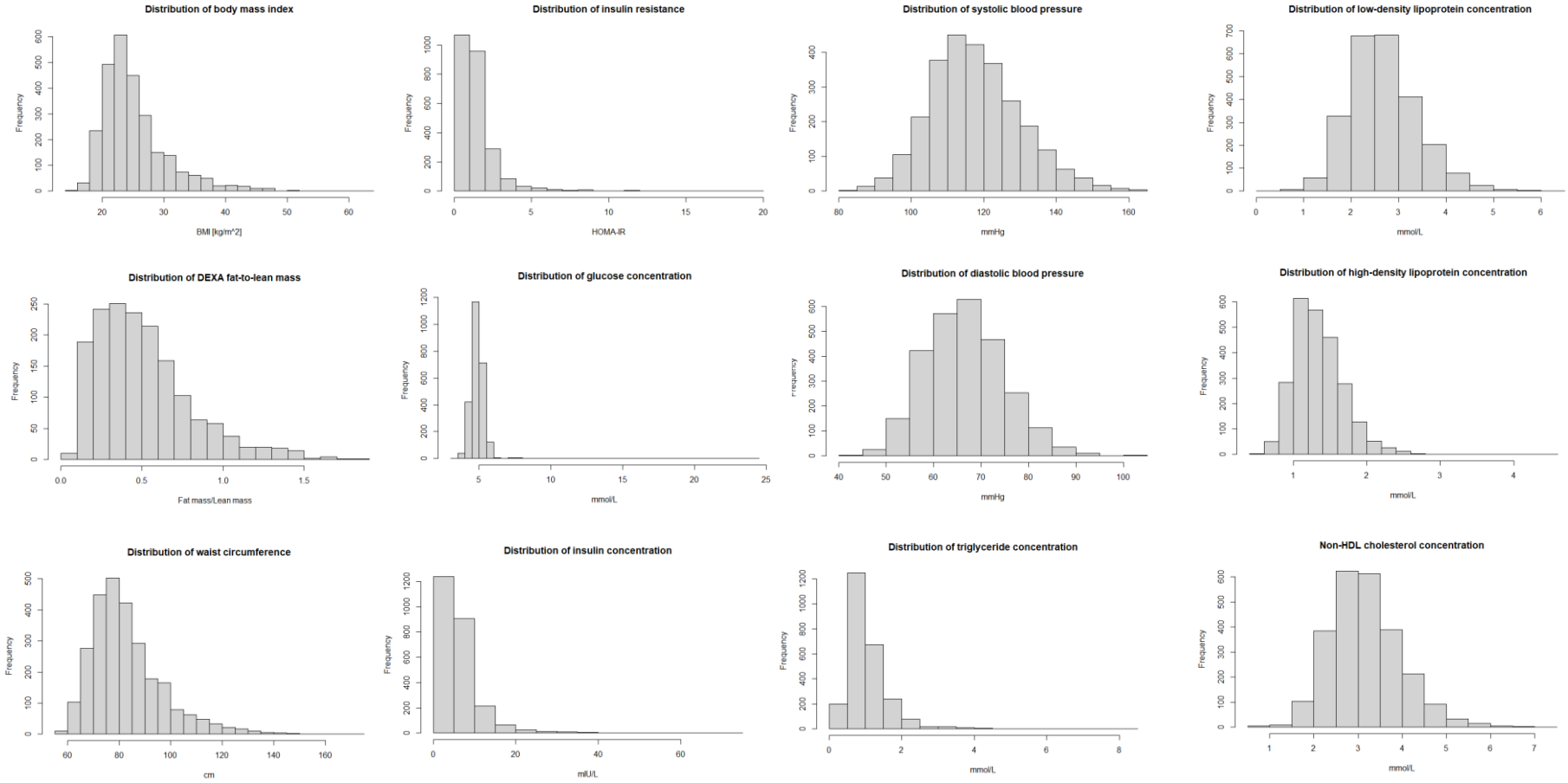
Supplementary materials

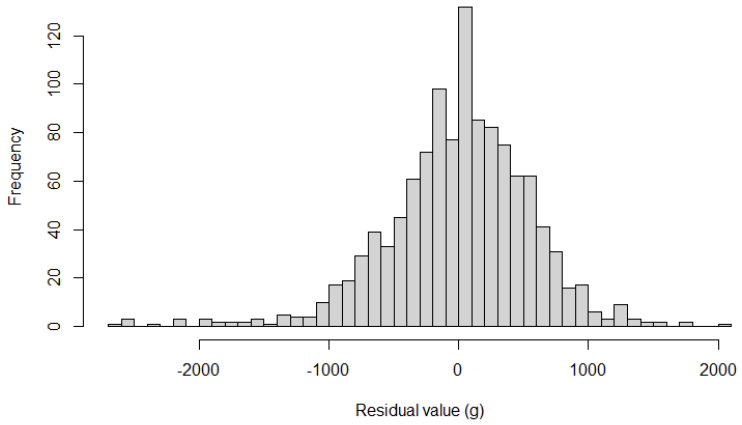
Supplementary Figure 1 Histograms of cardiometabolic outcome variables



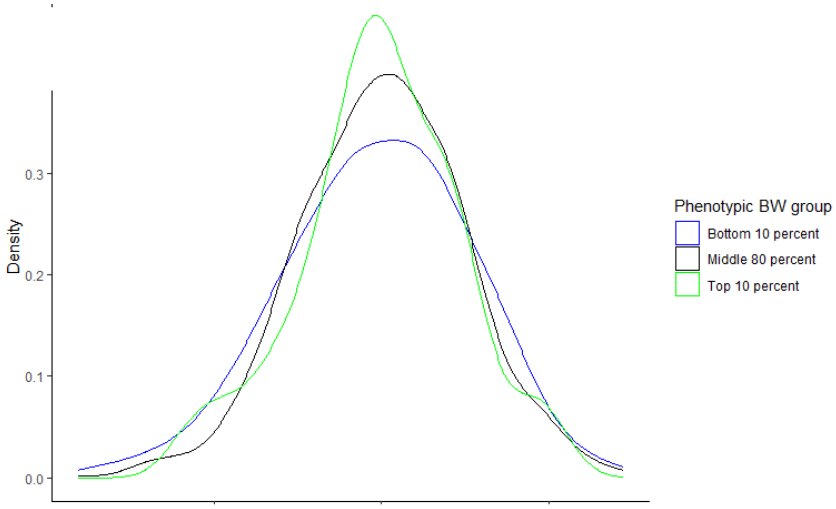
