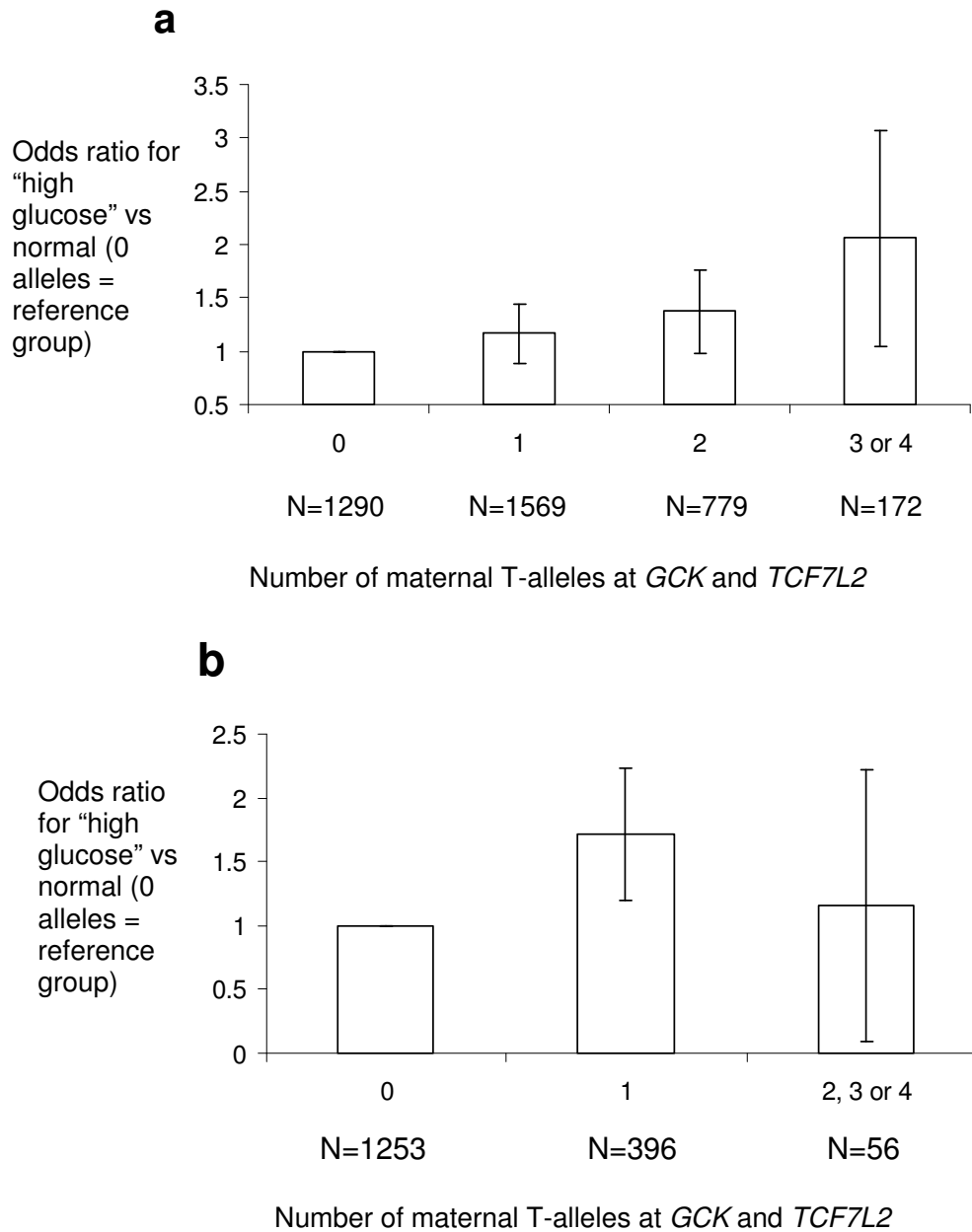


**Supplementary Online Material**

**Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: common genetic variants in *GCK* and *TCF7L2* are associated with fasting and post-challenge glucose levels in pregnancy and with the new consensus definition of gestational diabetes from the International Association of Diabetes and Pregnancy Study Groups**

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**Supplementary Figure 1.** Association between odds of “high glucose” and combined number of maternal T-alleles at *GCK* and *TCF7L2* in (a) Europeans and (b) Thais (final two allele groups combined due to low numbers). All error bars represent 95% CIs. Analyses are adjusted for field center, age and BMI at OGTT and mean arterial pressure.



