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Research Article

Associations between cardiovascular risk factors and cognitive function: a cross-sectional study of twins in the United Kingdom

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Short Title: Cardiovascular Risk Scores and Cognitive Function among twins

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Abstract

Introduction: Cardiovascular risk factors (CVRF) have been associated with cognitive impairment; however, the underlying mechanisms remain unclear. This study used twins modelling, to investigate whether shared twin factors contribute to the associations between CVRFs and cognitive function.

Methods: This study used a cross-sectional design and participants were from the UK adult twin registry. Clinically validated cognitive tests were administered during routine clinical research visits between 2013 and 2016, measuring overall global cognition, recall, verbal fluency, processing speed, episodic memory and learning. CVRFs were total cholesterol (TC), high-density lipoprotein (HDL), systolic blood pressure (SBP), type 2 diabetes (T2D), and smoking status.

Results: Participants were between 1300-2300 twins (depending on the cognitive test) and the mean age of twins was approximately 56 years. Cholesterol levels (both TC and HDL) were significantly associated ($p<0.05$) with overall global cognition, recall, and verbal fluency with effect sizes (standardised) ranging from 0.5 to 0.11. In the twins modelling, after adjusting for genetic and shared environmental factors, the associations disappeared. Similarly, higher SBP levels were associated with poorer verbal fluency performance (-0.05 [-0.10 to 0.00]), and while between-pair effects were significant found (-0.09 [-0.15 to -0.03]), within-pair effects (after adjusting of shared environmental factors) were not.

Conclusion: Higher TC, HDL, and lower SBP were all associated with better performance on a range of validated cognitive tests. However, findings suggest that the association between CVRFs and cognitive function is predominantly explained by shared twin-pair factors which may be genetic or shared environment.

Introduction

In years to come, there will be a substantial surge in the number of people living with dementia, including Alzheimer's Disease.[1] Dementia is a clinical syndrome characterised by marked impairment in two or more cognitive domains, which interferes with the ability to perform everyday activities. [2] Cognitive function, however, varies considerably across individuals,[3] and understanding the sources of this variability is a critical step toward clarifying mechanisms underlying cognitive decline. Twin studies provide a powerful approach for this purpose, enabling estimation of heritability (the variance in cognition due to genetic influences), as well as contributions from shared and unique environmental factors.[4] Such investigations are essential not only for understanding dementia, but also for distinguishing patterns of normal cognitive aging from those indicative of pathological processes.

Cardiovascular risk factors (CVRFs), including systolic blood pressure (SBP), type 2 diabetes (T2D) and smoking, have been associated with poorer cognitive performance.[5-9] Despite these associations, the underlying mechanisms remain unclear. Observed relationships may be confounded by unmeasured factors, such as genetic influences, highlighting the need for designs that account for these potential confounders.[10] Twin-based approaches are well suited to address this issue because they allow separation of genetic and shared environmental influences from individual-specific effects. Two previous studies have examined the association between CVRFs and cognition using twin designs, but both were limited by relatively small samples.[11,12] The twin decomposition approach extends these methods by comparing effects between families and within twin pairs, thereby evaluating whether associations persist after accounting for factors shared by twins.

Therefore, the aims of this study were to (i) estimate the heritability of cognitive function using the classical twin modelling; (ii) examine association between CVRFs and cognitive performance; and (iii) apply a twin decomposition approach, to assess whether shared familial factors contribute to these associations. We hypothesised that cognitive function would show significant heritability, that higher cardiovascular risk would be associated with poorer cognitive performance, and that within-pair comparisons would attenuate these association relative to between-family analyses.

Methods

Study population

Participants were from the UK Adult Twin Registry (TwinsUK), the UK's largest registry of monozygotic (MZ) and dizygotic (DZ) twins, curated by the Department of Twin Research & Genetic Epidemiology, King's College London. Participant characteristics have been described in detail elsewhere.[13] Briefly, this registry comprises over 16,000 twins; is predominantly female (82%), with a mean age of 59 years.[13] Data are collected approximately every four years during routine research visits to the clinical research facility, and via bi-annual telephone or postal questionnaires. Our study utilises a cross-sectional design and includes all twins with data available on [at least one] cognitive test which was collected between 2013-2016. The number of twins who had cognitive function testing ranged from 1344 to 2284 pairs.

