Title: Association between cognition and gene polymorphisms involved in thrombosis and haemostasis

Running title: Thrombosis and haemostasis associations with cognition

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Abstract:

An association between blood markers of thrombosis and haemostasis and cognitive decline has been described. These results may be confounded by lifestyle and environmental factors. We used a Mendelian Randomisation approach to describe association between thrombosis/haemostasis genotypes and cognition.

We studied genetic variants (single nucleotide polymorphisms) of circulating markers of thrombosis and haemostasis. Our chosen blood factors and associated polymorphisms were: D-dimer [rs12029080], fibrinogen [rs1800789], plasminogen activator inhibitor [rs2227631], von Willebrand factor [rs1063857]). We described association with multi-domain cognitive test scores using data from the Scottish Family Health Study. Cognitive data were analysed for individual tests and combined to give a general cognitive factor.

In 20,288 subjects we found no evidence of association between cognitive function (individual tests and combined scores) and any of the above-mentioned single nucleotide polymorphisms. Lower scores on cognitive measures were associated with:increasing age, socioeconomic deprivation, blood pressure, waist-hip ratio, smoking, and vascular comorbidity (all $p<0.001$). In a post-hoc sensitivity analysis restricted to those aged over 50 years there was still no signal of association.

Our data add to our understanding of determinants of cognition but are not definitive, the variation in blood levels explained by SNPs was modest and our sample size may have been insufficient to detect a modest association.

Keywords: cognition disorders; dementia; hemostasis; genomics; Mendelian randomization analysis;

Introduction

Cognitive decline and dementia are a substantial and growing public health concern. To date, our understanding of pathogenesis and risk factors is limited and this has impacted on development of effective therapies.(Ritchie et al 2015)

Various cohort and case-control based studies have described an apparent association between higher levels of blood markers of thrombosis and haemostasis and incident dementia or cognitive decline.(Bots et al 1998, Gallacher et al 2010, Stott et al 2010)) Recent systematic review and meta-analysis has confirmed this link with blood markers, observed associations were strongest for “vascular” dementia but also apparent for “all cause” (undifferentiated) dementias.(Quinn et al 2011) The summary data on strength of associations were modest with wide confidence intervals but were consistent across the available data. A particular association between dementia and markers of thrombin generation (D-dimer and prothrombin fragment 1+2) and endothelial dysfunction (von Willebrand factor [vWF] and plasminogen activator inhibitor 1 [PAI1]) was apparent.

There are many typical biases that will affect the validity of these epidemiological studies. Association may be a result of disease rather than causal or may reflect confounding by other factors. For example, thrombosis/haemostasis factors may be associated with vascular disease that causes cognitive decline, thus representing an indirect association. Even in robust studies, statistical adjustment for confounding is often incomplete as only certain known factors will be measured.(Fewell et al 2007) Of particular importance in this context, haemostatic and thrombotic blood markers of interest are influenced by several demographic, clinical and lifestyle factors that may also impact on cognition and so may confound any apparent association.(Bath et al 2010)

A potential approach to establish causation is to describe the association of an outcome of interest (in this case, cognition) with genetic markers that relate to the postulated causative factor (in this case, genetic variants that determine thrombosis and haemostasis). This

"Mendelian randomisation" strategy can provide important suggestive evidence about causality by incorporating fixed genetic information into the traditional epidemiological study design.(Davey Smith et al 2014)

We performed Mendelian randomisation analyses of the genetic determinants of thrombosis/haemostasis and compared with population cognitive test scores in a large, community dwelling adult population. Our aim was to describe the role of thrombosis/haemostasis in cognitive capability, free from the usual lifestyle and environmental confounders.

Methods

Study protocol, data management and statistical analyses were in collaboration with the Robertson Centre for Biostatistics, University of Glasgow according to a pre-specified analysis plan (available on request from corresponding author).

Population: Our study used the Generation Scotland resource, specifically the Scottish Family Health Study (SFHS) component. SFHS contains biobanked materials suitable for genetic analyses in a well-phenotyped, heterogeneous population of volunteers. Both Generation Scotland and the SFHS have been described in detail elsewhere.(Smith et al 2012)

In brief, SFHS is a large, intensively phenotyped, cohort designed to study the genetic basis of common, complex diseases. Recruitment began in 2006 and was completed in 2011. Individuals were approached through primary care provider. SFHS contains data on 24 000 volunteers from across Scotland, aged 18-98.

