Supplementary Material

Electrocardiographic Predictors of Cognitive Decline and Dementia: A Systematic Review

Search strategy
A search was performed after combining appropriate keywords.

PubMed
("electrocardiography"[MeSH Terms] OR "electrocardiography"[Title/Abstract] OR "electrocardiogram"[Title/Abstract] OR "ECG"[Title/Abstract] OR "ECGs"[Title/Abstract] OR "EKG"[Title/Abstract] OR "EKGs"[Title/Abstract]) AND ("dementia"[MeSH Terms] OR "cognitive dysfunction"[MeSH Terms] OR "dementia"[Title/Abstract] OR "dement*"[Title/Abstract] OR "cognitive impairment"[Title/Abstract] OR "cognitive impair*"[Title/Abstract] OR "alzheimer"[Title/Abstract] OR "alzheimer's"[Title/Abstract] OR "cognitive decline"[Title/Abstract] OR "cognitive dysfunction"[MeSH Terms] OR "cognitive"[Title/Abstract] OR “cognition"[Title/Abstract] OR "mci"[Title/Abstract] OR "cind"[Title/Abstract] OR "cogn*"[Title/Abstract])

Web of Science (selecting topic and only articles)
("electrocardiography" OR "electrocardiogram" OR "ECG" OR "ECGs" OR "EKG" OR "EKGs") AND ("dementia" OR "dement*" OR “cognitive dysfunction” OR "cognitive impairment" OR "cognitive impair*" OR "alzheimer" OR "alzheimer's" OR "cognitive decline" OR "cognitive" OR “cognition" OR "mci" OR "cind" OR "cogn*")

Embase (selecting topic and only articles)
(electrocardiography OR electrocardiogram OR ECG OR ECGs OR EKG OR EKGs) AND (dementia OR dement* OR cognitive dysfunction OR cognitive impairment OR cognitive impair* OR alzheimer OR alzheimers OR cognitive decline OR cognitive OR cognition OR mci OR cind OR cogn*)

Inclusion
1. Cross-sectional study, case-control study, prospective study, secondary analysis of randomized controlled trial.
2. The association between specific electrocardiographic markers and cognitive function/ dementia is presented.
3. General population OR community-based participants OR disease-based population.
4. Exposure is specific ECG marker independent of clinical symptoms.
5. Outcome is objective diagnosis of dementia or cognitive function.
6. Adult population.
7. Written in English

Exclusion

1. Original data is not presented (i.e. reviews, guidelines/recommendations, letters to editor, commentaries, editorials, case reports, conference abstract).
2. Self-reported dementia or cognitive function.

3. ECG finding is heart rate variability (systematic reviews have been performed recently).
4. ECG finding is atrial fibrillation (several systematic reviews have been conducted).
5. The exposure is composite ECG markers or combination of ECG markers and clinical symptoms, and the association between specific ECG marker and outcomes are not presented separately.
6. The outcome is intermediate outcomes such as MRI imaging.
7. Animal studies or *in vitro* studies.
8. Written in languages other than English.
9. Participants experience life-threatening arrhythmia/require immediate interventions.

Information	
Names of databases/platforms searched	PubMed Web of Science Embase
Database time coverage	1945 (Web of Science)- Present
Date searched	1 July 2020
Number of records from each database before de-duplicating	PubMed: 1443 (1 July 2020) Web of Science (Topic): 1,050 (2 July 2020) Embase (Title or Abstract): 1,939 (1 July 2020) Total: 4,432
Number of records after de-duplicating	2,891

Supplementary Table 1. Excluded studies and the reasons for exclusion

Reference	Study authors, year	Reason(s) for exclusion
[1]	Barba, 2000	No association between ECG findings and cognition
[2]	Bart, 2012	Conference abstract
[3]	Bucht, 1984	ECG findings composite
[4]	Charles, 2014	Conference abstract, ECG findings: composite
[5]	Charles, 2014	Outcomes: MRI/CT findings, No association between ECG findings and cognition
[6]	Chen, 2011	Conference abstract, ECG findings: atrial fibrillation
[7]	Chen, 2014	Conference abstract, ECG findings: atrial fibrillation
[8]	Chen, 2014	Conference abstract
[9]	Chen, 2015	Conference abstract
[10]	Chen, 2016	Conference abstract
[11]	Chen, 2016	Conference abstract, No association between ECG findings and cognition check overlapping
[12]	Chen, 2018	ECG findings: atrial fibrillation
[13]	Chumakova, 2014	Conference abstract, ECG findings: atrial fibrillation
[14]	de Leeuw, 2000	Outcomes: MRI/CT findings, No association between ECG findings and cognition
[15]	Deme, 2009	Conference abstract, No association between ECG findings and cognition
[16]	Diaconu, 2013	Conference abstract, ECG findings: atrial fibrillation
[17]	Ding, 2017	Conference abstract, ECG findings: atrial fibrillation
[18]	Ding, 2018	ECG findings: atrial fibrillation
[19]	Evstigneeva, 2015	Conference abstract
[20]	Falsetti, 2018	ECG findings: atrial fibrillation
[21]	Galluzzi, 2009	ECG findings: heart rate variability (24 h)
[22]	Georgakis, 2017	Systematic literature review
[23]	Geroldi, 2003	ECG findings: composite
[24]	Gu, 2019	No association between ECG findings and cognition, selection based on serious disease
[25]	Halling, 2006	ECG findings: atrial fibrillation
[26]	Horstmann, 2014	ECG findings: atrial fibrillation
[27]	Ikram, 2008	Exposures are recognized MI and unrecognized MI, which were diagnosed based on not only ECG but also clinical information
[28]	Jackson, 2018	Conference abstract
[29]	Jeerakathil, 2004	Outcomes: MRI/CT findings, No association between ECG findings and cognition
[30]	Jin, 2009	Conference abstract
[31]	Jozwiak, 2006	ECG findings: atrial fibrillation
[32]	Kawabata-Yoshihara, 2012	ECG findings: atrial fibrillation
[33]	Kim, 2018	ECG findings: heart rate variability (5 min)
[34]	Lee, 2012	Conference abstract, ECG findings: heart rate variability
[35]	Lima-Costa, 2009	ECG findings: composite
[36]	Lin, 2017	Intervention study
[37]	Mahinrad, 2016	ECG findings: heart rate variability (10 s)