Supplementary figure 1 Distribution of outcome variables

Supplementary Figure 2 The birth weight polygenic score and phenotypic groupings

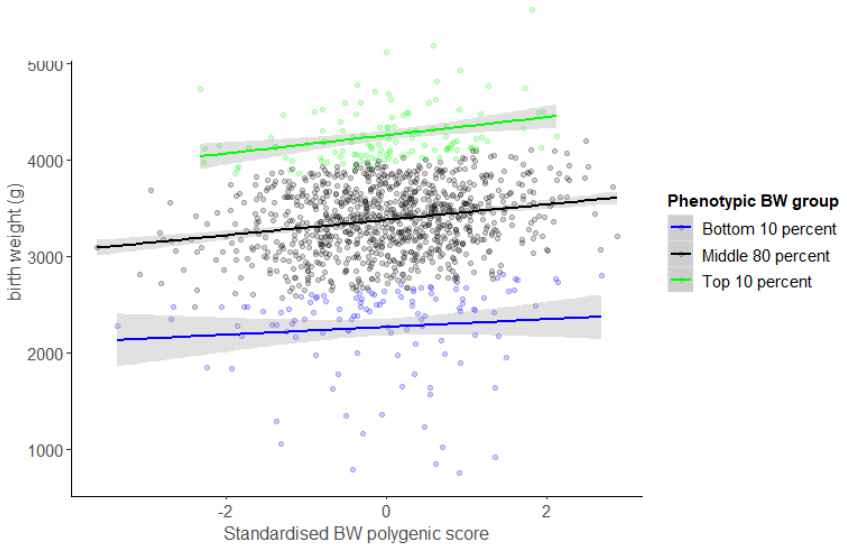
A)



