SHORT REPORT

Figures and figure supplements

Body mass index and adipose distribution have opposing genetic impacts on human blood traits

Christopher S Thom *et al*

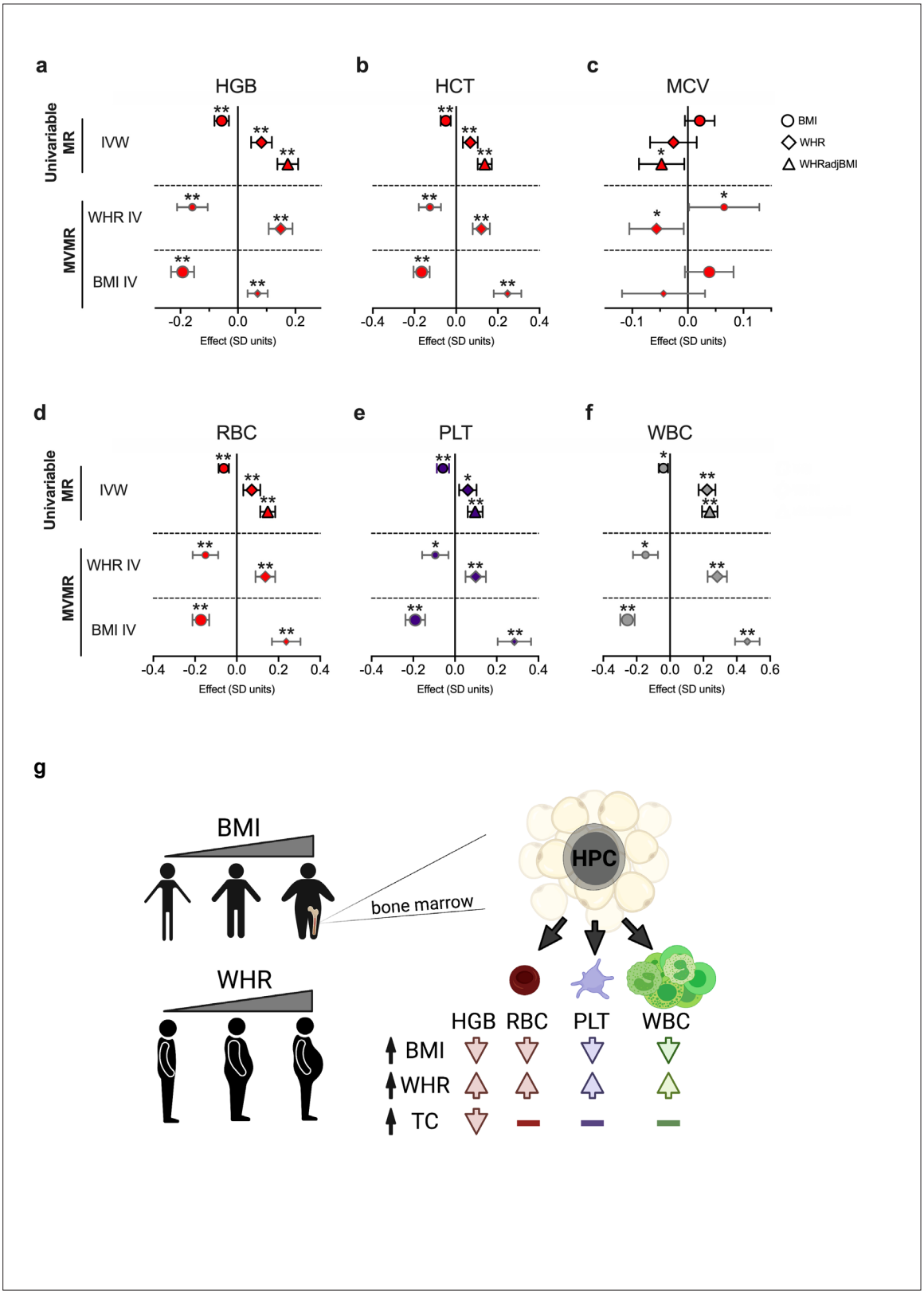


Figure 1. Body mass index (BMI) and waist-to-hip ratio (WHR) exert opposing effects on blood traits. (**a–f**) Effects of BMI, WHR, WHRadjBMI on (**a**) hemoglobin (HGB), (**b**) hematocrit (HCT), (**c**) mean corpuscular volume (MCV), (**d**) red blood cell count (RBC), (**e**) platelet count (PLT), or (**f**) white blood cell count (WBC). Shown in top panel are effects of BMI, WHR, or WHRadjBMI on HGB in univariable Mendelian randomization (MR) experiments by inverse variance weighted (IVW) method. Underneath univariable MR results, effects of BMI or WHR at 639 LD-independent WHR-associated single

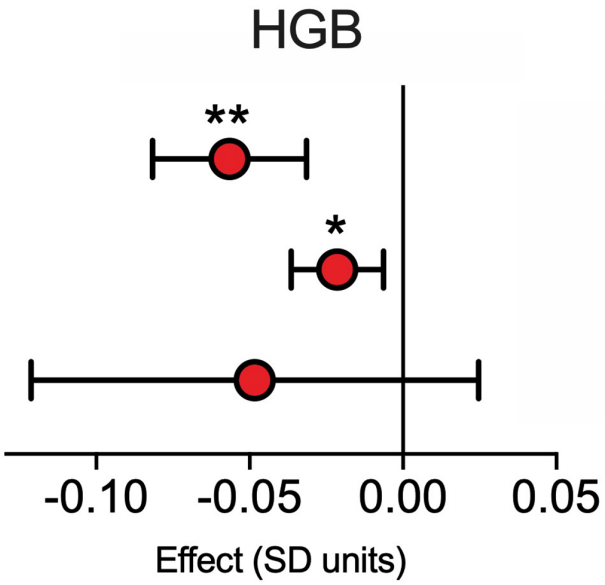
Figure 1 continued on next page

Figure 1 continued

nucleotide polymorphisms (SNPs) are shown. Bottom row of panels show effects of BMI or WHR at 1268 LD-independent BMI-associated SNPs. Effects are in SD units with 95% confidence intervals. *$p < 0.05$, **$p < 0.003$. (**g**) Schematic summarizing effects of indicated exposures on blood traits (created with https://BioRender.com).

a

Method	Effect (95% CI)	p-value
IVW	-0.057 (-0.081 - -0.031)	1.0×10^{-5}
WM	-0.050 (-0.074 - -0.026)	0.01
MR Egger	-0.048 (-0.121 - 0.025)	0.19
MR Egger (bias)		0.81



b

Method	Effect (95% CI)	p-value
IVW	-0.050 (-0.074 - -0.026)	4.4×10^{-5}
WM	-0.013 (-0.028 - 0.002)	0.09
MR Egger	-0.042 (-0.112 - 0.028)	0.24
MR Egger (bias)		0.80

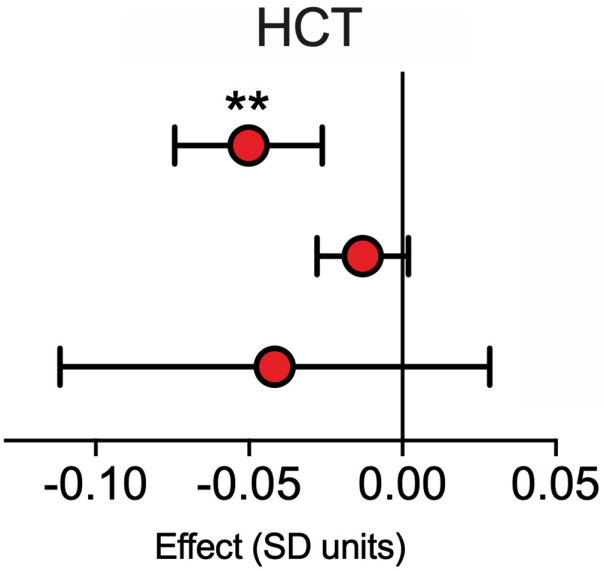


Figure 1—figure supplement 1. Genetically determined body mass index (BMI) decreases hemoglobin (HGB) and hematocrit (HCT) levels. (**a–b**) Effects of BMI on (**a**) HGB or (**b**) HCT by inverse variance weighted (IVW), weighted median (WM), or MR Egger methods. Effects are in standard deviation (SD) units. Error bars represent 95% confidence intervals. Insignificant MR Egger intercept p-values validate effect estimates. *$p < 0.05$.