[38]	Mahinrad, 2015	Conference abstract, ECG findings: heart rate variability (10 s)
[39]	Mahringer, 2018	Conference abstract
[40]	Mahringer, 2018	Conference abstract
[41]	Matei, 2015	Conference abstract
[42]	Matei, 2015	Conference abstract
[43]	McNicholas, 2018	Conference abstract, ECG findings: atrial fibrillation
[44]	Nadkarni, 2019	Conference abstract, No association between ECG findings and cognition
[45]	Norby, 2017	Conference abstract
[46]	Norby, 2018	Conference abstract
[47]	O'Connell, 1998	ECG findings: atrial fibrillation
[48]	Ott, 1997	ECG findings: atrial fibrillation
[49]	Pal, 2019	Conference abstract, ECG findings: atrial fibrillation
[50]	Podea, 2010	Conference abstract, ECG findings: atrial fibrillation
[51]	Puccio, 2009	ECG findings: atrial fibrillation
[52]	Räiha, 2013	Association not shown
[53]	Rastas, 2007	ECG findings: atrial fibrillation
[54]	Rooney, 2017	Conference abstract
[55]	Rooney, 2018	Conference abstract
[56]	Rydén, 2017	Conference abstract, ECG findings: atrial fibrillation
[57]	Rydén, 2017	Conference abstract, ECG findings: atrial fibrillation
[58]	Rydén, 2019	ECG findings: atrial fibrillation
[59]	Sabatine, 2000	ECG findings: atrial fibrillation
[60]	Shiohama, 1993	No association between ECG findings and cognition
[61]	Taranchuk, 2011	Conference abstract, ECG findings: atrial fibrillation
[62]	Thacker, 2013	ECG findings: atrial fibrillation
[63]	Thacker, 2012	Conference abstract, ECG findings: atrial fibrillation
[62]	Thacker, 2013	Duplication (same as Thacker, 2013 above)
[64]	Todoroki, 2015	Outcomes: MRI/CT findings, No association between ECG findings and cognition
[65]	Weinstein, 2019	Conference abstract, ECG findings: heart rate variability
[66]	Wozakowska-Kapłon, 2009	ECG findings: atrial fibrillation
[67]	Yaneva-Sirakova, 2016	Conference abstract, left ventricular hypertrophy assessed by echocardiography
[68]	Young, 2010	Conference abstract
[69]	Zhang, 2019	ECG findings: Atrial fibrillation
[70]	Zhang, 2019	Conference abstract, ECG findings: atrial fibrillation

Supplementary Table 2: A summary of unadjusted studies

Study, year, country	Population, N, Age (mean/median), males (%), Follow-up	Exclude	Type of ECG, ECG findings	Outcome, Diagnosis criteria	Effect size (95% confidence interval)	Quality
Outcome Dementia: cross-sectional analyses (n=5)						
De Pedis*, 1987, [71]	Patients admitted to a geriatric hospital, **N: Dementia 36, Control 27,** Age: Dementia 84 y, Control 83 y, Male: Dementia 22.0%, Controls 30.0%		AV block, SA block, sick sinus syndrome, Gaps (RR interval >1.5 s)		Difference in prevalence of each ECG finding between dementia group and control: Ventricular tachycardia p=0.02, gaps p=0.03, AV block NS, SA block NS, sick sinus syndrome NS	2/9
Sanna*, 2019, Italy [72]	Convenient sample of patients with AD without cardiovascular or systematic disease and controls, **N: AD 32, Control 34,** Age: AD 75.1±7.2 y, Control 73.3±6.2 y, Male: AD 69 %, Control 65%	Malignant tumors (n=4), systemic inflammatory diseases (n=12), amyloidosis (n=3), known or clinically suspected coronary artery disease (n=11), moderate to severe valvular disease (n=8), grade II to III arterial hypertension (blood pressure 160/100>mm Hg) (n=10), pericardial disease (n=1), and congenital heart disease (n=1)	Resting 12-lead ECG Right bundle branch block, Left bundle branch block, Low QRS voltage, Total QRS score, LV hypertrophy, Pathologic Q waves, Repolarization abnormalities, PR interval, QTc interval		ECG findings (Value or %) in AD patients versus controls Sinus rhythm: 94% versus 94% p=0.95, Atrial fibrillation: 6% versus 6% p=0.95, Right bundle branch block: 3% versus 3% p=0.97, Left bundle branch block: 0% versus 6% p=0.16, Low QRS voltage: 28% versus 3% **p=0.004**, Total QRS score: 96.5±26mm versus 111.6±34.3 **p=0.05**, LVH: 3% versus 0% p=0.51, Pathologic Q waves: 6% versus 3% p=0.52, Repolarization abnormalities: 16% versus 24% p= 0.42, PR interval: 160 (IQR150–180) ms versus 160 (160–180) ms p=0.87, QTc interval: 418±24 ms versus 424±30 ms p=0.37	4/9
Sonnesyn*, 2009, Norway [73]	Recruited from the DemVst study, a prospective cohort study of participants with mild dementia, **N: DLB 22, AD 81, Control 23,** Age: DLB 78.1±8.2 y,	Patients without dementia or with acute delirium, terminal illness, previous bipolar disorder or psychotic disorder, or having been recently	Resting 12-lead ECG QTc		Mean QTc ± SD in patients with AD versus patients with AD versus Control: 429.5±39.5 versus 424.2±28.2 versus 438.9±30.7 p=0.125 QTc >420 ms (%): 55 versus 56 versus 65 p=0.765	5/9

