Role of cardiac biomarkers in cognitive impairment and functional decline

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CHAPTER 4

LEFT VENTRICULAR HYPERTROPHY AND COGNITIVE IMPAIRMENT

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Abstract

Background: Patients with advanced heart failure run a greater risk of dementia. Whether early cardiac structural changes also associate with cognitive decline is yet to be determined. **Objective:** We tested whether left ventricular hypertrophy (LVH) derived from electrocardiogram associates with cognitive decline in older subjects at risk of cardiovascular disease. **Methods:** We included 4233 participants (mean age 75.2 years, 47.8% male) from PROSPER (PROspective Study of Pravastatin in the Elderly at Risk). LVH was assessed from baseline electrocardiograms by measuring the Sokolow-Lyon index. Higher levels of Sokolow-Lyon index indicate higher degrees of LVH. Cognitive domains involving selective attention, processing speed, immediate and delayed memory were measured at baseline and repeated during a mean follow-up of 3.2 years. **Results:** At baseline, LVH was not associated with worse cognitive function. During follow-up, participants with higher levels of LVH had a steeper decline in cognitive function including in selective attention ($p = 0.009$), processing speed ($p = 0.010$), immediate memory ($p < 0.001$) and delayed memory ($p = 0.002$). These associations were independent of cardiovascular risk factors, co-morbidities and medications. **Conclusion:** LVH assessed by electrocardiogram associates with steeper decline in cognitive function of older subjects independent of cardiovascular risk factors and co-morbidities. This study provides further evidence on the link between subclinical cardiac structural changes and cognitive decline in older subjects.

Introduction

Patients with advanced heart failure have an increased risk of dementia and Alzheimer's disease[1, 2]. Recent research suggests that subclinical cardiac dysfunction increases the risk of dementia and stroke in older subjects free of cardiac disease[3]. In line with this, a graded decrease in cardiac function has been also associated with structural and functional alterations in the brain of older subjects[4]. Together, these findings might suggest that not only overt cardiac dysfunction, but also suboptimal cardiac function contributes to development of cognitive impairment.

Left ventricular hypertrophy (LVH) is one of the early structural changes in the heart that occur in response to cardiovascular risk factors, particularly hypertension[5]. The anatomical remodeling of the heart during LVH results in diastolic dysfunction which might hamper cardiac output[6]. Since the heart is the driving force for cerebral perfusion, a chronic decrease in cardiac output might jeopardize the integrity of the brain[4]. In line with this premise, LVH has been associated with major cerebrovascular events such as stroke[7], as well as with asymptomatic brain lesions such as lacunar infarcts[8]. Hence, as LVH might be a potential marker of suboptimal cardiac function, we hypothesize that older patients with LVH are at increased risk of developing cognitive impairment.

In this study, we sought to investigate the cross-sectional and longitudinal association of LVH with various domains of cognitive function in older subjects at risk of cardiovascular disease. Furthermore, we tested whether the associations are independent of cardiovascular risk factors, cardiovascular co-morbidities and use of medications.

Methods

Study design

The data for this study were drawn from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER was a randomized controlled trial designed to assess the effect of pravastatin in prevention of vascular events in the elderly with pre-existing cardiovascular diseases or risk factors. A total of 5804 men and women aged 70 to 82 years were included from three collaborating centers in Ireland, Scotland and the Netherlands. About 50% of the participants had a history of vascular disease defined as stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction and vascular surgery. The rest of the participants had at least one major cardiovascular risk factor defined as smoking, hypertension and diabetes mellitus. The mean follow-up time was 3.2 years. A detailed description of PROSPER study design, inclusion and exclusion criteria has been published previously[9]. In brief, exclusion criteria included physical or mental inability to attend the clinic for study visits, poor cognitive function at baseline, congestive heart failure (New York Heart Association functional class III or IV), previous atrial fibrillation, significant arrhythmias and implanted cardiac pacemakers. This study was approved by the institutional ethics committees of the three collaborating centers and all participants gave written informed consent.

