



Does the South Asian 'thin-fat' phenotype develop in utero?



Background

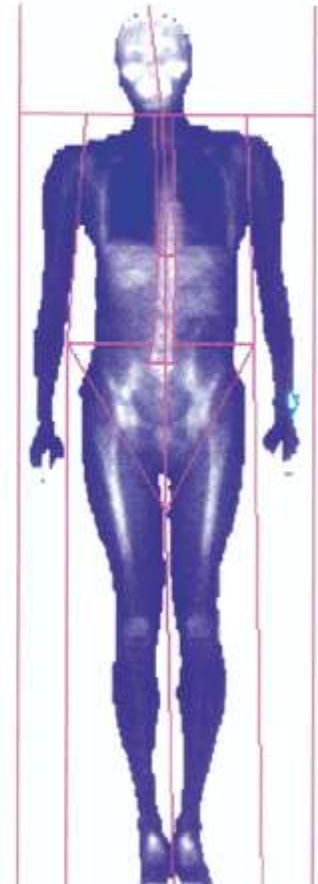
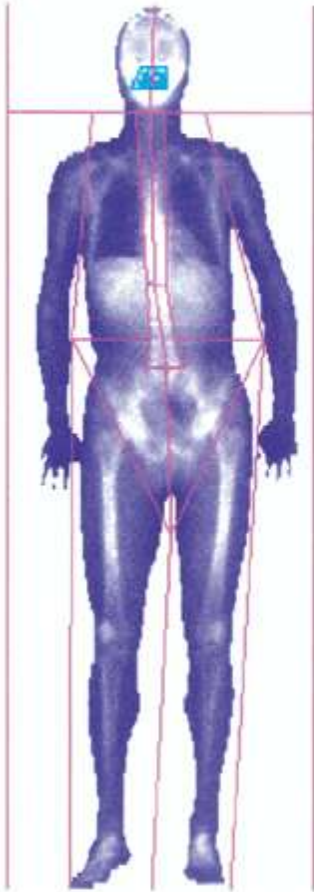
- South Asian adults:
 - Increased risk of insulin resistance, type 2 diabetes, CHD
 - For a given BMI are more adipose
 - ‘thin-fat (insulin resistant) phenotype’
- Might exist in childhood and even at birth
 - Suggesting developmental origin



BMI

22.3

22.3



Body fat

9.1%

21.2%



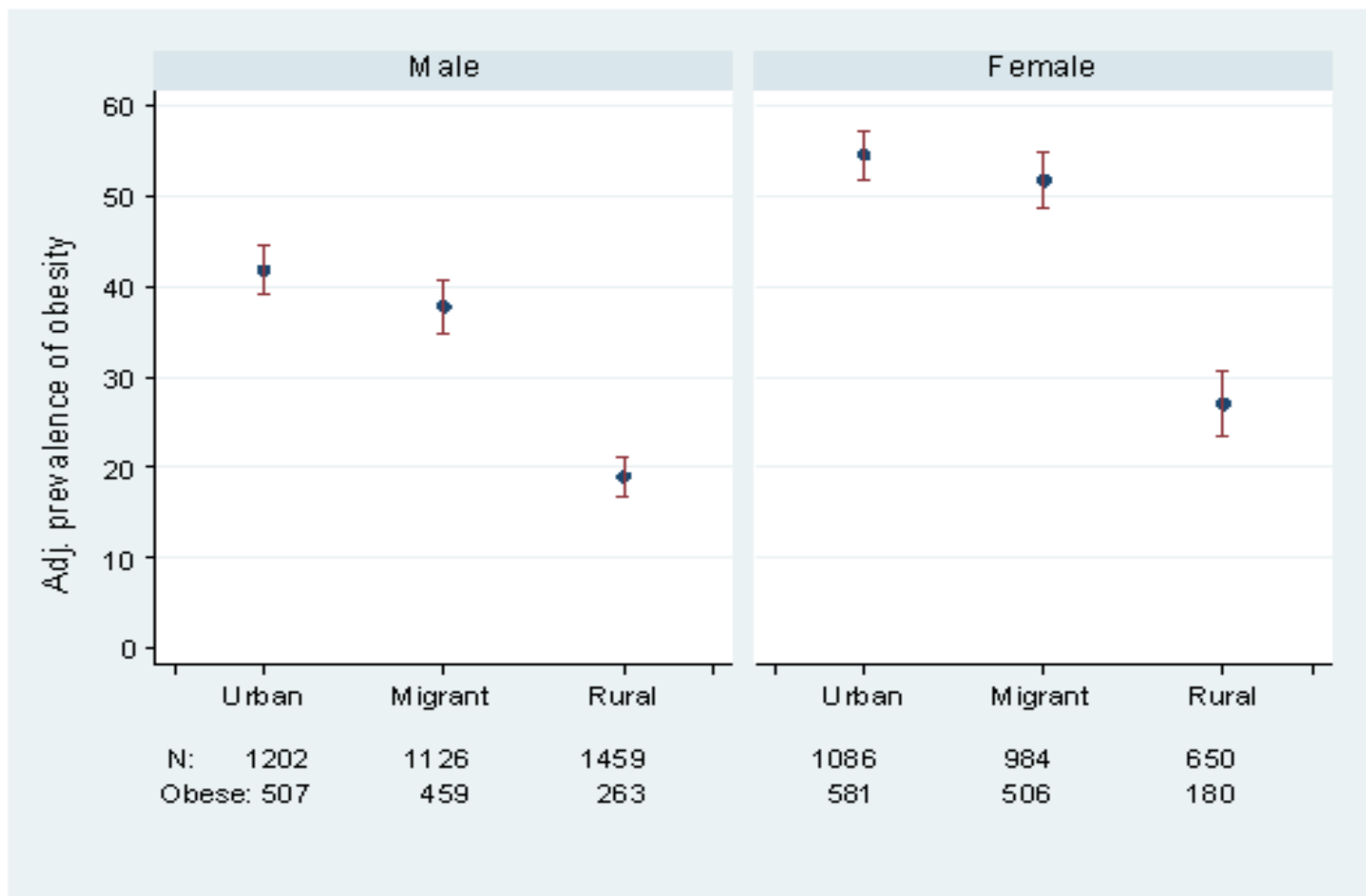
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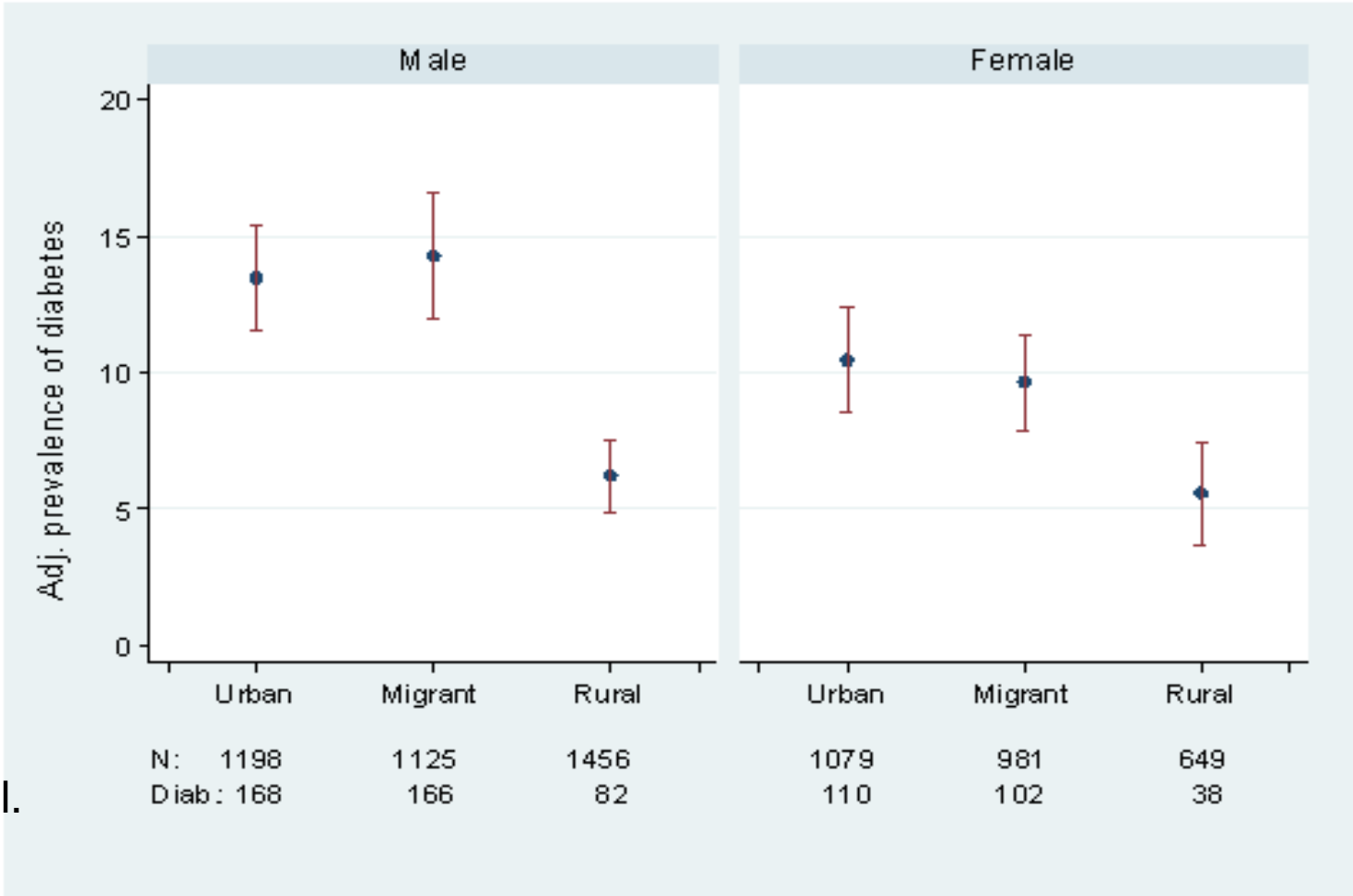
🔥 Indian Migration Study prevalence of obesity



