

## Tables and Figures (including Supplementary Figures and Tables)

Table 1.

Dataset	Training (n=1226)			Holdout (n=530)			All Dataset (n=1756)			ANOVA or Chi-square		Young Stroke (n=877)			Old Stroke (n=879)			ANOVA or Chi-square	
Feature	N	Mean±SD or Frequency(%)	%Missing	N	Mean±SD or Frequency(%)	%Missing	N	Mean±SD or Frequency(%)	%Missing	$F$ or $\chi^2$ statistics	pvalue	N	Mean±SD or Frequency(%)	%Missing	N	Mean±SD or Frequency(%)	%Missing	$F$ or $\chi^2$ statistics	pvalue
AGE_AT_INDEX	1226	66.42±12.03	0.00	530	66.35±12.76	0.00	1756	66.4±12.25	0.00	0.01	0.91	877	56.83±8.44	0.00	879	75.94±6.82	0.00	2720.50	0.00
AGE_AT_INDEX (≥66.8))	614	50.10	0.00	265	50.00	0.00	879	50.10	0.00	0.00	0.98	877	50.00	0.00	879	50.00	0.00	NA	NA
Hypertension	952	77.70	0.00	399	75.30	0.00	1351	76.90	0.00	1.17	0.28	606	69.10	0.00	745	84.76	0.00	60.64	6.84E-15
Systolic blood pressure	949	132.5±22.43	22.59	418	130.31±18.71	21.13	1367	131.83±21.38	22.15	3.05	0.08	734	131.57±21.42	16.31	633	132.12±21.34	27.99	0.23	0.63
Diastolic blood pressure	949	72.07±11.35	22.59	418	71.1±10.54	21.13	1367	71.78±11.11	22.15	2.22	0.14	734	73.43±11.40	22.59	633	69.86±10.45	21.13	36.00	2.52E-09
BMI	1225	29.6±7.23	<0.01	528	29.27±7.25	<0.01	1753	29.5±7.23	<0.01	0.78	0.38	875	30.89±7.66	0.23	878	28.12±6.49	0.11	18.62	1.79E-05
BMI ≥ 25	905	73.80	<0.01	365	68.90	<0.01	1270	72.30	<0.01	4.17	0.04	698	79.77	0.23	572	65.15	0.11	46.95	7.29E-12
BMI ≥ 30	507	41.40	<0.01	204	38.50	<0.01	711	40.50	<0.01	1.16	0.28	416	47.54	0.23	295	33.60	0.11	35.34	2.76E-09
Sex (Male)	671	54.70	0.00	281	53.00	0.00	952	54.20	0.00	0.44	0.51	485	55.30	0.00	467	53.13	0.00	0.84	0.36
Atrial fibrillation	311	25.37	0.00	141	26.60	0.00	452	25.74	0.00	0.30	0.59	122	13.91	0.00	330	37.54	0.00	128.26	9.86E-30
Coronary Artery Disease	414	33.80	0.00	186	35.10	0.00	600	34.20	0.00	0.29	0.59	236	26.91	0.00	364	41.41	0.00	41.04	1.49E-10
Diabetes	393	32.10	0.00	171	32.30	0.00	564	32.10	0.00	0.01	0.93	299	34.09	0.00	265	30.15	0.00	3.14	0.08
Dyslipidemia	601	49.00	0.00	247	46.60	0.00	848	48.30	0.00	0.87	0.35	432	49.26	0.00	416	47.33	0.00	0.66	0.42
Ever_smoke	679	55.40	19.25	289	54.50	18.11	968	55.10	18.91	0.55	0.46	544	72.73	14.71	424	62.72	23.09	16.33	5.32E-05
Alcohol	180	14.70	40.46	73	13.80	40.19	253	14.40	40.38	0.32	0.57	153	29.03	39.91	100	19.23	40.84	13.72	2.12E-04
NIHSS_7above	163	21.50	38.17	70	21.00	36.98	233	21.30	37.80	0.04	0.84	87	19.3	48.69	146	22.7	26.96	1.83	1.76E-01
NIHSS_10above	94	12.40	38.17	47	14.10	36.98	141	12.90	37.80	0.58	0.45	46	10.2	48.69	95	14.8	26.96	4.93	2.60E-02
NIHSS_16above	51	6.70	38.17	26	7.80	36.98	77	7.10	37.80	0.40	0.53	19	4.2	48.69	58	9	26.96	9.35	2.00E-03
Death up to 5yr	261	21.30	0.00	123	23.20	0.00	384	21.90	0.00	0.80	0.37	103	11.74	0.00	281	31.97	0.00	105.09	1.17E-24
Death up to 3yr	193	15.70	0.00	91	17.20	0.00	284	16.20	0.00	0.56	0.46	69	7.87	0.00	215	24.46	0.00	89.14	3.68E-21
Death up to 1yr	96	7.80	0.00	48	9.10	0.00	144	8.20	0.00	0.74	0.39	29	3.31	0.00	115	13.08	0.00	55.74	8.29E-14

Table 2.

Univariate p value cutoff	Features_Input	Features_selected (LASSO)	C-Index Mean±SE [95%CI]	median improvement again base model	Pathway-specific PRS selected
< 0.1	31 PRSs + Age	24 PRSs + Age	0.705±0.035 [0.637-0.773]	<0.001	GO_RECEPTOR_LOCALIZATION_TO_SYNAPSE //GO_POSITIVE_REGULATION_OF_MEMBRANE_DEPOLARIZATION //GO_POSITIVE_REGULATION_OF_AMYLOID_BETA_FORMATION //GO_ENERGY_RESERVE_METABOLIC_PROCESS //GO_SEROTONIN_RECEPTOR_SIGNALING_PATHWAY //GO_GLOMERULAR_BASEMENT_MEMBRANE_DEVELOPMENT //GO_AMYLOID_BETA_METABOLIC_PROCESS //GO_MONOCYTE_AGGREGATION //GO_NEGATIVE_REGULATION_OF_MAPK_CASCADE //GO_RESPONSE_TO_INTERLEUKIN_1 //GO_NEGATIVE_REGULATION_OF_HEMOPOIESIS //GO_GRANULOCYTE_DIFFERENTIATION //GO_T_CELL_DIFFERENTIATION //GO_FIBRINOLYSIS //GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION //GO_PROTEASOMAL_UBIQUITIN_INDEPENDENT_PROTEIN_CATABOLIC_PROCESS //GO_PROTEIN_LOCALIZATION_TO_PHA/GOPHORE_ASSEMBLY_SITE //GO_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_PEPTIDE_ANTIGEN //GO_ZYMOGEN_ACTIVATION //GO_IMPORT_INTO_NUCLEUS //GO_RESPONSE_TO_TUMOR_NECROSIS_FACTOR //GO_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE_TRANSLOCATION //GO_REGULATION_OF_ODONTOGENESIS //GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS // Age_at_index
< 0.05	20 PRSs + Age	16 PRSs + Age	0.684±0.033 [0.619-0.749]	<0.001	GO_RECEPTOR_LOCALIZATION_TO_SYNAPSE //GO_POSITIVE_REGULATION_OF_MEMBRANE_DEPOLARIZATION //GO_POSITIVE_REGULATION_OF_AMYLOID_BETA_FORMATION //GO_SEROTONIN_RECEPTOR_SIGNALING_PATHWAY //GO_AMYLOID_BETA_METABOLIC_PROCESS //GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION //GO_GRANULOCYTE_DIFFERENTIATION //GO_NEGATIVE_REGULATION_OF_HEMOPOIESIS //GO_FIBRINOLYSIS //GO_PROTEASOMAL_UBIQUITIN_INDEPENDENT_PROTEIN_CATABOLIC_PROCESS //GO_ZYMOGEN_ACTIVATION //GO_IMPORT_INTO_NUCLEUS //GO_RESPONSE_TO_TUMOR_NECROSIS_FACTOR //GO_REGULATION_OF_ODONTOGENESIS //GO_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE_TRANSLOCATION //GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS // Age_at_index
< 0.025	9 PRSs + Age	8 PRSs + Age	0.661±0.036 [0.592-0.731]	0.027	GO_POSITIVE_REGULATION_OF_MEMBRANE_DEPOLARIZATION //GO_POSITIVE_REGULATION_OF_AMYLOID_BETA_FORMATION //GO_AMYLOID_BETA_METABOLIC_PROCESS //GO_PROTEASOMAL_UBIQUITIN_INDEPENDENT_PROTEIN_CATABOLIC_PROCESS //GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION //GO_RESPONSE_TO_TUMOR_NECROSIS_FACTOR //GO_REGULATION_OF_ODONTOGENESIS //GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS // Age_at_index
< 0.01	3 PRSs + Age	2 PRSs + Age	0.643±0.034 [0.575-0.710]	0.233	GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION //GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS // Age_at_index
base model	0 PRSs + Age	0 PRSs + Age	0.626±0.024 [0.578-0.674]	NA	Age_at_index
< 0.1	31 PRSs + Age + 7	16 PRSs + Age + 7 clinical risk factors	0.754±0.031 [0.693-0.814]	<0.001	GO_AMYLOID_BETA_METABOLIC_PROCESS //GO_SEROTONIN_RECEPTOR_SIGNALING_PATHWAY //GO_MONOCYTE_AGGREGATION //GO_NEGATIVE_REGULATION_OF_MAPK_CASCADE //GO_POSITIVE_REGULATION_OF_AMYLOID_BETA_FORMATION //GO_ENERGY_RESERVE_METABOLIC_PROCESS //GO_IMPORT_INTO_NUCLEUS //GO_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_PEPTIDE_ANTIGEN //GO_FIBRINOLYSIS //GO_NEGATIVE_REGULATION_OF_HEMOPOIESIS //GO_ZYMOGEN_ACTIVATION //GO_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE_TRANSLOCATION //GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION //GO_REGULATION_OF_ODONTOGENESIS //GO_RESPONSE_TO_TUMOR_NECROSIS_FACTOR //GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS //Age_at_index //diabetes //dyslipidemia //smoking //coronary_artery_disease //BMI_overweight //atrial_fibrillation //hypertension
< 0.05	20 PRSs + Age + 7	11 PRSs + Age + 7 clinical risk factors	0.751±0.030 [0.693-0.809]	0.02	GO_AMYLOID_BETA_METABOLIC_PROCESS //GO_SEROTONIN_RECEPTOR_SIGNALING_PATHWAY //GO_POSITIVE_REGULATION_OF_AMYLOID_BETA_FORMATION //GO_IMPORT_INTO_NUCLEUS //GO_NEGATIVE_REGULATION_OF_HEMOPOIESIS //GO_FIBRINOLYSIS //GO_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE_TRANSLOCATION //GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION //GO_REGULATION_OF_ODONTOGENESIS //GO_RESPONSE_TO_TUMOR_NECROSIS_FACTOR //GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS //Age_at_index //diabetes //dyslipidemia //smoking //coronary_artery_disease //BMI_overweight //atrial_fibrillation //hypertension
< 0.025	9 PRSs + Age + 7	6 PRSs + Age + 7 clinical risk factors	0.740±0.030 [0.680-0.799]	0.066	GO_AMYLOID_BETA_METABOLIC_PROCESS //GO_POSITIVE_REGULATION_OF_AMYLOID_BETA_FORMATION //GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION //GO_REGULATION_OF_ODONTOGENESIS //GO_RESPONSE_TO_TUMOR_NECROSIS_FACTOR //GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS //Age_at_index //diabetes //dyslipidemia //smoking //coronary_artery_disease //BMI_overweight //atrial_fibrillation //hypertension
< 0.01	3 PRSs + Age + 7	2 PRSs + Age + 7 clinical risk factors	0.729±0.028 [0.674-0.783]	0.319	GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION ///GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS //Age_at_index //diabetes //dyslipidemia //smoking //coronary_artery_disease //BMI_overweight //atrial_fibrillation //hypertension
base model	0 PRSs + Age + 7	0 PRSs + Age + 7 clinical risk factors	0.729±0.027 [0.676-0.782]	NA	Age_at_index// diabetes //dyslipidemia //smoking //coronary_artery_disease //BMI_overweight //atrial_fibrillation //hypertension

Supplementary Table 1A.

Features	Association with IS			p value < 0.1 for univariate cox ph			p value < 0.1 for multivariate cox ph			p value < 0.05 for multivariate cox ph			p value < 0.025 for multiivariate cox ph			p value < 0.001 for multiivariate cox ph			Gene-Set
	MAF	Effect/SE	P.value	HR(MEAN/SE[95%CI])	z statistic	p.value	HR(MEAN/SE[95%CI])	z statistic	pvalue	HR(MEAN/SE[95%CI])	z statistic	pvalue	HR(MEAN/SE[95%CI])	z statistic	pvalue	HR(MEAN/SE[95%CI])	z statistic	pvalue	
AGE_AT_ONSET(Binary)				1.96/0.09[1.66-2.32]	7.83	5E-15	3.49/0.17[2.48-4.91]	7.20	6E-13	3.54/0.17[2.52-4.98]	7.29	3E-13	3.74/0.17[2.67-5.23]	7.65	1.96E-14	3.76/0.17[2.69-5.27]	7.71	1.23E-14	
V3259	1	564.91/139.72	5.270E-05	1.27/0.07[1.1-1.46]	3.31	0.001	1.2/0.08[1.04-1.4]	2.46	0.014	1.2/0.08[1.03-1.39]	2.37	0.018	1.25/0.07[1.08-1.45]	3.03	0.002	1.23/0.07[1.07-1.42]	2.85	4.37E-03	GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS
V992	1	853.53/220.5	1.085E-04	1.22/0.07[1.06-1.4]	2.75	0.006	1.03/0.09[0.86-1.22]	0.29	0.770	1.04/0.09[0.88-1.23]	0.43	0.669	1.08/0.08[0.92-1.26]	0.98	0.328	1.16/0.07[1.01-1.33]	2.14	0.032	GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION
V1359	1	549.11/156.5	4.503E-04	1.21/0.07[1.05-1.39]	2.59	0.010													GO_NEGATIVE_REGULATION_OF_EPITHELIAL_CELL_APOPTOTIC_PROCESS
V6819	0.03	-88.61/26.72	9.140E-04	0.83/0.08[0.71-0.97]	-2.39	0.017	0.9/0.11[0.73-1.1]	-1.04	0.300	0.89/0.11[0.72-1.09]	-1.12	0.262	0.88/0.1[0.72-1.08]	-1.20	0.229				GO_POSITIVE_REGULATION_OF_AMYLOID_BETA_FORMATION
V2007	0.03	230.35/48.97	2.550E-06	1.17/0.07[1.03-1.34]	2.38	0.017	1.16/0.07[1.02-1.33]	2.22	0.026	1.16/0.07[1.02-1.33]	2.21	0.027	1.16/0.07[1.02-1.33]	2.26	0.024				GO_REGULATION_OF_ODONTOGENESIS
V3447	1	1239.64/375.79	9.712E-04	1.18/0.07[1.03-1.36]	2.34	0.019	1.11/0.08[0.95-1.3]	1.35	0.177	1.12/0.07[0.97-1.3]	1.51	0.131	1.14/0.07[0.98-1.32]	1.75	0.081				GO_RESPONSE_TO_TUMOR_NECROSIS_FACTOR
V5675	0.03	-254.72/68.62	2.056E-04	0.84/0.07[0.73-0.97]	-2.33	0.020	0.92/0.11[0.74-1.13]	-0.81	0.416	0.91/0.11[0.74-1.12]	-0.91	0.361	0.91/0.1[0.74-1.11]	-0.97	0.334				GO_AMYLOID_BETA_METABOLIC_PROCESS
V4403	1	506.84/93.02	5.070E-08	1.18/0.07[1.02-1.36]	2.26	0.024	1.06/0.09[0.9-1.26]	0.69	0.488	1.09/0.08[0.92-1.28]	0.98	0.329	1.06/0.08[0.9-1.24]	0.66	0.512				GO_PROTEASOMAL_UBIQUITIN_INDEPENDENT_PROTEIN_CATABOLIC_PROCESS
V821	0.03	-159.96/43.79	2.589E-04	0.84/0.08[0.73-0.98]	-2.24	0.025	0.88/0.08[0.75-1.03]	-1.56	0.118	0.88/0.08[0.75-1.03]	-1.59	0.112	0.87/0.08[0.74-1.02]	-1.69	0.092				GO_POSITIVE_REGULATION_OF_MEMBRANE_DEPOLARIZATION
V6519	1	-1014.54/282.46	3.284E-04	0.85/0.07[0.74-0.98]	-2.20	0.028	0.89/0.07[0.77-1.02]	-1.64	0.101	0.88/0.07[0.76-1.01]	-1.79	0.074							GO_RECEPTOR_LOCALIZATION_TO_SYNAPSE
V2450	1	564.07/157.84	3.521E-04	1.17/0.07[1.02-1.35]	2.19	0.029	1.05/0.08[0.9-1.23]	0.66	0.509	1.06/0.08[0.91-1.24]	0.72	0.470							GO_GRANULOCYTE_DIFFERENTIATION
V1216	0.03	-310.83/61.14	3.710E-07	0.85/0.08[0.73-0.99]	-2.15	0.031													GO_REGULATION_OF_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS
V4219	0.03	62.89/17.01	2.178E-04	1.16/0.07[1.01-1.34]	2.14	0.032	1.14/0.07[0.99-1.32]	1.81	0.070	1.13/0.07[0.98-1.31]	1.72	0.085							GO_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE_TRANSLOCATION
V3699	1	585.81/148.78	8.240E-05	1.17/0.07[1.01-1.34]	2.11	0.034	1.07/0.08[0.92-1.26]	0.88	0.380	1.08/0.08[0.92-1.27]	0.98	0.329							GO_ZYMOGEN_ACTIVATION
V3046	1	311.34/89.28	4.882E-04	1.16/0.07[1.01-1.33]	2.10	0.035	1.05/0.08[0.89-1.23]	0.55	0.583	1.07/0.08[0.91-1.25]	0.83	0.405							GO_FIBRINOLYSIS
V5350	0.03	-262.97/67.18	9.060E-05	0.86/0.07[0.74-0.99]	-2.10	0.035													GO_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS
V5736	1	1343.5/284.17	2.270E-06	1.16/0.07[1.01-1.33]	2.08	0.037	1.09/0.07[0.94-1.26]	1.15	0.251	1.1/0.07[0.95-1.27]	1.27	0.205							GO_IMPORT_INTO_NUCLEUS
V6899	0.03	-140.19/38.54	2.752E-04	0.86/0.07[0.74-0.99]	-2.08	0.038													GO_POSITIVE_REGULATION_OF_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS
V1637	1	1212.42/272.06	8.330E-06	1.16/0.07[1.01-1.33]	2.07	0.038	1.03/0.09[0.87-1.22]	0.35	0.729	1.06/0.08[0.9-1.24]	0.70	0.483							GO_NEGATIVE_REGULATION_OF_HEMOPOIESIS
V4297	1	-442.9/129.72	6.396E-04	0.86/0.08[0.74-1]	-2.00	0.046	0.89/0.07[0.77-1.03]	-1.55	0.120	0.89/0.07[0.77-1.03]	-1.55	0.122							GO_SEROTONIN_RECEPTOR_SIGNALING_PATHWAY
V785	1	977.84/285.7	6.201E-04	1.15/0.07[1-1.33]	1.91	0.056	1.06/0.08[0.91-1.24]	0.77	0.443										GO_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_PEPTIDE_ANTIGEN
V6166	0.03	-62.3/15.06	3.510E-05	0.89/0.06[0.79-1.01]	-1.87	0.062	0.92/0.06[0.81-1.04]	-1.38	0.167										GO_MONOCYTE_AGGREGATION
V6818	0.03	-263.63/51.42	2.940E-07	0.87/0.08[0.75-1.01]	-1.84	0.066													GO_REGULATION_OF_AMYLOID_BETA_FORMATION
V333	0.03	-309/86.99	3.820E-04	0.88/0.07[0.77-1.01]	-1.80	0.072	0.89/0.07[0.77-1.03]	-1.60	0.109										GO_ENERGY_RESERVE_METABOLIC_PROCESS
V3197	1	770.44/205.09	1.723E-04	1.13/0.07[0.99-1.31]	1.75	0.080													GO_NEGATIVE_REGULATION_OF_MYELOID_CELL_DIFFERENTIATION
V1910	1	1098.97/318.28	5.546E-04	1.13/0.07[0.98-1.31]	1.73	0.084	1.02/0.08[0.86-1.2]	0.23	0.821										GO_RESPONSE_TO_INTERLEUKIN_1
V5065	0.03	103.88/28.71	2.966E-04	1.12/0.07[0.98-1.29]	1.72	0.086	1.06/0.07[0.93-1.21]	0.83	0.405										GO_PROTEIN_LOCALIZATION_TO_PHAGOPHORE_ASSEMBLY_SITE
V5029	0.03	-204.41/53.4	1.292E-04	1.292E-04	-1.70	0.090													GO_AMYLOID_BETA_FORMATION
V3511	0.03	458.52/137.94	8.870E-04	1.13/0.07[0.98-1.3]	1.69	0.090	1.06/0.08[0.9-1.25]	0.72	0.473										GO_T_CELL_DIFFERENTIATION
V939	0.03	-401.55/120.46	8.575E-04	0.89/0.07[0.77-1.02]	-1.67	0.095	0.94/0.07[0.81-1.09]	-0.85	0.396										GO_NEGATIVE_REGULATION_OF_MAPK_CASCADE
V4929	0.03	-218.54/53.55	4.490E-05	0.88/0.07[0.76-1.02]	-1.66	0.096	0.9/0.08[0.77-1.04]	-1.44	0.150										GO_GLOMERULAR_BASEMENT_MEMBRANE_DEVELOPMENT

Supplementary Table 1B.

