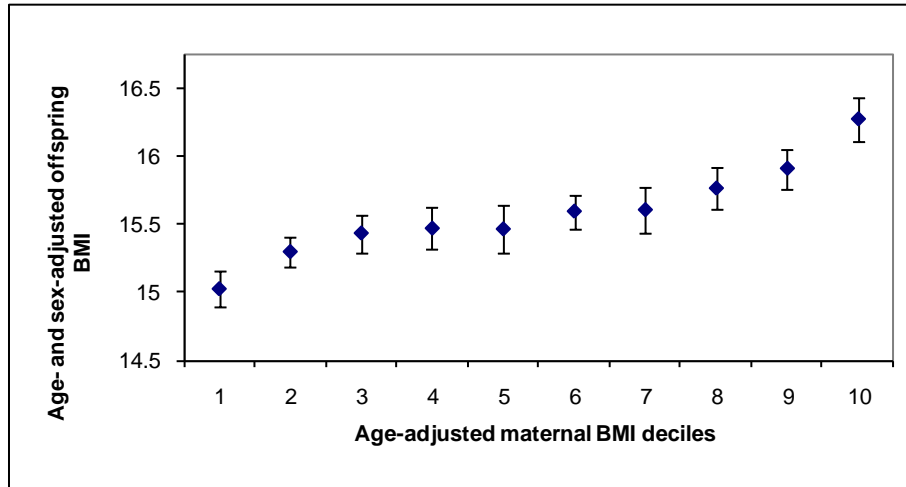
Association of maternal adiposity (across the distribution) with offspring adiposity in general (not clinically obese) populations

- Large number of cohorts consistently show positive association:
 - Genetic
 - Family (non-intrauterine) environment
 - Intrauterine
- Stronger association in mothers would support latter (or mothers influence offspring behaviour more than fathers)





Probit: Offspring BMI according to deciles of maternal and paternal BMI (N = 12,183). Offspring age = 6 years.

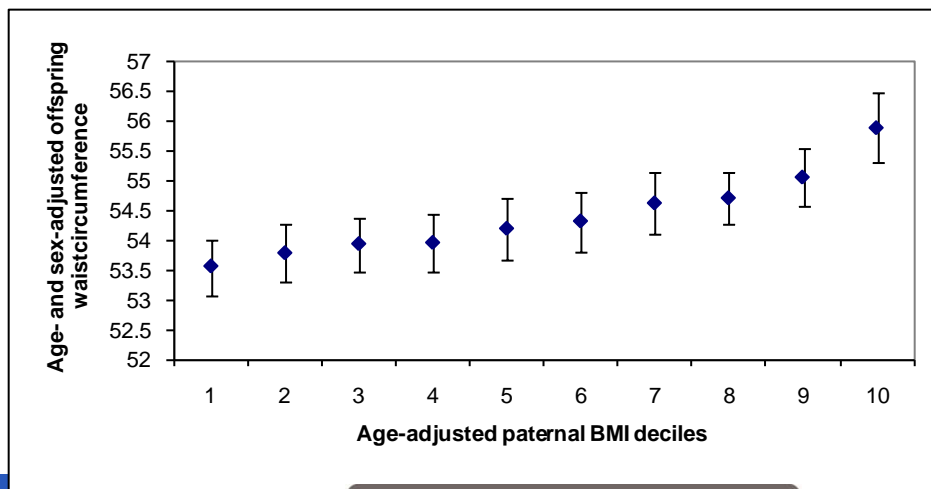
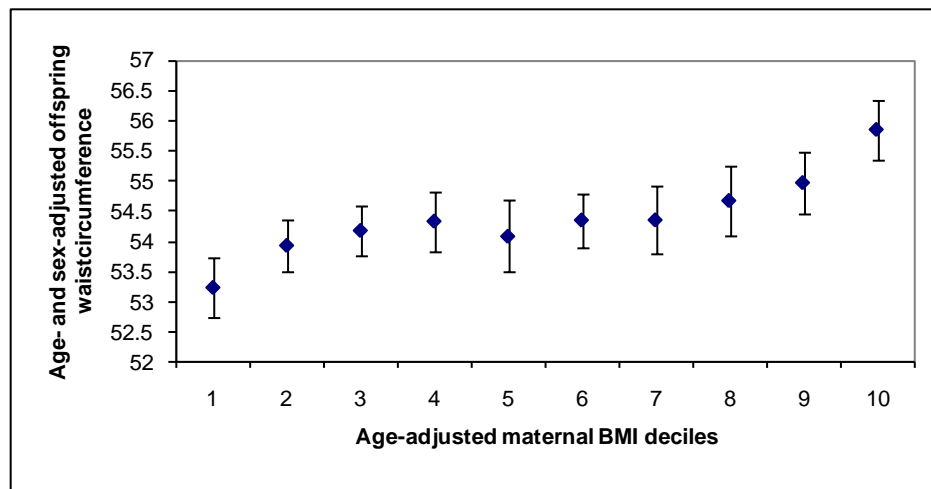


