SUPPLEMENTAL MATERIAL

Leveraging human genetics to estimate clinical risk reductions achievable by inhibiting Factor XI

Supplemental Methods

Definition of clinical endpoints in the UK Biobank

The UK Biobank (UKB) is a population cohort of 500,000 subjects from the United Kingdom [1]. It combines deep phenotyping in the form of electronic health records (EHR) with genome-wide genotyping and imputation. Clinical endpoints for cross-sectional association analyses were derived from EHRs based on International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD10) codes (UKB data field 41202 and 41204), ICD9 codes (UKB data fields 41203 and 41205), OPCS Classification of Interventions and Procedures (V4) codes (UKB field 41210 and 41200), death registry (UKB data field 40001 and 40002) and self-reported baseline questionnaire diagnostic codes (UKB data field 20001 and 20002). The codes used for the phenotypic definitions of specific endpoints are listed in Supplementary Table I. For the special cases of ischemic stroke (UKB data field 42008) and myocardial infarction (UKB data field 42000), the UKB-provided "date of first occurrence" phenotypes were used. Primary phenotypes (Figure 2A in the main manuscript) were defined by thorough review of the available data fields and diagnostic codes by a clinical expert, secondary (PheWAS) phenotypes (supplemental Figure IV) were defined based on previously reported UKB PheWAS [2]. For investigating subgroups within UKB (e.g. atrial fibrillation patients), subgroups were defined based on baseline and follow-up information, i.e. a person classed as atrial fibrillation patient had a documented diagnosis of atrial fibrillation at baseline or at any point during the prospective follow-up period.

Quality control of UK Biobank genotype data

For sample quality control (QC) the following filters were applied based on information in the UKB sample QC file "_002_ukb_sqc_v2.txt": a) samples with ethnicity other than white British (78,674 samples), b) samples with mismatch between reported and genetically inferred sex (378 samples) and c) samples with sex chromosomal aneuploidy (652 samples). In addition, we made use of UKB provided kinship coefficients generated by the KING software [3] to remove related samples. For each of 36,159 pairs of samples with 2nd degree relationship or closer (kinship coefficient >0.884), a single sample was excluded at random. After QC we retained 371,695 samples for further analysis. Genotypes were retrieved from the UKB Imputation V3 dataset, all variants under consideration passed a stringent INFO imputation quality check (INFO>0.99). Positions of genotype variants were given based on genome Build 37.

Analysis of predicted FXI loss-of-function variants

For the analysis of FXI loss-of-function (LOF) variants, the genotype data was supplemented with variant calls from whole exome sequencing (WES) of 49,958 subjects in the UK Biobank (supplemental Figure I). We downloaded WES variant calls generated by the UK Biobank FE variant calling pipeline. Positions of WES variants were provided based on genome Build 38. To identify putative LOF variants in FXI we applied the tool Loftee (https://github.com/konradjk/loftee) to both genotype and WES variants. Only variants with high confidence (HC) LOF annotation for FXI from Loftee were retained. Manual review of the genotype cluster plots of the seven putative LOF variants identified in the genotype data led to the rejection of five variants due to insufficient separation of the genotype groups. The two genotyped FXI LOF variants retained were Affx-80273409 and rs121965066. In the WES data 19 putative LOF variants were identified (Table II). As a quality control we compared the consistency of LOF carrier status for the two LOF variants from the genotype data in the WES data. LOF carrier status was 100% concordant between genotype and WES datasets for Affx-80273409 (4:187201469:CTG/C) and rs121965066, i.e. all subjects that were minor allele carriers in the genotype data also carried the allele in the WES dataset (if included). In total we identified 477 putative FXI LOF allele carriers, 120 and 357 in the WES and genotype datasets respectively. Putative F11 LOF variants were analyzed separately in the WES and genotype datasets and subsequently integrated using a fixed-effect meta-analysis (supplemental Figure II).

Definition of time-to-event data for survival analysis

Time-to-event data for subjects passing genotype QC was extracted from the UKB HES data set using the ICD10 codes in Table I. The observation period for each subject was set to from the date of the baseline visit to the date of the first event or the date of the last recorded diagnostic code in the dataset. Subjects with events before the baseline visit were excluded from the analysis.

Definition of the F11 activity genetic score

To define a genetic instrument for F11 activity, we made use of publically available summary level data of recent large-scale GWAS studies. We focused on SNPs with independent effects and genome-wide significant effect at the F11 locus. Effect sizes listed below are always expressed with respect to the F11 activity lowering allele.
A genetic risk score for F11 activity was derived based on a recent meta GWAS of ~16000 subjects [4]. Log effect sizes for two genome-wide significant SNPs at the F11 locus, rs4253417 (β=-0.0735, se=0.00248, P=2.86e-193, effect allele: C) and rs4253421 (β=-0.0498, se=0.00373, P=1.25e-40, effect allele: G), were combined in a simple additive score (see main Methods). The

two SNPs are only weakly linked (LD r^2=0.096 in UKB) and show independent effects on F11 activity in a conditional analysis [4]. rs4253421 is a proxy SNP for rs1593 (LD r^2=0.854 in UKB). This genetic score was subsequently rescaled to a 30% increase in relative aPTT (see main Methods). This rescaling was achieved by dividing the FXI score for each individual 0.3.
For prospective analysis of time-to-event data we also defined a binary score using the extreme tails of the FXI score distribution: the first group consisted of 60,629 subjects with no FXI activity lowering alleles ("no genetic FXI reduction") and the second of the 49,637 subjects with a relative aPTT effect > 0.4 ("strongest observed genetic FXI reduction").

Additional effect estimates for stroke and MI

To improve the power of the cross-sectional analysis, we integrated effect sizes of publically available GWAS summary datasets using fixed effect meta-analysis. For MI the CARDIoGRAMplusC4D [5] (http://www.cardiogramplusc4d.org) was used. For ischemic stroke we integrated data from the MEGASTROKE study [6] (http://www.megastroke.org). To combine the SNP-wise effects from these studies into a single score we a) harmonized effect alleles to the F11 activity lowering allele, b) rescaled the effect estimate to a 30% relative increase in aPTT based on a global aPTT mean of 29.0s in the ARIC study [7], c) integrated the SNP-wise effects into a score using a simple fixed-effect meta-analysis. This last step was justified due to the lack of LD between the markers [8]. This yielded a single risk estimate on an aPTT scale that could straightforwardly be combined with the UK Biobank estimates by fixed effect meta-analysis. The same meta-analysis procedure was also used to perform combined association analysis of estimates for the ischemic stroke subtypes cardioembolic stroke, small vessel stroke and large artery stroke from the MEGASTROKE study [6].

Statistical methods

Association analyses were performed using the R statistical programming language v. 3.4.3. Logistic regressions were carried out using the build-in *glm* function while Cox proportional hazard (CPH) regressions analyses were performed with the *survival* package (vs. 2.42-3). Regressions were carried out with age at baseline, sex, genotyping platform and the first 10 principal components of the genotypes as covariates. Deviation of the proportional hazards assumption for the Cox model was checked using the *cox.zph* function (Schoenfeld Residuals test). No significant deviation was observed. Random and fixed effect meta-analysis were performed using the *rma* function from R package metafor (vs 2.0-0) [9]. Meta analyses of UK Biobank and MEGASTROKE/ CARDIoGRAMplusC4D consortia data was carried out using fixed-effect meta analysis. As a sensitivity analysis we also performed random-effects meta analysis, obtaining highly consistent results.

Subgroup and Interaction analysis

The interaction analyses of venous thrombosis (VT) and ischaemic stroke (IS) consisted of three models for each of the 48 phenotypes tested. The subgroups for survival (Cox proportional hazard) and logistic regression analysis were defined by case status for the respective phenotype using both prevalent and incident diagnoses. Control of the false discovery rate (FDR) was achieved using the procedure by Benjamini & Yekutieli [10].
For each phenotype we estimated there models:

1) Test for significant effect as a risk factor: phenotypes were tested separately as independent variables in Cox regression models for effect on VT or IS.
2) Test for association of the F11 genetic score within the subgroup of cases: a Cox regression for effect of the F11 genetic score on IS/VT only within the cases of each phenotype.
3) Interaction analysis: A Cox regression model that included case/control status of a phenotype as a covariate and included an interaction term between the F11 score and risk factor case/control status.

For all Cox regression models the validity of the proportional hazard assumption was confirmed using the Schoenfeld Residuals test. Complementary to the Cox regression analysis, we also performed the same workflow using logistic regression in a cross-sectional manner. The results of both approaches were comparable (Tables II, II).