B)

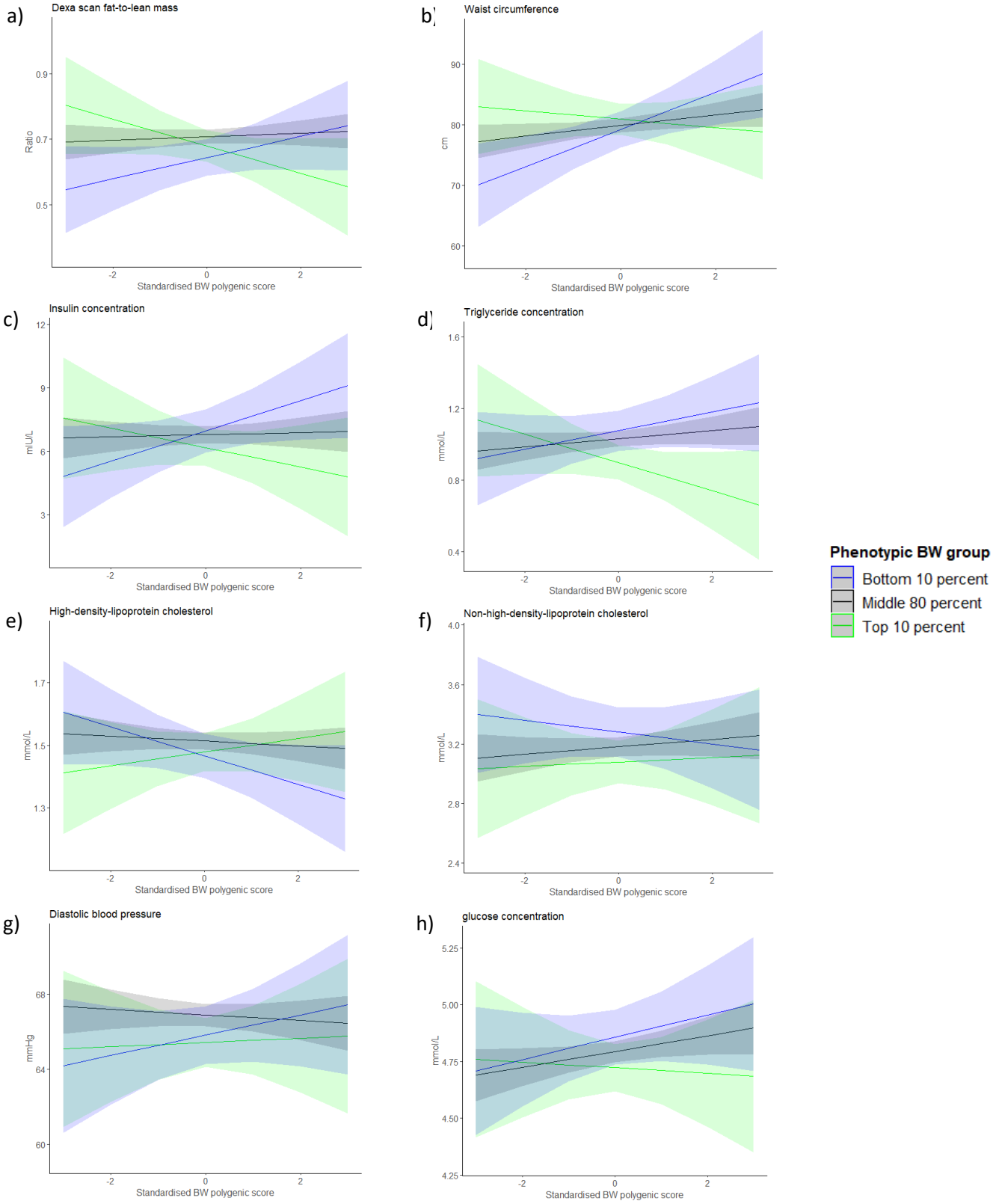


C)



Supplementary figure 2 A) Residual values following regression of BW-PGS on measured BW. This was subsequently used for phenotype grouping **B)** Density plot showing the distribution of the polygenic score among the phenotypic groupings for BW. C**)** Scatterplot and regression line showing the association between the polygenic score and measured birth weight in the three groupings. Shaded area: 95% CI.

