

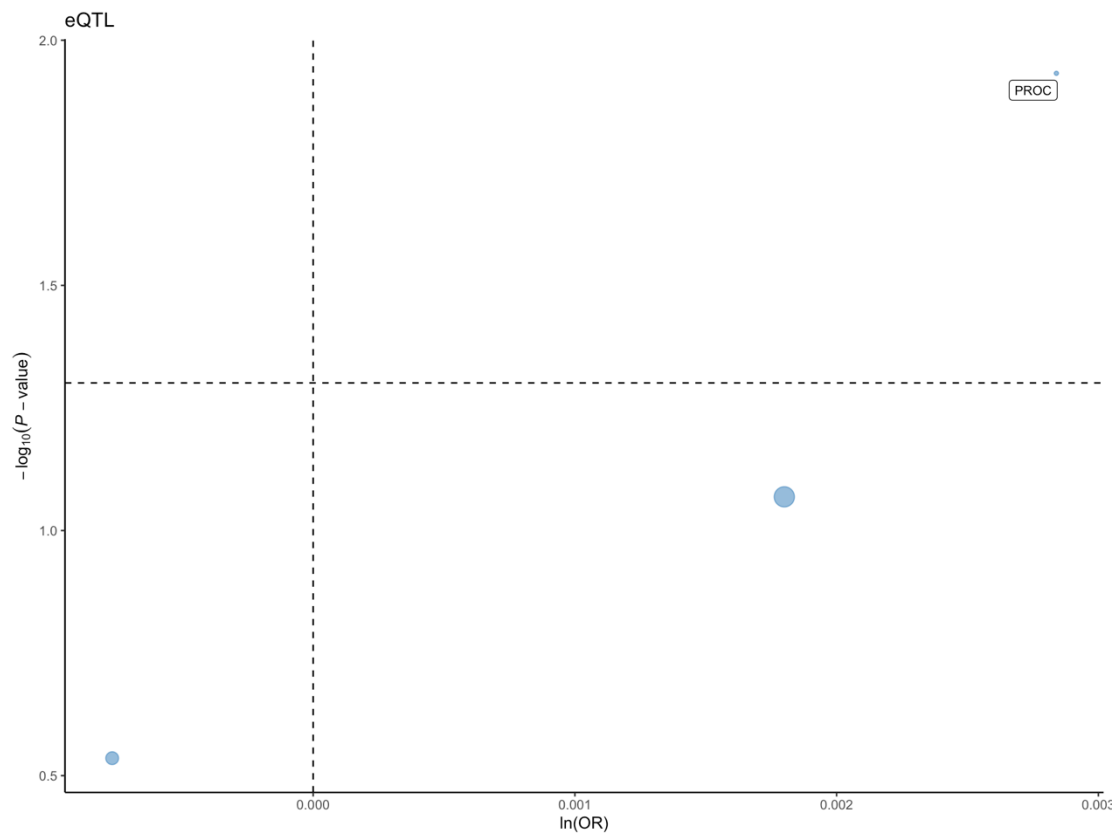
Supplementary Figure S1. Leaving out each SNP and funnel plot of PC with DVT

```
> STD
      id.exposure      id.outcome      exposure
1 ebi-a-GCST90019423 ebi-a-GCST90038615 Vitamin K-dependent protein C measurement || id:ebi-a-GCST90019423
      outcome snp_r2.exposure snp_r2.outcome correct_causal_direction steiger_pval
1 Deep venous thrombosis || id:ebi-a-GCST90038615      0.1492089      0.0001839076      TRUE      0
```

Supplementary Figure S2. Steiger Test for PC and DVT

```
> res_OR
      id.exposure      exposure
1 ebi-a-GCST90019417 Vitamin K-dependent protein S measurement || id:ebi-a-GCST90019417
2 ebi-a-GCST90019423 Vitamin K-dependent protein C measurement || id:ebi-a-GCST90019423
3 prot-a-2695      Antithrombin-III || id:prot-a-2695
      id.outcome      outcome nsnp      b      se
1 ebi-a-GCST90038615 Deep venous thrombosis || id:ebi-a-GCST90038615      4 -0.0041311605 0.002421867
2 ebi-a-GCST90038615 Deep venous thrombosis || id:ebi-a-GCST90038615      3 0.0048111170 0.002040126
3 ebi-a-GCST90038615 Deep venous thrombosis || id:ebi-a-GCST90038615      1 -0.0007103609 0.004766681
      pval      lo_ci      up_ci      or      or_lci95      or_uci95
1 0.08805001 -0.0088780207 0.0006156996 0.9958774 0.9911613 1.000616
2 0.01836156 0.0008124704 0.0088097635 1.0048227 1.0008128 1.008849
3 0.88153287 -0.0100530560 0.0086323342 0.9992899 0.9899973 1.008670
>
```

