

**Supplementary Table 1** - Demographic and clinical characteristics for individuals in the UK Biobank VTE GWAS analysis

	VTE Cases	VTE Controls
N Individuals	14,222	372,102
Age $\pm$ SD, years	60.3 $\pm$ 7.1	57.3 $\pm$ 7.9
Male, n (%)	6,374 (44.8%)	172,438 (46.3%)
Former Smoker, n (%)	5,517 (38.8%)	130,965 (35.2%)
Current Smoker, n (%)	1,767 (12.4%)	37,878 (10.2%)
Hypertension, n (%)	6,441 (45.3%)	119,426 (32.1%)
Diabetes, n (%)	1,436 (10.1%)	16,519 (4.4%)
Hyperlipidemia, n (%)	3,778 (26.6%)	63,964 (17.2%)
Body-Mass Index $\pm$ SD, kg/m <sup>2</sup>	29.0 $\pm$ 5.5	27.3 $\pm$ 4.7
Variants Included in Analysis	13,599,453	

Abbreviations: GWAS, Genome-wide Association Study; SD, Standard Deviation; VTE, Venous Thromboembolism

**Supplementary Table 2** - Demographic and clinical characteristics for veterans in the MVP VTE GWAS analysis

	<b>White</b>		<b>Black</b>		<b>Hispanic</b>	
	VTE Cases	VTE Controls	VTE Cases	VTE Controls	VTE Cases	VTE Controls
N Veterans	8,929	181,337	2,261	49,400	654	21,214
Age $\pm$ SD, years	71.0 $\pm$ 11.3	68.0 $\pm$ 12.8	66.1 $\pm$ 11.5	61.5 $\pm$ 11.6	66.8 $\pm$ 13.0	60.5 $\pm$ 14.7
Male, n (%)	8,490 (95.0%)	168,161 (92.7%)	2,402 (91.6%)	42,722 (86.5%)	613 (93.7%)	19,258 (90.8%)
Current Smoker, n (%)	1,697 (19.0%)	32,814 (18.1%)	680 (25.9%)	13,505 (27.3%)	77 (11.8%)	3,399 (16.0%)
Former Smoker, n (%)	5,122 (57.4%)	98,706 (54.4%)	1,244 (47.5%)	21,217 (42.9%)	398 (60.9%)	10,317 (48.6%)
Diabetes, n (%)	3,742 (41.9%)	62,283 (34.3%)	1,387 (52.9%)	20,857 (42.2%)	342 (52.3%)	8,431 (39.7%)
Hyperlipidemia, n (%)	3,812 (42.7%)	80,417 (44.3%)	1,057 (40.3%)	19,515 (39.5%)	291 (44.5%)	8,118 (38.3%)
Body-Mass Index $\pm$ SD, kg/m <sup>2</sup>	31.5 $\pm$ 6.7	30.3 $\pm$ 5.9	31.3 $\pm$ 7.0	30.5 $\pm$ 6.2	32.2 $\pm$ 7.0	30.8 $\pm$ 5.8
Variants Included in Analysis	19,972,400		31,960,759		28,192,968	

Abbreviations: GWAS, Genome-wide Association Study; MVP, Million Veteran Program; SD, Standard Deviation; VTE, Venous Thromboembolism

## Supplementary Note

### 1. Supplementary Results

Of the 22 novel loci, 6 contained at least one gene implicated in the coagulation cascade or platelet function (**Supplementary Table 5**). Three previously reported suggestive ( $5.0 \times 10^{-8} < P < 0.05$ ) VTE associations at the *GP6*<sup>4</sup>, *STXBP5*<sup>5</sup>, and *VWF*<sup>5</sup> loci were now observed at genome-wide significance. Across all 33 VTE loci (11 known and 22 novel), 31 were directionally consistent across whites, blacks, and Hispanics in MVP and 22 demonstrated at least nominal significance ( $P < 0.05$ ) in blacks and 7 in Hispanics (**Supplementary Table 13**). 2 known and 4 novel VTE loci demonstrated moderate heterogeneity across the three ethnicities ( $50\% < \text{heterogeneity } I^2 < 75\%$ ), but remained below our pre-specified heterogeneity threshold of 75%. In addition, we found no evidence of association for 3 African specific variants previously reported in an analysis of 393 African ancestry VTE cases that lacked independent replication<sup>6</sup> (**Supplementary Table 14**). In a conditional analysis using combined summary statistics from MVP Europeans and UK Biobank, we identified an additional 15 independent VTE variants across the 33 loci (**Supplementary Table 15**).