**Supplementary Figure 2. Investigating associations between fetal genotype and birth weight, stratified by maternal genotype. (All error bars represent 95% CIs.)**

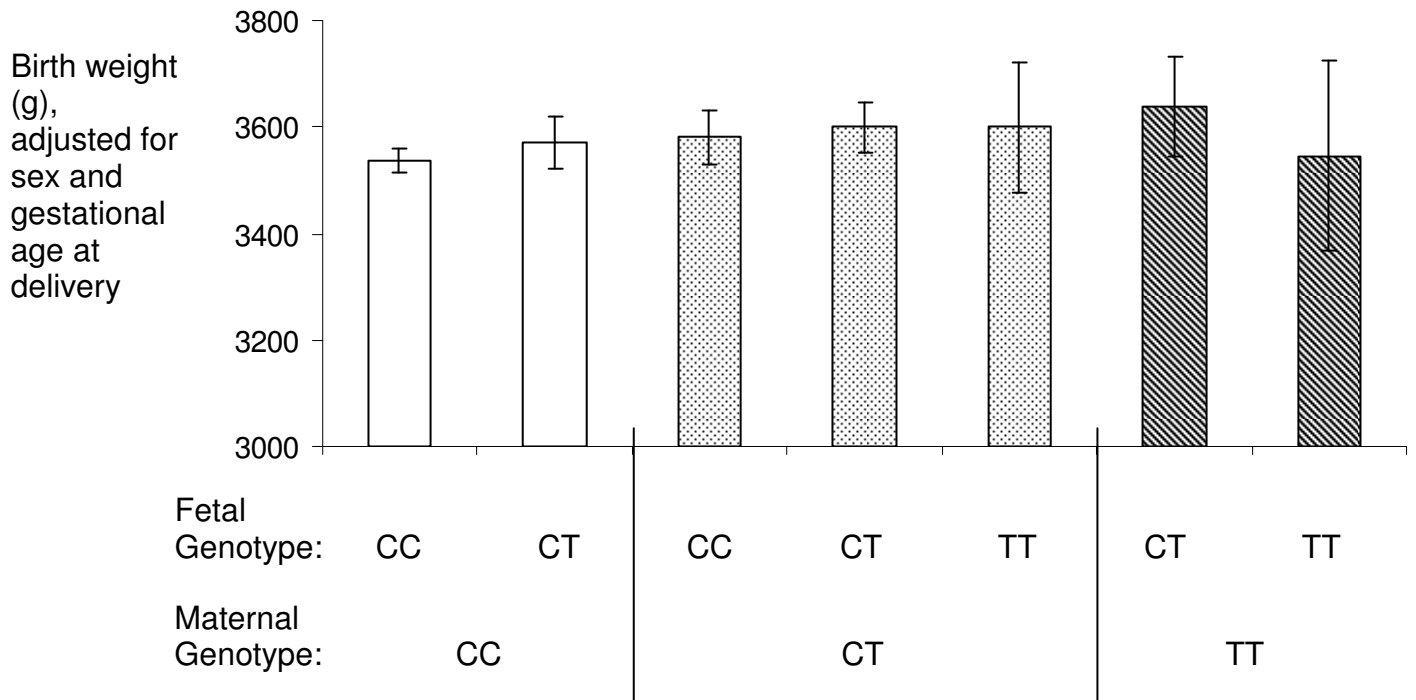
(a) Bar graph of birth weight against fetal *GCK* rs1799884 genotype in Europeans, stratified by maternal genotype. *P* values from linear regression (additive model) adjusted for sex and gestational age: *P*=0.25 (white bars); *P*=0.61 (dotted bars); *P*=0.28 (striped bars).

