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Spatial QRS-T angle and Cognitive Decline in Older Subjects

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Abstract

Background: An abnormally wide spatial QRS-T angle on an ECG is a marker of heterogeneity in electrical activity of cardiac ventricles and is linked with cardiovascular events. Growing evidence suggests that cardiac dysfunction might signal future cognitive decline.

Objective: In this study we investigated whether spatial QRS-T angle associates with future cognitive decline in older subjects at high cardiovascular risk.

Methods: We included 4172 men and women (mean age 75.2 ± 3.3 years) free of cardiac arrhythmias from the PROSPER cohort. Spatial QRS-T angle was calculated from baseline 12-lead ECGs using a matrix transformation method. Cognitive function was assessed using 4 neuropsychological tests including Stroop test, letter-digit coding test, immediate and delayed picture word learning tests. Cognitive function was assessed at baseline and repeatedly during a mean follow-up time of 3.2 years. Using linear mixed models, we calculated the annual changes of cognitive scores in sex-specific thirds of spatial QRS-T angle.

Results: Participants with wider spatial QRS-T angle had a steeper decline in letter-digit coding test (β= –0.0106, p=0.004), immediate picture-word learning test (β= –0.0049, p=0.001) and delayed picture-word learning test (β= –0.0055, p=0.013). All associations were independent of arrhythmias, cardiovascular risk factors, comorbidities, medication use, cardiovascular events and other ECG abnormalities including QRS duration, QTc interval, T wave abnormalities and left ventricular hypertrophy.

Conclusion: Abnormal cardiac electrical activity characterized by wide spatial QRS-T angle associates with accelerated cognitive decline independent of conventional cardiovascular factors. These findings suggest a link between a non-traditional ECG measure of pre-clinical cardiac pathology and future cognitive decline.

Keywords: Spatial QRS-T angle; Cognitive function; Cardiac dysfunction; Old age

Introduction

The electrical activity of the heart is generated by waves of myocardial depolarization and repolarization leading to a harmonized cardiac muscle contraction and relaxation [1]. Alterations in the sequence of ventricular depolarization and repolarization are not only associated with cardiovascular events [2, 3] but may also precede cerebrovascular events and increase risk of stroke [4]. Apart from overt cerebrovascular accidents, ventricular repolarization abnormality as measured by QT dispersion has been linked to cognitive impairment and Alzheimer's disease dementia [5]. Hence, early cardiac electrical abnormalities might signal future risk of cognitive impairment and such markers may assist in identification of high-risk populations.

The spatial QRS-T angle is a non-invasive subclinical marker of electrical activity of cardiac ventricles [6]. It quantifies the deviation in the direction of cardiac ventricular depolarization and repolarization in a three-dimensional space [7]. A wide spatial QRS-T angle reflects the pathophysiological changes in the ionic channels affecting the repolarization profiles, or structural abnormalities affecting the sequence of depolarization [8]. A wider spatial QRS-T angle has been associated with incident coronary heart disease [2], all-cause and cardiovascular mortality [9] and ischemic stroke [10]. Since a wide spatial QRS-T angle is a marker of greater inhomogeneity of electrical activity of cardiac ventricles, we aimed to study the independent link between spatial QRS-T angle and cognitive decline in older subjects at high risk of cardiovascular disease.

Methods

Study design

The study population consists of the participants from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER was a multicenter randomized clinical trial which aimed to assess the effect of pravastatin in prevention of vascular events in older subjects with pre-existing cardiovascular risk factors or diseases [11]. In brief, a total of 5804 men and women at high cardiovascular risk (defined as being due to smoking, hypertension or diabetes mellitus) or with a history of vascular disease (defined as stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction [MI] and vascular surgery), aged 70 to 82 years, were enrolled from three collaborating centers in Ireland, Scotland and the Netherlands. The mean follow-up time was 3.2 years. The original PROSPER study was approved by the Medical Ethics Committees of the three collaborating centres and complied with the Declaration of Helsinki. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Study participants

From the baseline electrocardiogram (ECG) recordings, we excluded participants with missing spatial QRS-T angle measurements and those with evidence of atrial fibrillation, atrial flutter, ectopic atrial rhythms, supraventricular arrhythmias, junctional rhythms, intermittent conduction defect and other arrhythmias (n=520). Furthermore, we included only participants with at least two cognitive measurements: the baseline and one follow-up measurement. Hence, a total of 4172 participants were included for analysis. Compared to the excluded participants, the included participants were younger and had a lower prevalence of cardiovascular risk factors and co-morbidities (Supplementary Table 1). We included participants from both treatment groups since it has been shown that treatment with pravastatin does not affect cognitive function [12].

Spatial QRS-T angle measurement

Standard 12-lead ECGs were recorded using a Burdick Eclipse 850i electrocardiograph in the resting supine position. All the ECGs were recorded in the morning of the first enrolment visit (at baseline) before initiation of statin treatment. A fully computerized automated method was used to ensure reproducibility of the measurements. The digital ECG recordings were transferred to the University of Glasgow ECG Core Lab in Scotland and interpreted using the University of Glasgow (Uni-G) ECG analysis program software [13]. The software provided

an interpretation of the ECG recordings, Minnesota Codes, and numerous measurements including the QRS complex and T waves [13-15]. To calculate the spatial QRS-T angle, we first reconstructed the Frank XYZ vectocardiographic leads from the 12-lead ECG recordings using the inverse Dower method [16]. We then measured the spatial QRS-T angle as the angle between the maximum QRS vector and the maximum T vector. The maximum QRS and T vectors were defined as the point of maximum magnitude of the spatial QRS vector and the spatial T vector within the 3-dimensional QRS loop and T loop, respectively [6]. Since the cut-point for spatial QRS-T angle has varied among previous studies [6], we first classified the spatial QRS-angle based on the sex-specific tertiles in three groups of low (0°-38° for women and 0°-45° for men), middle (39°-75° for women and 46°- 84° for men) and high (76°-180° for women and 85°-180° for men). Secondly, based on a cut-point used in previous studies for older subjects [9, 17], we classified the spatial QRS-T angle levels in three groups of normal (0° to 104°), borderline (105° to 134°), and abnormal (135° to 180°).