Participants were invited for a detailed clinical assessment, including cognitive tests and lifestyle questionnaires. Blood and urine samples were taken and stored in biobank facilities. After participants had given informed consent for data and sample collection and analysis, and completed a pre-clinic questionnaire, research nurses/technicians performed all measurements. Nurses and technicians were fully trained and validated in sample and data collection according to standard operating procedures, each of which was designed for the study, according to current best practice.

Polymorphisms of interest: We used a multi-modal approach to select SNPS of interest for our study. Candidate blood markers were chosen based on our previous meta-analysis of thrombosis/haemostasis and cognition. We reviewed the literature for credible genetic variables of blood markers using the HuGE Navigator online database resource (http://64.29.163.162:8080/HuGENavigator/home.do). We selected materials where data were available from meta-analyses or genetic consortium projects. We selected SNPs based on those with greatest strength of association (the greatest percentage variation in the factor) with our blood markers of interest. We cross referenced plausible SNPs against the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP/). As a final check of face validity we consulted with an independent expert in thrombosis/haemostasis (Prof GDO Lowe, Glasgow). We chose to focus our analysis on four exemplar markers of thrombosis / haemostasis. Our final choices of SNP were:

Fibrinogen:SNP rs1800789 (Chromosome: 4:154561591; gene:FGB. functional consequence: upstream variant 2KB). Chosen based on meta-analysis of GWA study data using 91,435 individuals from 28 cohorts of European ancestry with fibrinogen levels and genome-wide imputed data.(Dehgan et al 2009)

D-dimer: SNP rs12029080 (Chromosome: 1:94587797; closest gene: Coagulation factor 3 (F3)+46.0kb (also known as tissue factor)). Chosen based on data from Heart and Aging

Research in Genomic Epidemiology (CHARGE) Consortium, which includes data from several prospective, population-based cohorts of adults in the US and Europe (all European ancestry.(Smith et al 2011)

Von Willebrand factor (vWF): SNP rs1063857 (Chromosome: 12:6044348; Gene:VWF; functional consequence: synonymous codon). Chosen based on data from Atherosclerosis Risk in Communities (ARIC) study (European ancestry) (Campos et al 2011, Smith et al 2010) and data on expression in cardiovascular disease.(van Schie et al 2011)

Plasminogen activator inhibitor 1 (PAI-1): SNP rs2227631 (Chromosome: 7:101126257; gene:SERPINE1; functional consequence: upstream variant 2KB). Chosen based on data from Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, which includes data from several prospective, population-based cohorts of adults in the US and Europe (all European ancestry) and Framingham Heart Study data (European ancestry). (Huang et al 2012; Kathiresan et al 2005)

We note that studied SNPs account for only a proportion of variance seen in the markers of interest (maximal variance in blood levels explained by SNPs is 2% for fibrinogen variance; 1.8% for D-dimer; 13% for vWF; 3.7% for PAI-1).

DNA extraction and genotyping: DNA extraction was performed in the Wellcome Trust Clinical Research Facility Genetics Core, Edinburgh, UK, using a Nucleon Kit on 9 ml of blood sample (Tepnel Life Science). The Picogreen method (Invitrogen) was used to quantify DNA concentration in ng/µl, and 500 µl of each DNA master stock was transferred to a deep well plate and then normalised to 50 ng/µl to make working stock plates. The plates were then transferred to the British Heart Foundation-Glasgow Cardiovascular Research Centre and stored at -4°C for commencement of the genotyping procedure. Each plate held 380 DNA samples in a concentration of 50 ng/µl, with 4 empty wells used as no-template controls.

All genotyping was performed in the British Heart Foundation-Glasgow Clinical Research Centre using the TaqMan® OpenArrayTM Genotyping System (Applied Biosciences). 2.5 µl of the DNA samples and 2.5 µl of the TaqMan® OpenArray® Master Mix were mixed in the TaqMan OpenArray 384-Well sample plate. The OpenArray Autoloader was used to transfer the mixture to TaqMan OpenArray plate. Thermal cycling was performed using the Dual Flat Block GeneAmp® PCR System 9700, applying the appropriate protocol for the TaqMan OpenArray plate. The loaded plates were then scanned using the OpenArray® NT Cycler. Genotype calling and results analysis were performed using TaqMan Genotyper Software V1.3 (Life Technologies), where results were checked manually to remove samples with poor genotype quality. Genotypes of our 4 SNPs of interest were cross-validated with another project that genotyped the same SNPs.