Kinra et al.
BMJ



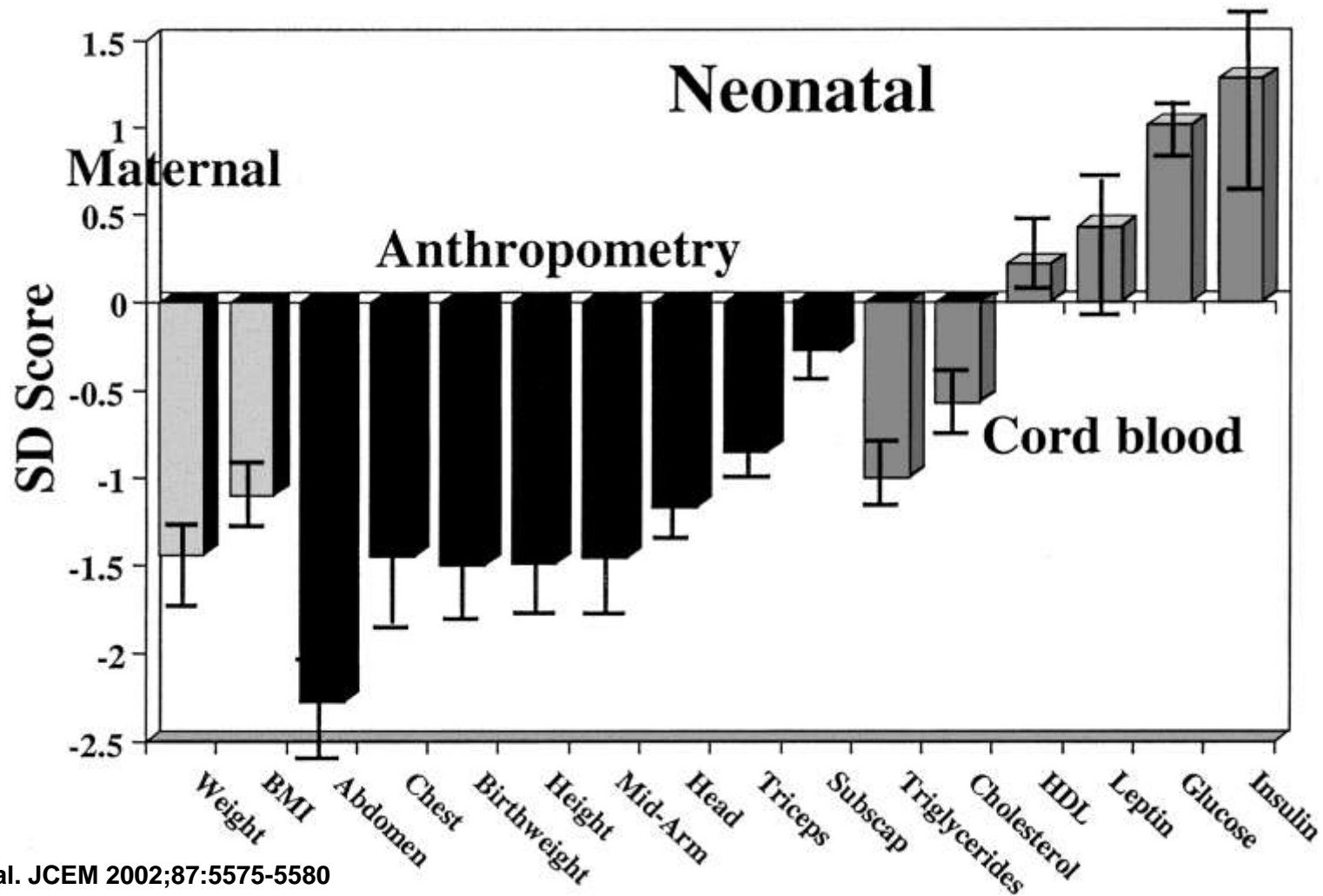
Indian Migration Study: prevalence of diabetes



Kinra et al.
BMJ



sd scores for Indian mothers and babies in Pune compared with white Caucasian mothers and babies in London. sd score Indian = individual value – UK mean/UK sd.



Yajnik C S et al. JCEM 2002;87:5575-5580

🌟 The Born in Bradford Study



Bradford



- Population ~ 500,000
- “**Capital of the wool world**”
(population increase from 6,000 to 180,000 between 1800 and 1850)
- One of the most deprived cities in the UK
- 20% of the population South Asian
 - 90% from Pakistan
 - Mostly from Mirpur
 - Now a 3 generation settled population
- > 50% of births to parents of Pakistani origin



Upwards and Onwards

photographs by Ian Beckett

words by Ian McMillan

Foreword by David Clarke and the Mayor

commissioned for Bristol's World City 2015 initiative
by Bristol's Learning Partnership & the Foundation Trust



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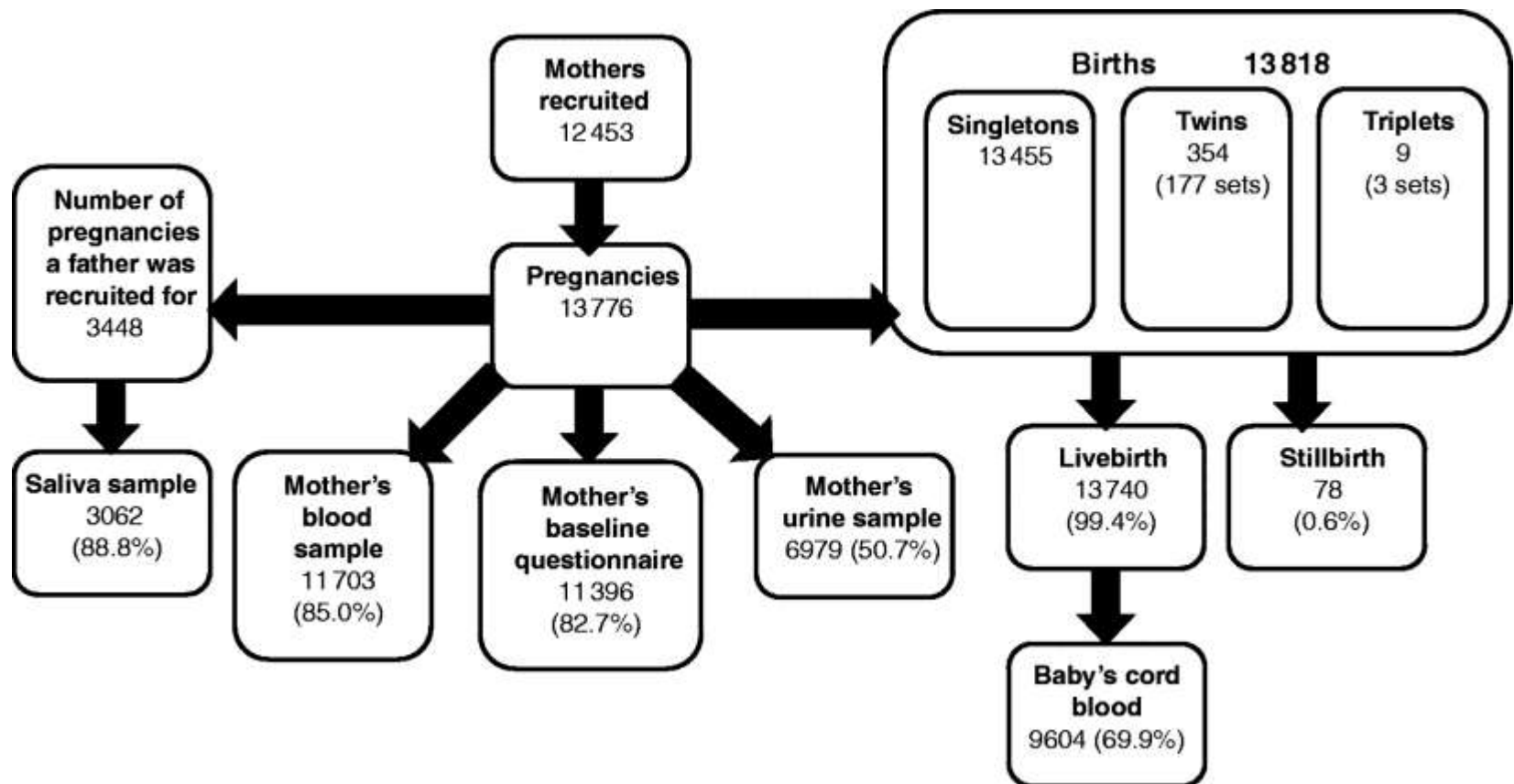