Patel R, et al. *Plos-One* 2011



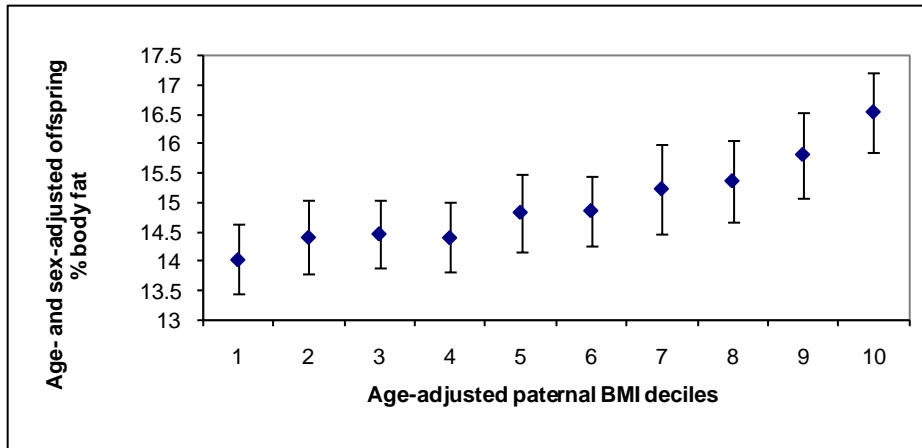
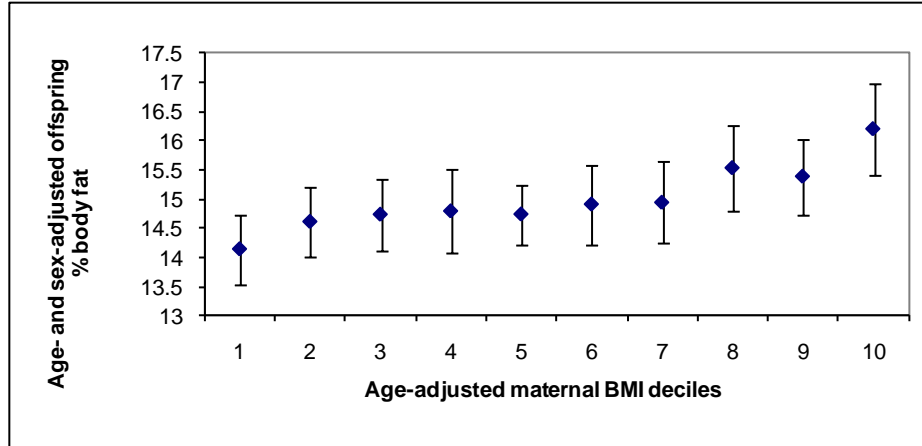


Probit: Offspring Waist according to deciles of maternal and paternal BMI (N = 12,183). Offspring age = 6 years.