(b) Bar graph of birth weight against fetal *GCK* rs1799884 genotype in Thais, stratified by maternal genotype (CT and TT are combined due to lower minor allele frequency). *P* values from linear regression adjusted for sex and gestational age: *P*=0.57 (white bars); *P*=0.43 (striped bars).

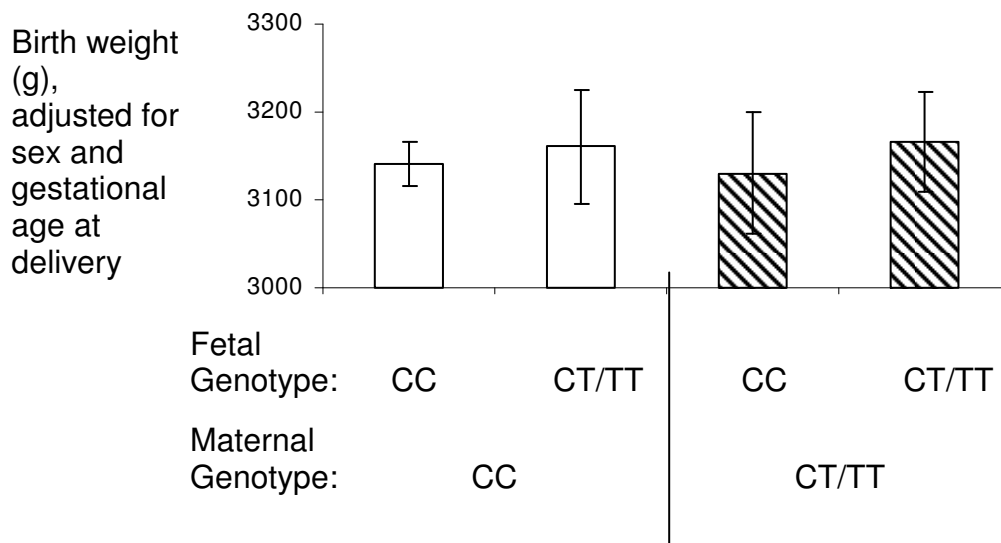
(c) Bar graph of birth weight against fetal *TCF7L2* rs7903146 genotype in Europeans, stratified by maternal genotype. *P* values from linear regression (additive model) adjusted for sex and gestational age: *P*=0.97 (white bars); *P*=0.92 (dotted bars); *P*=0.65 (striped bars).

(d) Bar graph of birth weight against fetal *TCF7L2* rs7903146 genotype in Thais, stratified by maternal genotype (CT and TT are combined due to lower minor allele frequency). *P* values from linear regression adjusted for sex and gestational age: *P*=0.01 (white bars); *P*=0.96 (striped bars).