Understanding the full spectrum of phenotypic consequences of a given variant may reveal the mechanism by which a variant or gene leads to disease. Termed a phenome-wide association study (PheWAS), this approach examines the association of a risk variant across a range of phenotypes<sup>7,8</sup>. Using a median of 63 distinct EHR-derived ICD-9/10 diagnosis codes per participant and available clinical laboratory data, we tested each of the 30 autosomal VTE lead risk variants across 1,249 disease phenotypes, symptoms, injuries, and 4 continuous cardiometabolic traits. We found that several of the VTE risk variants demonstrated a range of pleiotropy (**Supplementary Table 16**). For example, rs2074492 near *HLA-C*, was associated with multiple autoimmune diseases including an increased risk for celiac disease, a disorder previously associated with a greater risk of developing VTE<sup>9</sup>. Interestingly, 4 of the VTE risk loci demonstrated known associations with LDL cholesterol<sup>10-12</sup> (*MYRF*, *HLA-C*, *ABO*, and *SLC44A2*), and 2 with HDL (high-density lipoprotein) cholesterol/triglycerides<sup>10,11</sup> (*MYRF*, *PEPD*). In total, we identified 142 statistically significant ( $P < 1.1 \times 10^{-6}$ ) PheWAS associations across the 30 genetic variants. Results of a PheWAS of the PRS<sub>VTE</sub> in MVP are also shown in **Supplementary Table 16**.

Next, we sought to better understand how DNA sequence variants might differ in their contribution to vascular disease risk in the arterial and venous territories. Analysis of shared heritability provides a mechanism to better understand the relationship of common variant risk across phenotypes<sup>3,13</sup>. Using linkage disequilibrium score regression<sup>3</sup>, we examined the genetic correlation between VTE and i) coronary artery disease (CAD), ii) peripheral artery disease (PAD), and iii) large artery stroke (LAS). We used summary statistics from the European UK Biobank VTE analysis, data from a European MVP release 2.1 PAD analysis<sup>14</sup>, summary data of 60,801 CAD cases and 123,504 controls from the CARDIoGRAMplusC4D consortium<sup>15</sup>, and 6,688 LAS cases and 454,450 controls from the 2018 MEGASTROKE analysis<sup>16</sup>. We noted a stronger positive correlation between VTE and PAD ( $r_g = 0.47$ ,  $P = 2.0 \times 10^{-15}$ ) than for VTE and CAD ( $r_g = 0.27$ ,  $P = 1.2 \times 10^{-7}$ ) or VTE and LAS ( $r_g = 0.35$ ,  $P = 0.02$ , **Supplementary**

**Fig. 7)**, suggesting that common variant risk links thrombotic complications across venous and arterial beds, but more greatly with peripheral vasculature. In a sensitivity analysis, the correlation between VTE and myocardial infarction (MI) was similar in direction and magnitude as that for VTE-CAD (VTE-MI  $r_g = 0.29$ ,  $P = 2.2 \times 10^{-7}$ ). Association results for the 30 autosomal genome-wide lead VTE risk variants for PAD, CAD, and LAS in the MVP, CARDIoGRAMplusC4D, and MEGASTROKE analyses, respectively, are shown in **Supplementary Table 17**.