Patel R, et al. *Plos-One* 2011

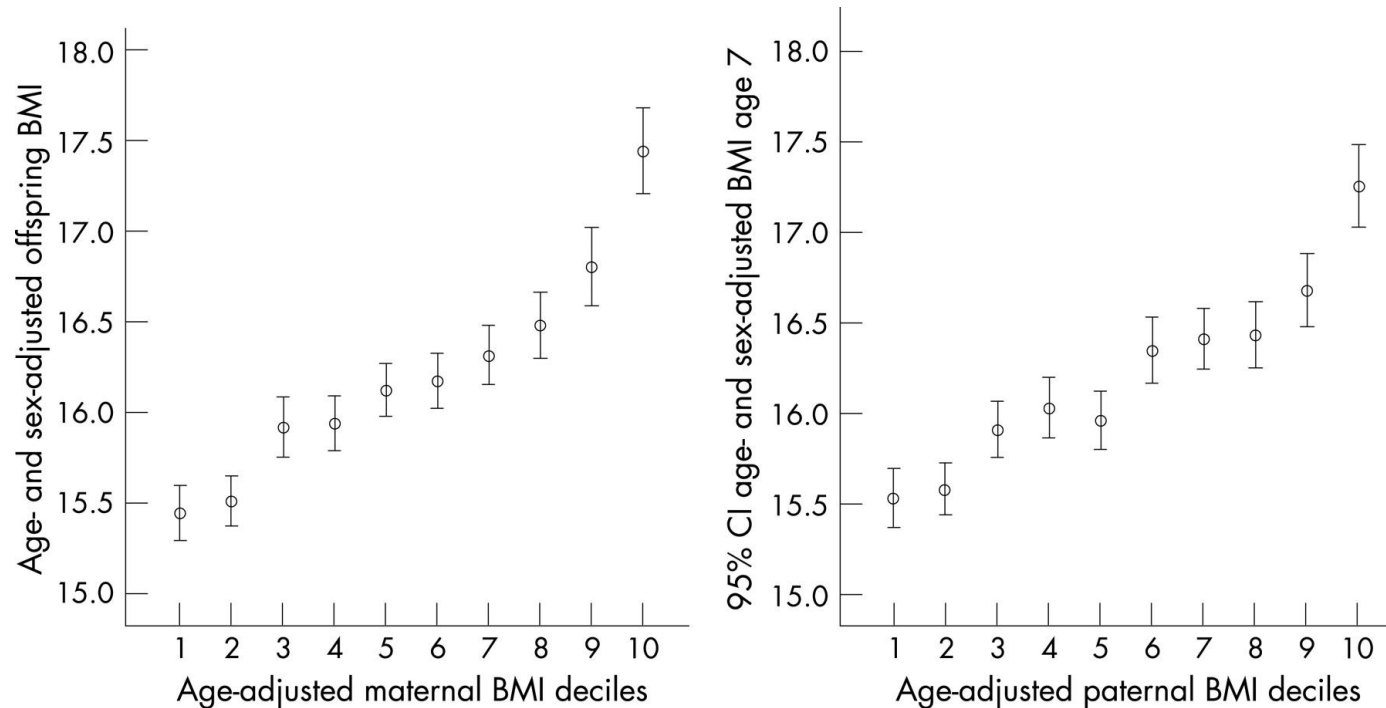
✦ Probit: Offspring % body fat according to deciles of maternal and paternal BMI (N = 12,183). Offspring age = 6 years.