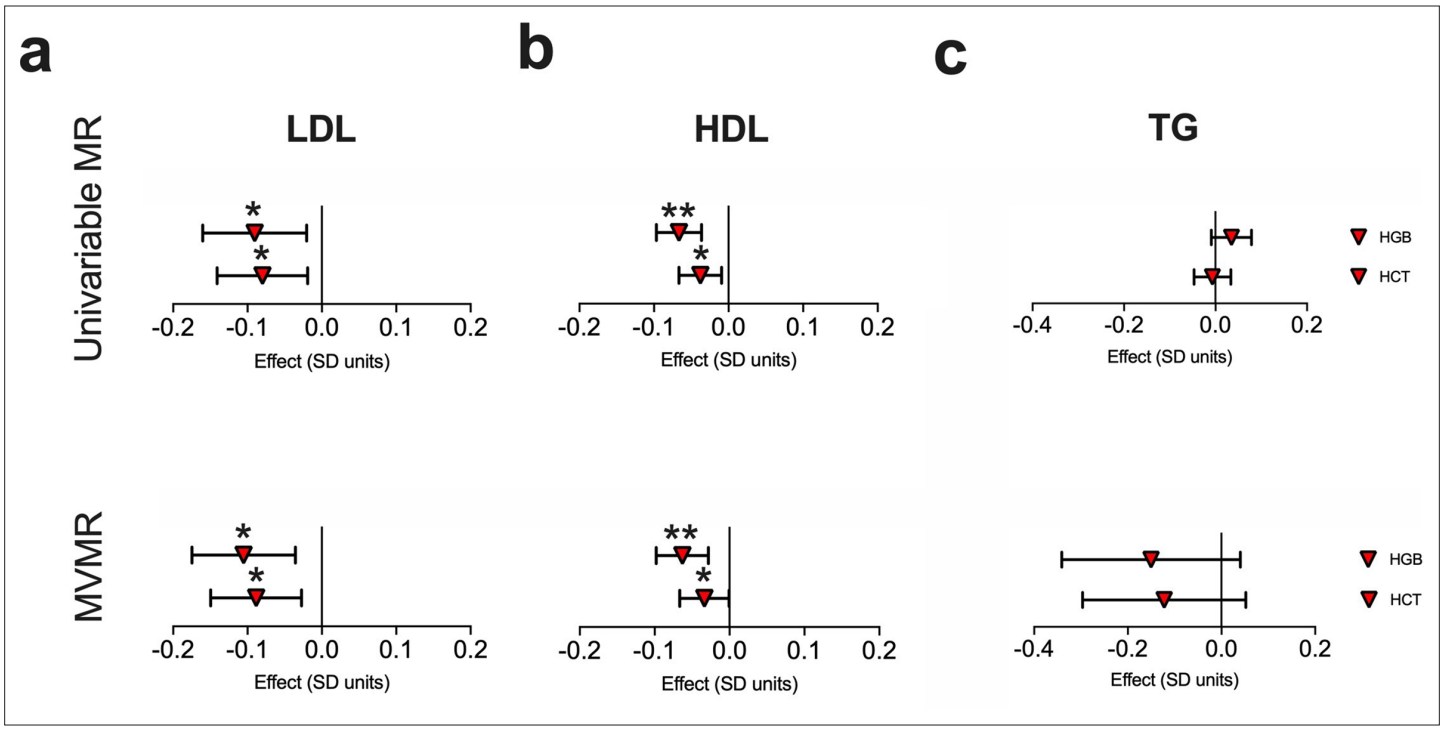
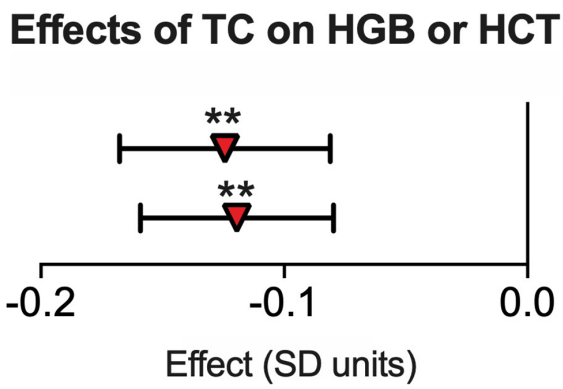


Figure 1—figure supplement 2. Effects of lipid fractions or triglyceride level (TG) on erythroid traits. (**a–c**) Effect sizes (standard deviation [SD] units) with 95% confidence intervals for (**a**) low density lipoprotein (LDL), (**b**) high density lipoprotein (HDL), or (**c**) TG, on erythroid traits (hemoglobin [HGB] or hematocrit [HCT]) by univariable Mendelian randomization (MR) (top) or multivariable MR (MVMR) (bottom). MVMR experiments adjusted for body mass index (BMI) effects. Shapes are centered at mean and error bars represent 95% confidence intervals. *$p < 0.05$, **$p < 0.003$.

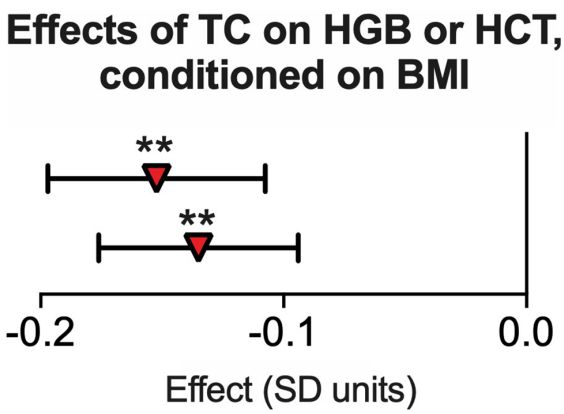
a

Outcome	Effect (95% CI)	p-value
HGB	-0.104 (-0.169 - -0.038)	2.0×10^{-3}
HCT	-0.103 (-0.164 - -0.042)	8.9×10^{-4}



b

Outcome	Effect (95% CI)	p-value
HGB	-0.127 (-0.195 - -0.059)	3.2×10^{-4}
HCT	-0.118 (-0.181 - -0.056)	2.9×10^{-4}



c

Outcome	Effect (95% CI)	p-value
HGB	-0.057 (-0.083 - -0.031)	1.4×10^{-5}
HCT	-0.051 (-0.075 - -0.026)	5.1×10^{-5}

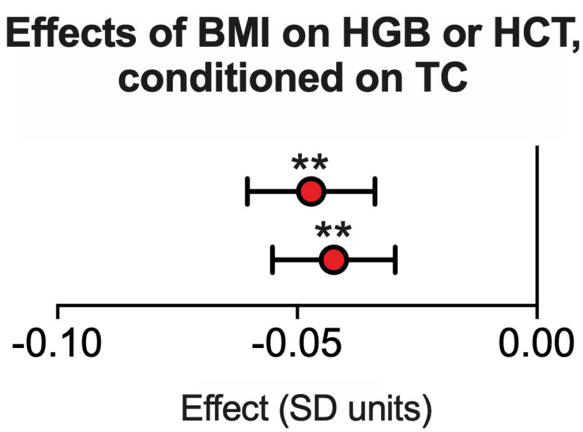


Figure 1—figure supplement 3. Total cholesterol (TC) decreases hemoglobin (HGB) and hematocrit (HCT) levels independent of body mass index (BMI) effects. (**a**) Effects of TC on HGB or HCT by inverse variance weighted (IVW) method. (**b**) Effects of TC on HGB or HCT by IVW after adjusting for BMI. (**c**) Effects of BMI on HGB or HCT by IVW after adjusting for TC. Effects are in standard deviation (SD) units. Error bars represent 95% confidence intervals. **$p < 0.003$.