Cognitive function

Four different clinically validated tests of cognitive function were used: i) Mini Mental State Examination (MMSE) , ii) Verbal Fluency Test, iii) Deary-Liewald Reaction Time Test (DLRT) and iv) Cambridge Neuropsychological Test Automated Battery-Paired-Associated Learning Test (CANTAB-PAL) The MMSE is a standardised cognitive screening tool to assess global cognitive function and higher scores indicate better performance on MMSE.[14] Additionally, the recall score (0-3) was used separately as a measure of memory (recall) function. Verbal fluency was measured using the verbal fluency, which is a subtest of the Addenbrookes Cognitive Examination III [15], here too, higher scores indicate better performance. The DLRT measures processing speed and for DLRT, a higher mean (time taken to complete a task) indicates worse performance.[16] Finally, the CANTAB-PAL test assesses visual memory and learning and higher scores indicate worse performance.[17] All the cognitive assessments were administered in person by trained research assistants and research nurses during routine study visits.

Cardiovascular risk factors

We included total cholesterol (TC), high density lipoprotein (HDL), SBP, smoking status, and T2D. The data on TC, HDL and SBP were collected during participants' visits to the clinical research facility, further information is included in the supplementary methods. Smoking history was self-reported via questionnaires with participants indicating whether they were former, current or never smokers (prompt question "*Have you ever smoked cigarettes, cigars or a pipe?*"). In this study, former and current smokers were combined to form two categories: never smoked (0) and ever smoked (1). Participants also self-reported on T2D (prompt question "*Has a doctor*

ever told you that you have/had any of the following conditions? \ Type 2 diabetes (or 'adult onset')") which was also coded as a binary variable (no diabetes:0, diabetes: 1).

Statistical analyses

Statistical analyses were performed in RStudio, using R version 4.3.1.[18] The raw MMSE score was log transformed and verbal fluency and CANTAB-PAL were square root transformed to account for skew in the data. DLRT scores were normally distributed and did not require any transformation. Further, all the continuous variables (for both CVRFs and cognitive function) were converted to standardised z-scores to obtain standardised scores for comparison. Descriptive statistics were examined separately for each of the cognitive tests, continuous variables were described as mean (standard deviation) (SD) and categorical variables as frequency (percentages). The heritability for the cognitive domains (.i.e. the proportion of variance in cognition between twins due to additive genetic influences) was utilising univariate ACE twin models in the 'OpenMx' R package.[19] The model partitions the observed variance in cognitive function into additive genetic influences (A), shared environmental influences (C), and nonshared environmental influences (E).[20] The ACE models use the genetic relatedness of MZ and DZ twin pairs who share 100% (MZ) or 50% (DZ) of their genes. The assumption is that shared environment is similar for MZ and DZ pairs.

We tested if CVRFs and cognitive function were associated in individual-level analyses using linear generalized estimating equations (GEE) models with an exchangeable correlation structure. Finally, using the co-twin control analyses, we tested whether CVRFs were associated with cognitive function independent of genetic and early life shared environmental factors. To do this, we used GEE models to estimate between-pair (the expected change in outcome for one unit change in the twin-pair average of the exposure) and within-pair (expected change in outcome for a unit change in the difference between the individual and the twin pair average) effects of CVRFs on cognitive function.[21] All models were adjusted for age and sex. For the co-twin control analyses, we additionally included additionally included years of education, socioeconomic status, and BMI as covariates to account for potential confounding related to cognitive performance.

Results

Descriptive statistics

There were a total of 2284 twin pairs (MZ n = 1465; DZ n = 819) with MMSE scores, 2266 (MZ n = 1452; DZ n = 814) with verbal fluency, 1454 (MZ n = 915; DZ n = 539) with DLRT, and 1344 (MZ n = 806; DZ n = 538) with CANTAB-PAL. For the MMSE cohort, the mean age of twins was 56.4 (Standard Deviation (SD) = 15.8); 87.7% were female; and 96.0% were white. The proportion with Type 2 diabetes was 3.2%, and 39.6% were either current or former smokers. The DZ twins were slightly older with a higher proportion of female twins and more likely to have diabetes or ever smoked (Table 1). Descriptive statistics for the other cognitive outcomes were similar (Supplementary tables ST1-ST3).