Outcomes of interest: We used data pertaining to a variety of tests that assess differing cognitive domains:

Logical Memory test 1 and 2 (LM1+2) is a test of immediate and delayed auditory memory using one story taken from the Wechsler Memory Scale III. In this test a paragraph was read to subjects. They were asked to recall the content immediately and after a delay of 30 minutes. Scores were total number of memory elements recalled, scores from both tests were added together.(Weschler 1998)

Digit Symbol Test (DST), a measure of processing speed (taken from Wechsler Adult Intelligence Scale III). The participants were instructed to enter symbols according to a given number-symbol code. The score recorded was the number of completed symbols within 2 min. (Weschler 2013)

Verbal Fluency test (VF), a measure of phonemic fluency. Participants were asked to name as many words as possible beginning with the letters C,F and L for one minute each.

Proper names or repeated words are not credited. The score used was the total number of words generated across the three tasks. (Raven 1977)

We also collected data on the **Mill Hill Vocabulary Test** (MHVT), a measure of acquired verbal knowledge (Junior and Senior synonyms combined) that we used to estimate peak prior cognitive ability. (Lezak 1995)

To assess the importance of other, non-genetic co-variates we included data pertaining to demographic factors (age, sex, deprivation [Scottish Index of Multiple Deprivation (National Statistics Scotland 2012)]; education [highest level of schooling completed]); lifestyle factors (smoking, alcohol, sedentary time [participant estimate]) and clinical factors (blood pressure; comorbidity; waist to hip ratio). Operationalisation of each co-variate has been described previously.(Smith et al 2012) From comorbidity data, we recognised that certain disease labels collected in SFHS are potentially associated with reduced scores on cognitive tests and so we grouped these (Alzheimer's Disease; Parkinson's Disease and severe depression) under a rubric of "cognitive comorbidity". For ease of analysis we also created a "vascular comorbidity" grouping (hypertension, heart disease [any], stroke, diabetes).

Statistical analysis: Continuous variables were summarised as median (standard deviation), median (interquartile range) and range. Categorical variables were summarised as number and proportion per category. Distributions of continuous variables were visualised using violin plots. All continuous measures showed approximately normal distributions. To obtain maximal statistical power all non-missing data were used resulting in potential different sample sizes across variables.

We assessed the correlation of cognitive variables by Pearson correlation coefficients prior to principal component analysis(Table S1). Then we used principal components analysis to derive a **general fluid cognitive factor**, traditionally called g, (Luciano et al 2011) from the

three cognitive tests described above (LM1+2, DST, VF) as the first unrotated component. This component explained 49% of the variance from the full cognitive battery.

To account for family structure, we used mixed models to analyse the relation of the SNP of interest to cognitive outcome. To assess whether these relations differ according to age, the interaction of the SNP with age group was also entered into the model.

We analysed the SNPs in four ways, treating them as categorical variables (labelled as "factor" in the results tables), as each homozygous category against the two other categories (e.g. AA vs. AG or GG and GG vs. AA orAG) and as continuous (labelled as "additive" in the results tables).

We also created multivariable models including socioeconomic and lifestyle factors, comorbidities, body measurements and blood pressure variables. Models were derived using a three step process.

1. Within each domain (socio-economic, blood pressure, body measurements, lifestyle, comorbidities), we entered all univariately significant variables into a model predicting cognitive factor and used stepwise elimination for all variables with $p>0.01$.
2. We entered the remaining variables from all domains together into a model predicting cognitive factor and eliminated all variables with $p>0.01$.
3. We predicted cognitive factor from all variables identified in step 2 and the SNP.

We adjusted all mixed models for age, sex and prior peak intelligence (MHVT) and assumed a compound symmetry correlation structure within families.

Recognising that our population was relatively young, and that differences in cognition may become apparent with ageing, we conducted a post-hoc sensitivity analysis restricted to those aged over 50 years. In the sensitivity analyses we described scores on cognitive tests by allele and mixed models correcting for age, sex and prior peak intelligence.

All analyses were performed using R v3.0.1.(R Core Team 2013). The P-values presented are not corrected for multiple testing and have to be considered as descriptive.

Results

Genotyping was performed for 20,753 samples in total, (data on genotype frequencies and Hardy Weinberg equilibrium are presented in supplementary materials, Tables S2, S3).

Of these samples n=465 (2.2%) samples were removed due to poor quality, n=1132 (5.6%) were excluded due to implausible SNP data in their family; n=109 (0.5%) were excluded due to missing data and n= 121 (0.6%) due to implausible cognitive data. Genotypes discrepancy was less than 1% in over 10,000 genotypes that were cross validated between two projects.