Comparison of absolute differences between survival curves for subgroups

For showing that the absolute difference in ischaemic stroke event rate is different for subjects with atrial fibrillation compared to subject without, we define the null hypothesis for a chosen time t (here: $t = 6$ years) as:

$$C: = S_{AF,gH}(t) - S_{AF,gL}(t) - S_{nAF,gH}(t) + S_{nAF,gL}(t) = 0,$$

where $S_{AF,gH}(t)$ gives the survival rate of subjects with atrial fibrillation and the strongest observed genetic effect on FXI and where $S_{nAF,gL}(t)$ represents the survival rate for subjects without atrial fibrillation and no genetic effect on FXI. The other terms are defined accordingly. Intuitively, this means that the difference between the survival rates for subjects with extreme genetic scores is identical for subjects with AF and subjects without AF under the null hypothesis.
This null hypothesis is assessed using a permutation test and p-values are derived based on the generated distribution of the test statistic under the null hypothesis [11]. For that, it is important to note that one special case under the null hypothesis is the situation that all four survival rates are equal. For the permutation test, the following steps are performed:

1) Calculate the absolute value of the realization of test statistic C (denoted as c) for the given dataset by estimating the Kaplan-Meier curves for each group and extracting the observed survival rates at time t.
2) Permutate the group labels of the four groups (AF,gH; AF,gL; nAF,gH; nAF,gL) $i = 1000000$ times. In each iterations, calculate the absolute value of the realization of the test statistic C for the permutated dataset (denoted as $c_i;\ i = 1, \dots, 1000000$).
3) Calculate the number of cases in which $c_i > c$ and denote this number by k. The estimated p-value is then given by $P = \frac{k+1}{i+1}$.

The approach based on the covariate-adjusted Cox regression uses an identical procedure, only the estimation of the survival rates is then based on the Cox model equation.

Calibration of clinical and genetic risk estimates

The first prerequisite for the risk calibration procedure is the availability of risk estimates from a genetic analyses and clinical studies for the same phenotype on an identical scale (aPTT in our case). Given that, a calibration factor can be estimated that quantifies the relative difference in risk impact of a genetically determined activity reduction and the effect of a temporary pharmacological target modulation. This calibration factor can then be applied to genetic risk estimates for other phenotypes to make predictions about the outcome of future trials.
A critical component of this procedure is the principled propagation of the uncertainty (i.e. standard errors) of the estimators involved. Let β_1 and β_2 be two independent effect estimators with standard deviations σ_1 and σ_2. Then, the standard deviation σ_f of $f = \frac{\beta_1}{\beta_2}$ or $f = \beta_1 \beta_2$ can be approximated by $\sigma_f \approx |f| \sqrt{\left(\frac{\sigma_1}{\beta_1}\right)^2 + \left(\frac{\sigma_2}{\beta_2}\right)^2}$ [12]. Similarly, for $f = \beta_1 + \beta_2$ we obtain $\sigma_f = \sqrt{\sigma_1^2 + \sigma_1^2}$.

For F11 specifically, we make use of a) clinical trial data for F11 inhibition in venous thromboembolism (VT) and b) genetic risk estimates for VT based on the aPTT score to anticipate the effect of F11 inhibition in a trial of ischemic stroke.
For the former, we leverage clinical Phase 2a trial data for the effect of two different dosages of an F11 antisense (F11-ASO) on VT risk after total knee arthroplasty (TKA) [13].
The study compared the effect of F11-ASO against 40 mg of Enoxaparin.
Using the reported event counts, we calculated odds ratios (ORs) of 0.839 (CI 0.681 - 1.034) and 0.1 (CI 0.044 - 0.22) for 200mg and 300mg of F11-ASO respectively. To arrive at the desired comparison of F11-ASO vs. placebo, the estimates from [13] were combined with a VT risk estimate for Enoxaparin vs. Placebo of OR=0.27 (CI=0.19, 0.38) (supplemental Figure VII) from a fixed random effect meta-analysis of event counts of four trials [14-17] (retrieved from [18]) using standard indirect adjusted comparison methods for odds ratios [19]. This yielded final risk estimates

for F11-ASO vs. Placebo of OR=0.22 (CI 0.15- 0.33) and OR= 0.027 (CI 0.01-0.065) for 200mg and 300mg F11-ASO respectively.
The effect of the 200mg and 300mg dosages of F11-ASO on aPTT was measured in [13]. The relative increase in aPTT from day zero to day 36 (day before surgery) was ~20% (aPTT ratio 1.2) and 40% (aPTT ratio 1.4) for the 200mg and 300mg F11-ASO dosages respectively. To arrive at the final clinical VT risk estimate, the estimates for 200mg and 300mg F11-ASO were rescaled to a 100% relative aPTT increase by division through the respective relative aPTT effects and combined using a fixed effect meta-analysis. For a 30% increase in relative aPTT (i.e. a 1.3 fold change), this yielded an estimate of OR= 0.086 (CI 0.06-0.13) for the clinical VTE data. The calibration factor can now be estimated as a simple ratio of the clinical and genetic effect sizes for VT. Multiplication of the calibration factor with the genetic risk estimate of a different phenotype yields a prediction of the clinical effect for that endpoint.

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Supplementary figures & tables

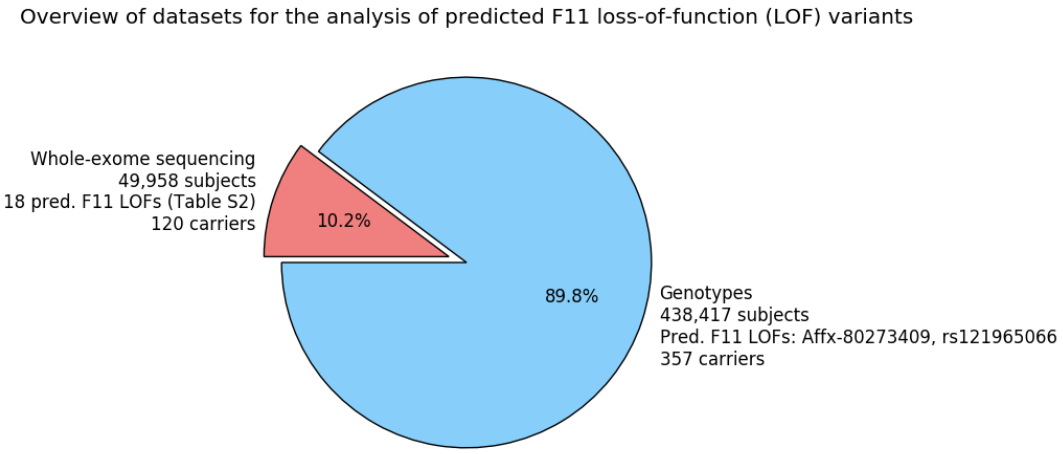

Figure I: Overview of genetic data for analysis of predicted F11 loss-of-function variants

In total 477 carriers of predicted F11 loss-of-function variants were identified in the whole-exome sequence and genotype datasets.