Study participants

From the original PROSPER cohort, we excluded 148 participants with missing ECG measurements at baseline, 475 participants with ECG data indicative of cardiac arrhythmias and/or rhythms not generated by the sino-atrial node (including atrial fibrillation, atrial flutter, ectopic atrial rhythms, supraventricular arrhythmias, junctional rhythms, intermittent conduction defect and other arrhythmias); and 948 participants with missing cognitive measurements at baseline or during follow-up. Participants with at least the baseline and one follow-up cognitive measurement were included. Therefore, we included a total of 4233 participants in the present study. Compared to the excluded participants, those included

were younger and had lower prevalence of cardiovascular risk factors and co-morbidities (Supplementary Table 1a, b).

ECG measurements

On the morning of the first enrolment visit, standard 12-lead ECGs were recorded in the resting supine position using a Burdick Eclipse 850i electrocardiograph before initiation of statin treatment. These digital data were transferred to the University of Glasgow ECG Core Lab based at Glasgow Royal Infirmary in Scotland and interpreted using the University of Glasgow (Uni-G) ECG analysis program. We used a fully automated method to ensure reproducibility of the measurements[10]. In addition, all the automated ECG recordings were reviewed by two experts (P.W.M and E.N.C) and any incorrect recordings were replaced by the correct interpretation[11]. The software provided numerous measurements including QRS durations, R-wave amplitudes in leads V5 and V6 and S-wave amplitude in lead V1, from which we determined the Sokolow-Lyon voltage index for LVH (sum of S wave amplitude in lead V1 and R wave amplitude in lead V5 or V6, whichever is the higher)[12]. Previous studies have shown that the product of QRS duration and voltage index significantly improves the accuracy of LVH detection from the ECG[13, 14]. Therefore, we computed the product of Sokolow-Lyon voltage by multiplying it with QRS duration: Sokolow-Lyon product=Sokolow-Lyon voltage×QRS duration. Higher Sokolow-Lyon product values indicate higher degrees of LVH.

Cognitive function measurements

In PROSPER, the global cognitive function was assessed using the mini-mental state examination test (MMSE) at baseline and participants with a MMSE score of < 24 were excluded. In this study, we used four tests to assess different domains of cognitive function. The Stroop interference test was used to test selective attention. The participants were asked to read the name of a color which was typed with ink of color different from the color being named. The outcome was the total number of seconds to complete the test; a higher score indicates worse performance. The Letter-Digit Coding Test was used to assess general

cognitive speed. The subjects had to match digits with letters according to a key provided. The outcome parameter was the total number of correct digits entered in 60 seconds; higher scores indicate better performance. Immediate and delayed memory were tested by the Picture-Word Learning Test. 15 pictures were shown to the participants and they were asked to recall as many pictures as possible in three trials. To measure their delayed recall, participants were asked to repeat the test after 20 minutes. The outcome variable was the accumulated number of correctly recalled pictures; and a higher score indicates better performance. The test/re-test correlations of the four cognitive tests were shown to be high and acceptable, indicating the reliability of cognitive tests (r = 0.80, 0.88, 0.66 and 0.63 for Stroop interference test, Letter-Digit Coding test, immediate and delayed Picture-Word Learning tests, respectively). To avoid learning effect, we used different versions of cognitive tests at each visit[15]. Cognitive function was measured at five time points: at baseline, after 9, 18 and 30 months and at the end of the study, which varied among participants ranging from 36 to 48 months. The baseline cognitive function was assessed before initiation of PROSPER clinical trial. A more detailed description of the cognitive tests has been published elsewhere[15].

Statistical analysis

We used linear regression models to assess the cross-sectional association of LVH with cognitive function. The dependent variable was the score of each cognitive test at baseline. Linear mixed models were used to test the longitudinal association between LVH and cognitive decline over time. The models incorporated Sokolow-Lyon product levels, time (in years) and the interaction between time and Sokolow-Lyon product. Subjects were defined as random factors and all other variables were defined as fixed factors. Probability values were calculated using the interaction term between time and Sokolow-Lyon product. The Stroop interference test scores were log-transformed because they were not normally distributed. All analyses were performed in two steps. In the first step (Model 1), analyses were adjusted for age, sex, education (age at which the participant left school), country of enrolment and version of cognitive tests where applicable. In the second step (Model 2),