Features	Association with IS			p value <0.1 for univariate cox ph			p value <0.1 for multivariate cox ph			p value <0.05 for multivariate cox ph			p value <0.025 for multiivariate cox ph			p value <0.01 for multiivariate cox ph			Gene-Set
	MAF	Effect/SE	P.value	HR(MEAN/SE[95%CI])	z statistic	p.value	HR(MEAN/SE[95%CI])	z statistic	pvalue	HR(MEAN/SE[95%CI])	z statistic	pvalue	HR(MEAN/SE[95%CI])	z statistic	pvalue	HR(MEAN/SE[95%CI])	z statistic	pvalue	
hypertension				1.905/0.171[1.364-2.6	3.78	1.58E-04	1.816/0.22[1.18-2.795]	2.714	6.647E-03	1.805/0.219[1.175-2.774]	2.694	7.070E-03	1.858/0.219[1.209-2.856]	2.825	4.730E-03	1.66/0.215[1.089-2.532]	2.354	1.858E-02	
diabetes				0.764/0.133[0.588-0.9	-2.02	4.37E-02	0.742/0.178[0.524-1.052]	-1.676	9.375E-02	0.742/0.178[0.524-1.052]	-1.677	9.359E-02	0.749/0.178[0.529-1.061]	-1.629	1.033E-01	0.729/0.177[0.516-1.032]	-1.784	7.447E-02	
dyslipidemia				0.478/0.127[0.372-0.6	-5.81	6.42E-09	0.507/0.166[0.367-0.702]	-4.092	4.270E-05	0.499/0.165[0.361-0.689]	-4.22	2.440E-05	0.49/0.164[0.355-0.675]	-4.352	1.350E-05	0.48/0.164[0.348-0.661]	-4.49	7.130E-06	
smoking				2.106/0.231[1.339-3.3	3.22	1.27E-03	0.464/0.16[0.339-0.634]	-4.809	1.520E-06	0.465/0.16[0.34-0.636]	-4.795	1.630E-06	0.472/0.159[0.346-0.644]	-4.739	2.150E-06	0.479/0.159[0.351-0.654]	-4.636	3.560E-06	
coronary artery				1.988/0.119[1.575-2.5	5.79	7.21E-09	1.513/0.152[1.124-2.037]	2.727	6.383E-03	1.51/0.151[1.123-2.03]	2.729	6.343E-03	1.541/0.15[1.147-2.069]	2.874	4.055E-03	1.63/0.149[1.216-2.184]	3.272	1.070E-03	
atrial_fib				2.191/0.121[1.729-2.7	6.49	8.35E-11	1.397/0.155[1.031-1.894]	2.155	3.120E-02	1.411/0.155[1.042-1.91]	2.227	2.597E-02	1.386/0.154[1.024-1.875]	2.112	3.468E-02	1.371/0.154[1.013-1.854]	2.043	4.107E-02	
AGE_AT_INDEX_BINARY				3.506/0.138[2.673-4.5	9.06	1.30E-19	2.455/0.184[1.71-3.524]	4.868	1.130E-06	2.453/0.185[1.708-3.522]	4.862	1.160E-06	2.489/0.184[1.736-3.57]	4.956	7.210E-07	2.479/0.184[1.729-3.555]	4.937	7.940E-07	
BMI_Overweight				0.497/0.12[0.392-0.62	-5.82	5.86E-09	0.577/0.153[0.428-0.779]	-3.592	3.280E-04	0.566/0.152[0.42-0.762]	-3.749	1.780E-04	0.564/0.152[0.419-0.759]	-3.778	1.580E-04	0.552/0.15[0.411-0.742]	-3.949	7.840E-05	
V3259	1	564.91/139.72	5.270E-05	1.27/0.07[1.1-1.46]	3.31	0.001	1.203/0.077[1.035-1.398]	2.415	0.015741	1.193/0.076[1.028-1.385]	2.315	0.021	1.241/0.074[1.073-1.435]	2.911	3.598E-03	1.243/0.074[1.075-1.437]	2.935	3.330E-03	GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS
V992	1	853.53/220.5	1.085E-04	1.22/0.07[1.06-1.4]	2.75	0.006	1.08/0.076[0.93-1.254]	1.009	0.313206	1.093/0.076[0.943-1.268]	1.181	0.238	1.11/0.073[0.962-1.28]	1.428	0.153	1.152/0.071[1.003-1.323]	2.005	4.497E-02	GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION
V1359	1	549.11/156.5	4.503E-04	1.21/0.07[1.05-1.39]	2.59	0.010													GO_NEGATIVE_REGULATION_OF_EPITHELIAL_CELL_APOPTOTIC_PROCESS
V6819	0.025	-88.61/26.72	9.140E-04	0.83/0.08[0.71-0.97]	-2.39	0.017	0.935/0.109[0.755-1.157]	-0.621	0.53463	0.933/0.109[0.753-1.156]	-0.631	0.528	0.912/0.108[0.738-1.127]	-0.854	0.393				GO_POSITIVE_REGULATION_OF_AMYLOID_BETA_FORMATION
V2007	0.025	230.35/48.97	2.550E-06	1.17/0.07[1.03-1.34]	2.38	0.017	1.133/0.069[0.99-1.296]	1.817	0.069285	1.132/0.068[0.99-1.294]	1.812	0.070	1.133/0.067[0.993-1.294]	1.856	0.063				GO_REGULATION_OF_ODONTOGENESIS
V3447	1	1239.64/375.79	9.712E-04	1.18/0.07[1.03-1.36]	2.34	0.019	1.134/0.079[0.971-1.324]	1.59	0.111753	1.13/0.077[0.972-1.313]	1.594	0.111	1.154/0.076[0.994-1.34]	1.877	0.061				GO_RESPONSE_TO_TUMOR_NECROSIS_FACTOR
V5675	0.025	-254.72/68.62	2.056E-04	0.84/0.07[0.73-0.97]	-2.33	0.020	0.875/0.104[0.714-1.073]	-1.286	0.198583	0.854/0.104[0.697-1.046]	-1.529	0.126	0.875/0.102[0.717-1.068]	-1.314	0.189				GO_AMYLOID_BETA_METABOLIC_PROCESS
V4403	1	506.84/93.02	5.070E-08	1.18/0.07[1.02-1.36]	2.26	0.024													GO_PROTEASOMAL_UBIQUITIN_INDEPENDENT_PROTEIN_CATABOLIC_PROCESS
V821	0.025	-159.96/43.79	2.589E-04	0.84/0.08[0.73-0.98]	-2.24	0.025													GO_POSITIVE_REGULATION_OF_MEMBRANE_DEPOLARIZATION
V6519	1	-1014.54/282.46	3.284E-04	0.85/0.07[0.74-0.98]	-2.20	0.028													GO_RECEPTOR_LOCALIZATION_TO_SYNAPE
V2450	1	564.07/157.84	3.521E-04	1.17/0.07[1.02-1.35]	2.19	0.029													GO GRANULOCYTE_DIFFERENTIATION
V1216	0.025	-310.83/61.14	3.710E-07	0.85/0.08[0.73-0.99]	-2.15	0.031													GO_REGULATION_OF_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS
V4219	0.025	62.89/17.01	2.178E-04	1.16/0.07[1.01-1.34]	2.14	0.032	1.169/0.075[1.009-1.355]	2.083	0.037252	1.149/0.075[0.993-1.33]	1.86	0.063						GO_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE_TRANSLOCATION	
V3699	1	585.81/148.78	8.240E-05	1.17/0.07[1.01-1.34]	2.11	0.034	1.094/0.083[0.929-1.287]	1.078	0.280943										GO_ZYMOGEN_ACTIVATION
V3046	1	311.34/89.28	4.882E-04	1.16/0.07[1.01-1.33]	2.10	0.035	1.019/0.082[0.868-1.198]	0.232	0.816317	1.086/0.074[0.94-1.255]	1.123	0.262						GO_FIBRINOLYSIS	
V5350	0.025	-262.97/67.18	9.060E-05	0.86/0.07[0.74-0.99]	-2.10	0.035													GO_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS
V5736	1	1343.5/284.17	2.270E-06	1.16/0.07[1.01-1.33]	2.08	0.037	1.09/0.077[0.937-1.268]	1.119	0.263	1.094/0.076[0.943-1.269]	1.183	0.237						GO_IMPORT_INTO_NUCLEUS	
V6899	0.025	-140.19/38.54	2.752E-04	0.86/0.07[0.74-0.99]	-2.08	0.038													GO_POSITIVE_REGULATION_OF_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS
V1637	1	1212.42/272.06	8.330E-06	1.16/0.07[1.01-1.33]	2.07	0.038	1.074/0.076[0.925-1.248]	0.938	0.348481	1.076/0.076[0.927-1.248]	0.958	0.338						GO_NEGATIVE_REGULATION_OF_HEMOPOIESIS	
V4297	1	-442.9/129.72	6.396E-04	0.86/0.08[0.74-1]	-2.00	0.046	0.886/0.072[0.77-1.02]	-1.682	0.092622	0.883/0.072[0.767-1.016]	-1.738	0.082						GO_SEROTONIN_RECEPTOR_SIGNALING_PATHWAY	
V785	1	977.84/285.7	6.201E-04	1.15/0.07[1-1.33]	1.91	0.056	1.05/0.075[0.907-1.215]	0.652	0.514326										GO_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_PEPTIDE_ANTIGEN
V6166	0.025	-62.3/15.06	3.510E-05	0.89/0.06[0.79-1.01]	-1.87	0.062	0.919/0.067[0.805-1.048]	-1.258	0.208239										GO_MONOCYTE_AGGREGATION
V6818	0.025	-263.63/51.42	2.940E-07	0.87/0.08[0.75-1.01]	-1.84	0.066													GO_REGULATION_OF_AMYLOID_BETA_FORMATION
V333	0.025	-309/86.99	3.820E-04	0.88/0.07[0.77-1.01]	-1.80	0.072	0.908/0.073[0.786-1.048]	-1.32	0.187										GO_ENERGY_RESERVE_METABOLIC_PROCESS
V3197	1	770.44/205.09	1.723E-04	1.13/0.07[0.99-1.31]	1.75	0.080													GO_NEGATIVE_REGULATION_OF_MYELOID_CELL_DIFFERENTIATION
V1910	1	1098.97/318.28	5.546E-04	1.13/0.07[0.98-1.31]	1.73	0.084													GO_RESPONSE_TO_INTERLEUKIN_1
V5065	0.025	103.88/28.71	2.966E-04	1.12/0.07[0.98-1.29]	1.72	0.086													GO_PROTEIN_LOCALIZATION_TO_PHAGOPHORE_ASSEMBLY_SITE
V5029	0.025	-204.41/53.4	1.292E-04	0.88/0.07[0.76-1.02]	-1.70	0.090													GO_AMYLOID_BETA_FORMATION
V3511	0.025	458.52/137.94	8.870E-04	1.13/0.07[0.98-1.3]	1.69	0.090													GO_T_CELL_DIFFERENTIATION
V939	0.025	-401.55/120.46	8.575E-04	0.89/0.07[0.77-1.02]	-1.67	0.095	0.924/0.074[0.799-1.069]	-1.058	0.289924										GO_NEGATIVE_REGULATION_OF_MAPK_CASCADE
V4929	0.025	-218.54/53.55	4.490E-05	0.88/0.07[0.76-1.02]	-1.66	0.096													GO_GLOMERULAR_BASEMENT_MEMBRANE_DEVELOPMENT

Figure 1.

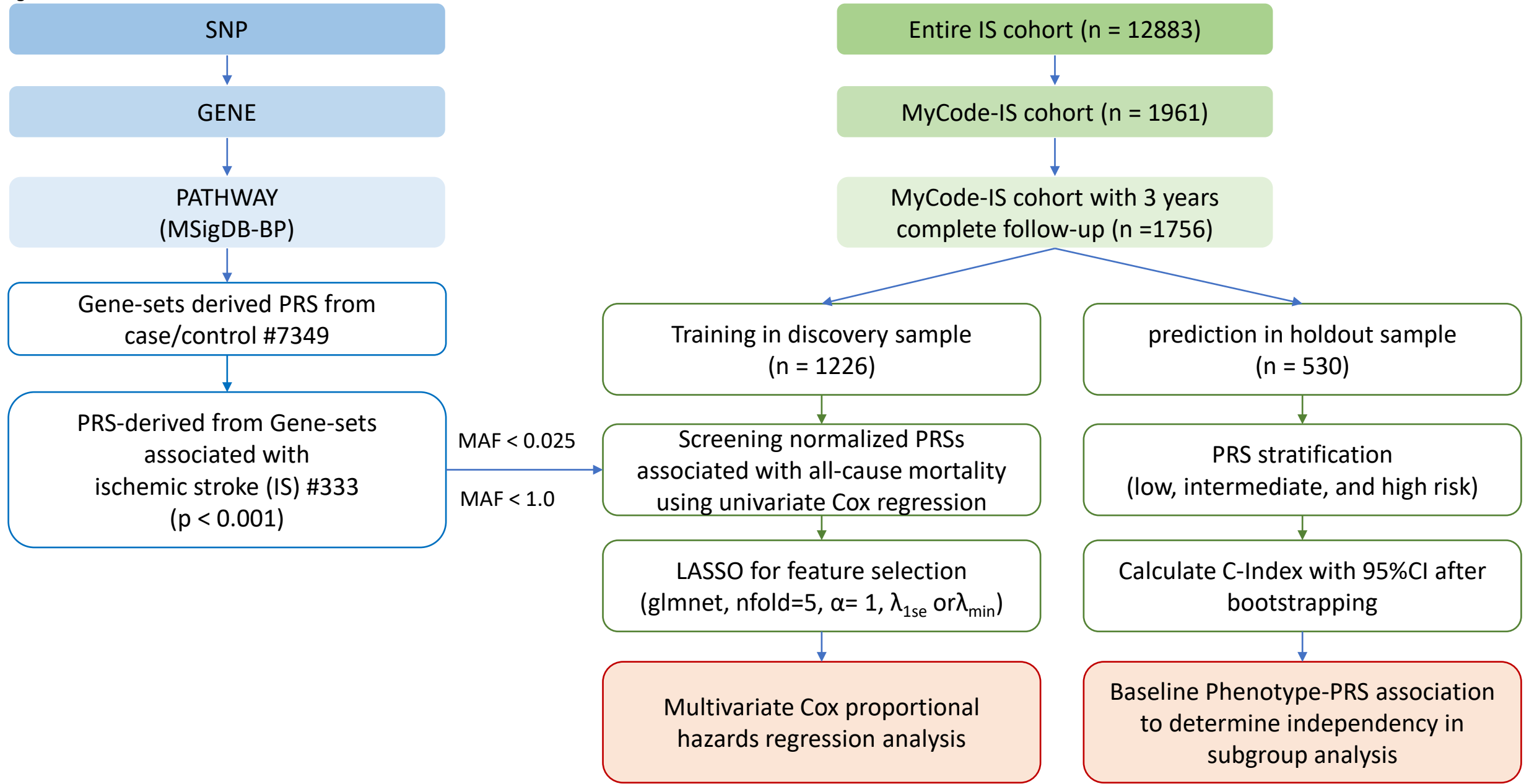


Figure 2.

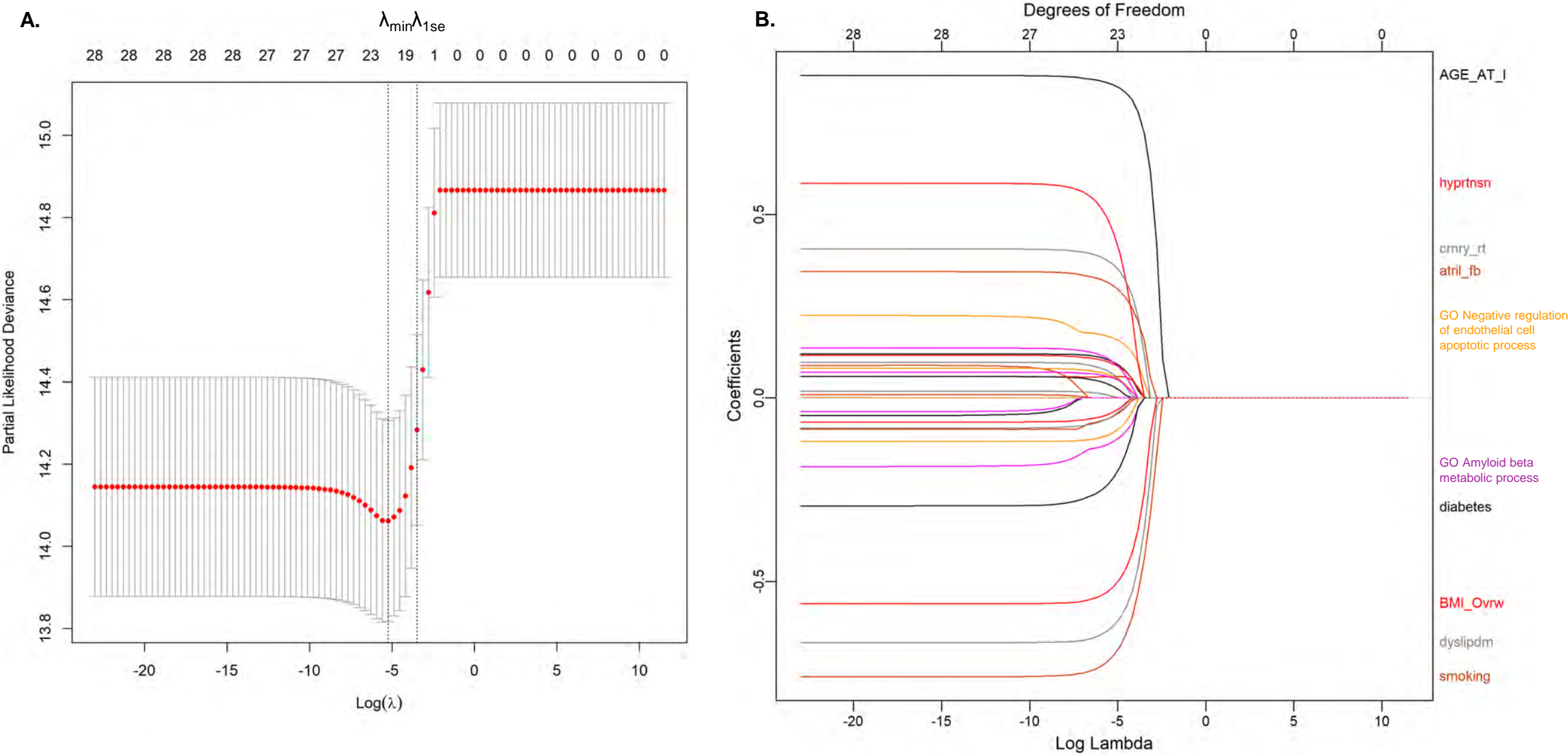
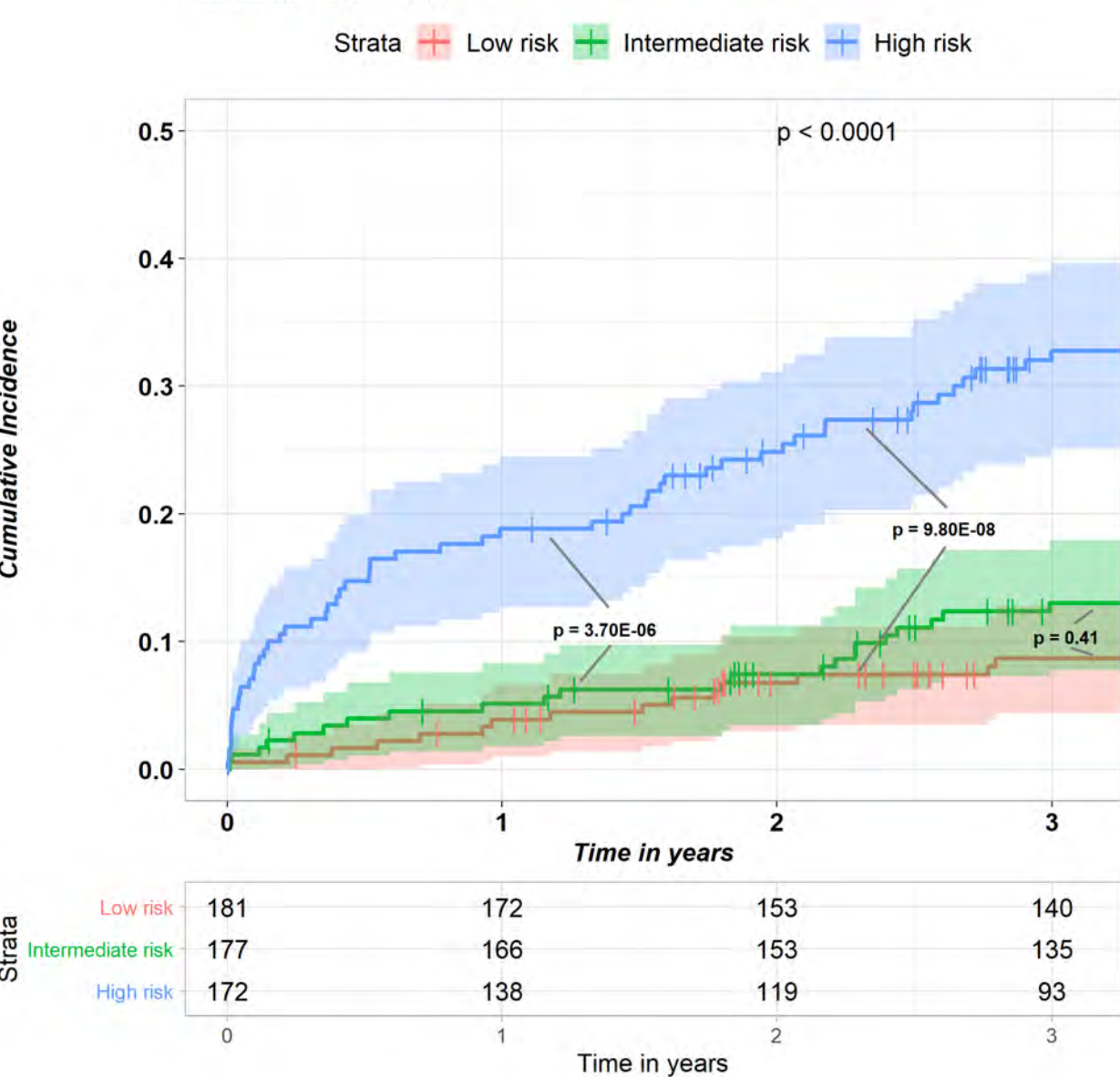
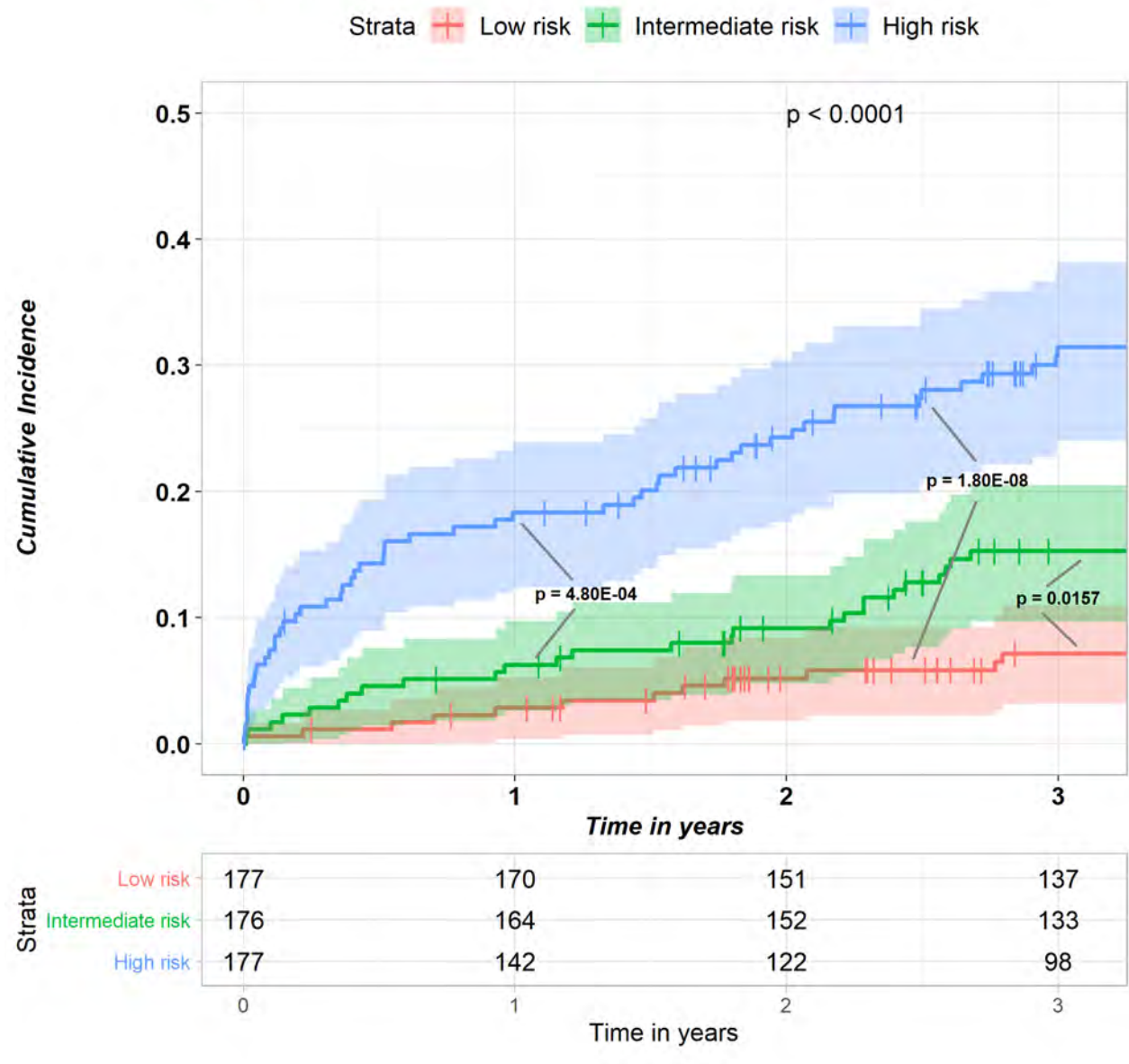