FA CUP WINNERS



The Born in Bradford Study

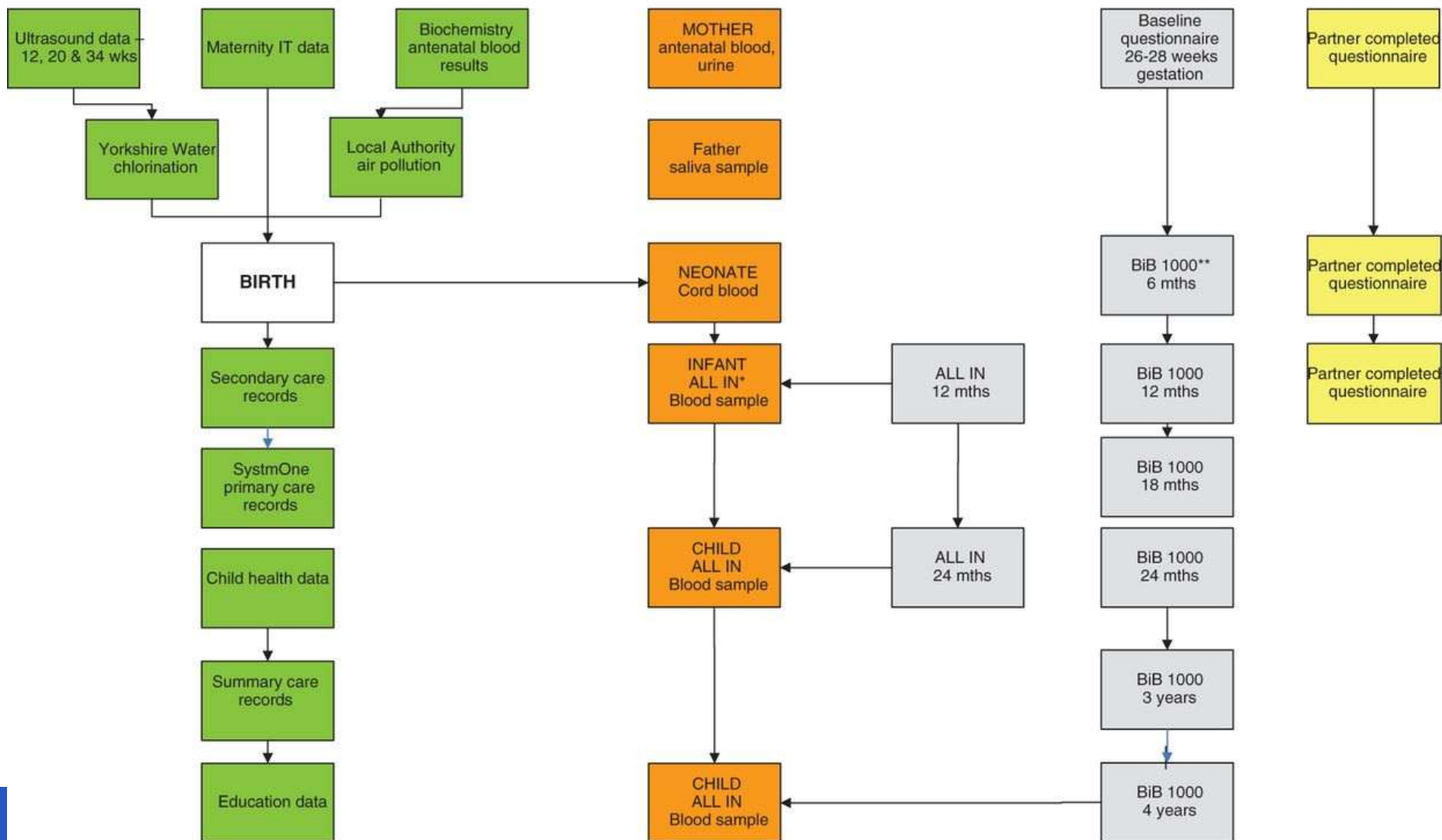


BiB – Data

ROUTINE DATA

BIOBANK

RESEARCH – EXAMINATION & QUESTIONNAIRE DATA



*ALL IN = Allergy and Infection sub cohort

** BiB 1000 = Obesity sub cohort

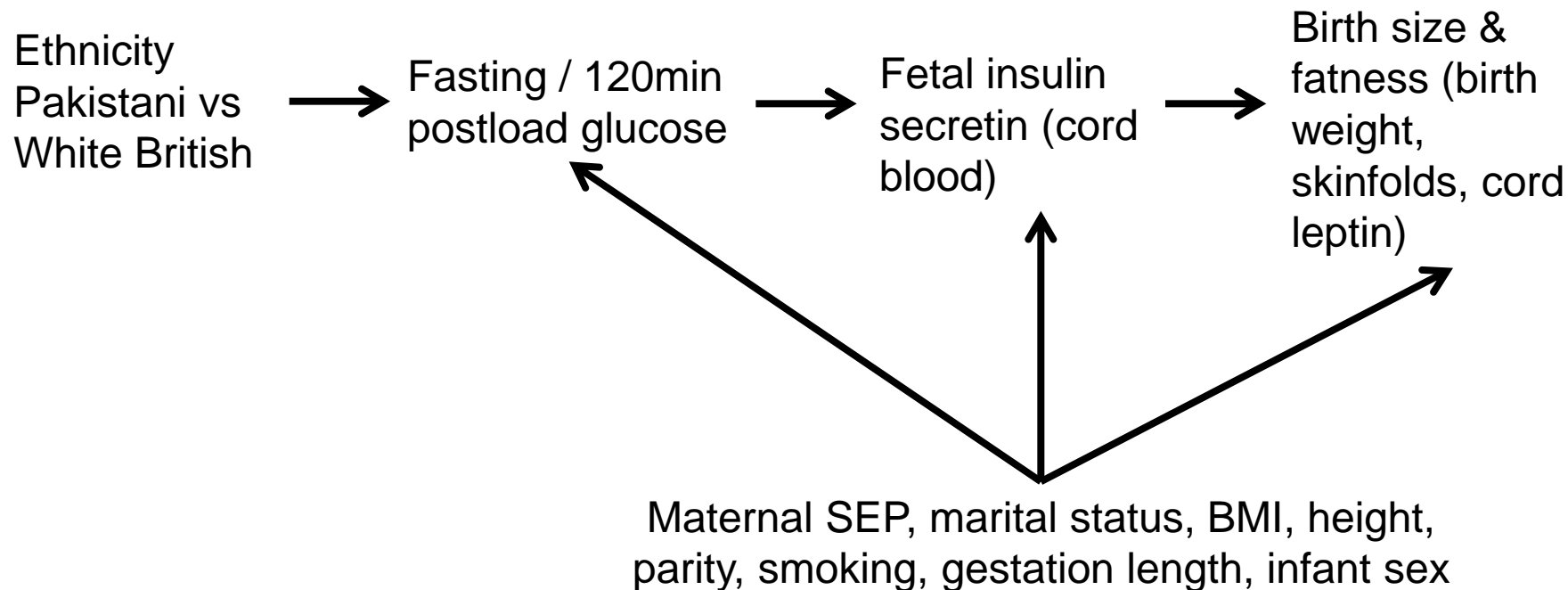
BiB unique features

- Biethnic population
- At risk population
- Pregnancy OGTT (26-28 weeks)
- Repeat in utero USS assessment
- Substantial biobank
 - Maternal pregnancy fasting blood
 - Maternal pregnancy urine
 - Cord blood
 - Infant blood 12 & 24 months (subgroup 1000)
 - Extracted DNA & funds for GWAS and DNA methylation
- Birth & follow-up anthropometry to age 5



Research questions

1. Are Pakistani infants fatter at birth than White British?
 - i. Do any Pakistani versus White British differences vary by generation of the Pakistani infants?
2. Does maternal pregnancy fasting/postload glucose mediate the association of ethnicity with birth fatness?



Determining generation

- Details of the baby's parents' and grandparents' place of birth were obtained from the maternal questionnaire for all Pakistani origin infants
- 66 potential categories
- Reviewed numbers and mean birthweight in each group