The QT interval was calculated from the onset of QRS complex to the T offset and was corrected for heart rate (QTc interval) using the Hodges formula [18]. T wave abnormalities were defined as Minnesota Codes 5-1, 5-2 and 5-3 [14]. Left ventricular hypertrophy (LVH) was defined by using the Sokolow-Lyon voltage criteria [19].

Cognitive function assessment

In PROSPER, the mini-mental state examination test (MMSE) was used at baseline for screening purposes and participants with poor cognitive function (MMSE score <24) were excluded from enrolment in the study [20]. Four cognitive tests were used to assess different domains of cognitive function. The cognitive tests included the Stroop test, the letter-digit coding test (LDCT), immediate picture-word learning test (PLTi) and delayed picture-word learning test (PLTd). A detailed description of the cognitive assessments has been published elsewhere [20]. In brief, the Stroop test measures selective attention and reaction time. The outcome variable is the total number of seconds to complete the test. In contrast to the other cognitive tests used in this study, a higher score in Stroop test indicates worse performance. The LDCT measures the processing speed and the outcome variable is the total number of correct digits entered in 60 seconds; a higher score indicates better performance. The PLTi and PLTd tests measure immediate and delayed memory, respectively. The outcome variables are the accumulated number of correctly recalled pictures for the immediate and delayed trials; a higher score indicates better performance. Cognitive function was assessed at baseline, after 9,

18, 30 months and at the end of the study which varied between 36 and 48 months. During each visit, different versions of cognitive tests were used to avoid learning effects [20].

Statistical analysis

A p-value<0.05 was considered as statistically significant. Differences in baseline characteristics of participants in the three groups of spatial QRS-T angle were compared using the ANOVA test for continuous variables and Chi-squared test for categorical variables. Linear regression models were used to test the cross-sectional association between spatial QRS-T angle and cognitive function at baseline. The dependent variable was the score of each cognitive test at baseline. Using analysis of covariance, we calculated the adjusted mean score of cognitive tests in sex-specific thirds of spatial QRS-T angle. The Stroop test scores were log-transformed because they were not normally distributed. Linear mixed models (random regression model with random intercepts and slopes) were used to test the longitudinal association between spatial QRS-T angle and changes in cognitive scores over time. The models incorporated spatial QRS-T angle, time (in years) and the interaction term between time and spatial QRS-T angle. Subjects were defined as random factors and all other variables were defined as fixed factors. To assess the mean annual change of cognitive scores in thirds of spatial QRS-T angle, we computed the estimates of interaction between time and sex-specific thirds of spatial QRS-T angle using linear mixed models. To calculate the estimate of change in cognitive scores per 10 degree increase in spatial QRS-T angle, we divided the spatial QRS-T angle levels by ten. All probability values were calculated using continuous values of spatial QRS-T angle. Both cross-sectional and longitudinal analyses were first adjusted for age, sex, education (age at which the participant left school), country of enrolment and version of cognitive tests where appropriate (model 1). In the next step, adjustment for cardiovascular diseases, cardiovascular risk factors and medication use (diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors [ACEI] and angiotensin receptors blockers [ARB]) were added (model 2). In longitudinal analysis, further adjustment for statin treatment groups was added in model 2. To test the effect of other ECG parameters on the longitudinal associations, adjustments for T wave abnormalities, QTc interval, QRS duration and LVH were added in model 3.

To test the effect of cardiovascular events on the longitudinal associations, a series of sensitivity analyses were performed in which we stratified for the participants according to who did and who did not develop incident atrial fibrillation, heart failure hospitalization, coronary

events, fatal or non-fatal stroke or transient ischemic attack (TIA) and non-fatal MI during follow-up. To test whether the difference between participants who did and who did not develop cardiovascular events is significant, p for interactions were calculated using linear mixed models. Furthermore, we tested the effect of baseline apolipoprotein e4 phenotype on longitudinal associations by stratifying participants in two groups of E4+ carriers (including $E_{4/4}$, $E_{3/4}$ and $E_{2/4}$) and E4- carriers. Finally, we tested the effect of baseline cardiovascular co-morbidities and use of anti-arrhythmic medications on longitudinal associations by excluding participants who had history of hypertension, history of diabetes mellitus, history of MI, history of stroke or TIA, and participants using anti-arrhythmic medications.

Results

Of the 4172 participants in this study, the mean age was 75.2 ± 3.3 years and 1998 (47.9%) participants were male. A total of 2593 (62.2%) had history of hypertension, 427 (10.2%) had history of diabetes mellitus, 541 (13.0%) had history of MI and 430 (10.3%) had history of stroke or TIA. The mean systolic blood pressure was 154.5 ± 21.8 mmHG, mean diastolic blood pressure was 83.7 ± 11.3 mmHG and mean body mass index was 26.9 ± 4.1 kg/m². Subjects with higher spatial QRS-T angle were slightly older, had higher prevalence of cardiovascular diseases and risk factors, were more likely to have T-wave abnormalities, had higher QTc interval and QRS duration, used ACEI more frequently and used beta-blockers less frequently (Table 1). Moreover, participants with higher spatial QRS-T angle were more likely to develop incident atrial fibrillation, heart failure hospitalization, coronary events, and non-fatal MI during follow-up period (Table 1).

Table 2 shows the cross-sectional association between spatial QRS-T and cognitive function at baseline. In model 1, higher spatial QRS-T angle was not associated with performance of participants in any of the cognitive tests at baseline. Full adjustments for cardiovascular risk factors, cardiovascular co-morbidities and medication use did not change the observed associations.

Table 3 and Figure 1 show the longitudinal association between spatial QRS-T angle and cognitive decline over a period of 3.2 years. In model 1, higher spatial QRS-T angle was significantly associated with a steeper decline in the LDCT (β=-0.0106; p-value= 0.004), PLTi (β=0-0.0049; p-value= 0.001) and PLTd (β=-0.0055; p-value= 0.013) scores during follow-up. After full adjustment for cardiovascular risk factors, cardiovascular co-morbidities and medication use, the mean annual change of cognitive scores in thirds of spatial QRS-T angle remained essentially the same (Table 3, model 2). Adjustment for baseline level of cognitive scores did not essentially change these results (data not shown). Furthermore, we found no significant difference in the annual change of cognitive scores between the low and middle thirds of spatial QRS-T angle (Supplementary Table 2).