Patel R, et al. *Plos-One* 2011



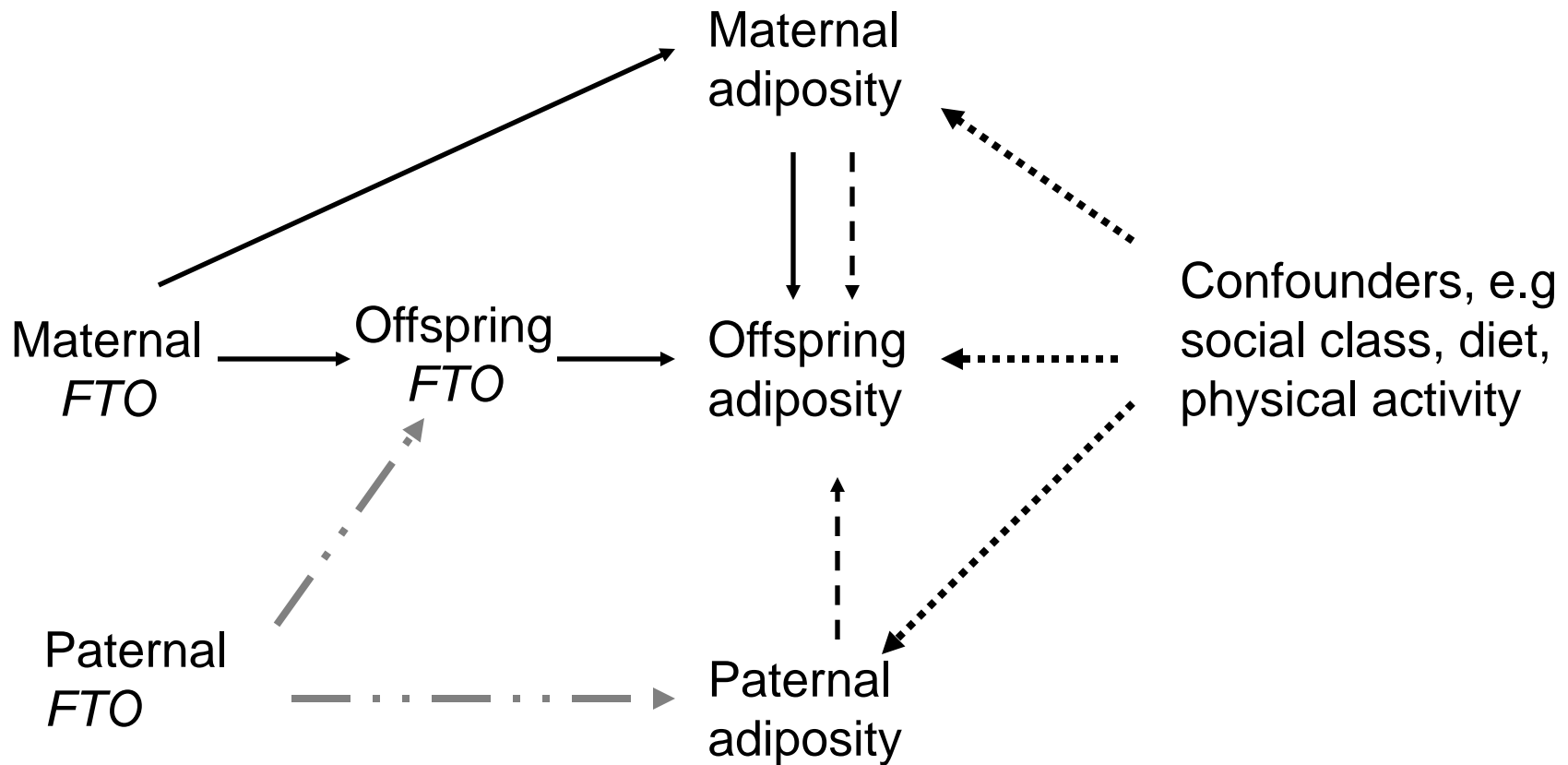
ALSPAC: Offspring body mass index (BMI) according to deciles of maternal and paternal BMI (N = 4654). Offspring age = 9



Davey Smith, G. et al. *Arch Dis Child* 2007;92:876-880



ALSPAC: Mendelian randomisation & parental comparisons.
Offspring Age = 12



Lawlor et al. *Plos-Med* 2008

Results 1

	Difference in total offspring fat / lean mass per SD parental BMI (95%CI)		P – for difference in association mums v dads
	Mothers	Fathers	
Fat mass (z-score)	0.25 (0.22, 0.27)	0.13 (0.11, 0.15)	< 0.0001
Lean mass (z-score)	0.10 (0.08, 0.12)	0.08 (0.06, 0.10)	0.31

Adjusted for offspring sex, age, height & puberty; parental SEP, education, smoking & maternal parity & mutually adjusted for each parents BMI (NB: full adjusted associations no different to simple sex, age and height)

🌟 Results 2: Sensitivity analyses for non-paternity with total fat mass

Assumed non-paternity (%)	Coefficient for <u>mothers</u> BMI	Coefficient for <u>fathers</u> BMI	P for difference in coefficients
0	0.236	0.127	< 0.0001
5	0.235	0.139	< 0.0001
10	0.233	0.151	< 0.0001
15	0.231	0.165	0.001
20	0.229	0.181	0.017