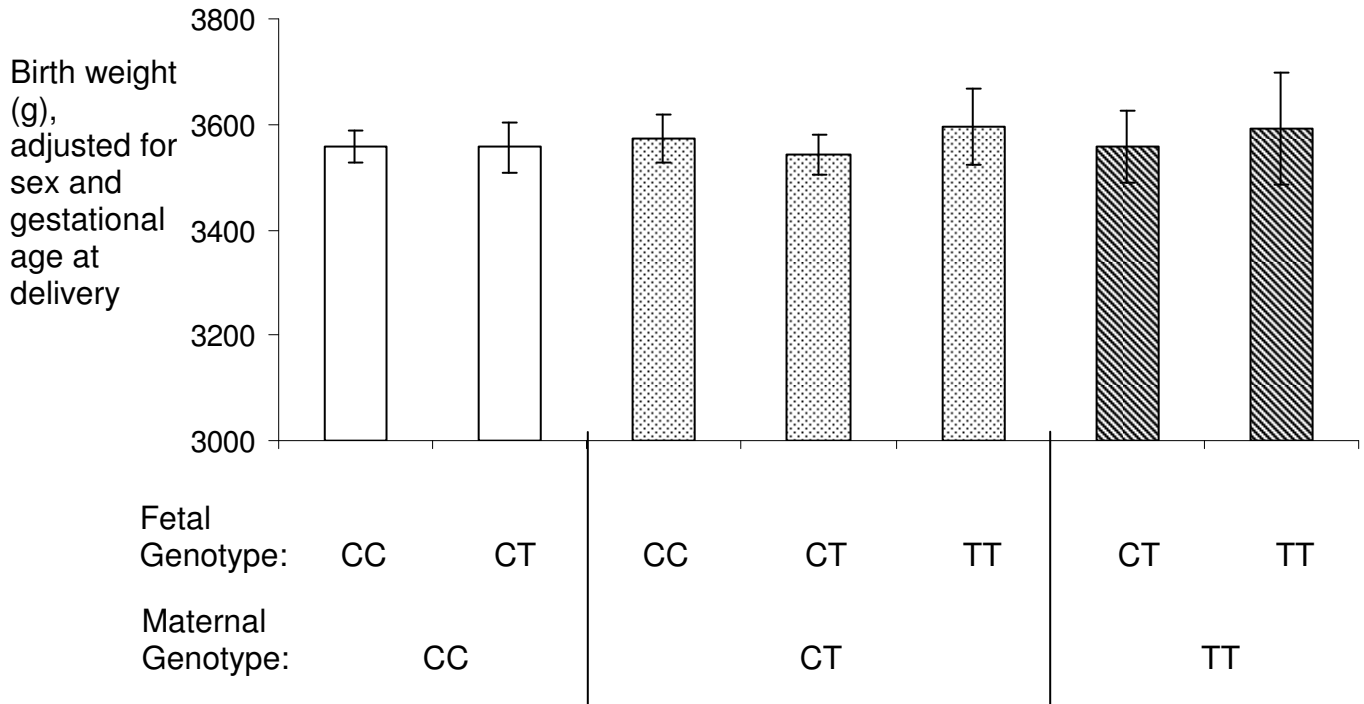
**a**



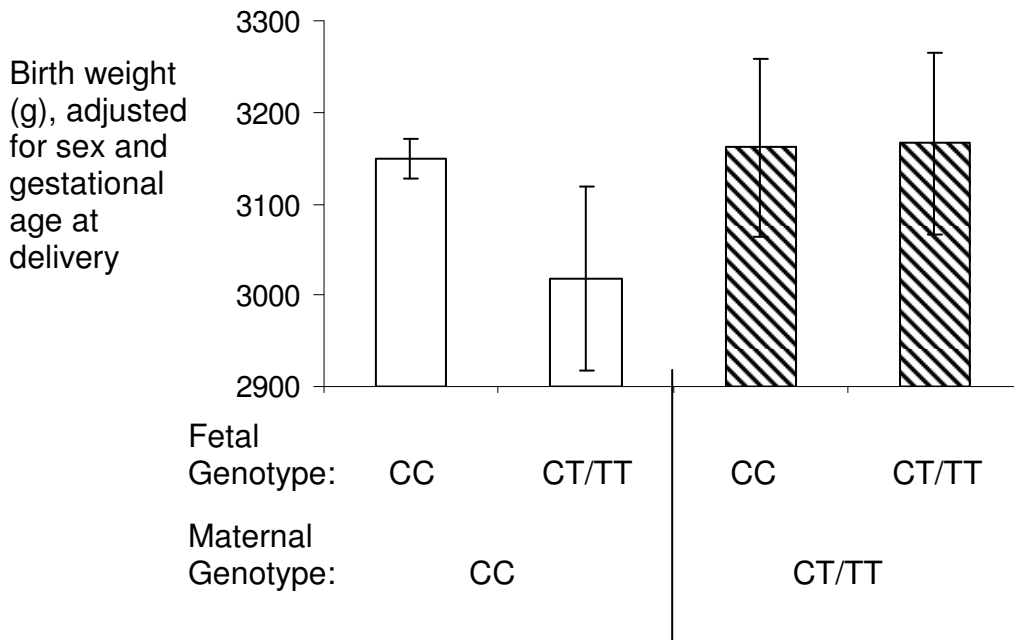
**b**



**c**



**d**



**Supplementary Table 1. Maternal plasma glucose levels by *GCK* rs1799884 genotype, presented by European field center**