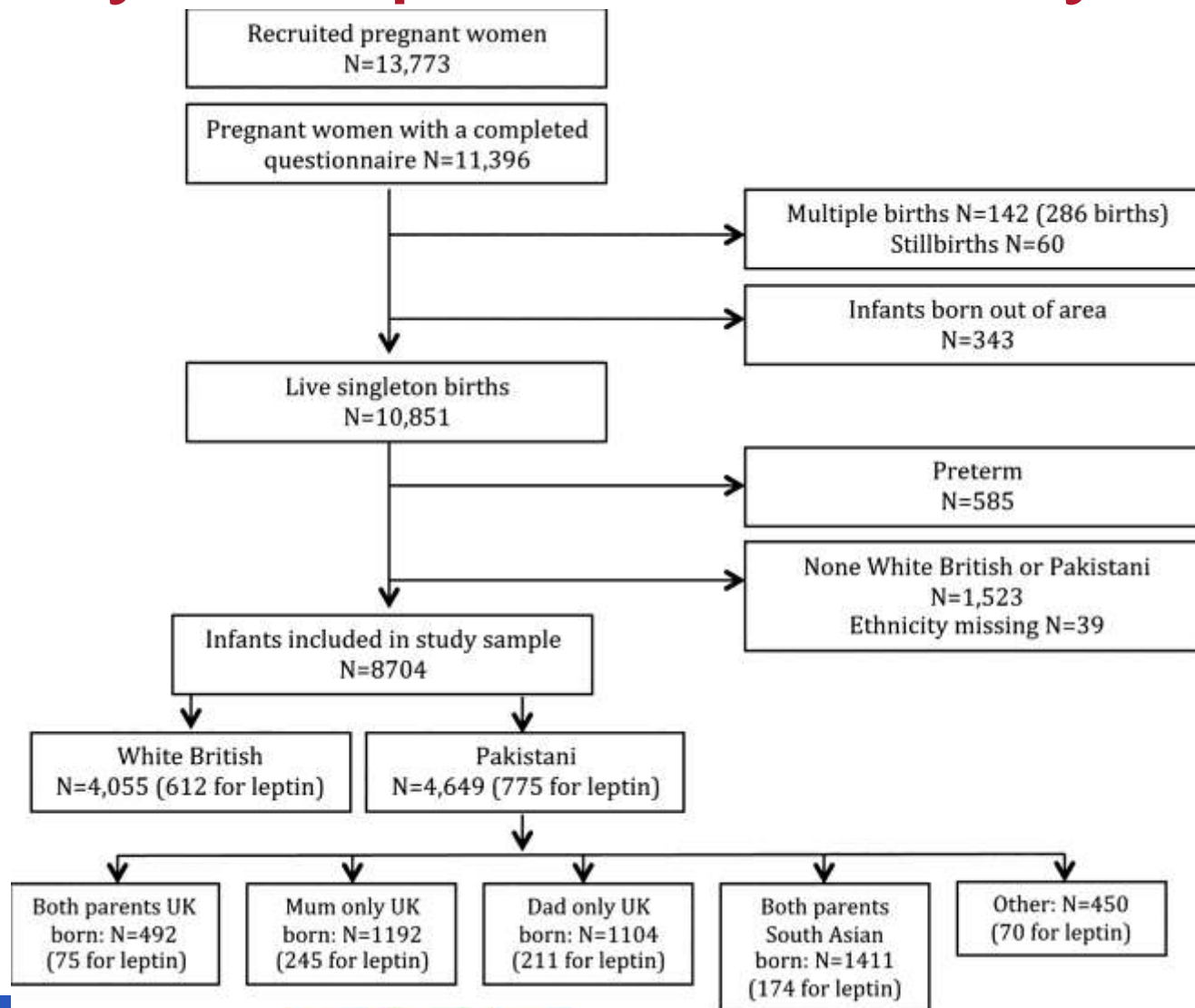


- Number of groups reduced to 17
- Within the 17 groups, **90%** fell into one of four main categories:
 1. ***Both parents UK born & all 4 grandparents SA born***
 2. ***Mum UK born, dad and all 4 grandparents SA born***
 3. ***Dad UK born, mum & all 4 grandparents SA born***
 4. ***Both parents SA born & all 4 grandparents SA born***

Jane West et al. *JECH* 2013;67:544-551

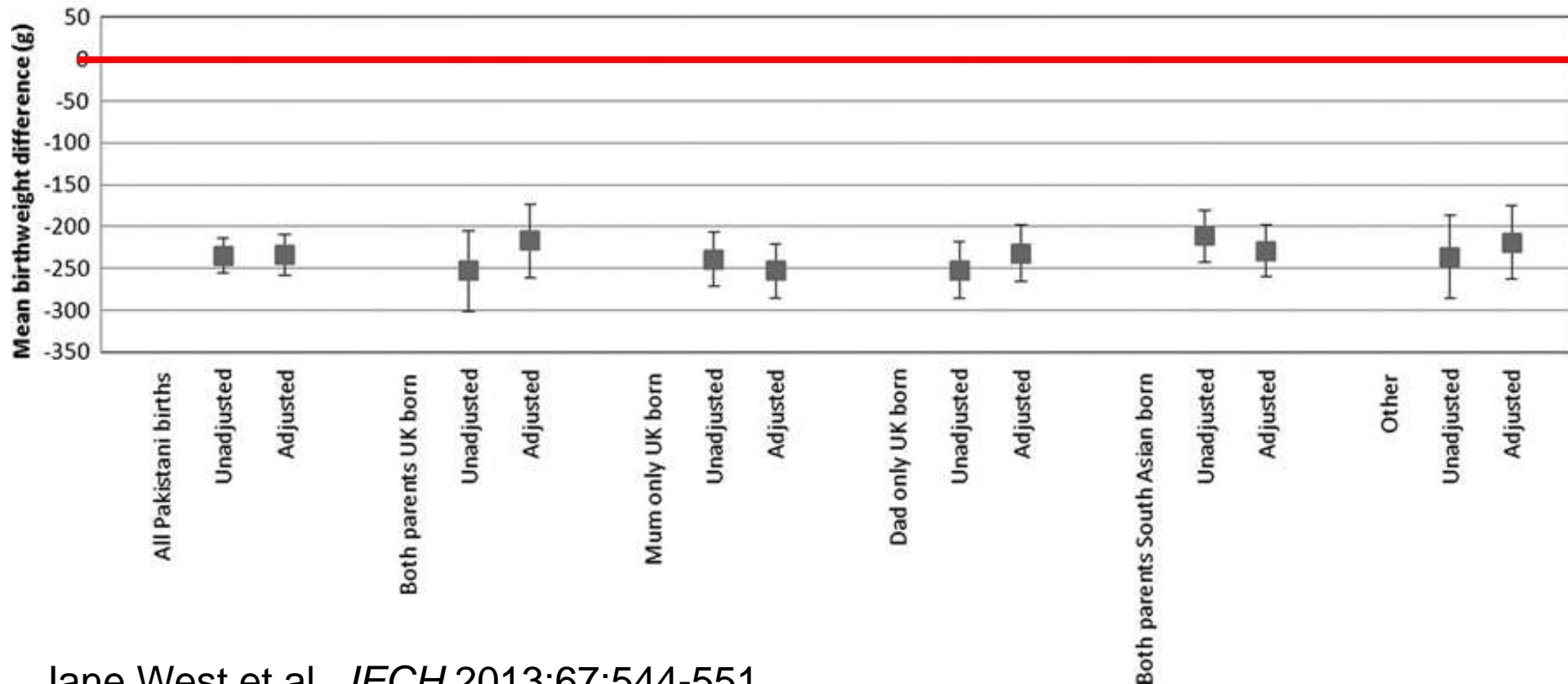


Study sample for 1st study



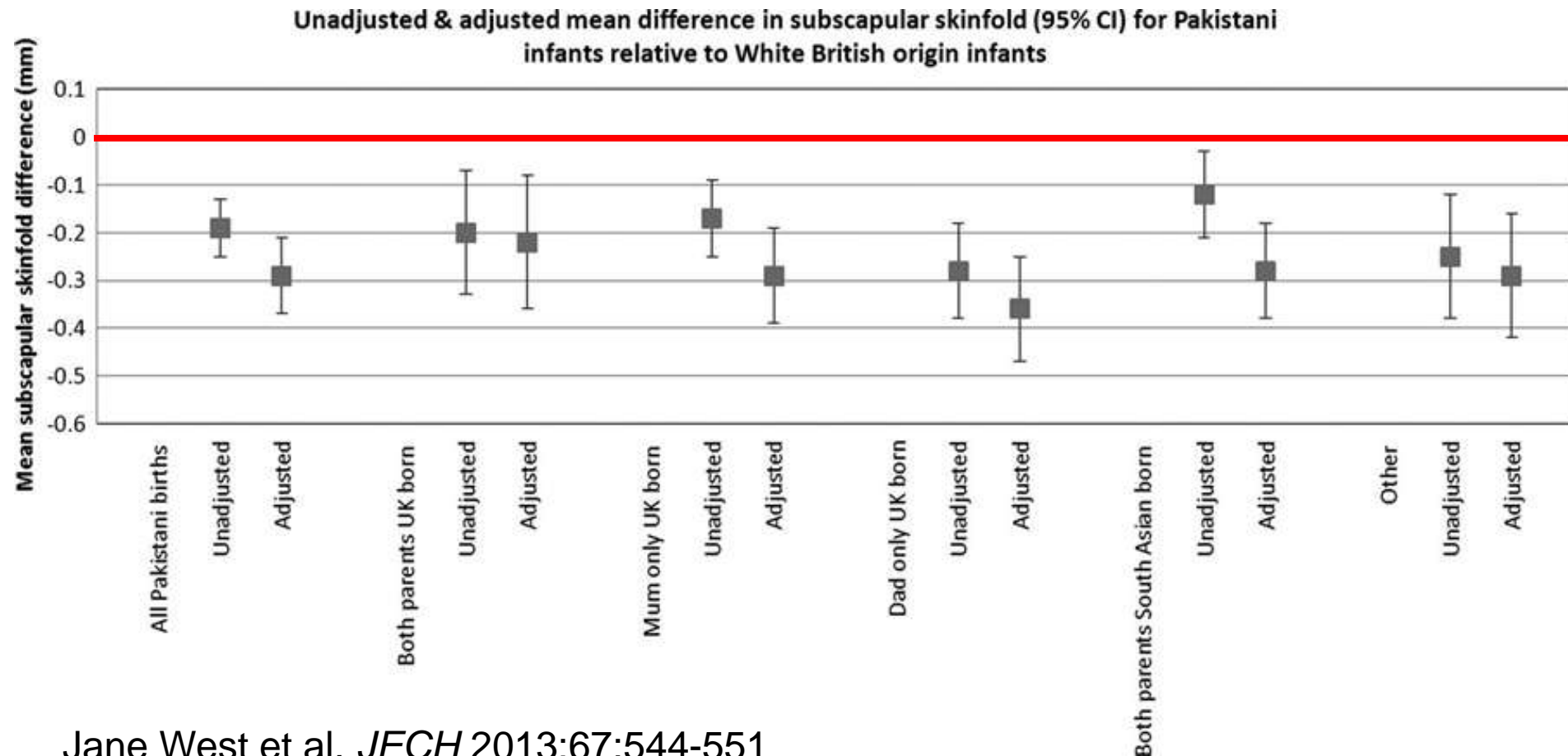
Mean difference in birthweight

Unadjusted & adjusted mean difference in birthweight (95% CI) for Pakistani infants relative to White British origin infants