Supplementary Figure 3 Phenotype-genotype interactions for secondary outcomes



Supplementary figure 3 Birth weight phenotype-genotype interactions for secondary outcomes.

a-d) The significant phenotype-genotype interaction for the fat-to-lean mass ratio, waist circumference and insulin levels and triglyceride concentration. e-h) The insignificant phenotype-genotype interaction models for high-density lipoprotein cholesterol, non high-density-lipoprotein cholesterol concentration, diastolic blood pressure and glucose concentration. BW: Birth weight, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance. Shaded area: 95% CI

Supplementary Table 1 Maternal characteristics by phenotypic group (n=1167)

	≤10th phenotypic centile (n=118)	**>10th to <90th phenotypic centile** (n=931)	**≥ 90th phenotypic centile** (n=118)
Maternal age (years)			
Mean (SD)	29.1 (±5.9)	29.2 (±5.8)	29.4 (±5.9)
Missing	9 (7.6%)	2 (0.2%)	0 (0%)
Maternal smoking level†			
Mean (SD)	0.8 (±1.4)	0.5 (±1.2)	0.2 (±0.6)
Missing	32 (27.1%)	39 (4.2%)	6 (5.1%)
Maternal BMI (kg/m^2)			
Mean (SD)	21.8 (±4.1)	22.3 (±4.1)	23.4 (±4.9)
Missing	9 (7.6%)	2 (0.2%)	0 (0%)
Maternal ethnicity			
European descent	107 (90.7%)	894 (96.0%)	115 (97.5%)
Other	2 (1.7%)	35 (3.8%)	3 (2.5%)
Missing	9 (7.6%)	2 (0.2%)	0 (0.0%)
Family income level			
> 12.000 AUD	92 (78.0%)	795 (85.4%)	102 (86.4%)
< 12.000 AUD	12 (10.2%)	107 (11.5%)	12 (10.2%)
Missing	14 (11.9%)	29 (3.1%)	4 (3.4%)
Maternal education level			
No formal education beyond high school	53 (44.9%)	402 (43.2%)	51 (43.2%)
Some formal education beyond high school	56 (47.5%)	527 (56.6%)	67 (56.8%)
Missing	9 (7.6%)	2 (0.2%)	0 (0.0%)

† 0=None, 1=1 to 5 daily, 2=6 to 10 daily, 3=11 to 15 daily, 4=16 to 20 daily, 5=21 or more per day

Supplementary Table 2 Secondary outcome variables (n=1167)

