BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045896
Article Type:	Original research
Date Submitted by the Author:	15-Oct-2020
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Keywords:	Heart failure < CARDIOLOGY, PREVENTIVE MEDICINE, Delirium & cognitive disorders < PSYCHIATRY

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Associations of subclinical heart failure and atrial fibrillation with mild cognitive impairment: Implications for screening

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Short title; Cognition in subclinical HF and AF

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Word count: Abstract 266; text 3228

Abstract

Objectives. Effective identification and management of subclinical left ventricular dysfunction (LVD) and subclinical atrial fibrillation (AF) by screening elderly populations might be compromised by mild cognitive impairment (MCI). We sought to characterize the prevalence and profile of MCI and evaluate associations with LV and left atrial dysfunction and AF, in a trial of screening for subclinical LVD and AF.

Design. Cross-sectional.

Setting. Australian, community-based intervention trial.

Participants. Adults aged ≥ 65 years with ≥ 1 non-ischaemic LVD risk factors (n=337).

Outcome measures. The Montreal cognitive assessment (MoCA) was obtained Subclinical LVD was defined as echocardiographic global longitudinal strain (GLS) ≤16%, diastolic dysfunction or left ventricular hypertrophy; abnormal left atrial reservoir strain (LARS) was defined as <24%. Subclinical AF was detected using a single-lead portable electrocardiographic device in those without pre-existing AF who gave consent (n=293).

Results. Subclinical LVD was found in 155 (46%), abnormal LARS in 9 (3.6%) and subclinical AF in 11 (3.8%). MoCA score consistent with MCI (<26) was found in 101 (30%); executive function (69%) and delayed recall (93%), were the most frequently abnormal domains. Compared with normal cognition, MCI was associated with non-adherence to AF screening (25% vs 40%, p=0.01). In multivariable logistic regression modelling, educational achievement, systolic blood pressure, body mass index and waist-to-hip ratio were independently associated with MCI. However, neither subclinical AF nor any measure of cardiac dysfunction, were associated with MCI.

Conclusions. The 30% prevalence of MCI among elderly subjects with risk factors for subclinical LVD and AF has important implications for screening strategies and management. However, MCI is not associated with subclinical myocardial dysfunction nor subclinical AF.

Article summary

Strengths and limitations of this study

- A community-based study representative of a cardiovascular screening population.
- A validated and easily applied cognitive assessment was used.
- The most sensitive measures of left ventricular and atrial function were evaluated.
- A longitudinal design would have provided additional insights into impact of subclinical left ventricular dysfunction and subclinical atrial fibrillation on incident cognitive impairment.
- Brain MRI may have provided mechanistic insight.

Keywords: Subclinical left ventricular dysfunction, subclinical atrial fibrillation, cognitive impairment

Introduction

Mild cognitive impairment (MCI) describes test-based evidence of cognitive impairment without significant compromise to independent functioning (1). It is a prelude to dementia - a major contributor to mortality and morbidity in our ageing population (2). Heart failure (HF) and atrial fibrillation (AF) increase risk of cognitive impairment (CI) (3,4), with between 54% and 74% of HF patients affected (5). Furthermore, MCI in HF compromises self-management and leads to worse outcomes (6). Early detection and prevention of HF and AF may consequently serve to reduce the burden of MCI. Trials evaluating screening for subclinical left ventricular dysfunction (LVD) and AF, should incorporate cognitive assessment, not only to inform future screening and prevention strategies but to elucidate clinical associations and mechanisms.

Cognitive impairment in symptomatic HF is largely attributed to cerebral hypoperfusion resulting from low cardiac output (7). While this is unlikely to play a significant role in subclinical HF other factors may predominate. Vascular risk factors, particularly hypertension, predispose to cerebral small-vessel disease, lacunar infarcts and compromise auto-regulatory responses that maintain cerebral perfusion (5). Limited data suggest subclinical LVD is independently associated with MCI (8), suggesting a direct causal relationship. In addition, reduced systolic function assessed by global longitudinal strain (GLS) has been associated with silent cerebral infarcts, independent of vascular risk factors (9). Left atrial (LA) enlargement has been linked with MCI but this does not appear independent of AF, particularly in longitudinal analyses (10). AF may exert its effect on cognitive function via silent cerebral infarcts, presumably due to cardiogenic embolism. What is not known is the impact of subclinical AF or LA function on cognition.

Should screening programs for subclinical HF and AF be advocated, the cognitive status of the target population must be quantified to inform effective program design and

implementation. Furthermore, the presence of an independent link between subclinical LV and LA dysfunction, subclinical AF, and cognitive impairment remains unclear. Accordingly, assessment of cognitive function was undertaken at baseline in participants enrolled in the Victorian Study of Echocardiographic detection of Subclinical Left Ventricular Dysfunction (Vic-ELF) to establish a) prevalence and profile of MCI in this population and b) identify associations between MCI and left ventricular (LV) function, LA function and subclinical AF.

Methods

Study population. All subjects were participants in the Victorian Study of Echocardiographic detection of Subclinical Left Ventricular Dysfunction (Vic-ELF; ACTRN:12617000116325). Baseline data were used for this cross-sectional sub-study. Subjects were recruited from the community via primary care and advertising. Those who were asymptomatic and ≥ 65 years with hypertension (self-reported, on medication or systolic blood pressure (SBP) ≥140/90mm Hg), type II diabetes mellitus or obesity (BMI ≥ 30kg/m^2) were eligible for inclusion. Those with a history or symptoms of HF or ischaemic heart disease (based on existing clinical indication for echocardiography), LV ejection fraction ≤40%, > moderate valvular disease or oncologic life expectancy <1 year were excluded. The study was approved by a Human Research Ethics Committee (Bellberry, HREC number 2016-10-727) and all participants gave written informed consent.

Patient and public involvement. Patients were not involved in study design and no evaluation of patient involvement burden was undertaken. All participants will receive information regarding the impact of the research findings after study conclusion.

Clinical assessment. Comprehensive medical and medication history were taken along with clinical examination. Heart rate, resting averaged blood pressures, body mass index (BMI), waist and hip circumference and serum N-terminal pro-brain natriuretic peptide (NT-proBNP)

were recorded along with a six-minute walk test to assess functional capacity, in accordance with standard procedure (11). Patient–reported functional capacity was assessed using the Duke activity score index (DASI). Health-related quality of life, depression and anxiety were evaluated with the EQ-5D-5L, generalized anxiety disorder 7-item scale (GAD-7) and the patient health questionnaire-9 (PHQ-9), respectively. Habitual physical activity was measured (n=201) using waist-worn accelerometers (ActiLife, ActiGraph, Pensacola, FL) for 7 days. Recordings of less than 4 days were excluded, leaving a total of 190 suitable for analysis.

Cognitive assessment. The MoCA was conducted in accordance with instructions (12). In brief the MoCA is a short (10-12 minutes) office-based assessment that evaluates the cognitive domains of executive and visuospatial function; attention, concentration and working memory; short term memory, language skills and orientation. It is validated in ages 55-85 years and is the preferred screening tool for mild cognitive impairment (13). MCI is diagnosed by a score of <26/30. Graded severity levels of 18-25, 10-17 and <10, are suggested for mild, moderate and severe CI respectively, although supportive data are lacking. Therefore, all cognitive impairment will be referred to as MCI. A deficit in a domain is defined herein as ≥1 point deficit in that domain. MoCA result was unknown to the investigator (SR) evaluating subclinical AF and atrial function.

Echocardiography. Resting 2D and Doppler echocardiography was performed with standard equipment (ACUSON SC2000, Siemens Healthcare USA, Mountain View, CA) and transducer (4V1c, 1.25 to 4.5 MHz; 4Z1c, 1.5 to 3.5 MHz) in accordance with guidelines (14). A vector-velocity imaging algorithm (Syngo VVI, Siemens Medical Solutions, Siemens Healthcare USA, Mountain View, CA) was used for GLS quantification and averaged from apical, 2-, 3- and 4-chamber views. Diastolic function was assessed by measuring mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, septal and lateral mitral annular early diastolic velocities (e') and E/e' ratio. Biplane method of disks (Simpson's

modified rule) was used for left atrial volume quantification and indexed to body surface area (LAVI). Diastolic dysfunction was diagnosed using current recommendations (15). Left ventricular mass (LVM) was calculated using the 2D linear method and indexed to body surface area. LVH was defined as LVMI (LVM indexed to body surface area) 95 g/m^2 in women, 115 g/m^2 in men. Subclinical LVD was defined as presence of GLS ≤16%, DD or LVH.

LA reservoir strain (LARS) was assessed by speckle-tracking using a third-party software program (TomTec-Arena™ (Version TTA2), Tomtec, Munich, Germany). Apical four and two chamber images were selected with a frame rate of 60-80 frames/sec. The endocardial border of the LA was manually traced, and strain analysis performed using the LV strain algorithm, with the average of both the four- and two-chamber values. The reference point for image analysis was taken at the onset of the QRS complex (R-R gating). Abnormal LARS was defined as <24 %.

