Association of cardiovascular system medications with cognitive function and dementia in older adults living in nursing homes in Australia

Enwu Liu1,2, Suzanne M Dyer1,2, Lisa Kouladjian O’Donnell1,2, Rachel Milte1,2,4, Clare Bradley1,2,5, Stephanie L Harrison1,2, Emmanuel Gnanamanickam1,2, Craig Whitehead1,2, Maria Crotty1,2

1Department of Rehabilitation, Aged and Extended Care, Faculty of Medicine, Nursing and Health Sciences, School of Health Sciences, Flinders University, Daw Park, Australia
2NHMRC Cognitive Partnership Centre, The University of Sydney, Sydney NSW, Australia
3Kolling Institute of Medical Research, St Leonards, NSW, Australia and Sydney Medical School, University of Sydney, Sydney NSW, Australia
4Institute for Choice, University of South Australia, GPO Box 2471, Adelaide SA, Australia
5Infection & Immunity – Aboriginal Health, SAHMRI, PO Box 11060, Adelaide SA, Australia

Abstract

Objective To examine associations between cardiovascular system medication use with cognition function and diagnosis of dementia in older adults living in nursing homes in Australia. Methods As part of a cross-sectional study of 17 Australian nursing homes examining quality of life and resource use, we examined the association between cognitive impairment and cardiovascular medication use (identified using the Anatomical Therapeutic Classification System) using general linear regression and logistic regression models. People who were receiving end of life care were excluded. Results Participants included 541 residents with a mean age of 85.5 years (± 8.5), a mean Psychogeriatric Assessment Scale–Cognitive Impairment (PAS-Cog) score of 13.3 (± 7.7), a prevalence of cardiovascular diseases of 44% and of hypertension of 47%. Sixty-four percent of participants had been diagnosed with dementia and 72% had received cardiovascular system medications within the previous 12 months. Regression models demonstrated the use of cardiovascular medications was associated with lower (better) PAS-Cog scores (Coefficient (β) = −3.7; 95% CI: −5.2 to −2.2; P < 0.0001) and a lower probability of a dementia diagnosis (OR = 0.44; 95% CI: 0.26 to 0.75, P = 0.0022). Analysis by subgroups of medications showed cardiac therapy medications (C01), beta blocking agents (C07), and renin-angiotensin system agents (C09) were associated with lower PAS-Cog scores (better cognition) and lower dementia diagnosis probability. Conclusions This analysis has demonstrated an association between greater cardiovascular system medication use and better cognitive status among older adults living in nursing homes. In this population, there may be differential access to health care and treatment of cardiovascular risk factors. This association warrants further investigation in large cohort studies.

Keywords: Cardiovascular agents; Cognitive dysfunction; Dementia; Residential facilities

1 Introduction

Dementia is a condition that has a number of causes, most commonly Alzheimer’s disease, and is characterised by a gradual decline in cognitive function. Cognitive functions that may be affected include memory, orientation, learning, problem-solving, attention, language and the ability to perform activities of daily living. It has been estimated that worldwide there are 47 million people living with dementia and the number of people living with dementia is expected to be more than 131 million by 2050 and the total estimated cost of dementia is about US$818 billion in 2015. Whilst Alzheimer’s disease is the most common type of dementia, there is increasing awareness that dementia of mixed pathology is more common than dementia of discrete types. Neurodegeneration and cerebrovascular damage to the brain are the two main causes of age-related cognitive decline and dementia. Cardiovascular and cerebrovascular diseases share many pathophysiological traits and risk factors and even heart disease itself could be a risk factor for...
Many classes of cardiovascular drugs have demonstrated effectiveness in the primary prevention, acute treatment and secondary prevention of stroke which is a risk factor for cognitive impairment and dementia.\[11\] In addition, in some trials of cardiovascular medications a protective effect against cognitive decline and dementia has been demonstrated, in particular with lipid lowering agents, although findings are inconsistent.\[12–18\] People in nursing homes have high prevalence of cardiovascular disease (CVD) risk factors and high use of CVD medications.\[19\] For these reasons, the high rate of use of these medications in aged care may have associations with cognitive status.

There is often a lengthy delay between the appearance of symptoms of dementia and it’s diagnosis.\[20\] Diagnosis is based upon clinical criteria following assessment of the patient’s history, cognitive and mental state assessment, physical examination and medication review.\[21\] A large proportion of dementia is undetected in community and institutional settings and it is estimated that approximately half of people living with dementia in nursing homes are not diagnosed.\[22\] In Australian nursing home settings, cognitive function is routinely assessed using the Psychogeriatric Assessment Scale–Cognitive Impairment (PAS-Cog) instrument.\[23\] The PAS-Cog consists of nine questions to test the subject’s memory and other cognitive functions, with higher scores indicating greater impairment. The aim of this analysis is to examine associations of cardiovascular system medications with cognitive function and diagnosis of dementia in older adults living in nursing homes in Australia.