We then examined whether the identified VTE risk variants were associated with changes in protein concentrations in circulating plasma and queried recently published protein quantitative trait loci (pQTL) data derived from the plasma samples of 3,301 participants of the INTERVAL study<sup>2,17</sup>. We observed 102 pQTL associations in human plasma at genome-wide significance ( $P < 5 \times 10^{-8}$ , **Supplementary Table 18**) including 5 VTE lead variant-protein associations directly related to the coagulation cascade (**Supplementary Table 19**). VTE risk alleles were associated with decreased concentration of tissue factor pathway inhibitor (TFPI), and increased concentrations of plasminogen activator-inhibitor 1 (PAI-1), Factor VIII (F8), Factor X (F10) and its active form, Factor Xa. In each case, the VTE risk allele was associated with changes in protein concentration resulting in a pro-coagulant effect on the coagulation cascade.

We then attempted to identify causal VTE variants through a fine-mapping analysis leveraging our multi-ethnic summary statistics and the MR-MEGA software<sup>18</sup>. After excluding chromosome X and the major histocompatibility complex because of the complex LD structures across the regions, we constructed credible sets for 29 VTE loci that in aggregate account for  $\geq 99\%$  of the posterior probability of driving the VTE association based on the UK Biobank and trans-ethnic MVP summary statistics. At 12 VTE signals, the credible set included 6 or fewer VTE associated variants (**Supplementary Table 20**). These credible sets included the known causal *F5* Leiden<sup>19</sup> and *F2* G20210A<sup>20</sup> variants, and also included 4 variants at the *ZFPM2* locus - all of which were genome-wide trans-pQTL associations with PAI-1 (**Supplementary Table 9**).

For our VTE PRS analysis, we provide MVP release 3.0 results stratified by sex in **Supplementary Table 21**, and results of the incident event analysis in WHI stratified by WHI sub-study as well as by hormone replacement therapy use are shown in **Supplementary Tables 22-23**.

Lastly, in MVP we performed a manual chart review of 50 VTE cases and 50 controls, which demonstrated that our phenotyping algorithm had a positive predictive value of 96% (95% CI = 85.1-99.3%), and negative predictive value of 100% (95% CI = 91.1-100%).

## 2. Supplementary Methods

### *Cohort Descriptions*

The design of the Million Veteran Program (MVP) was previously described<sup>21</sup>. In brief, individuals aged 19 to >100 years have been recruited from more than 50 VA Medical Centers nationwide since 2011. Each veteran's electronic health record (EHR) data are

being integrated into the MVP biorepository, including inpatient International Classification of Diseases (ICD-9/10) diagnosis codes, Current Procedural Terminology (CPT) procedure codes, clinical laboratory measurements, and reports of diagnostic imaging modalities. MVP received ethical and study protocol approval by the VA Central Institutional Review Board and informed consent was obtained from all participants.

In UK Biobank, individuals aged 45 to 69 years old were recruited from across the United Kingdom for participation<sup>22</sup>. At enrollment, a trained healthcare provider ascertained participants' medical histories through verbal interview. In addition, participants' EHR including inpatient ICD-9/10 diagnosis codes and Office of Population and Censuses Surveys (OPCS-4) procedure codes, were integrated into UK Biobank. Informed consent was obtained for all participants, and UK Biobank received ethical approval from the Research Ethics Committee (reference number 11/NW/0382). Our study was approved by a local Institutional Review Board at Partners Healthcare (protocol 2013P001840).

We also examined incident VTE data from the Women's Health Initiative (WHI) randomized clinical trial of Hormone Therapy (HT) for our PRS analysis. The overall design of the WHI study has been described previously<sup>23</sup>. In brief, at the inception of the WHI study (1993-1998), 161,808 postmenopausal women between the ages of 50 and 79 years were eligible for inclusion in multiple clinical trials. Exclusion criteria related to the presence of medical conditions predisposing to shortened survival or safety concerns. The protocol and consent forms were approved at each site by institutional review committees and all participants provided written informed consent. The WHI-HT initially comprised 27,347 postmenopausal women who were randomized to receive either estrogen plus progestin or estrogen alone versus placebo until the trials were stopped early in July 2002 and March 2004, respectively. All WHI-HT participants subsequently continued to be followed without intervention until close-out. Of the various components of WHI, VTE was adjudicated by physician adjudicators for participants who were enrolled in the HT trials. The WHI-HT trial was approved by the local institutional review board at the Fred Hutchinson Cancer Research Center.