Atrial fibrillation screening and echocardiographic risk markers for AF. Participants without a history of atrial fibrillation or flutter were asked to provide separate consent (n=293). Screening for subclinical AF was performed using a portable, single-lead ECG device (Remon RM-100; Semacare, Beijing, China) using three finger contact electrodes. Recordings lasted 60-seconds and were undertaken 3 times per day for 2 weeks (i.e. 42 recordings). Instructions were given verbally face-to-face and in written form. Battery failure, device malfunction or problems relating to dexterity were recorded. ECG recordings were exported as PDF files for interpretation, and all were assessed by a physician. The presence of AF was defined as an irregular rhythm of ≥30 sec with a variable R-R interval and absent P waves.

A stepwise risk stratification tool for atrial fibrillation using GLS, LAVI and LA reservoir strain (LARS) has been devised (16). GLS >14.3% determines low risk; GLS <14.3% and LAVI >39ml/m^2 determines high risk; GLS <14.3% and LAVI ≤39ml/m^2 determines

intermediate risk, which can be reclassified to intermediate-high if LARS <33.9%. Participants were dichotomised by low/intermediate or high (including intermediate-high) risk based on these criteria. Association between this risk assessment with MCI was assessed individually and combined with detected subclinical AF i.e. a group combining those at high risk of subclinical AF plus those with detected subclinical AF.

Statistical analysis. Continuous variables are presented as median with interquartile ranges (IQR) or mean ± standard deviation, based on distribution testing using the Shapiro-Wilk test. Categorical variables are presented as frequencies and percentages. Differences between two independent groups were determined using χ^2 and unpaired Student's t-test for categorical and continuous variables, respectively. Variables with a p-value <0.1 in univariable analysis were selected for inclusion in multivariable logistic regression modelling. Effect sizes are expressed as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as a two-tailed p-value <0.05. Analyses were conducted using STATA 15.1 (StataCorp, College Station, TX).

Results

Of the 337 subjects (age 70 years (68-73), 58% female), 292 (87%) had hypertension with a median duration of 13 years, 108 (32%) had type 2 diabetes mellitus with a median duration of 8 years and 214 (64%) were obese (Table 1). The majority (65%) were dyslipidaemic, a significant proportion were current or ex-smokers (45%) and a small proportion had a history of stroke or transient ischaemic attack (6%) and alcohol abuse (7%). On average, the group spent 66% of waking time sedentary with levels of moderate to physical activity (MVPA) falling well below guideline recommendations. Serum NT-proBNP was, on average, in the low risk range i.e. <125pg/ml (51pg/ml (30-100)).

With regards cognitive assessment by MoCA, 101 (30%) exhibited MCI with an overall average MoCA score of 27 (25-29). Of the 101 participants with MCI, severity staging showed none with severe CI and only 3 with moderate CI thus the majority had MCI corresponding to a MoCA score between 18 and 25. Overall, delayed recall and executive function had the highest proportion of deficits (237 (70%) and 145 (43%), respectively (Table 2). There were no differences in the proportion of cognitive domain deficits between those with and without subclinical LVD (Table 1), except for orientation, although only 2% of participants had deficits in this domain.

Those with MCI were less obese and reported significantly fewer years of formal education (Table 1). There was a non-significant trend towards higher blood pressure and longer duration of a diagnosis of hypertension and type II diabetes. The proportion with at least moderate anxiety or depression did not differ by presence of MCI, and while on average functional capacity by 6MWT and minutes per week of MVPA were less in those with MCI, neither were statistically significant (Table 1). Overall, 155 (46%) had subclinical LVD. Echocardiographic markers of systolic and diastolic LV function did not differ by presence of MCI (Table 3). However, LVMI was significantly higher in those with MCI compared to normal cognition (75g/m^2 (60-84) vs. 67g/m^2 (55-79), p=0.04, respectively), although this did not translate into a greater proportion of those with MCI having LVH (7 (7%) vs. 13 (5.5%), p=0.62, respectively). LA function measured by LARS was abnormal (<24%) in 9 (3.6%) with a mean value of 36.2±7%. LARS did not differ by presence of MCI, nor did the proportion of those with abnormal LARS (Table 3).

Subclinical AF was detected in 11 (3.8%) of the 293 screened. Subclinical AF was equally incident in those with and without MCI, as was pre-existing AF (Table 1). In those with pre-existing AF, only 13 (57%) were taking an anticoagulant. By echocardiographic AF risk stratification, 9 (2.7%) were deemed high risk and again there was no association with

MCI (Table 1). However, after instances of battery/device malfunction were excluded (n=10), MCI was significantly associated with a reduced number of recordings (<30 recordings), 51 (25%) and 33 (40%) for no MCI and MCI, respectively, p=0.01. Therefore, in those undergoing AF screening with a hand-held device a 12% (33/283) rate of non-adherence, related to MCI, was observed.

In univariable logistic regression modelling, prior cerebrovascular accident (CVA), education duration, SBP, BMI and waist-to-hip ratio (WHR) were associated with MCI, (p<0.1) (Table 4). No echocardiographic markers of LV or LA function, nor presence of atrial fibrillation showed an association. In multivariable analysis, MCI was independently associated with higher SBP (OR 1.02 (1.00-1.04), p=0.03) and WHR (OR 40 (2.3-708), p=0.01), while greater numbers of years in formal education (0.9 (0.86-0.98), p=0.01) and higher BMI (0.9 (0.85-0.95), p<0.001) were independently associated with normal cognition.

Discussion

Up to 30% of individuals included in a screening program for subclinical LVD and AF had MCI, manifest most commonly as executive dysfunction, and poor recall of recently delivered information. This is more prevalent than in unselected people aged >65 years, among whom the prevalence of MCI is 3-19% (17). The higher prevalence in our population supports the notion that MCI can be expected in people at risk of HF and AF. This is consistent with evidence that CV risk factors compromise executive function, which is especially true for hypertension – even at subclinical levels (18).

For the first time, associations were sought between sensitive deformation markers of LV and LA function (strain) and none were found, nor did we find evidence that subclinical AF or high AF risk was associated with MCI, although the number of subjects concerned was low. However, consistent with existing data, lower educational achievement, higher systolic

blood pressure and visceral adiposity, but lower BMI were independently associated with MCI (19,20) (Figure 1).

Cognition and cardiac disease. There is contemporary focus on cognitive dysfunction in the setting of cardiac diseases, principally HF and AF. Cognitive impairment, specifically vascular cognitive impairment shares well documented risk factors with HF and AF. Exposure to hypertension, diabetes, smoking and abdominal obesity in mid-life is associated with an accelerated decline in executive function a decade later. This is coupled with magnetic resonance imaging (MRI) evidence of cerebral vascular damage and atrophy (20).

Symptomatic heart failure is independently associated cognitive impairment, although data with robust adjustment for shared risk factors is sparse. Nevertheless, the impact is significant, with most recent estimates of incidence being around 30% over 3.5 years (21), with cerebral hypoperfusion and subclinical cardiogenic emboli likely mechanisms (22). Population studies demonstrate conflicting results regarding associations between LV function and cognition. Cross-sectional data from the Framingham Heart Study found a U-shaped relationship between LVEF quintiles and cognition with the extremes displaying worse cognitive performance (memory and executive function) (23). Conversely, longitudinal data from the Netherlands demonstrated that LAVI but not LVEF at baseline was associated with lower performances in attention and executive function at follow-up (24). Furthermore, another cross-sectional population study found lower systolic function, assessed by tissue Doppler early systolic peak velocity, was not associated with poor cognitive performance but was associated with lower total brain volume (25). With regards LA size, several studies have demonstrated an association between greater LA size and cognitive impairment by global assessment or specific domain testing (6,24,25). However, adjustment for atrial fibrillation is inconsistent and recent evidence suggests the association is not independent of known AF (10).

Less is known about the link between cardiac dysfunction and cognition in asymptomatic patients. In patients with chronic heart disease (e.g. coronary disease) but without symptomatic HF, diastolic filling pressure estimated by E/e', was associated with significantly higher odds of MCI after comprehensive adjustment for clinical factors, although effect size was small (OR 1.07, 1.01-1.13, p=0.022) (8). This finding did not extend to LVMI, LAVI or stroke volume index (8). In a population without symptomatic cardiac or cerebrovascular disease, those with silent cerebral infarcts (SCIs) on MRI had significantly lower systolic function, as assessed by GLS (26). Moreover, GLS in those with SCIs was in the abnormal range.