	≤10th phenotypic centile (n=118)	**>10th to <90th phenotypic centile** (n=931)	**≥ 90th phenotypic centile** (n=118)
Fat mass age 20 (g)			
Mean (SD)	21219.9 (±11690.0)	22735.7 (±12650.4)	21516.5 (±12105.9)
Missing	28 (23.7%)	164 (17.6%)	30 (25.4%)
Lean mass age 20 (g)			
Mean (SD)	46547.8 (±12064.2)	47153.3 (±11966.3)	51596.1 (±13408.2)
Missing	28 (23.7%)	164 (17.6%)	30 (25.4%)
Fat-to-lean mass ratio age 20			
Mean (SD)	0.5 (±0.3)	0.5 (±0.3)	0.5 (±0.3)
Missing	28 (23.7%)	164 (17.6%)	30 (25.4%)
Fat mass age 27 (g)			
Mean (SD)	24182.4 (±12380.4)	24750.9 (±12819.0)	25245.0 (±12670.4)
Missing	47 (39.8%)	379 (40.7%)	42 (35.6%)
Lean mass age 27 (g)			
Mean (SD)	49118.8 (±10918.2)	51229.3 (±11043.1)	54676.0 (±12002.0)
Missing	47 (39.8%)	379 (40.7%)	42 (35.6%)
Fat-to-lean mass ratio age 27			
Mean (SD)	0.5 (±0.2)	0.5 (±0.2)	0.5 (±0.2)
Missing	47 (39.8%)	379 (40.7%)	42 (35.6%)
Glucose age 20 (mmol/L)			
Mean (SD)	5.0 (±0.6)	5.0 (±0.4)	5.0 (±0.5)
Missing	32 (27.1%)	183 (19.7%)	31 (26.3%)
Glucose age 22 (mmol/L)			
Mean (SD)	5.1 (±1.6)	5.0 (±0.9)	4.9 (±0.3)
Missing	40 (33.9%)	325 (34.9%)	45 (38.1%)
Glucose age 27 (mmol/L)			
Mean (SD)	4.9 (±0.7)	4.8 (±0.6)	4.7 (±0.4)
Missing	32 (27.1%)	294 (31.6%)	31 (26.3%)
Insulin age 20 (mIU/L)			
Mean (SD)	4.8 (±5.4)	4.6 (±5.2)	4.5 (±4.7)
Missing	32 (27.1%)	183 (19.7%)	31 (26.3%)
Insulin age 22 (mIU/L)			
Mean (SD)	12.3 (±30.3)	8.5 (±5.7)	7.2 (±3.3)
Missing	40 (33.9%)	325 (34.9%)	45 (38.1%)
Insulin age 27 (mIU/L)			
Mean (SD)	9.1 (±22.5)	6.6 (±4.6)	5.8 (±2.8)
Missing	32 (27.1%)	292 (31.4%)	31 (26.3%)
HDL cholesterol age 20 (mmol/L)			
Mean (SD)	1.3 (±0.3)	1.3 (±0.3)	1.3 (±0.3)
Missing	32 (27.1%)	183 (19.7%)	31 (26.3%)
HDL cholesterol age 22 (mmol/L)			
Mean (SD)	1.3 (±0.3)	1.4 (±0.4)	1.3 (±0.3)
Missing	40 (33.9%)	325 (34.9%)	45 (38.1%)
HDL cholesterol age 27 (mmol/L)			
Mean (SD)	1.4 (±0.4)	1.5 (±0.4)	1.5 (±0.3)
Missing	32 (27.1%)	293 (31.5%)	31 (26.3%)
Diastolic blood pressure age 20 (mmHg)			
Mean (SD)	65.4 (±8.6)	65.4 (±7.9)	63.9 (±8.0)
Missing	16 (13.6%)	94 (10.1%)	16 (13.6%)
Diastolic blood pressure age 22 (mmHg)			
Mean (SD)	66.8 (±8.5)	67.4 (±7.8)	66.6 (±7.7)
Missing	35 (29.7%)	269 (28.9%)	40 (33.9%)
Diastolic blood pressure age 27 (mmHg)			
Mean (SD)	69.5 (±8.4)	69.6 (±7.6)	67.3 (±7.9)
Missing	32 (27.1%)	286 (30.7%)	28 (23.7%)

Supplementary table 2 (continued)

Waist circumference age 20 (cm)			
Mean (SD)	80.2 (±13.6)	80.4 (±12.9)	81.7 (±12.1)
Missing	17 (14.4%)	96 (10.3%)	17 (14.4%)
Waist circumference age 22 (cm)			
Mean (SD)	84.0 (±15.7)	83.6 (±13.7)	84.4 (±11.7)
Missing	35 (29.7%)	269 (28.9%)	41 (34.7%)
Waist circumference age 27 (cm)			
Mean (SD)	85.3 (±16.9)	85.0 (±14.9)	87.1 (±15.1)
Missing	32 (27.1%)	286 (30.7%)	28 (23.7%)
Non-HDL cholesterol age 20 (mmol/L)			
Mean (SD)	3.2 (±0.7)	3.0 (±0.7)	2.9 (±0.7)
Missing	32 (27.1%)	183 (19.7%)	31 (26.3%)
Non-HDL cholesterol age 22 (mmol/L)			
Mean (SD)	3.5 (±0.8)	3.2 (±0.8)	3.1 (±0.9)
Missing	40 (33.9%)	325 (34.9%)	45 (38.1%)
Non-HDL cholesterol age 27 (mmol/L)			
Mean (SD)	3.6 (±0.9)	3.4 (±2.9)	3.3 (±0.8)
Missing	32 (27.1%)	293 (31.5%)	31 (26.3%)
Triglyceride concentration age 20 (mmol/L)			
Mean (SD)	1.1 (±0.6)	1.1 (±0.6)	1.0 (±0.5)
Missing	32 (27.1%)	184 (19.8%)	31 (26.3%)
Triglyceride concentration age 22 (mmol/L)			
Mean (SD)	1.2 (±0.6)	1.1 (±0.5)	1.0 (±0.4)
Missing	40 (33.9%)	325 (34.9%)	45 (38.1%)
Triglyceride concentration age 27 (mmol/L)			
Mean (SD)	1.1 (±0.5)	1.0 (±0.6)	0.9 (±0.5)
Missing	32 (27.1%)	294 (31.6%)	31 (26.3%)