Jane West et al. *JECH* 2013;67:544-551

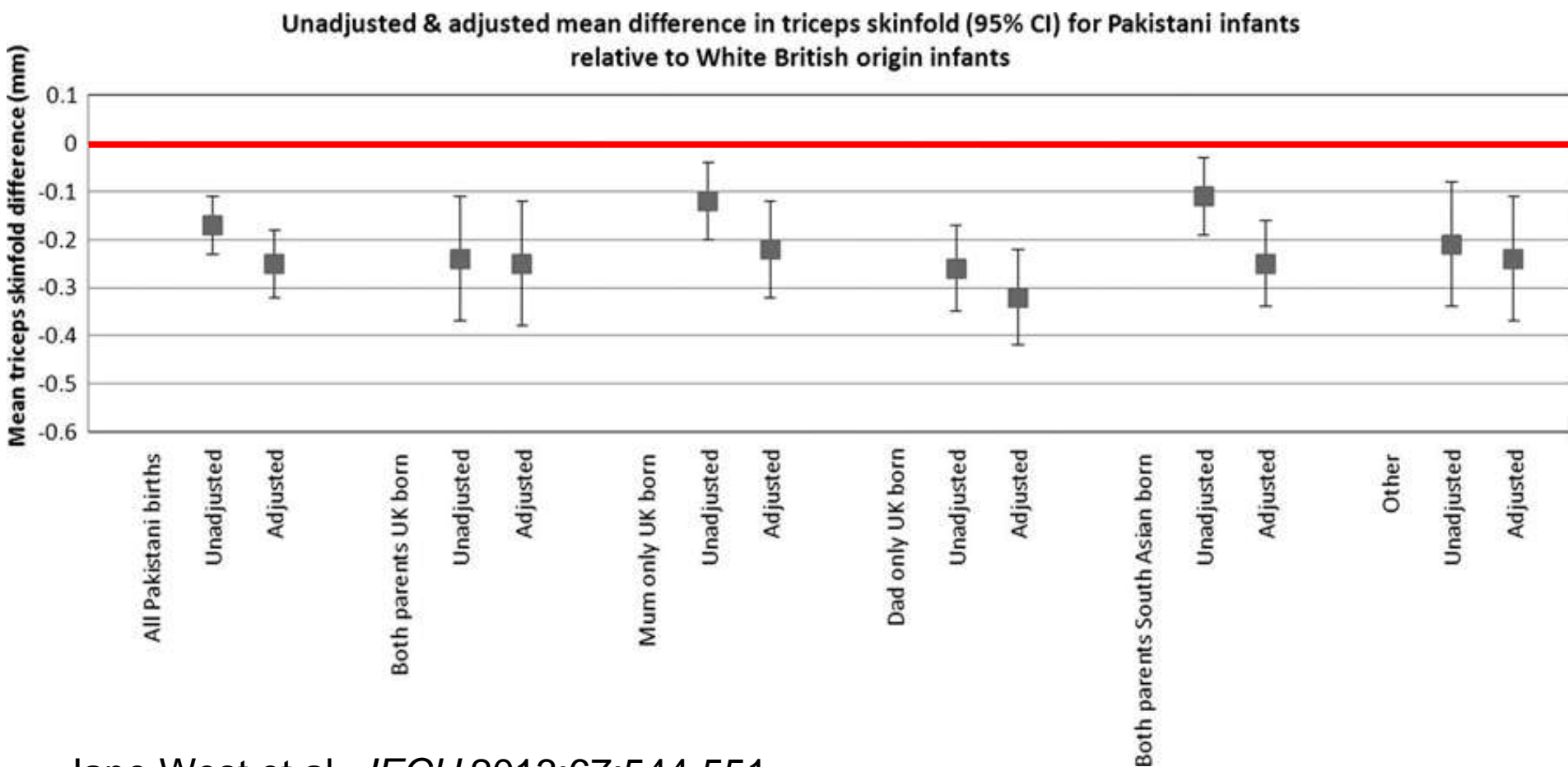
🔥 Mean difference in subscapular skinfolds



Jane West et al. *JECH* 2013;67:544-551

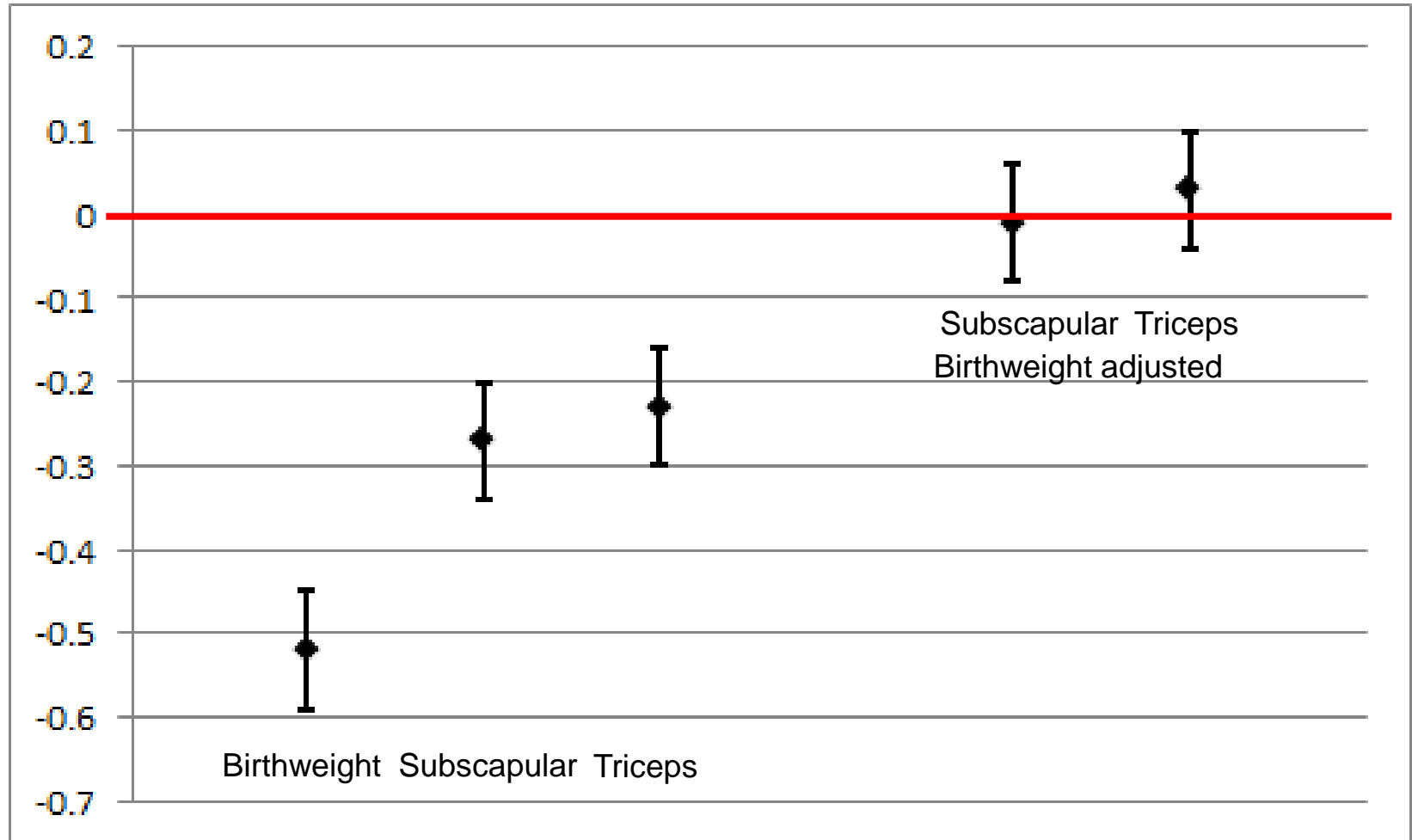


🔥 Mean difference in triceps skinfolds



Jane West et al. *JECH* 2013;67:544-551

🔥 Differences in size by SD; all participants



Ethnic differences in cord-blood leptin levels

	Ratio of geometric mean (RGM) in cord-blood leptin compared to white British (N= 612 for all)				
	All Pakistani N = 775	Both parents UK born N = 75	Mum only UK born N = 245	Dad only UK born N = 211	Both South Asian born N = 174
No adjustment	1.11 (1.01, 1.21)	1.10 (0.89, 1.33)	1.20 (1.06, 1.36)	1.07 (0.94, 1.22)	1.07 (0.93, 1.23)
Adjusted for birthweight	1.30 (1.17, 1.44)	1.43 (1.17, 1.76)	1.33 (1.16, 1.52)	1.30 (1.14, 1.49)	1.27 (1.08, 1.46)

Jane West et al. *JECH* 2013;67:544-551



Do ethnic differences in cord blood leptin levels differ by birthweight?