Atrial fibrillation is associated with a 42% increase in risk of dementia, independent of age and cardiovascular risk factors (4,27). Interestingly, this association appears strongest in those <70 years with data suggesting no association > 67 years, presumably due to the influence of neurodegenerative pathophysiology (27,28). This is significant given the median age in our study was 70 years. The most prominent mechanism behind the association between AF and cognitive impairment is SCIs, the presence of which determine cognitive decline associated with AF, and conversely those with AF without SCIs do not exhibit cognitive decline (29). However, no study has examined the distribution of SCIs preventing inference about the pathophysiologic mechanism i.e. small vessel versus embolic disease. Anticoagulation in AF is associated with up to a 60% reduction in cognitive decline and incident dementia, supporting a cardioembolic mechanism (30). Neuroimaging would have strengthened our study and revealed whether those with AF were free of SCIs thus potentially explaining the lack of association with MCI.

Clinical implications. Clinicians involved in management of patient with CV risk factors must be alert to the significant proportion of patients who will have MCI – affecting their ability to recall medical information and self-manage aspects of their condition. Indeed, those with MCI

progress to dementia at a rate of over 50% in 5 years (17). Our data highlight that even in the early stages of cognitive compromise modifiable risk factors i.e. systolic hypertension and abdominal obesity are contributors, and it may be argued that cognitive screening be undertaken routinely in this scenario. We did not find evidence of an association between certain echocardiographic measures, even sensitive markers of LV and LA function. So, based on these data, echocardiographic abnormality alone should not prompt cognitive evaluation.

In terms of HF prevention, while management of subclinical disease largely rests on risk factor control, the onus is on the patient to recognize the often-insidious transition to a symptomatic state. Current ACC/AHA HF management guidelines suggest that patients with subclinical HF undertake self-surveillance for symptoms and our data highlight one of the problems with this approach i.e. the potential for under-recognition due to cognitive impairment. While screening for subclinical LVD is not currently advocated, it is plausible that early institution of therapy may preserve cognition if progression to symptomatic HF is delayed or prevented. Indeed, anticoagulation for AF, whether permanent or paroxysmal, is associated with a significant reduction in cognitive impairment (30), an observation that could extend to subclinical AF detected by screening.

One of the primary objectives of this study was to assess the prevalence of MCI and therefore the consequences to delivery of screening programs for HF and AF. This study population may have been subject to selection bias given they had sufficient cognition to apply for the trial, meaning the true prevalence is likely higher. However, for those with established dementia, prevention of HF or AF is not their primary care goal. Population-based screening for dementia or MCI is not presently advocated, however a novel proposal may be that HF/AF screening be used as a platform for cognitive screening given the high yield in this cohort. Our data suggest that strategies to optimize engagement and follow-up with a HF/AF screening program should be considered. For example, engagement of services beyond the screening

program and consideration given to the impact of reduced cognition and health literacy. When cognition is compromised, close relatives can assist with health literacy to promote use of health services. Our finding of a 12% rate of non-adherence to self-initiated AF screening, that related to MCI, is also of importance in considering the mode of delivery of AF screening. Technologies like monitoring patches or smartwatches may be more effective than devices that participants are required to operate.

Limitations. The study would have been strengthened by a longitudinal design, to additionally assess impact on incident MCI. While our sample size was not based on calculation, it is comparable to other studies in specific populations. As mentioned previously, brain MRI would have provided additional mechanistic insights. Our method of assessment for MCI was chosen both for its speed and validity. However, use of more detailed tests for individual cognitive domains may have added more depth to our results and made comparisons with other studies easier. Indeed, variation in the literature surrounding CV disease and cognition may be largely due to inconsistencies in methods. Finally, it should be borne in mind that while a significant proportion of subjects exhibited subclinical LVD, the number with reduced atrial function and/or subclinical AF was low, limiting the certainty of our observations.

Conclusion. Elderly subjects enrolled in a trial screening for subclinical LVD and AF exhibited a 30% prevalence of MCI. There was no association between sensitive measures of LV and LA function nor subclinical AF and presence of MCI.

Author contributions. ELP and THM contributed to the conception and design of the work. All authors contributed to the acquisition and interpretation of data. ELP analysed the data and drafted the manuscript. SR and LW critically revised the manuscript. THM obtained funding for the study and critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding. The work was partially supported by a Partnership grant (1149692) from the National Health and Medical Research Council, Canberra, the Ian Potter Foundation, Melbourne, and the Baker Heart and Diabetes Institute. Dr Potter is supported by a Monash University postgraduate scholarship.

Competing interests. None declared.

Patient consent for publication. Not required.

Data availability statement. Data available upon reasonable request.

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Table 1: Clinical, anthropometric, functional, and physical activity measures by presence or absence of mild cognitive impairment (MCI).

	All (n=337)	No MCI (n=236)	MCI (n=101)	p-value
Age, yrs (IQR)	70 (68-73)	70 (68-73)	70 (67-73)	0.83
Gender, female (%)	194 (58)	140 (59)	54 (54)	0.32
Hypertension (%)	292 (87)	201 (85)	91 (90.1)	0.22
Hypertension duration, years (IQR)	13 (7-20)	12 (7-20)	15 (7-20)	0.56
Type II Diabetes (%)	108 (32)	72 (31)	36 (36)	0.36
Diabetes duration, years (IQR)	8 (5-15)	7 (4.5-12.5)	10 (5-18)	0.1
Obesity (%)	214 (64)	158 (68)	56 (56)	0.04
Dyslipidaemia (%)	208 (62)	145 (62)	63 (62)	0.9
Ever smoker (%)	152 (45)	110 (47)	42 (42)	0.34
AF, known (%)	23 (7)	14 (6)	9 (9)	0.32
AF, detected by screening* (%)	11 (4)	8 (4)	3 (4)	0.88
High risk for AF† (%)	9 (3)	8 (3)	1 (1)	0.21
Stroke/TIA	21 (6)	11 (5)	10 (10)	0.07
Alcohol abuse (%)	25 (7)	21 (9)	4 (4)	0.12
ACE-I/ARB (%)	264 (78)	183 (78)	81 (80)	0.59
Beta blocker (%)	37 (11)	22 (9)	15 (15)	0.14
Statin (%)	179 (53)	123 (52)	56 (55)	0.58
Antiplatelet agent (%)	68 (20)	43 (18)	25 (25)	0.17
Anticoagulant (%)	16 (5)	10 (4)	6 (6)	0.5
Education, years (IQR)	12 (10-15)	12 (10-15)	11 (10-14)	0.02
PHQ9 >6 (moderate depression)	27 (8)	20 (8.5)	7 (6.9)	0.63
GAD7 >6 (moderate anxiety)	26 (8)	19 (8)	7 (6.9)	0.72
EQ-5D-L score (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	0.77
Systolic BP, mm Hg (IQR)	138 (131-150)	137 (129-149)	141 (133-151)	0.07
Diastolic BP, mm Hg (IQR)	83 (78-90)	83 (77-89)	85 (79-91)	0.09
BMI, kg/m^2 (IQR)	31 (28-35)	32 (28-36)	30 (27-33)	0.002
Waist-hip ratio (SD)	0.93 (0.09)	0.92 (0.09)	0.94 (0.09)	0.07
Duke activity score index (IQR)	51.7 (46.7-52.7)	52 (49.5-52.7)	50.7 (46-52.7)	0.39
Six-minute walk test, m (IQR)	441 (403-476)	445 (403-477)	438 (405-472)	0.49
MVPA, minutes/week (IQR)	63 (18-144)	65 (18-135)	48 (17-152)	0.89
Sedentary time, % (SD)	66 (10)	67 (10)	64 (9)	0.15
NT-proBNP, pg/ml (IQR)	51 (30-100)	55 (31-101)	49 (24-95)	0.34

* total screened = 293, †echocardiographic criteria

TIA – transient ischaemic attack, ACE-I/ARB – angiotensin converting enzyme inhibitor/receptor blocker, BP – blood pressure, BMI – body mass index, MVPA – moderate-vigorous physical activity, NT-proBNP – N terminal pro-brain natriuretic peptide.

Table 2: Mild cognitive impairment (MCI) and deficits in individual cognitive domains according to presence or absence of subclinical left ventricular dysfunction (LVD). P-value for comparison of normal LV function vs. subclinical LVD.