Genetic and environmental influences of cognitive function

The mean cognitive function scores and intraclass correlations are shown in Supplementary Table ST4. Twins were most similar in DLRT (correlation co-efficient 0.53 [0.50-0.57]) and CANTAB-PAL scores (0.49 [0.45-0.53]) and least similar in MMSE recall (0.24 [0.20-0.28]). Model estimates from the univariate ACE models are shown in Table 2 and Supplementary Tables ST5-ST9. Results from the AE models indicate a moderate degree of variance in all cognitive abilities attributable to genetics, with heritability ranging from 0.19 in CANTAB-PAL to 0.45 in verbal fluency. The rest of the variance was attributable to non-shared environmental factors (Table 2 and Supplementary Tables ST5-ST9) across all cognitive domain tests except for CANTAB-PAL. For this cognitive domain, the ACE model was the best fitting with 0.26 variance attributable to shared environmental factors and 0.55 variance to non-shared environmental factors (Table 2 and Supplementary Table ST9).

Individual regression model: Association between cardiovascular risk factors and cognitive function

The results from the regression analysis used to determine individual level associations between CVRFs and cognitive function are shown in Figure 1 and Supplementary Table ST10). Higher TC (β = 0.08 [95% Confidence Interval (95% CI) = 0.04, 0.12]) and HDL levels (β = 0.09 [95% CI = 0.05,0.13]) showed a statistical association with better performance on MMSE. Higher TC (β = 0.08 [95% CI = 0.04; 0.12]) and HDL (β = 0.07 [95% CI = 0.03; 0.11]) were statistically associated with better MMSE recall scores. Likewise, higher TC (β = 0.08 [95% CI = 0.04,0.13]) and HDL (β = 0.05 [95% CI = 0.00,0.09]) were statistically associated with better verbal fluency performance; additionally, higher SBP (β = -0.05 [95% CI = -0.10; -0.00]) scores was statistically associated with worse performance on verbal fluency. For DLRT alone, diabetes showed a statistical association with lower performance (β = 0.39 [95% CI = 0.01; 0.78]). There were no significant associations found CVRFs and CANTAB-PAL after

adjusting for age and sex. The results from the regression analysis used to determine individual level associations between CVRFs and cognitive function for the MZ and DZ cohorts separately, are presented in supplementary tables ST11 and ST12, and the results were similar to the main findings. For DZ twins, lower HDL levels were statistically associated with better DLRT performance (β = -0.08 [95% CI = -0.15,-0.00]).

Co-twin control model: Comparison of between- and within-twin pair associations between cardiovascular risk factors and cognitive function

