Electronic Supplementary Material

Low birthweight and risk of type 2 diabetes: a Mendelian randomisation study

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ESM Table 1 Association between the low-birthweight GRS and metabolic traits

Baseline variable	NHS		HPFS	
	β ± SE	*p*	β ± SE	*p*
BMI (kg/m^2)	0.004 ± 0.029	0.89	0.025 ± 0.027	0.36
Waist circumference (cm)	-0.264 ± 0.207	0.20	-0.222 ± 0.299	0.46
Hypercholesterolaemia	0.002 ± 0.002	0.37	-0.001 ± 0.003	0.71
Hypertension	0.001 ± 0.002	0.65	-0.005 ± 0.003	0.13

Data are β ± SE, adjusted for age and genotyping sources

ESM Table 2 Mendelian randomisation estimate of the relation between low birthweight and risk of type 2 diabetes using summary statistics

SNP	Effect allele /Other [a]	$\beta_1 \pm$ SE for birthweight [b]	OR (95% CI) for type 2 diabetes [c]	Mendelian randomisation analysis, $\beta_3 \pm$ SE [d]
rs900400	C/T	0.072 ± 0.006	1.02 (0.99-1.05)	0.28 ± 0.21
rs724577	C/A	0.042 ± 0.006	1.03 (1.00-1.06)	0.70 ± 0.35
rs4432842	C/T	0.034 ± 0.006	1.00 (0.97-1.02)	0.00 ± 0.37
rs1801253	G/C	0.041 ± 0.007	1.05 (1.02-1.09)	1.19 ± 0.41
rs1042725	T/C	0.047 ± 0.005	1.04 (1.01-1.06)	0.83 ± 0.26
Meta-analysis [e]	-	0.050 ± 0.003	1.03 (1.01-1.04)	0.53 ± 0.13

[a]Allele coding based on the forward strand. Effect allele is associated with low birthweight; and other allele is the reference allele

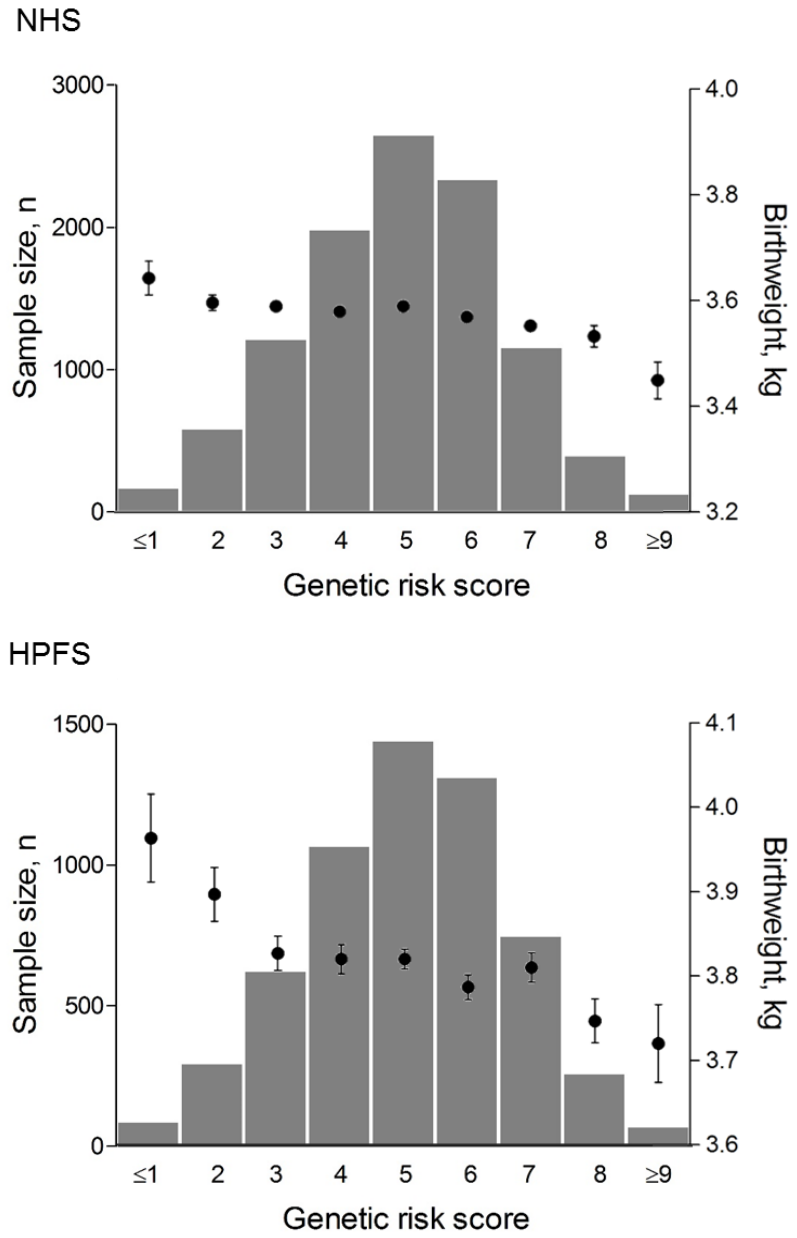
[b]The β_1 coefficients were derived from the GWAS meta-analysis of birthweight reported by Horikoshi M et al [1]

[c]ORs were derived from the GWAS meta-analysis of type 2 diabetes reported by the DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium et al [2]

[d]The β_3 was calculated from β_1 and β_2 ($\log_e$-OR for type 2 diabetes) for each SNP: $\beta_3=\beta_2/\beta_1$, and the SE of β_3 is given by: $S_3 = \sqrt{\frac{1}{\beta 1^2 S2^{-2}}}$, where S_2 is the SE of β_2. The overall β_3 estimate was obtained by using inverse variance weights fixed effects meta-analysis (*p* for heterogeneity =0.105), and can be interpreted as an OR of 1.70 (95% CI: 1.32-2.19) for type 2 diabetes per 1-SD lower genetically-determined birthweight (*p* <0.001)

[e]Meta-analysis was based on data for 5 analyzed SNPs using inverse variance weights fixed effects to obtain an overall estimate (all *p* for heterogeneity >0.05)

ESM Fig. 1 Distribution of the low-birthweight GRS among US women and men



The histograms indicate sample size, and the plots and bars indicate mean (SE) of birthweight. The GRS was significantly associated with birthweight among women (β = -0.014 kg, p =0.001) and men (β = -0.018 kg, p =0.001)

References

1. Horikoshi M, Yaghootkar H, Mook-Kanamori DO et al (2013) New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism. Nat Genet 45: 76-82

2. DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium; Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium et al (2014) Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nat Genet 46: 234-44