#### *Quality Control Analysis*

In MVP, we excluded: duplicate samples, samples with more heterozygosity than expected, an excess (>2.5%) of missing genotype calls, or discordance between genetically inferred sex and phenotypic gender. In addition, one individual from each pair of related individuals (as measured by the KING<sup>24</sup> software) were removed. Veterans were then divided into three mutually exclusive ethnic groups based on self-identified race/ethnicity and admixture analysis using the ADMIXTURE v1.3 software<sup>25</sup>: 1) non-Hispanic whites (self-identified as "non-Hispanic," "white," and > 80% genetic European ancestry), 2) non-Hispanic blacks (self-identified as "non-Hispanic," "black," and > 50% genetic African ancestry), and 3) Hispanics (self-identified only). In total, 312,571 white, black, and Hispanic MVP participants passed our sample-level quality control. Prior to imputation, variants that were poorly called or that deviated from their expected allele frequency based on reference data from the 1000 Genomes Project<sup>26</sup> were excluded. After pre-phasing using EAGLE<sup>27</sup> v2, genotypes from the 1000 Genomes Project<sup>26</sup> phase 3, version 5 reference panel were imputed into Million Veteran Program (MVP)

participants via Minimac3 software<sup>28</sup>. Ethnicity-specific principal component analysis was performed using the EIGENSOFT software<sup>29</sup>.

Following imputation, variant level quality control was performed using the EasyQC R package<sup>30</sup> (www.R-project.org), and exclusion metrics included: ancestry specific Hardy-Weinberg equilibrium<sup>31</sup>  $P < 1 \times 10^{-20}$ , posterior call probability  $< 0.9$ , imputation quality  $< 0.3$ , minor allele frequency (MAF)  $< 0.003$ , call rate  $< 97.5\%$  for common variants (MAF  $> 1\%$ ), and call rate  $< 99\%$  for rare variants (MAF  $< 1\%$ ). Variants were also excluded if they deviated  $> 10\%$  from their expected allele frequency based on reference data from the 1000 Genomes Project<sup>26</sup>.

In UK Biobank, approximately 500,000 individuals were genotyped and subsequently imputed to the haplotype reference consortium (HRC) and UK10K reference panels. Details of these procedures are described elsewhere<sup>32</sup>. We performed genome-wide association testing for VTE in the UK Biobank using all variants in the v3 release with minor allele frequency greater than 0.3% and imputation quality INFO  $> 0.4$ . To avoid potential population stratification, only European-ancestry samples were included in the analysis. This subset was selected based on self-reported white ethnicity that was subsequently confirmed using genetic principal components analysis. Outliers within the self-reported white samples in the first 6 principal components of ancestry were detected and subsequently removed using the R package *aberrant*<sup>33</sup>. In addition, individuals with sex chromosome aneuploidy (neither XX or XY), discordant self-reported and genetic sex, or excessive heterozygosity or missingness, as defined centrally by the UK Biobank were removed. Finally, one individual from each pair of second-degree or closer relatives (kinship  $> 0.0884$ ) was removed, selectively retaining VTE cases when possible.

#### *VTE Phenotype and Manual Chart Review*

Manual chart review was performed by two blinded trained clinician chart abstractors with a vascular surgeon reviewing discordant cases; the results of chart review for 50 cases and 50 controls otherwise representative of the overall cohort were used for determining the positive and negative predictive values of the phenotyping algorithm, which was standardized to the 50% prevalence of VTE in the validation set. Positive predictive value refers to the ratio of (true positives)/(true positives + false positives) and negative predictive value the ratio of (true negatives)/(true negatives + false negatives). In UK Biobank, individuals were defined as having VTE based on the definition by Klarin and colleagues as previously described<sup>34</sup>. All other individuals were defined as controls.