To further explore the effect of other ECG parameters affecting the sequence of ventricular repolarization/depolarization on the longitudinal associations, adjustment for T wave abnormalities, QTc interval, QRS duration and LVH were added in model 3. Further adjustment for these parameters did not essentially change the results, meaning that higher

spatial QRS-T angle remained significantly associated with a steeper decline in LDCT, PLTi and PLTd test scores (all p-values<0.05) (Table 3, model 3). Furthermore, we tested whether an interaction exists between spatial QRS-T angle and these ECG parameters in relation to cognitive function and found no significant interaction (all p for interactions > 0.05). The estimate (β) and 95% confidence intervals that were assessed using continuous levels of spatial QRS-T angle are presented in Supplementary Table 3. When we categorized the spatial QRS-T angle according to a cut-point that is reported in literature (Normal: 0° to 104°, Borderline: 105° to 134° and Abnormal: 135° to 180°), the abnormal group was associated with a steeper decline in the Stroop, LDCT, PLTi and PLTd tests performances (Supplementary Table 4).

Over a period of 3.2 years, a total of 351 participants developed incident atrial fibrillation, 146 participants were hospitalized for heart failure, 424 participants developed coronary events, 279 participants developed stroke or TIA and 335 participants developed non-fatal MI. A total of 3235 subjects were free of these cardiovascular events during follow-up. Figure 2 shows the longitudinal association of spatial QRS-T angle and cognitive function stratified by incident cardiovascular events during follow-up. We did not observe a significant difference in annual changes of cognitive function between participants who did and those who did not develop incident atrial fibrillation, coronary events, stroke or TIA, heart failure hospitalization and non-fatal MI during follow-up (all p for interactions > 0.05). Furthermore, there was no interaction between baseline apolipoprotein e-4 carriers and spatial QRS-T angle during follow-up (Supplementary Table 5). Finally, when we excluded participants with additional cardiovascular co-morbidities at baseline and participants taking anti-arrhythmic medications, the longitudinal results did not change except that after exclusion of participants with history of hypertension (n=1579, >37% of the population) higher spatial QRS-T angle was not associated with steeper decline in Stroop and LDCT tests performances (Supplementary Table 6).

Discussion

Our findings suggest that a wide spatial QRS-T angle, as a reflection of greater heterogeneity in electrical activity of cardiac ventricles, associates with accelerated decline in cognitive function of older subjects at high cardiovascular risk. These associations were independent of arrhythmias, cardiovascular risk factor and co-morbidities, medication use, incident cardiovascular events and other ECG parameters.

Previous research has shown that different ECG-parameters measuring either the excitation or relaxation phase of the cardiac ventricles are related to cerebrovascular accidents and cognitive impairment. For example, men with pathologic Q waves suggesting unrecognized MI have a two-fold increased risk of dementia and carry a higher burden of cerebral small vessel disease [21]. Similarly, patients with Alzheimer's disease and mild cognitive impairment have higher values of QT dispersion and QT corrected dispersion [5]. Our current study suggests that an abnormal spatial QRS-T angle might precede the decline in cognitive function in a large cohort of older adults at high cardiovascular risk. Furthermore, the persistence of longitudinal associations in subjects without cardiac arrhythmias suggests that even subtle alterations in the ventricular electrical activity are linked to cognitive decline.

The observed association between spatial QRS-T angle and cognitive decline can be explained through a number of pathophysiological mechanisms. First, a wide spatial QRS-T angle and cognitive decline may both reflect cardiovascular damage and hence share a common cause. Previous research has shown that spatial QRS-T angle is a strong non-invasive predictor of cardiovascular morbidity and mortality [2, 22, 23] and a wide angle is linked with higher electric instability of the cardiac ventricles that might increase the risk of cardiac arrhythmias and ischemia [7]. The role of cardiovascular risk factors and diseases in development of cognitive impairment is well established [24]. In line with this, our results show that subjects with higher spatial QRS-T angle have higher prevalence of cardiovascular co-morbidities and are more likely to develop incident cardiovascular events during follow-up. Furthermore, exclusion of subjects with a history of hypertension at baseline attenuated the longitudinal relation of spatial QRS-T angle and executive function as measured by Stroop and LDCT tests. However, the relation between spatial QRS-T angle and memory function was independent of measured cardiovascular co-morbidities and incident cardiovascular events during follow-up. An abnormal spatial QRS-T angle might reflect cardiac changes that results in hemodynamic stress and altered brain perfusion, which might in turn lead to global cognitive decline [25]. In

line with this, a wide QRS-T angle have been associated with cardiac abnormalities such as ventricular remodelling, diastolic dysfunction, impaired ionic channel and calcium homeostasis in heart failure patients [26]. Moreover, a wide QRS-T angle has been linked to worse left ventricular myocardial performance index in diabetic patients free of cardiovascular diseases [27]. Such alterations may cause subtle hemodynamic instability, which may over time, lead to cerebral small vessel disease and ultimately to parenchymal damage manifesting as cognitive impairment [24, 28]. Nevertheless, we cannot rule out the effect of residual confounding and unmeasured cardiovascular factors in our study, which might affect both cognitive function and spatial QRS-T angle. Finally, it is also possible that a wide QRS-T angle mirrors the already established cerebrovascular damage in the brain which may in turn contribute to cognitive impairment [10].

It is important to mention that the spatial QRS-T angle is superior to other traditional ECG parameters measuring cardiac electrical activity since it quantifies the spatial aspects of ventricular action potential that are not measured by other ECG-parameters [17]. Furthermore, spatial QRS-T angle is a more robust parameter since it is less susceptible to measurement errors and noises due to determination of the T wave end on the surface of ECG [7, 29]. Other ECG measures of ventricular electrical activity such as QT dispersion and QTc interval are highly dependent on the determination of ECG wave points [30]. Moreover, the spatial QRS-T angle is distinct from other well-known markers of cardiac dysfunction such as troponin and B-type natriuretic peptide. Such plasma markers of cardiac dysfunction are released from cardiac muscles in response to cardiac wall stretch and/or cardiac muscle damage [31]. However, the spatial QRS-T angle is suggested to be increased as a result of subtle cardiac ionic channel disturbances and/or cardiac structural abnormalities [7]. As such, spatial QRS-T angle might be a non-invasive marker for detection of subtle cardiac abnormalities in an early stage [23, 32].