	Overall (n=337)	MCI (n=101)	Normal LV function (n=175)	Subclinical LVD (n=162)	p-value
MCI (MoCA <26)	101 (30)		52 (29.7)	49 (30.2)	0.9
Moderate CI (MoCA <18)	3 (3)		2 (4)	1 (2)	0.7
Executive and visuospatial (%)	145 (43)	70 (69)	75 (43)	70 (43)	0.9
Naming (%)	15 (4.5)	9 (9)	6 (3.4)	9 (5.6)	0.34
Attention (%)	5 (1.5)	5 (5)	4 (2.3)	1 (0.62)	0.21
Language (%)	124 (37)	69 (68)	70 (40)	54 (33)	0.2
Abstraction (%)	88 (26)	61 (60)	50 (29)	38 (23)	0.29
Delayed recall (%)	237 (70)	94 (93)	121 (69)	116 (72)	0.62
Orientation (%)	7 (2)	6 (6)	7 (4)	0 (0)	0.01

Table 3: Echocardiographic variables by presence or absence of mild cognitive impairment (MCI)

	No MCI (n=236)	MCI (n=101)	p-value
LV ejection fraction, % (SD)	62 (6.8)	62 (5.8)	0.7
GLS, % (IQR)	18.7 (17-20)	18.7 (17-20)	0.87
EA, (IQR)	0.8 (0.68-0.95)	0.82 (0.69-0.99)	0.63
e', cm/s (IQR)	7.5 (6.3-8.9)	7.5 (6.5-8.7)	0.67
E/e' (IQR)	8.2 (6.9-10.2)	8.7 (7.2-11)	0.32
LAVI, ml/m^2 (IQR)	34 (28-40)	33 (29-42)	0.56
LA reservoir strain*, % (SD)	36.2 (7)	36.1 (7)	0.9
LARS <24%* (%)	7 (4)	2 (3)	0.61
Relative wall thickness (IQR)	0.37 (0.34-0.43)	0.39 (0.33-0.43)	0.96
LV mass indexed, g/m^2 (IQR)	67 (55-79)	75 (60-84)	0.04
Subclinical LV dysfunction (%)	113 (48)	49 (48.5)	0.9
Systolic dysfunction (GLS≤16%)	42 (18)	13 (13)	0.26
Diastolic dysfunction (%)	54 (23)	26 (26)	0.54
LV hypertrophy (%)	13 (5.5)	7 (7)	0.62

*available in 248 participants

LV – left ventricular, GLS – global longitudinal strain, LAVI – left atrial volume indexed to body surface area, LARS – left atrial reservoir strain

Table 4: Logistic regression modelling for prediction of mild cognitive impairment (abbreviations as per tables 1 and 3)

	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years	1.00 (0.95-1.06)	0.88		
Female gender	0.8 (0.49-1.26)	0.32		
Hypertension	1.58 (0.75-3.33)	0.23		
Hypertension duration	1.00 (0.97-1.03)	0.76		
Type II diabetes	1.26 (0.77-2.06)	0.36		
Diabetes duration	1.03 (0.98-1.09)	0.22		
Dyslipidaemia	1.03 (0.63-1.66)	0.9		
Ever smoker	0.88 (0.23-3.44)	0.86		
Stroke/TIA	2.2 (0.87-5.6)	0.09	2.5 (0.93-6.8)	0.07
AF (known)	1.54 (0.65-3.69)	0.33		
AF (detected or high risk)	0.63 (0.2-1.96)	0.43		
Education, years	0.92 (0.86-0.98)	0.02	0.9 (0.86-0.98)	0.011
Depression (PHQ9 >6), %	0.8 (0.32-2)	0.6		
Anxiety (GAD7 >6), %	0.85 (0.33-2.1)	0.72		
ACE-I/ARB	1.17 (0.65-2)	0.59		
Beta blocker	1.7 (0.84-3.4)	0.14		
Statin	1.14 (0.7-1.8)	0.58		
Antiplatelet	1.47 (0.84-2.59)	0.17		
Anticoagulant	1.43 (0.5-4)	0.5		
Systolic BP, mm Hg	1.02 (0.99-1.03)	0.07	1.02 (1.00-1.04)	0.03
Diastolic BP, mm Hg	1.02 (0.99-1.04)	0.2		
BMI, kg/m^2	0.93 (0.88-0.97)	0.001	0.9 (0.85-0.95)	<0.001
Waist-hip ratio	11 (0.8-161)	0.07	40 (2.3-708)	0.01
NT-proBNP, pg/ml	0.99 (0.99-1.00)	0.7		
MVPA, hr/week	0.99 (0.99-1.00)	0.98		
Sedentary time, %	0.98 (0.94-1.01)	0.15		
Echocardiographic classifications				
Subclinical LV dysfunction	1.03 (0.64-1.63)	0.9		
Systolic dysfunction (GLS ≤16%)	0.68 (0.35-1.33)	0.26		
Diastolic dysfunction	1.18 (0.69-2)	0.54		
LV hypertrophy	1.27 (0.49-3.3)	0.62		
Echocardiographic continuous measures				
LV ejection fraction, %	0.99 (0.95-1.03)	0.7		
GLS, %	1.01 (0.92-1.11)	0.82		
e', cm/s	0.96 (0.84-1.09)	0.57		
E/e'	1.03 (0.94-1.12)	0.4		
LAVI ml/m^2	1 (0.98-1.03)	0.56		
LA reservoir strain, %	0.98 (0.96-1.04)	0.91		
LARS <24%	0.66 (0.13-3.27)	0.61		

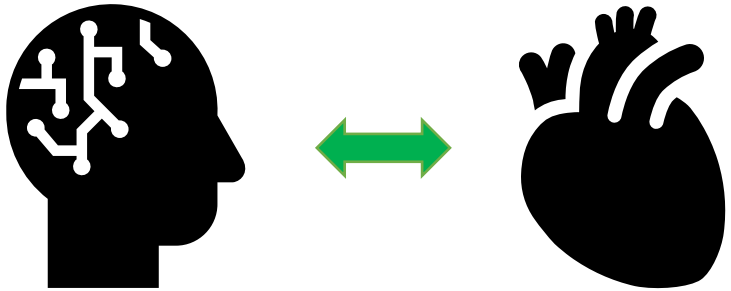
LV mass indexed, g/m²	1.00 (0.99-1.02)	0.13

Figure legends:

Figure 1: Summary of study findings.

ELDERLY WITH RISK FACTORS FOR LEFT VENTRICULAR DYSFUNCTION AND ATRIAL FIBRILLATION UNDERGOING SCREENING

30% prevalence of **mild cognitive impairment**



Implications for screening

- 1.6 x more likely to be non-adherent to hand-held AF screening
- Consideration of strategies to optimise engagement e.g. wearables, family involvement

Associations with clinical factors and cardiac function

- No association with **subclinical AF**
- No association with **LV global longitudinal strain** or **diastolic parameters**
- No association **with left atrial reservoir strain**
- Systolic blood pressure, educational attainment, body mass index and abdominal adiposity are independently associated

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	5
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5-7

Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	14
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6,7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	NA
Statistical methods	#12c	Explain how missing data were addressed	NA
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	NA
Statistical methods	#12e	Describe any sensitivity analyses	NA
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	8,9
Participants	#13b	Give reasons for non-participation at each stage	NA

Participants	#13c	Consider use of a flow diagram	NA
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	9
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
Main results	#16b	Report category boundaries when continuous variables were categorized	NA
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13-14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

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Associations of Subclinical Heart Failure and Atrial Fibrillation with Mild Cognitive Impairment: A Cross-Sectional Study in a Subclinical Heart Failure Screening Program

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-045896.R1
Article Type:	Original research
Date Submitted by the Author:	03-Mar-2021
Complete List of Authors:	Potter, Elizabeth ; Baker Heart and Diabetes Institute; Monash University School of Public Health and Preventive Medicine Ramkumar, Satish; Baker Heart and Diabetes Institute; Monash University School of Public Health and Preventive Medicine Wright, Leah; Baker Heart and Diabetes Institute Marwick, Tom; Baker Heart and Diabetes Institute; Monash University School of Public Health and Preventive Medicine
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Geriatric medicine
Keywords:	Heart failure < CARDIOLOGY, PREVENTIVE MEDICINE, Delirium & cognitive disorders < PSYCHIATRY

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Associations of Subclinical Heart Failure and Atrial Fibrillation with Mild Cognitive Impairment: A Cross-Sectional Study in a Subclinical Heart Failure Screening Program

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Short title; Cognition in subclinical HF and AF

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Word count: Abstract 266; text 3228

Abstract

Objectives. Effective identification and management of subclinical left ventricular dysfunction (LVD) and subclinical atrial fibrillation (AF) by screening elderly populations might be compromised by mild cognitive impairment (MCI). We sought to characterize the prevalence and profile of MCI and evaluate associations with LV and left atrial dysfunction and AF, in a trial of screening for subclinical LVD and AF.

Design. Cross-sectional.

Setting. Australian, community-based intervention trial.

Participants. Adults aged ≥ 65 years with ≥ 1 LVD risk factors without ischaemic heart disease (n=337).

Outcome measures. The Montreal cognitive assessment (MoCA) was obtained Subclinical LVD was defined as echocardiographic global longitudinal strain (GLS) ≤16%, diastolic dysfunction or left ventricular hypertrophy; abnormal left atrial reservoir strain (LARS) was defined as <24%. Subclinical AF was detected using a single-lead portable electrocardiographic device in those without pre-existing AF who gave consent (n=293).