#### *Discovery and Replication Association Analysis*

In MVP, genotyped and imputed DNA sequence variants were tested for association with VTE through logistic regression adjusting for age, sex, and 5 principal components of ancestry assuming an additive model using the SNPTTEST (mathgen.stats.ox.ac.uk/genetics\_software/snptest/snptest.html) statistical software program. In our discovery analysis, we performed association analyses separately for each ancestral group (whites, blacks, and Hispanics) and then meta-analyzed using an inverse variance-weighted fixed effects method implemented in the METAL software

program<sup>35</sup>. We excluded variants with a high amount of heterogeneity ( $I^2$  statistic > 75%) across the three ancestries.

In UK Biobank, association testing was performed using a logistic regression model adjusted for age at baseline, sex, genotyping array, and the first 5 principal components of ancestry. All testing was performed in PLINK2 (<https://www.cog-genomics.org/plink/2.0/>).

We combined results across MVP and UK Biobank cohorts using inverse-variance weighted fixed effects meta-analysis and set a significance threshold of  $P < 5 \times 10^{-8}$  (genome-wide significance). In addition, we also required a replication  $P < 0.01$  in each of the MVP and UK Biobank analyses (e.g. MVP discovery and subsequent UK Biobank replication, and vice versa), with concordant direction of effect, to minimize false positive findings. Novel loci were defined as being greater than 500,000 base-pairs away from a known VTE genome-wide associated lead variant. Additionally, linkage disequilibrium information from the 1000 Genomes Project<sup>26</sup> was used to determine independent variants where a locus extended beyond 500,000 base-pairs. All logistic regression  $P$  values were two-sided.

#### *Conditional Analysis*

We used the COJO-GCTA software to perform an approximate, stepwise conditional analysis to identify independent variants within VTE-associated loci. We used summary statistics from the European specific meta-analysis of UK Biobank and MVP datasets (23,151 VTE cases, 553,439 controls) to conduct this analysis combined with an LD-matrix obtained from 20,000 unrelated European individuals randomly sampled from the UK Biobank release v3. We set a threshold  $P < 5 \times 10^{-8}$  (genome-wide significance) to declare statistical significance.

#### *PheWAS Disease Definitions, and Association Analysis*

Understanding the full spectrum of phenotypic consequences of a given DNA sequence variant may shed light on the mechanism by which a variant/gene leads to disease. For 30 autosomal lead VTE risk variants and the  $PRS_{VTE}$  identified in our study, we performed a PheWAS of 1,249 distinct diseases, symptoms, and injuries in MVP leveraging the full catalog of EHR ICD-9/10 diagnosis codes in 227,817 white veterans using the R package PheWAS<sup>36</sup>. We additionally included 4 continuous cardiometabolic traits - LDL cholesterol, HDL cholesterol, triglycerides, and body mass index - given their possible links with VTE causality<sup>34,37</sup>. In total, 1,249 disease phenotypes and 4 continuous traits were available for analysis and we set a statistical threshold of  $P < 1.2 \times 10^{-6}$  [ $0.05/(31 \times (1,249 \text{ diseases} + 4 \text{ continuous traits}))$ ]. Of 312,571 genotyped veterans passing quality control, we identified 23,172,451 distinct, prevalent ICD-9 diagnosis codes available for analysis. We focused on the largest ethnic group of 227,817 white participants, in which the mean age was  $64.3 \pm 13.1$  years, and 93.3% (212,465) were male.