In our analysis, we did not find a cross-sectional association between spatial QRS-T angle and cognitive function at baseline. This might be due to the characteristics of participants in the original PROSPER cohort in which subjects with poor cognitive function were excluded [11]. Since our population consists of older subjects with a fairly preserved cognitive function at baseline, the observed association between QRS-T angle and cognitive function might be underestimated. Nevertheless, a wide spatial QRS-angle was associated with a significant decline in all four cognitive tests during follow-up, strengthening the temporal order of the

associations. Furthermore, the threshold for abnormal spatial QRS-T angle varied among studies [17, 23, 33] and there is no established cut-off point. When we repeated our analysis using a cut-off point from previous literature [9, 17], the results did not essentially change. Future research should determine the optimal age and gender specific threshold for abnormal spatial QRS-T angle.

The strengths of this study include the large sample size (more than 4000 participants), prospective multicentre design and the use of different cognitive tests assessing various domains of cognitive function. Furthermore, the non-invasive nature of ECG makes the QRS-T angle a suitable tool for use in clinical practice and supports its use for cardiovascular prevention strategies as well as efforts to prevent cognitive decline. Although measurement of spatial QRS-T angle requires a computer program, the implementation of this program using modern electrocardiographs is quite easy [17]. One limitation is that the participants had pre-existing cardiovascular risk factors or disease which might limit generalizability of our findings to a healthy older population. Another limitation is that PROSPER had a relatively short duration of follow-up which might result in small magnitude of associations and limit the clinical significance of our findings. Of note, although the magnitude of associations were small, the effect estimates were comparable with the effect estimates of left ventricular hypertrophy and apolipoprotein E4 in relation to cognitive decline in the same population [34, 35]. Moreover, only 10% of the population developed incident events during follow-up which might have under-powered our analysis in finding moderating effects of cardiovascular events on the reported associations. Finally, this was a secondary analysis of a randomized-controlled trial and was not designed to investigate a causal association between ECG abnormalities and cognitive decline.

In conclusion, we found that wider spatial QRS-T angle as a reflection of electrical instability in cardiac ventricles associates with accelerated cognitive decline independent of several conventional cardiovascular risk factors and comorbidities. These findings provide insight into the link between pre-clinical cardiac pathologies and development of cognitive decline in future. Future work should investigate the prognostic accuracy of a widened QRS-T angle and future cognitive decline, with the aim of early intervention into subtle cardiovascular abnormality in order to prevent cerebrovascular alterations and cognitive impairment.

Conflict of Interest:

None

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Table 1. Baseline characteristics of participants in thirds of Spatial QRS-T angle

	Spatial QRS-T angle thirds			
	Low n=1383	Middle n=1393	High n=1396	p-value
Demographics				
Age, years, mean (SD)	75.04 (3.29)	75.09 (3.30)	75.33 (3.37)	0.049
Age left school, years, mean (SD)	15.22 (2.15)	15.25 (2.11)	15.12 (2.08)	0.253
Country, n (%)				0.262
Scotland	608 (44.0)	586 (42.1)	624 (44.7)	
Ireland	489 (35.4)	490 (35.2)	502 (36.0)	
Netherlands	286 (20.7)	317 (22.8)	270 (19.3)	
Cardiovascular diseases and risk factors				
History of vascular disease, n (%)	543 (39.3)	568 (40.8)	713 (51.1)	<0.001
History of stroke or TIA, n (%)	126 (9.1)	140 (10.1)	164 (11.7)	0.068
History of MI, n (%)	116 (8.4)	156 (11.2)	269 (19.3)	<0.001
History of DM, n (%)	123 (8.9)	134 (9.6)	170 (12.2)	0.011
History of hypertension, n (%)	841 (60.8)	883 (63.4)	869 (62.2)	0.373
LVH, n (%)[*]	41 (3.0)	112 (8.0)	157 (11.3)	<0.001
BMI, kg/m^2, mean (SD)	26.87 (4.17)	26.69 (3.97)	27.19 (4.25)	0.006
SBP, mmHG, mean (SD)	152.17 (21.48)	154.78 (21.51)	156.58 (22.33)	<0.001
DBP, mmHG, mean (SD)	83.09 (11.40)	83.67 (10.74)	84.35 (11.61)	0.012
Current smoking, n (%)	373 (27.0)	362 (26.0)	351 (25.1)	0.547
ECG parameters				
Heart rate, beats/min, mean (SD)	65.70 (11.06)	65.48 (11.47)	66.67 (11.62)	0.014
T wave abnormality, n (%)†	184 (13.3)	353 (25.3)	560 (40.1)	<0.001
QTc interval, sec, mean (SD)	0.424 (0.02)	0.426 (0.03)	0.433 (0.03)	<0.001
QRS duration, sec, mean (SD)	0.095 (0.02)	0.094 (0.01)	0.105 (0.02)	<0.001
Medications				
Beta-blocker, n (%)	413 (29.9)	379 (27.2)	325 (23.3)	<0.001
Diuretic, n (%)	538 (38.9)	561 (40.3)	557 (39.9)	0.747
ACE inhibitor, n (%)	188 (13.6)	208 (14.9)	268 (19.2)	<0.001
ARB, n (%)	26 (1.9)	24 (1.7)	39 (2.8)	0.107
Calcium channel blocker, n (%)	324 (23.4)	350 (25.1)	376 (26.9)	0.103
Incident cardiovascular events during follow-up				
Atrial fibrillation, n (%)	105 (7.6)	105 (7.5)	141 (10.1)	0.021
HF hospitalization, n (%)	34 (2.5)	37 (2.7)	75 (5.4)	<0.001
Coronary events, n (%)	110 (8.0)	123 (8.8)	191 (13.7)	<0.001
Non-fatal MI, n (%)	99 (7.2)	99 (7.1)	137 (9.8)	0.011
Stroke or TIA, n (%)	89 (6.4)	91 (6.5)	99 (7.1)	0.756