Phenotype	Total N	Field Center	Mean plasma glucose level (SE) by <i>GCK</i> rs1799884 genotype		
			CC	CT	TT
FPG (mmol/l)	1284	Belfast	4.62 (0.01)	4.66 (0.02)	4.64 (0.06)
	1085	Manchester	4.59 (0.01)	4.64 (0.02)	4.67 (0.05)
	959	Brisbane	4.42 (0.01)	4.44 (0.02)	4.59 (0.06)
	483	Newcastle	4.53 (0.02)	4.56 (0.03)	4.55 (0.10)
1-hr PG (mmol/l)	1284	Belfast	7.41 (0.05)	7.70 (0.08)	7.51 (0.27)
	1085	Manchester	7.44 (0.06)	7.43 (0.10)	7.96 (0.26)
	959	Brisbane	7.33 (0.06)	7.54 (0.09)	7.80 (0.27)
	483	Newcastle	7.29 (0.09)	7.42 (0.14)	7.24 (0.42)
2-hr PG (mmol/l)	1284	Belfast	6.06 (0.04)	6.15 (0.06)	5.95 (0.19)
	1085	Manchester	6.01 (0.05)	5.91 (0.07)	6.30 (0.20)
	959	Brisbane	6.27 (0.05)	6.20 (0.07)	6.40 (0.22)
	483	Newcastle	6.16 (0.07)	6.35 (0.11)	6.03 (0.34)

FPG, fasting plasma glucose; PG, plasma glucose.

Mean values by genotype (SE) are adjusted for age, BMI and mean arterial pressure, measured at a median of 28-29 weeks of gestation.

**Supplementary Table 2. Maternal plasma glucose levels by *TCF7L2* rs7903146 genotype, presented by European field center**

Phenotype	Total N	Field Center	Mean plasma glucose level (SE) by <i>TCF7L2</i> rs7903146 genotype		
			CC	CT	TT
FPG (mmol/l)	1285	Belfast	4.61 (0.01)	4.64 (0.01)	4.72 (0.03)
	1085	Manchester	4.61 (0.02)	4.59 (0.02)	4.66 (0.03)
	959	Brisbane	4.43 (0.01)	4.43 (0.02)	4.50 (0.04)
	482	Newcastle	4.57 (0.02)	4.51 (0.03)	4.49 (0.06)
1-hr PG (mmol/l)	1285	Belfast	7.34 (0.06)	7.62 (0.07)	7.76 (0.14)
	1085	Manchester	7.40 (0.07)	7.49 (0.08)	7.61 (0.16)
	959	Brisbane	7.32 (0.07)	7.47 (0.07)	7.53 (0.16)
	482	Newcastle	7.26 (0.11)	7.35 (0.11)	7.61 (0.25)
2-hr PG (mmol/l)	1285	Belfast	5.94 (0.05)	6.23 (0.05)	6.18 (0.10)
	1085	Manchester	5.94 (0.06)	6.01 (0.06)	6.16 (0.12)
	959	Brisbane	6.20 (0.05)	6.26 (0.06)	6.47 (0.13)
	482	Newcastle	6.18 (0.08)	6.19 (0.09)	6.46 (0.20)

FPG, fasting plasma glucose; PG, plasma glucose.

Mean values by genotype (SE) are adjusted for age, BMI and mean arterial pressure, measured at a median of 28-29 weeks of gestation.