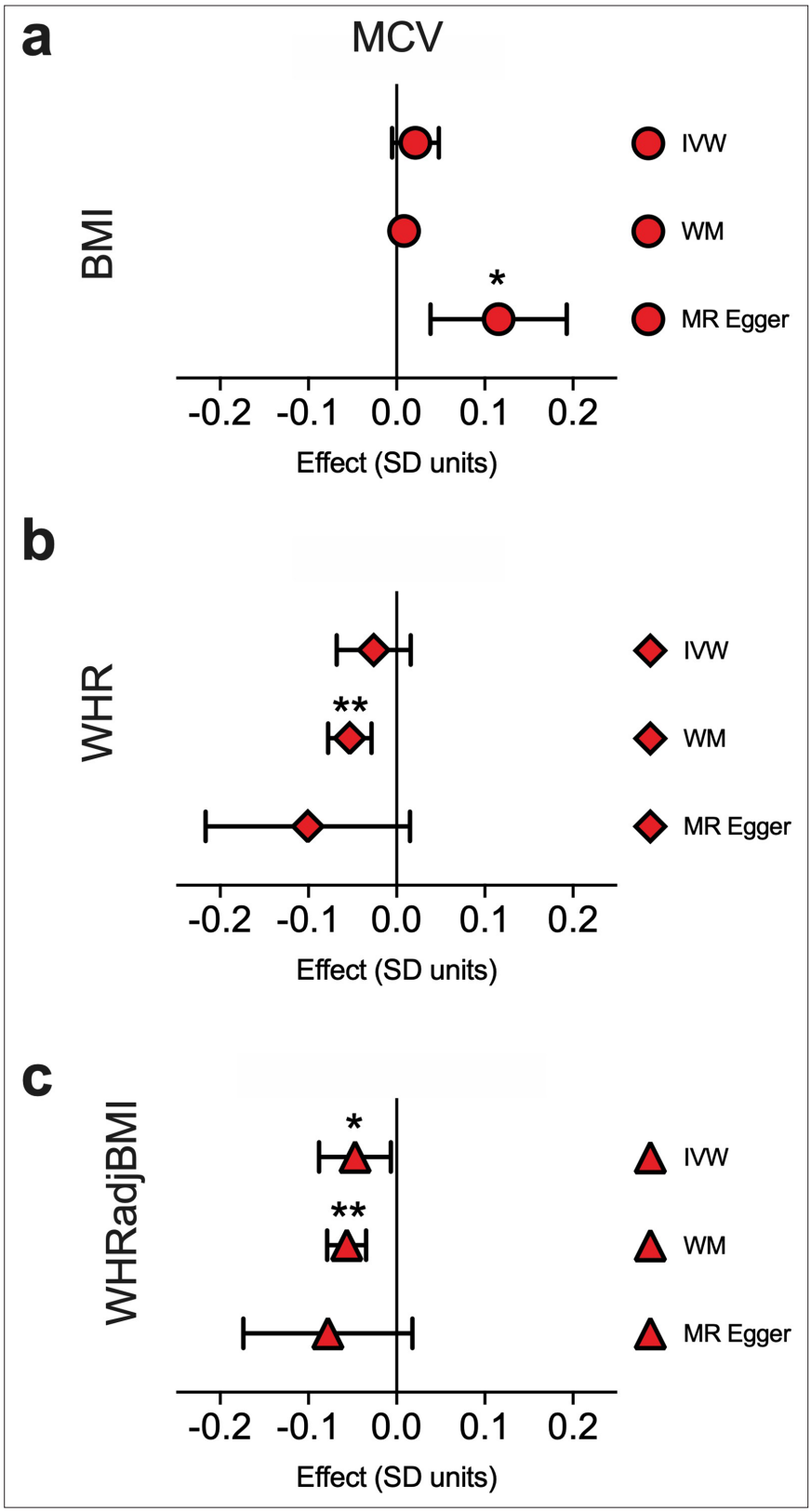


Figure 1—figure supplement 4. Effects of body mass index (BMI), waist-to-hip ratio (WHR), and WHRadjBMI on mean corpuscular volume (MCV) across Mendelian randomization (MR) methodologies. (**a–c**) Effects of (**a**) BMI, (**b**) WHR, or (**c**) WHRadjBMI on MCV by univariable MR. Shapes are centered at mean and error bars represent 95% confidence intervals. *$p < 0.05$, **$p < 0.003$.

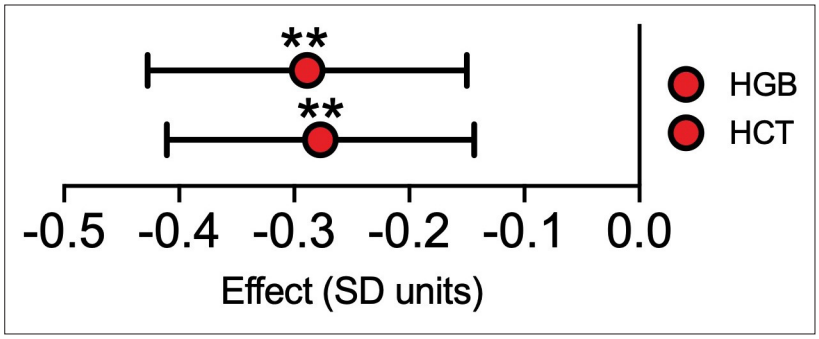


Figure 1—figure supplement 5. Effects of hemoglobin (HGB) or hematocrit (HCT) on body mass index (BMI). Two-sample Mendelian randomization (MR) experiments show effects (standard deviation [SD] units) with 95% confidence intervals for indicated erythroid traits on BMI by inverse variance weighted (IVW) method. **$p < 0.003$.

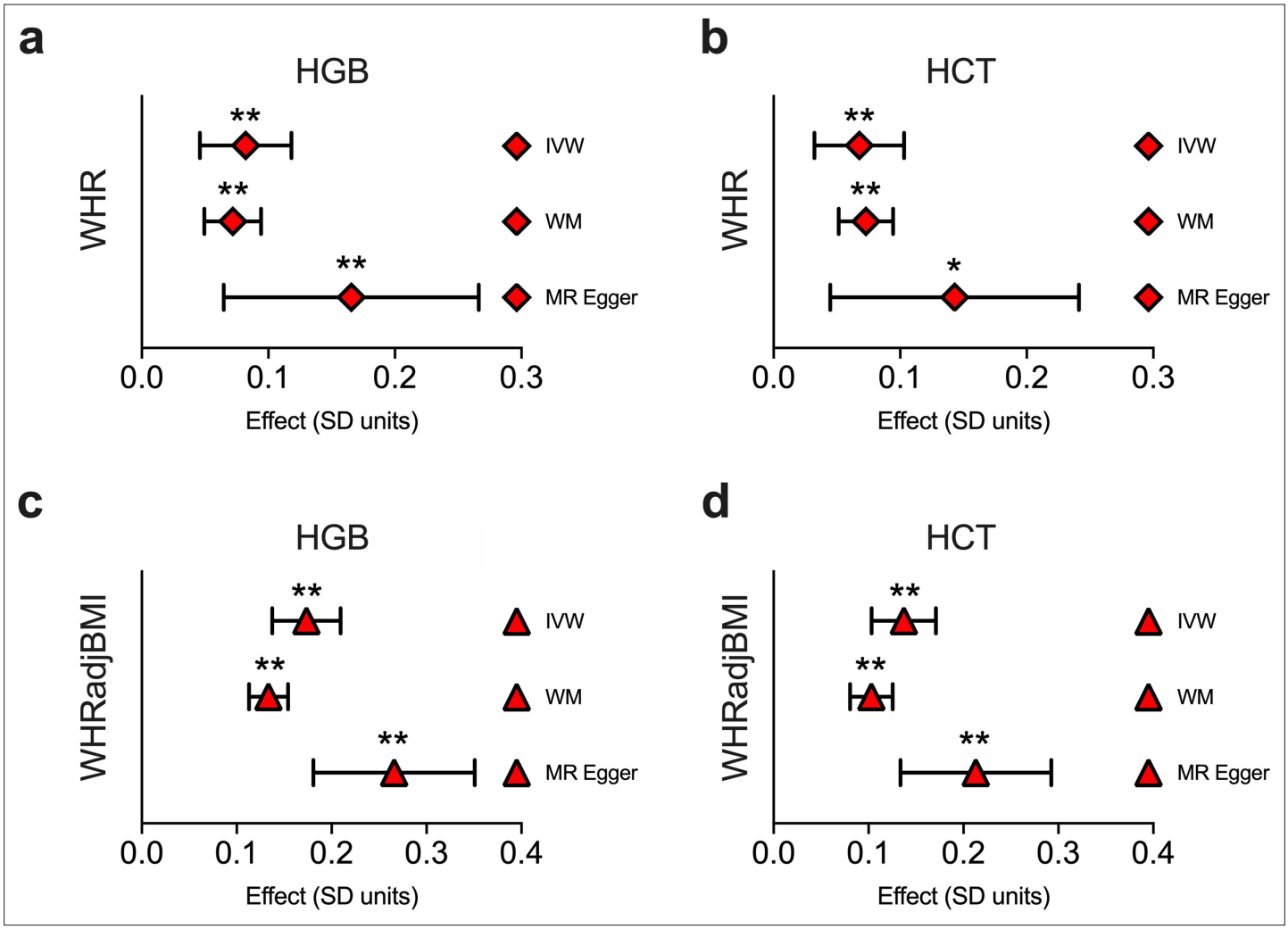


Figure 1—figure supplement 6. Effects of waist-to-hip ratio (WHR) and WHRadjBMI are consistent across Mendelian randomization (MR) methodologies. (**a–b**) By univariable MR, WHR exerts a positive effect on (**a**) hemoglobin (HGB) and (**b**) hematocrit (HCT). (**c–d**) In analogous experiments, WHRadjBMI exerts a positive effect on (**c**) HGB and (**d**) HCT. Effects were larger after WHR was adjusted for BMI at the individual level (WHRadjBMI). Shapes are centered at mean and error bars represent 95% confidence intervals. *p < 0.05, **p < 0.003.