Cut-points for low, middle and high groups for women are: 0°-38°, 39°-75°, 76°-180°, respectively; and for men: 0°-45°, 46°-84°, 85°-180°, respectively. [*]LVH: LVH based on Sokolow-Lyon index cut points (≥3500 µV); †T wave abnormality: Minnesota code 5-1, 5-2 and 5-3. Abbreviations: SD: Standard Deviation; n: Number; TIA: Transient Ischemic Attack; MI: Myocardial Infarction; DM: Diabetes Mellitus; LVH: Left Ventricular Hypertrophy; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ACE inhibitors: Angiotensin Converting Enzyme inhibitors; ARBs: Angiotensin Receptor Blockers; HF: Heart Failure.

Table 2. Cognitive function in relation to spatial QRS-T angle at baseline

	Spatial QRS-T angle thirds			
	Low n=1383	Middle n=1393	High n=1396	p-value*
Stroop, seconds, mean (SE):				
Model 1	63.45 (0.61)	62.90 (0.61)	64.64 (0.61)	0.049
Model 2	66.04 (1.57)	65.46 (1.57)	66.84 (1.52)	0.166
LDCT, digits coded, mean (SE):				
Model 1	24.21 (0.18)	24.06 (0.18)	23.87 (0.18)	0.064
Model 2	23.21 (0.45)	23.05 (0.45)	22.99 (0.44)	0.171
PLTi, pictures remembered, mean (SE):				
Model 1	9.50 (0.05)	9.55 (0.05)	9.46 (0.05)	0.299
Model 2	9.40 (0.12)	9.46 (0.12)	9.39 (0.12)	0.436
PLTd, pictures remembered, mean (SE):				
Model 1	10.38 (0.07)	10.47 (0.07)	10.35 (0.07)	0.530
Model 2	10.25 (0.17)	10.35 (0.17)	10.28 (0.17)	0.876

*p-values were calculated using continuous values of spatial QRS-T angle

Model 1: adjusted for age, sex, country, education and version of cognitive tests where applicable; Model 2: adjusted for all the variables in model 1 + history of vascular disease, history of diabetes, systolic and diastolic blood pressure, body mass index, smoking status and antihypertensive medications. Abbreviations: SE: Standard Error; LDCT: Letter Digit Coding Test; PLTi: Picture-Word Learning Test immediate; PLTd: Picture-Word Learning Test delayed.

Table 3. Cognitive function in relation to spatial QRS-T angle during follow-up

	Spatial QRS-T angle thirds			
	Low	Middle	High	
	n=1383	n=1393	n=1396	p-value*
Stroop, seconds, mean annual decline (SE):				
Model 1	0.488 (0.13)	0.622 (0.13)	0.775 (0.13)	0.055
Model 2	0.491 (0.13)	0.625 (0.13)	0.781 (0.13)	0.054
Model 3	0.492 (0.13)	0.622 (0.13)	0.781 (0.13)	0.052
LDCT, digits coded, mean annual decline (SE):				
Model 1	-0.350 (0.03)	-0.345 (0.03)	-0.461 (0.03)	0.004
Model 2	-0.350 (0.03)	-0.346 (0.03)	-0.462 (0.03)	0.004
Model 3	-0.350 (0.03)	-0.346 (0.03)	-0.463 (0.03)	0.004
PLTi, pictures remembered, mean annual decline (SE):				
Model 1	0.007 (0.01)	-0.009 (0.01)	-0.034 (0.01)	0.001
Model 2	0.007 (0.01)	-0.009 (0.01)	-0.034 (0.01)	0.001
Model 3	0.007 (0.01)	-0.010 (0.01)	-0.035 (0.01)	0.001
PLTd, pictures remembered, mean annual decline (SE):				
Model 1	-0.060 (0.02)	-0.054 (0.02)	-0.094 (0.02)	0.013
Model 2	-0.060 (0.02)	-0.054 (0.02)	-0.095 (0.02)	0.013
Model 3	-0.060 (0.02)	-0.054 (0.02)	-0.095 (0.02)	0.012

*p-values were calculated using the interaction term between continuous values of spatial QRS-T angle and time.

Means represent the mean annual decline in the score of each cognitive test.