Study, year, country	Population, N, Age (mean/median), males (%), Follow-up	Exclude	Type of ECG, ECG findings	Outcome, Diagnosis criteria	Effect size (95% confidence interval)	Quality
	AD 75.6±7.7 y, Control not mentioned, Male: DLB 49%, AD 30%, Control 30%	diagnosed with life-threatening or severe somatic illness. Patients with missing or unreadable ECGs, ECGs showing rhythms other than sinus rhythm, or with right or left bundle branch block.			QTc>450 ms (%): 18 versus 20 versus 39 p=0.211	
Zulli*, 2005, Italy [74]	Community population-based sample of patients admitted to an Alzheimer's disease center for investigation of cognitive disturbances, **N: AD 33, MCI 39, Controls 29,** Age: AD 72.1±8.2 y, MCI 70.0±7.2 y, Controls 69.8±5.3 y, Male: AD 39.4%, MCI 41.0%, Control 34.5%	Individuals with heart failure, clinical evidence of coronary artery disease, significant valvular disease, diabetes mellitus, or severe clinical conditions; patients with ECG changes or those who were taking drugs that could potentially interfere with the measurements of QT parameters; patients with major depressive or cerebrovascular disorders; and patients with abnormalities in levels of serum folate, vitamin B12, and thyroid hormones, positive syphilis serology, history of traumatic brain injury, or other neurological diseases. Only patients with AD who had never undergone cholinesterase	Resting 12-lead ECG QT maximal QT interval (Qtmax), maximal QT corrected interval (QTcmax), minimal QT interval (QTmin), minimal QT corrected interval (QTcmin), QTD, and QT corrected dispersion (QTcD)		QTcmax (ms) AD 434.2 ±25.1 MCI 421.8 ± 24.8 control 432.0 ±22.3 p-values AD versus MCI 0.08, AD versus C 0.90, MCI versus C 0.14 QTmax (ms) AD 410.3 ± 23.9, MCI 402.7 ± 29,1, control 397.6 ±21.8 p-values AD versus MCI 0.31, AD versus C 0.08, MCI versus C 0.29 QTcmin (ms) AD 376.7 ± 22.4, MCI 377.1 ± 23.0, control 389.6 ± 20.3 p-values AD versus MCI 0.95, AD versus C 0.07, MCI versus C 0.68 QTmin (ms) AD 356 ± 20.8, MCI 359.3 ±21.7, control 361.3 ± 20.6 p-values AD versus MCI 0.57, AD versus C 0.41, MCI versus C 0.75 QTcD (ms) AD 59.8 ± 13.3, MCI 47.2 ± 11.7, control 39.1 ±14.8 p-values AD versus MCI **0.001**, AD versus C **<0.001**, MCI versus C **0.03** QTD (ms)	2/9

Study, year, country	Population, N, Age (mean/median), males (%), Follow-up	Exclude	Type of ECG, ECG findings	Outcome, Diagnosis criteria	Effect size (95% confidence interval)	Quality
		inhibitor therapy were included.			AD 56.3 ±12.8, MCI 45.6 ± 12.8, control 36.2 ±13.7 p-values AD versus MCI **0.001**, AD versus C **<0.001**, MCI versus C **0.01**	
Zulli*, 2008, Italy [75]	Patients with AD, MCI, and cognitive healthy control without clinical evidence of coronary artery disease, **N: AD 33, MCI 39, Control 29,** Age: AD 72.1±8.2 y, MCI 70.0±7.2 y, Controls 69.8±5.3 y, Male: AD 39.4%, MCI 41.0%, Control 34.5%	Individuals with heart failure, clinical or instrumental evidence of coronary artery disease, significant valvular disease, diabetes mellitus and severe clinical conditions were excluded. Patients with ECG change or taking antiarrhythmic drugs, including beta blockers, or drugs potentially interfering with the measurements of QT parameters did not enter the study as well. Also patients taking inhibitors of the rennin–angiotensin–aldosternoe system were excluded. Patients with bundle branch blocks and patients with left ventricular hypertrophy-subendocardial strain pattern were excluded too, because they prevent the evaluation of SMI. Patients with major depressive disorders, cerebrovascular	24-h ECG any episode of myocardial ischemia, number of premature ventricular beats (PVBs), their morphology, the number of couplets and runs of ventricular tachycardia in each subject. Repetitive premature ventricular beats (RPVBs) were defined as those ventricular beats forming couplets or ventricular tachycardia episodes; non-sustained ventricular tachycardia (NSVT) was characterized as >3 consecutive premature beats occurring at a rate of >100 beats/min lasting less than 30 s (24-h ECG)		The mean number of ventricular couplets: AD =3.44±5.2, MIC=0.8±2.2 C=0.33±0.86; AD versus MCI, p=**0.005**; AD versus C, p=**0.002** The mean number of repetitive PVB: AD=8.56±13.1, MCI =1.8±7.2, C=0.7±1.7; AD versus MCI, p=**0.02**; AD versus C, p=**0.02** Supraventricular arrhythmias: No significant difference	2/9

Study, year, country	Population, N, Age (mean/median), males (%), Follow-up	Exclude	Type of ECG, ECG findings	Outcome, Diagnosis criteria	Effect size (95% confidence interval)	Quality
		disorders, abnormalities in serum folate, vitamin B12 and thyroid hormones levels, positive syphilis serology, history of traumatic brain injury or other neurologic diseases were excluded too. Further, only AD patients who had never experienced cholinesterase inhibitors therapy were included, to avoid confounders.				
Outcome Dementia: longitudinal analyses (n=1)						
Katzman, 1989, US [76]	Ambulatory, functional, presumably nondemented volunteers aged 75 to 85 were recruited from senior citizen centers, by local newspaper advertisements, and by word of mouth, **N=434**, 79 y, 35.5%, 5 y	The presence of Parkinson's disease, terminal illnesses, or visual or hearing impairments that precluded psychological testing	Unclear for LVH, 24-h ECG for sinus bradycardia, LVH, sinus bradycardia (detail not mentioned)	Incident dementia (AD), multiinfarct dementia/mix AD and cerebrovascular disease (MID/MIX)) Dementia: DSM-3, AD: McKhann and colleagues	LHV(%) in nondemented participants versus participants with AD versus participants with MID/MIX: 12.6% versus 6.3% versus 20.0%, sinus bradycardia at baseline 29.4% versus 25.0% versus 20.0%	5/9
Outcome Cognitive function: cross-sectional analyses (n=4)						
Bernal, 2018, Spain [77]	IFFANIAM study Patients with myocardial infarction, **N=254**, 82.1±4.5 y, 57.5%		IAB	Cognitive impairment (Pfieffer test>3)	Cognitive impairment (%) in those with no IAB/partial versus those with advanced IAB; 26.9% versus 26.5%	1/8
Elmståhl, 2009,	General population (all men born in the year		24-hour ECG,	Cognitive test battery (binary)	During 24 h	3/8