HDL: High-density lipoprotein

Supplementary Table 3 Modelling birth weight with the polygenic score

	The overall effect of the polygenic score on birth weight (g) when including predetermined covariables		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	-4018.63	-4551.59 – -3485.66	**<0.001**
Standardised BW-PGS (SD)	**85.62**	**61.45 – 109.78**	**<0.001**
Fetal sex [male]	115.10	66.82 – 163.39	**<0.001**
Gestational duration (weeks)	179.37	167.68 – 191.06	**<0.001**
Principal component 1	22198.86	-4902.56 – 49300.29	0.108
Principal component 2	-634.49	-10636.67 – 9367.69	0.901
Observations	1167		
R^2 / R^2 adjusted	0.459 / 0.457		

BW-PGS: Birth weight polygenic score

Supplementary Table 4 Birth weight phenotype-genotype interactions for the remaining secondary outcomes

	Participants	Observations	Estimate	boot se	Boot 95% CI	p-value
Glucose concentration						
PGS in largest decile	n = 1111	o = 2486	-0.01	0.023	-0.07, 0.03	0.60
Interaction middle deciles			0.05	0.033	-0.01, 0.12	0.15
Interaction smallest decile			0.06	0.0376	-0.00, 0.15	0.10
High-density lipoprotein cholesterol						
PGS in largest decile	n = 1112	o = 2489	0.018	0.022	-0.02, 0.06	0.40
Interaction middle deciles			-0.025	0.023	-0.07, 0.02	0.28
Interaction smallest decile			-0.063	0.029	-0.12, -0.01	0.03
Non high-density lipoprotein cholesterol						
PGS in largest decile	n = 1112	o = 2488	0.01	0.055	-0.10, 0.12	0.85
Interaction middle deciles			0.01	0.058	-0.10, 0.13	0.82
Interaction smallest decile			-0.04	0.076	-0.19, 0.11	0.61
Diastolic blood pressure						
PGS in largest decile	n = 1153	o = 2685	0.11	0.527	-0.92, 1.15	0.82
Interaction middle deciles			-0.26	0.552	-1.32, 0.85	0.63
Interaction smallest decile			0.43	0.700	-1.01, 1.73	0.54

Supplementary table 4 Output from models of the remaining secondary outcomes including BW phenotype-genotype interactions.

* Linear mixed model of cardiometabolic parameters adjusted for fetal sex, gestational duration, genetic principal components and age at assessment. Estimate SE was derived using 5000 repeats of a non-parametric bootstrap at the participant ID level. **Bold** indicates significant effects.

Supplementary Table 5 Birth weight phenotype-genotype interactions for log-transformed outcome variables

	Participants	Observations	Estimate	boot se	Boot 95% CI	p-value
Body mass index						
PGS in largest decile	n = 1150	o = 2675	-0.01	0.013	-0.04, 0.01	0.29
Interaction middle deciles			0.02	0.014	-0.00, 0.05	0.08
Interaction smallest decile			**0.06**	**0.018**	**0.02, 0.09**	**0.001**
HOMA-IR						
PGS in largest decile	n = 1112	o = 2486	-0.07	0.041	-0.16, 0.00	0.07
Interaction middle deciles			0.08	0.043	-0.00, 0.17	0.08
Interaction smallest decile			**0.15**	**0.053**	**0.05, 0.26**	**0.005**
LDL-c						
PGS in largest decile	n = 1111	o = 2483	0.02	0.018	-0.02, 0.05	0.35
Interaction middle deciles			-0.01	0.019	-0.05, 0.03	0.67
Interaction smallest decile			-0.04	0.024	-0.08, 0.01	0.14
SBP						
PGS in largest decile	n = 1153	o = 2685	-0.01	0.006	-0.02, -0.00	0.03
Interaction middle deciles			0.01	0.006	-0.00, 0.02	0.07
Interaction smallest decile			0.01	0.008	-0.00, 0.03	0.09

Supplementary table 5 Repeating the primary analysis with a log-transformation of the primary outcome variables.