Figure 3. A. Cumulative probability for 3yrs mortality in the testing dataset clinical (8) + genetics (0)



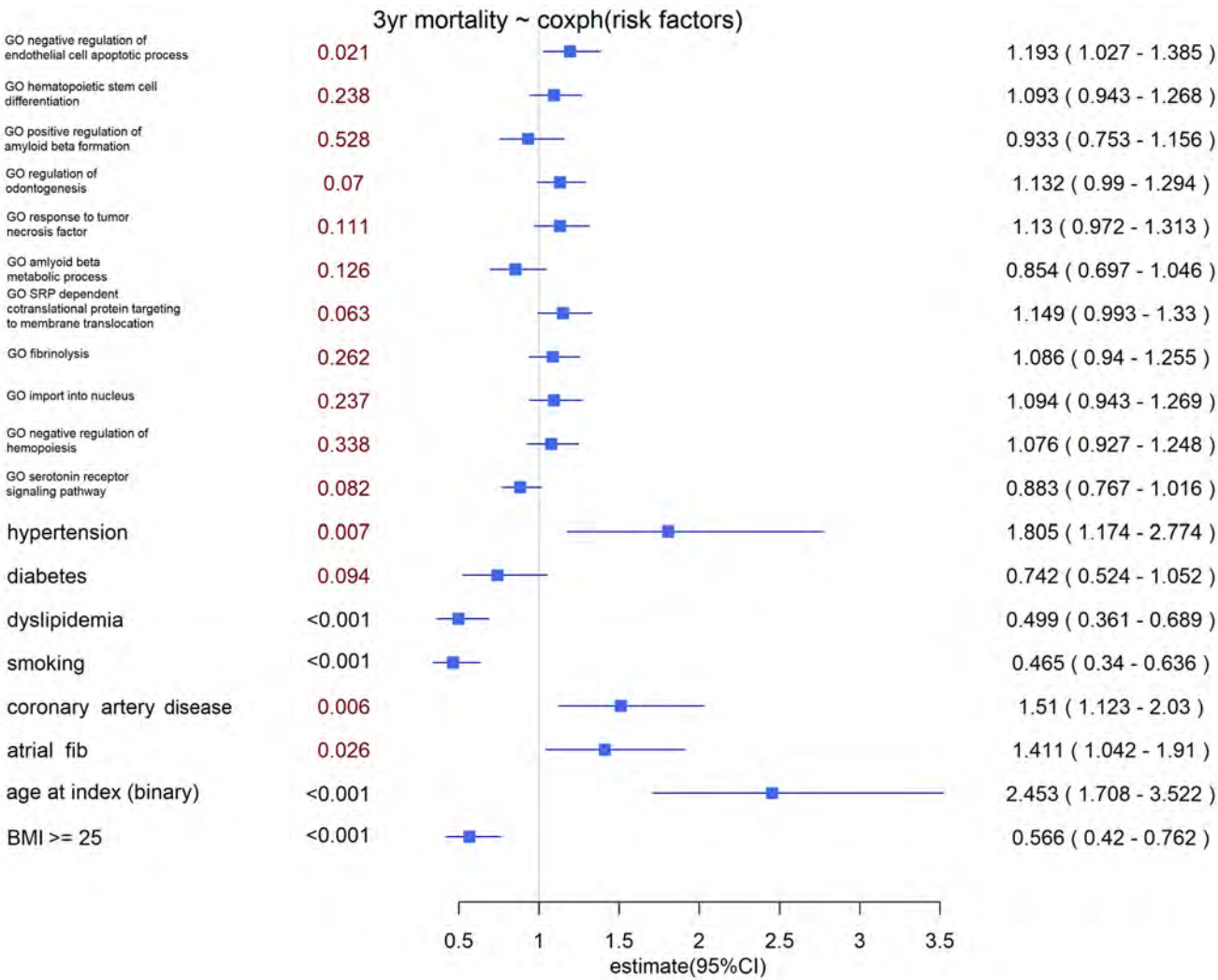
B. Cumulative probability for 3yrs mortality in the testing dataset clinical (8) + genetics (11)



(%)



C.



D.

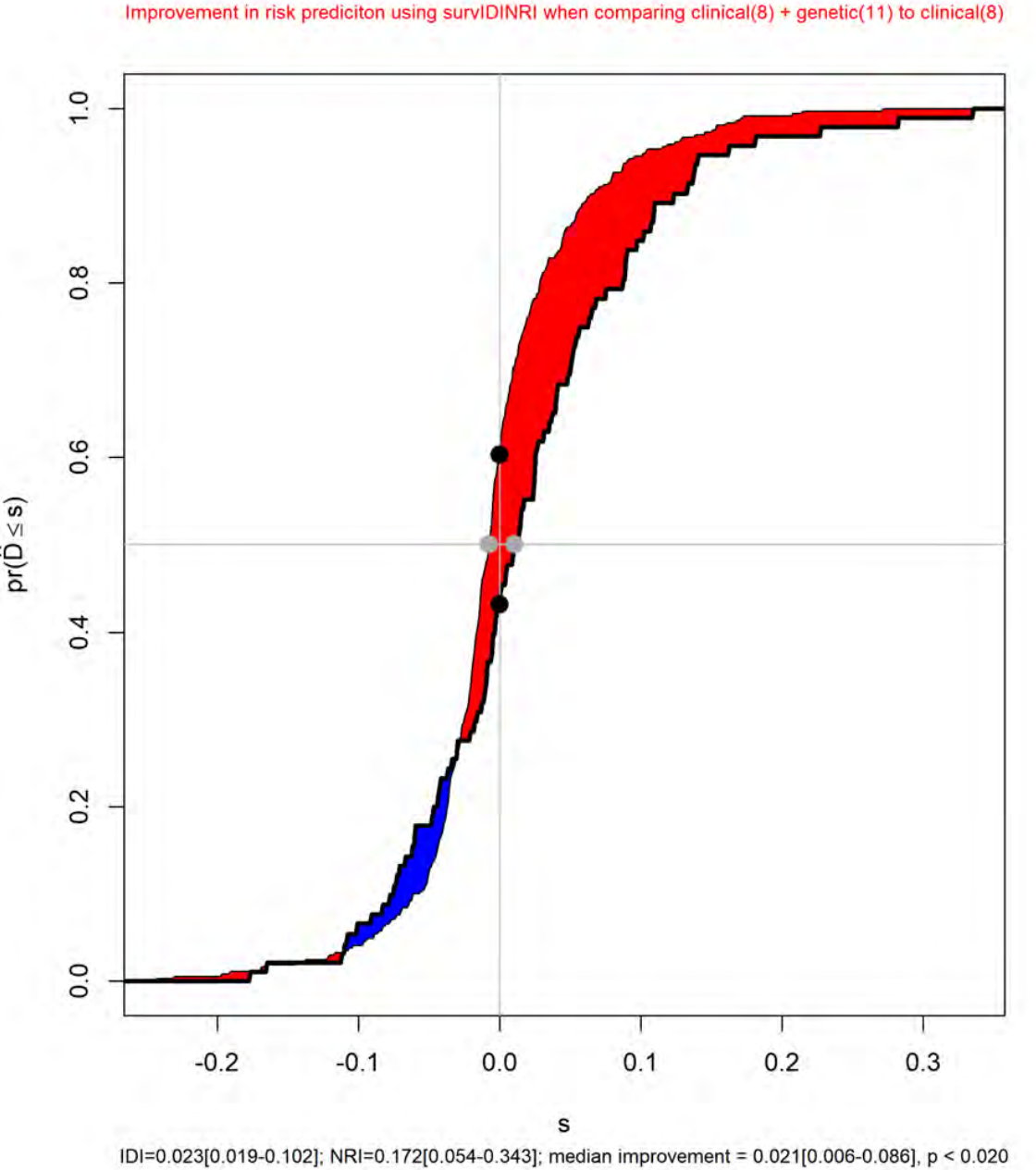


Figure 4 (old).

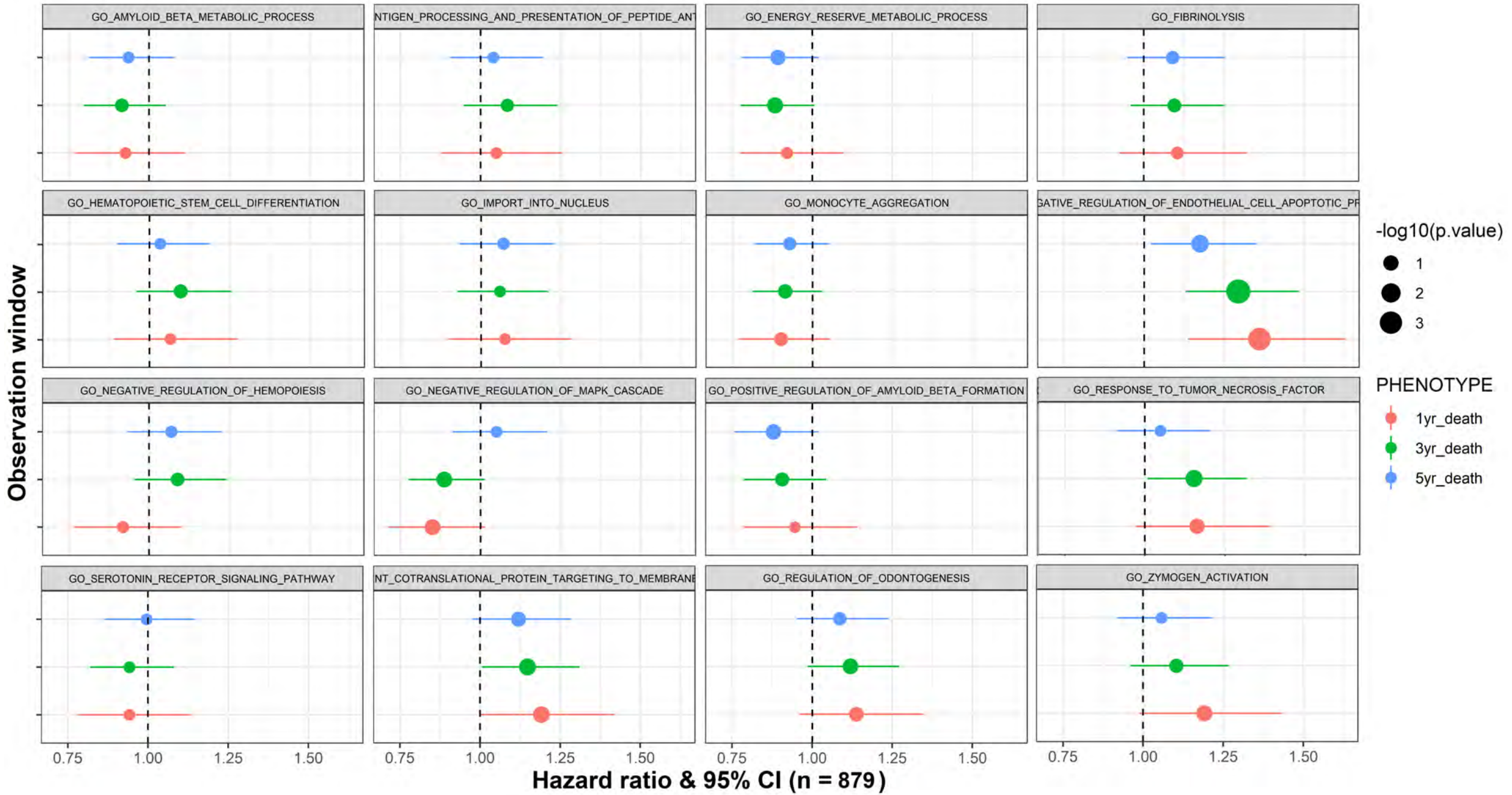
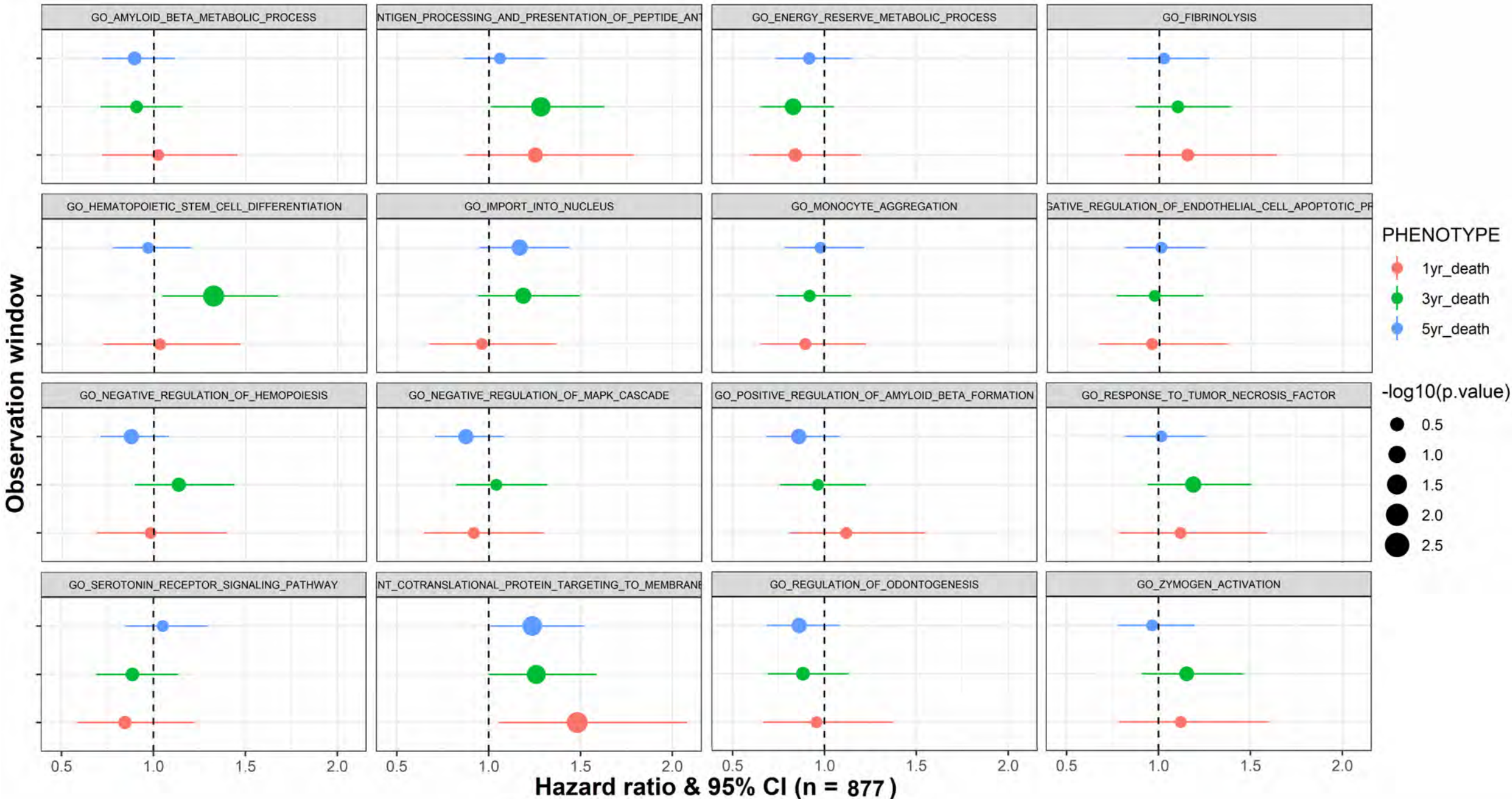
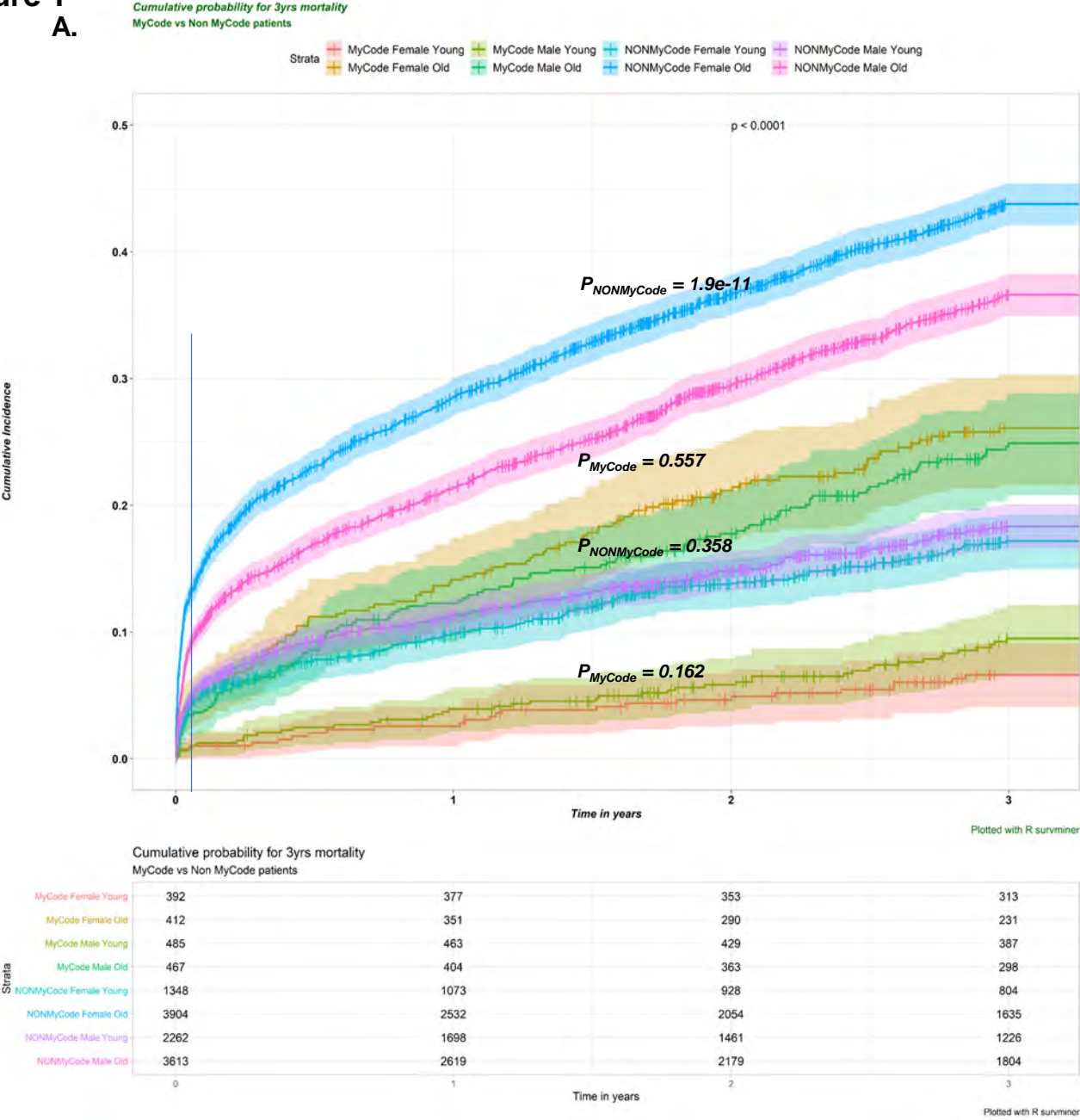


Figure 4 (young).