Participants showed a range of cognitive ability on our chosen tests, cognitive scores for each test and for combined test (g) are tabulated and presented stratified by age (supplementary materials, Table S4).

The mean age of subjects was 47.3 years (SD:15.0, range:18-99), with11,135 female participants (59%). Level of education was relatively high in the sample with 5,654 (32%) having a College/University degree; n=1825 (9.8%) had a marker of cognitive comorbidity. Other socio-demographic, clinical, and lifestyle covariates are tabulated (Table 1 and supplementary materials, Table S5).

At traditional significance thresholds, there was no evidence of association between any of our four chosen thrombosis/haemostasis related SNPs and any single or combined cognitive measures, in uncorrected analyses (Table 1). Using mixed models accounting for age, sex and estimated peak prior intelligence, again there was no evidence of any relevant association between SNPs and cognitive ability (Table 2, supplementary materials Tables S6).

Correcting for co-variates of age, sex and prior peak intelligence, higher scores on (g) were significantly associated with lower age, blood pressure, waist-hip ratio, smoking and vascular comorbidity and were also associated with higher educational achievement and socioeconomic status (all <0.001), albeit effect sizes were small (Table 3 and supplementary materials, Tables S7).

Our post-hoc sensitivity analyses did not show evidence of association in those aged 50 years and older.(Table 2 and table 3)

Discussion

We found no relevant association between genetic polymorphisms associated with thrombosis/haemostasis and cognitive abilities in a middle and older age population.

We postulated that the associations previously described for cognition and circulating markers of thrombin generation and endothelial dysfunction were confounded by clinical, lifestyle and sociodemographic factors. We found association between clinical, lifestyle and sociodemographic factors and our cognitive domains of interest. However, we found no association between SNPs and cognitive measures, even on uncorrected analysis. As a further check of the robustness of our results, we ran the categorical and additive models correcting for plausible demographic, clinical and lifestyle factors that may impact on cognition. Again in these corrected models there was no signal of association.

Although our data add to our knowledge of determinants of later life cognition, our results are not definitive. We studied a predominantly middle aged and healthy cohort, thrombosis/haemostasis genetic associations may still be apparent in older populations with greater prevalence of pathological cognitive ageing. Recognising that our population was relatively young, albeit there was a spread of age, we performed post-hoc sensitivity

analyses restricted to those aged over 50 years. Cognitive scores were poorer in the older group but again there was no signal of association with our SNPs of interest.

It is also possible that a modest association may have been missed. The SNPs studied account for only a proportion of variance seen in the markers of interest (2% of fibrinogen variance; 1.8% for D-dimer; 13% for vWF; 3.7% for PAI-1). For this reason, many published studies using Mendelian Randomisation approaches to describe association with thrombosis/haemostasis may have been "under-powered" despite relatively large sample sizes.(Welsh 2014; Marioni et al 2011) Thus, given that association between SNPs and blood markers is modest and that the association between blood markers and insensitive cognitive measures is also modest, even with a large mid-age sample there is potential that we lacked statistical "power" to detect a true association. Confounded association as an explanation of previous findings suggesting links between thrombosis and haemostasis are also still plausible as our study may have been underpowered to definitively answer this question. Combining our data with other large cohorts that have cognitive and genetic data may be necessary to avoid type II statistical error.

Higher cognitive test scores were seen in those with "healthier" lifestyle, higher education and socioeconomic status. Lower scores were seen in those with vascular risk factors of increased blood pressure and waist-hip ratio. Associations of these factors with cognition have been previously described in other cohorts and emphasise the importance of lifestyle factors in cognitive ageing.(Barnes et al 2011, Gow et al 2012) We described prevalent psychiatric and neurodegenerative diseases at baseline but numbers were modest. In a population with high prevalence vascular risk factors and disease we had hoped to explore possible vascular and non-vascular cognitive decline associations. Our data do not allow us to comment on possible underlying mechanisms for differing cognitive scores.

Strengths of our approach were access to a large dataset with comprehensive clinical, demographic and lifestyle phenotyping including cognitive data and markers of peak prior

intelligence. We used a hypothesis-driven gene-centric analysis informed by systematic review of available published data.(Quinn et al 2011)

A limitation of our work was that we did not have access to participant samples to allow quantification of blood levels of D-dimer, fibrinogen, PAI-1 and vWF and this complicates the interpretation of our "neutral" result. We know the strength of association of each SNP with the thrombosis/haemostasis markers from pooled genetic data and we know the association of each thrombosis/haemostasis marker with cognitive domains of interest from our previous meta-analysis. There is no reason to think the SFHS cohort would be systematically different from the cohorts that informed these analyses, but we accept the ideal would have been direct blood measures.