Study, year, country	Population, N, Age (mean/median), males (%), Follow-up	Exclude	Type of ECG, ECG findings	Outcome, Diagnosis criteria	Effect size (95% confidence interval)	Quality
Sweden [78]	1984 and residing in the municipality of Malmo), **N=88,** 81 y, 100%		ST segment depression (STDE) assessed using 24-h Holter ECG	(Swedish version of Block Design, a Swedish version of the original Verbal Paired Associates of Wechsler, Digit Symbol Substitution Test, the Benton Visual Retention Test)	Low block design (%) in those without STDE versus those with STDE: 59 versus 84 p=0.014, Low synonyms (%): 67 versus 78 p=0.775, Low paired associates (%): 68 versus 69 p=0.887, Low digit symbol substitution (%): 68 versus 71 p=1.000, Low Benton Visual Retention (%): 54 versus 63 p=0.285 Night-time Low block design (%) in those without STDE versus those with <60 min STDE versus those with >60 min STDE: 71 versus 83 versus 88, p=0.209, p for trend 0.079, Low synonyms (%): 79 versus 83 versus 71 p=0.701 p for trend 0.692, Low paired associates (%): 63 versus 92 versus 82 p=0.089 p for trend 0.045, Low digit symbol substitution (%): 92 versus 91 versus 94 p=0.335 p for trend 0.404, Low Benton Visual Retention (%): 65 versus 91 versus 92 p=0.059 p for trend 0.022	
Formiga, 2018, Spain [79]	Substudy from the OCTABAIX project, General population (substudy of a prospective population-based study of community dwelling older inhabitants), **N=75**, 85 y, 46.7%	AF,pacemaker rhythm, the presence of a severe cognitive impairment MEC<10, functional dependence Barthel Index<30	IAB	MEC (Spanish version of the Mini-Mental State Examination)	MEC>23 (%) in those with IAB versus those without IAB: 100% versus 70.6%, p=0.004	2/8
Rabuñal-Rey, 2012,	99-year-old and older patients living in the		Resting 12-lead ECG	The cognition mini-exam	% in those with CME≥ versus those with CME<20:	2/8

Study, year, country	Population, N, Age (mean/median), males (%), Follow-up	Exclude	Type of ECG, ECG findings	Outcome, Diagnosis criteria	Effect size (95% confidence interval)	Quality
Spain [80]	Lugo area (Galicia, northwest Spain), **N=80**, 100.8±1.3 y		Various findings according to Minnesota code (Arrhythmias: (premature supraventricular, junctional or ventricular beats, AF, other arrhythmias), QRS axis deviation (left-axis deviation, right-axis deviation, extreme axis deviation), high amplitude R waves (left ventricular hypertrophy), AV conduction defect (second-degree AB block, First-degree AV block), Ventricular conduction defect (left bundle branch block, right bundle branch block, right bundle branch block incomplete, left bundle branch block incomplete, nonspecific intraventricular conduction delay), Repolarization abnormalities (ST depression, T	(CME) (Spanish version of the Folstein Mini-mental State Exam) (cognitive impairment CME<20)	QRS axis: 26.1% versus 36.8% p=0.357, High amplitude R waves: 8.7% versus 8.8% p=0.999, AV conduction defect: 8.7% versus 12.3% p=0.999, Ventricular conduction defect: 26.1% versus 35.1% p=0.437, Repolarization abnormalities: 21.7% versus 35.1% p=0.244, ST depression: 8.7% versus 26.3% p=0.130, T amplitude zero, negative or diphasic: 17.4% versus 24.6% p=0.487, Q and QS patterns: 13.0% versus 17.5%, p=0.747 Miscellaneous items: 17.4% versus 40.4%, p=0.068	

Study, year, country	Population, N, Age (mean/median), males (%), Follow-up	Exclude	Type of ECG, ECG findings	Outcome, Diagnosis criteria	Effect size (95% confidence interval)	Quality
			amplitude zero, negative or diphasic, other repolarization)			

*Cross-sectional study.

AD, Alzheimer's disease; DLB, dementia with Lewy bodies; IAB, interatrial block; IQR, interquartile range; LVH, left ventricular hypertrophy; MCI, mild cognitive impairment; MI, myocardial infarction; QTc, corrected heart rate values of QT interval; QTcD, QT dispersion

Supplementary Table 3. A summary of appropriately adjusted disease-based studies

Study, year, country	Population, N, Age (mean/median), males (%), Follow-up	Type of ECG, ECG findings	Outcome, Diagnosis criteria	Effect size (95% confidence interval)	Adjustment	Quality
Outcome: dementia						
Buss, 2012, India [81]	Patients with dementia and controls, N=305, 68.4±6.4 y, 52.8%	Resting 12-lead ECG, LVH, ST and T abnormalities, Q waves, Bundle branch block	All dementia, AD, VaD Diagnosis criteria not mentioned	Dementia in participants with LVH: All dementia OR: **4.53 (1.52, 13.51),** AD OR: 0.89 (0.10, 8.25), VaD OR: **11.74 (3.15, 43.71)** Dementia in participants with ST and T abnormalities All dementia OR: 2.03 (0.82, 5.00) AD OR: 1.00 (0.25, 3.96) VaD OR:**3.06 (1.06, 8.85)** Dementia in participants with Bundle branch block: All dementia OR: 1.14 (0.21, 6.21) AD OR: 1.26 (0.14, 11.25) VaD OR: 0.98 (0.10, 9.16)	Age, sex, education	3/8
Cacciatore, 2012, Italy [82]	Patients with cognitive impairment recruited at university hospital, N=358, 73.7±7.1 y, 40.5%, 10 y	24-h ECG, Ventricular rate response (binary): moderate (>50/<90 bpm), low/ high (<50/>90)	Incident dementia, Dementia: DSM-4, AD: the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association VaD: the California Alzheimer's Disease Diagnostic and Treatment Centers	Incident dementia in participants with ventricular rate response low/high: HR: **2.40 (1.10, 5.20)**	Age, sex, heart rate (beats per minute), pulse blood pressure, number of concomitant diseases, number of drugs taken, administration of warfarin or aspirin, CHF, diabetes, CAD, the geriatric depression scale, the Basic Activities of Daily Living Index, social support	7/9