## 2 Methods

### 2.1 Design, settings and participants

The Investigating Services Provided in the Residential Environment for Dementia (INSPIRED) Study is a cross-sectional study designed to determine and compare the quality of life, quality of care, utilisation of healthcare resources and costs of various residential care facilities that provide alternative models of dementia care for people with cognitive impairment and dementia. We collected data from 17 not-for profit nursing homes across 4 Australian states between January 2015 and February 2016. The inclusion criteria for INSPIRED were: (1) being permanent residents of the facility; (2) residing in the facility for 12 months or more; (3) not in immediate palliative care; (4) if not able to self-consent, have family who are able to provide proxy consent and/or participate on the resident’s behalf; and (5) no other complex medical or family issues that would prevent participation. Written informed consents were obtained from participants or their legal guardians. Ethics approval for the study was obtained from the Flinders University social and behavioural research ethics committee. As part of this study we collected comprehensive data on medication use.

### 2.2 Cognitive and comorbidities measures

We collected the most recent (within three months) PAS-Cog scale data from nursing home records. If a participant had a PAS-Cog score older than three months and that score was higher than 18 (of a possible 21) points we retained that score as the most recent score based on an assumption that an additional PAS-Cog score would not substantially improve. If there was a PAS-Cog score older than three months but less than 18 points, a trained research nurse conducted a face-to-face interview to obtain the PAS-Cog data. A diagnosis of dementia was collected from the residential facility’s medical records. In Australia, the Aged Care Act 1997 requires that all nursing homes must keep records about a resident’s medical conditions, the treatment they are receiving and the type of care that is being provided under a resident’s care plan.\[24\] Data on participants’ comorbidities were also collected from residential facility medical records.

### 2.3 Cardiovascular medication use

The exposure variable for this analysis was whether a subject had been using medications active on the cardiovascular system within the last 12 months. We classified medication use according to the Anatomical Therapeutic Chemical (ATC) classification system.\[25\] Cardiovascular (C-class) medications that are considered predominantly to be used to manage cardiovascular risk factors were examined. Cardiovascular system medications are coded as follows: C01: cardiac therapy (cardiac glycosides, antiarrhythmics and vasodilators and other preparations used in cardiac diseases), C02: antihypertensives (antiadrenergics, agents acting on areolar smooth muscle), C03: diuretics, C04: peripheral vasodilators, C05: vasoprotective agents, C07: beta blocking agents, C08: calcium channel blockers, C09: agents acting on the renin-angiotensin system and C10: lipid modifying agents.\[25\]

Medication use information was obtained from three possible sources: (1) Pharmaceutical Benefits Scheme (PBS) data,\[26\] with the federal Department of Human Services of Australia providing details of the service records for consenting participants; (2) Pharmacy data records from nursing home-contracted pharmacists, or (3) Facility-based medication charts when pharmacy data could not be obtained.

For this analysis a participant was considered to have
been exposed if they had been prescribed cardiovascular system medications at any point during the previous 12 months.

2.4 Statistical methods

Means, standard deviations and percentages were used to describe the sample. Analysis of variance (ANOVA), Chi-square test and Fisher exact test were used to compare the means and proportions across PAS-Cog categories corresponding to no (score 0 to 4), mild (score 5 to 9), moderate (score 10 to 15) or severe (score 16 to 21) cognitive impairment and whether or not participants had a dementia diagnosis. We used general linear regression models to test the associations between cognitive impairment (measured by the continuous PAS-Cog score) and cardiovascular medications. Logistic regression models were used to test associations between diagnosis of dementia (yes vs. no) and cardiovascular medications. Unadjusted analyses were initially conducted and adjusted analyses controlling for potential confounding factors were performed. For multivariable general linear regression and multivariable logistic regression, adjustments were made for residents’ age and gender, comorbidities related to cognition, dementia and cardiovascular disease, total number of comorbidities and the use of agents predominantly used for secondary prevention of cardiovascular disease, i.e. antithrombotic agents (B01) and antihemorrhagics (B02). Further analysis to investigate associations between the subgroups of the cardiovascular system medications and cognitive impairment and dementia were also performed using the same models.