* Linear mixed model of cardiometabolic parameters adjusted for fetal sex, gestational duration, genetic principal components and age at assessment. Estimate SE was derived using 5000 repeats of a non-parametric bootstrap at the participant ID level. **Bold** indicates significant effects.

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, LDL-c: low-density lipoprotein cholesterol, SBP: Systolic blood pressure, PGS: Polygenic Score

Supplementary Table 6 Birth weight phenotype-genotype interaction for 20th and 80th centile cuts and continuous BW-phenotype

	Participants	Observations	Estimate	boot se	Boot 95% CI	p-value
Body mass index						
PGS in largest quintile	n = 1150	o = 2675	0.17	0.285	0.38, 0.74	0.54
Interaction smallest quintile			0.75	0.417	-0.08, 1.56	0.07
Interaction continuous model			-0.17	0.119	-0.41, 0.06	0.14
HOMA-IR						
PGS in largest quintile	n = 1112	o = 2486	-0.06	0.039	-0.14, 0.01	0.10
Interaction smallest quintile			**0.19**	**0.067**	**0.06, 0.32**	**0.003**
Interaction continuous model			-0.05	0.023	-0.09, -0.00	0.04
LDL-c						
PGS in largest quintile	n = 1111	o = 2483	-0.00	0.034	-0.07, 0.07	0.96
Interaction smallest quintile			-0.03	0.048	-0.13, 0.06	0.55
Interaction continuous model			0.02	0.016	-0.01, 0.05	0.24
SBP						
PGS in largest quintile	n = 1153	o = 2685	-0.15	0.436	-0.98, 0.73	0.73
Interaction smallest quintile			0.31	0.679	-1.09, 1.57	0.65
Interaction continuous model			0.02	0.231	-0.44, 0.47	0.95

Supplementary table 6 Exploring an alternative cut-off and a continuous interaction between BW-PGS and BW-phenotype.

* Linear mixed model of cardiometabolic parameters adjusted for fetal sex, gestational duration, genetic principal components and age at assessment. Estimate SE was derived using 5000 repeats of a non-parametric bootstrap at the participant ID level. In the continuous model the residuals from regressing measured BW on BW-PGS were normalised explaining the negative estimate. **Bold** indicates significant effects.

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, LDL-c: low-density lipoprotein cholesterol, SBP: Systolic blood pressure, PGS: Polygenic Score

Supplementary Table 7 Gestational duration excluded as covariable

	Participants	Observations	Estimate	boot se	Boot 95% CI	p-value
Body mass index						
PGS in largest decile	n = 1150	o = 2675	-0.39	0.381	-1.13, 0.36	0.30
Interaction middle deciles			0.72	0.407	-0.08, 1.52	0.08
Interaction smallest decile			**1.65**	0.508	**0.61, 2.64**	**0.001**
HOMA-IR						
PGS in largest decile	n = 1112	o = 2486	-0.11	0.058	-0.23, -0.00	0.05
Interaction middle deciles			0.13	0.066	0.01 0.27	0.05
Interaction smallest decile			**0.29**	**0.096**	**0.10, 0.48**	**0.002**
LDL-c						
PGS in largest decile	n = 1111	o = 2483	0.04	0.049	-0.05, 0.14	0.40
Interaction middle deciles			-0.02	0.051	-0.12, 0.08	0.67
Interaction smallest decile			-0.09	0.066	-0.22, 0.04	0.18
SBP						
PGS in largest decile	n = 1153	o = 2685	-1.36	0.657	-2.65, -0.07	0.04
Interaction middle deciles			1.20	0.716	-0.18, 2.63	0.09
Interaction smallest decile			1.39	0.916	-0.43, 3.16	0.13

Supplementary table 7 Sensitivity analysis of primary models without gestational duration included in models.