ICD-9 diagnosis codes were collapsed to clinical disease groups and corresponding controls using the groupings proposed by Denny et al<sup>8</sup>. Diseases were required to have a prevalence of > 0.13% (~300 cases) to be included in the PheWAS analysis. 30 autosomal lead VTE risk DNA sequence variants and the  $PRS_{VTE}$  were tested using logistic regression adjusting for age, sex, and five principal components under the assumption of additive effects using the PheWAS R package

(<https://github.com/PheWAS/PheWAS>) in R v3.2.0 ([www.R-project.org](http://www.R-project.org)). In total, 1,249 disease phenotypes and 4 continuous traits were available for analysis and we set a statistical threshold of  $P < 1.1 \times 10^{-6}$  [ $0.05/(31 \times (1,249 \text{ diseases} + 4 \text{ continuous traits}))$ ]. For the lipid continuous traits (LDL cholesterol, HDL cholesterol, and triglycerides), maximal LDL cholesterol/triglycerides (after log transformation) and minimal HDL cholesterol were used after inverse normal transformation in MVP as previously described<sup>38</sup>. The body-mass index (BMI) phenotype was formulated in both UK Biobank and MVP and results were combined in an inverse-variance weighted fixed effects meta-analysis. In UK Biobank, BMI was calculated in 374,942 unrelated individuals from the measurement acquired at enrollment. In MVP, BMI was calculated in 218,382 participants from the mean height and mean weight over the 3 years prior to the enrollment date. Outliers were excluded if their mean measurement was  $< 17$  or  $> 60$  kg/m<sup>2</sup>. In each case, the BMI phenotype was adjusted for age, age squared, and principal components of ancestry in a linear regression model. The resulting residuals were transformed to approximate normality using inverse normal scores separately by sex as previously described<sup>39</sup>. All logistic and linear regression P values were two-sided.

#### *Shared Heritability within PAD, CAD, and LAS*

To better understand the how common genetic variation influences risk for atherosclerosis in multiple vascular beds, we used linkage disequilibrium score regression<sup>3</sup> to calculate the genetic correlation between VTE-PAD, VTE-CAD/VTE-MI and VTE-LAS. Summary statistics from the European UK Biobank VTE GWAS, European MVP PAD GWAS<sup>14</sup>, the CARDIoGRAMplusC4D CAD/MI GWAS<sup>15</sup> (predominantly European), and the transancestral LAS MEGASTROKE GWAS meta-analysis ( $>2/3$  European)<sup>16</sup> were used for this analysis. Of note, we used the transancestral meta-analysis statistics from MEGASTROKE because the sample size of the European-ancestry only analysis lacked sufficient power for estimation of genetic correlation. We then queried association results for the 30 autosomal genome-wide lead VTE risk variants for PAD, CAD, and LAS in the MVP PAD<sup>14</sup>, CARDIoGRAMplusC4D<sup>15</sup> CAD, and MEGASTROKE<sup>16</sup> LAS GWAS analyses, respectively.

#### *VTE Variant-Plasma Protein Associations*

To identify loci that might influence plasma protein concentrations potentially implicated in thromboembolism, we used published protein quantitative trait locus (pQTL) data generated from an aptamer-based multiplex protein assay to quantify 3,622 plasma proteins in 3,301 healthy participants from the INTERVAL study<sup>2,17</sup>. We queried the 30 autosomal VTE risk variants identified in our study for overlap with genome-wide significant (two-sided  $P < 5.0 \times 10^{-8}$ ) variant-protein pairs.

#### *Fine-Mapping of VTE Association Signals*

For 29 non-MHC, autosomal, VTE association signals, we used the MR-MEGA<sup>18</sup> software and VTE summary statistics from the UK Biobank (European) and MVP (African, European, and Hispanic) analyses. We first defined a genomic region 1 megabase on either side of the VTE lead variant restricting to variants with MAF  $> 1\%$ . Under the assumption of one causal variant at a given locus, we then used multi-dimensional scaling of the Euclidean distance matrix to generate axes of genetic variation to each set



of association statistics between ancestry groups as implemented in MR-MEGA. For each GWAS signal we applied the “meta-regression model,” including one axis of genetic variation as a covariate, to each variant passing quality control. From this model, we examined the VTE association for each variant and the heterogeneity in allelic effects that is correlated with ancestry. Subsequently, we derived a posterior probability (using the resultant Bayes’ factor) of VTE association and constructed a 99.99% credible set of variants driving each GWAS signal.