Although our cognitive tests describe various domains these short test data are not comparable to the detailed neuropsychological testing that has been used in some previous studies looking at associations with later life cognition.(Gow et al 2011)

We studied only four SNPs that relate to specific circulating factors. Our chosen SNPs represented those with the strongest association with the blood marker of interest. We recognise that other SNPs also contribute to variation in levels of the blood markers (for example FV Leiden [rs6025] or prothrombin 3'UTR mutation [rs1799963]) but we were limited in the SNPs we could include in our analysis. Association between thrombosis/haemostasis and cognition may still be apparent for those genetic variants that make up the remaining variance not accounted for in our chosen SNPs or indeed for other genetic markers of thrombosis/haemostasis. Future studies may wish to explore the aggregate effect of combined associated SNPs.

In conclusion, our Mendelian Randomisation approach did not suggestive a causative relationship between circulating markers of thrombosis and haemostasis and cognition. Associations were seen with various clinical, demographic and lifestyle factors. We

focussed on a limited number of SNPs and our sample may have been underpowered so a causative role for thrombosis/haemostasis is not definitively excluded based on our data.

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Prof Deary, Gallacher and Stott assisted with supervision, analysis of cognitive data, interpretation of data and drafting of manuscript.

Dr Messow performed the statistical analyses and assisted with drafting of the manuscript.

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Table 1: Demographic, clinical and lifestyle measures in the Scottish Family Health Study cohort

	Demographic measures	value
Age	Mean(SD) [Range]	47.3 (15.0) [18.0, 99.0]
Sex	Female - N(%)	11135 (58.8%)
Education	College or University degree - N(%)	5654 (32.2%)
	Other professional - N(%)	3600 (20.5%)
	Higher grade, A level or equivalent - N(%)	1948 (11.1%)
	Standard grade or equivalent - N(%)	2118 (12.1%)
	No qualifications - N(%)	1424 (8.1%)
SIMD quintile	1 - N(%) [poorest]	2329 (13.3%)
	5 - N(%)[richest]	5525 (31.6%)
	Clinical measures	
SBP (mmHG)	Mean (SD) [Range]	131.5 (17.8) [80.0, 239.0]
Waist-hip ratio	Mean (SD) [Range]	0.9 (0.1) [0.5, 1.7]
Vasc morbidity	Yes - N(%)	3164 (17.1%)
Cog morbidity	Yes - N(%)	1825 (9.8%)
	Lifestyle measures	
Units alcohol in last week	Mean (SD)	10.1 (13.6)
	[Range]	[0.0, 326.0]
Smoking status	Never - N(%)	9700 (52.9%)
	Stopped more than 1 year ago - N(%)	4866 (26.5%)
	Current - N(%)	3221 (17.6%)
Sitting hours	Mean (SD) [Range]	24.1 (27.9) [0.0, 192.0]

Table 1: Demographic, clinical and lifestyle measures in the Scottish Family Health Study cohort

This is an abbreviated table and full details are available in supplementary materials (Table S5).

N obs = Number of observations; N miss= Participants with missing data; SD=Standard Deviation; SIMD=Scottish Index of Multiple Deprivation; SBP – Systolic Blood Pressure

Vasc morbidity = vascular comorbidity; Cog morbidity = Cognitive comorbidity. Vascular and cognitive comorbidity are operationalised in the main manuscript.

Table 2: Cognitive test scores by single nucleotide polymorphism (SNP) and allele