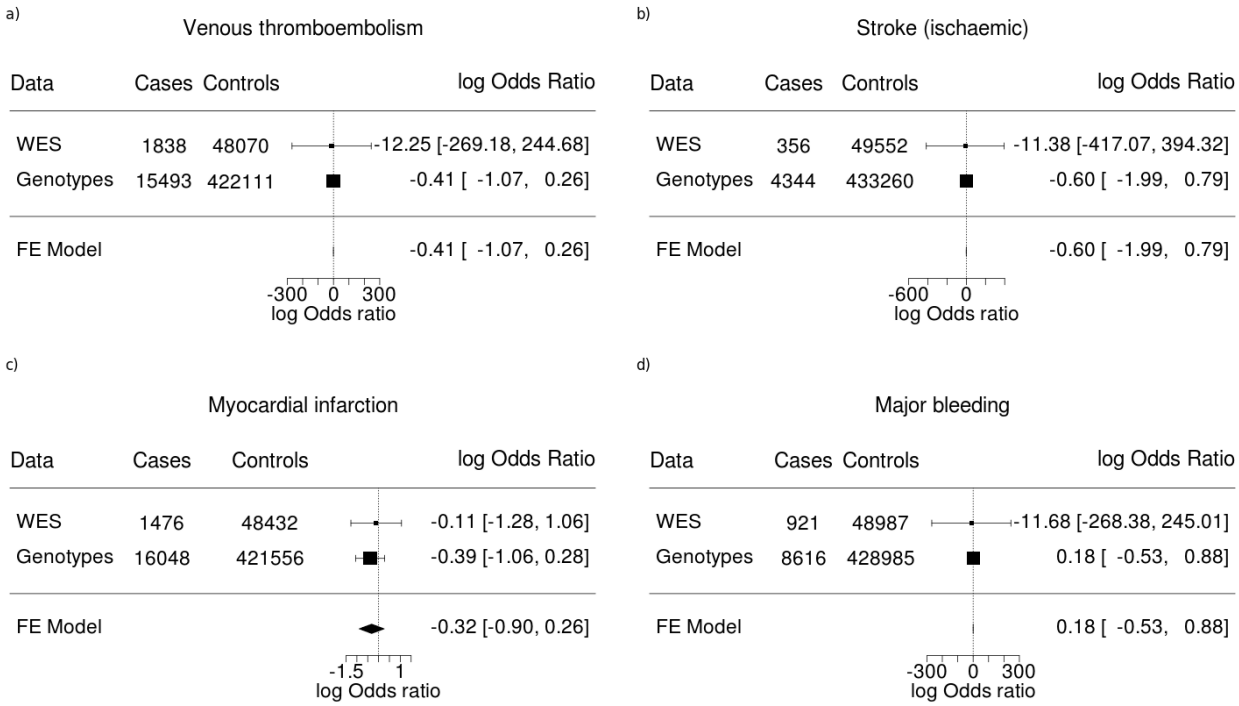

Figure II: Fixed-effect meta-analysis of predicted F11 loss-of-function variants

Loss-of-function (LOF) variant carriers vs. non-carriers were analyzed in genotype and whole-exome sequence (WES) datasets separately. Effects from both datasets were combined by fixed-effect meta-analysis.

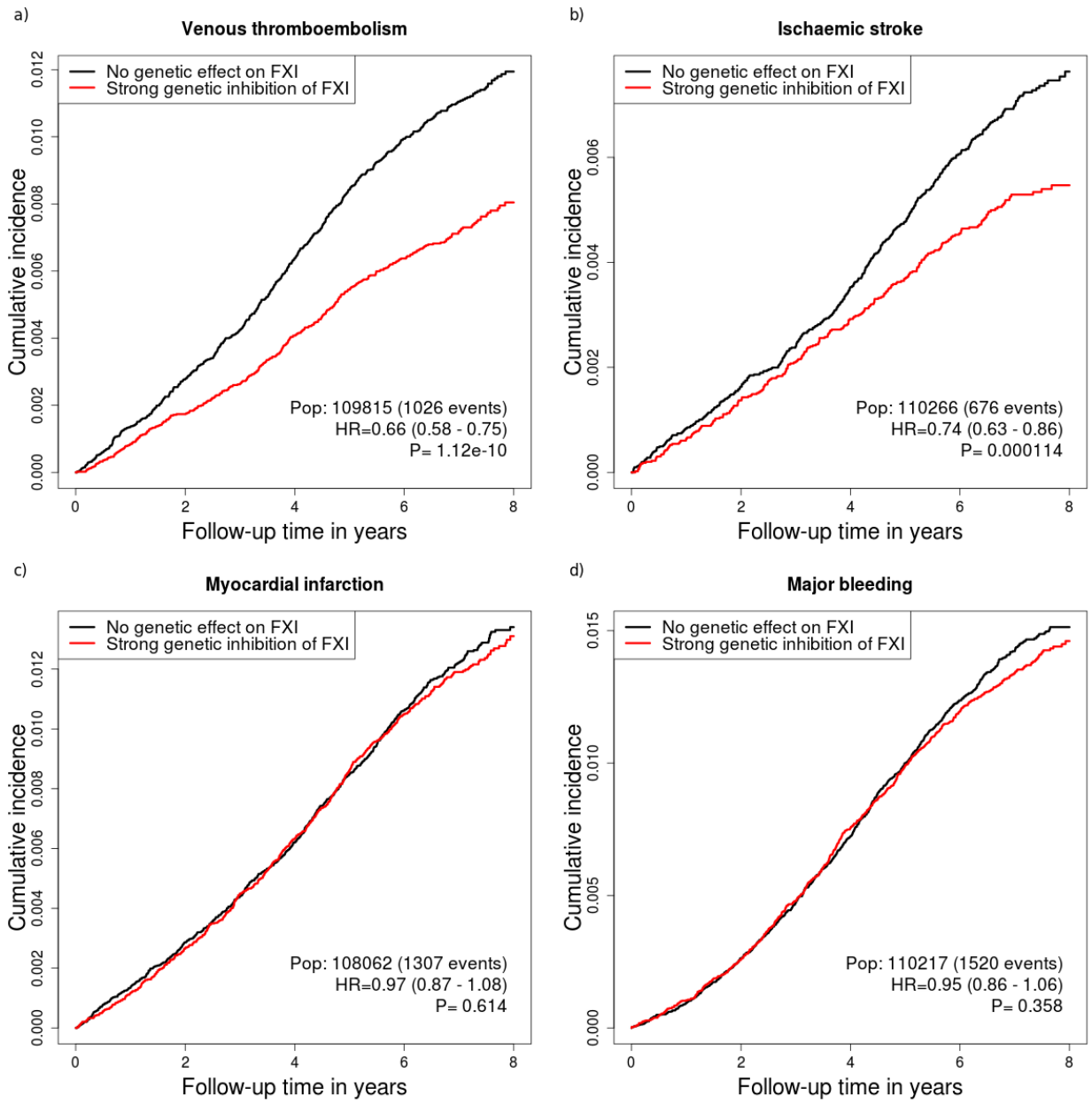

Figure III: Prospective analyses of for primary efficacy and safety endpoints in UK Biobank for two extreme groups of the FXI genetic score. The two groups correspond to all subjects without an aPTT lowering allele in our genetic score (~60k subjects, black) and all subjects with a strong effect on aPTT (> 1.4s, ~50k subjects, red). Size of base populations differed for the endpoints pre-defined by UK Biobank (b,c) or derived from the hospital episode data (a,d). In each case subjects with events before the start of the observation period were dropped from the analysis. We observed significant associations for venous thromboembolism (a) (HR=0.66 (0.58- 0.75), P=1.12x10^{-10}) and ischemic stroke (b) (HR=0.74 (0.63-0.86), P=0.000114) but not myocardial infarction (c) or major bleeding (d).