- Greater relative fatness at birth raises the possibility that efforts to increase birthweight could have adverse effects because of increases in fatness
- Muthaya et al. *Public Health Nutrition* 2006:
 - Greater relative adiposity (arm fat index) comparing Indian infants (born in India) to White US infants was more marked amongst those LGA than NGA
 - But, small study with just 16 (10 White US, 6 Indian) infants in LGA group



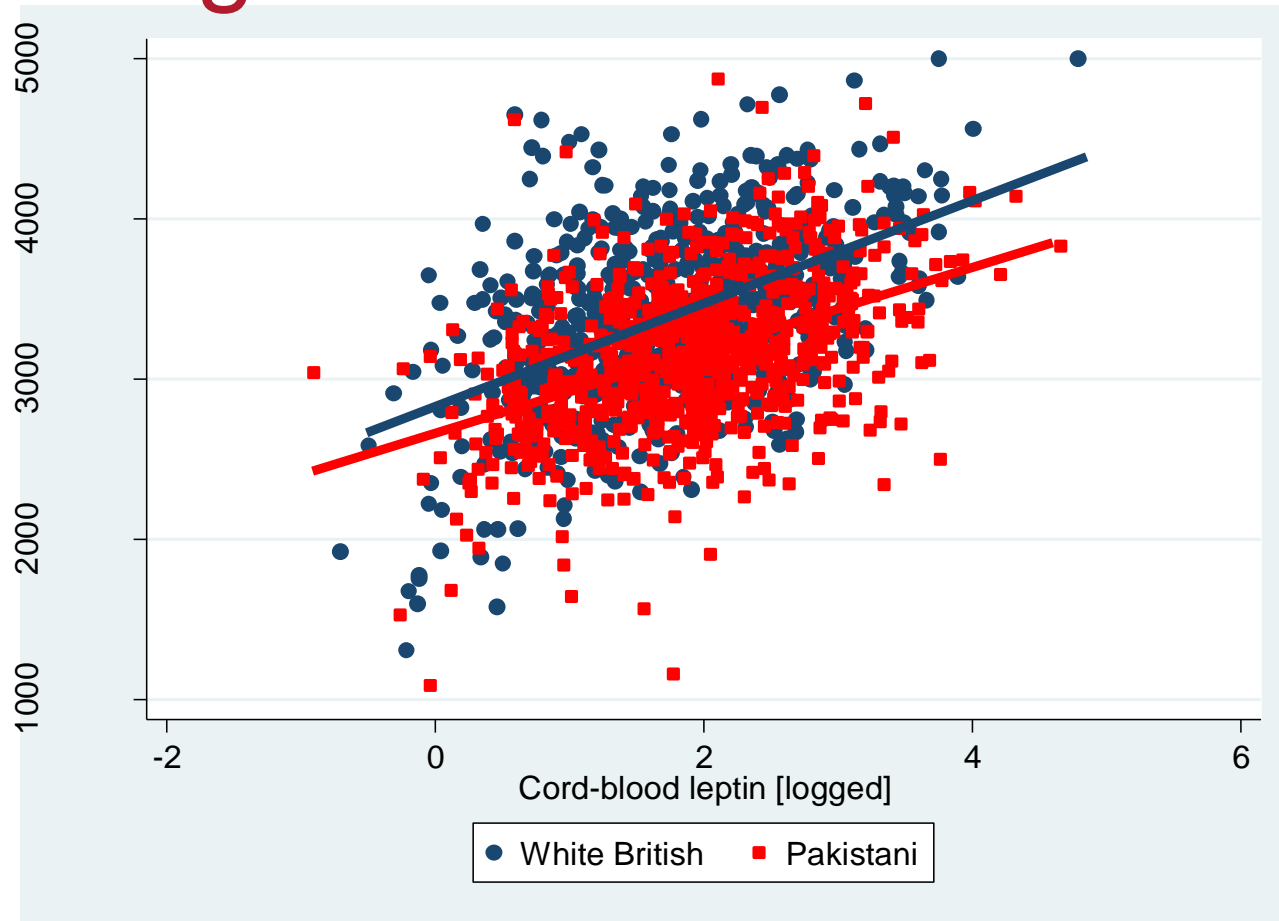
RGM cord leptin Pakistani vs White British infants by thirds of birthweight

	Unadjusted	Sex adjusted	Sex & birthweight adjusted
Lowest 1/3 rd N = 509	1.29 (1.12, 1.49)	1.31 (1.15, 1.51)	1.37 (1.20, 1.57)
Middle 1/3 rd N = 497	1.30 (1.14, 1.48)	1.34 (1.18, 1.52)	1.36 (1.20, 1.54)
Highest 1/3 rd N = 476	1.31 (1.13, 1.51)	1.26 (1.10, 1.44)	1.31 (1.16, 1.52)