#### *Genetic Analysis of Incident VTE Events in WHI*

After assessing the associated VTE risk for *F5* p.R506Q and *F2* G20210A carriers as well as the 5% of individuals with the highest PRS<sub>VTE</sub> relative to the rest of the population in MVP, we sought replication of our findings using incident VTE data from the WHI. The design of the WHI-HT study has been described previously<sup>23</sup>. In brief, at the inception of the WHI study postmenopausal women between the ages of 50 and 79 years were eligible for inclusion in multiple clinical trials. Data used in this analysis included incident VTE events from participants belonging to one of three GWAS sub-studies: 1) the WHI Genomics and Randomized Trials Network (WHI-GARNET, 457 incident VTE events among 4,233 participants), 2) the WHI Memory Study (WHIMS, 180 incident VTE events among 5,637 participants), 3) the WHI Long Life Study (WHI-LLS, 53 incident VTE events among 1,105 participants).

The WHI-GARNET sub-study consisted of individuals selected as a nested case-control sample of coronary heart disease, stroke, venous thrombosis, and incident diabetes events from the parent WHI Hormone Therapy Trial. From 27,347 women who participated in the Hormone Therapy Trial, 4,894 were genotyped on the Illumina Omni-Quad as part of WHI GARNET and imputed using the 1000 Genomes reference panel<sup>26</sup> phase 3, version 5. VTE cases were identified that occurred during the active phase of the Hormone Trial and afterwards. Controls were participants in the Hormone Therapy Trial free of all 4 case conditions. Matching criteria for controls were age, race/ethnicity, hysterectomy status, and enrollment date. GARNET WHI participants were predominantly European (87%), and only European individuals were included in the analysis. In total, 457 VTE incident events were identified among 4,233 individuals after removing 21 observations due to missingness.

The WHIMS sub-study consisted of WHI Hormone Trial women of European ancestry from the following sources: 1) WHI Memory Study (WHIMS) participants<sup>40</sup> who were not in WHI-GARNET, 2) women from the WHI-HT at least 65 years old at enrollment who were neither in WHIMS nor GARNET, and 3) women from the WHI-HT younger than age 65 at enrollment who were neither in WHIMS nor GARNET. In total, 180 incident VTE events were identified among 5,637 individuals after removing 50 observations due to missingness. Participants were genotyped using the Illumina HumanOmniExpress platform and imputed using the 1000 Genomes reference panel<sup>26</sup> phase 3, version 5.

The WHI-LLS (GWAS) sub-study consisted of the phase III cohort of additional eligible women who were added to the LLS study after the decision was made to expand the study population in 2012. In total, 53 VTE incident events were identified among 1,105 individuals after removing 13 observations due to missingness. Participants were

genotyped using the Illumina HumanOmniExpress platform and imputed using the 1000 Genomes reference panel<sup>26</sup> phase 3, version 5.

Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals for the associations of the *F5* p.R506Q and *F2* G20210A mutations with VTE adjusting for age, 10 principal components of ancestry, and hormone therapy intervention status during the active phase of the WHI-HT. We then tested the associated VTE risk for the 5% of individuals with the highest  $PRS_{VTE}$  relative to the rest of the population using Cox proportional hazards models adjusting for age, 10 principal components of ancestry, and hormone therapy intervention status during the active phase of the WHI-HT. Results from WHIMS, WHI-LLS, and WHI-GARNET were combined using an inverse-variance weighted fixed effects meta-analysis. Bonferroni-corrected 2-sided P values ( $P=0.016$ ;  $0.05/3$ ) for 3 tests were used to declare statistical significance. Analyses were performed using the R software program (version 3.5.1; Vienna, Austria).

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