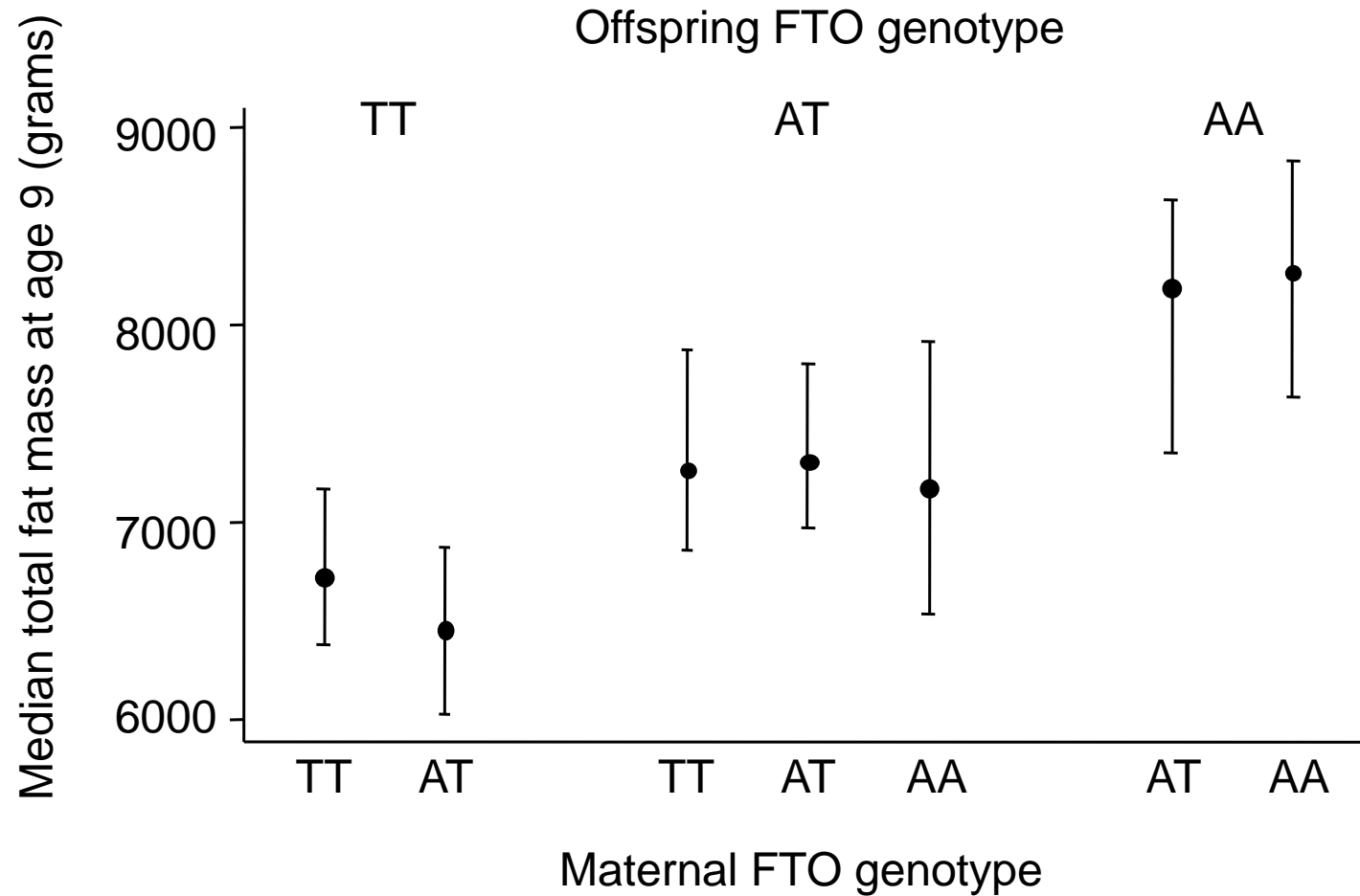
Results 3: IV analyses

	Change in total offspring fat mass per SD <u>mothers</u> BMI (95%CI)		P – for difference in association OLS v IV
	OLS	IV	
Fat mass (z-score)	0.26 (0.23, 0.29)	-0.08 (-0.56, 0.41)	0.17

OLS: Ordinary Least Squares (conventional) regression; IV: Instrumental variable analysis, instrumental variable = mothers FTO controlling for offspring FTO

NB: OLS adjusted as in results 1, but slightly fewer participants included here

Results 4: graphical representation of IV analyses



👉 Could developmental overnutrition be a major contributor to obesity epidemic?