Model 1: adjusted for age, sex, country, education and version of cognitive tests where applicable; Model 2: adjusted for all the variables in model 1+ history of vascular disease, history of diabetes, systolic and diastolic blood pressure, body mass index, smoking status, antihypertensive medications and statin treatment groups. Model 3: adjusted for all the variables in model 2 + LVH, T wave abnormalities, QTc interval and QRS duration. Abbreviations: SE: Standard Error; LDCT: Letter Digit Coding Test; PLTi: Picture-Word Learning Test immediate; PLTd: Picture-Word Learning Test delayed.
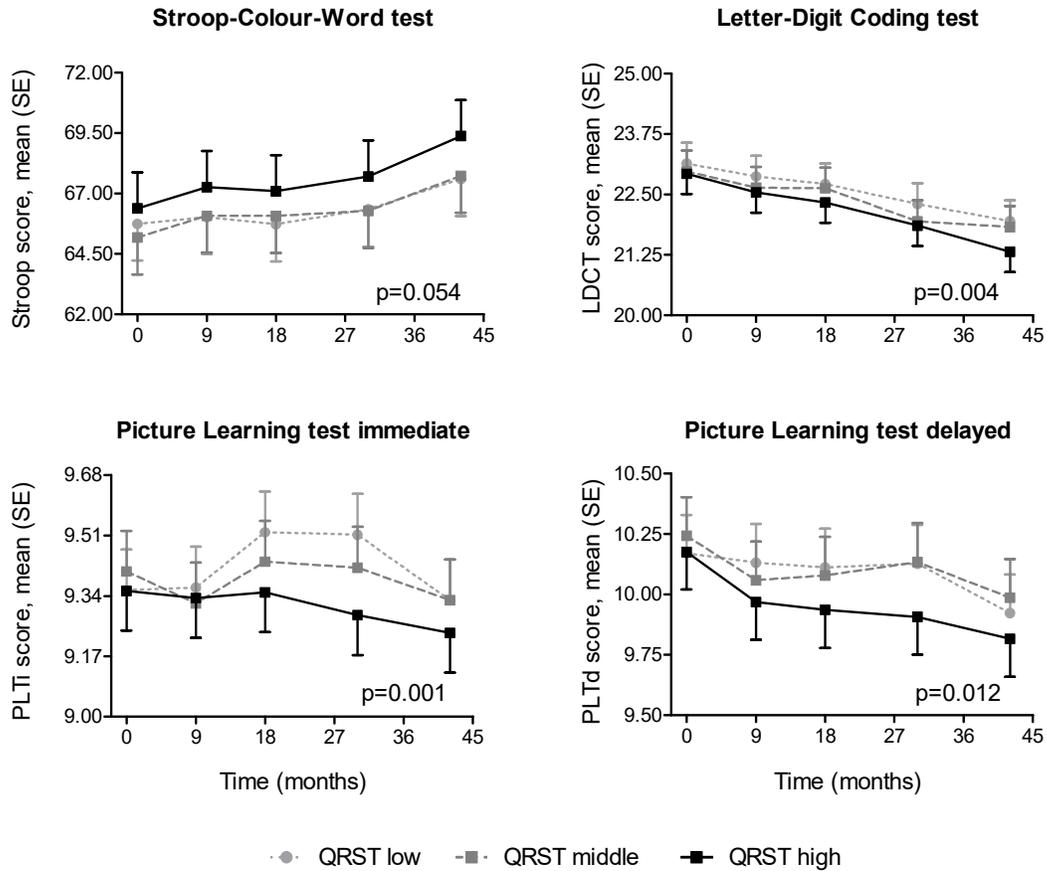
Figure 1. Cognitive function in relation to spatial QRS-T angle during follow-up. Data represent mean (standard error) decline in the score of each cognitive test in three groups of spatial QRS-T angle. The time point at the end of the study is the mean of end time points (36 to 48 months). Analyses were adjusted for age, country, education, version of cognitive tests where applicable, history of diabetes, history of vascular disease, body mass index, smoking status, systolic blood pressure, diastolic blood pressure, antihypertensive medications and statin treatment groups.
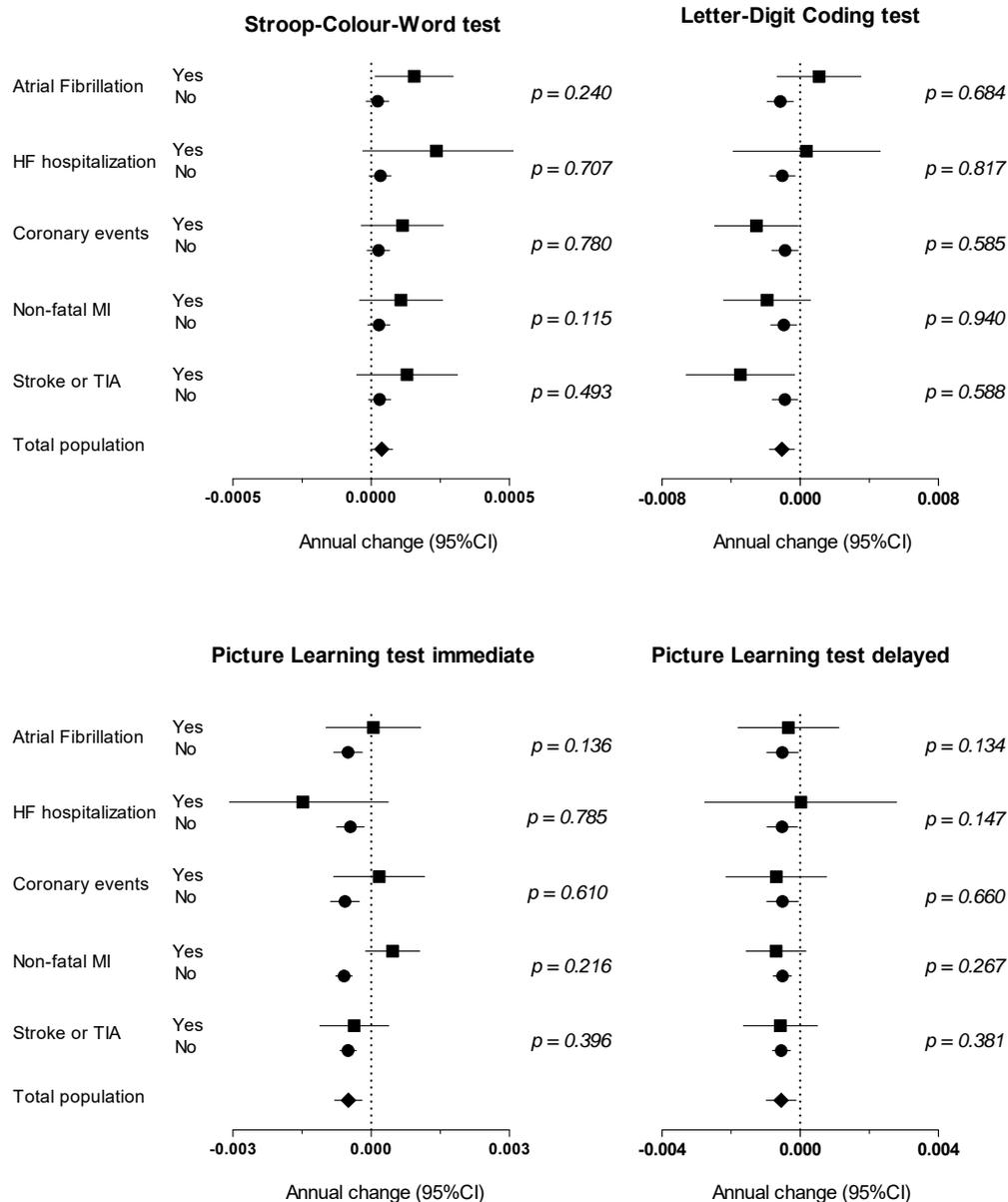
Figure 2. Association of spatial QRS-T angle and annual changes of cognitive function stratified for cardiovascular events during follow-up. Data represent annual change (95% confidence interval) in cognitive function per each unit (degree) increase in spatial QRS-T angle (the X axis), stratified for subjects who did and those who did not develop cardiovascular events during follow-up. Dark circles and squares correspond to the annual change (estimate) and the lines correspond to the 95% confidence intervals. P-values show the p for interaction. Analyses were performed in the fully adjusted model. Abbreviation: MI: myocardial infarction; HF: heart failure hospitalization and TIA: transient ischemic attack