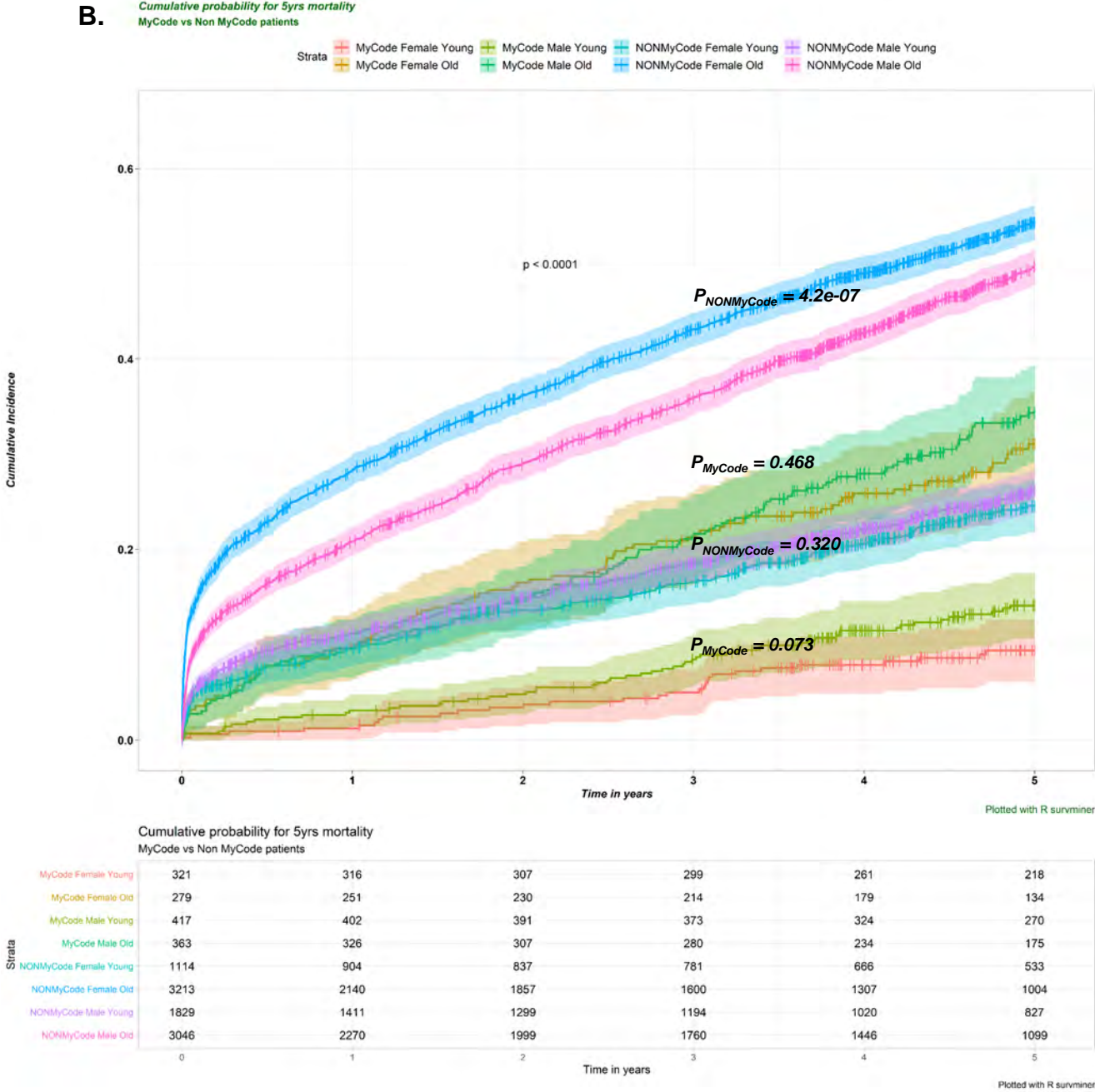


Supplementary Figure 1  
A.



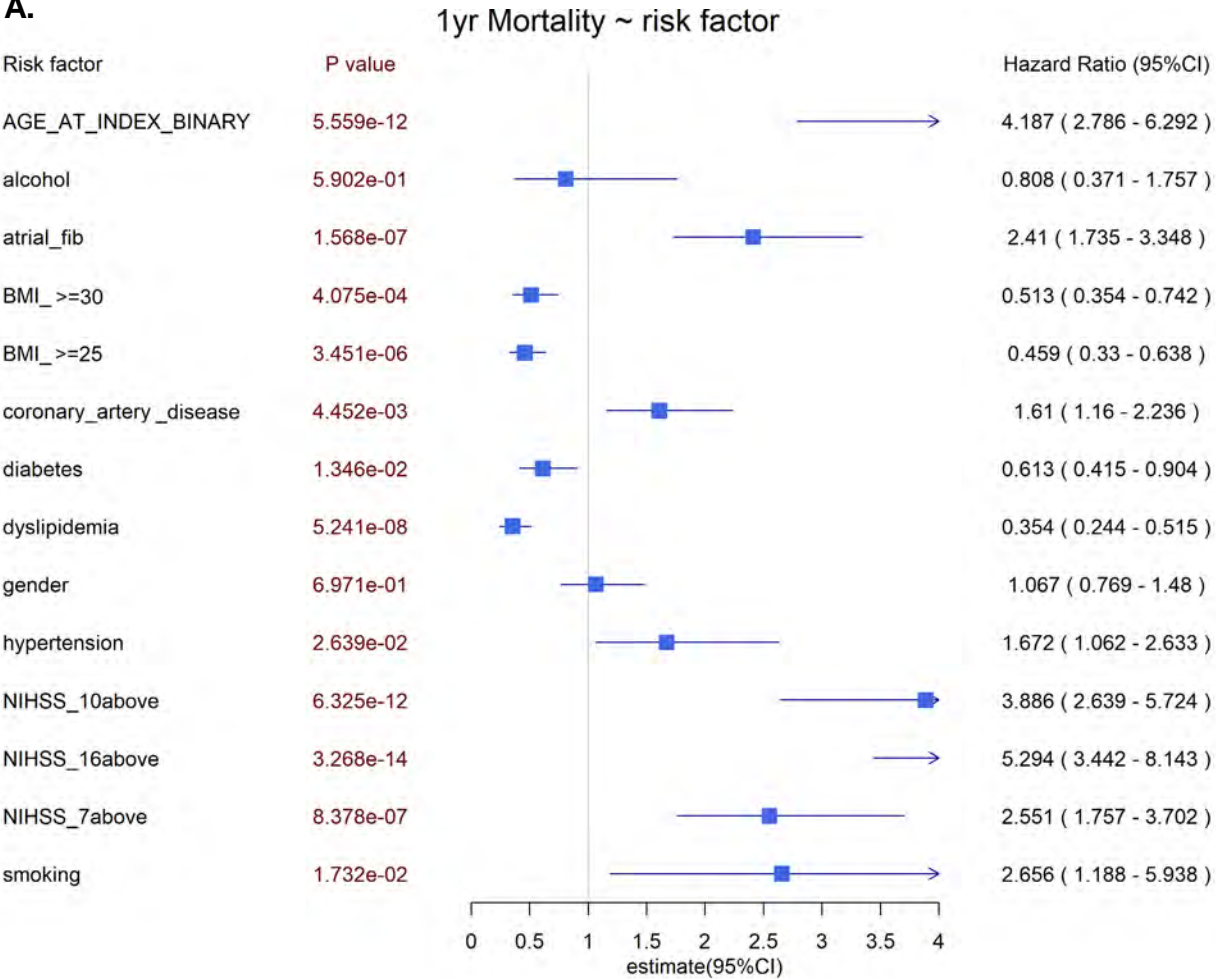
Supplementary Figure 1

B.

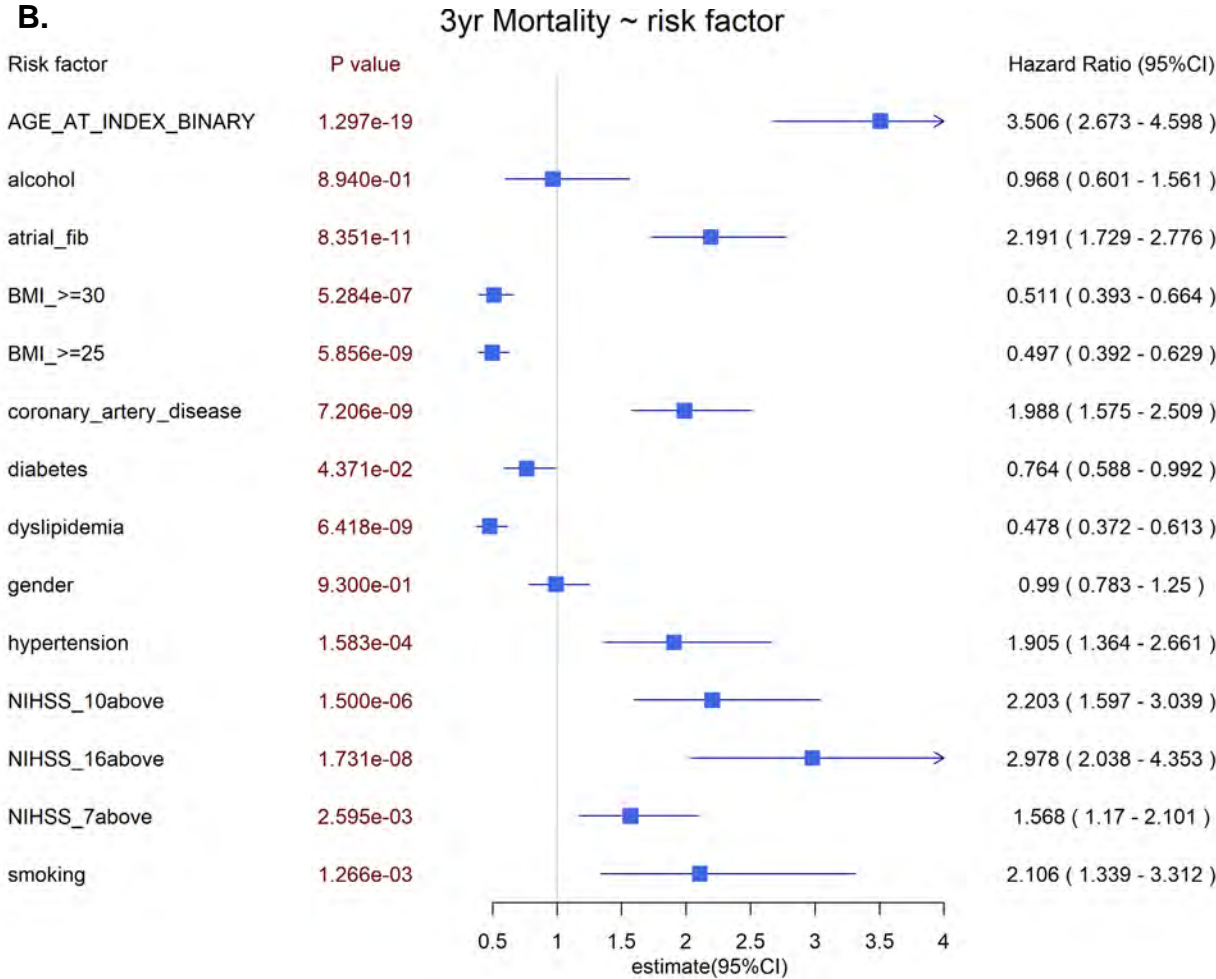


Supplementary Figure 2.

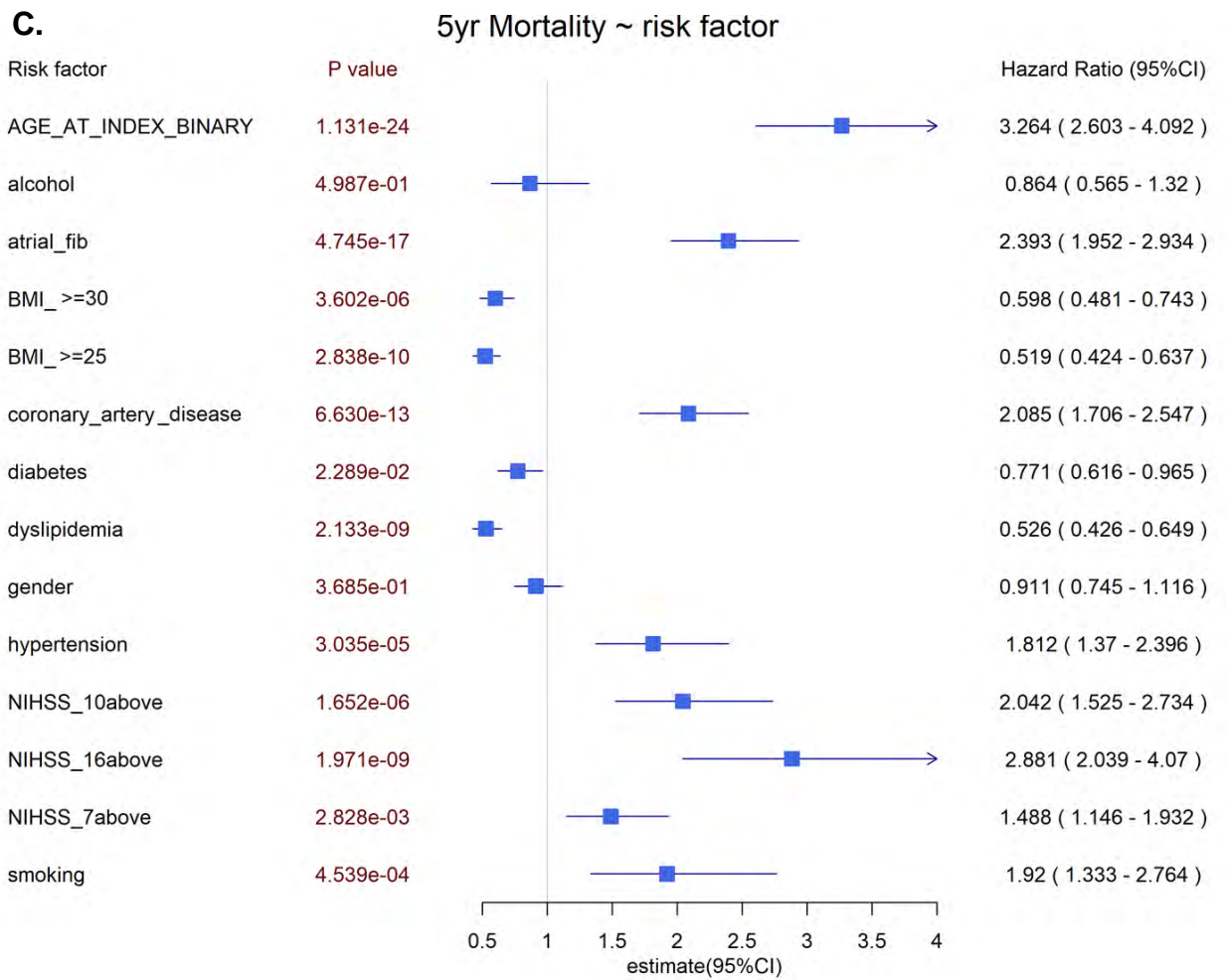
A.



B.



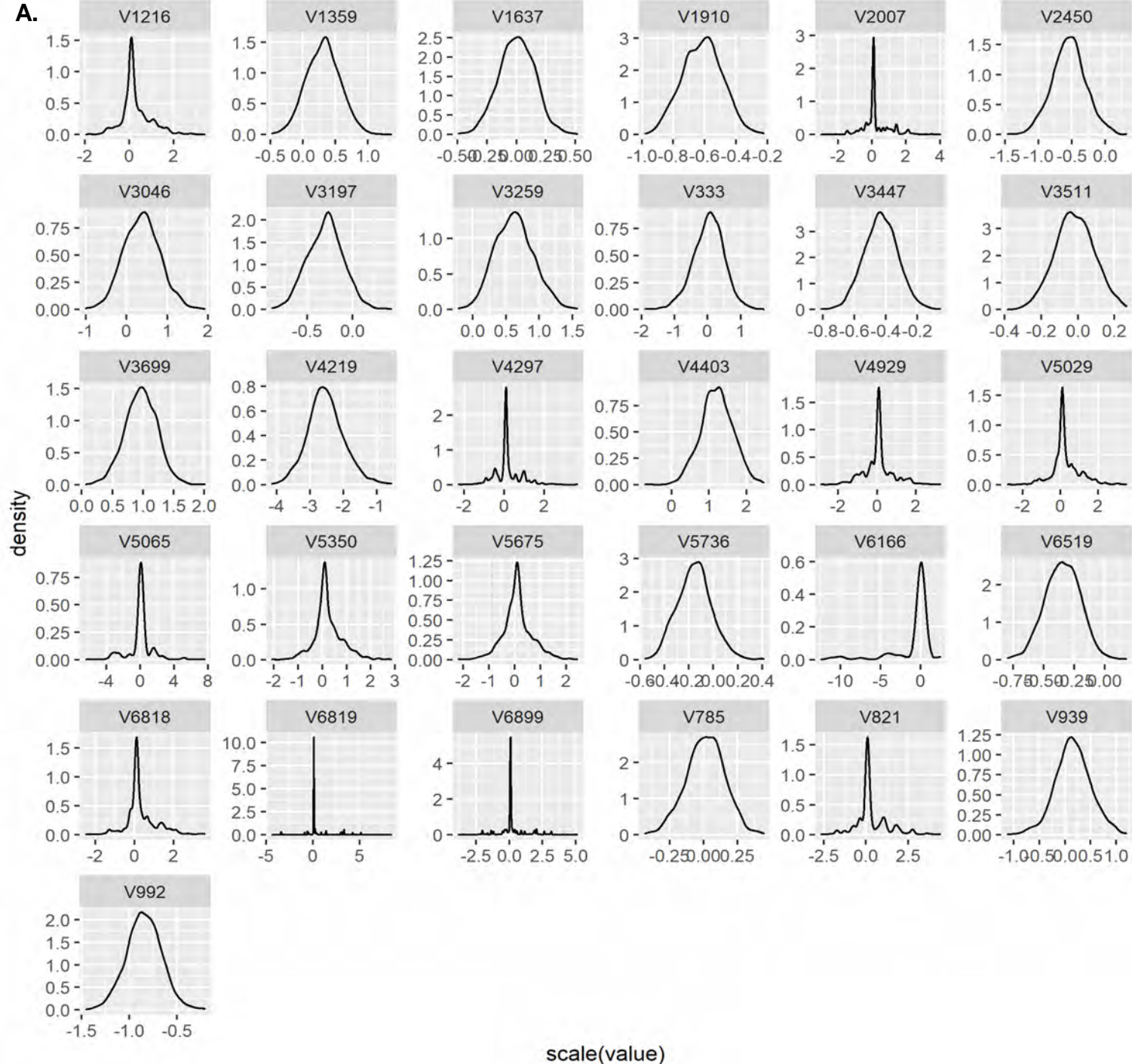
Supplementary Figure 2.





Supplementary Figure 3.

A.