analyses were further adjusted for cardiovascular risk factors and co-morbidities (history of diabetes, history of vascular disease, body mass index, smoking status, systolic blood pressure, diastolic blood pressure, total cholesterol and HDL-cholesterol levels), antihypertensive medications (diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors [ACEI] and angiotensin receptors blockers [ARB]) and anticoagulant medications. In the longitudinal analyses, adjustments for statin treatment groups were added. In an additional analysis, we categorized the participants in two groups based on the clinical cut-off value of Sokolow-Lyon voltage, since there is no well-established clinical cut-off value for Sokolow-Lyon product[16]. Participants were categorized as follow: 1) participants with Sokolow-Lyon voltage < 3500 μV; 2) participants with Sokolow-Lyon voltage ≥ 3500 μV. We then repeated the cross-sectional and longitudinal analyses in these two groups. Probability values were calculated using the interaction term between time and continuous values of Sokolow-Lyon voltage.

Furthermore, to explore the effect of cardiovascular events on longitudinal associations, we stratified for participants who did and did not develop coronary events, stroke or transient ischemic attack events, incident atrial fibrillation and heart failure hospitalization during follow-up. The interaction terms were tested in linear mixed models for composite executive function and memory function scores. The composite executive function was calculated by averaging the Z scores of the Stroop interference test and Letter-Digit Coding tests. The composite memory function was calculated by averaging the Z scores of the immediate and delayed Picture-Word Learning tests. To test the effect of ACEI and ARB medications, participants were stratified in two groups of ACEIs users and ARBs users and tested for interaction. Similarly, to test the effect of sex on longitudinal associations participants were stratified in two groups of males and females. Finally, to test the effect of cardiovascular risk factors and co-morbidities on longitudinal associations, a series of additional analyses were performed in which we excluded participants with a history of hypertension, history of diabetes mellitus, history of myocardial infarction, history of stroke or transient ischemic attack, high cholesterol levels (>6.21 mmol/L) and current smokers and repeated the longitudinal analyses.

Results

The mean age of the participants was 75.2 years and a total of 2025 (47.8%) participants were male. The mean Sokolow-Lyon product and Sokolow-Lyon voltage were 224.3 µVs and 2285.1 µV, respectively (Table 1). Participants with higher Sokolow-Lyon product were older, more likely to be male, had lower body mass index, had lower prevalence of diabetes mellitus, had higher systolic and diastolic blood pressure, and used calcium channel blockers and beta-blockers more frequently (all p values < 0.05) (Supplementary Table 2).

Table 2 shows the cross-sectional association of Sokolow-Lyon product and cognitive function at baseline. In Model 1, higher Sokolow-Lyon product was not associated with worse performance of participants in the Stroop interference test, Letter-Digit Coding test and delayed Picture-Word Learning tests. Participants with higher Sokolow-Lyon product had a non-significant trend of better performance in the immediate Picture-Word Learning test. Consistently, full adjustment for cardiovascular risk factors, co-morbidities and use of medications in Model 2 did not change the observed associations (estimates and 95% confidence intervals are presented in Supplementary Table 3).

Table 3 shows the longitudinal association of Sokolow-Lyon product and cognitive function during follow-up. In Model 1, participants with higher Sokolow-Lyon product had a steeper decline in Stroop interference test performance (p = 0.009), Letter-Digit Coding Test score (p = 0.010), immediate Picture-Word Learning Test score (p < 0.001) and delayed Picture-Word Learning Test score (p = 0.002). These results were similar after adjustment for cardiovascular risk factors, co-morbidities and use of medication (Model 2) (estimates and 95% confidence intervals are presented in Supplementary Table 3). Exclusion of outliers (>3 SD, < 2% of the data) did not change the results.