- IV and OLS results statistically consistent with each other, so maternal adiposity could be positively causally related to offspring adiposity
- Parental comparisons suggest that the offspring of mothers who have a pregnancy BMI greater by 1SD than other mothers will have on average 0.12 SD greater fat mass at age ~12 as a result of a unique maternal effect (i.e. difference in maternal and paternal coefficients)
- Amongst UK children aged 12 years BMI increased by 0.47SD in males and 0.53SD in females between 1987 and 1997 – i.e. more than x5 that **possibly** due to developmental overnutrition (remember the unique maternal effect may not be intrauterine)

🌟 Mean difference in BMI at age 18 years by maternal pregnancy exposures: sibling study of 280,866 singleton born Swedish men from 248, 293 families

	Within brothers	Between unrelated men	P-value for difference
Maternal diabetes in pregnancy (yes versus no)	0.94 (0.35, 1.52)	0.87 (0.68, 1.07)	0.87
Maternal pre-pregnancy BMI (per 1kg)	-0.04 (-0.07, -0.01)	0.32 (0.31, 0.32)	< 0.001

Lawlor DA, Lichtenstein P, Långström N. *Circulation* 2011



Gestational weight gain and offspring adiposity

- At least 14 studies
 - All in European origin populations
 - 13 show positive association; 1 null
 - Most use IOM categories of GWG
 - Most examined outcomes in offspring up to age ~10-11



ALSPAC

- Mothers and offspring enrolled in the Avon Longitudinal Study of Parents and Children, a population-based birth cohort study that recruited 14,541 pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992
- Gestational weight available for 12,484 mothers; of whom 12,449 had a term pregnancy and offspring who survived 1 year.

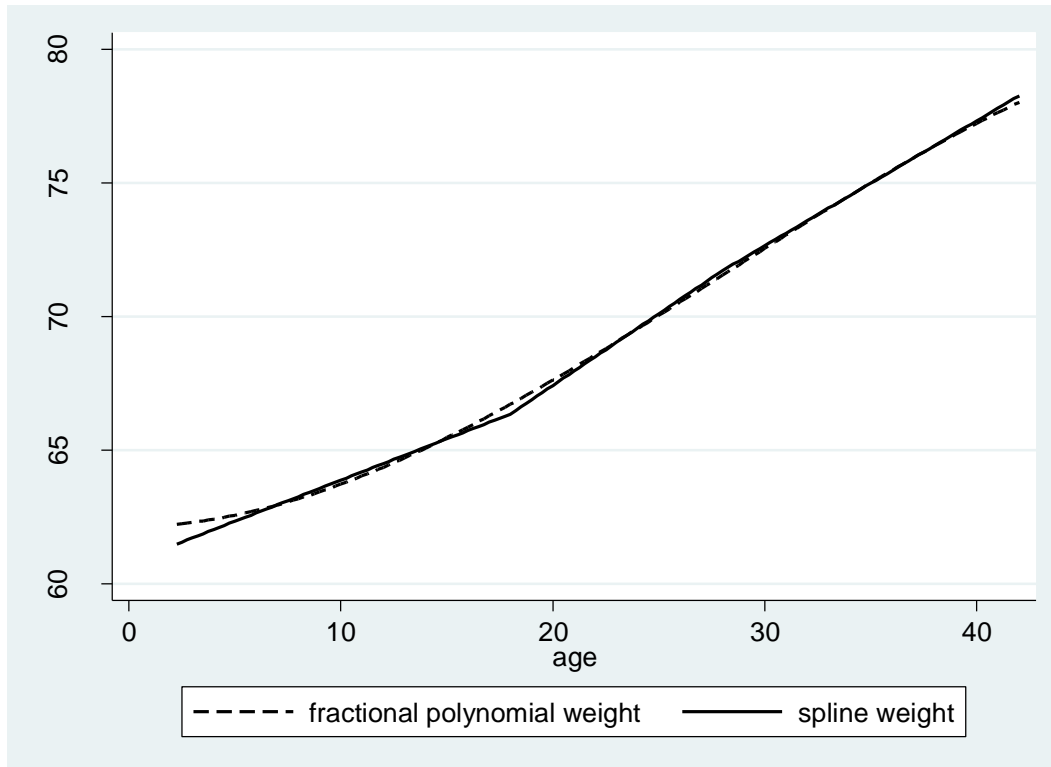
Statistical methods

1. Categorise women according to IOM categories; using pre-pregnancy weight and highest gestational weight
2. Use all of the available repeat ANC weight measurements
 - Median (IQR): 10 (8, 11)
 - MLwiN - linear spline random effects model with two knots (fractional polynomials to identify position of knots)