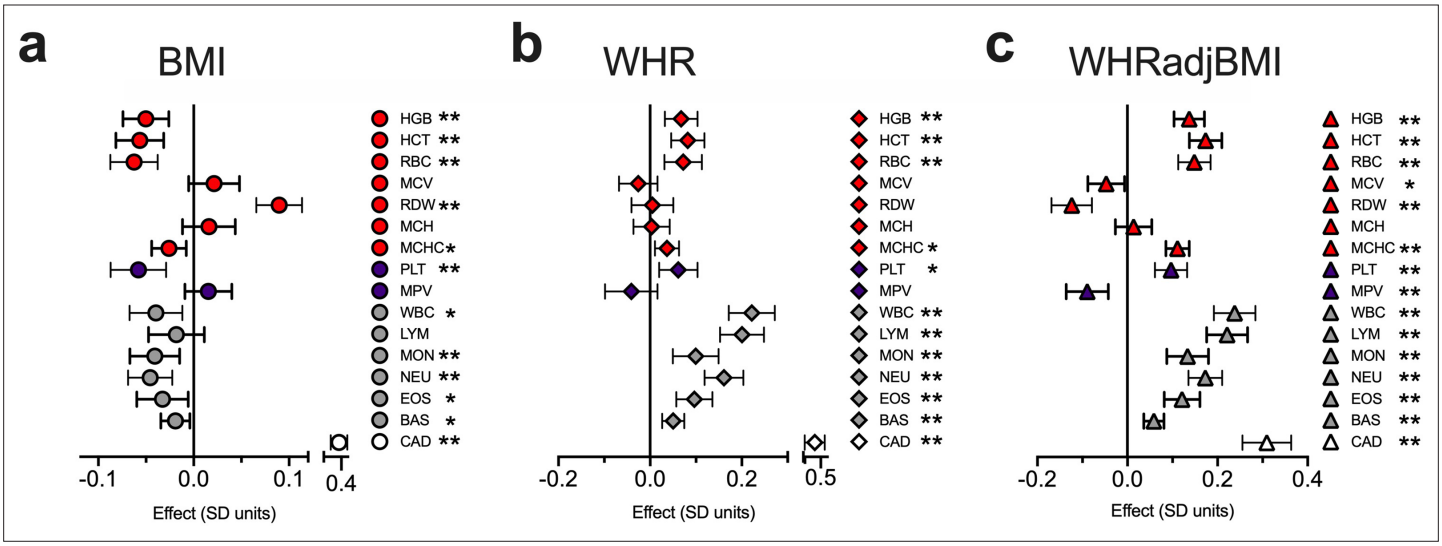


Figure 1—figure supplement 7. Genetically determined waist-to-hip ratio (WHR) and body mass index (BMI) exert opposing effects on multilineage quantitative blood traits, including red blood cell (RBC), platelet (PLT), and white blood cell (WBC) count. (**a–c**) Univariable Mendelian randomization (MR) experiments showing the effects of genetically determined (**a**) BMI, (**b**) WHR, or (**c**) WHRadjBMI on blood traits or coronary artery disease risk (CAD) by inverse variance weighted method. Shapes are centered at mean and error bars represent 95% confidence intervals. *p < 0.05, **p < 0.003.

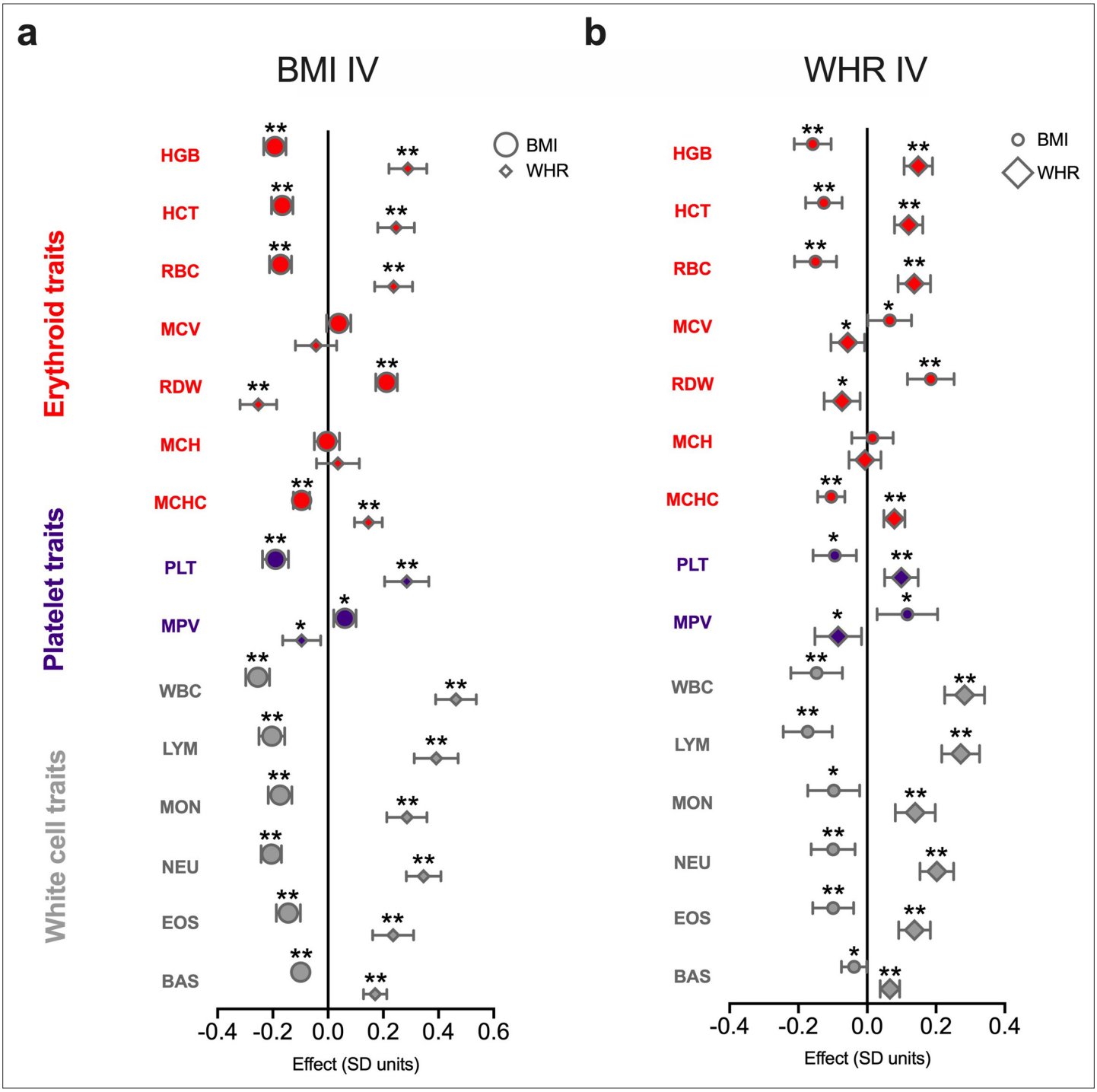


Figure 1—figure supplement 8. Effects of body mass index (BMI) and waist-to-hip ratio (WHR) on quantitative blood traits by multivariable Mendelian randomization (MVMR). (**a–b**) Effects of BMI or WHR, as quantified by MVMR using instrumental variables based on single nucleotide polymorphisms (SNPs) significant for (**a**) BMI or (**b**) WHR. Shapes are centered at mean and error bars represent 95% confidence intervals. *p < 0.05, **p < 0.003.