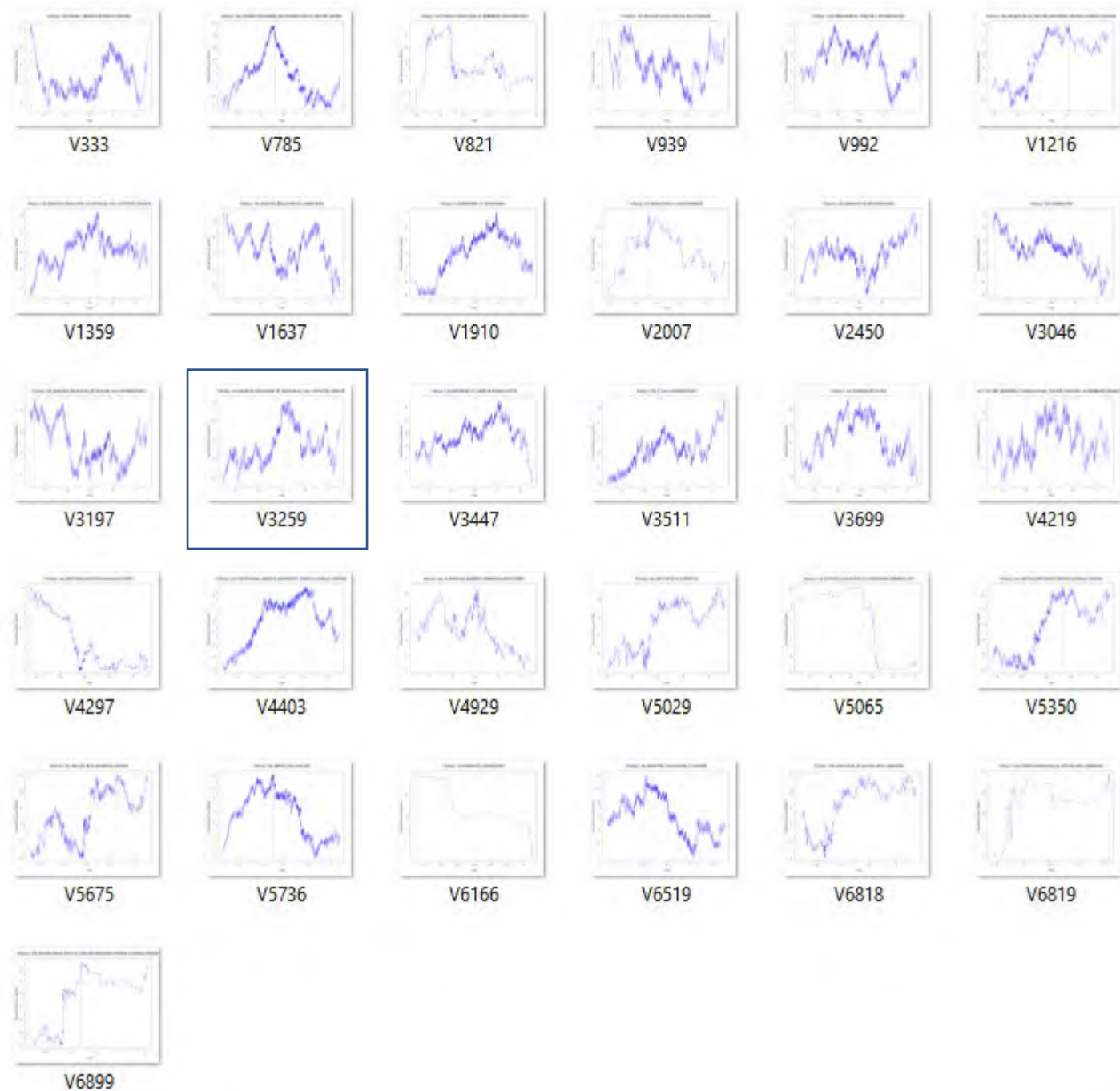
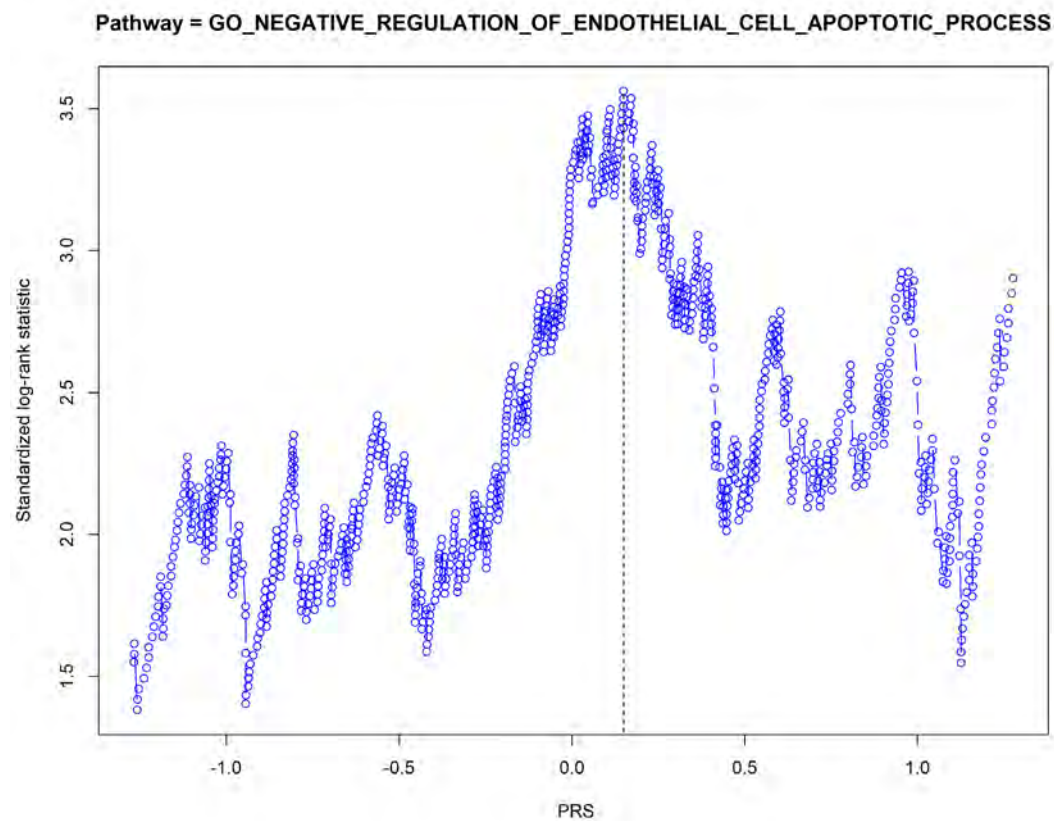


B.

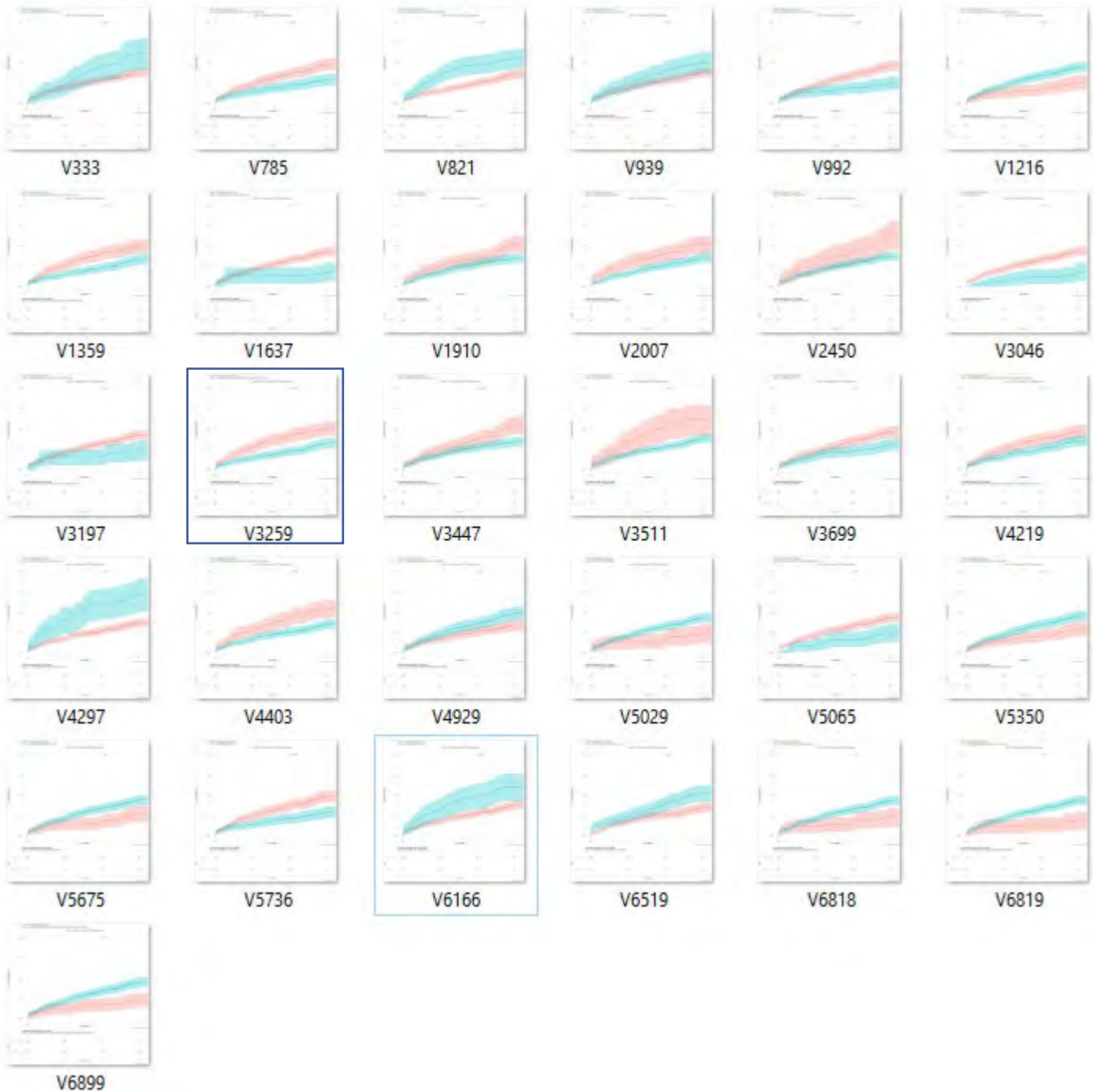
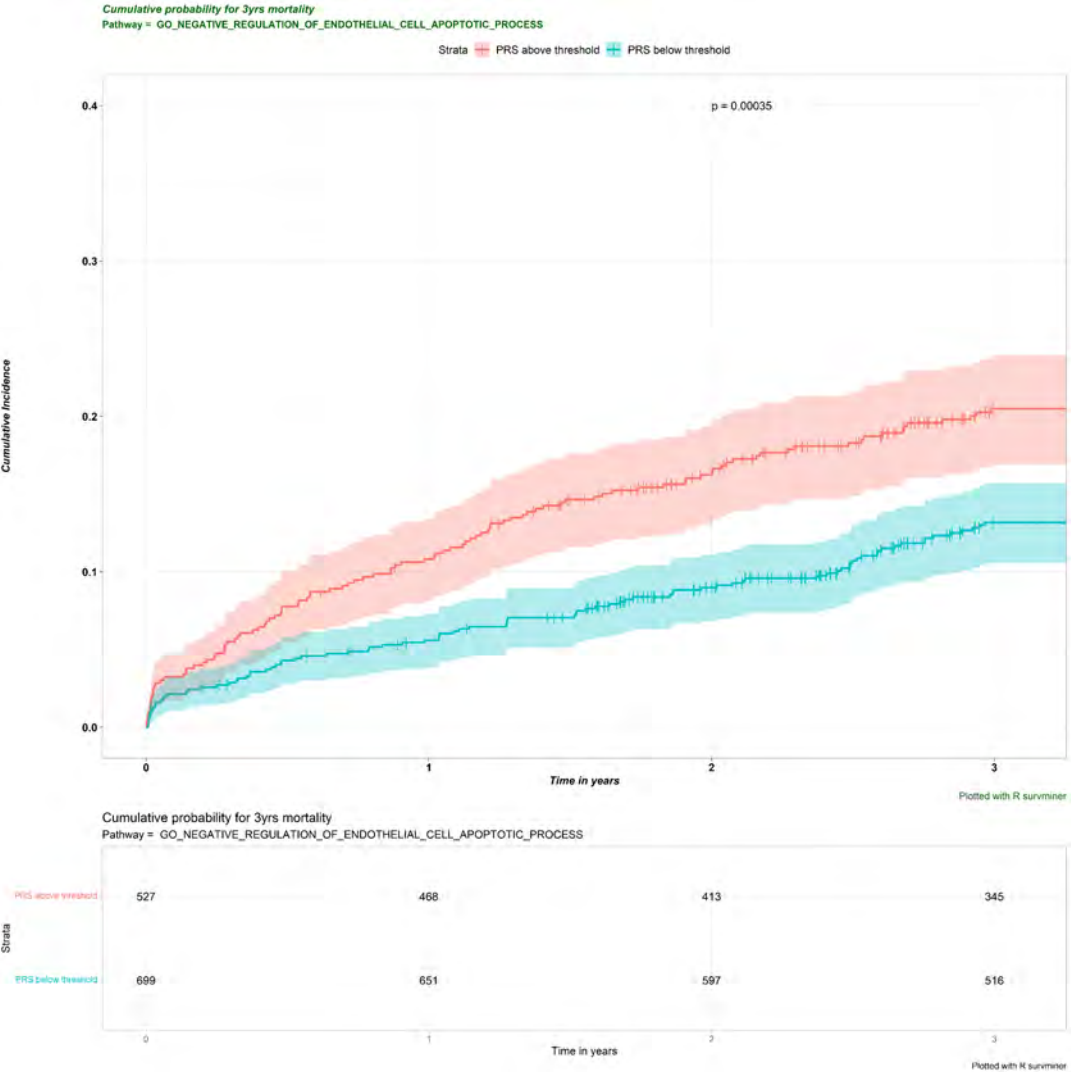
Category	Pathway
AGE_tr	AGE_AT_ONSET(Binary)
V3259	GO_NEGATIVE_REGULATION_OF_ENDOTHELIAL_CELL_APOPTOTIC_PROCESS
V992	GO_HEMATOPOIETIC_STEM_CELL_DIFFERENTIATION
V1359	GO_NEGATIVE_REGULATION_OF_EPITHELIAL_CELL_APOPTOTIC_PROCESS
V6819	GO_POSITIVE_REGULATION_OF_AMYLOID_BETA_FORMATION
V2007	GO_REGULATION_OF_ODONTOGENESIS
V3447	GO_RESPONSE_TO_TUMOR_NECROSIS_FACTOR
V5675	GO_AMYLOID_BETA_METABOLIC_PROCESS
V4403	GO_PROTEASOMAL_UBIQUITIN_INDEPENDENT_PROTEIN_CATABOLIC_PROCESS
V821	GO_POSITIVE_REGULATION_OF_MEMBRANE_DEPOLARIZATION
V6519	GO_RECEPTOR_LOCALIZATION_TO_SYNAPSE
V2450	GO GRANULOCYTE DIFFERENTIATION
V1216	GO_REGULATION_OF_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS
V4219	GO_SRP_DEPENDENT_COTRANSLATIONAL_PROTEIN_TARGETING_TO_MEMBRANE_TRANSLOCATION
V3699	GO_ZYMOGEN_ACTIVATION
V3046	GO_FIBRINOLYSIS
V5350	GO_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS
V5736	GO_IMPORT_INTO_NUCLEUS
V6899	GO_POSITIVE_REGULATION_OF_AMYLOID_PRECURSOR_PROTEIN_CATABOLIC_PROCESS
V1637	GO_NEGATIVE_REGULATION_OF_HEMOPOIESIS
V4297	GO_SEROTONIN_RECEPTOR_SIGNALING_PATHWAY
V785	GO_ANTIGEN_PROCESSING_AND_PRESENTATION_OF_PEPTIDE_ANTIGEN
V6166	GO_MONOCYTE_AGGREGATION
V6818	GO_REGULATION_OF_AMYLOID_BETA_FORMATION
V333	GO_ENERGY_RESERVE_METABOLIC_PROCESS
V3197	GO_NEGATIVE_REGULATION_OF_MYELOID_CELL_DIFFERENTIATION
V1910	GO_RESPONSE_TO_INTERLEUKIN_1
V5065	GO_PROTEIN_LOCALIZATION_TO_PHAGOPHORE_ASSEMBLY_SITE
V5029	GO_AMYLOID_BETA_FORMATION
V3511	GO_T_CELL_DIFFERENTIATION
V939	GO_NEGATIVE_REGULATION_OF_MAPK_CASCADE
V4929	GO_GLOMERULAR_BASEMENT_MEMBRANE_DEVELOPMENT



Supplementary Figure 4.

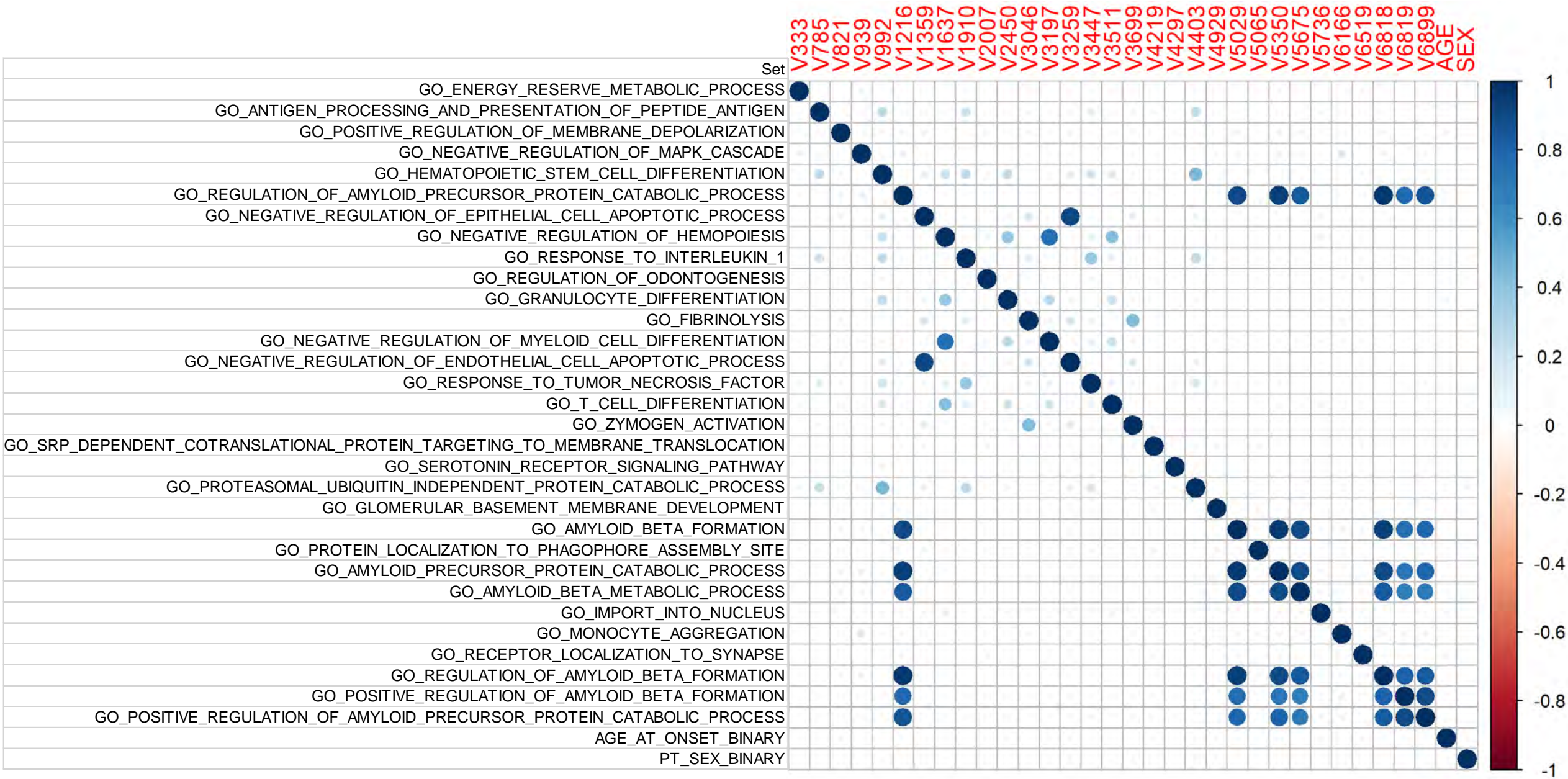


Supplementary Figure 5

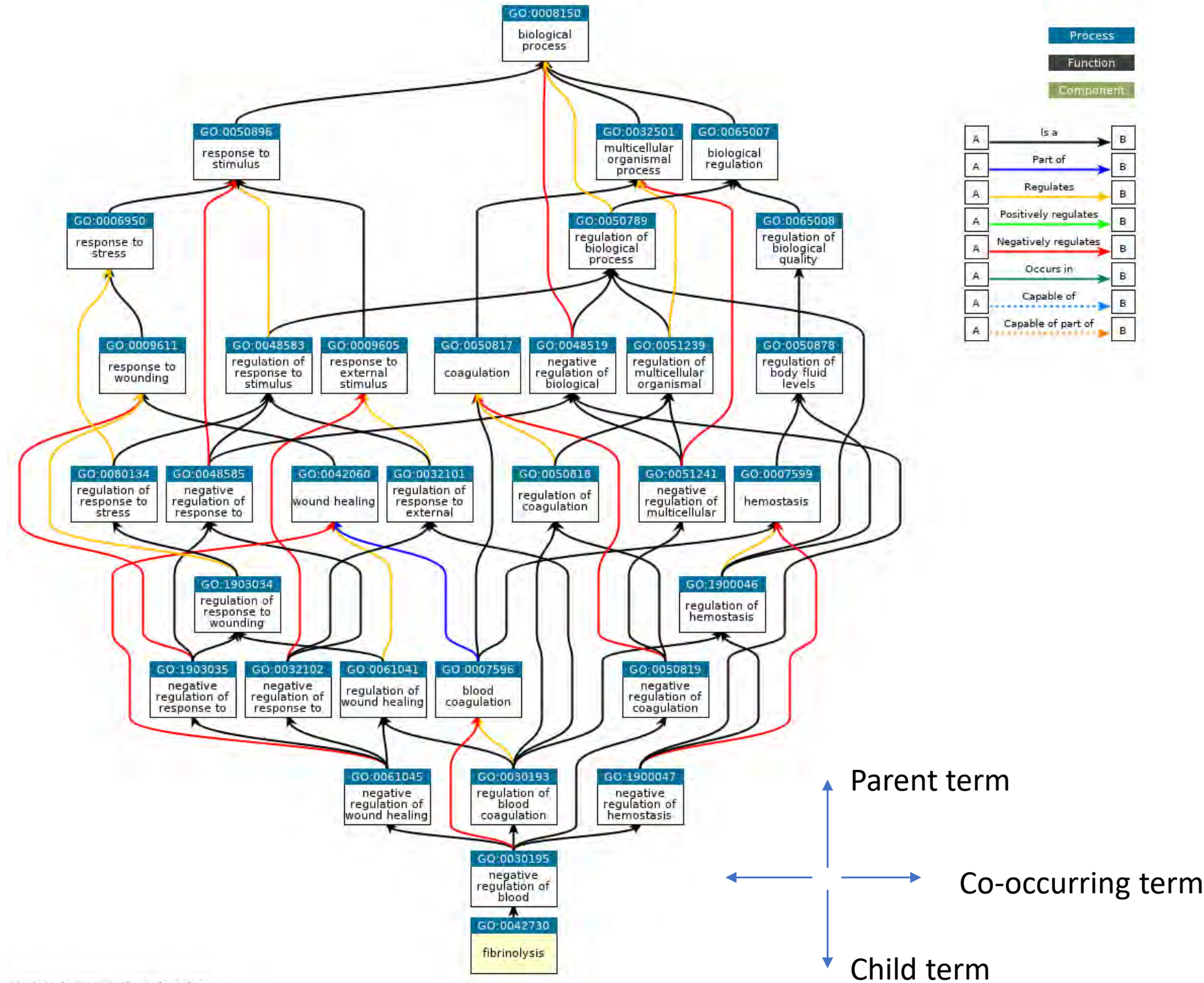




Supplementary Figure 6.