Supplementary Data

Supplementary Table 1. Baseline characteristics of included and excluded participants

Characteristics	Included n=4172	Excluded n=1632	p-value
Socio-demographics:			
Age, years, mean (SD)	75.2 (3.3)	75.8 (3.4)	<0.001
Male, n (%)	1998 (47.9)	806 (49.4)	0.305
Age left school, years, mean (SD)	15.2 (2.1)	15.0 (1.8)	<0.001
Cardiovascular risk factors:			
History of vascular disease, n (%)	1824 (43.7)	741 (45.4)	0.245
History of stroke or TIA, n (%)	430 (10.0)	219 (13.4)	0.001
History of MI, n (%)	541 (13.0)	235 (14.4)	0.097
History of DM, n (%)	427 (10.2)	196 (12.0)	0.050
SBP, mmHg, mean (SD)	154.5 (21.8)	155.0 (21.8)	0.431
DBP, mmHg, mean (SD)	83.7 (11.3)	83.9 (11.9)	0.480
BMI, kg/m ^{2} ,mean (SD)	26.9 (4.1)	26.6 (4.3)	0.015
Current smoking, n (%)	1086 (26.0)	472 (28.9)	0.025
Antihypertensive medications:			
Beta-blockers, n (%)	1117 (26.8)	385 (23.6)	0.013
Diuretics, n (%)	1656 (39.7)	702 (43.0)	0.021
ACE inhibitors, n (%)	664 (15.9)	287 (17.6)	0.122
ARBs, n (%)	89 (2.1)	27 (1.7)	0.241
Calcium channel blockers, n (%)	1050 (25.2)	408 (25.0)	0.895

Abbreviations: SD: Standard Deviation; n: number; TIA: Transient Ischemic Attack; MI: Myocardial Infarction; DM: Diabetes Mellitus; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; ACE inhibitors: Angiotensin Converting Enzyme Inhibitors; ARBs: Angiotensin Receptor Blockers.

Supplementary Table 2. Comparison of annual changes in cognitive scores between low and middle thirds of spatial QRS-T angle

	Difference of low and middle thirds (95 % CI)	p-value
Stroop, seconds	0.13 (-0.023, 0.49)	0.479
LDCT, digits coded	0.004 (-0.08, 0.09)	0.924
PLTi, pictures remembered	-0.02 (-0.04, 0.02)	0.229
PLTd , pictures remembered	0.006 (-0.05, 0.06)	0.832

Analyses were performed in the fully adjusted model

Abbreviations: LDCT: Letter Digit Coding Test; PLTi: Picture-Word Learning Test immediate; PLTd: Picture-Word Learning Test delayed.

Supplementary Table 3. The estimates (β) and 95% confidence intervals for cross-sectional and longitudinal analyses

	Cross-sectional Estimate (95% CI)	Change over time Estimate (95% CI)	Additional annual change Estimate (95% CI)
Stroop test, seconds:			
Model 1*	0.002 (0.00001, 0.004)	0.004 (0.0006, 0.007)	0.0004 (-0.000007, 0.0008)
Model 2*	0.001 (-0.001, 0.003)	0.004 (0.0007, 0.007)	0.0004 (-0.000006, 0.0008)
LDCT, digits coded:			
Model 1	-0.042 (-0.086, 0.002)	-0.312 (-0.37, -0.25)	-0.0106 (-0.018, -0.003)
Model 2	-0.031 (-0.076, 0.013)	-0.312 (-0.37, -0.25)	-0.0106 (-0.018, -0.003)
PLTi, pictures remembered:			
Model 1	-0.006 (-0.018, 0.006)	0.022 (-0.002, 0.047)	-0.0049 (-0.008, -0.002)
Model 2	-0.005 (-0.017, 0.007)	0.022 (-0.002, 0.047)	-0.0049 (-0.008, -0.002)
PLTd, pictures remembered:			
Model 1	-0.005 (-0.022, 0.011)	-0.031 (-0.067, 0.005)	-0.0055 (-0.098, -0.001)
Model 2	-0.001 (-0.018, 0.016)	-0.031 (-0.067, 0.005)	-0.0055 (-0.098, -0.001)

* estimates and 95% CIs for the natural log-transformed values of Stroop test.

The term *cross-sectional* represents the cross-sectional association between spatial QRS-T angle and cognitive function at baseline. The term *changes over time* represents the annual changes of cognitive scores during follow-up. The term *additional annual change* represents the extra yearly change in cognitive scores per 10 degree increase in the spatial QRS-T angle values. Model 1 is adjusted for age, sex, country, education and version of cognitive tests where appropriate; Model 2 is additionally adjusted for history of vascular disease, history of diabetes, systolic and diastolic blood pressure, body mass index, smoking status, antihypertensive medications and statin treatment groups. Abbreviations: LDCT: Letter Digit Coding Test; PLTi: Picture-Word Learning Test immediate; PLTd: Picture-Word Learning Test delayed.