**Supplementary Table 3. Association between maternal *GCK* rs1799884 genotype and glucose levels under different models**

Phenotype	Ancestry	Model 1			Model 2			Model 3		
		Total N	Effect size per T allele (SE) in mmol/l	<i>P</i> value	Total N	Effect size per T allele (SE) in mmol/l	<i>P</i> value	Total N	Effect size per T allele (SE) in mmol/l	<i>P</i> value
FPG (mmol/l)	European	3816	0.04 (0.01)	0.001	3811	0.03 (0.01)	0.001	3745	0.04 (0.01)	0.0002
	Thai	1706	0.09 (0.02)	4x10 <sup>-5</sup>	1706	0.08 (0.02)	7x10 <sup>-5</sup>	1655	0.08 (0.02)	6x10 <sup>-5</sup>
1-hr PG (mmol/l)	European	3816	0.17 (0.05)	0.0009	3811	0.15 (0.05)	0.001	3745	0.16 (0.05)	0.0006
	Thai	1706	0.15 (0.10)	0.13	1706	0.11 (0.09)	0.24	1655	0.07 (0.09)	0.46
2-hr PG (mmol/l)	European	3816	0.03 (0.04)	0.44	3811	0.02 (0.04)	0.56	3745	0.02 (0.04)	0.53
	Thai	1706	0.24 (0.08)	0.002	1706	0.21 (0.07)	0.005	1655	0.16 (0.07)	0.02

FPG, fasting plasma glucose; PG, plasma glucose.

Model 1: Linear regression of maternal glucose level against genotype (coded zero, one, or two T alleles), with field center as a covariate in the European samples only.

Model 2: Linear regression of maternal glucose level against genotype (coded zero, one, or two T alleles), with field center (Eur only), age, BMI and mean arterial pressure as covariates.

Model 3: Linear regression of maternal glucose level against genotype (coded zero, one, or two T alleles), with field center (Eur only), age, BMI, BMI-squared, gestational age at OGTT, parity, sex of the baby, mean arterial pressure and maternal height as covariates.



**Supplementary Table 4. Association between maternal *TCF7L2* rs7903146 genotype and glucose levels under different models**

Phenotype	Ancestry	Model 1			Model 2			Model 3		
		Total N	Effect size per T allele (SE) in mmol/l	P value	Total N	Effect size per T allele (SE) in mmol/l	P value	Total N	Effect size per T allele (SE) in mmol/l	P value
FPG (mmol/l)	European	3816	0.01 (0.01)	0.16	3811	0.02 (0.01)	0.03	3745	0.01 (0.01)	0.09
	Thai	1706	0.02 (0.03)	0.51	1706	0.01 (0.03)	0.66	1655	0.01 (0.03)	0.61
1-hr PG (mmol/l)	European	3816	0.14 (0.04)	0.0006	3811	0.16 (0.04)	5x10 <sup>-5</sup>	3745	0.14 (0.04)	0.0005
	Thai	1706	0.27 (0.14)	0.06	1706	0.23 (0.14)	0.09	1655	0.17 (0.14)	0.22
2-hr PG (mmol/l)	European	3816	0.11 (0.03)	0.0003	3811	0.13 (0.03)	2x10 <sup>-5</sup>	3745	0.10 (0.03)	0.0004
	Thai	1706	0.21 (0.11)	0.06	1706	0.17 (0.11)	0.11	1655	0.07 (0.11)	0.49

FPG, fasting plasma glucose; PG, plasma glucose.

Model 1: Linear regression of maternal glucose level against genotype (coded zero, one, or two T alleles), with field center as a covariate in the European samples only.

Model 2: Linear regression of maternal glucose level against genotype (coded zero, one, or two T alleles), with field center (Eur only), age, BMI and mean arterial pressure as covariates.

Model 3: Linear regression of maternal glucose level against genotype (coded zero, one, or two T alleles), with field center (Eur only), age, BMI, BMI-squared, gestational age at OGTT, parity, sex of the baby, mean arterial pressure and maternal height as covariates.