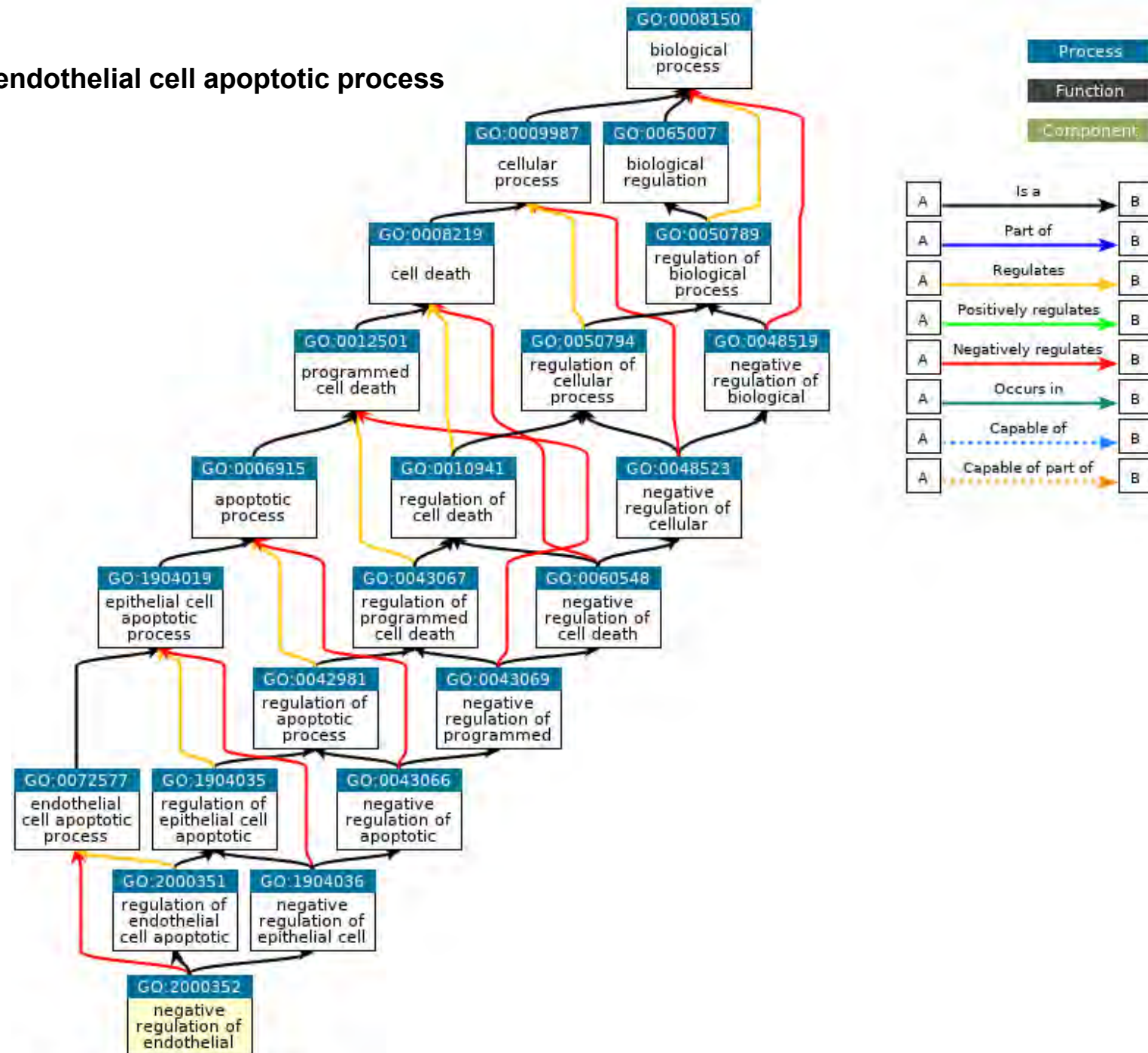


Supplementary Figure 7.  
GO:0042730 fibrinolysis



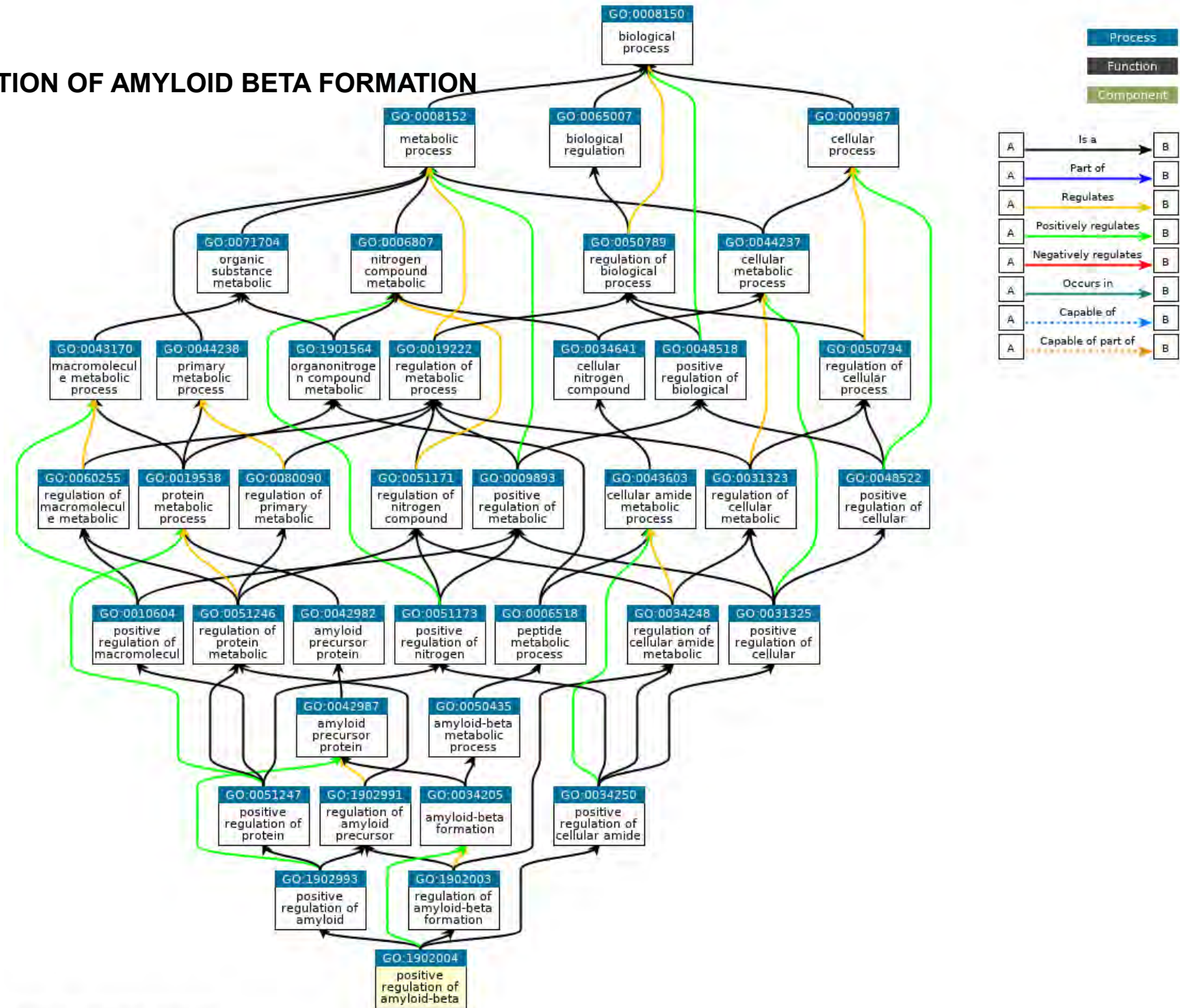


**GO:2000352 negative regulation of endothelial cell apoptotic process**



**GO:1902004 POSITIVE REGULATION OF AMYLOID BETA FORMATION**

**GO:1902004 POSITIVE REGULATION OF AMYLOID BETA FORMATION**



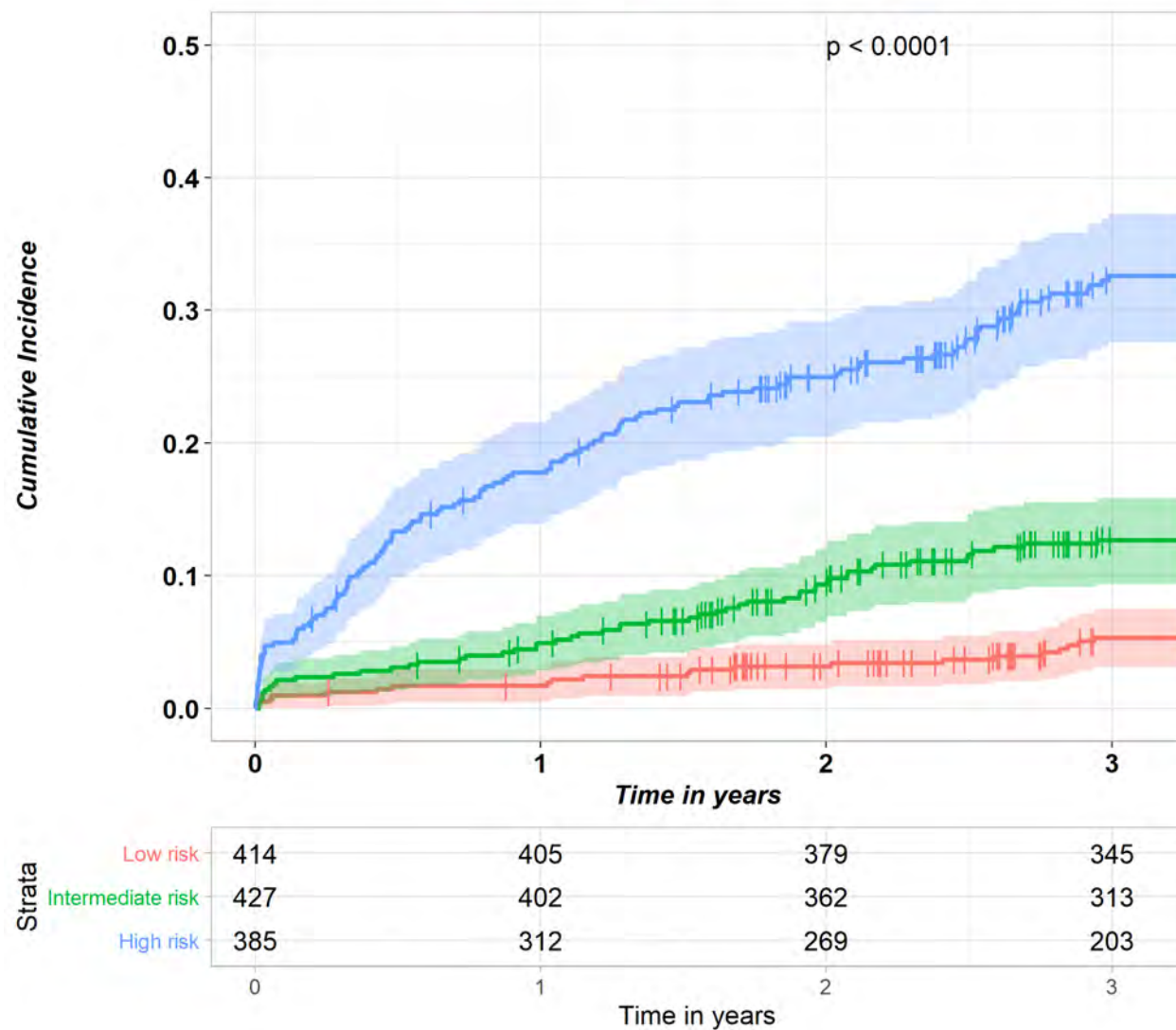


**Cumulative probability for 3yrs mortality in the training dataset**  
clinical (8) + genetics (0)

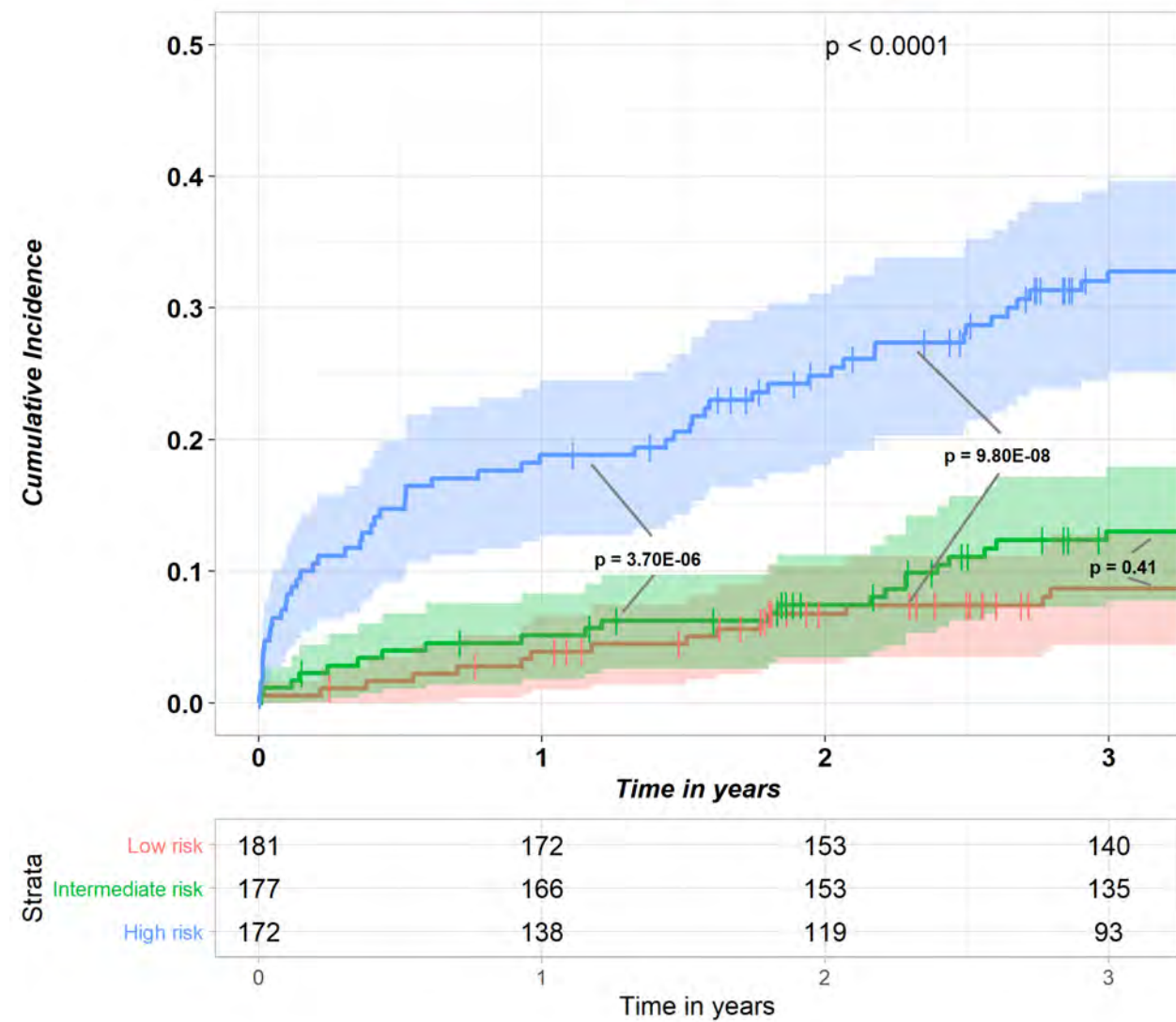
**Supplementary Figure 8. Cumulative probability for 3yrs mortality in the testing dataset**  
clinical (8) + genetics (0)

Strata + Low risk + Intermediate risk + High risk

Strata + Low risk + Intermediate risk + High risk



Plotted with R survminer



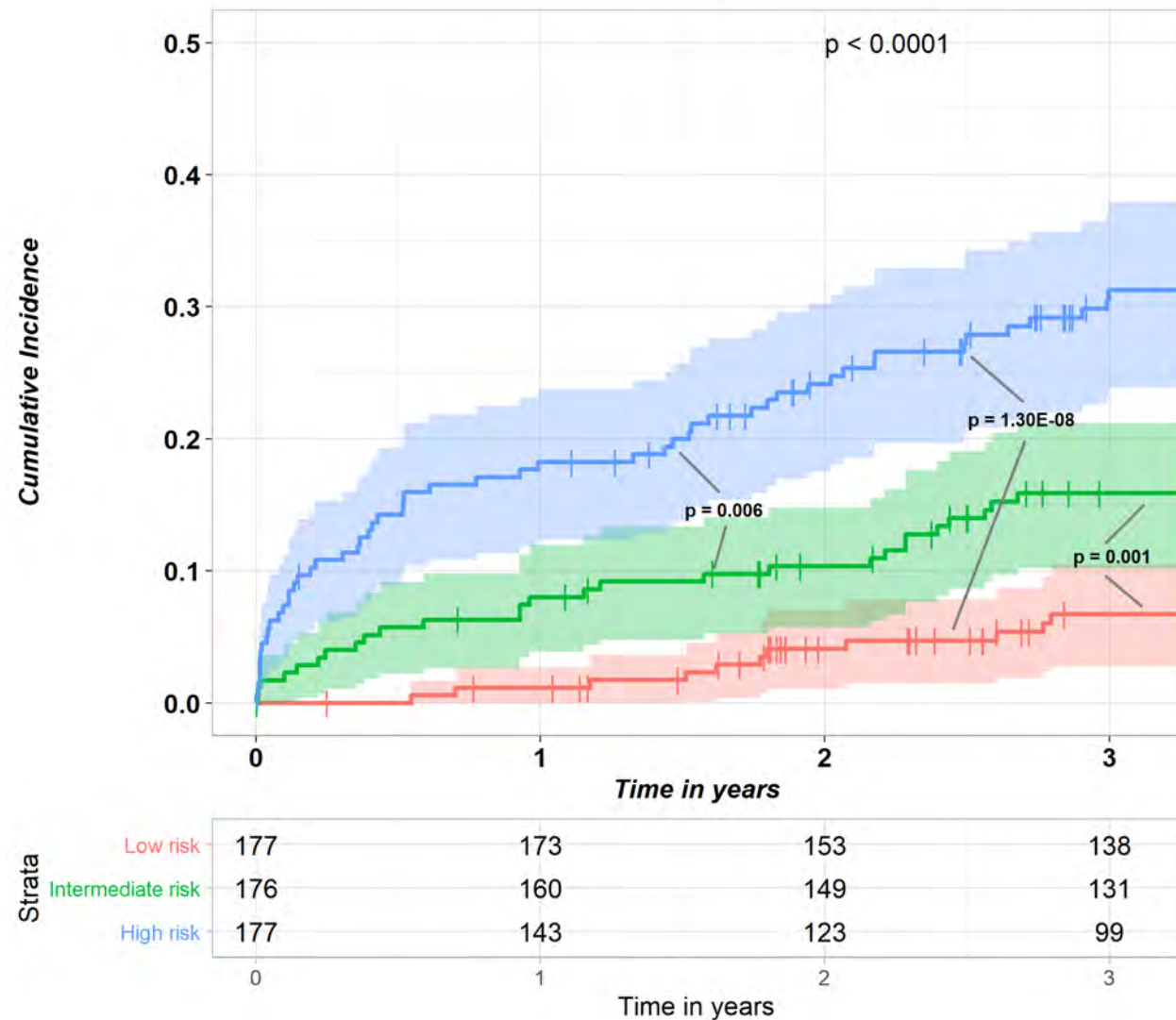
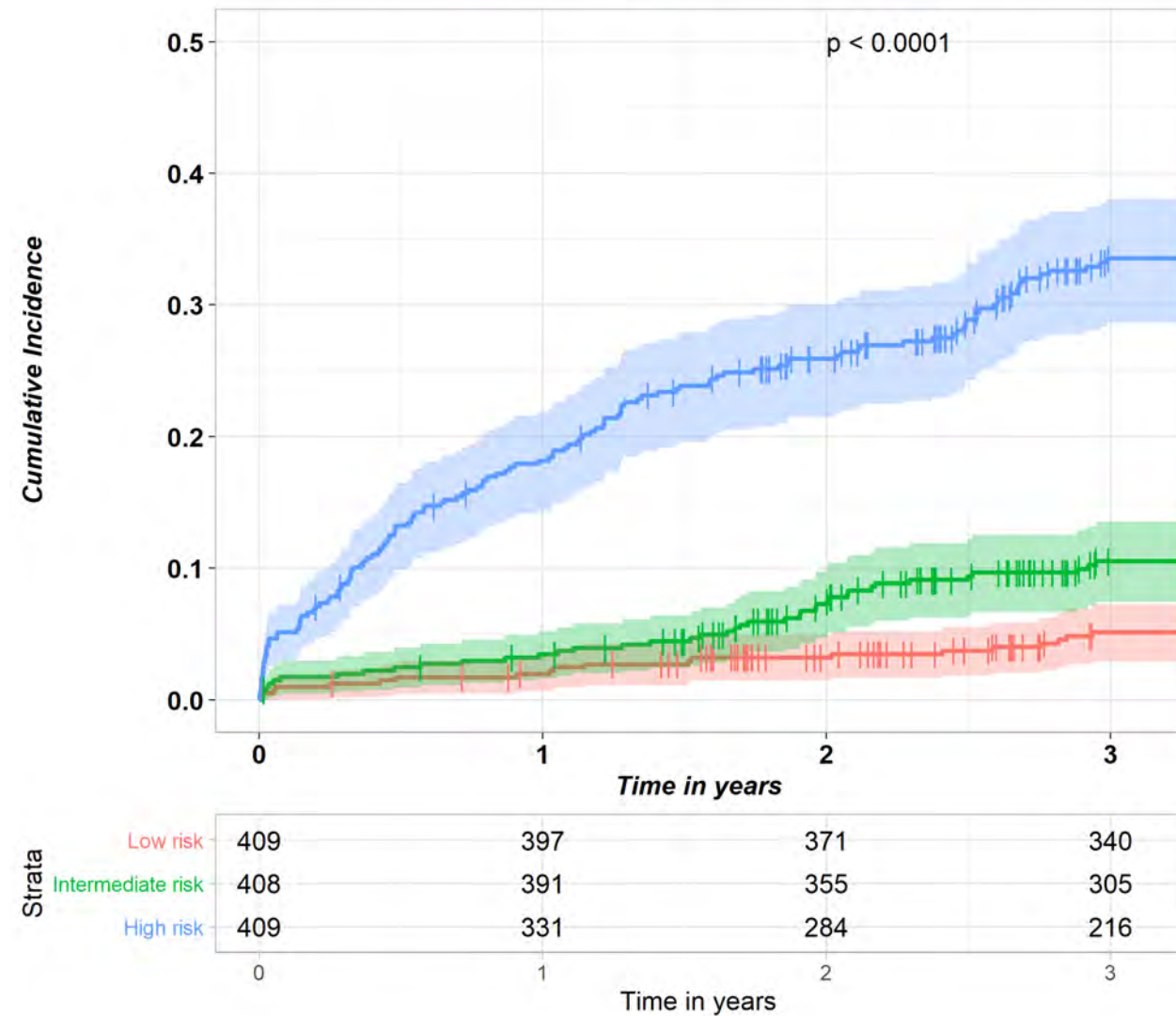
Plotted with R survminer