Table 1. Baseline characteristics of participants

Characteristics	Value
Socio-demographics	
Age, y, mean (SD)	75.2 (3.3)
Male, n (%)	2025 (47.8)
Age left school, y, mean (SD)	15.2 (2.1)
Vascular risk factors	
History of vascular disease, n (%)	1850 (43.7)
History of MI, n (%)	546 (12.9)
History of stroke or TIA, n (%)	438 (10.3)
History of diabetes mellitus, n (%)	435 (10.3)
SBP, mmHg, mean (SD)	154.6 (21.9)
DBP, mmHg, mean (SD)	83.7 (11.3)
BMI, kg/m^2, mean (SD)	26.9 (4.1)
Current smoking, n (%)	1099 (26.0)
Cognitive function	
MMSE, score, median (IQR)	28.0 (27.0-29.0)
Stroop interference, seconds, median (IQR)	58.2 (48.0-73.5)
LDCT, mean (SD)	23.7 (7.8)
PLTi, mean (SD)	9.4 (1.8)
PLTd, mean (SD)	10.3 (2.6)
Medications	
Diuretics, n (%)	1689 (39.9)
Beta-blockers, n (%)	1130 (26.7)
Calcium channel blockers, n (%)	1070 (25.3)
ACE inhibitors, n (%)	675 (15.9)
ARBs, n (%)	90 (2.1)
Anti-diabetic medication, n (%)	281 (6.6)
ECG indices for LVH	
Sokolow-Lyon voltage, µV, mean (SD)	2285.1 (799.4)
Sokolow-Lyon product, µVs, mean (SD)	224.3 (90.5)

Abbreviations: MI: myocardial infarction; TIA: transient ischemic attack; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; MMSE: Mini-Mental State Examination test; LDCT: Letter Digit Coding Test; PLTi: Picture-Word Learning Test immediate; PLTd: Picture-Word Learning Test delayed; ACE: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers.

At baseline, participants in the high Sokolow-Lyon voltage group did not have worse performance in any of the cognitive tests (Supplementary Table 4). Figure 1 shows the longitudinal association of Sokolow-Lyon voltage categories and cognitive function after full

adjustment for measured cardiovascular risk factors, co-morbidities and use of medications. Participants in the high Sokolow-Lyon voltage group had a steeper decline in Letter-Digit Coding test score (p = 0.007), immediate Picture-Word Learning test score (p < 0.001), and delayed Picture-Word Learning test score (p = 0.024). The relation between high Sokolow-Lyon voltage and decline in Stroop interference test performance was marginally significant (p = 0.072). All these associations were similar in Model 1 (data not shown).

Table 2. The association between LVH and cognitive function at baseline

	Sokolow-Lyon product (µVs)			
	Low 17.11 – 177.16 n = 1411	Medium 177.20 – 245.55 n = 1411	High 245.70 – 902.53 n = 1411	*p* Value*
Stroop interference, seconds, mean (SE)				
Model 1	63.60 (0.61)	63.79 (0.60)	63.80 (0.61)	0.978
Model 2	65.69 (1.98)	66.17 (1.96)	66.35 (1.96)	0.712
LDCT, digits coded, mean (SE)				
Model 1	24.07 (0.18)	24.26 (0.18)	23.74 (0.18)	0.351
Model 2	23.25 (0.57)	23.33 (0.57)	22.72 (0.57)	0.119
PLTi, pictures remembered, mean (SE)				
Model 1	9.41 (0.05)	9.53 (0.05)	9.56 (0.05)	0.090
Model 2	9.29 (0.15)	9.41 (0.15)	9.46 (0.15)	0.065
PLTd, pictures remembered, mean (SE)				
Model 1	10.35 (0.07)	10.34 (0.07)	10.45 (0.07)	0.240
Model 2	10.14 (0.22)	10.12 (0.21)	10.23 (0.21)	0.238

*p values were calculated using continuous values of Sokolow-Lyon product. Model 1: adjusted for age, sex, country, education and version of cognitive tests where applicable. Model 2: adjusted for age, sex, country, education, version of cognitive tests where applicable, body mass index, smoking status, systolic blood pressure, diastolic blood pressure, history of diabetes, history of vascular disease, total cholesterol level, HDL-cholesterol level, antihypertensive medications (diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers) and anticoagulant medications. SE: standard error; LDCT: letter digit coding test; PLTi: picture-word learning test immediate; PLTd: picture-word learning test delayed.