Results. Subclinical LVD was found in 155 (46%), abnormal LARS in 9 (3.6%) and subclinical AF in 11 (3.8%). MoCA score consistent with MCI (<26) was found in 101 (30%); executive function (69%) and delayed recall (93%), were the most frequently abnormal domains. Compared with normal cognition, MCI was associated with non-adherence to AF screening (25% vs 40%, p=0.01). In multivariable logistic regression modelling, educational achievement, systolic blood pressure, body mass index and waist-to-hip ratio were independently associated with MCI. However, neither subclinical AF nor any measure of cardiac dysfunction, were associated with MCI.

Conclusions. The 30% prevalence of MCI among elderly subjects with risk factors for subclinical LVD and AF has important implications for screening strategies and management. However, MCI is not associated with subclinical myocardial dysfunction nor subclinical AF.

Article summary

Strengths and limitations of this study

- A community-based study representative of a cardiovascular screening population.
- A validated and easily applied cognitive assessment was used.
- The most sensitive measures of left ventricular and atrial function were evaluated.
- A longitudinal design would have provided additional insights into impact of subclinical left ventricular dysfunction and subclinical atrial fibrillation on incident cognitive impairment.
- Brain MRI may have provided mechanistic insight.

Keywords: Subclinical left ventricular dysfunction, subclinical atrial fibrillation, cognitive impairment

Introduction

Mild cognitive impairment (MCI) describes objective evidence of cognitive impairment without significant compromise to independent functioning (1). It is a prelude to dementia - a major contributor to mortality and morbidity in our ageing population (2). Heart failure (HF) and atrial fibrillation (AF) increase risk of cognitive impairment (CI) (3,4), with between 54% and 74% of HF patients affected (5). Furthermore, MCI in HF compromises self-management and leads to worse outcomes (6). Early detection and prevention of HF and AF may consequently serve to reduce the burden of MCI. Trials evaluating screening for subclinical left ventricular dysfunction (LVD) and AF, should incorporate cognitive assessment, not only to inform future screening and prevention strategies but to elucidate clinical associations and mechanisms.

Cognitive impairment in HF is associated with medial temporal lobe atrophy and lower cerebral grey matter volume on neuroimaging (7,8), changes that are more marked compared with those with risk factors but without HF. Whether this is the case in the subclinical phase of HF failure i.e., LVD without HF symptoms, is uncertain. Limited data suggest subclinical LVD is independently associated with MCI (9). In addition, reduced systolic function assessed by global longitudinal strain (GLS) has been associated with silent cerebral infarcts, independent of vascular risk factors (10). Left atrial (LA) enlargement has been linked with MCI but this does not appear independent of AF, particularly in longitudinal analyses (11). AF may exert its effect on cognitive function via silent cerebral infarcts, presumably due to cardiogenic embolism. The impact of subclinical AF (asymptomatic AF, unrecognised without screening) or LA function on cognition are unknown.

Should screening programs for subclinical HF and AF be advocated, the cognitive status of the target population must be quantified to inform effective program design and implementation. Furthermore, the presence of an independent link between subclinical LV and

LA dysfunction, subclinical AF, and cognitive impairment remains unclear. Accordingly, assessment of cognitive function was undertaken at baseline in participants enrolled in the Victorian Study of Echocardiographic detection of Subclinical Left Ventricular Dysfunction (Vic-ELF) to establish a) prevalence and profile of MCI in this population and b) identify associations between MCI and left ventricular (LV) function, LA function and subclinical AF.

Methods

Study population. All subjects were participants in the Victorian Study of Echocardiographic detection of Subclinical Left Ventricular Dysfunction (Vic-ELF; ACTRN:12617000116325). Baseline data were used for this cross-sectional sub-study. Subjects were recruited from the community via primary care and advertising. Those who were asymptomatic and ≥ 65 years with hypertension (self-reported, on medication or systolic blood pressure (SBP) ≥140/90mm Hg), type II diabetes mellitus or obesity (BMI ≥ 30kg/m^2) were eligible for inclusion. Those with a history or symptoms of HF or ischaemic heart disease (based on existing clinical indication for echocardiography), LV ejection fraction ≤40%, > moderate valvular disease or oncologic life expectancy <1 year were excluded. The study was approved by a Human Research Ethics Committee (Bellberry, HREC number 2016-10-727) and all participants gave written informed consent.

Patient and public involvement. Patients were not involved in study design and no evaluation of patient involvement burden was undertaken. All participants will receive information regarding the impact of the research findings after study conclusion.

Clinical assessment. Comprehensive medical and medication history were taken along with clinical examination. Heart rate, resting averaged blood pressures, body mass index (BMI), waist and hip circumference and serum N-terminal pro-brain natriuretic peptide (NT-proBNP) were recorded along with a six-minute walk test to assess functional capacity, in accordance

with standard procedure (12). Patient–reported functional capacity was assessed using the Duke activity score index (DASI), which has shown good correlation with peak oxygen uptake, and is readily expressed in metabolic equivalents (METS), a metric familiar to most cardiologists. Health-related quality of life, depression and anxiety were evaluated with the EQ-5D-5L, generalized anxiety disorder 7-item scale (GAD-7) and the patient health questionnaire-9 (PHQ-9), respectively. Habitual physical activity was measured (n=201) using waist-worn accelerometers (ActiLife, ActiGraph, Pensacola, FL) for 7 days. Recordings of less than 4 days were excluded, leaving a total of 190 suitable for analysis.

Cognitive assessment. The MoCA was conducted in accordance with instructions (13). In brief the MoCA is a short (10-12 minutes) office-based assessment that evaluates the cognitive domains of executive and visuospatial function; attention, concentration and working memory; short term memory, language skills and orientation (supplemental material). It is validated in ages 55-85 years and is the preferred screening tool for mild cognitive impairment (14). MCI is diagnosed by a score of <26/30. Graded severity levels of 18-25, 10-17 and <10, are suggested for mild, moderate and severe CI respectively, although supportive data are lacking. Therefore, all cognitive impairment will be referred to as MCI. A deficit in a domain is defined herein as ≥1 point loss in that domain. MoCA result was unknown to the investigator (SR) evaluating subclinical AF and atrial function.

Echocardiography. Resting 2D and Doppler echocardiography was performed with standard equipment (ACUSON SC2000, Siemens Healthcare USA, Mountain View, CA) and transducer (4V1c, 1.25 to 4.5 MHz; 4Z1c, 1.5 to 3.5 MHz) in accordance with guidelines (15). A vector-velocity imaging algorithm (Syngo VVI, Siemens Medical Solutions, Siemens Healthcare USA, Mountain View, CA) was used for GLS quantification and averaged from apical, 2-, 3- and 4-chamber views. Diastolic function was assessed by measuring mitral inflow peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, septal and lateral

mitral annular early diastolic velocities (e') and E/e' ratio. Biplane method of disks (Simpson's modified rule) was used for left atrial volume quantification and indexed to body surface area (LAVI). Diastolic dysfunction was diagnosed using current recommendations (16). Left ventricular mass (LVM) was calculated using the 2D linear method and indexed to body surface area. LVH was defined as LVMI (LVM indexed to body surface area) 95 g/m^2 in women, 115 g/m^2 in men. Subclinical LVD was defined as presence of GLS ≤16%, DD or LVH.

LA reservoir strain (LARS) measures passive LA stretch during LA filling and is associated with diastolic dysfunction grade, may improve diastolic assessment and is independently predicts incident HF (17-19). LARS was assessed by speckle-tracking using a third-party software program (TomTec-Arena™ (Version TTA2), Tomtec, Munich, Germany). Apical four and two chamber images were selected with a frame rate of 60-80 frames/sec. The endocardial border of the LA was manually traced, and strain analysis performed using the LV strain algorithm, with the average of both the four- and two-chamber values. The reference point for image analysis was taken at the onset of the QRS complex (R-R gating). Abnormal LARS was defined as <24 %.

Atrial fibrillation screening and echocardiographic risk markers for AF. Participants without a history of atrial fibrillation or flutter were asked to provide separate consent (n=293). Screening for subclinical AF was performed using a portable, single-lead ECG device (Remon RM-100; Semacare, Beijing, China) using three finger contact electrodes. Recordings lasted 60-seconds and were undertaken 3 times per day for 2 weeks (i.e. 42 recordings). Instructions were given verbally face-to-face and in written form. Battery failure, device malfunction or problems relating to dexterity were recorded. ECG recordings were exported as PDF files for interpretation, and all were assessed by a physician. The presence of AF was defined as a

continuous episode of an irregular rhythm ≥30 sec with a variable R-R interval and absent P waves.