**Cumulative probability for 3yrs mortality in the training dataset**  
clinical (8) + genetics (16)

**Supplementary Figure 8. Cumulative probability for 3yrs mortality in the testing dataset**  
clinical (8) + genetics (16)

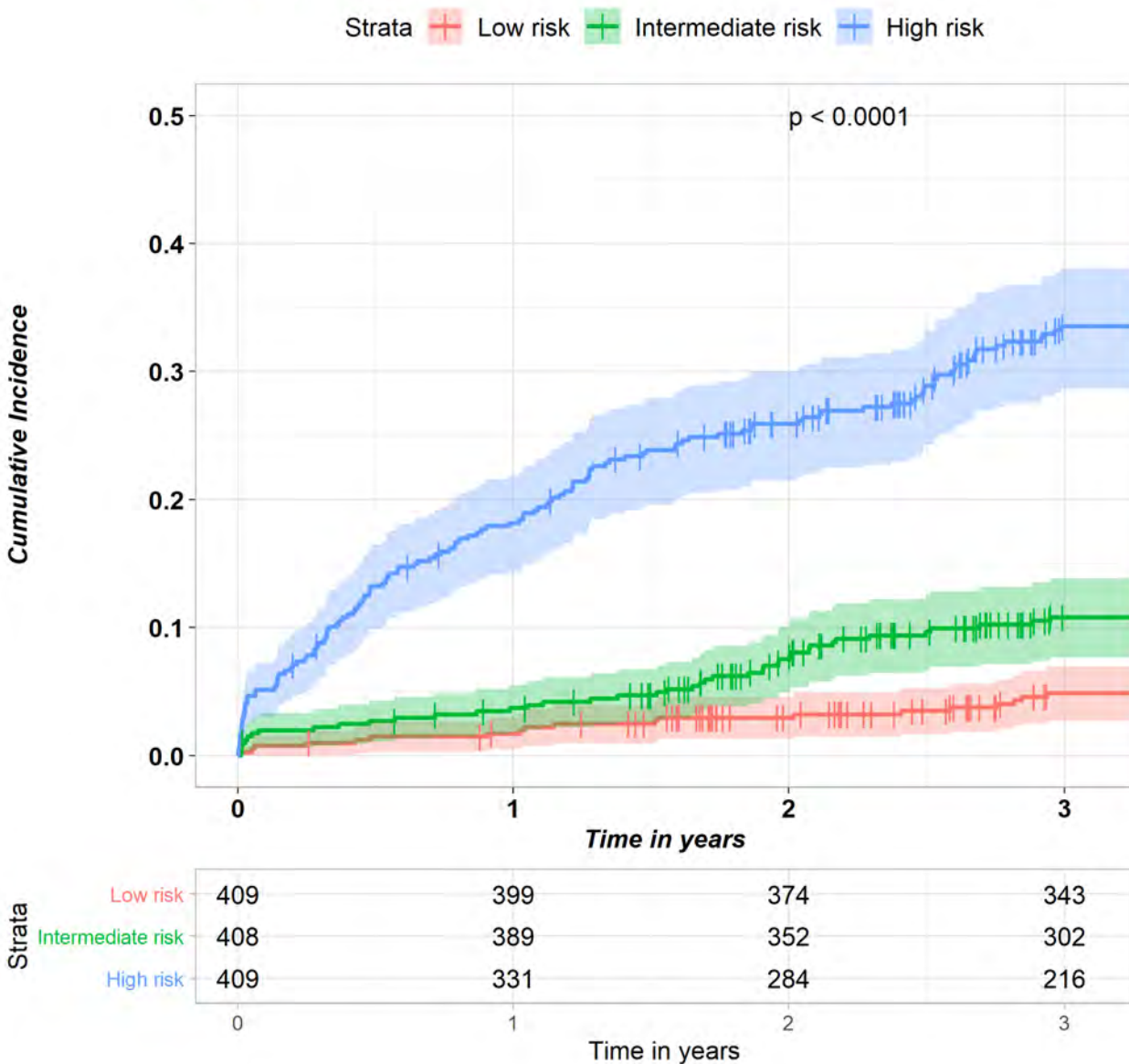
Strata Low risk Intermediate risk High risk

Strata Low risk Intermediate risk High risk



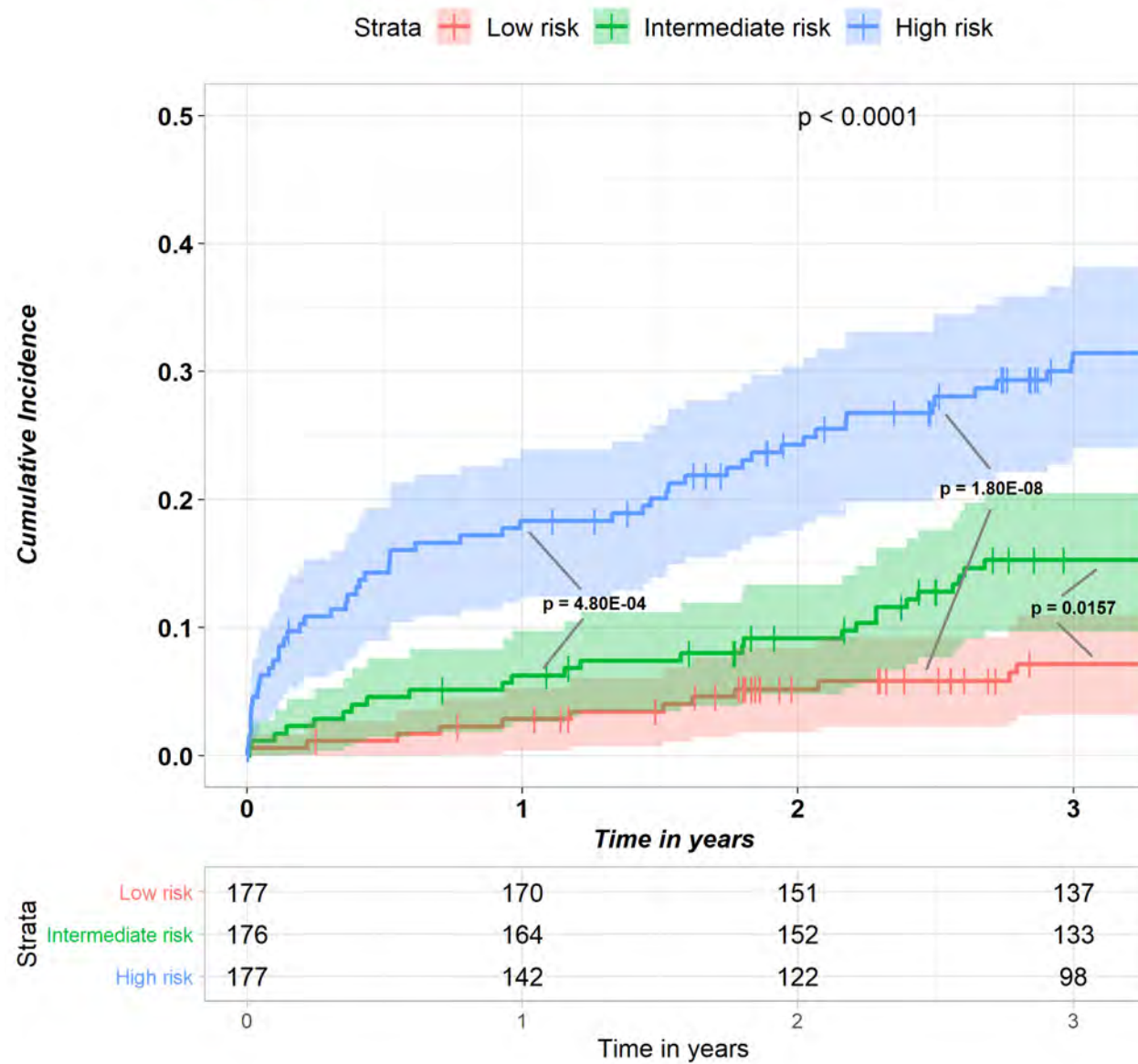


**Cumulative probability for 3yrs mortality in the training dataset**  
clinical (8) + genetics (11)



Plotted with R survminer

**Supplementary Figure 8. Cumulative probability for 3yrs mortality in the testing dataset**  
clinical (8) + genetics (11)

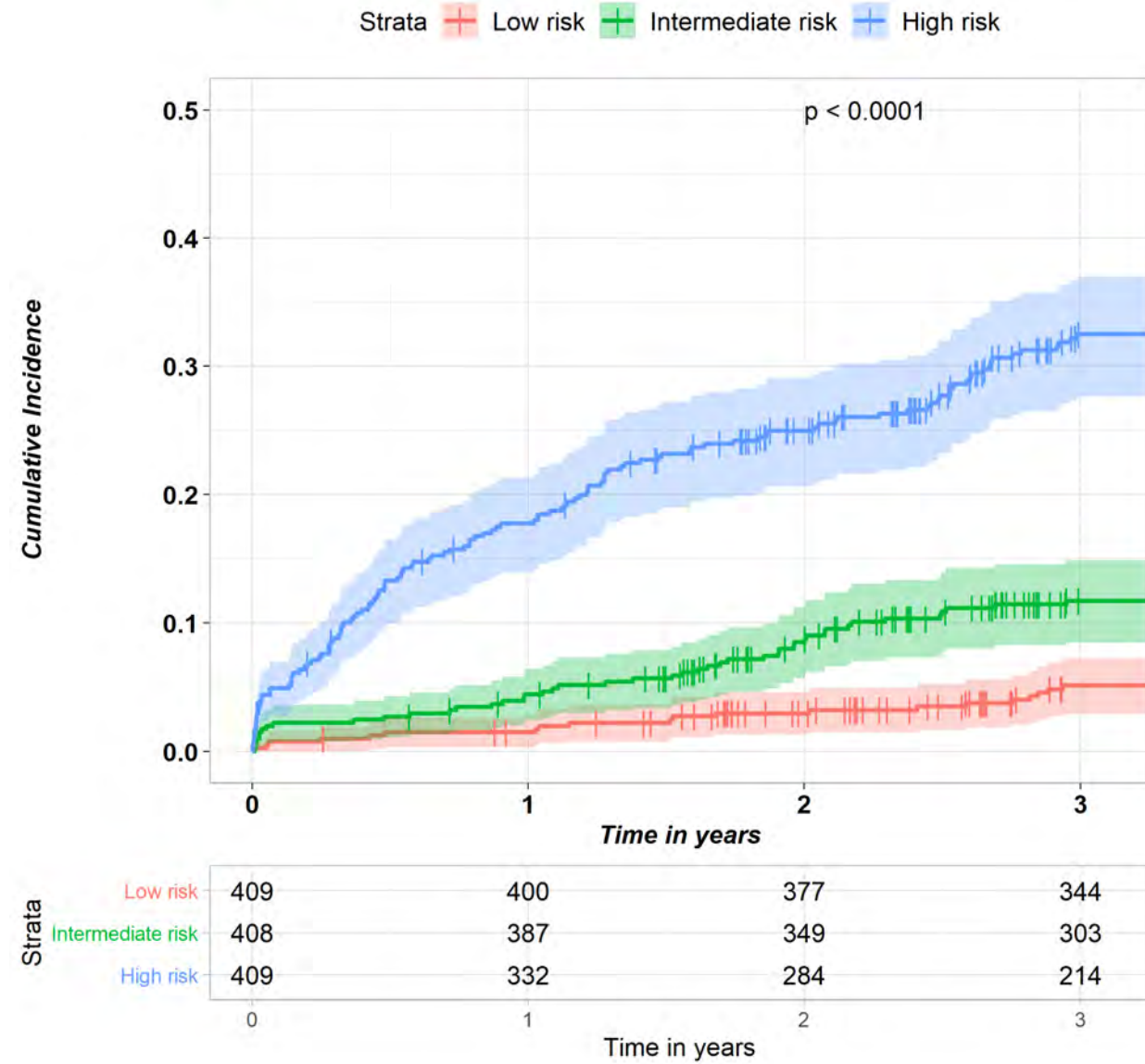


Plotted with R survminer

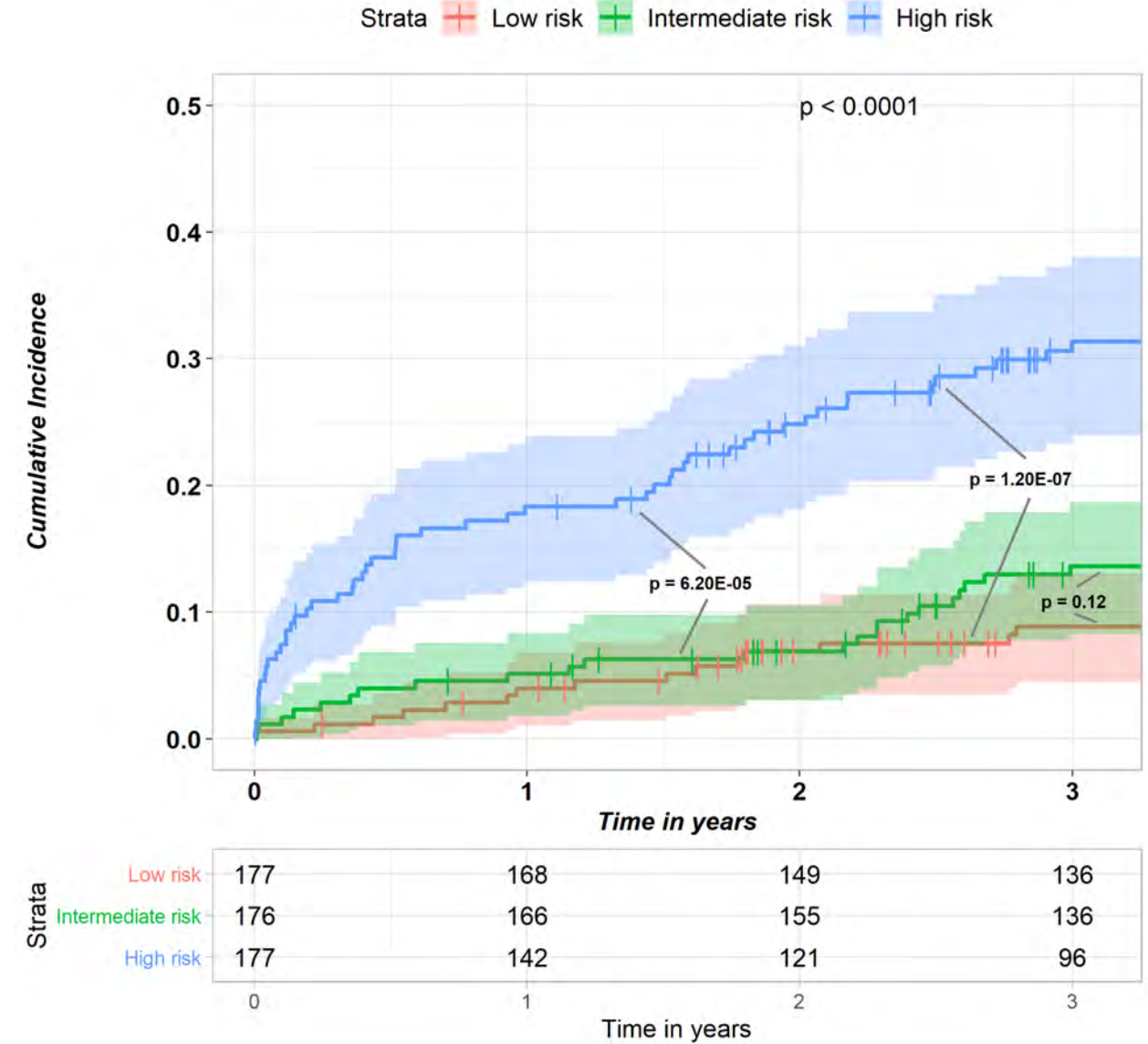
Cumulative probability for 3yrs mortality in the training dataset  
clinical (8) + genetics (5)

Supplementary Figure 8.

Cumulative probability for 3yrs mortality in the testing dataset  
clinical (8) + genetics (5)



Plotted with R survminer



Plotted with R survminer

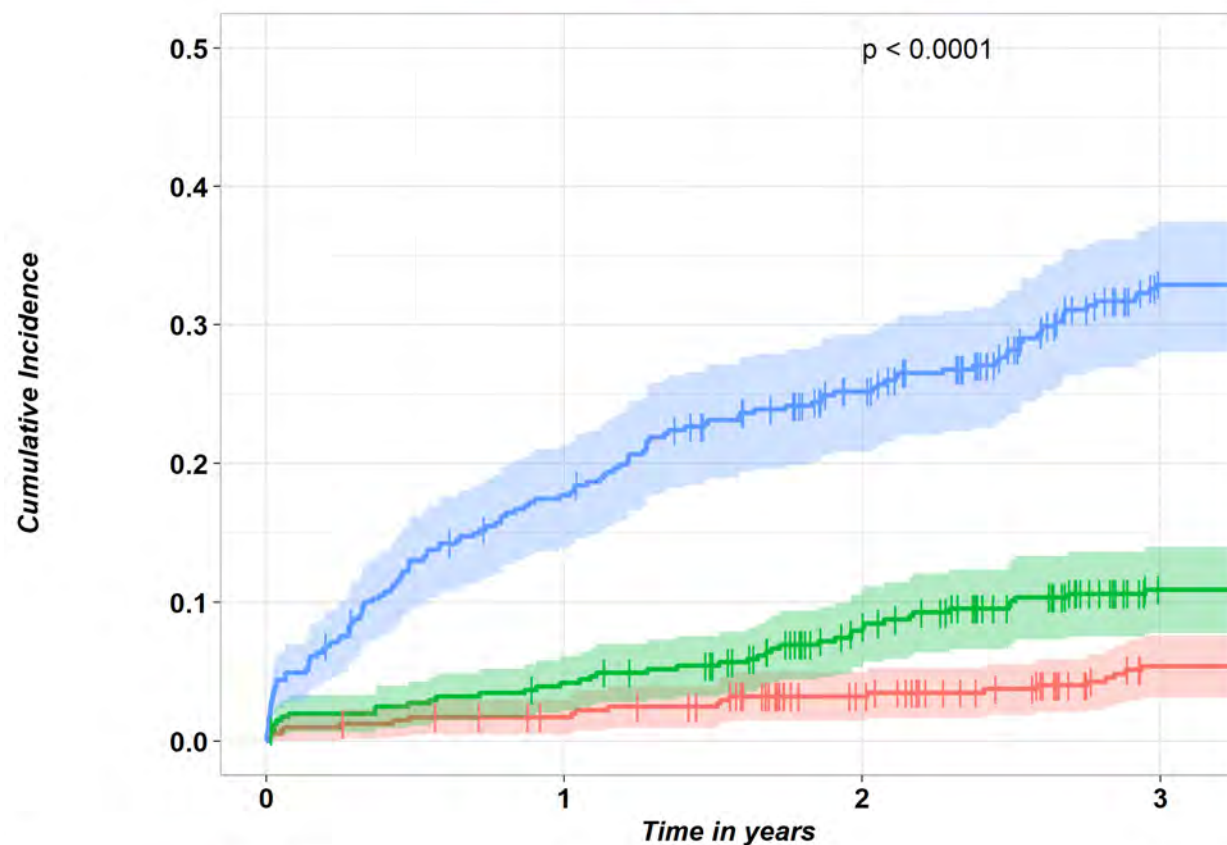


**Cumulative probability for 3yrs mortality in the training dataset**  
clinical (8) + genetics (2)

**Supplementary Figure 8.**

**Cumulative probability for 3yrs mortality in the testing dataset**  
clinical (8) + genetics (2)

Strata + Low risk + Intermediate risk + High risk

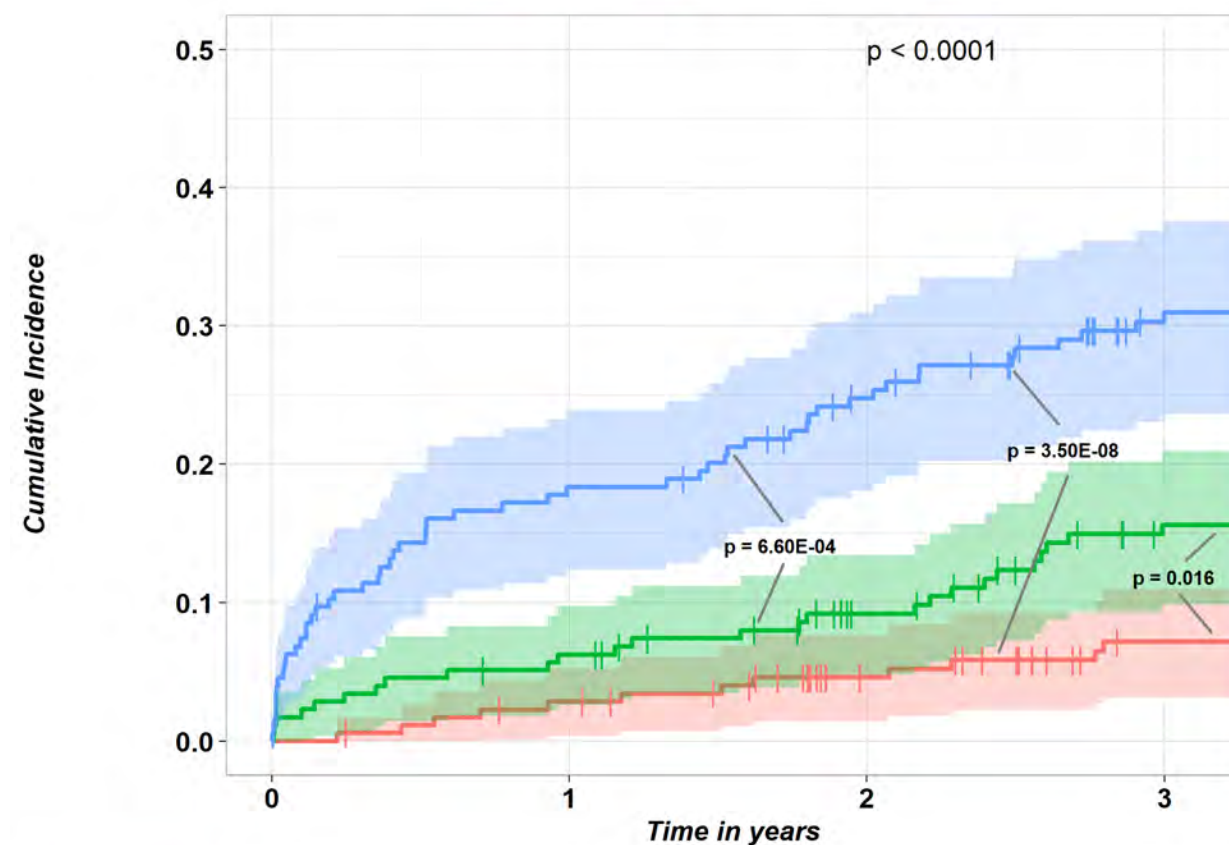


Strata	Low risk	409	397	372	338
	Intermediate risk	408	389	353	308
	High risk	409	333	285	215
		0	1	2	3