For MMSE (both cognitive domains) and verbal fluency, the between-pair coefficients for TC (MMSE overall β = 0.11[95% CI = 0.06; 0.16]; MMSE recall β = 0.11[95% CI = 0.06; 0.16]; verbal fluency β = 0.10 [95% CI = 0.05; 0.16]) and HDL (MMSE overall β = 0.11[95% CI = 0.06; 0.15]; MMSE recall β = 0.08[0.03; 0.12]; verbal fluency β = 0.06[95% CI = 0.01; 0.10]) were significant, not equal to zero, and mirrored the results from the previous model (.i.e. individual level association between CVRFs and cognitive function) (Figure 1 and Supplementary Table ST10). However, the within-pair effect associations were not significant ($p > .05$) and approximately equal to 0 for all these associations. Additionally, SBP was also associated with MMSE overall for between-pair effect (β = -0.06 [95% CI = -0.12 to -0.00]) but not significant and approximately 0 for the within-pair effect (β = 0.03 [95% CI = -0.05; 0.12]). Higher SBP were associated with worse performance on verbal fluency for between-pairs (β = -0.09 [95% CI = -0.15 to -0.03]) but likewise were not significant for within-pairs. Lastly, higher SBP was also associated with worse performance (.i.e. increased errors) on CANTAB-PAL for between-pairs (β = 0.07 [95% CI = 0.00; 0.13]) but not significant and approximately 0 for within-pair (β = 0.01 [95% CI = -0.09; 0.10]). The results from the co-twin control models used to determine the between- and within-pair associations between CVRFs and cognitive function for the MZ and DZ cohorts were again similar to the overall group, presented in supplementary tables ST11 and ST12. For MZ twins alone, there was a statistically significant association between higher TC and worse performance on CANTAB-PAL for the within-pair effect (β = 0.19 [95% CI = 0.06; 0.32]). This association was not significant for the between-pair effect. After further adjustment for education and socioeconomic status (Supplementary Table ST13), the direction and magnitude of associations remained largely comparable to the main analyses, with modest attenuation of effect estimates. The positive association between smoking and verbal fluency in the between-twin model, and the negative association between T2D and CANTAB-PAL in the individual-level and within-twin models, reached statistical significance following adjustment. Additional adjustment for BMI (Supplementary Table ST14) resulted in slight further attenuation of some associations. For example, the positive association between HDL and verbal fluency in the individual-level model was no longer statistically significant, although the corresponding between-twin estimate remained borderline. Most other associations showed minimal additional change after adjustment for BMI.

Discussion

In a cohort of UK twins, a co-twin control analysis was used to explore associations between CVRFs and cognitive function. In this dataset overall, higher cholesterol levels (both TC and HDL) were associated with better performance on MMSE(both overall and recall) and verbal fluency, and lower SBP was associated with better performance on verbal fluency at the individual level. The twin decomposition approach showed that these results were significant for the between-pair effects but not for within pair effects. The between-pair beta coefficients were similar to the individual level beta coefficients and the within-pair coefficients were approximately zero; that is, once shared twin-pair factors (such as genetics) are adjusted for, the association disappeared. For the MZ twins alone, higher TC was significantly associated and worse performance on CANTAB-PAL for the within-pair effects only (the individual and between-pair associations are not significant and approximately equal to 0). While this suggests that the association between TC and CANTAB-PAL is not explained by genotype, we are cautious in interpreting this due to the lower sample size of MZ pairs. Overall, observed relationships between cognitive function and three CVRFs (TC, HDL, and SBP) were predominantly explained by factors that are shared by twins. There were no significant associations for smoking and diabetes, or with the other two cognitive tests (DLRT and CANTAB-PAL).

Our findings that, overall and between families, increased TC and HDL are associated with better performance in cognitive function are similar to some previous studies of unrelated individuals. A 2022 study included 1309 female participants, all aged above 60 years, concluded that a higher concentration of total cholesterol appeared to be associated with better cognitive performance.[22] Similarly, another study examining the association between HDL and cognition among women reported a positive effect of HDL on cognitive function.[23] Our results might align with these studies, given that a significant proportion of our participants (87.7%) were predominantly female, potentially influencing the overall results. However, further research in balanced (.i.e.

equal male and female participants) cohorts is required to clarify the differences between sex.[24] Our findings in relation to cholesterol might be expected given the complex relationship between cholesterol and brain health.[25] The strongest genetic risk factor for cognitive decline (APOE Epsilon4 genotype) is itself associated with circulating TC. MZ twin pairs share ~100% of their genetic material including APOE genotype, which might explain why a different direction of effect was seen in the MZ within-pair model. Further, APOE ε4 may confer early-life advantages but increases risk for cognitive decline later in life (antagonistic pleiotropy), with recent evidence suggesting these effects are more pronounced in middle-aged women than men.[26] This underscores the complexity of genetic influences on cognition across the life course and may partly explain why associations between cholesterol and cognition are not straightforward, including our finding that within MZ pairs, higher TC was linked to poorer CANTAB-PAL performance.