Study, year, country	Population, N, Age (mean/median), males (%), Follow-up	Type of ECG, ECG findings	Outcome, Diagnosis criteria	Effect size (95% confidence interval)	Adjustment	Quality
Outcome: cognitive decline						
Van der Veen, 2015, The Netherlands [83]	Second Manifestations of Arterial Disease–Magnetic Resonance (SMART-MR) study Patients newly referred to the hospital with manifest coronary artery disease, cerebrovascular disease, peripheral arterial disease or an abdominal aortic aneurysm, N=663, 57±9 y, 81%, Mean 3.9 y	Resting 12-lead ECG LVH (Yes/No) Sokolow–Lyon criterion: S in V1 + (R in V5 or V6, whichever is larger) ≥3.5 mV and/or Cornell voltage criterion: S in V3 + R in aVL >2.8 mV (in men), >2.0 mV (in women)	Change in memory and executive function tests. The composite score for memory performance included immediate recall, delayed recall, and retention score of the 15-word learning test and the delayed recall of the Rey-Osterrieth Complex Figure test. The composite score for executive functioning included the Visual Elevator test, the Brixton Spatial Anticipation test, and the Verbal Fluency test (letter N for baseline and letter A for follow-up, 1-minutetime frame).	Additional change in cognitive functioning in patients with LVH Change in memory: Model1 -0.00 (-0.19, 0.18) Model2 -0.00 (-0.19, 0.18) Model3 -0.01 (-0.20, 0.18) Change in executive functioning: Model1 0.03 (-0.20, 0.26) Model2 0.02 (-0.21, 0.25) Model3 0.00 (-0.23, 0.23)	Model 1: Age, sex, educational level, Dutch version of the National Adult Reading test score, baseline memory or executive functioning z-score, and follow-up time; Model 2: additionally adjusted for systolic and diastolic BP and use of antihypertensives; Model 3: additionally adjusted for cardiovascular risk factors (BMI, alcohol use, smoking, hyperlipidemia, diabetes mellitus).	5/9

AD, Alzheimer's disease; BMI, body mass index; BP, blood pressure; CAD, coronary arterial disease; CHF, chronic heart failure; HR, hazard ratio; IAB, interatrial block; LVH, left ventricular hypertrophy; OR, odds ratio; VaD, vascular dementia

REFERENCES

[1] Barba R, Martinez-Espinosa S, Rodriguez-Garcia E, Pondal M, Vivancos J, Del Ser T (2000) Poststroke dementia - Clinical features and risk factors. *Stroke* **31**, 1494-1501.

[2] Bart B, Larina V, Runikhina N (2012) Cognitive functioning in hypertensive postmenopausal women. *Maturitas* **71**, S35.

[3] Bucht G, Adolfsson R, Winblad B (1984) Dementia of the Alzheimer type and multi-infarct dementia: a clinical description and diagnostic problems. *J Am Geriatr Soc* **32**, 491-498.

[4] Charles S, Verhgese J (2014) The association between objective cardiac markers and cerebrovascular lesions in patients with dementia. *J Am Geriatr Soc* **62**, S284.

[5] Charles SH, Tow AC, Verghese J (2014) Objective cardiac markers and cerebrovascular lesions in Indian seniors. *J Epidemiol Glob Health* **4**, 245-247.

[6] Chen LY, Lopez F, Gottesman R, Huxley R, Agarwal SK, Loehr L, Mosley T, Alonso A (2011) Atrial fibrillation is associated with higher risk of dementia and post-dementia hospitalization mortality in individuals without stroke: the atherosclerosis risk in communities (ARIC) study. *Circulation* **124 (Suppl 21)**, Abstract 8684

[7] Chen LY, Agarwal SK, Lopez FL, Gottesman RF, Loehr LR, Soliman EZ, Mosley TH, Folsom AR, Coresh J, Alonso A (2014) Higher burden of atrial fibrillation is independently associated with lower cognitive function: The atherosclerosis risk in communities (ARIC) study. *Circulation* **130 (Suppl 2)**, Abstract 12946.

[8] Chen LY, Agarwal SK, Lopez FL, Gottesman RF, Loehr LR, Soliman EZ, Mosley TH, Folsom AR, Coresh J, Alonso A (2014) Nonsustained ventricular tachycardia is independently associated with lower cognitive executive function: The atherosclerosis risk in communities (ARIC) study. *Circulation* **130 (Suppl 2)**, Abstract 12962.

[9] Chen LY, Lopez FL, Gottesman RF, Wruck LM, Mosley TH, Soliman EZ, Agarwal SK, Loehr LR, Folsom AR, Coresh J, Alonso A (2015) Atrial fibrillation and its association with cognitive decline over 20 years: The atherosclerosis risk in communities neurocognitive study (ARIC-NCS). *Heart Rhythm* **12**, S30.

[10] Chen LY, Norby FL, Gottesman RF, Mosley TH, Folsom AR, Kamel H, Soliman EZ, Alonso A (2016) Left atrial abnormality is associated with greater cognitive decline independent of atrial fibrillation: The atherosclerosis risk in communities neurocognitive study (ARIC-NCS). *Circulation* **134 (Suppl 1)**, Abstract 16711.

[11] Chen LY, Norby FL, Gottesman RF, Mosley TH, Konety SH, Cogswell RJ, Shah AM, Solomon SD, Alonso A (2016) Left atrial enlargement is associated with lower

cognitive function independent of atrial fibrillation: the atherosclerosis risk in communities neurocognitive study (ARIC-NCS). *Heart Rhythm* **13**, S331-S332.

[12] Chen LY, Norby FL, Gottesman RF, Mosley TH, Soliman EZ, Agarwal SK, Loehr LR, Folsom AR, Coresh J, Alonso A (2018) Association of atrial fibrillation with cognitive decline and dementia over 20 years: The ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study). *J Am Heart Assoc* **7**, e007301.

[13] Chumakova G, Demenko TN, Gritzenko OV (2014) Cognitive and psychosomatic impairments in patients with different forms of atrial fibrillation. *Eur Heart J* **35**, 440.

[14] de Leeuw FE, de Groot JC, Oudkerk M, Kors JA, Hofman A, van Gijn J, Breteler MM (2000) Atrial fibrillation and the risk of cerebral white matter lesions. *Neurology* **54**, 1795-1801.