All $p_{\text{interaction}} > 0.5$

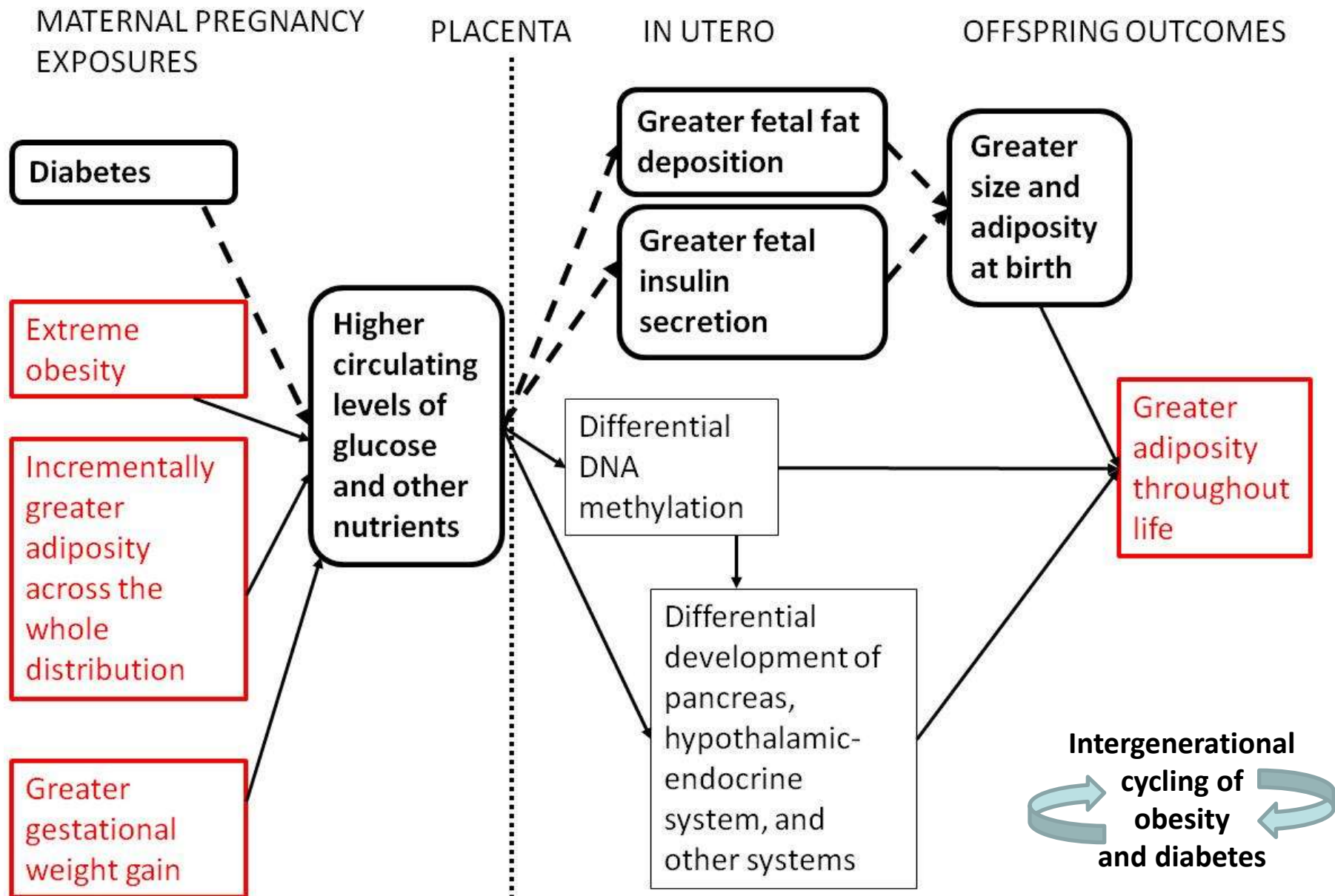
Jane West et al. *IJE* 2013 in press

🌿 Association of cord-blood leptin with birthweight

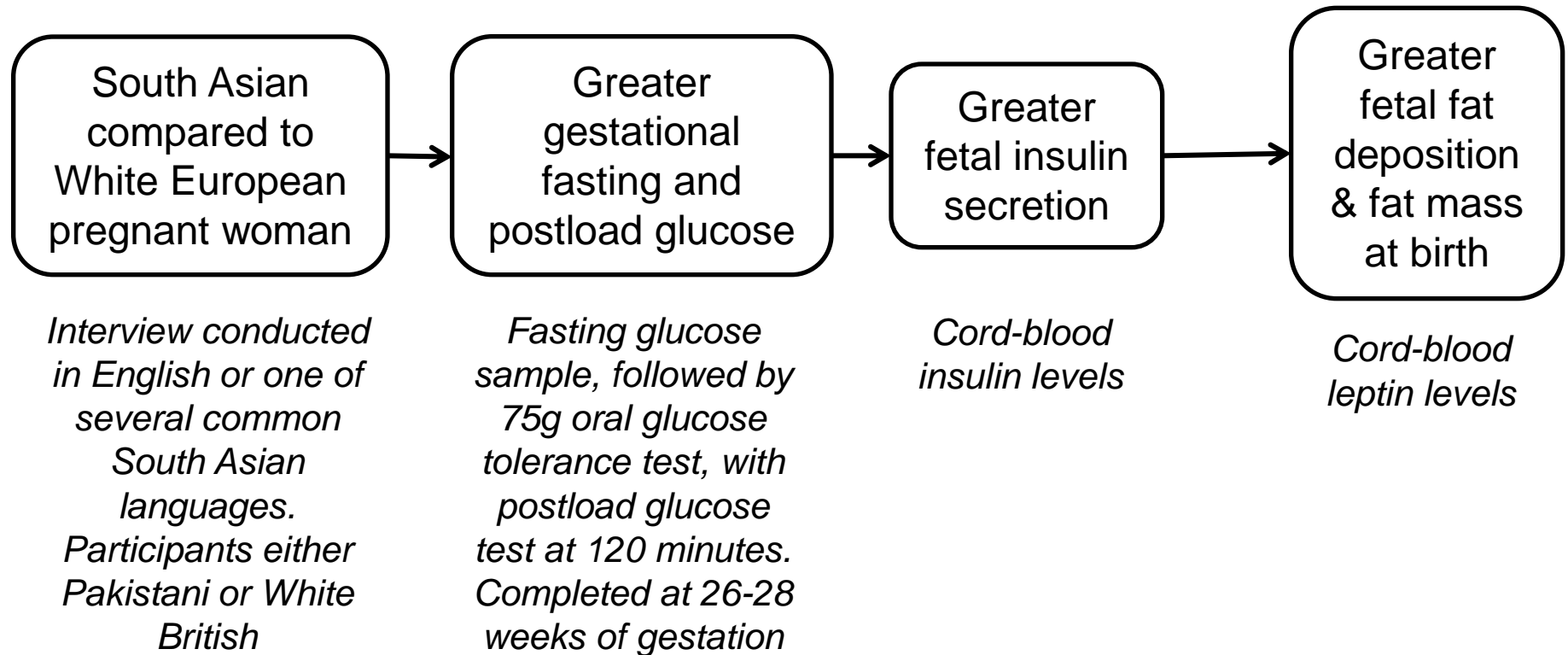


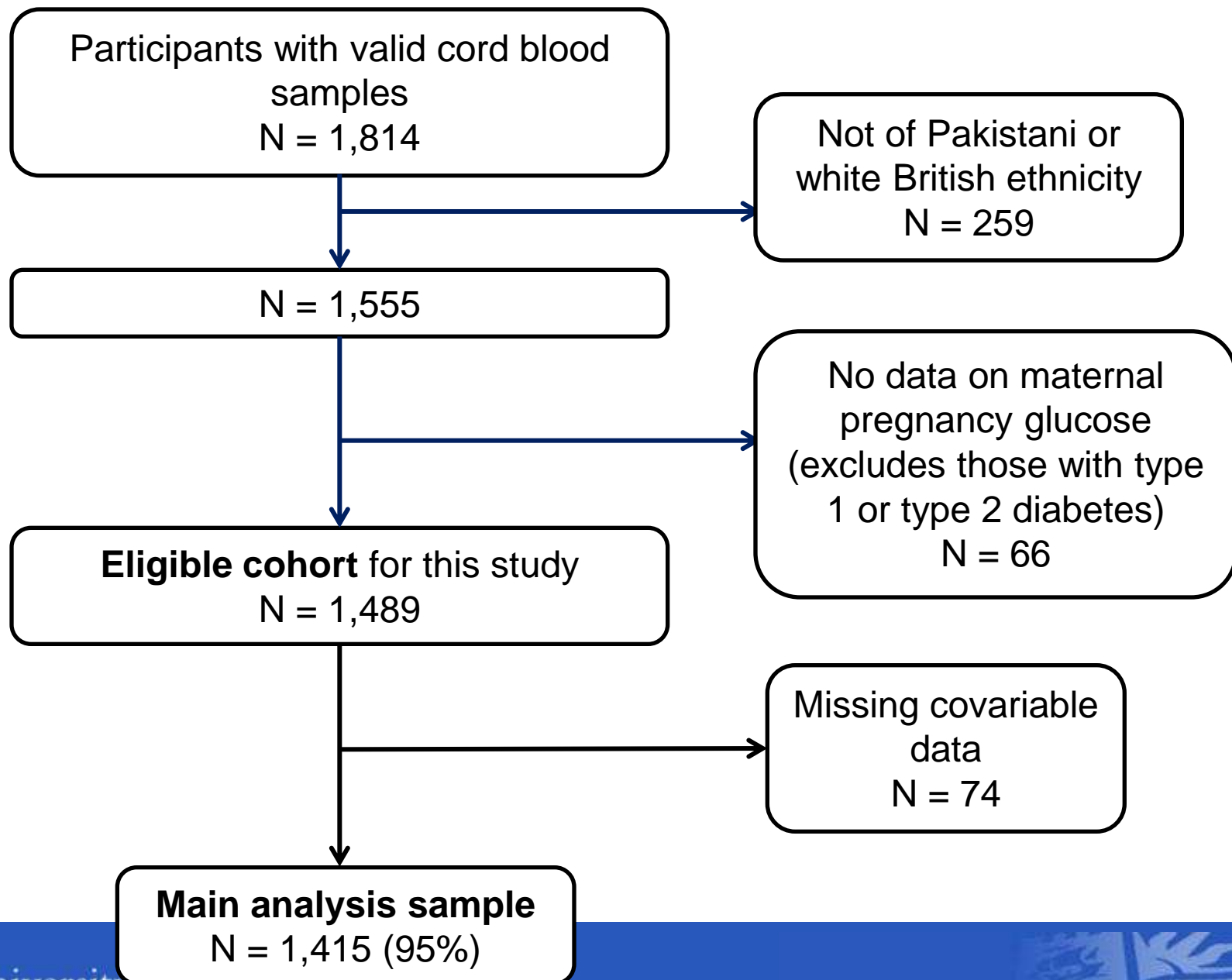
🌟 To what extent does greater gestational glucose 'cause' greater fatness at birth in South Asian infants?