Our study's findings also suggest the relationship between CVRFs and cognition is primarily influenced by factors shared between twins, aligns with results from a previous study conducted among male twin participants.[11] Using data (n=272 twin pairs) from the Vietnam Era Twin Registry, it was observed that the relationship between cardiovascular health and cognition is largely explained by early environmental factors.[11] Notably, in addition to the demographic differences between the two studies, our study sample was larger and included 2284 twin pairs. Therefore, CVRFs could potentially serve as markers of some common risk in early life; however, might not be good candidates for directly causing cognitive change among relatively healthy middle-older age women.

The shared factors driving the relationship between cognition and CVD risk might involve genetic and common environmental factors in combination. It is not clear from our study on how or which of these two factors predominantly influences the association. Another twin study explored genetic and environmental influences using the classical twin model using data from 379 twin pairs.[12] They reported mild-to-high (0.27-0.74) shared heritability between several CVRFs and cognition. Using bivariate analysis, they reported significant positive correlations between cognition and TC (genetic correlations r_G= 0.33) and HDL (r_G= 0.41) i.e. the genes influencing an increase or decrease in total cholesterol and HDL were also associated with intact or impaired cognition. Additionally, they observed negative correlations between cognition and SBP (r_G= -0.56), indicating a shared genetic basis that moderately mediated the elevated SBP and decreased cognitive function and vice versa.[12] Some studies have utilized Mendelian randomisation technique to investigate the relationship between CVRFs and cognition, which facilitates the examination of a causal link between an exposure and an outcome variable.[27] Low HDL was found to be a potential causal risk factor for impaired cognition in one study.[28] Multiple studies reported genetically elevated SBP was associated with poorer cognitive function, (including dementia and Alzheimer's disease) thereby supporting a causal effect of SBP on cognition however, the estimated effects were small.[29, 30] Mendelian randomisation studies rest on the assumption of assortative mating, which may, particularly in relation to cognition, be violated, and therefore triangulation with other study designs, such as experimental models (e.g. the natural experiment of twins or formal trials) is useful.

Our heritability analysis for cognition suggests contribution of genetics towards cognitive measures in our study was relatively modest, and shared familial environmental factors, such as educational history, socio-economic status, early dietary patterns, potentially even intra-uterine factors related to maternal health, may also contribute to the association between CVRF and cognitive function. A previous study [31] using a smaller sample (n=324 twin pairs) from the previous time-points in TwinsUK investigated cognitive change over a 10-year period found differences in physical fitness (measured by leg power) were associated with subsequent cognitive decline within twins. Further research could focus on finding and changing the earlier life environments which might be driving both these factors and premorbid prevention of CVRFs and promotion of healthy lifestyle beginning early in life should achieve the best results for promoting not only cardiovascular but also cognitive health.

This is the first study to use a co-twin control design to examine the relationship between CVRFs and cognitive function in a large cohort, but the findings should be interpreted in light of some limitations. First, the cohort consisted predominantly of healthy female participants, which may limit generalisability. Second, the cross-sectional design prevents assessment of temporal relationships od cognitive change over time, longitudinal studies incorporating multiple cognitive assessments over time can measure cognitive decline relative to an individual's baseline scores thereby allowing investigation of within-person associations rather than between-person associations while exploring this relationship between CVRFs and cognition. Third, cross-sectional analyses assume linear associations, whereas some CVRFs particularly cholesterol,[32, 33] may have non-linear relationships with cognition. Finally, certain relevant confounders, including hormone status, medication use, and some shared versus non-shared environmental factors, were not fully accounted for due to limited or self-

reported data. Future research should incorporate objective and comprehensive measures of these variables to reduce residual confounding.

In conclusion, our study found that increased TC, increased HDL, and lower SBP were all associated with better performance on cognitive function but this relationship was predominantly driven by factors that are common between twins, such as genetic or shared environmental factors, and therefore unlikely to be causal. Within MZ twin pairs, higher TC was observed to be associated with worse performance on CANTAB-PAL. Future studies should aim to elucidate whether differences in findings between and within families are explained by shared genetics or shared environments.

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Statement of Ethics

This study received ethical approval from the London Westminster REC 07/H0802/84. All adult participants provided written informed consent to participate in this study.