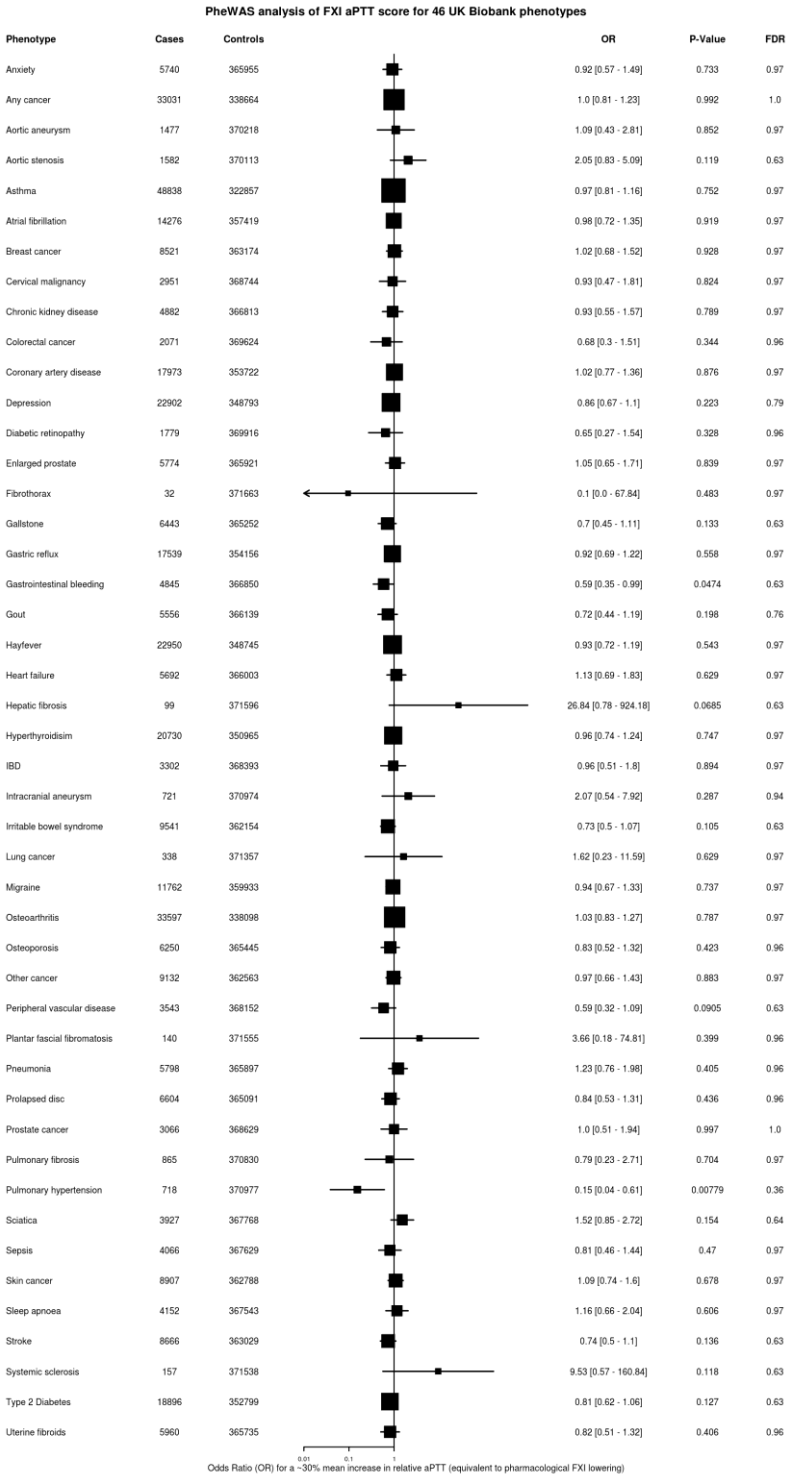

Figure IV: PheWAS analysis of F11 aPTT score in the UK Biobank. Cross-sectional association analysis by logistic regression of 46 phenotypes did not identify additional associations after accounting for multiple testing by False Discovery Rate [20].

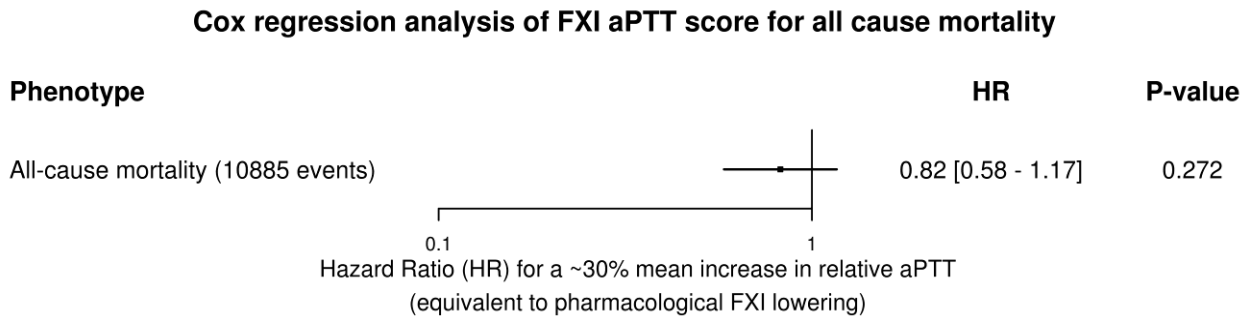

Figure V: Cox proportional hazard regression analysis all-cause mortality in the UK Biobank did not show a significant effect of the FXI aPTT score.

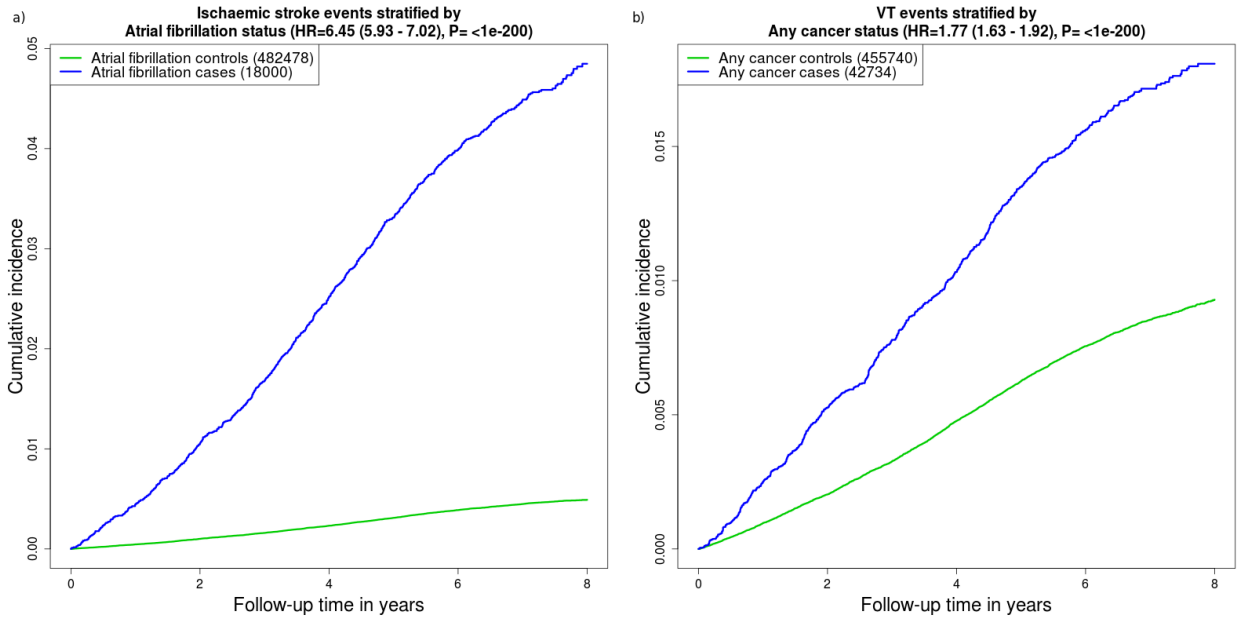

Figure VI: Prospective analyses of risk impact of strongest identified factors.

a) Effect of atrial fibrillation (AF) diagnosis on incidence of ischaemic stroke. AF case status confers major increase in ischaemic stroke risk (HR=6.45 (5.93-7.02), P<1e-200). b) Effect of any cancer diagnosis on incidence of venous thromboembolism. Cancer case status confers a major increase in VTE risk (HR=1.77 (1.63-1.92), P<1e-200).

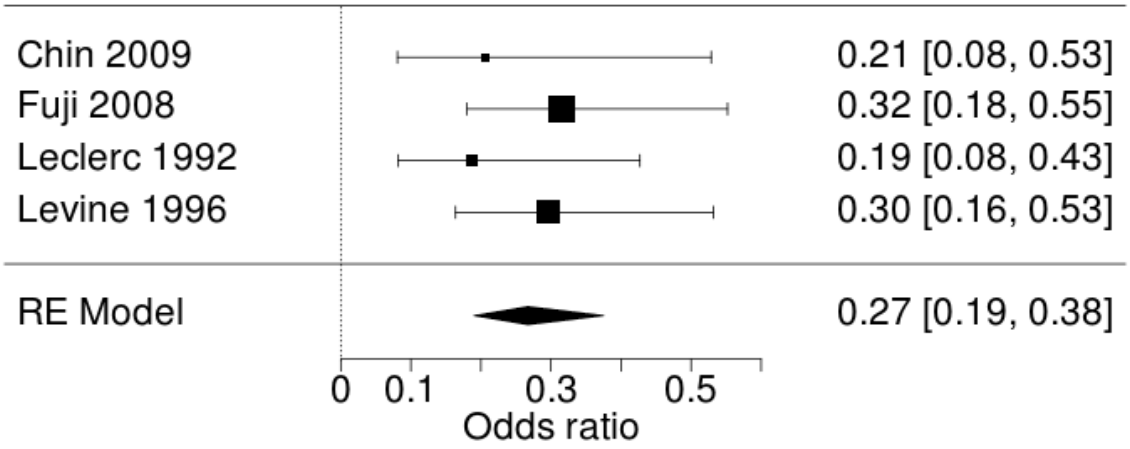

Figure VII: Random effect meta-analysis of four studies of Endoxaparin vs. Placebo in venous thromboembolism after total knee arthoplasty. A combined risk reduction of OR=0.27 (CI 0.19 – 0.38) was observed.