Figure 2 shows the longitudinal association of Sokolow-Lyon product and cognitive function, stratified by incident cardiovascular events. During follow-up, 432 participants

developed coronary events, 281 participants developed stroke or transient ischemic attack events, 357 participants developed incident atrial fibrillation and 151 participants were hospitalized for heart failure. There was no significant difference in annual changes of cognitive function between participants who did and those who did not develop cardiovascular events, except that participants with atrial fibrillation had a less prominent decline in executive function (marginal p for interaction = 0.055). There was no significant difference in annual changes of cognitive function between participants taking ACEI medications vs participants taking ARB medications (Supplementary Table 5). Similarly, we did not observe sex dependent differences in annual changes of cognitive function during follow-up (data not shown).

Table 3. The association between LVH and cognitive function during follow-up

	Sokolow-Lyon product (μVs)			
	Low	Medium	High	
	17.11 – 177.16	177.20 – 245.55	245.70 – 902.53	*p* Value*
	n = 1411	n = 1411	n = 1411	
*Stroop interference, seconds, mean** (SE)*				
Model 1	0.523 (0.13)	0.507 (0.13)	0.841 (0.13)	0.009
Model 2	0.525 (0.13)	0.510 (0.13)	0.845 (0.13)	0.009
LDCT, digits coded, mean (SE)				
Model 1	-0.329 (0.03)	-0.389 (0.03)	-0.437 (0.03)	0.010
Model 2	-0.329 (0.03)	-0.390 (0.03)	-0.438 (0.03)	0.010
PLTi, pictures remembered, mean (SE)				
Model 1	0.016 (0.01)	-0.009 (0.01)	-0.043 (0.01)	<0.001
Model 2	0.015 (0.01)	-0.010 (0.01)	-0.043 (0.01)	<0.001
PLTd, pictures remembered, mean (SE)				
Model 1	-0.054 (0.02)	-0.060 (0.02)	-0.094 (0.02)	0.002
Model 2	-0.054 (0.02)	-0.060 (0.02)	-0.095 (0.02)	0.002

**p* values were calculated using the interaction term between continuous levels of Sokolow-Lyon product and time. ** represents mean annual decline in cognitive scores during follow-up. Model 1: adjusted for age, sex, country, education and version of cognitive test where applicable. Model 2: Model 1 + body mass index, smoking, systolic blood pressure, diastolic blood pressure, history of diabetes, history of vascular disease, antihypertensive medications (diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers), statin treatment groups, HDL, total cholesterol and anticoagulants. SE: standard error; LDCT: letter digit coding test; PLTi: picture-word learning test immediate; PLTd: picture-word learning test delayed.

After exclusion of participants with a history of hypertension (n=2634), diabetes mellitus (n=435), myocardial infarction (n=546), stroke or transient ischemic attack (n=438), high cholesterol levels (n=1174) and current smokers (n=1099) at baseline, the longitudinal associations did not materially change (Supplementary Table 6)