Conflict of Interest Statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author contributions

SV (conceptualization, data curation, formal analysis, methodology, software, writing – original draft), EJT (data curation, formal analysis, methodology, software, supervision, writing – review & editing), RSP (methodology, writing – review & editing), RCEB (methodology, writing – review & editing), CM (conceptualization, writing – review & editing), IH (conceptualization, supervision, writing – review & editing), JR (conceptualization, supervision, writing – review & editing), CJS (conceptualization, methodology, supervision, writing – review & editing). All authors contributed substantially to this study and have read and approved the final version of the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to ethical reasons but are available from the corresponding author upon request.

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Figure Legend

Figure 1 - **Individual and co-twin control analysis for MMSE overall, MMSE recall, DLRT, and CANTAB-PAL.**
Abbreviations: TC, total cholesterol; HDL, high density lipoprotein, SBP, systolic blood pressure; SMK, smoking; DBT, Diabetes; β, effect size; CI, confidence interval; MMSE, Mini-Mental State Examination; DLRT, Deary-Liewald Reaction Time Test; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery-Paired-Associated Learning Test

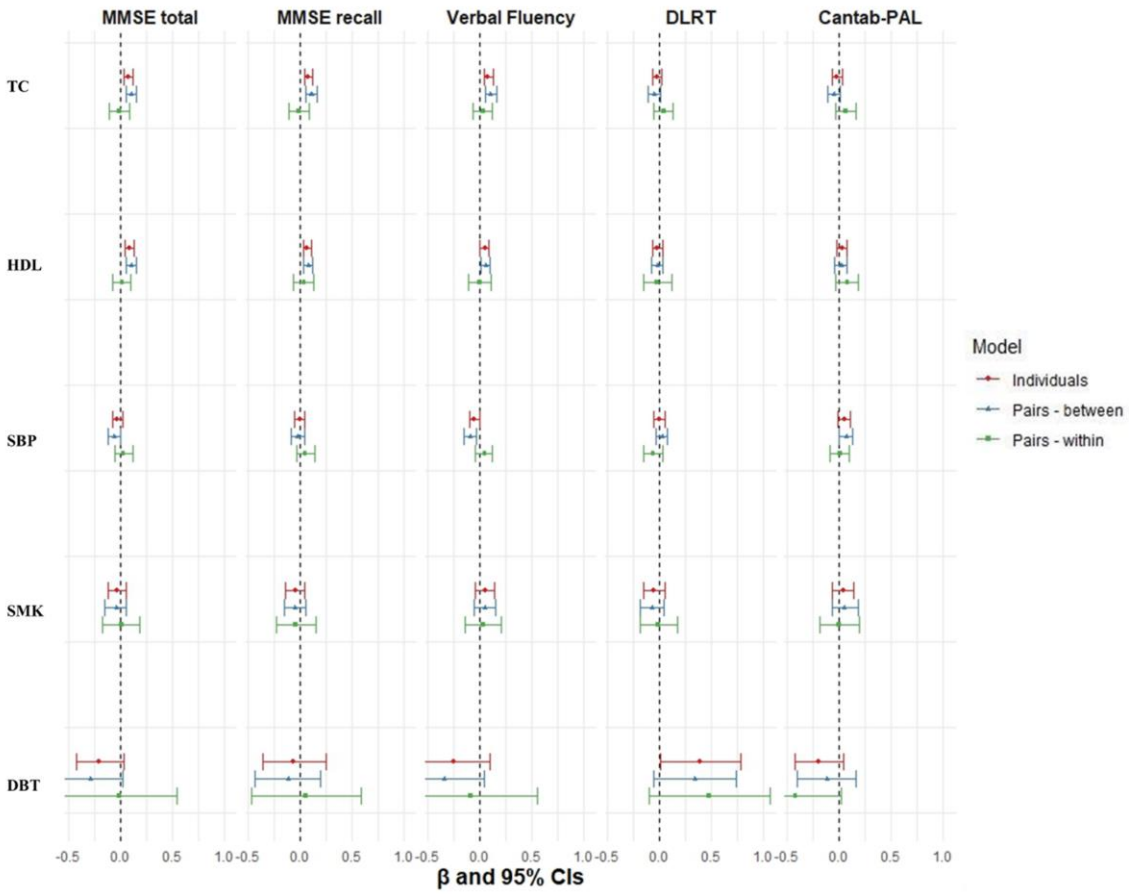

Table 1. Descriptive characteristics of participants included for MMSE

	All (n=2284)	MZ (n=1465)	DZ (n=819)
Age [mean(SD)]	56.4 (15.8)	53.9 (16.6)	60.8 (13.1)
Sex [female n(%)]	2002 (87.7%)	1251 (85.4%)	751 (88.4%)
Ethnicity[$] [n(%)]	Asian – 16 (0.7%) Black – 45 (2.0%) Chinese – 2 (0.0%) Mixed – 26 (1.1%) Other – 4 (0.2%) White – 2176 (96.0%)	Asian – 14 (0.1%) Black – 33 (2.3%) Chinese – 1 (0.0%) Mixed – 16 (1.1%) Other – 3 (0.2%) White – 1390 (95.4%)	Asian – 2 (0.2%) Black – 12 (1.5%) Chinese – 1 (0.1%) Mixed – 10 (1.2%) Other – 1 (0.1%) White – 786 (96.8%)