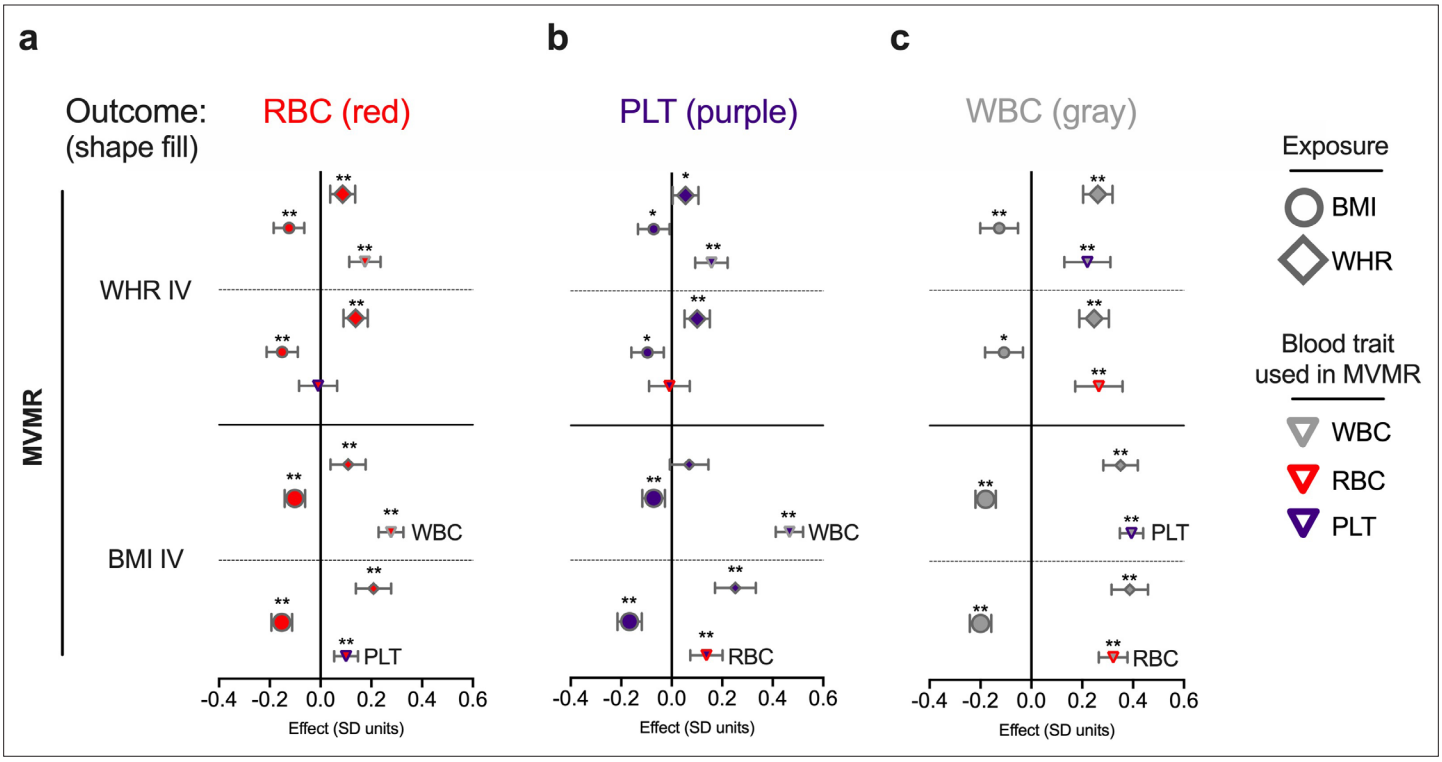


Figure 1—figure supplement 9. Effects of waist-to-hip ratio (WHR) and body mass index (BMI) on quantitative blood traits by multivariable Mendelian randomization (MVMR) after regressing out effects of other blood traits. (**a–c**) Effects of WHR, BMI, or WHRadjBMI on (**a**) red blood cell (RBC) count, (**b**) platelet (PLT) count, or (**c**) white blood cell (WBC) count. Left panel indicates trait used to create instrumental variables (IVs) (639 LD-independent statistically significant single nucleotide polymorphisms [SNPs] for WHR or 1268 SNPs for BMI). Exposure and mediator traits are listed at right. Within plots, large labels indicate effects from the IV trait with smaller symbols denoting potential mediating traits. Shapes are centered at mean and error bars represent 95% confidence intervals. *p < 0.05, **p < 0.003.

Figure 2. Conditional blood trait analysis based on body mass index (BMI) and/or waist-to-hip ratio (WHR) modifies interpretation of genomic loci that impact blood trait variation. (**a**) Violin plots showing the dispersion in effect size at genome-wide significant loci after adjusting erythroid traits (hemoglobin [HGB] or hematocrit [HCT]) for BMI, or WHR and BMI. **p < 0.0001 by F-test to compare variances. (**b**) Scatterplots depicting changes in effect sizes and p-values for all genome-wide significant sentinel loci before or after adjustment. Novel loci (red) had $p < 5 \times 10^{-8}$ only after adjustment

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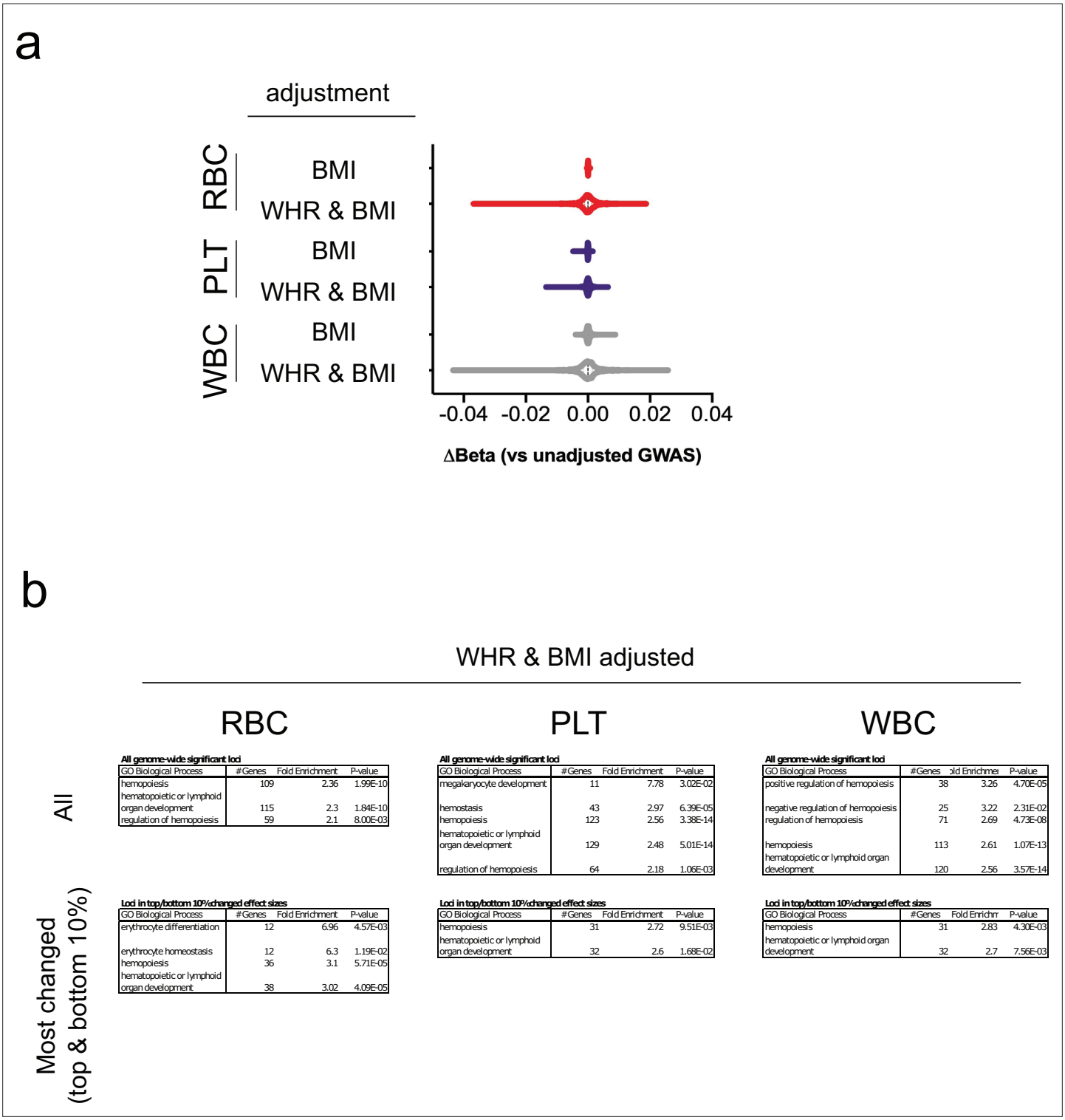
and represent new loci (not in LD with genome-wide significant single nucleotide polymorphisms [SNPs] before adjustment). Clarified loci (pink) are sentinel SNPs with $p < 5 \times 10^{-8}$ after adjustment and are in linkage disequilibrium with significant pre-adjustment SNPs. Missing loci (blue) are those with adjusted $p > 5 \times 10^{-8}$, which were significant pre-adjustment. Shared SNPs (gray) are sentinel SNPs before and after adjustment for the indicated factors. (**c**) After adjustment for WHR and BMI, the common coding SNP (rs145878042) in *RAPGEF3* significantly impacts HGB level. (**d**) Adjustment for WHR and BMI alters interpretation of SNP effects at the *RSPO3* locus, including more significant effects for new sentinel variant rs72959041 (unadjusted $p = 2.1 \times 10^{-10}$, adjusted $p = 3.4 \times 10^{-40}$). (**e**) Gene-based Manhattan plots for HGB, before or after BMI/WHR adjustment. (**f**) Gene ontology analyses for hematopoietic, mesenchymal, and vascular biological processes for HGB loci before and after mtCOJO adjustment for BMI and WHR. Significance reflects Fisher's exact test after multiple testing.