SNP	Allele	Allele frequency	Logical memory 1+2 (Total correct) [Range: 0-50]	Digit Symbol Testing (Total Correct) [Range: 0-125]	Verbal Fluency (Total words) [Range:0-89]	Cognitive function principal component (g)
		N (%)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
rs1800789	AA	623 (3.3%)	30.7 (8.6)	72.0 (17.1)	38.9 (11.5)	0.07 (1.25)
	AG	5740 (30.5%)	31.0 (7.7)	72.3 (16.8)	39.7 (11.7)	0.00 (1.19)
	GG	12471 (66.2%)	31.0 (8.0)	72.3 (17.1)	39.8 (11.7)	0.00 (1.23)
rs12029080	GG	1456 (7.7%)	31.2 (8.1)	72.1 (16.9)	39.5 (11.8)	0.00 (1.26)
	GT	7694 (40.9%)	31.0 (7.9)	72.1 (17.0)	39.8 (11.7)	0.00 (1.20)
	TT	9658 (51.4%)	31.0 (8.0)	72.3 (17.0)	39.7 (11.6)	0.00 (1.22)
rs1063857	GG	2611 (14.3%)	31.0 (7.8)	71.7 (17.0)	40.1 (11.7)	0.01 (1.21)
	GA	8670 (47.5%)	31.0 (8.0)	72.3 (17.1)	39.8 (11.7)	-0.01 (1.22)
	AA	6956 (38.1%)	31.1 (7.9)	72.5 (16.9)	39.6 (11.6)	-0.01 (1.21)
rs2227631	AA	6649 (36.4%)	31.2 (8.0)	72.3 (17.2)	39.7 (11.6)	-0.01 (1.23)
	AG	8772 (48.1%)	31.0 (7.9)	72.1 (16.8)	39.8 (11.7)	0.00 (1.21)
	GG	2831 (15.5%)	30.8 (8.0)	72.6 (16.8)	39.7 (11.5)	0.01 (1.20)
Sensitivity analysis, cognitive test scores by SNP and allele in participants aged 50 years and older						
rs1800789	AA	306 (3.4%)	29.3 (8.5)	63.8 (15.1)	39.5 (11.7)	0.45 (1.22)
	AG	2777 (30.5%)	29.8 (7.7)	64.8 (15.5)	40.5 (12.2)	0.34 (1.21)
	GG	6027 (66.2%)	29.7 (8.0)	64.9 (15.8)	40.9 (12.1)	0.33 (1.22)
rs12029080	GG	698 (7.7%)	29.4 (8.2)	64.4 (15.1)	40.1 (12.1)	0.40 (1.22)
	GT	3763 (41.3%)	29.8 (7.8)	64.7 (15.8)	40.8 (12.1)	0.32 (1.21)
	TT	4645 (51.0%)	29.6 (8.0)	65.0 (15.8)	40.7 (12.1)	0.33 (1.22)
rs1063857	GG	1281 (14.5%)	29.6 (7.9)	64.6 (16.2)	41.1 (12.3)	0.33 (1.25)
	GA	4215 (47.6%)	29.7 (7.9)	64.8 (15.7)	40.8 (12.2)	0.33 (1.22)
	AA	3353 (37.9%)	29.8 (7.9)	65.1 (15.6)	40.5 (12.0)	0.32 (1.20)

SNP	Allele	Allele frequency	Logical memory 1+2 (Total correct) [Range: 0-50]	Digit Symbol Testing (Total Correct) [Range: 0-125]	Verbal Fluency (Total words) [Range:0-89]	Cognitive function principal component (g)
		N (%)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
rs2227631	AA	3251 (36.7%)	29.8 (8.0)	64.9 (16.1)	40.6 (12.0)	0.33 (1.23)
	AG	4262 (48.1%)	29.7 (7.8)	64.8 (15.5)	40.6 (12.2)	0.34 (1.21)
	GG	1341 (15.1%)	29.5 (8.0)	65.1 (15.5)	41.0 (11.9)	0.33 (1.19)

Table 3: Cognitive function and thrombosis/haemostasis genotypes

		P value for variable	P value (aged 50 years or older)	P value (adjusted mixed models)
rs1800789	AG vs. AA GG vs. AA	p=0.363	p=0.151	p=0.356
	Additive	p=0.550	p=0.233	p=0.992
rs12029080	GT vs. GG TT vs. GG	p=0.731	p=0.254	p=0.552
	Additive	p=0.546	p=0.683	p=0.423
rs1063857	GA vs. GG AA vs. GG	p=0.742	p=0.939	p=0.449
	Additive	p=0.566	p=0.757	p=0.522
rs2227631	AG vs. AA GG vs. AA	p=0.569	p=0.850	p=0.181
	Additive	p=0.351	p=0.600	p=0.072

P-values from mixed models predicting cognitive principal component “g” from single nucleotide polymorphism alleles adjusting for age, interaction of age with single nucleotide polymorphism, sex and prior peak intelligence.

Second results column is sensitivity analyses restricted to those aged over 50 years.

Third results column presents models predicting cognitive principal component from SNPs and interaction of SNP with age category. Models adjusting for age, sex, mill hill vocabulary test, household income, education, blood pressure, heart rate, BMI, waist-hip ratio, alcohol consumption, smoking, vascular and cognitive comorbidity history.