[15] Deme SM, Jianu CD, Nanu PD, Kory-Calomfirescu ST (2009) The correlations between Type 2 Diabetes mellitus, cerebral stroke, coronary heart disease and cognitive status. *Cerebrovasc Dis* **27**, 217.

[16] Diaconu N, Grosu A, Gratii C, Racila V, Pavlic G (2013) Chronic atrial fibrillation is a risk factor for cognitive impairment? *Europace* **15**, ii19.

[17] Ding M, Fratiglioni L, Johnell K, Marengoni A, Ljungman P, Qiu C (2017) Atrial fibrillation, cognitive decline, and dementia among older people: A longitudinal population-based study. *Alzheimers Dement* **13**, P238.

[18] Ding M, Fratiglioni L, Johnell K, Santoni G, Fastbom J, Ljungman P, Marengoni A, Qiu C (2018) Atrial fibrillation, antithrombotic treatment, and cognitive aging: A population-based study. *Neurology* **91**, e1732-e1740.

[19] Evstigneeva AJU, Razin VA, Krestjyaninov MV (2015) Cognitive disorders in patients with ST-elevation myocardial infarction. *Eur Heart J* **4**, 188-189.

[20] Falsetti L, Viticchi G, Buratti L, Grigioni F, Capucci A, Silvestrini M (2018) Interactions between atrial fibrillation, cardiovascular risk factors, and ApoE genotype in promoting cognitive decline in patients with Alzheimer's disease: a prospective cohort study. *J Alzheimers Dis* **62**, 713-725.

[21] Galluzzi S, Nicosia F, Geroldi C, Alicandri A, Bonetti M, Romanelli G, Zulli R, Frisoni GB (2009) Cardiac autonomic dysfunction is associated with white matter lesions in patients with mild cognitive impairment. *J Gerontol A Biol Sci Med Sci* **64**, 1312-1315.

[22] Georgakis MK, Synetos A, Mihas C, Karalexi MA, Tousoulis D, Seshadri S, Petridou ET (2017) Left ventricular hypertrophy in association with cognitive impairment: a systematic review and meta-analysis. *Hypertens Res* **40**, 696-709.

[23] Geroldi C, Ferrucci L, Bandinelli S, Cavazzini C, Zanetti O, Guralnik JM, Frisoni GB (2003) Mild cognitive deterioration with subcortical features: prevalence, clinical characteristics, and association with cardiovascular risk factors in community-dwelling older persons (The InCHIANTI Study). *J Am Geriatr Soc* **51**, 1064-1071.

[24] Gu SZ, Beska B, Chan D, Neely D, Batty JA, Adams-Hall J, Mossop H, Qiu W, Kunadian V (2019) Cognitive decline in older patients with non-ST elevation acute coronary syndrome. *J Am Heart Assoc* **8**, e011218.

[25] Halling A, Berglund J (2006) Association of diagnosis of ischaemic heart disease, diabetes mellitus and heart failure with cognitive function in the elderly population. *Eur J Gen Pract* **12**, 114-119.

[26] Horstmann S, Rizos T, Rauch G, Fuchs M, Arden C, Veltkamp R (2014) Atrial fibrillation and prestroke cognitive impairment in stroke. *J Neurol* **261**, 546-553.

[27] Ikram MA, van Oijen M, de Jong FJ, Kors JA, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM (2008) Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. *Stroke* **39**, 1421-1426.

[28] Jackson JD, Gibbons LE, Thacker E, Suemoto CK, Satizabal CL, Bettcher BM, Mez J, White LR, Power MC (2018) Midlife incident prolonged rate-corrected QT interval does not predict late-life cognitive performance: The Honolulu-Asia Aging Study. *Alzheimers Dement* **14**, P1500.

[29] Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, DeCarli C (2004) Stroke risk profile predicts white matter hyperintensity volume - The Framingham Study. *Stroke* **35**, 1857-1861.

[30] Jin Kang H, Shin Yoon Y, Eun Kim J, Ko S, Young Yeom J, Duk Park K, Gyu Choi K, Jeong JH (2009) The association between vascular risk factors and korean Alzheimer's disease patients. *Alzheimers Dement* **5**, 388-389.

[31] Jozwiak A, Guzik P, Mathew A, Wykretowicz A, Wysocki H (2006) Association of atrial fibrillation and focal neurologic deficits with impaired cognitive function in hospitalized patients >= 65 years of age. *Am J Cardiol* **98**, 1238-1241.

[32] Kawabata-Yoshihara LA, Scazufca M, Santos Ide S, Whitaker A, Kawabata VS, Benseñor IM, Menezes PR, Lotufo PA (2012) Atrial fibrillation and dementia: results from the Sao Paulo ageing & health study. *Arq Bras Cardiol* **99**, 1108-1114.

[33] Kim MS, Yoon JH, Hong JM (2018) Early differentiation of dementia with Lewy bodies and Alzheimer's disease: Heart rate variability at mild cognitive impairment stage. *Clin Neurophysiol* **129**, 1570-1578.

[34] Lee JK, Chen YH, Lin MS, Kao HL (2012) Heart rate variability change predicts neurocognitive improvement after carotid artery stenting in patients with chronic internal carotid artery occlusion. *Eur Heart J* **33**, 244.

[35] Lima-Costa MF, Castro-Costa E, Uchôa E, Firmo J, Ribeiro AL, Ferri CP, Prince M (2009) A population-based study of the association between Trypanosoma cruzi infection and cognitive impairment in old age (the Bambuí Study). *Neuroepidemiology* **32**, 122-128.

[36] Lin F, Heffner KL, Ren P, Tadin D (2017) A role of the parasympathetic nervous system in cognitive training. *Curr Alzheimer Res* **14**, 784-789.

[37] Mahinrad S, Jukema JW, van Heemst D, Macfarlane PW, Clark EN, de Craen AJ, Sabayan B (2016) 10-Second heart rate variability and cognitive function in old age. *Neurology* **86**, 1120-1127.

[38] Mahinrad S, Van Heemst D, Macfarlane PW, Stott DJ, Jukema JW, De Craen AJM, Sabayan B (2015) Short-term heart rate variability and cognitive function in older subjects at risk of cardiovascular disease. *J Hypertens* **33**, e57.

[39] Mahringer C, Lunglmayr M, Boeck C, Ransmayr G, Struhal W (2018) PDQI-an ECG modulation quality index for the assessment of the autonomic nervous system in dementia patients. *Clin Autonom Res* **28**, 260.