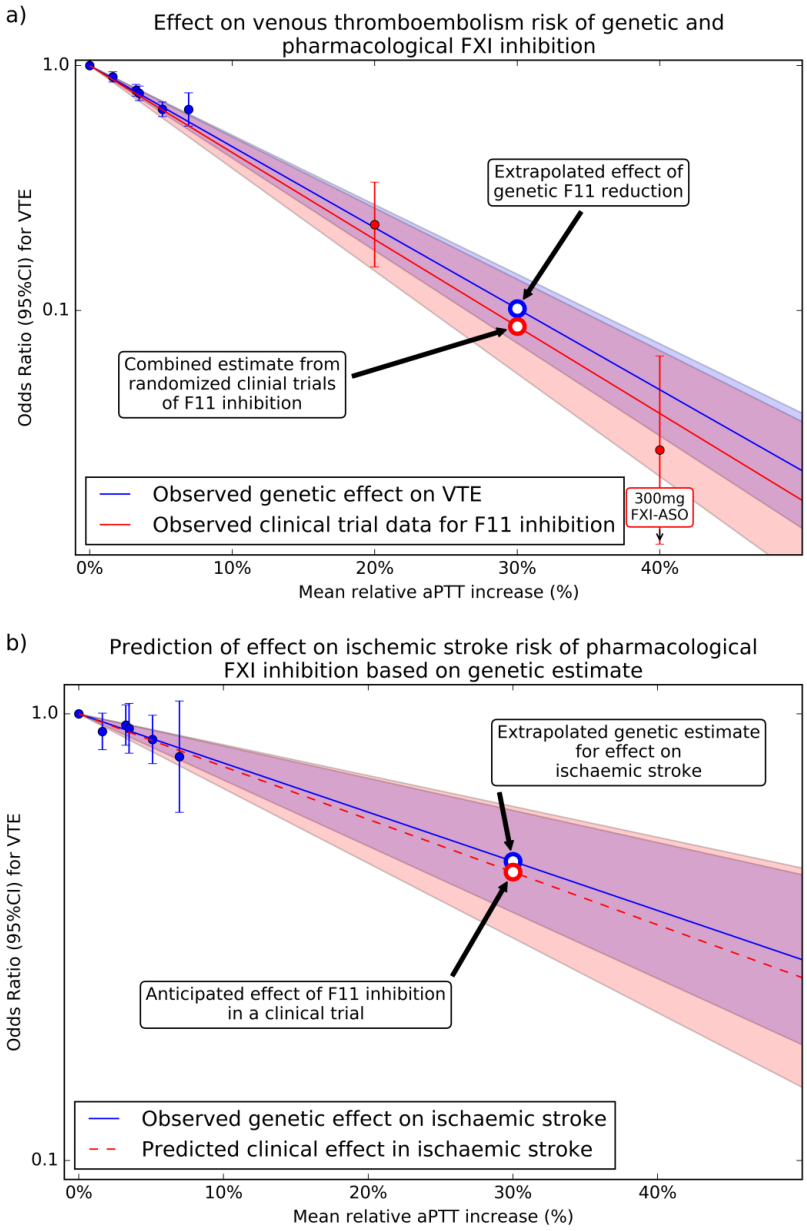

Figure VIII: Anticipation of achievable clinical effect of FXI inhibition on ischemic stroke.

a) Comparison of effects for genetic (blue) and pharmacological (red) modulation of F11 on venous thrombosis risk, enabling derivation of a calibration factor of of 0.93 (SE 0.11). b) Application of the calibration factor to the genetic risk estimate for ischemic stroke (blue) to predict achievable effects with pharmacological modulation (red) yields a predicted odds ratio of OR=0.44 (CI 0.31 – 0.62) for a pharmacological intervention equivalent to a relative increase in aPTT of 30%.

Supplemental Table I: Definitions of clinical endpoints based on UKB EHR records. ICD10 and ICD9 codes were checked in UKB primary and secondary diagnoses data fields (data fields 41202&41204 and 41203&41205 for ICD10 and ICD9 respectively, primary and secondary causes of death (ICD10 coded, UKB data fields 40001&40002),OPCS operation codes were checked against UKB data fields 41210&41200. "UKB baseline codes" refer to UKB data fields 20001 (for non-cancer) and 20002 (for cancer). "OP code, self reported" corresponds to UKB data field 20004. Additional UKB data fields used are referenced directly within the table.

Phenotype	UK Biobank codes
Anxiety	UKB baseline: 1287
Any cancer	UKB baseline: 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1015, 1016, 1017, 1018, 1019, 1020, 1021, 1022, 1023, 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1050, 1051, 1052, 1053, 1055, 1056, 1058, 1059, 1060, 1061, 1062, 1063, 1064, 1065, 1066, 1067, 1068, 1070, 1071, 1072, 1073, 1074, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1084, 1085, 1086, 1087, 1088
Aortic aneurysm	UKB baseline: 1492, 1591, 1592 ICD10: I71 ICD9: 4410, 4411, 4414, 4416 OPCS: L464, L271, L272, L274, L275, L276, L278, L279, L281, L283, L284, L285, L286, L288, L289, L181, L182, L183, L184, L185, L186, L188, L189, L191, L192, L193, L194, L195, L196, L198, L199 OP code, self-reported: 1104
Aortic stenosis	UKB baseline: 1490 ICD10: I350

Asthma	UKB baseline: 1111 ICD10: J45 UKB Field 6152 "Blood clot, DVT, bronchitis, emphysema, asthma, rhinitis, eczema, allergy diagnosed by doctor" = 8 (Asthma)
Atrial fibrillation	UKB baseline: 1483, 1471 ICD10: I48.4, I48.2, I48.3, I48.0, I48.1, I48.9, I48 ICD9: 4273 OPCS: K62.4, K57.1, K62.1, K62.2, K62.3 OP code, self reported: 1524
Breast cancer	UKB baseline: 1002
Cervical malignancy	UKB baseline: 1041, 1072
Chronic kidney disease	UKB baseline: 1520, 1193, 1192, 1519, 1607 ICD10: N18.8, I12.0, N18.2, N18.3, N18, N18.1, I13.2, N18.4, I13.1, N18.9, N18.5, N18.0 ICD9: 585, 5859 OPCS: M01.3, M01.2, M01.1, M01.5, M01.4, M01.9, M01.8, M01 OP code, self reported: 1195
Colorectal cancer	UKB baseline: 1020, 1022, 1023
Coronary artery disease	OPCS: K50.2, K49.1, K49.2, K49.9, K49.8, K75.4, K40.4, K75.1, K75.2, K75.3, K75.8, K75.9, K45.5, K45.4, K45.1, K45.3, K45.2, K40.1, K41.1, K41.3, K41.2, K41.4, K40.2, K40.3 UKB data field 42001 "Adjudicated MI phenotype" = 0 (Self-report only), 1 (Hospital admission) or 2 (Death only)
Depression	UKB baseline: 1286
Diabetic retinopathy	UKB baseline: 1276

	ICD10: E103, E113
Enlarged prostate	UKB baseline: 1396
Fibrothorax	ICD10: J94.1
Gallstone	UKB baseline: 1162
Gastric reflux	UKB baseline: 1138
Gastrointestinal bleeding	UKB baseline: 1191 ICD10: K922 ICD9: 5789
Gout	UKB baseline: 1466
Hayfever	UKB baseline: 1387
Heart failure	UKB baseline: 1076, 1079 ICD10: I43.8, I43.0, I43.2, I42.8, I42.9, I43.1, I13.2, I42.6, I42.7, I42.0, I13.0, I50.1, I50.0, I42.5, I11.0, I50.9, I25.5 ICD9: 4289, 4280, 4281, 4254
Hepatic fibrosis	ICD10: K74.0
Hyperthyroidisim	UKB baseline: 1225, 1226
IBD	UKB baseline: 1461, 1462, 1463
Intracranial aneurysm	UKB baseline: 1425 ICD10: I671, I607 ICD9: 4373, 74780 OPCS: L331, L332, L333, L334, L338
Irritable bowel syndrome	UKB baseline: 1154
Lung cancer	UKB baseline: 1001, 1027, 1028
Major bleeding	UKB baseline: 1191, 1491, 1445, 1083,