**Supplementary Table 5. Associations between maternal *GCK* rs1799884 genotype and neonatal anthropometric traits**

Phenotype	Ancestry	Model 1			Model 2		
		Total N	Effect size per T allele (SE)	<i>P</i> value	Total N	Effect size per T allele (SE)	<i>P</i> value
Log cord C-peptide level	European	2721	0.013 (0.009)	0.16	2717	0.010 (0.009)	0.26
	Thai	1462	0.016 (0.015)	0.26	1462	0.013 (0.014)	0.36
Birth weight (g)	European	3558	30 (14)	0.03	3553	23 (13)	0.07
	Thai	1505	23 (23)	0.32	1505	17 (21)	0.42
Fat mass at birth (g)	European	3175	12 (5.4)	0.03	3171	10 (5)	0.05
	Thai	1456	4 (8)	0.64	1456	1 (7)	0.94
Percent body fat at birth (%)	European	3175	0.27 (0.11)	0.02	3171	0.24 (0.11)	0.02
	Thai	1456	0.14 (0.20)	0.48	1456	0.06 (0.18)	0.72
Birth length (cm)	European	3480	0.07 (0.07)	0.31	3475	0.04 (0.06)	0.51
	Thai	1502	0.12 (0.09)	0.19	1502	0.10 (0.09)	0.26
Birth head circumf.(cm)	European	3532	0.06 (0.04)	0.09	3527	0.05 (0.04)	0.18
	Thai	1503	0.04 (0.07)	0.59	1503	0.02 (0.07)	0.74
Triceps skinfold thickness (mm)	European	3191	0.06 (0.03)	0.03	3187	0.06 (0.03)	0.05
	Thai	1464	0.00 (0.05)	0.94	1464	-0.02 (0.05)	0.64
Flank skinfold thickness (mm)	European	3192	0.06 (0.03)	0.04	3188	0.05 (0.03)	0.08
	Thai	1464	0.04 (0.05)	0.40	1464	0.03 (0.04)	0.56
Subscap. skinfold thickness (mm)	European	3195	0.07 (0.03)	0.03	3191	0.06 (0.03)	0.06
	Thai	1465	0.07 (0.06)	0.22	1465	0.05 (0.05)	0.34
Sum of skinfolds (mm)	European	3189	0.19 (0.08)	0.02	3185	0.16 (0.08)	0.04
	Thai	1464	0.10 (0.14)	0.48	1464	0.05 (0.14)	0.71

Model 1: Linear regression of trait against genotype (coded zero, one, or two T alleles), with field center (Eur only), sex and gestational age at delivery as covariates.

Model 2: Linear regression of trait against genotype (coded zero, one, or two T alleles), with field center (Eur only), with sex, gestational age at delivery, maternal age at OGTT, maternal BMI at OGTT, maternal BMI at OGTT-squared, parity, maternal smoking (yes/no), mean arterial pressure and maternal height as covariates.

All analyses excluded births before 37 completed weeks of gestation and pregnancies in which caregivers were not blinded to maternal glucose levels.