Diabetes^ – Yes [n(%)]	*Concordant* Non-diabetic – 1899 (94.7%) Diabetic – 22 (1.1%) *Discordant* 86 (4.3%)	*Concordant* Non-diabetic – 1234 (96.3%) Diabetic – 18 (1.4%) *Discordant* 29 (2.3%)	*Concordant* Non-diabetic – 665 (91.6%) Diabetic – 4 (0.1%) *Discordant* 57 (7.9%)
Smoking*– Yes [n(%)]	*Concordant* Non-smokers – 916 (46.6%) Smokers – 496 (25.2%) *Discordant* 554 (28.2%)	*Concordant* Non-smokers – 668 (53.4%) Smokers – 314 (25.1%) *Discordant* 268 (21.4%)	*Concordant* Non-smokers – 248 (34.6%) Smokers – 182 (25.4%) *Discordant* 286 (39.9%)
SBP[#] [mean(SD)]	126.7 (17.5)	125.9 (17.2)	129.7 (17.5)
Total Cholesterol[†] [mean(SD)]	5.3 (1.1)	5.3 (1.1)	5.4 (1.1)
HDL[†] [mean(SD)]	1.9 (0.5)	1.9 (0.5)	1.9 (0.5)

Notes:
[$]n=2268 twin pairs; ^n=2007 twin pairs; *n=1966 twin pairs; [#]n=2280 twin pairs; [†]n=2256 twin pairs
Abbreviations: MMSE, Mini-Mental State Examination; MZ, Monozygotic twins; DZ, Dizygotic twins; n, Sample size; SD, Standard deviation; SBP, Systolic Blood Pressure; HDL, High Density Lipoprotein

Table 2. Results of the twins (ACE) model for cognitive function adjusted for age and sex

	Variance components			Model fit		
Cognitive function	**A**	**C**	**E**	**AIC**	**df**	**p**
MMSE overall	0.25 [0.21, 0.30]	-	0.75 [0.70, 0.79]	-15484.03	1	0.120
MMSE recall	0.22 [0.17, 0.26]	-	0.78 [0.74, 0.83]	-1149.289	1	0.492
Verbal fluency	0.45 [0.41-0.48]	-	0.55 [0.52-0.59]	502.345	1	1
DLRT	0.44 [0.40-0.49]	-	0.56 [0.51-0.60]	35064.74	1	1
CANTAB-PAL	0.19 [0.03-0.37]	0.26 [0.11-0.40]	0.55 [0.50-0.61]	7053.828	3	0.656

Notes:
Abbreviations: A, additive genetic effects; C, common shared environment; E, non-shared environmental influences; AIC, Akaike Information Criterion; df, degrees of freedom; p, significance value; MMSE, Mini-Mental State Examination; DLRT, Deary-Liewald Reaction Time Test; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery-Paired-Associated Learning Test