Supplementary Table 4. Cognitive function in relation to spatial QRS-T angle during follow-up, using cut-offs from previous studies

	Spatial QRS-T angle thirds			
	Normal (0°-104°) 3223	Borderline (105°-134°) 370	Abnormal (135°-180°) 579	p-value*
Stroop, seconds, mean annual decline (SE):				
Model 1	0.536 (0.08)	0.933 (0.25)	0.954 (0.20)	0.055
Model 2	0.540 (0.08)	0.941 (0.25)	0.956 (0.20)	0.054
LDCT, digits coded, mean annual decline (SE):				
Model 1	-0.362 (0.02)	-0.463 (0.05)	-0.467 (0.04)	0.004
Model 2	-0.363 (0.02)	-0.465 (0.05)	-0.467 (0.04)	0.004
PLTi, pictures remembered, mean annual decline (SE):				
Model 1	-0.002 (0.008)	-0.028 (0.02)	-0.059 (0.02)	0.001
Model 2	-0.002 (0.008)	-0.028 (0.02)	-0.059 (0.02)	0.001
PLTd, pictures remembered, mean annual decline (SE):				
Model 1	-0.054 (0.01)	-0.100 (0.03)	-0.132 (0.03)	0.013
Model 2	-0.055 (0.01)	-0.101 (0.03)	-0.133 (0.03)	0.013

*p-values were calculated using the interaction term between continuous values of spatial QRST angle and time.

Means represent the mean annual decline in the score of each cognitive test. Model 1: adjusted for age, sex, country, education and version of cognitive tests where applicable; Model 2: adjusted for all the variables in model 1+ history of vascular disease, history of diabetes, systolic and diastolic blood pressure, body mass index, smoking status, antihypertensive medications and statin treatment groups. Abbreviations: SE: Standard Error; LDCT: Letter Digit Coding Test; PLTi: Picture-Word Learning Test immediate; PLTd: Picture-Word Learning Test delayed.

Supplementary Table 5. Cognitive function in relation to spatial QRS-T angle during follow-up stratified by APOE e4 at baseline

	Spatial QRS-T angle	
	Beta (95% CI)	P for interaction
Stroop, seconds*		
E4+ , n=996	0.00005 (-0.00003, 0.0001)	0.540
E4-, n=3063	0.00003 (-0.00001, 0.00008)	
LDCT, digits coded		
E4+ , n=996	-0.0009 (-0.002, 0.0005)	0.747
E4-, n=3063	-0.001 (-0.002, -0.0002)	
PLTi, pictures remembered		
E4+ , n=996	-0.0004 (-0.001, 0.0002)	0.699
E4-, n=3063	-0.0006 (-0.0009, -0.0002)	
PLTd, pictures remembered		
E4+ , n=996	0.0002 (-0.0007, 0.001)	0.603
E4-, n=3063	-0.0009 (-0.001, -0.0004)	

Estimates and 95% CI for the natural log-transformed values of Stroop test.

Analyses were performed in the fully adjusted models. E4+ carriers include participants with APOE $E_{4/4}$, $E_{3/4}$ and $E_{2/4}$ alleles.

Abbreviations: LDCT: Letter Digit Coding Test; PLTi: Picture-Word Learning Test immediate; PLTd: Picture-Word Learning Test delayed.

Supplementary Table 6. Cognitive function in relation to spatial QRS-T angle during follow-up, after exclusion of participants with cardiovascular co-morbidities at baseline

	Spatial QRS-T angle thirds			
	Low	Medium	High	p-value*
Stroop, seconds, mean (SE):				
No history of hypertension (n=1579)	0.785 (0.20)	0.707 (0.21)	1.008 (0.20)	0.152
No history of DM (n=3745)	0.422 (0.13)	0.624 (0.13)	0.725 (0.13)	0.035
No history of MI (n=3631)	0.487 (0.14)	0.582 (0.14)	0.836 (0.14)	0.029
No history of stroke or TIA(n=3742)	0.415 (0.14)	0.593 (0.14)	0.724 (0.14)	0.045
No anti-arrhythmic use (n= 4079)	0.524 (0.13)	0.637 (0.13)	0.737 (0.13)	0.117
LDCT, digits coded, mean (SE):				
No history of hypertension (n=1579)	-0.431 (0.04)	-0.355 (0.04)	-0.418 (0.04)	0.943
No history of DM (n=3745)	-0.326 (0.03)	-0.323 (0.03)	-0.459 (0.03)	0.002
No history of MI (n=3631)	-0.359 (0.03)	-0.338 (0.03)	-0.446 (0.03)	0.029
No history of stroke or TIA(n=3742)	-0.345 (0.03)	-0.347 (0.03)	-0.472 (0.03)	0.002
No anti-arrhythmic use (n= 4079)	-0.355 (0.03)	-0.347 (0.03)	-0.461 (0.03)	0.009
PLTi, pictures remembered, mean (SE):				
No history of hypertension (n=1579)	0.010 (0.02)	-0.035 (0.02)	-0.037 (0.02)	0.017
No history of DM (n=3745)	0.007 (0.01)	0.001 (0.01)	-0.028 (0.01)	0.008
No history of MI (n=3631)	0.004 (0.01)	-0.007 (0.01)	-0.037 (0.01)	0.001
No history of stroke or TIA(n=3742)	0.007 (0.01)	-0.001 (0.01)	-0.034 (0.01)	0.002
No anti-arrhythmic use (n= 4079)	0.006 (0.01)	-0.008 (0.01)	-0.034 (0.01)	0.002
PLTd, pictures remembered, mean (SE):				
No history of hypertension (n=1579)	-0.010 (0.03)	-0.111 (0.03)	-0.074 (0.03)	0.030
No history of DM (n=3745)	-0.061 (0.02)	-0.042 (0.02)	-0.088 (0.02)	0.040
No history of MI (n=3631)	-0.066 (0.02)	-0.058 (0.02)	-0.094 (0.02)	0.025
No history of stroke or TIA(n=3742)	-0.053 (0.02)	-0.047 (0.02)	-0.096 (0.02)	0.009
No anti-arrhythmic use (n= 4079)	-0.059 (0.02)	-0.052 (0.02)	-0.095 (0.02)	0.014

*p-values were calculated using continuous values of spatial QRS-T angle.

All analyses were performed in the fully adjusted models (model 2). Abbreviations: SE: Standard Error; PLTi, Picture-Word Learning Test immediate; PLTd, Picture-Word Learning Test delayed; LDCT: Letter-Digit Coding Test; DM: Diabetes Mellitus; MI: Myocardial Infarction; TIA: Transient Ischemic Attack.