	IOM recommendations		ALSPAC	
Pre-pregnancy BMI	Absolute weight gain in kg	Mean rate of weight gain in 2nd and 3rd trimesters in kg/week	Mean (range) absolute weight gain in kg*	Mean rate (SD) of weight gain in 2nd and 3rd trimesters in kg/week
Underweight (<18.5kg/m ²)	12.5-18	0.51	12.9 (-2.0, 30.5)	0.54 (0.14)
Normal weight (18.5-24.9kg/m ²)	11.5-16	0.42	12.8 (-2.2, 37.8)	0.53 (0.14)
Overweight (25-29.9kg/m ²)	7-11.5	0.28	11.9 (-3.0, 33.5)	0.49 (0.17)
Obese (>=30kg/m ²)	5-9	0.22	9.5 (-6.9, 30.9)	0.41 (0.20)

🌿 Results: Descriptive



IOM categories

Less than recommended: 35%
Recommended: 38%
More than recommended: 27%

--- 18 weeks

--- 28 weeks

Association of GWG with offspring CVD risk factors

- Offspring of women with higher than IOM recommended GWG were more adipose and had more adverse CVD risk factor levels; those with lower than IOM recommended GWG were less adipose but had similar CVD risk factor levels to those with recommended IOM GWG.
- Offspring of women with greater GWG up to 28 weeks were more adipose and had more adverse CVD risk factor levels
- The associations of greater GWG with more adverse offspring CVD risk factor levels were largely mediate by associations with offspring adiposity



Mean difference in BMI at age 18 years by maternal pregnancy exposures: Swedish sibs

	Within brothers	Between unrelated men	P-value for difference
Maternal diabetes in pregnancy (yes versus no)	0.94 (0.35, 1.52)	0.87 (0.68, 1.07)	0.87
Maternal pre-pregnancy BMI (per 1kg)	-0.04 (-0.07, -0.01)	0.32 (0.31, 0.32)	< 0.001
Weight retention (per 1kg) in normal weight mums	0.00 (-0.02, 0.02)	0.07 (0.06, 0.07)	< 0.001
Weight retention (per 1kg) in overweight /obese mums	0.06 (0.01, 0.12)	0.02 (0.01, 0.03)	0.13