* Linear mixed model of cardiometabolic parameters adjusted for fetal sex, genetic principal components and age at assessment. Estimate SE was derived using 5000 repeats of a non-parametric bootstrap at the participant ID level. **Bold** indicates significant effects.

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, LDL-c: low-density lipoprotein cholesterol, SBP: Systolic blood pressure, PGS: Polygenic Score

Supplementary Table 8 Term born only.

	Participants	Observations	Estimate	boot se	Boot 95% CI	p-value
Body mass index						
PGS in largest decile	n =1054	o = 2460	-0.50	0.416	-1.30, 0.33	0.23
Interaction middle deciles			0.82	0.440	-0.05, 1.67	0.06
Interaction smallest decile			1.24	0.624	0.01, 2.44	0.05
HOMA-IR						
PGS in largest decile	n = 1018	o = 2290	-0.14	0.064	-0.28, -0.02	0.07
Interaction middle deciles			0.16	0.071	0.03, 0.31	0.02
Interaction smallest decile			0.24	0.125	-0.02, 0.47	0.06
LDL-c						
PGS in largest decile	n = 1017	o = 2285	0.00	0.051	-0.1, 0.1	0.96
Interaction middle deciles			0.02	0.054	-0.08, 0.13	0.70
Interaction smallest decile			-0.01	0.080	-0.16, 0.15	0.93
SBP						
PGS in largest decile	n = 1153	o = 2685	**-1.76**	**0.688**	**-3.12, -0.42**	**0.01**
Interaction middle deciles			1.43	0.743	0.04, 2.95	0.05
Interaction smallest decile			2.09	1.226	-0.33, 4.48	0.09

Supplementary table 8 Repeating the primary analysis with a term-born only cohort.

* Linear mixed model of cardiometabolic parameters adjusted for fetal sex, gestational duration, genetic principal components and age at assessment. Estimate SE was derived using 5000 repeats of a non-parametric bootstrap at the participant ID level. **Bold** indicates significant effects.

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, LDL-c: low-density lipoprotein cholesterol, SBP: Systolic blood pressure, PGS: Polygenic Score

Supplementary Table 9 Using measured birth weight to create phenotypic groupings

	Participants	Observations	Estimate	boot se	Boot 95% CI	p-value
Body mass index						
PGS in largest decile	n = 1150	o = 2675	0.48	0.358	-0.21, 1.19	0.18
Interaction middle deciles			-0.30	0.383	-1.06, 0.45	0.44
Interaction smallest decile			1.15	0.517	0.11, 2.14	0.03
HOMA-IR						
PGS in largest decile	n = 1112	o = 2486	-0.05	0.056	-0.16, 0.06	0.39
Interaction middle deciles			0.06	0.063	-0.06, 0.19	0.35
Interaction smallest decile			**0.32**	**0.119**	**0.09 0.55**	**0.007**
LDL-c						
PGS in largest decile	n = 1111	o = 2483	0.04	0.052	-0.13, 0.00	0.43
Interaction middle deciles			-0.02	0.054	-0.12, 0.09	0.73
Interaction smallest decile			-0.09	0.073	-0.24, 0.05	0.22
SBP						
PGS in largest decile	n = 1153	o = 2685	-0.35	0.61	-1.53, 0.870	0.57
Interaction middle deciles			0.17	0.66	-1.14, 1.46	0.80
Interaction smallest decile			0.06	0.98	-1.90, 1.96	0.95

Supplementary table 9 Repeating the primary analysis with phenotypic grouping based on the crude measured birth weight.

* Linear mixed model of cardiometabolic parameters adjusted for fetal sex, gestational duration, genetic principal components and age at assessment. Estimate SE was derived using 5000 repeats of a non-parametric bootstrap at the participant ID level. **Bold** indicates significant effects.

HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, LDL-c: low-density lipoprotein cholesterol, SBP: Systolic blood pressure, PGS: Polygenic Score