[40] Mahringer C, Lunglmayr M, Boeck C, Ransmayr G, Struhal W (2018) PDQI-an ECG quality index for autonomic nervous system evaluation by heart rate variability analysis in dementia patients. *Clin Autonom Res* **28**, 449.

[41] Matei D, Constantinescu V, Corciova C, Popescu CD (2015) QT interval in patients with ischemic stroke with or without cognitive impairment. *Eur Psychiatry* **30**, 593.

[42] Matei D, Corciova C, Matei R, Constantinescu I, Cuciureanu ID, Ieee (2015) QT interval in vascular dementia and Alzheimer's disease. In *2015 E-Health and Bioengineering Conference*.

[43] McNicholas T, Tobin K, Carey D, Claffey P, Kenny RA (2018) Atrial fibrillation and cognition at four year follow up - Data from the Irish Longitudinal Study on Ageing (TILDA). *Age and Ageing* **47 (Suppl 5)**, v13–v60,

[44] Nadkarni NK, Perera S, Barinas-Mitchell E, Klunk W, Lopez O, Dekosky S, Kuller L (2019) Relationship between gait speed, arterial and cardiac stiffness, and cerebral

amyloid-β deposition and cerebral blood flow in cognitively normal older adults. *J Am Geriatr Soc* **67**, S94.

[45] Norby FL, Chen LY, Soliman EZ, Gottesman RF, Mosley TH, Alonso A (2017) Left ventricular hypertrophy is associated with incident dementia: The atherosclerosis risk in communities-neurocognitive study. *Circulation* **135 (Suppl 1)**, Abstract P016.

[46] Norby FL, Alonso A, Rooney MR, Maheshwari A, Koene RJ, Zhang M, Soliman EZ, Loehr LR, Mosley TH, Coresh J, Chen LY (2018) The association of nonsustained ventricular tachycardia with dementia and mild cognitive impairment: The Atherosclerosis Risk in Communities Study. *Circulation* **138 (Suppl 1)**, Abstract 16174.

[47] O'Connell JE, Gray CS, French JM, Robertson IH (1998) Atrial fibrillation and cognitive function: case-control study. *J Neurol Neurosurg Psychiatry* **65**, 386-389.

[48] Ott A, Breteler MM, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A (1997) Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke* **28**, 316-321.

[49] Pal T, German-Sallo M, Preg Z, Szentendrey D, Tripon RG, Nemes-Nagy E (2019) Atrial fibrillation causes cognitive impairment-which cognitive domains are affected? *Eur Heart J* **40**, 3530.

[50] Podea DM, Chenderes RM, Nanu PD, Mila C (2010) Atrial fibrillation and the risk for conversion from mild cognitive impairment to dementia in subjects aged over 65. *Eur Psychiatry* **25**, 1501.

[51] Puccio D, Novo G, Baiamonte V, Nuccio A, Fazio G, Corrado E, Coppola G, Muratori I, Vernuccio L, Novo S (2009) Atrial fibrillation and mild cognitive impairment: what correlation? *Minerva Cardioangiol* **57**, 143-150.

[52] Räihä I, Tarvonen S, Kurki T, Rajala T, Sourander L (1993) Relationship between vascular factors and white matter low attenuation of the brain. *Acta Neurol Scand* **87**, 286-289.

[53] Rastas S, Verkkoniemi A, Polvikoski T, Juva K, Niinistö L, Mattila K, Länsimies E, Pirttilä T, Sulkava R (2007) Atrial fibrillation, stroke, and cognition: a longitudinal population-based study of people aged 85 and older. *Stroke* **38**, 1454-1460.

[54] Rooney MR, Norby FL, Koene RJ, Maheshwari A, Lutsey PL, Soliman EZ, Loehr LR, Mosley TH, Coresh J, Alonso A, Chen LY (2017) Excessive supraventricular ectopic activity and cognitive function: The atherosclerosis risk in communities (ARIC) study. *Circulation* **136 (Suppl 1)**, Abstract 16492.

[55] Rooney MR, Norby FL, Koene RJ, Maheshwari A, Lutsey PL, Soliman EZ, Loehr LR, Mosley TH, Coresh J, Alonso A, Chen LY (2018) Frequent premature atrial contractions are associated with higher prevalence of dementia and mild cognitive impairment: The atherosclerosis risk in communities (ARIC) study. *Circulation* **138 (Suppl 1)**, Abstract 12601.

[56] Rydén L, Skoog I (2017) Atrial fibrillation and incidence dementia among older adults: A population-based study. *Alzheimers Dement* **13**, P238-P239.

[57] Rydén L, Skoog I (2017) Atrial fibrillation and incidence of dementia among older adults: A population-based study. *Alzheimers Dement* **13**, P517.

[58] Rydén L, Zettergren A, Seidu NM, Guo X, Kern S, Blennow K, Zetterberg H, Sacuiu S, Skoog I (2019) Atrial fibrillation increases the risk of dementia amongst older adults even in the absence of stroke. *J Intern Med* **286**, 101-110.

[59] Sabatini T, Frisoni GB, Barbisoni P, Bellelli G, Rozzini R, Trabucchi M (2000) Atrial fibrillation and cognitive disorders in older people. *J Am Geriatr Soc* **48**, 387-390.

[60] Shiohama N, Shinomiya S, Nagaoka M (1993) Clinical features of anterior bradyrhythmia. *Clin Electroencephalogr* **24**, 194-201.

[61] Taranchuk VV, Plenova ON (2011) Arterial hypertension, atrial fibrillation and cognitive function. *Europace* **13**.

[62] Thacker EL, McKnight B, Psaty BM, Longstreth WT, Jr., Sitlani CM, Dublin S, Arnold AM, Fitzpatrick AL, Gottesman RF, Heckbert SR (2013) Atrial fibrillation and cognitive decline: a longitudinal cohort study. *Neurology* **81**, 119-125.

[63] Thacker EL, McKnight B, Psaty BM, Longstreth WT, Sitlani CM, Arnold AM, Fitzpatrick AL, Dublin S, Gottesman RF, Heckbert SR (2012) Atrial fibrillation and cognitive decline: The cardiovascular health study. *Circulation* **125 (Suppl 10)**, Abstract 022.