Lawlor DA, Lichtenstein P, Långström N. *Circulation* 2011 & *AJCN* 2011



Developmental overnutrition and inequalities

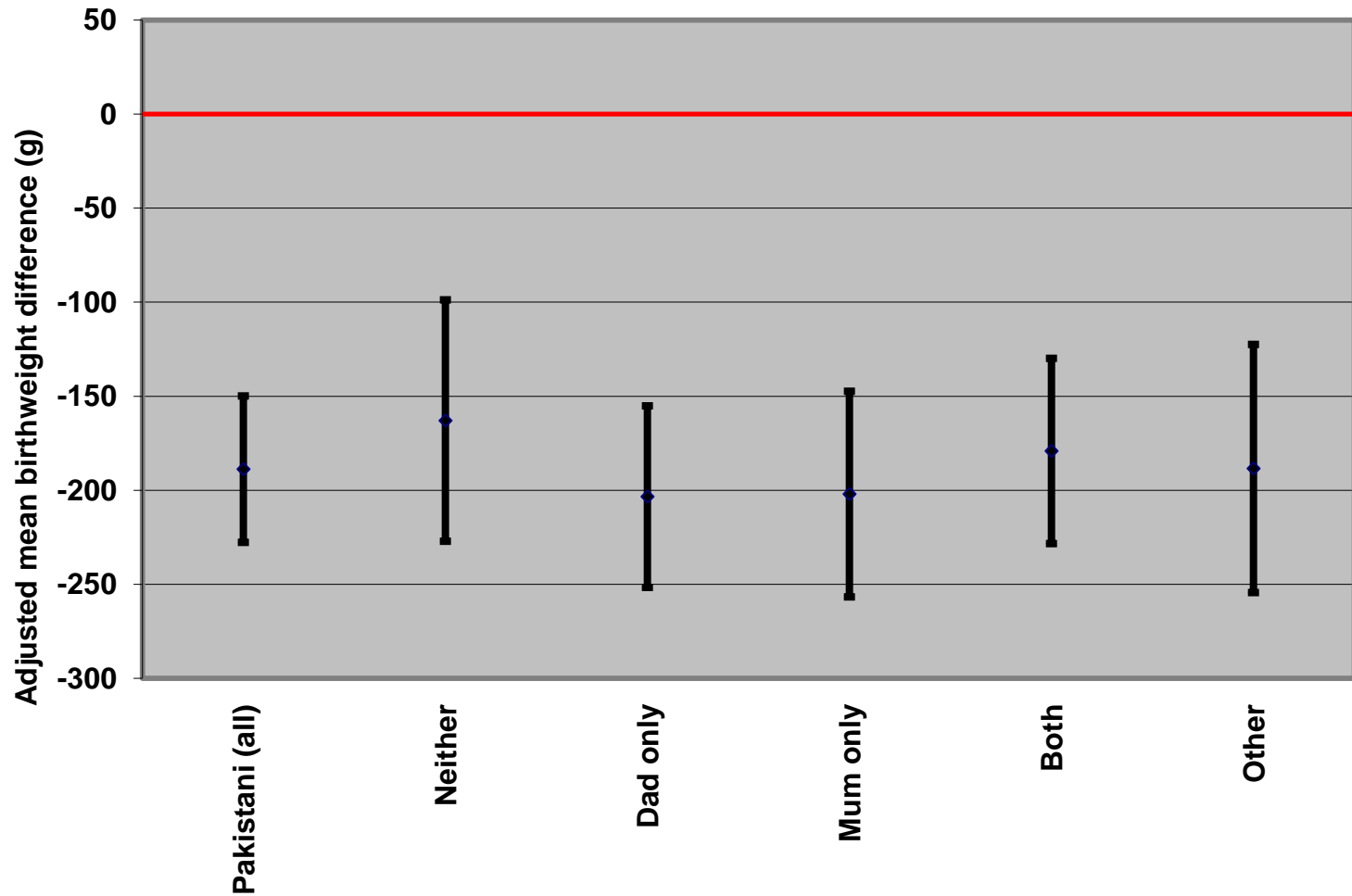
- Greater adiposity and associated diabetes more common:
 - More deprived individuals in Western populations
 - South Asian individuals



🌟 The Born in Bradford cohort



Adjusted mean birthweight difference (95% CI) by ethnic & generation group relative to White British infants



Jane West, PhD 2011

Mean z-score difference

	Birthweight	Subscapular skinfold thickness	Triceps skinfold thickness
Pakistani NO birthweight adjustment	-0.44 (0-.51, -0.37)	-0.21 (-0.30, -0.12)	-0.20 (-0.29, -0.11)
With birthweight adjustment	-	0.02 (0.06, 0.10)	0.04 (-0.04, 0.12)

Jane West, PhD 2011

✦ Ratio of geometric means of cord leptin comparing to Pakistani to White British

	Number	Unadjusted ratio of geometric means (95% CI)	Adjusted ratio of geometric means** (95% CI)
Pakistani (All)	1388 - 613 White British; 775 Pakistani	1.09 (0.99, 1.19)	1.35 (1.23, 1.49)

Jane West, PhD 2011

Summary

- **OLD HYPOTHESIS:** Good evidence that maternal glycaemia in pregnancy linearly (across whole distribution) associated with greater fetal/infant adiposity & insulin secretion
- **NEW RELEVANCE:** At extremes of maternal adiposity/diabetes phenotype (extreme obesity or existence of diabetes in pregnancy) there is evidence of an intrauterine effect on future offspring greater BMI/adiposity
- Across the whole distribution of maternal BMI little evidence that this is related to offspring greater BMI/adiposity through intrauterine mechanisms & intergenerational cycling of adiposity via intrauterine programming unlikely to have driven obesity epidemic to date
- BUT if epidemic continues and more women go into pregnancy with more extreme obesity and diabetes could become a major public health driver of further epidemic
- AND likely to increase ethnic and socioeconomic inequalities



Possible ways forward

- Better assessment of maternal (and paternal) exposures – balance of study size vs detailed measurements ('2012'; BiB; HAPO)
- Mendelian randomization & family based studies in large sample sizes – large record linkage studies, collaboration
- Long-term follow-up of currently on-going trials (e.g. LIMIT)



 **THANK YOU**