All genome-wide significant loci

GO Biological Process	#Genes	Fold Enrichment	P-value
hemopoiesis	109	2.36	1.99E-10
hematopoietic or lymphoid organ development	115	2.3	1.84E-10
regulation of hemopoiesis	59	2.1	8.00E-03

Loci in top/bottom 10% changed effect sizes

GO Biological Process	#Genes	Fold Enrichment	P-value
erythrocyte differentiation	12	6.96	4.57E-03
erythrocyte homeostasis	12	6.3	1.19E-02
hemopoiesis	36	3.1	5.71E-05
hematopoietic or lymphoid organ development	38	3.02	4.09E-05

All genome-wide significant loci

GO Biological Process	#Genes	Fold Enrichment	P-value
megakaryocyte development	11	7.78	3.02E-02
hemostasis	43	2.97	6.39E-05
hemopoiesis	123	2.56	3.38E-14
hematopoietic or lymphoid organ development	129	2.48	5.01E-14
regulation of hemopoiesis	64	2.18	1.06E-03

Loci in top/bottom 10% changed effect sizes

GO Biological Process	#Genes	Fold Enrichment	P-value
hemopoiesis	31	2.72	9.51E-03
hematopoietic or lymphoid organ development	32	2.6	1.68E-02

All genome-wide significant loci

GO Biological Process	#Genes	Fold Enrichment	P-value
positive regulation of hemopoiesis	38	3.26	4.70E-05
negative regulation of hemopoiesis	25	3.22	2.31E-02
regulation of hemopoiesis	71	2.69	4.73E-08
hemopoiesis	113	2.61	1.07E-13
hematopoietic or lymphoid organ development	120	2.56	3.57E-14

Loci in top/bottom 10% changed effect sizes

GO Biological Process	#Genes	Fold Enrichment	P-value
hemopoiesis	31	2.83	4.30E-03
hematopoietic or lymphoid organ development	32	2.7	7.56E-03

Figure 2—figure supplement 1. Conditional blood trait analysis based on body mass index (BMI) and/or waist-to-hip ratio (WHR) modifies interpretation of genomic loci that impact variation in red blood cell (RBC), platelet (PLT), and white blood cell (WBC) counts. (**a**) Violin plots show adjustment for indicated trait(s) via mtCOJO (BMI and/or WHR) modifies effect sizes at genome-wide significant blood trait loci. WHR disperses effect sizes more than BMI adjustment alone. (**b**) After mtCOJO adjustment for WHR and BMI, significant single nucleotide polymorphisms (SNPs) and nearby genes excluded some blood cell-specific gene ontology pathways. Shown are significant pathways related to hemopoiesis/hematopoiesis, erythrocyte biology, or megakaryocyte/platelet biology (Fisher's exact test $p < 0.05$ after multiple testing).

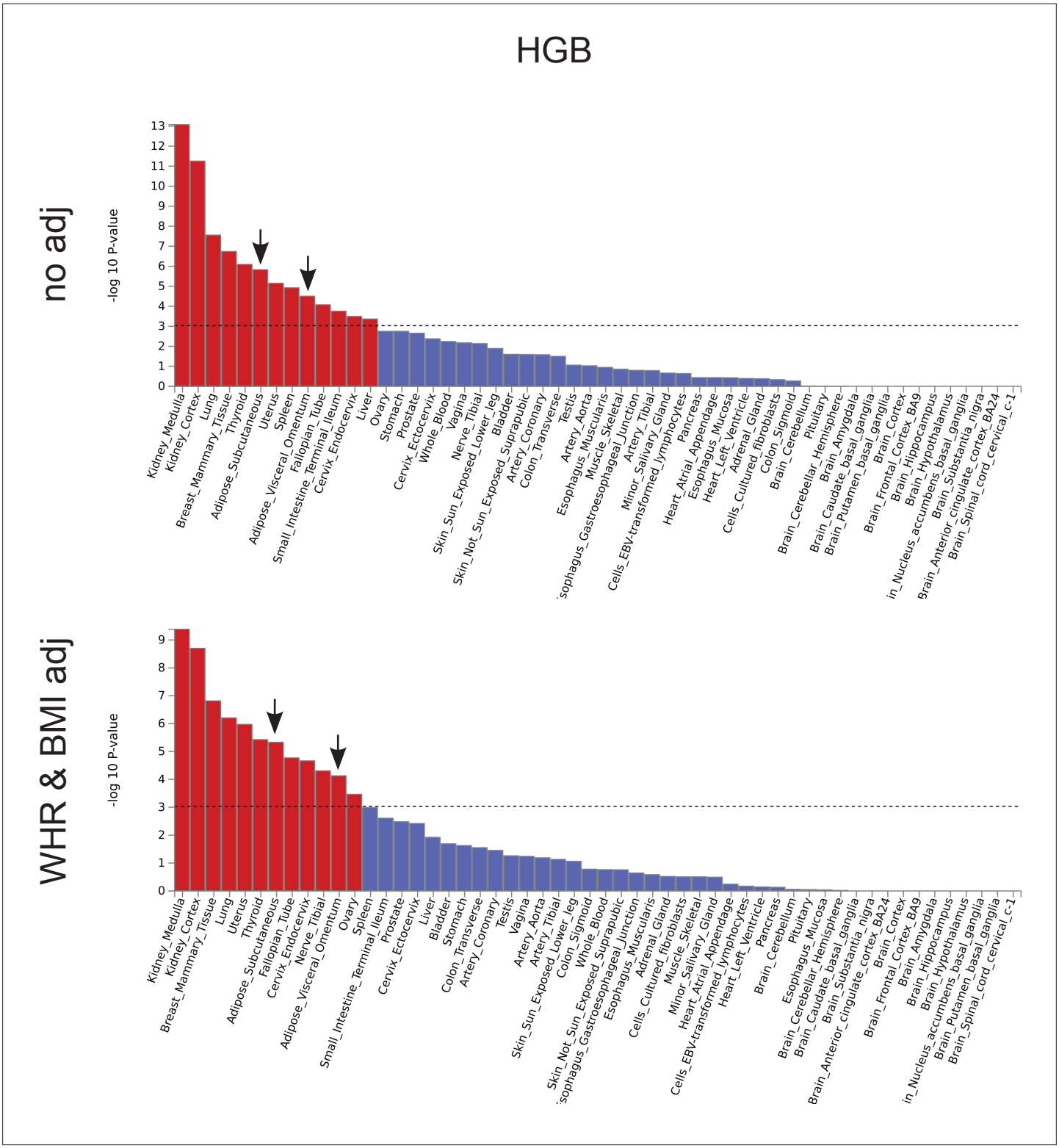


Figure 2—figure supplement 2. MAGMA tissue enrichment analyses for original and body mass index (BMI)/waist-to-hip ratio (WHR)-adjusted hemoglobin (HGB) data. Significantly enriched adipose populations are identified by arrows in each plot.