**Supplementary Table 6. Associations between maternal *TCF7L2* rs7903146 genotype and neonatal anthropometric traits**

Phenotype	Ancestry	Model 1			Model 2		
		Total N	Effect size per T allele (SE)	P value	Total N	Effect size per T allele (SE)	P value
Log cord C-peptide level	European	2721	0.001 (0.008)	0.85	2717	0.004 (0.007)	0.56
	Thai	1461	0.002 (0.022)	0.93	1461	0.001 (0.021)	0.95
Birth weight (g)	European	3558	8 (11)	0.49	3553	11 (10)	0.27
	Thai	1504	29 (34)	0.39	1504	14 (31)	0.66
Fat mass at birth (g)	European	3175	0 (4)	0.91	3171	1 (4)	0.80
	Thai	1455	15 (12)	0.21	1455	11 (11)	0.33
Percent body fat at birth (%)	European	3175	-0.01 (0.09)	0.94	3171	0.02 (0.09)	0.80
	Thai	1455	0.50 (0.29)	0.11	1455	0.36 (0.26)	0.18
Birth length (cm)	European	3480	0.05 (0.05)	0.38	3475	0.06 (0.05)	0.26
	Thai	1501	-0.01 (0.13)	0.96	1501	-0.07 (0.13)	0.55
Birth head circumf.(cm)	European	3532	0.03 (0.03)	0.39	3527	0.04 (0.03)	0.22
	Thai	1502	-0.14 (0.10)	0.18	1502	-0.17 (0.10)	0.08
Triceps skinfold thickness (mm)	European	3191	0.02 (0.02)	0.45	3187	0.03 (0.02)	0.28
	Thai	1463	0.02 (0.08)	0.82	1463	0.01 (0.08)	0.95
Flank skinfold thickness (mm)	European	3192	-0.01 (0.02)	0.61	3188	-0.01 (0.02)	0.81
	Thai	1463	0.14 (0.07)	0.03	1463	0.13 (0.06)	0.04
Subscap. skinfold thickness (mm)	European	3195	0.01 (0.03)	0.78	3191	0.01 (0.02)	0.58
	Thai	1464	0.12 (0.08)	0.15	1464	0.11 (0.08)	0.17
Sum of skinfolds (mm)	European	3189	0.01 (0.07)	0.85	3185	0.03 (0.06)	0.61
	Thai	1463	0.29 (0.21)	0.17	1463	0.26 (0.20)	0.20

Model 1: Linear regression of trait against genotype (coded zero, one, or two T alleles), with field center (Eur only), sex and gestational age at delivery as covariates.

Model 2: Linear regression of trait against genotype (coded zero, one, or two T alleles), with field center (Eur only), with sex, gestational age at delivery, maternal age at OGTT, maternal BMI at OGTT, maternal BMI at OGTT-squared, parity, maternal smoking (yes/no), mean arterial pressure and maternal height as covariates.

All analyses excluded births before 37 completed weeks of gestation and pregnancies in which caregivers were not blinded to maternal glucose levels.

**Supplementary Table 7. Using ROC curves to evaluate the impact of maternal genotype vs maternal glucose on birth weight and neonatal adiposity**

Outcome	N	Model 1*	Model 2 Model 1 variables Maternal fasting glucose at OGTT	Model 3 Model 1 variables Maternal <i>GCK</i> rs1799884 Maternal <i>TCF7L2</i> rs7903146	Model 4 Model 1 variables Maternal fasting glucose at OGTT Maternal 1h glucose at OGTT Maternal 2h glucose at OGTT	Model 5 Model 1 variables Maternal fasting glucose at OGTT Maternal <i>GCK</i> rs1799884 Maternal <i>TCF7L2</i> rs7903146				
		Area under ROC curve (SE)	Area under ROC curve (SE)	P value model 2 vs model 1	Area under ROC curve (SE)	P value model 3 vs model 1	Area under ROC curve (SE)	P value model 4 vs model 2	Area under ROC curve (SE)	P value model 5 vs model 2
BW >90 <sup>th</sup> percentile	5059	0.73 (0.01)	0.74 (0.01)	0.01	0.73 (0.01)	0.35	0.75 (0.01)	0.01	0.74 (0.01)	0.56
Percent fat >90 <sup>th</sup> percentile	4649	0.67 (0.01)	0.69 (0.01)	0.003	0.68 (0.01)	0.48	0.70 (0.01)	0.04	0.69 (0.01)	0.75
Skinfolds >90 <sup>th</sup> percentile	4650	0.66 (0.01)	0.68 (0.01)	0.003	0.66 (0.01)	0.42	0.69 (0.01)	0.008	0.68 (0.01)	0.47

BW, birth weight; ROC, receiver operating characteristic.

\*Model 1 explanatory variables: Study centre; Maternal age at OGTT; Maternal BMI at OGTT; Maternal BMI at OGTT-squared; Gestational age at delivery; Maternal MAP (mean arterial pressure); Parity; Sex of the baby; Maternal height; Maternal smoking.