Supplementary Figure S3. MVMR analysis of protein C, protein S and AT-III on DVT



Supplementary Figure S4. Bubble plot shows only the PROC gene (encoding protein C) in the upper right quadrant, indicating that it has a positive relationship with the outcome (eqtl-a-ENSG00000115718 against ebi-a-GCST90038615)

Supplementary Table SI. Characteristics of contributing studies

Exposures	Dataset	Sample size	No. SNPs	Population
Vitamin K-dependent protein S measurement	ebi-a-GCST90019417	10,708	15,567,420	European
Vitamin K-dependent protein C measurement	ebi-a-GCST90019423	10,708	15,567,760	European
Antithrombin-III	prot-a-2695	3,301	10,534,735	European
Major outcome				
DVT	ebi-a-GCST90038615	484,598	9,587,836	European
Secondary outcome				
Self-reported DVT	ukb-a-65	337,159	10,894,596	European
BMI	ukb-b-19953	461,460	9,851,867	European

Supplementary Table SII. Two-sample Mendelian randomization estimations showing the effect of protein C on DVT

Methods	Exposure	Odds ratio	P-value	PRESSO	Q-statistics
MR Egger	ebi-a-GCST90019423	1.009 (1.003–1.014)	0.190	0.075	0.100
Weighted median		1.005 (1.003–1.007)	1.085e-06		
Inverse-variance weighted		1.005 (1.001–1.010)	0.022		
Simple mode		1.000 (0.985–1.006)	0.503		
Weighted mode		1.006 (1.004–1.009)	0.029		

Supplementary Table SIII. Characteristics of contributing studies in the mediation study

Exposures	Dataset	Sample size	No. SNPs	Population
BMI	ebi-a-GCST90019417	10,708	15,567,420	European
Smoking	ebi-a-GCST90019423	10,708	15,567,760	European
SBP	ieu-b-38	757,601	7,088,083	European
DM	ebi-a-GCST006867	655,666	5,030,727	European
Obesity	ebi-a-GCST90038615	484,598	9,587,836	European

Data source is listed in supplementary files.

Supplementary Table SIV. Two-sample Mendelian randomization estimations showing the effect of protein C on BMI

Methods	Exposure	Odds ratio	P-value	PRESSO	Q-statistics
MR Egger	ebi-a-GCST90019423	0.974 (0.933–1.016)	3.476 e-01	0.085	0.200
Weighted median		0.973 (0.964–0.982)	1.317e-08		
Inverse-variance weighted		0.976 (0.957–0.995)	1.403e-02		
Simple mode		0.974 (0.962–0.986)	2.616e-02		
Weighted mode		0.973 (0.963–0.983)	1.299e-02		

Supplementary Table SV. Two-sample Mendelian randomization estimations showing the effect of BMI on DVT

Methods	Exposure	Odds ratio	<i>P</i> -value	PRESSO	Q-statistics
MR Egger	ukb-b-19953	1.004 (0.999–1.009)	0.144	0.067	0.080
Weighted median		1.003 (1.000–1.006)	0.063		
Inverse-variance weighted		1.003 (1.001–1.005)	0.000		
Simple mode		1.006 (0.997–1.014)	0.199		
Weighted mode		1.003 (0.997–1.008)	0.329		

Supplementary Table SVI. Multivariable MR analysis estimating the effect of relative protein C, protein S and AT-III on DVT

Item	beta	Odds ratio (95% CI)	<i>P</i> -value
IVW			
Vitamin K-dependent protein C	0.003	1.003 (1.001–1.004)	0.0002
BMI	0.004	1.004 (1.002–1.006)	0.0002