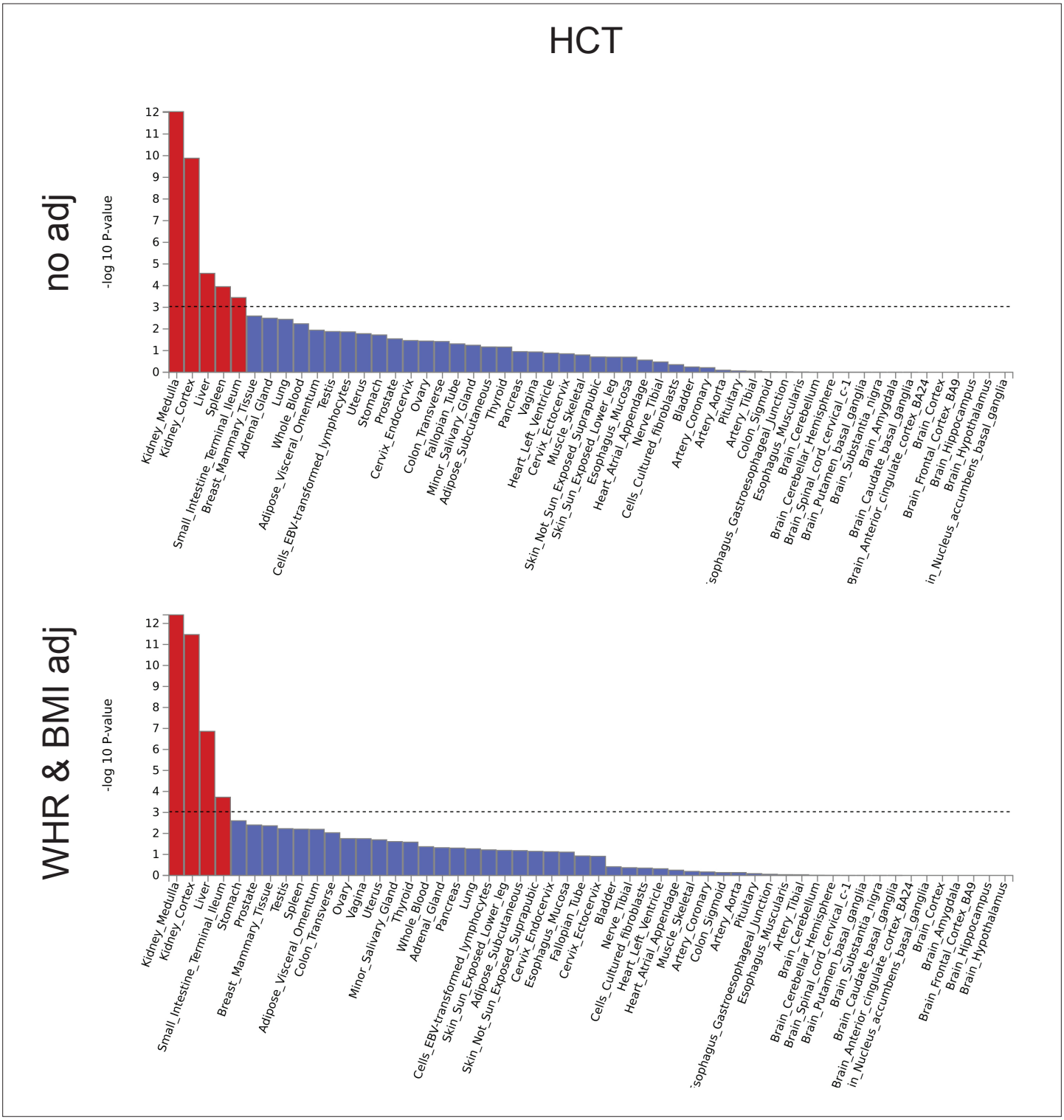


Figure 2—figure supplement 3. MAGMA tissue enrichment analyses for original and body mass index (BMI)/waist-to-hip ratio (WHR)-adjusted hematocrit (HCT) data. There were no significantly enriched adipose populations.

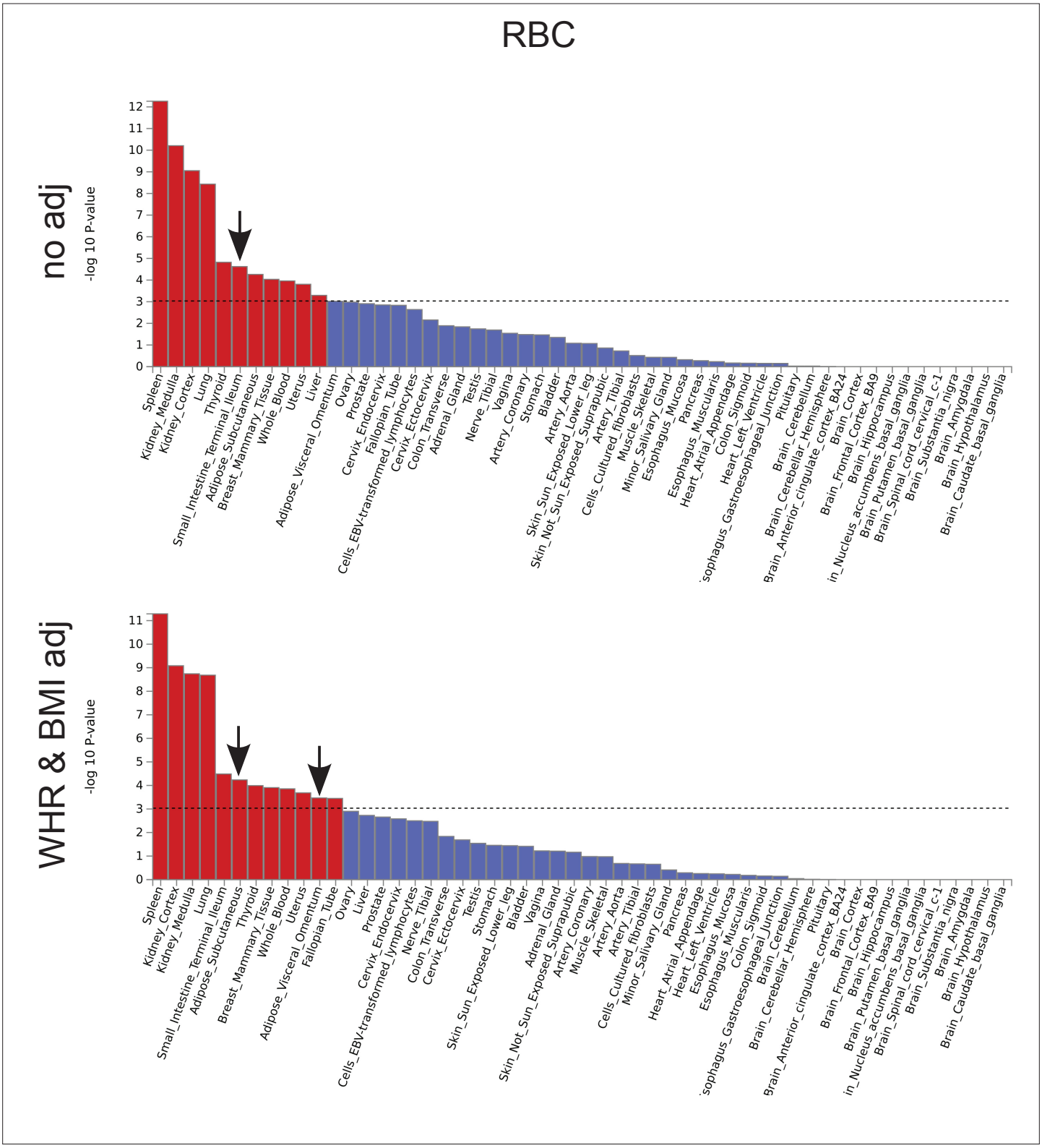


Figure 2—figure supplement 4. MAGMA tissue enrichment analyses for original and body mass index (BMI)/waist-to-hip ratio (WHR)-adjusted red blood cell count (RBC) data. Significantly enriched adipose populations are identified by arrows in each plot.