**Time in years**

Plotted with R survminer

Strata + Low risk + Intermediate risk + High risk



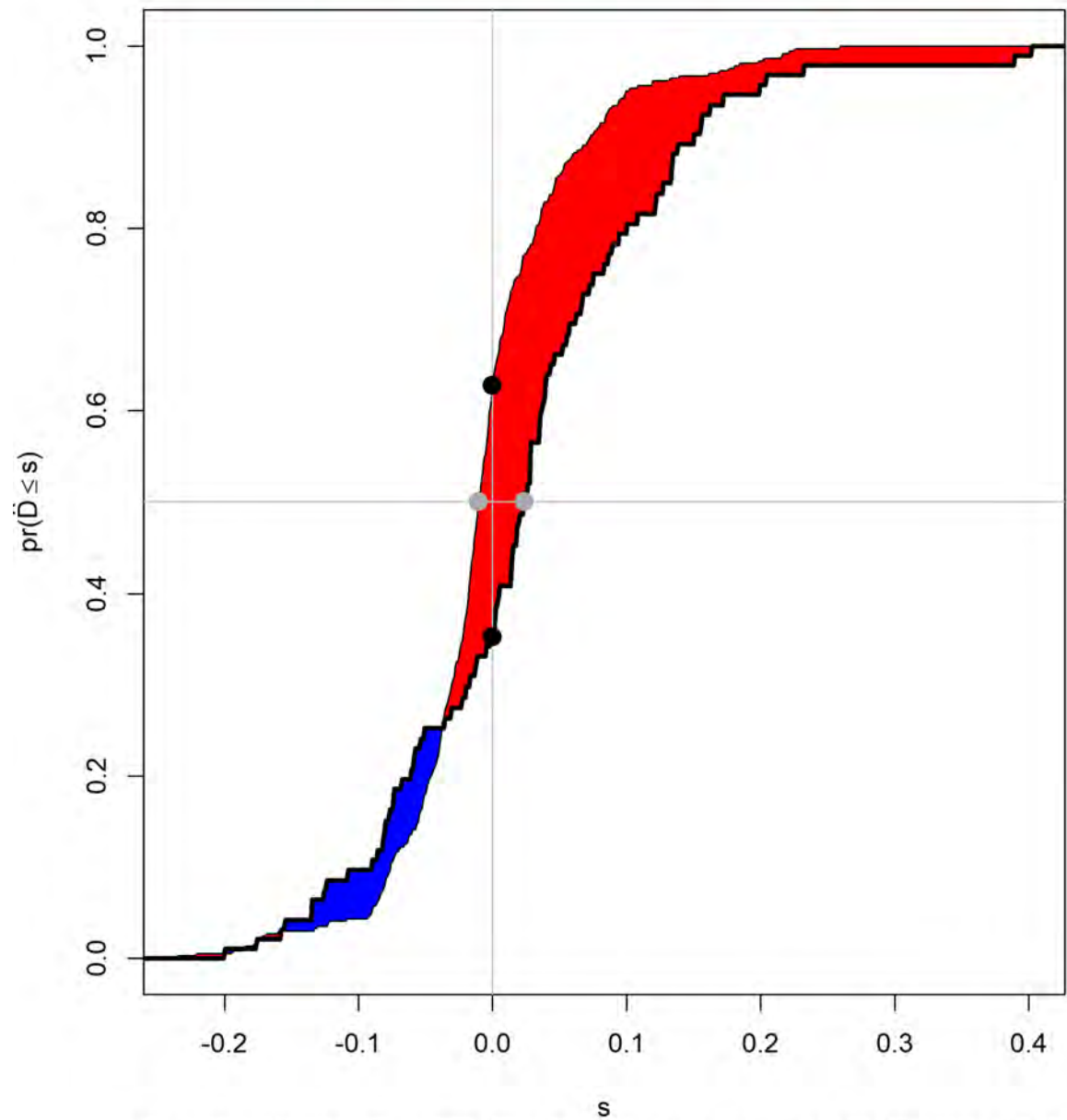
Strata	Low risk	177	170	153	138
	Intermediate risk	176	164	146	127
	High risk	177	142	126	103
		0	1	2	3

**Time in years**

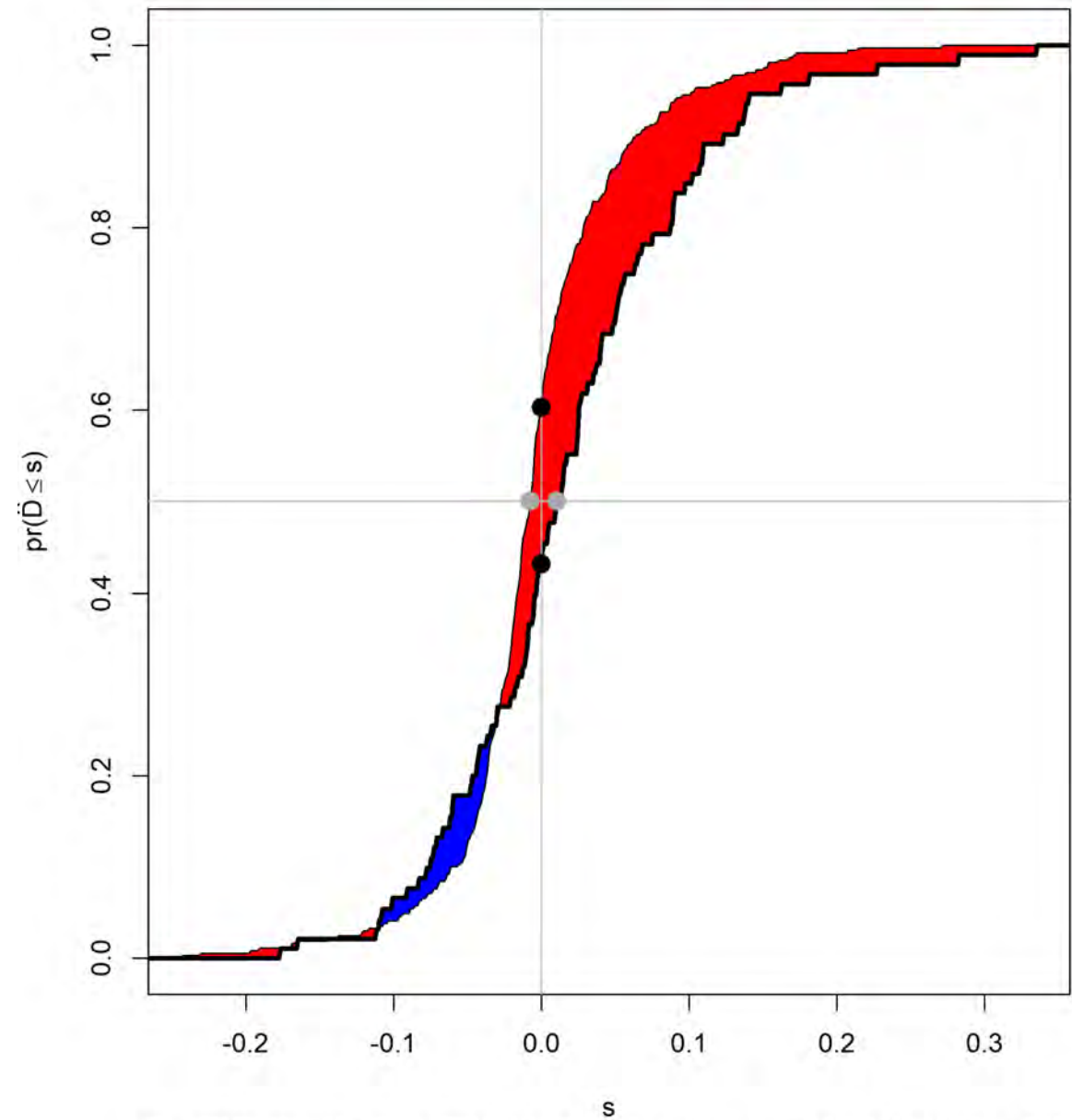
Plotted with R survminer

**Supplementary Figure 9.**

Improvement in risk prediction using survIDINRI when comparing clinical(8) + genetic(16) to clinical(8)

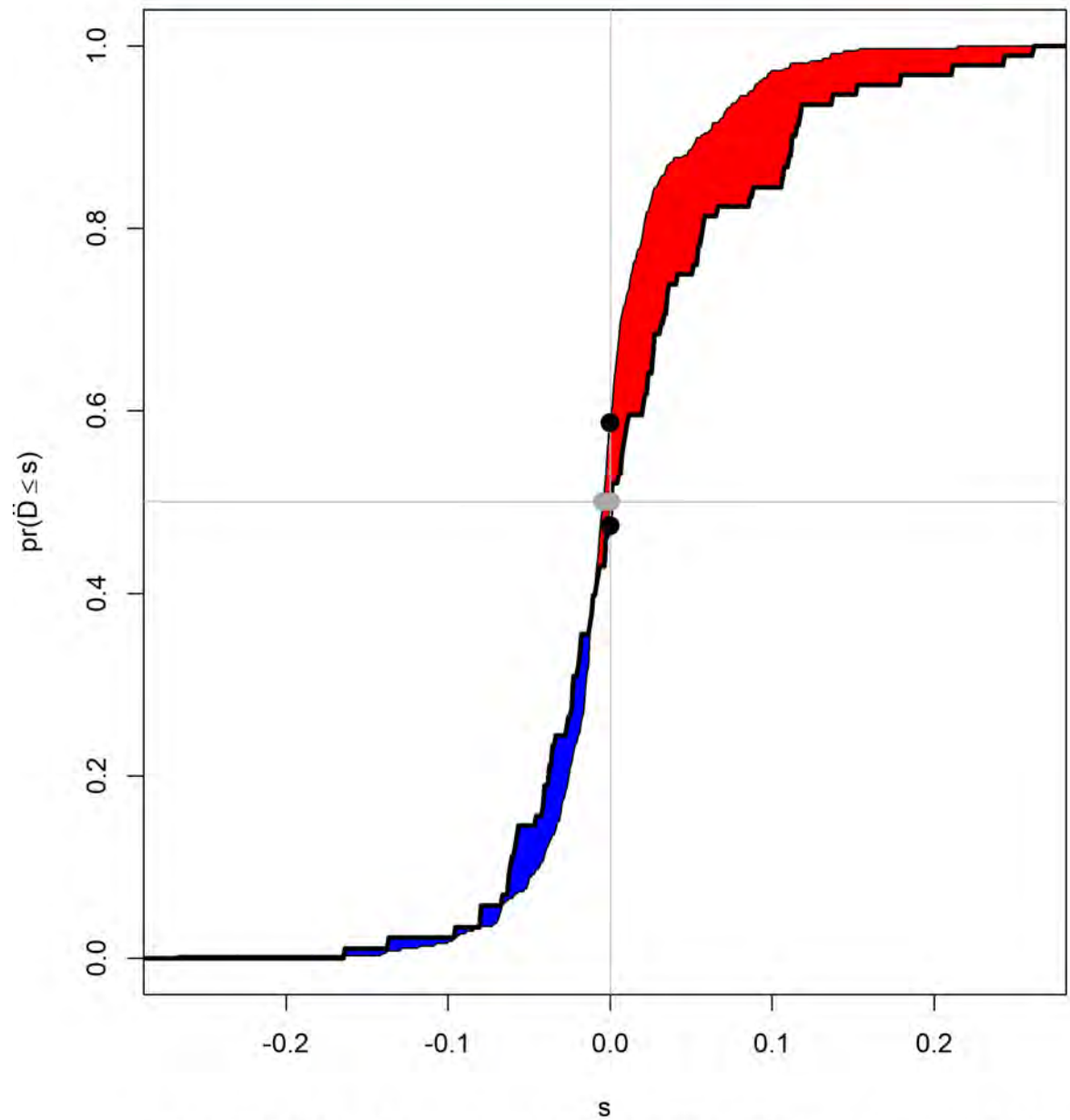


Improvement in risk prediction using survIDINRI when comparing clinical(8) + genetic(11) to clinical(8)

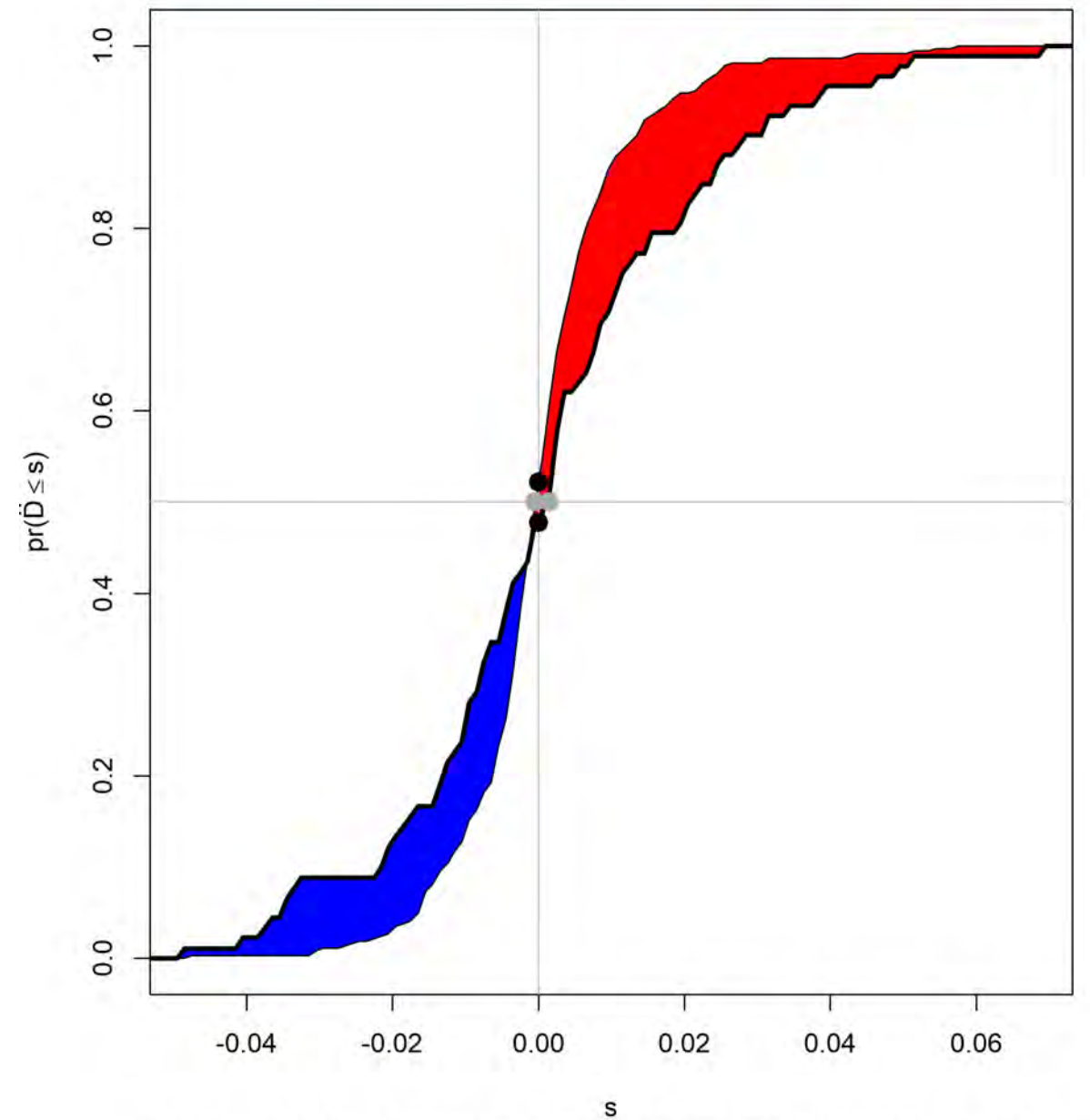


**Supplementary Figure 9.**

Improvement in risk prediction using survIDINRI when comparing clinical(8) + genetic(6) to clinical(8)

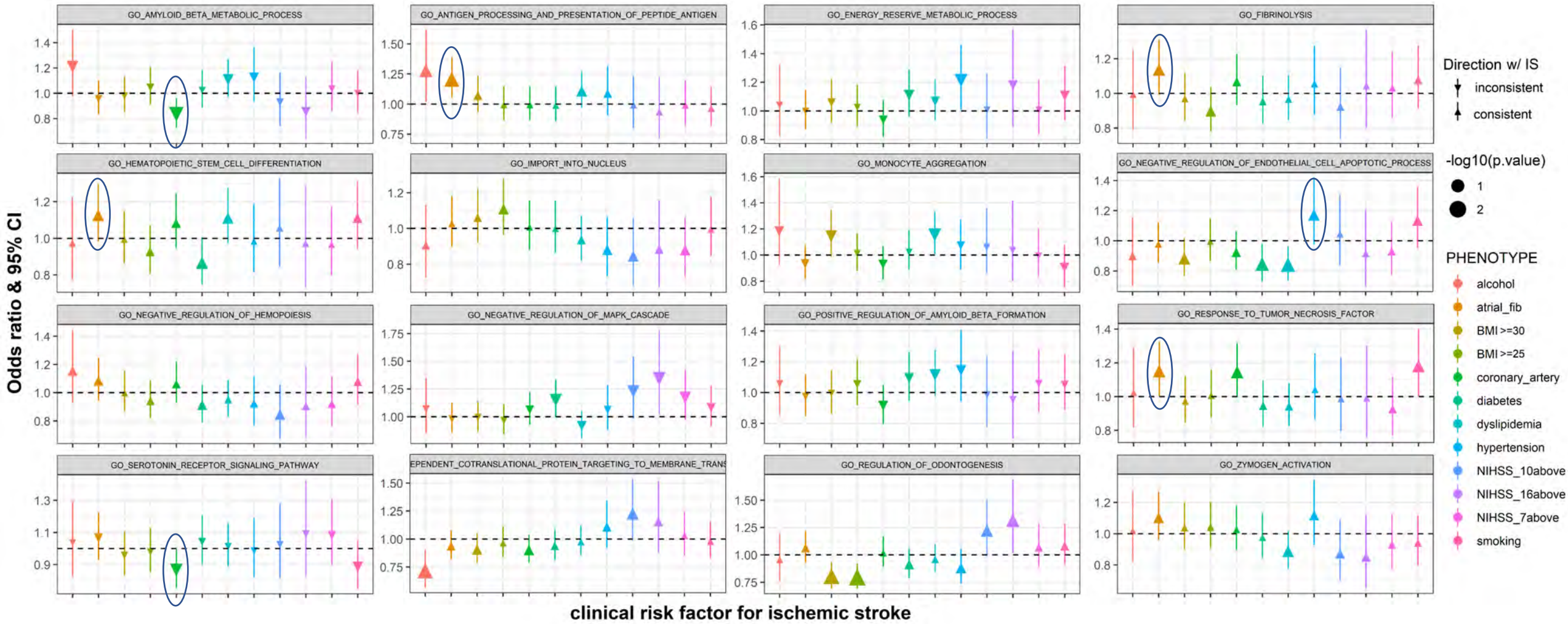


Improvement in risk prediction using survIDINRI when comparing clinical(8) + genetic(2) to clinical(8)





Supplementary Figure 10 (old).



Supplementary Figure 10 (young).