	1086 ICD10: H45.0, H35.6, I31.2, K25.2, K25.0, S06.60, I60, H43.1, I62, K92.2, S06.40, S06.50, K26.0, K26.2, I61 ICD9: 4321, 4309, 5310, 5789, 5320
Migraine	UKB baseline: 1265
Myocardial infarction	Cases identified by UKB data field 42000 "Date of first myocardial infarction"
Osteoarthritis	UKB baseline: 1465
Osteoporosis	UKB baseline: 1309
Other cancer	UKB baseline: 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1015, 1016, 1017, 1018, 1019, 1021, 1024, 1025, 1026, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1042, 1043, 1045, 1046, 1047, 1048, 1050, 1051, 1052, 1053, 1055, 1056, 1058, 1063, 1064, 1065, 1066, 1067, 1068, 1070, 1071, 1073, 1074, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1084, 1085, 1086, 1087, 1088
Peripheral vascular disease	UKB baseline: 1067, 1087 ICD10: I74, I1739
Plantar fascial fibromatosis	ICD10: M72.2
Pneumonia	UKB baseline: 1398 ICD10: B01.2, B05.2, J10.0, J11.0, J18, J12, J13, J14, J15, J16, J17, J18, J85.1 ICD9: 0551, 4809, 4809, 4808, 4802, 4801, 4800, 4819, 4820, 4821, 4822, 4823, 4824, 4828, 4829, 4839, 4869, 4859, 4870
Prolapsed disc	UKB baseline: 1312

Prostate cancer	UKB baseline: 1044
Pulmonary fibrosis	UKB baseline: 1121 ICD10: J84.1 UKB data field 22135 "Doctor diagnosed PF (work environment online follow-up)" = 1
Pulmonary hypertension	ICD10: I27
Sciatica	UKB baseline: 1476
Sepsis	UKB baseline: 1657 ICD10: A40, A41, B377, A021, A327, P369 ICD9: 0380, 0381, 0384, 0388, 0389
Skin cancer	UKB baseline: 1060, 1003, 1059, 1060, 1061, 1062
Sleep apnoea	UKB baseline: 1121 ICD10: G473
Stroke	UKB data field 42006 "Date of first stroke"
Systemic sclerosis	ICD10: M34
Type 2 Diabetes	UKB baseline: 1223 ICD10: E10 UKB data field 2443 "Diabetes diagnosed by doctor"=1 or UKB data field 6177 "Medication for cholesterol, blood pressure or diabetes" = 3 (Insulin)
Uterine fibroids	UKB baseline: 1351
Venous thromboembolism	UKB baseline: 1093, 1094, 1068 ICD10: I26, I80-I82

Table II: High confidence FXI loss-of-function variants identified in 50k whole-exome sequences from the UK Biobank

UKB WES SNP ID	Position (B38)	SNP ID	Impact
4:186273071:G:A	chr4:186273071	rs762013077	stop_gained
4:186273178:G:A	chr4:186273178	rs140190776	splice_donor_variant
4:186274193:G:T	chr4:186274193	COSM5866154	stop_gained
4:186274198:C:A	chr4:186274198	COSM6166867	stop_gained
4:186274228:C:A	chr4:186274228	rs121965066	stop_gained
4:186274277:T:C	chr4:186274277	rs1464239583	splice_donor_variant
4:186276392:T:C	chr4:186276392	rs1220869989	splice_donor_variant
4:186280094:I:4	chr4:186280094	NA	frameshift_variant
4:186280262:D:1	chr4:186280262	rs1263707656	frameshift_variant
4:186280274:D:1	chr4:186280274	COSM3602612	frameshift_variant
4:186280315:D:2	chr4:186280315	rs1352561237	frameshift_variant
4:186280374:C:A	chr4:186280374	rs745901569	stop_gained
4:186280516:D:1	chr4:186280516	rs1391198995	frameshift_variant
4:186285809:C:G	chr4:186285809	NA	stop_gained
4:186285814:G:T	chr4:186285814	COSM5778326	splice_donor_variant
4:186286423:C:T	chr4:186286423	rs375422404	stop_gained
4:186287822:D:1	chr4:186287822	NA	frameshift_variant
4:186288560:C:A	chr4:186288560	CM051918	stop_gained

Supplemental Table III: Results of the interaction analysis for venous thromboembolism