A stepwise risk stratification tool for atrial fibrillation using GLS, LAVI and LA reservoir strain (LARS) has been devised (20). GLS >14.3% determines low risk; GLS <14.3% and LAVI >39ml/m^2 determines high risk; GLS <14.3% and LAVI ≤39ml/m^2 determines intermediate risk, which can be reclassified to intermediate-high if LARS <33.9%. Participants were dichotomised by low/intermediate or high (including intermediate-high) risk based on these criteria. Association between this risk assessment with MCI was assessed individually and combined with detected subclinical AF i.e. a group combining those at high risk of subclinical AF plus those with detected subclinical AF.

Statistical analysis. Continuous variables are presented as median with interquartile ranges (IQR) or mean ± standard deviation, based on distribution testing using the Shapiro-Wilk test. Categorical variables are presented as frequencies and percentages. Differences between two independent groups were determined using χ^2 and unpaired Student's t-test for categorical and continuous variables, respectively. Variables with a p-value <0.1 in univariable analysis were selected for inclusion in multivariable logistic regression modelling. Effect sizes are expressed as odds ratios (OR) with 95% confidence intervals (CI). Statistical significance was defined as a two-tailed p-value <0.05. Analyses were conducted using STATA 15.1 (StataCorp, College Station, TX).

Results

Participant characteristics. Of the 337 subjects (age 70 years (IQR 68-73), 58% female), 292 (87%) had hypertension with a median duration of 13 years, 108 (32%) had type 2 diabetes mellitus with a median duration of 8 years and 214 (64%) were obese (Table 1). The majority (65%) were dyslipidaemic, a significant proportion were current or ex-smokers (45%) and a

small proportion had a history of stroke or transient ischaemic attack (6%) and alcohol abuse (7%). On average, the group spent 66% of waking time sedentary with levels of moderate to physical activity (MVPA) falling well below guideline recommendations. Serum NT-proBNP was, on average, in the low-risk range i.e. <125pg/ml (51pg/ml (IQR 30-100)).

Characteristics of cognitive impairment and relation to LV function. With regards cognitive assessment by MoCA, 101 (30%) exhibited MCI with an overall average MoCA score of 27 (IQR 25-29). Of the 101 participants with MCI, severity staging showed none with severe CI and only 3 with moderate CI thus the majority had MCI corresponding to a MoCA score between 18 and 25. Overall, delayed recall and executive function had the highest proportion of deficits (237 (70%) and 145 (43%), respectively (Table 2). There were no differences in the proportion of cognitive domain deficits between those with and without subclinical LVD (Table 1), except for orientation, although only 2% of participants had deficits in this domain.

Subclinical AF screening and cognitive impairment. Of the 293 screened, there were 10 instances of device malfunction leaving 283 for analysis. Subclinical AF was detected in 11 (3.9%). Subclinical AF was equally incident in those with and without MCI, as was pre-existing AF (Table 1). In those with pre-existing AF, only 13 (57%) were taking an anticoagulant. By echocardiographic AF risk stratification, 9 (2.7%) were deemed high risk and again there was no association with MCI (Table 1). MCI was significantly associated with a reduced number of recordings (<30 recordings), 51 (25%) and 33 (40%) for no MCI and MCI, respectively, p=0.01. Therefore, in those undergoing AF screening with a hand-held device a 12% (33/283) rate of non-adherence, related to MCI, was observed.

Clinical and echocardiographic associations with cognitive impairment. Those with MCI were less obese and reported significantly fewer years of formal education (Table 1). There was a non-significant trend towards higher blood pressure and longer duration of a diagnosis

of hypertension and type II diabetes. The proportion with at least moderate anxiety or depression did not differ by presence of MCI, and while on average functional capacity by 6MWT and minutes per week of MVPA were less in those with MCI, neither were statistically significant (Table 1). Overall, 155 (46%) had subclinical LVD. Echocardiographic markers of systolic and diastolic LV function did not differ by presence of MCI (Table 3). However, LVMI was significantly higher in those with MCI compared to normal cognition (75g/m^2 (IQR 60-84) vs. 67g/m^2 (IQR 55-79), p=0.04, respectively), although this did not translate into a greater proportion of those with MCI having LVH (7 (7%) vs. 13 (5.5%), p=0.62, respectively). LA function measured by LARS was abnormal (<24%) in 9 (3.6%) with a mean value of 36.2±7%. LARS did not differ by presence of MCI, nor did the proportion of those with abnormal LARS (Table 3).

In univariable logistic regression modelling, no echocardiographic markers of LV or LA function, nor presence of atrial fibrillation showed an association with MCI (Table 4). Prior cerebrovascular accident (CVA), education duration, SBP, BMI and waist-to-hip ratio (WHR) were associated with MCI, (p<0.1) (Table 4). In multivariable analysis, MCI was independently associated with higher SBP (OR 1.02 (1.00-1.04), p=0.03) and WHR (OR 40 (2.3-708), p=0.01), while greater numbers of years in formal education (0.9 (0.86-0.98), p=0.01) and higher BMI (0.9 (0.85-0.95), p<0.001) were independently associated with normal cognition.

Discussion

Up to 30% of individuals included in a screening program for subclinical LVD and AF had MCI, manifest most commonly as executive dysfunction, and poor recall of recently delivered information. This is more prevalent than in unselected people aged >65 years, among

whom the prevalence of MCI is 3-19% (21). The higher prevalence in our population supports the notion that MCI can be expected in people at risk of HF and AF. This is consistent with evidence that CV risk factors compromise executive function, which is especially true for hypertension – even at subclinical levels (22).

For the first time, associations were sought between sensitive deformation markers of LV and LA function (strain) and none were found, nor did we find evidence that subclinical AF or high AF risk was associated with MCI, although the number of subjects concerned was low. However, consistent with existing data, lower educational achievement, higher systolic blood pressure and visceral adiposity, but lower BMI were independently associated with MCI (23,24) (Figure 1). If an independent association exists between HF and cognitive impairment, then our data suggest this is not apparent in the subclinical phase of HF.

Cognition and cardiac disease. There is contemporary focus on cognitive dysfunction in the setting of cardiac diseases, principally HF and AF. Cognitive impairment, specifically vascular cognitive impairment shares well documented risk factors with HF and AF. Exposure to hypertension, diabetes, smoking and abdominal obesity in mid-life is associated with an accelerated decline in executive function a decade later. This is coupled with magnetic resonance imaging (MRI) evidence of cerebral vascular damage and atrophy (24).

Symptomatic heart failure is independently associated cognitive impairment, although data with robust adjustment for shared risk factors is sparse. Nevertheless, the impact is significant, with most recent estimates of incidence being around 30% over 3.5 years (25), with cerebral hypoperfusion and subclinical cardiogenic emboli likely mechanisms (26). Population studies demonstrate conflicting results regarding associations between LV function and cognition. Cross-sectional data from the Framingham Heart Study found a U-shaped relationship between LVEF quintiles and cognition with the extremes displaying worse

cognitive performance (memory and executive function) (27). Conversely, longitudinal data from the Netherlands demonstrated that LAVI but not LVEF at baseline was associated with lower performances in attention and executive function at follow-up (28). Furthermore, another cross-sectional population study found lower systolic function, assessed by tissue Doppler early systolic peak velocity, was not associated with poor cognitive performance but was associated with lower total brain volume (29). With regards LA size, several studies have demonstrated an association between greater LA size and cognitive impairment by global assessment or specific domain testing (6,28,29). However, adjustment for atrial fibrillation is inconsistent and recent evidence suggests the association is not independent of known AF (11).

Less is known about the link between cardiac dysfunction and cognition in asymptomatic patients. In patients with chronic heart disease (e.g. coronary disease) but without symptomatic HF, diastolic filling pressure estimated by E/e', was associated with significantly higher odds of MCI after comprehensive adjustment for clinical factors, although effect size was small (OR 1.07, 1.01-1.13, p=0.022) (9). This finding did not extend to LVMI, LAVI or stroke volume index (9). In a population without symptomatic cardiac or cerebrovascular disease, those with silent cerebral infarcts (SCIs) on MRI had significantly lower systolic function, as assessed by GLS (30). Moreover, GLS in those with SCIs was in the abnormal range.

Atrial fibrillation is associated with a 42% increase in risk of dementia, independent of age and cardiovascular risk factors (4,31). Interestingly, this association appears strongest in those <70 years with data suggesting no association > 67 years, presumably due to the influence of neurodegenerative pathophysiology (31,32). This is significant given the median age in our study was 70 years. The most prominent mechanism behind the association between AF and cognitive impairment is SCIs, the presence of which determine cognitive decline associated with AF, and conversely those with AF without SCIs do not exhibit cognitive decline (33).

However, no study has examined the distribution of SCIs preventing inference about the pathophysiologic mechanism i.e. small vessel versus embolic disease. Anticoagulation in AF is associated with up to a 60% reduction in cognitive decline and incident dementia, supporting a cardioembolic mechanism (34). Neuroimaging would have strengthened our study and revealed whether those with AF were free of SCIs thus potentially explaining the lack of association with MCI.