[64] Todoroki K, Ikeya Y, Fukui S, Yanagimachi N, Okazaki T, Tanaka C, Tanaka E, Shizuma T, Fukuyama N, Mori H (2015) Severity of white matter hyperintensities in older adults aged in their mid 80s and its relationship with hemodynamic and cardiac parameters. *Geriatr Gerontol Int* **15 Suppl 1**, 66-73.

[65] Weinstein G, Davis-Plourde K, Beiser AS, Seshadri S (2019) Autonomic balance indices and risk of dementia: The Framingham Study. *Alzheimers Dement* **15**, P1524.

[66] Wozakowska-Kapłon B, Opolski G, Kosior D, Jaskulska-Niedziela E, Maroszyńska-Dmoch E, Włosowicz M (2009) Cognitive disorders in elderly patients with permanent atrial fibrillation. *Kardiol Pol* **67**, 487-493.

[67] Yaneva-Sirakova T, Tarnovska-Kadreva R, Traykov L, Vassilev D, Vladimirova L, Shumkova M, Gruev I (2016) Left ventricular hypertrophy and mild cognitive impairment as markers for target organ damage in hypertensive patients with multiple risk factors. *Eur Heart J Cardiovasc Imaging* **17**, ii232.

[68] Young K, Abbott R, Petrovitch H, Chen R, White L, Ross G, Launer L, Bell C, Masaki K (2010) Resting heart rate and cognitive function: The Honolulu-Asia aging study. *J Am Geriatr Soc* **58**, S65.

[69] Zhang MJ, Norby F, Lutsey P, Gottesman R, Mosley TH, Cogswell R, Konety S, Chao TF, Shah A, Solomon S, Alonso A, Chen LY (2019) Association of atrial fibrillation and left atrial enlargement with cognitive function and decline: The atherosclerosis risk in communities neurocognitive study. *Circulation* **140 (Suppl 1)**, Abstract 9609.

[70] Zhang MJ, Norby FL, Lutsey PL, Mosley TH, Cogswell RJ, Konety SH, Chao TF, Shah AM, Solomon SD, Alonso A, Chen LY (2019) Association of left atrial enlargement and atrial fibrillation with cognitive function and decline: The ARIC-NCS. *J Am Heart Assoc* **8**, e013197.

[71] De Pedis G, Hedner K, Johansson BW, Steen B (1987) Cardiac arrhythmia in geriatric patients with organic dementia. *Compr Gerontol A* **1**, 115-117.

[72] Sanna GD, Nusdeo G, Piras MR, Forteleoni A, Murru MR, Saba PS, Dore S, Sotgiu G, Parodi G, Ganau A (2019) Cardiac abnormalities in Alzheimer disease: clinical relevance beyond pathophysiological rationale and instrumental findings? *JACC Heart Fail* **7**, 121-128.

[73] Sonnesyn H, Nilsen DW, Rongve A, Nore S, Ballard C, Tysnes OB, Aarsland D (2009) High prevalence of orthostatic hypotension in mild dementia. *Dement Geriatr Cogn Disord* **28**, 307-313.

[74] Zulli R, Nicosia F, Borroni B, Agosti C, Prometti P, Donati P, De Vecchi M, Romanelli G, Grassi V, Padovani A (2005) QT dispersion and heart rate variability abnormalities in Alzheimer's disease and in mild cognitive impairment. *J Am Geriatr Soc* **53**, 2135-2139.

[75] Zulli R, Nicosia F, Borroni B, Agosti C, Prometti P, Donati P, De Vecchi M, Turini D, Romanelli G, Grassi V, Padovani A (2008) Increased prevalence of silent myocardial ischaemia and severe ventricular arrhythmias in untreated patients with Alzheimer's disease and mild cognitive impairment without overt coronary artery disease. *Clin Neurol Neurosurg* **110**, 791-796.

[76] Katzman R, Aronson M, Fuld P, Kawas C, Brown T, Morgenstern H, Frishman W, Gidez L, Eder H, Ooi WL (1989) Development of dementing illnesses in an 80-year-old volunteer cohort. *Ann Neurol* **25**, 317-324.

[77] Bernal E, Bayés-Genís A, Ariza-Solé A, Formiga F, Vidán MT, Escobar-Robledo LA, Aboal J, Alcoberro L, Guerrero C, Ariza-Segovia I, Hernández de Benito A, Vilardell P, Sánchez-Salado JC, Lorente V, Bayés de Luna A, Martinez-Sellés M (2018) Interatrial block, frailty and prognosis in elderly patients with myocardial infarction. *J Electrocardiol* **51**, 1-7.

[78] Elmståhl S, Furuäng L (2009) Ambulatory recorded ST segment depression on ECG is associated with lower cognitive function in healthy elderly men. *Int J Gen Med* **2**, 145-151.

[79] Formiga F, Guerrero C, Ferrer A, Padros G, Ariza A (2018) Prevalence and clinical significance of interatrial block in very older persons. *Eur Geriatr Med* **9**, 155-159.

[80] Rabuñal-Rey R, Monte-Secades R, Gomez-Gigirey A, Pértega-Díaz S, Testa-Fernández A, Pita-Fernández S, Casariego-Vales E (2012) Electrocardiographic abnormalities in centenarians: impact on survival. *BMC Geriatr* **12**, 15.

[81] Buss S, Noone ML, Tsai R, Johnson B, Pradeep VG, Salam KA, Mathuranath PS, Verghese J (2013) Objective cardiac markers in dementia: results from the Kerala-Einstein study. *Int J Cardiol* **167**, 595-596.

[82] Cacciatore F, Testa G, Langellotto A, Galizia G, Della-Morte D, Gargiulo G, Bevilacqua A, Del Genio MT, Canonico V, Rengo F, Abete P (2012) Role of ventricular rate response on dementia in cognitively impaired elderly subjects with atrial fibrillation: a 10-year study. *Dement Geriatr Cogn Disord* **34**, 143-148.

[83] van der Veen PH, Geerlings MI, Visseren FL, Nathoe HM, Mali WP, van der Graaf Y, Muller M (2015) Hypertensive target organ damage and longitudinal changes in brain structure and function: the second manifestations of Arterial Disease-Magnetic Resonance Study. *Hypertension* **66**, 1152-1158.