		Survival analysis									Cross-sectional analysis								
		Venous thrombosis events in individuals with risk factor			Venous thrombosis events for genetically lower F11			Venous thrombosis events - interaction between risk			Risk of venous thrombosis in individuals with risk factor			Risk of venous thrombosis for genetically lower F11			Risk of venous thrombosis - interaction between risk		
Putative risk factor	Number individuals with risk factor present	HR	P-value	FDR	HR	P-value	FDR	HR ratio	P-value	FDR	OR	P-value	FDR	OR	P-value	FDR	Effect size (beta) of interaction	P-value	FDR
Peripheral vascular disease	3543	3.746242655	0	0	3.142251542	0.453975658	1	33.90741219	0.023168974	1	5.012019796	4.2822E-273	8.3567E-271	0.13336242	0.016724845	0.199879226	0.539738631	0.850182325	1
Sepsis	4095	9.285059998	0	0	0.106649931	0.026716466	0.81684551	1.199617026	0.864032724	1	4.709368608	8.2264E-273	8.3567E-271	0.095939054	0.003755363	0.069360748	0.03813855	0.98895386	1
Heart failure	5692	3.818480998	0	0	0.244154791	0.243637445	1	2.586467866	0.449126176	1	3.137707099	1.6484E-161	1.1163E-159	0.232535737	0.056613367	0.426000101	2.990487855	0.252897669	1
Stroke	8666	2.589395015	0	0	0.408501713	0.457311754	1	4.022253785	0.263375044	1	2.679144179	2.1766E-156	1.1055E-154	0.228277607	0.026564797	0.269855321	2.836695555	0.215554567	1
Chronic kidney disease	4882	4.393308531	0	0	0.156972312	0.124557655	1	1.579933899	0.714180893	1	3.208153442	1.2582E-151	5.1126E-150	0.179921364	0.034176894	0.294837904	2.067073282	0.454210564	1
Atrial fibrillation	14276	2.755557629	0	0	0.340047727	0.220765271	1	4.2209119	0.12592236	1	2.189888272	1.2448E-134	4.2151E-133	0.08035258	7.09344E-06	0.00036029	-0.717279221	0.713818491	1
Major bleeding	7957	2.845846526	0	0	0.017674399	0.001394428	0.099479542	0.147420629	0.142232319	1	2.336851225	9.111E-93	2.64437E-91	0.032158834	9.84372E-06	0.000399985	-4.329675363	0.102865667	1
Any cancer	33031	1.767835375	0	0	0.12079657	0.009105869	0.487214654	1.155281576	0.869874593	1	1.578427348	5.20885E-73	1.17585E-71	0.122681218	1.56741E-06	0.000106149	0.691897555	0.66030404	1
Coronary artery disease	17973	1.398605832	2.42775E-10	2.36179E-09	1.246725077	0.832151824	1	15.32269187	0.012398775	1	1.70887974	2.78284E-63	5.65382E-62	0.161045138	0.001122884	0.032590516	1.44286874	0.460452002	1
Other cancer	9132	2.2045237	0	0	0.882998127	0.921978699	1	9.371290213	0.08811694	1	1.97606477	1.41125E-62	2.60654E-61	0.187764648	0.023700203	0.253427036	2.072773882	0.413196778	1
Type 2 Diabetes	18896	1.41439862	1.9556E-11	2.20285E-10	0.189479318	0.118275645	1	1.809851199	0.594807676	1	1.643833561	1.25639E-55	2.12714E-54	0.113763583	0.00012559	0.004252645	0.407799722	0.836712942	1
Asthma	48838	1.478340902	0	0	0.24050233	0.063872557	1	2.885754073	0.20929101	1	1.438332455	1.03536E-54	1.61808E-53	0.356156548	0.009186663	0.124428831	5.056341967	0.000504155	0.102427884
Sleep apnoea	4152	2.301555773	0	0	3.281718741	0.520335757	1	36.40984517	0.055553815	1	2.354891882	1.54108E-49	2.23641E-48	0.446190027	0.447174879	1	4.887047979	0.171765228	1
Gastrointestinal bleeding	4845	2.826156857	0	0	0.003033018	0.000489876	0.099479542	0.021735395	0.024007686	1	2.051360316	4.18564E-38	5.66924E-37	0.037489597	0.001948921	0.049494695	-3.596556299	0.31518183	1
Osteoarthritis	33597	1.333261662	1.04587E-10	1.1192E-09	0.055601482	0.000929868	0.099479542	0.478923025	0.431302467	1	1.379281596	4.40458E-35	5.59293E-34	0.094676571	1.61284E-07	3.27676E-05	-0.26927607	0.867321098	1
Pneumonia	5798	1.3668906	0.001635411	0.011290788	2.201339419	0.683307554	1	23.77054968	0.104657562	1	1.855601941	9.63419E-32	1.15139E-30	0.219396311	0.116534101	0.763740491	2.695631557	0.408393431	1
Aortic aneurysm	1477	2.66234353	1.66533E-15	2.09658E-14	0.524014922	0.807348346	1	7.897014903	0.436298001	1	2.628385112	8.23534E-31	8.80607E-30	0.009915396	0.005025825	0.076850889	-6.908673432	0.207761595	1
Colorectal cancer	2071	2.18235479	1.37004E-10	1.39628E-09	0.237670088	0.582895801	1	2.217066399	0.763987518	1	2.366340941	8.15922E-31	8.80607E-30	0.104132134	0.114930261	0.763740491	0.047284006	0.99211942	1
Pulmonary fibrosis	865	4.854618141	0	0	0.004500925	0.067668659	1	0.050759865	0.309344659	1	3.003490027	3.02601E-26	3.07393E-25	0.250991798	0.476321217	1	3.27456648	0.612816203	1
IBD	3302	1.439788287	0.006241585	0.039289359	0.011747157	0.131563755	1	0.119146837	0.468303983	1	2.000476185	8.73952E-24	8.45518E-23	0.025161786	0.005295689	0.076850889	-4.609178455	0.295105536	1
Depression	22902	1.241219179	0.000276547	0.001972907	0.090378962	0.049726116	1	0.869852812	0.912452205	1	1.327376813	3.81128E-17	3.51968E-16	0.047880936	9.13156E-07	9.27618E-05	-2.796702219	0.191420185	1
Gallstone	6443	1.438640224	0.000117422	0.00096657	0.024214927	0.068119954	1	0.262063632	0.514794904	1	1.54733691	1.74078E-16	1.53769E-15	0.050186272	0.002739823	0.061849256	-2.154846365	0.52171374	1
Osteoporosis	6250	1.340710309	0.002060311	0.013779766	1.513182203	0.831136074	1	14.89690763	0.169558614	1	1.532058294	2.67785E-16	2.26689E-15	0.261656459	0.162060646	0.997741658	2.961659471	0.360937102	1
Aortic stenosis	1582	2.249428039	3.60963E-10	3.35888E-09	0.017392484	0.140718747	1	0.24799929	0.608449511	1	2.02882094	2.49188E-15	2.02508E-14	0.019234693	0.0223037	0.251743862	-5.510765385	0.338730287	1
Breast cancer	8521	1.942995535	0	0	0.046349891	0.064133402	1	0.417742782	0.605068366	1	1.426938598	1.3847E-13	1.08203E-12	0.146959033	0.029532949	0.285720895	1.209783437	0.685875146	1
Cervical malignancy	2951	1.254270992	0.183846495	1	0.003210859	0.114039099	1	0.030908588	0.336950979	1	1.663399553	3.52098E-10	2.55482E-09	0.252418015	0.361181971	1	3.219045651	0.522342661	1
Gastric reflux	17539	1.256279601	0.000189213	0.001446279	0.591655259	0.666589403	1	6.604437446	0.134661803	1	1.253765638	6.23286E-10	4.36661E-09	0.187689064	0.011306174	0.143565522	2.161844005	0.3414986	1
Hayfever	22950	0.88904734	0.081867619	0.461091926	0.106722624	0.119096049	1	1.001734025	0.999059348	1	0.798378099	6.08877E-08	3.99046E-07	0.196652783	0.032633829	0.294837904	2.251628191	0.385942038	1
Intracranial aneurysm	721	2.016770478	0.00228014	0.0147879	0.078485848	0.675444163	1	0.369748949	0.863795571	1	2.109903119	9.59876E-08	6.09424E-07	0.044409376	0.28182146	1	-6.01861698	0.523902173	1
Prolapsed disc	6604	1.28029713	0.01316373	0.078259205	0.010064745	0.024711955	0.81684551	0.101939675	0.266311402	1	1.332164842	1.09834E-06	6.76204E-06	0.037580928	0.003252572	0.066081725	-3.271290722	0.38143558	1
Gout	5556	1.260496864	0.017399017	0.100642624	1.42923845	0.857035371	1	11.30120537	0.225371346	1	1.335463976	2.68007E-06	1.60148E-05	0.536076453	0.58087008	1	5.362298722	0.157393951	1
Hyperthyroidisim	20730	1.079219187	0.230501452	1	0.696679601	0.77603536	1	7.691431721	0.119023722	1	1.171749746	6.04869E-06	3.51113E-05	0.348836475	0.088066508	0.61697456	4.336541769	0.042313434	1
Irritable bowel syndrome	9541	0.904188131	0.332323426	1	0.463269387	0.715388595	1	4.040488239	0.513441308	1	1.248205848	1.36882E-05	7.72499E-05	1.080283638	0.933050785	1	8.015361073	0.010006733	1
Uterine fibroids	5960	0.88270327	0.336967288	1	5.98220186	0.502526291	1	57.88727525	0.129935928	1	1.198036229	0.00393479	0.021037419	0.036240333	0.005003054	0.076850889	-3.211405628	0.416209245	1
Skin cancer	8907	1.029812573	0.746351814	1	0.025734796	0.063491291	1	0.212903828	0.439018185	1	1.119943127	0.027741626	0.144517945	0.171324785	0.063897454	0.463639044	1.756136645	0.585243927	1
Diabetic retinopathy	1779	1.747564374	5.45706E-05	0.000486639	0.070604061	0.380762124	1	0.561564022	0.850259385	1	0.794605179	0.078153118	0.387272743	0.111074911	0.188435331	1	-0.361029012	0.964482304	1
Migraine	11762	1.12030149	0.192153634	1	0.008271335	0.014147001	0.605554655	0.065516926	0.168936106	1	1.065778242	0.204882459	0.99108286	0.146823111	0.038177964	0.298327918	1.31354329	0.674229734	1
Anxiety	5740	1.000293916	0.998152603	1	11.68524686	0.334367545	1	124.5331515	0.06071956	1	1.024596743	0.735326277	1	0.354449465	0.436893362	1	4.146532552	0.354448779	1
Pulmonary hypertension	718	8.369518848	0	0	0.255900712	0.581143214	1	4.481696072	0.542524875	1	0.92096947	0.680839195	1	0.107472707	0.244013546	1	2.169530576	0.860137772	1
Sciatica	3927	0.931095223	0.626301663	1	0.5318195	0.839628419	1	4.686415525	0.620190608	1	0.953410281	0.582128718	1	0.084929551	0.133290437	0.846259371	-0.806968318	0.882898102	1