Clinical implications. Clinicians involved in management of patient with CV risk factors must be alert to the significant proportion of patients who will have MCI – affecting their ability to recall medical information and self-manage aspects of their condition. Indeed, those with MCI progress to dementia at a rate of over 50% in 5 years (21). Our data highlight that even in the early stages of cognitive compromise modifiable risk factors i.e. systolic hypertension and abdominal obesity are contributors, and it may be argued that cognitive screening be undertaken routinely in this scenario. We did not find evidence of an association between certain echocardiographic measures, even sensitive markers of LV and LA function. So, based on these data, echocardiographic abnormality alone should not prompt cognitive evaluation.

In terms of HF prevention, while management of subclinical disease largely rests on risk factor control, the onus is on the patient to recognize the often-insidious transition to a symptomatic state. Current ACC/AHA HF management guidelines suggest that patients with subclinical HF undertake self-surveillance for symptoms and our data highlight one of the problems with this approach i.e. the potential for under-recognition due to cognitive impairment. While screening for subclinical LVD is not currently advocated, it is plausible that early institution of therapy may preserve cognition if progression to symptomatic HF is delayed or prevented. Indeed, anticoagulation for AF, whether permanent or paroxysmal, is associated with a significant reduction in cognitive impairment (34), an observation that could extend to subclinical AF detected by screening.

One of the primary objectives of this study was to assess the prevalence of MCI and therefore the consequences to delivery of screening programs for HF and AF. This study population may have been subject to selection bias given they had sufficient cognition to apply for the trial, meaning the true prevalence is likely higher. However, for those with established dementia, prevention of HF or AF is not their primary care goal. Population-based screening for dementia or MCI is not presently advocated, however a novel proposal may be that HF/AF screening be used as a platform for cognitive screening given the high yield in this cohort. Our data suggest that strategies to optimize engagement and follow-up with a HF/AF screening program should be considered. For example, engagement of services beyond the screening program and consideration given to the impact of reduced cognition and health literacy. When cognition is compromised, close relatives can assist with health literacy to promote use of health services. Our finding of a 12% rate of non-adherence to self-initiated AF screening, that related to MCI, is also of importance in considering the mode of delivery of AF screening. Technologies like monitoring patches or smartwatches may be more effective than devices that participants are required to operate.

Limitations. The study would have been strengthened by a longitudinal design, to additionally assess impact on incident MCI. While our sample size was not based on calculation, it is comparable to other studies in specific populations. Furthermore, a larger sample size would have yielded more accurate effect sizes. As mentioned previously, brain MRI would have provided additional mechanistic insights. Our method of assessment for MCI was chosen both for its speed and validity. However, use of more detailed tests for individual cognitive domains may have added more depth to our results and made comparisons with other studies easier. Indeed, variation in the literature surrounding CV disease and cognition may be largely due to inconsistencies in methods. Finally, it should be borne in mind that while a significant

proportion of subjects exhibited subclinical LVD, the number with reduced atrial function and/or subclinical AF was low, limiting the certainty of our observations.

Conclusion. Elderly subjects enrolled in a trial screening for subclinical LVD and AF exhibited a 30% prevalence of MCI. There was no association between sensitive measures of LV and LA function nor subclinical AF and presence of MCI.

Author contributions. ELP and THM contributed to the conception and design of the work. All authors contributed to the acquisition and interpretation of data. ELP analysed the data and drafted the manuscript. SR and LW critically revised the manuscript. THM obtained funding for the study and critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Funding. The work was partially supported by a Partnership grant (1149692) from the National Health and Medical Research Council, Canberra, the Ian Potter Foundation, Melbourne, and the Baker Heart and Diabetes Institute. Dr Potter is supported by a Monash University postgraduate scholarship.

Competing interests. None declared.

Patient consent for publication. Not required.

Data availability statement. Data available upon reasonable request.

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Table 1: Clinical, anthropometric, functional, and physical activity measures by presence or absence of mild cognitive impairment (MCI).

	All (n=337)	No MCI (n=236)	MCI (n=101)	p-value
Age, yrs (IQR)	70 (68-73)	70 (68-73)	70 (67-73)	0.83
Gender, female (%)	194 (58)	140 (59)	54 (54)	0.32
Hypertension (%)	292 (87)	201 (85)	91 (90.1)	0.22
Hypertension duration, years (IQR)	13 (7-20)	12 (7-20)	15 (7-20)	0.56
Type II Diabetes (%)	108 (32)	72 (31)	36 (36)	0.36
Diabetes duration, years (IQR)	8 (5-15)	7 (4.5-12.5)	10 (5-18)	0.1
Obesity (%)	214 (64)	158 (68)	56 (56)	0.04
Dyslipidaemia (%)	208 (62)	145 (62)	63 (62)	0.9
Ever smoker (%)	152 (45)	110 (47)	42 (42)	0.34
AF, known (%)	23 (7)	14 (6)	9 (9)	0.32
AF, detected by screening* (%)	11 (4)	8 (4)	3 (4)	0.88
High risk for AF† (%)	9 (3)	8 (3)	1 (1)	0.21
Stroke/TIA	21 (6)	11 (5)	10 (10)	0.07
Alcohol abuse (%)	25 (7)	21 (9)	4 (4)	0.12
ACE-I/ARB (%)	264 (78)	183 (78)	81 (80)	0.59
Beta blocker (%)	37 (11)	22 (9)	15 (15)	0.14
Statin (%)	179 (53)	123 (52)	56 (55)	0.58
Antiplatelet agent (%)	68 (20)	43 (18)	25 (25)	0.17
Anticoagulant (%)	16 (5)	10 (4)	6 (6)	0.5
Education, years (IQR)	12 (10-15)	12 (10-15)	11 (10-14)	0.02
PHQ9 >6 (moderate depression)	27 (8)	20 (8.5)	7 (6.9)	0.63
GAD7 >6 (moderate anxiety)	26 (8)	19 (8)	7 (6.9)	0.72
EQ-5D-L score (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	0.77
Systolic BP, mm Hg (IQR)	138 (131-150)	137 (129-149)	141 (133-151)	0.07
Diastolic BP, mm Hg (IQR)	83 (78-90)	83 (77-89)	85 (79-91)	0.09
BMI, kg/m^2 (IQR)	31 (28-35)	32 (28-36)	30 (27-33)	0.002
Waist-hip ratio (SD)	0.93 (0.09)	0.92 (0.09)	0.94 (0.09)	0.07
Duke activity score index (IQR)	51.7 (46.7-52.7)	52 (49.5-52.7)	50.7 (46-52.7)	0.39
Six-minute walk test, m (IQR)	441 (403-476)	445 (403-477)	438 (405-472)	0.49
MVPA, minutes/week (IQR)	63 (18-144)	65 (18-135)	48 (17-152)	0.89
Sedentary time, % (SD)	66 (10)	67 (10)	64 (9)	0.15
NT-proBNP, pg/ml (IQR)	51 (30-100)	55 (31-101)	49 (24-95)	0.34

* total screened = 293, †echocardiographic criteria

TIA – transient ischaemic attack, ACE-I/ARB – angiotensin converting enzyme inhibitor/receptor blocker, BP – blood pressure, BMI – body mass index, MVPA – moderate-vigorous physical activity, NT-proBNP – N terminal pro-brain natriuretic peptide.

Table 2: Mild cognitive impairment (MCI) and deficits in individual cognitive domains according to presence or absence of subclinical left ventricular dysfunction (LVD). P-value for comparison of normal LV function vs. subclinical LVD.

	Overall (n=337)	MCI (n=101)	Normal LV function (n=175)	Subclinical LVD (n=162)	p-value
MCI (MoCA <26)	101 (30)		52 (29.7)	49 (30.2)	0.9
Moderate CI (MoCA <18)	3 (3)		2 (4)	1 (2)	0.7
Executive and visuospatial (%)	145 (43)	70 (69)	75 (43)	70 (43)	0.9
Naming (%)	15 (4.5)	9 (9)	6 (3.4)	9 (5.6)	0.34
Attention (%)	5 (1.5)	5 (5)	4 (2.3)	1 (0.62)	0.21
Language (%)	124 (37)	69 (68)	70 (40)	54 (33)	0.2
Abstraction (%)	88 (26)	61 (60)	50 (29)	38 (23)	0.29
Delayed recall (%)	237 (70)	94 (93)	121 (69)	116 (72)	0.62
Orientation (%)	7 (2)	6 (6)	7 (4)	0 (0)	0.01

Table 3: Echocardiographic variables by presence or absence of mild cognitive impairment (MCI)