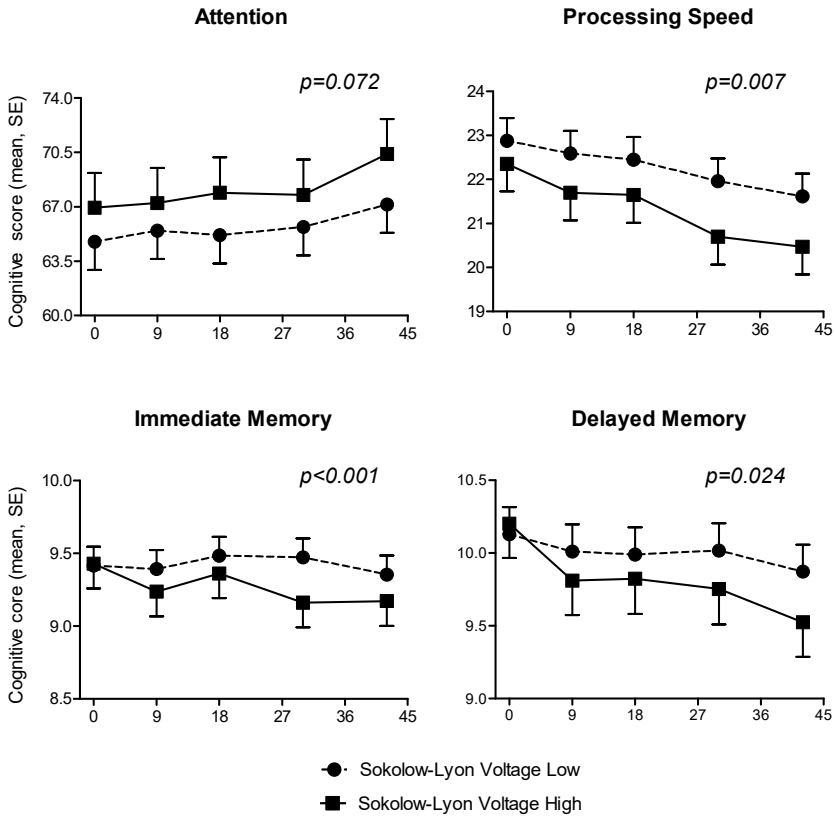

Figure 1. The association between clinical categories of left ventricular hypertrophy and annual changes of cognitive function during follow-up. The time point at the end of study is the mean of the end time points (36 to 48). Data shows fully adjusted models. Abbreviations: LDCT: letter digit coding test; PLTi: picture-word learning test immediate; PLTd: picture-word learning test delayed.

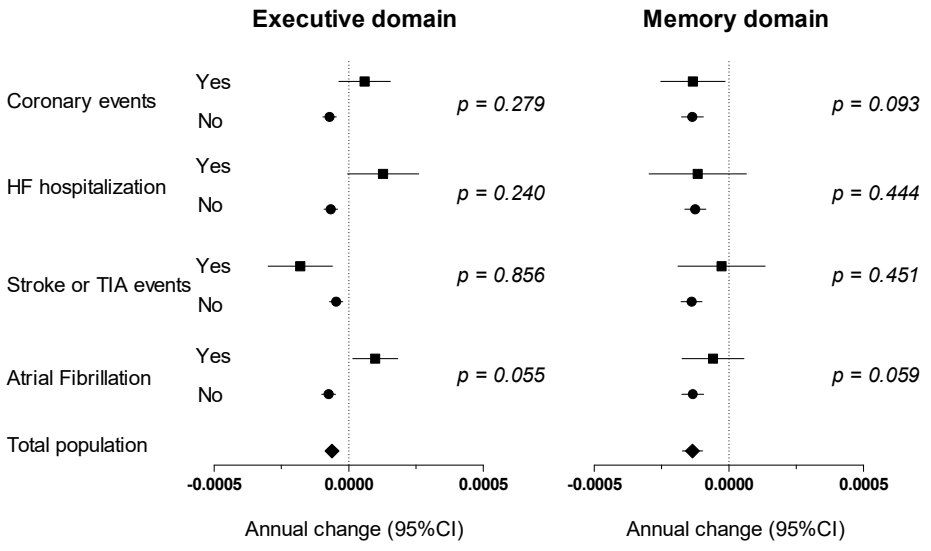

Figure 2. The association between left ventricular hypertrophy and annual changes of cognitive function, stratified for cardiovascular events during follow-up. Data represent annual change (95%CI) per each unit (μVs) increase in Sokolow-Lyon product for each cognitive test, stratified by cardiovascular events during follow-up. P-values were show p for interaction. Adjusted for age, sex, 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, total cholesterol level, HDL-cholesterol level, antihypertensive medications, anticoagulant medications and statin treatment groups.

Discussion

In this study we found that higher degrees of LVH as assessed by ECG associate with a steeper decline in cognitive function of older subjects independent of measured cardiovascular risk factors, cardiovascular co-morbidities and use of medications.