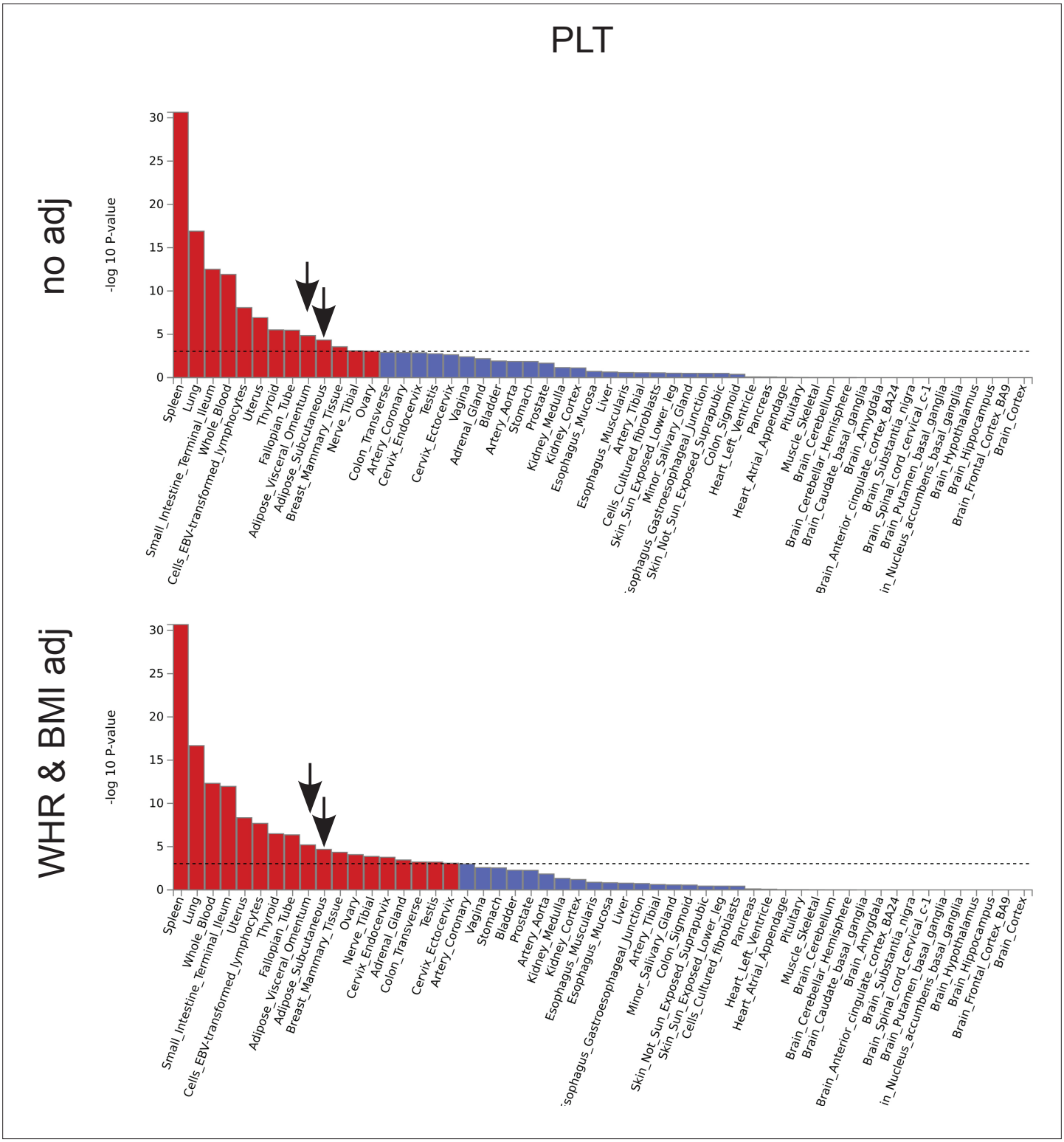


Figure 2—figure supplement 5. MAGMA tissue enrichment analyses for original and body mass index (BMI)/waist-to-hip ratio (WHR)-adjusted platelet count (PLT) data. Significantly enriched adipose populations are identified by arrows in each plot.

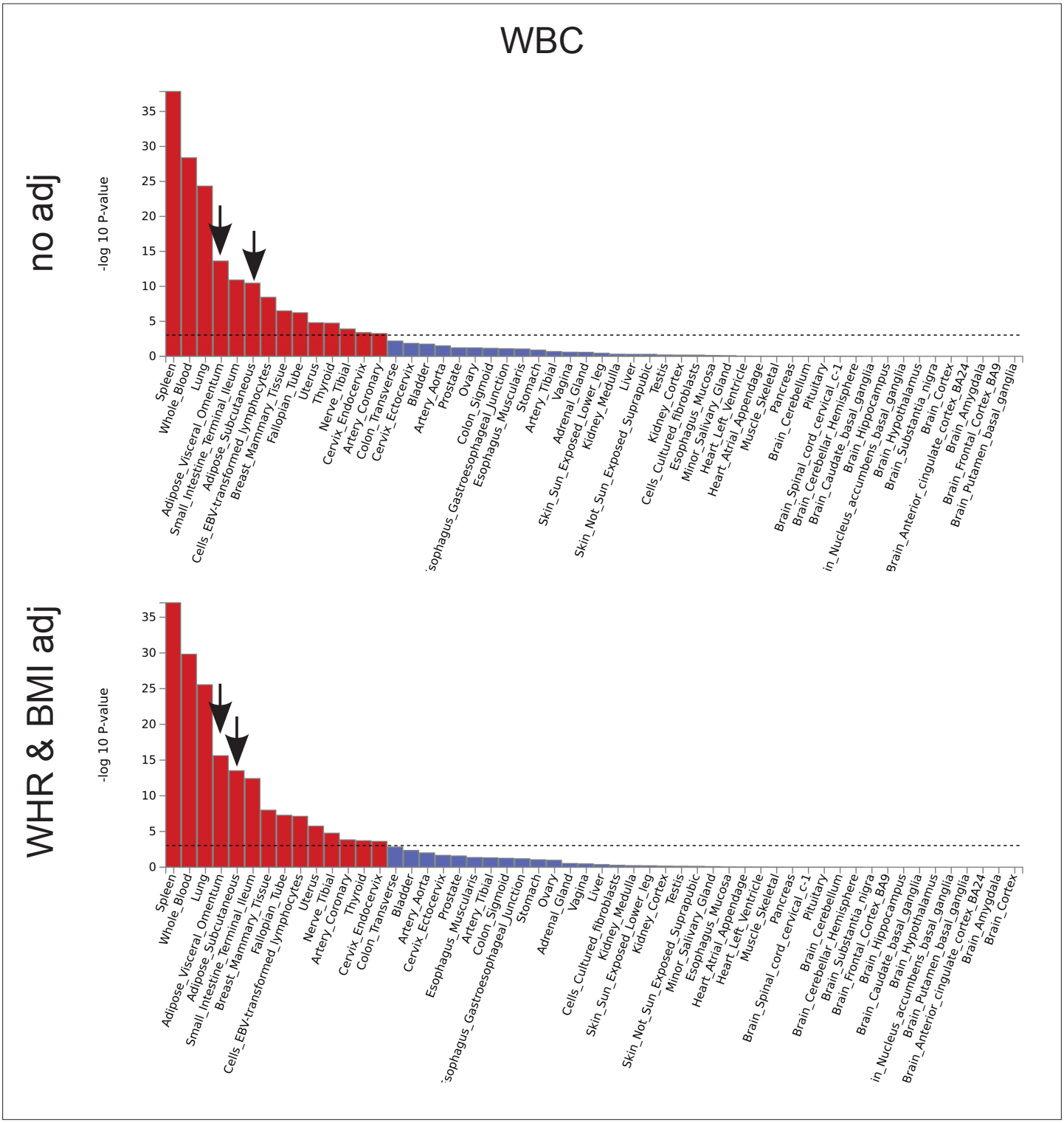


Figure 2—figure supplement 6. MAGMA tissue enrichment analyses for original and body mass index (BMI)/waist-to-hip ratio (WHR)-adjusted white blood cell count (WBC) data. Significantly enriched adipose populations are identified by arrows in each plot.