Cord leptin and mediation



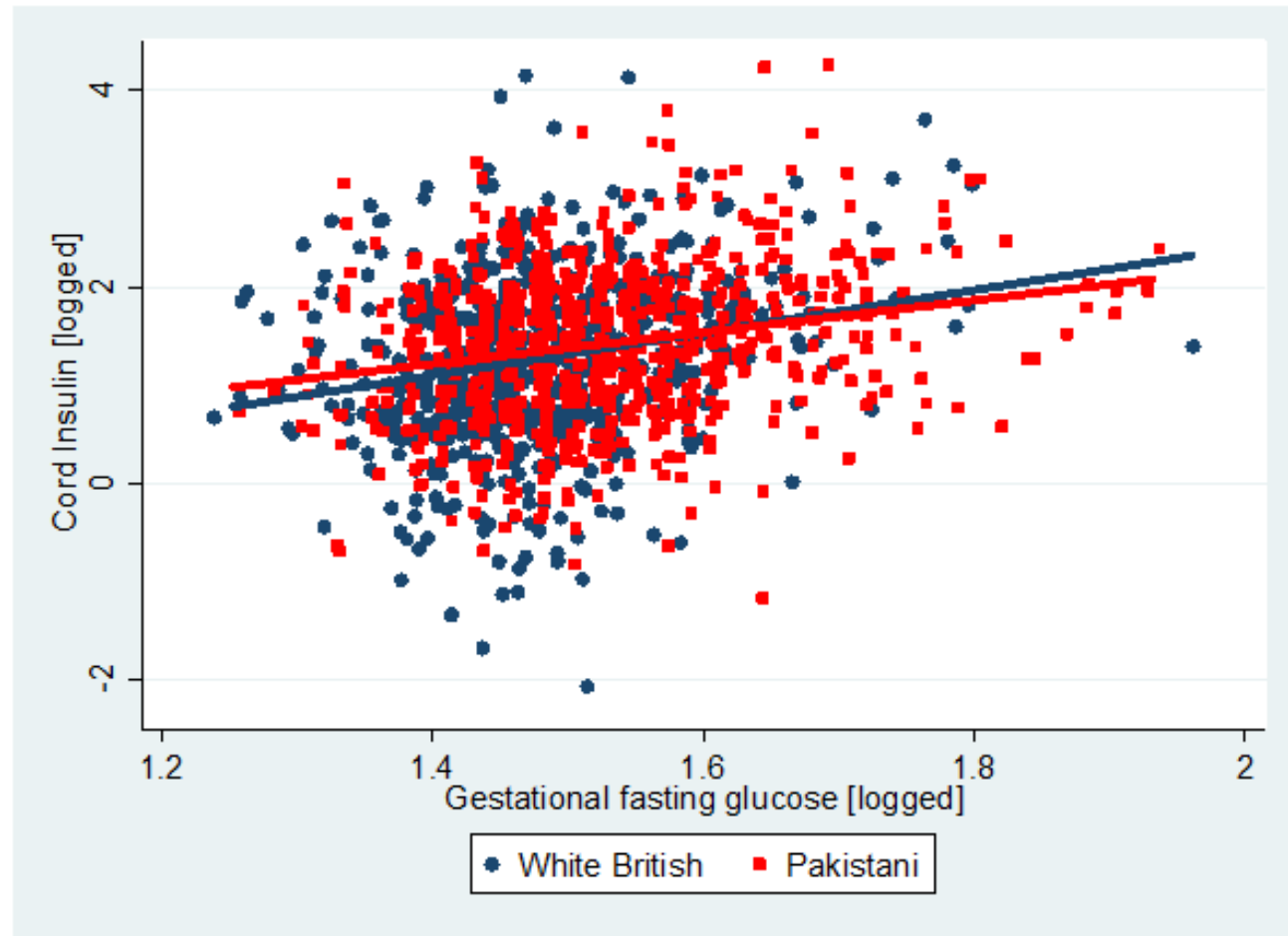


Associations of fasting glucose with infant outcomes

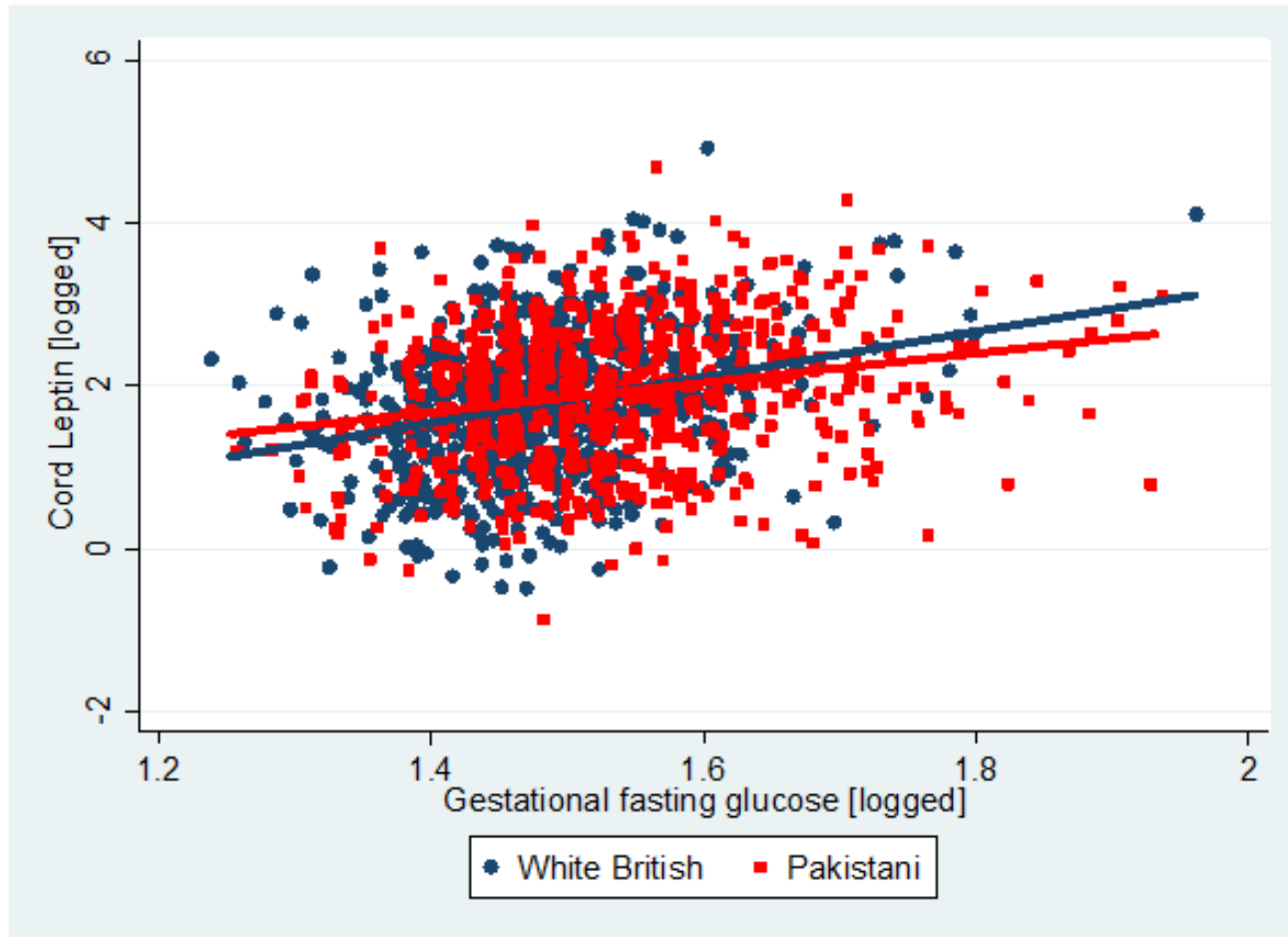
Outcome		Mean difference per doubling fasting glucose (95% CI)		P ethnic difference
		White British N = 629	Pakistani N = 786	
Cord insulin (%)	Unadjusted	132 (85, 179)	117 (87, 149)	0.60
	Adjusted	105 (55, 155)	91 (58, 123)	0.59
Cord leptin (%)	Unadjusted	174 (127, 220)	121 (88, 154)	0.07
	Adjusted	145 (100, 190)	116 (83, 149)	0.26



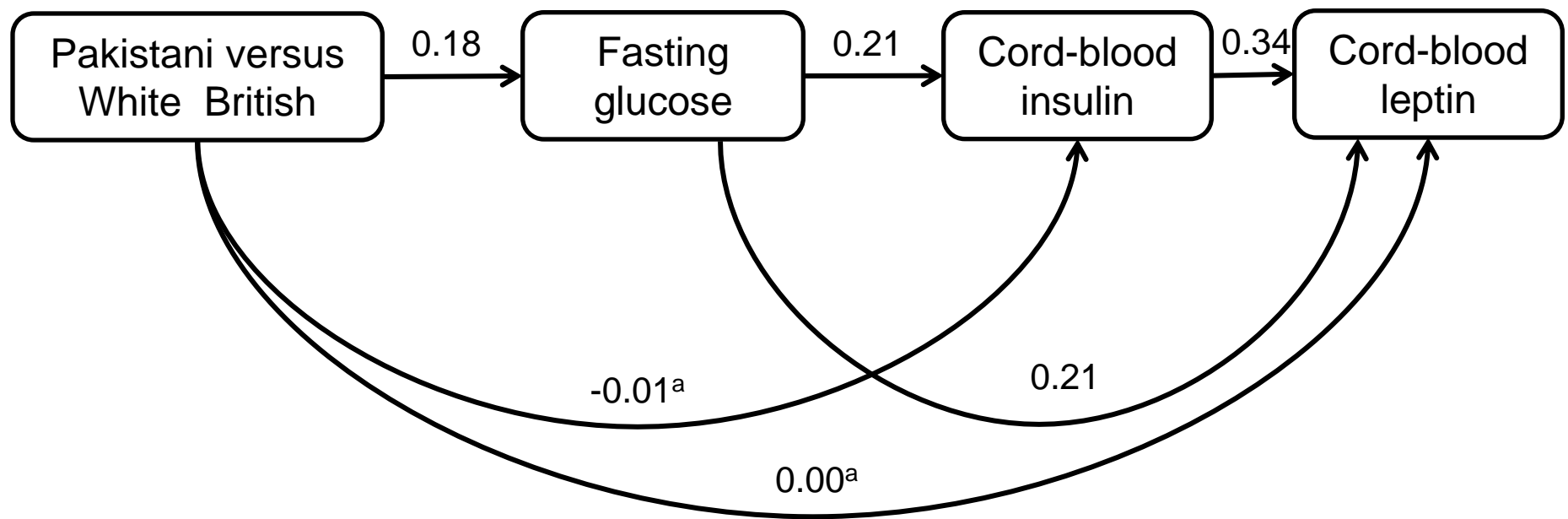
Association of fasting glucose with cord insulin



🔥 Association of fasting glucose with cord leptin



Path analysis



The numbers are all standardised regression coefficients and are adjusted for maternal age, parity, smoking and education and infant sex and gestational age, in addition to other variables shown in the path analyses.

They are correctly interpreted as the adjusted change in outcome (box at the end of the arrow head) in standard deviation units per category (for ethnic group) or per standard deviation of the exposure (arrow start).

P-values are < 0.001 for all results except that indicated with ^a $p \geq 0.75$

Conclusions – birth size

- Marked differences in birth size between Pakistani & White British babies
 - Pakistani infants have lower birthweight and thinner skinfolds
 - Differences are much less for skinfolds compared with birthweight
 - Where two infants have the same birthweight (i.e. adjusting for birthweight) triceps and subscapular skinfolds are the same, suggesting that Pakistani compared with White British have greater fat mass and less lean mass
 - Differences similar whether parents SA or UK born



Conclusions – cord-blood leptin

- Cord-blood leptin concentrations (a valid measure of birth fat mass) are higher among Pakistani infants, even without birthweight adjustment.
- Higher cord-blood leptin in Pakistani vs White British is consistent across the birthweight distribution
- Higher cord-blood leptin concentrations in Pakistani infants are mediated by higher maternal fasting glucose - directly and via a pathway involving fetal insulin secretion



Further research

- *BiB specific*
 - Metabolomics
 - Epigenomics
 - Longer-term associations to adiposity (to age 6) and metabolomics (to age 2)
- *Broader developmental overnutrition area*
 - Effect of pregnancy lifestyle intervention in overweight/obese women (LIMIT & UPBEAT RCT)
 - Intergenerational associations (ALSPAC-G2)



Acknowledgements 1

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- Derek Tuffnell
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🌟 Acknowledgements 2

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 - Obstetricians
 - Paediatricians
 - Data managers
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- NHS
- LA, local business & charities
- NIHR, MRC, Wellcome Trust

Ian Beesley BiB photo gallery
<http://www.borninbradford.nhs.uk/gallery.htm>