Previous cross-sectional studies have reported an association between echocardiographic measured LVH and cognitive function. For example, Scuteri et al. showed that increased left ventricular mass associated with worse MMSE score in 400 participants (mean age 79 ± 6 years) independent of blood pressure and large artery stiffness[17]. The

Framingham Offspring Study on 1673 participants (mean age 57 ± 9 years) showed similar results. However, this association was attenuated after adjustment for cardiovascular risk factors and morbidities[18]. Echocardiographic measured LVH was also associated with a 5-year decline in MMSE score in a small group of older adults in the Helsinki Ageing study[19]. Nevertheless, very few studies have tested the link between LVH assessed by ECG and cognitive function. Of note, ECG detected LVH has been shown to predict development of cognitive impairment in stroke free individuals in The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study[20]. In that study, cognitive function was assessed using a single-item measure of global cognitive function (The Six-item Screener) while the population consisted of middle aged adults (mean age 64 years).

The observed link between LVH and cognitive function can be explained through a number of pathophysiological mechanisms. First, LVH is recognized as cardiovascular target organ damage[6] and the role of vascular risk factors in development of cognitive impairment is well-established[21]. This suggests that cardiovascular risk factors and morbidities might play role as confounders in the association between LVH and cognitive function. Nevertheless, adjustment of our analyses for several well-established cardiovascular risk factors and co-morbidities, and exclusion of participants with cardiovascular co-morbidities at baseline, did not alter the observed associations. Second, LVH has been associated with future cardiovascular events[6], which might in turn contribute to neurovascular damage and cognitive impairment. Finally, it can be hypothesized that a subclinical decrease in cardiac output predisposes subjects to chronic cerebral hypoperfusion, which might adversely affect structural and functional integrity of the brain[1]. Consistent with this hypothesis, Jefferson et al. have shown that a lower cardiac index (cardiac output divided by body surface area), even in subjects without prevalent cardiovascular disease, associates with abnormal brain aging[2]. Recently, we have shown that a graded decrease in cardiac function is linked to lower brain parenchymal and grey matter volume, as well as worse cognitive function [4].

We did not observe a cross-sectional association between LVH and cognitive function at baseline. It should be noted that the participants in this study had preserved cognitive

function at baseline (due to PROSPER inclusion criteria: MMSE ≥ 24 points), which might have underestimated the relation between LVH and cognitive function. Furthermore, the presence of longitudinal association between LVH and cognitive function strengthens the temporality of the observed associations. We used the ECG to detect LVH in our patients. Although the ECG has a low sensitivity for LVH compared to echocardiography, both ECG and echocardiography measured LVH have been shown to associate with silent cerebral lesions such as punctate lesions, lacunas and cerebral artery territorial lesions[8]. This is in line with our results, suggesting that the ECG might be able to detect the presence of previously established vascular brain damage. Moreover, the specificity of ECG detected LVH compared to various diagnostic standards (e.g. echocardiography[14, 22], cardiac magnetic resonance imaging[23] and left ventricular mass at autopsy[13]), is shown to be quite high ranging from 85% to 90%[16]. As a result, the rate of false-positive detection is low and participants with higher values of ECG indices for LVH are very likely to actually have LVH.

This study has certain strengths and limitations. The major strengths are the large sample size, the prospective design, and the usage of an extensive set of neuropsychological tests to assess different domains of cognitive function. Furthermore, we show that the results are independent of several cardiovascular risk factors and co-morbidities. As limitations, the participants in this study were at high risk of cardiovascular disease which makes it difficult to generalize our findings to a healthy elderly population. Nevertheless, older adults frequently have a number of cardiovascular pathologies and our results were independent of measured cardiovascular risk factors, cardiovascular co-morbidities and use of medications. The observational nature of this study makes it difficult to infer any causality. Finally, we cannot exclude the possibility of selection bias given that some participants had missing cognitive measurements.

In conclusion, a higher degree of LVH assessed from ECG associates with a steeper decline in cognitive function independent of cardiovascular risk factors, cardiovascular co-morbidities and use of medications. Older adults with LVH may need to be recognized as a potentially high risk group for cognitive impairment. To establish a potential causal link,

future research should determine whether interventions that halt or slow down the pace of LVH have favorable effects on cognitive function of older subjects at risk of cardiovascular disease.

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