	No MCI (n=236)	MCI (n=101)	p-value
LV ejection fraction, % (SD)	62 (6.8)	62 (5.8)	0.7
GLS, % (IQR)	18.7 (17-20)	18.7 (17-20)	0.87
EA, (IQR)	0.8 (0.68-0.95)	0.82 (0.69-0.99)	0.63
e', cm/s (IQR)	7.5 (6.3-8.9)	7.5 (6.5-8.7)	0.67
E/e' (IQR)	8.2 (6.9-10.2)	8.7 (7.2-11)	0.32
LAVI, ml/m^2 (IQR)	34 (28-40)	33 (29-42)	0.56
LA reservoir strain*, % (SD)	36.2 (7)	36.1 (7)	0.9
LARS <24%* (%)	7 (4)	2 (3)	0.61
Relative wall thickness (IQR)	0.37 (0.34-0.43)	0.39 (0.33-0.43)	0.96
LV mass indexed, g/m^2 (IQR)	67 (55-79)	75 (60-84)	0.04
Subclinical LV dysfunction (%)	113 (48)	49 (48.5)	0.9
Systolic dysfunction (GLS≤16%)	42 (18)	13 (13)	0.26
Diastolic dysfunction (%)	54 (23)	26 (26)	0.54
LV hypertrophy (%)	13 (5.5)	7 (7)	0.62

*available in 248 participants

LV – left ventricular, GLS – global longitudinal strain, LAVI – left atrial volume indexed to body surface area, LARS – left atrial reservoir strain

Table 4: Logistic regression modelling for prediction of mild cognitive impairment (abbreviations as per tables 1 and 3)

	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years	1.00 (0.95-1.06)	0.88		
Female gender	0.8 (0.49-1.26)	0.32		
Hypertension	1.58 (0.75-3.33)	0.23		
Hypertension duration	1.00 (0.97-1.03)	0.76		
Type II diabetes	1.26 (0.77-2.06)	0.36		
Diabetes duration	1.03 (0.98-1.09)	0.22		
Dyslipidaemia	1.03 (0.63-1.66)	0.9		
Ever smoker	0.88 (0.23-3.44)	0.86		
Stroke/TIA	2.2 (0.87-5.6)	0.09	2.5 (0.93-6.8)	0.07
AF (known)	1.54 (0.65-3.69)	0.33		
AF (detected or high risk)	0.63 (0.2-1.96)	0.43		
Education, years	0.92 (0.86-0.98)	0.02	0.9 (0.86-0.98)	0.011
Depression (PHQ9 >6), %	0.8 (0.32-2)	0.6		
Anxiety (GAD7 >6), %	0.85 (0.33-2.1)	0.72		
ACE-I/ARB	1.17 (0.65-2)	0.59		
Beta blocker	1.7 (0.84-3.4)	0.14		
Statin	1.14 (0.7-1.8)	0.58		
Antiplatelet	1.47 (0.84-2.59)	0.17		
Anticoagulant	1.43 (0.5-4)	0.5		
Systolic BP, mm Hg	1.02 (0.99-1.03)	0.07	1.02 (1.00-1.04)	0.03
Diastolic BP, mm Hg	1.02 (0.99-1.04)	0.2		
BMI, kg/m^2	0.93 (0.88-0.97)	0.001	0.9 (0.85-0.95)	<0.001
Waist-hip ratio	11 (0.8-161)	0.07	40 (2.3-708)	0.01
NT-proBNP, pg/ml	0.99 (0.99-1.00)	0.7		
MVPA, hr/week	0.99 (0.99-1.00)	0.98		
Sedentary time, %	0.98 (0.94-1.01)	0.15		
Echocardiographic classifications				
Subclinical LV dysfunction	1.03 (0.64-1.63)	0.9		
Systolic dysfunction (GLS ≤16%)	0.68 (0.35-1.33)	0.26		
Diastolic dysfunction	1.18 (0.69-2)	0.54		
LV hypertrophy	1.27 (0.49-3.3)	0.62		
Echocardiographic continuous measures				
LV ejection fraction, %	0.99 (0.95-1.03)	0.7		
GLS, %	1.01 (0.92-1.11)	0.82		
e', cm/s	0.96 (0.84-1.09)	0.57		
E/e'	1.03 (0.94-1.12)	0.4		
LAVI ml/m^2	1 (0.98-1.03)	0.56		
LA reservoir strain, %	0.98 (0.96-1.04)	0.91		
LARS <24%	0.66 (0.13-3.27)	0.61		

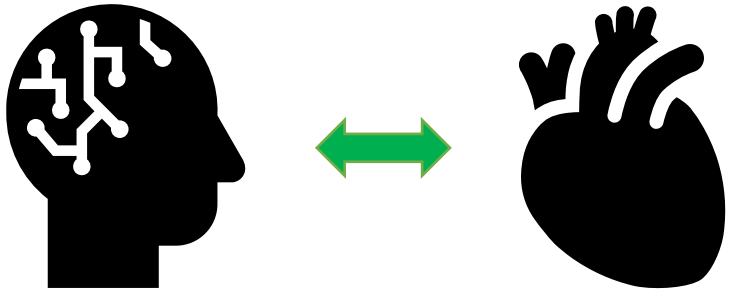
LV mass indexed, g/m²	1.00 (0.99-1.02)	0.13

Figure legends:

Figure 1: Summary of study findings.

ELDERLY WITH RISK FACTORS FOR LEFT VENTRICULAR DYSFUNCTION AND ATRIAL FIBRILLATION UNDERGOING SCREENING

30% prevalence of **mild cognitive impairment**



Implications for screening

- 1.6 x more likely to be non-adherent to hand-held AF screening
- Consideration of strategies to optimise engagement e.g. wearables, family involvement

Associations with clinical factors and cardiac function

- No association with **subclinical AF**
- No association with **LV global longitudinal strain** or **diastolic parameters**
- No association **with left atrial reservoir strain**
- Systolic blood pressure, educational attainment, body mass index and abdominal adiposity are independently associated

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Version 7.1 Original Version

NAME :

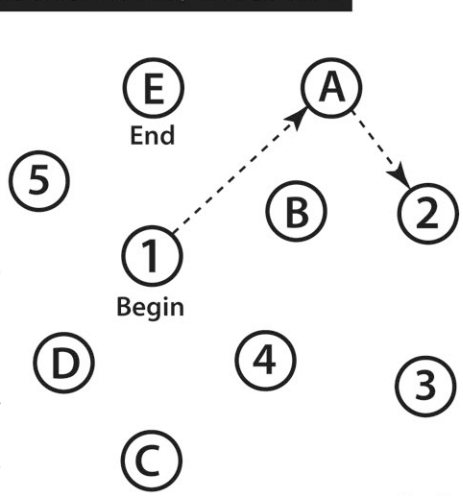
Education :

Sex :

Date of birth :

DATE :

VISUOSPATIAL / EXECUTIVE



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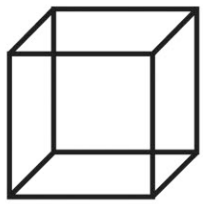

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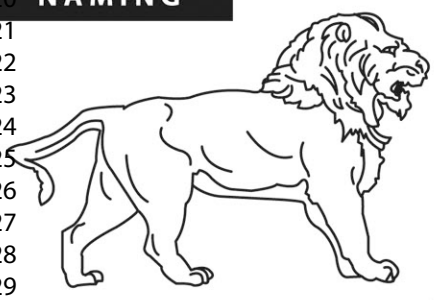
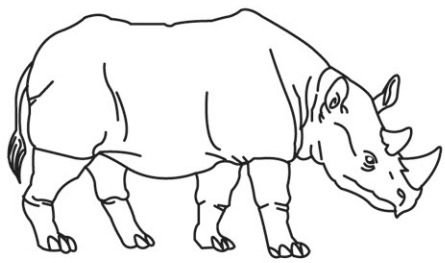
___/5

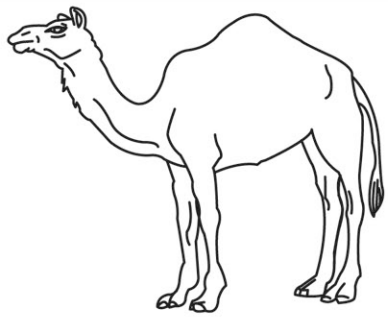
NAMING



[ ]



[ ]



[ ]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

Optional

	FACE	VELVET	CHURCH	DAISY	RED
Has to recall words **WITH NO CUE**	[ ]	[ ]	[ ]	[ ]	[ ]
Category cue					
Multiple choice cue					

Points for UNCUED recall only

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

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Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	5
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5-7

Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	14
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6,7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	8
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	NA
Statistical methods	#12c	Explain how missing data were addressed	NA
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	NA
Statistical methods	#12e	Describe any sensitivity analyses	NA
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	8,9
Participants	#13b	Give reasons for non-participation at each stage	NA

Participants	#13c	Consider use of a flow diagram	NA
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	9
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	9
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
Main results	#16b	Report category boundaries when continuous variables were categorized	NA
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	#18	Summarise key results with reference to study objectives	10

Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	14
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	13-14
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14