Supplemental Table IV: Results of the interaction analysis for ischaemic stroke

		Survival analysis									Cross-sectional analysis								
		Ischaemic stroke events in individuals with risk factor			Ischaemic stroke events for genetically lower F11			Ischaemic stroke events - interaction between risk			Risk of ischaemic stroke in individuals with risk factor			Risk of ischaemic stroke for genetically lower F11			Risk of ischaemic stroke - interaction between risk		
Putative risk factor	Number individuals with risk factor present	HR	P-value	FDR	HR	P-value	FDR	HR ratio	P-value	FDR	OR	P-value	FDR	OR	P-value	FDR	Effect size (beta) of interaction	P-value	FDR
Atrial fibrillation	14276	6.449539297	0	0	0.177591452	0.020053773	1	0.677272404	0.656587805	1	5.742887704	0	0	0.323305711	0.076550719	1	-2.535648465	0.297794076	1
Heart failure	5692	4.936108817	0	0	0.441119099	0.510271709	1	2.265710299	0.532125467	1	4.865988505	1.4914E-166	1.5554E-164	0.561665438	0.566679189	1	0.227006738	0.948914708	1
Coronary artery disease	17973	2.852306671	0	0	0.178881251	0.058321452	1	0.759485704	0.785178984	1	2.953869915	8.0378E-132	4.1914E-130	0.540406335	0.391800095	1	0.069958458	0.979018852	1
Major bleeding	7957	3.948306395	0	0	1.167393997	0.905521266	1	5.191598788	0.228696094	1	3.959386527	9.3973E-118	3.9203E-116	1.187425549	0.870297923	1	2.136933187	0.561684373	1
Chronic kidney disease	4882	4.231741106	0	0	1.54464481	0.763231809	1	10.58622097	0.113937563	1	4.393131776	3.0029E-115	1.0439E-113	0.666771912	0.724332439	1	1.618544108	0.683659007	1
Peripheral vascular disease	3543	4.257865026	0	0	0.30688259	0.467747955	1	1.519241494	0.801351825	1	4.711163666	5.5795E-101	1.6626E-99	0.177553517	0.191165908	1	-3.917389381	0.386359224	1
Venous thromboembolism	13563	2.534881535	0	0	0.37947018	0.443876781	1	1.651564806	0.705878926	1	2.66859663	1.08363E-71	2.82534E-70	1.175042811	0.869354888	1	2.567809024	0.456513935	1
Type 2 Diabetes	18896	2.156054462	0	0	0.25819136	0.230854754	1	1.179903628	0.890658987	1	2.282651177	8.37039E-65	1.93992E-63	1.117464112	0.893238255	1	2.811792612	0.344861924	1
Sepsis	4095	3.736407537	0	0	1.449480996	0.833531634	1	7.444118013	0.26758793	1	3.621137524	6.53149E-59	1.36237E-57	0.654952853	0.769870161	1	0.612898793	0.901408374	1
Intracranial aneurysm	721	6.225646054	0	0	0.028734616	0.387206244	1	0.349404671	0.787919524	1	8.463249999	2.66821E-49	5.05952E-48	0.093436688	0.415348326	1	-3.4000471	0.721577156	1
Aortic stenosis	1582	4.014990583	0	0	0.029493842	0.149935308	1	0.141722014	0.430188855	1	3.88670398	2.21391E-35	3.84823E-34	0.252251769	0.496059835	1	-2.426194924	0.72082903	1
Aortic aneurysm	1477	3.114271173	0	0	6.688088356	0.488429511	1	35.18589166	0.196903812	1	3.081089725	9.63119E-22	1.54532E-20	15.33437551	0.206999981	1	11.1668445	0.120140447	1
Depression	22902	1.382536007	1.08636E-05	0.000116253	0.337775142	0.483702268	1	1.420339619	0.826823667	1	1.583428734	2.55378E-13	3.80484E-12	1.088255981	0.939753108	1	2.221611454	0.567434839	1
Gastrointestinal bleeding	4845	2.032918186	3.46932E-11	4.36772E-10	0.152874597	0.432327273	1	0.445138958	0.738126582	1	2.062623611	3.08331E-13	4.28753E-12	0.076412482	0.171299464	1	-7.421486312	0.243282154	1
Sleep apnoea	4152	2.256997062	2.498E-14	3.34143E-13	0.43641528	0.712938547	1	1.543581581	0.848043264	1	2.064443935	1.44157E-12	1.87931E-11	1.469488652	0.836897398	1	2.952042167	0.637328026	1
Other cancer	9132	1.699974418	3.81792E-10	4.53956E-09	0.09739955	0.176187994	1	0.39273703	0.597268317	1	1.689926185	1.07775E-11	1.32236E-10	0.306488898	0.399553737	1	-2.257505376	0.637893016	1
Pulmonary fibrosis	865	2.596416622	3.30619E-07	3.7242E-06	9.704613656	0.567172113	1	90.40197213	0.255270864	1	2.588488968	7.70728E-08	8.93121E-07	1.680109674	0.878342275	1	4.830421348	0.663678609	1
Hayfever	22950	0.751011015	0.002142609	0.018342645	0.118556354	0.272806777	1	0.458588325	0.695563264	1	0.652087309	1.48218E-06	1.62716E-05	0.184778395	0.301078622	1	-4.005327841	0.471611383	1
Hyperthyroidisim	20730	1.267249744	0.001987821	0.017726584	1.483693478	0.798236165	1	8.320651272	0.183928109	1	1.329112008	4.84044E-05	0.00050482	1.228979502	0.865778718	1	3.025417282	0.470806638	1
Any cancer	33031	1.247790069	7.27733E-05	0.000741672	0.332515625	0.311375609	1	1.585361193	0.69317221	1	1.180362381	0.001374555	0.013652889	0.751378557	0.749777307	1	1.175616101	0.711957519	1
Osteoporosis	6250	1.313445152	0.024045684	0.177459026	5.588914841	0.484782243	1	27.02464521	0.184152558	1	1.41639849	0.001795152	0.017020021	7.400136798	0.31853131	1	8.538579365	0.204065397	1
Pneumonia	5798	1.123197243	0.377151722	1	0.018446069	0.135338364	1	0.08210478	0.354783961	1	1.36953876	0.003584468	0.031152656	0.395258267	0.635642547	1	-1.139898271	0.86307862	1
Gout	5556	1.191969198	0.123946823	0.828980619	0.497834822	0.776712156	1	2.485910317	0.711716958	1	1.268610707	0.01591265	0.127658811	0.041184631	0.087613445	1	-8.528016811	0.173729024	1
IBD	3302	1.599531828	0.002819906	0.023212412	0.00070399	0.044967779	1	0.004868258	0.139727183	1	1.383322691	0.032275328	0.2404331	0.001431003	0.029103512	1	-19.24515115	0.054743265	1
Asthma	48838	1.163761236	0.003895838	0.030881339	0.827603737	0.860070211	1	4.444185679	0.195959754	1	1.092567092	0.070201454	0.504928314	1.963931523	0.420432543	1	4.760007461	0.113061895	1
Uterine fibroids	5960	0.790437371	0.203845396	1	2.90786835	0.79128354	1	9.705130759	0.570919579	1	0.734151286	0.090338634	0.628107358	28.68394776	0.301625328	1	12.55408044	0.244585181	1
Anxiety	5740	1.155711472	0.346485135	1	8.663942228	0.508608427	1	24.47621083	0.329188376	1	1.183497209	0.214693935	1	1.338417996	0.906845671	1	2.152436955	0.79623189	1
Breast cancer	8521	1.060492826	0.645839957	1	0.23768872	0.597534978	1	1.165583505	0.956233621	1	0.95285737	0.707940091	1	0.311508878	0.618550311	1	-1.744338885	0.827154847	1
Cervical malignancy	2951	1.050952706	0.848394406	1	0.760001955	0.957575687	1	2.039390693	0.889560691	1	1.062212086	0.800160224	1	0.151061934	0.676974329	1	-3.946508248	0.78979656	1
Colorectal cancer	2071	1.175808009	0.386001078	1	1.242415147	0.957791889	1	7.07141415	0.635921503	1	1.014778762	0.935863128	1	3.330292297	0.724461878	1	7.064036456	0.535404961	1
Diabetic retinopathy	1779	4.253646798	0	0	0.624913273	0.84633078	1	2.663715156	0.690901713	1	1.050625409	0.818826446	1	0.861310089	0.938061757	1	-15.5075196	0.271024937	1
Gallstone	6443	0.83842557	0.247094215	1	0.000813024	0.044040327	1	0.005436236	0.13787814	1	0.950945054	0.701913368	1	0.00921616	0.065180623	1	-13.28033219	0.118624294	1
Gastric reflux	17539	0.997289446	0.973772777	1	0.209425956	0.35309334	1	0.937488214	0.970284089	1	0.972387682	0.709369206	1	1.090849816	0.9480756	1	2.220134627	0.62809761	1
Irritable bowel syndrome	9541	1.022712353	0.860364242	1	18.15325699	0.254328058	1	76.88530992	0.091682608	1	0.843165962	0.179355165	1	5.767594609	0.444173252	1	7.463210026	0.331221647	1
Migraine	11762	0.980072753	0.870135979	1	1.156084257	0.95400521	1	3.502534583	0.623399632	1	0.95669575	0.69452177	1	1.335824414	0.886706945	1	1.970116695	0.774166834	1
Osteoarthritis	33597	1.139028876	0.022983692	0.175679347	0.274157945	0.251136034	1	1.184031868	0.88812903	1	1.075166492	0.174342724	1	0.547354436	0.515863785	1	-0.33458386	0.918380323	1
Prolapsed disc	6604	0.874821934	0.368168047	1	2.239531924	0.791581483	1	9.064753612	0.4739876	1	0.881709888	0.340805531	1	2.053326901	0.766081702	1	4.371357546	0.588146929	1
Pulmonary hypertension	718	4.501125807	0	0	10.93348095	0.478076738	1	69.26191538	0.209606033	1	0.789495231	0.565276492	1	2.258271216	0.782827255	1	-20.41802301	0.450436187	1
Sciatica	3927	1.131345641	0.455697786	1	1.612218973	0.896630994	1	8.615249917	0.555230416	1	1.041455187	0.795134175	1	2.999298024	0.70261428	1	6.315947744	0.509831161	1
Skin cancer	8907	1.003555737	0.974302774	1	1.259860059	0.914699204	1	6.299146718	0.404653747	1	1.016077707	0.870981368	1	3.418545007	0.485300556	1	6.230039368	0.297172064	1

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