3 Results

In total, 1323 residents from the facilities were assessed and 901 were eligible to participate, of these 541 consented to be part of the INSPIRED study. The mean age was 85.5 years (± 8.5); 74.5% were female; the average PAS-Cog score was 13.3 (± 7.7); 83% (448) of the participants had some level of cognitive impairment based on the PAS-Cog score, and 64.6% had been diagnosed with dementia. There was a high prevalence of cardiovascular disease in the study sample; 44% had a history of cardiovascular disease (including angina, congestive cardiac failure, atrial fibrillation, ischaemic heart disease, or stroke) and 47% a history of hypertension (Table 1). Seventy-two percent (390) of the participants had been prescribed medications acting on the cardiovascular system during the previous 12 months. Table 1 summarises the use of individual classes of medications. Table 2 and Table 3 summarise the distributions of considered covariates according to PAS-Cog score and dementia diagnosis. These include ATC code B level 2 medications considered likely to be used to treat existing cardiovascular disease and comorbidities associated with cardiovascular disease and cognition that may confound the analysis. Significant differences in the distribution of age, cardiovascular medication use, the use of antithrombotic agents, the total number of comorbidities and a history of congestive heart failure, ischaemic heart disease and cardiovascular disease were noted by PAS-Cog category. Significant differences in the use of cardiovascular medication use, the use of antithrombotic agents, the total number of comorbidities and a medical history of hypertension, congestive heart failure, ischaemic heart disease, stroke and diabetes between those diagnosed with dementia or not were observed.

Unadjusted general linear regression models on PAS-Cog score and unadjusted logistic regression models on diagnosis

Table 1. Characteristics of INSPIRED study sample.

| Characteristic | Total sample size (n = 541) |
|---------------|---------------------------|
| Age, yrs      | 85.5 ± 8.5                |
| Female        | 403 (74.5%)               |
| Cardiovascular disease history | 239 (44.2%) |
| Hypertension history | 254 (47.1%) |
| Hypercholesterolemia history | 120 (22.3%) |
| DVT history   | 5 (0.93%)                 |
| PAS-Cog score | 13.3 ± 7.7                |
| PAS-Cog score 0–4, no cognitive impairment | 93 (17.2%) |
| PAS-Cog score 5–9, mild cognitive impairment | 100 (18.5%) |
| PAS-Cog score 10–15, moderate cognitive impairment | 82 (15.2%) |
| PAS-Cog 16–21, severe cognitive impairment | 266 (49.2%) |
| Dementia      | 348 (64.6%)               |
| Use of any ATC C-class Cardiovascular System Medication | 390 (72.1%) |
| C01 Cardiac therapy | 95 (17.6%) |
| C02 Antihypertensives | 16 (3.0%) |
| C03 Diuretics | 161 (29.8%)               |
| C04 Peripheral vasodilators | 4 (0.74%) |
| C05 Vasoprotective | 15 (2.8%) |
| C07 Beta blocking agents | 114 (21.1%) |
| C08 Calcium channel blockers | 81 (15.0%) |
| C09 Agents acting on the renin-angiotensin system | 193 (35.7%) |
| C10 Lipid modifying agents | 169 (31.2%) |
| Other considered drug use |                     |
| B01 Antithrombotic agents | 131 (24.2%) |
| B02 Antihemorrhagics | 3 (0.56%)                 |

Data were presented as mean ± SD or n (%). *Including those with a history of angina, congestive cardiac failure, atrial fibrillation, ischaemic heart disease and stroke. ATC: Anatomical Therapeutic Chemical Classification System, DVT: deep vein thrombosis, PAS-Cog: Psychogeriatric Assessment Scale–Cognitive Impairment.
Table 2. Characteristics and comorbidities of study sample by PAS-Cog score.

| Characteristic                        | No cognitive impairment (PAS-Cog 0–4) | Mild cognitive impairment (PAS-Cog 5–9) | Moderate cognitive impairment (PAS-Cog 10–15) | Severe cognitive impairment (PAS-Cog 16–21) | P values |
|---------------------------------------|---------------------------------------|----------------------------------------|-----------------------------------------------|---------------------------------------------|----------|
| Age, yrs                              | 85.1 ± 8.6                            | 86.8 ± 8.6                             | 87.3 ± 7.3                                    | 84.5 ± 8.7                                  | 0.0200   |
| Female                                | 68 (73.1%)                            | 68 (68.0%)                             | 64 (78.1%)                                    | 203 (76.3%)                                 | 0.3446   |
| Any ATC C-class Cardiovascular System Medication | 84 (90.3%)                            | 81 (81.0%)                             | 60 (73.2%)                                    | 165 (62.0%)                                 | <0.0001  |
| CO1 Cardiac therapy                   | 30 (32.3%)                            | 27 (27.0%)                             | 13 (15.9%)                                    | 29 (10.9%)                                  | <0.0001  |
| CO2 Antihypertensives                 | 5 (5.4%)                              | 4 (4.0%)                               | 3 (3.7%)                                      | 6 (2.3%)                                    | 0.5063   |
| CO3 Diuretics                         | 37 (39.8%)                            | 38 (38.0%)                             | 26 (31.7%)                                    | 61 (22.9%)                                  | 0.0033   |
| CO4 Peripheral vasodilators           | 0 (0.0%)                              | 1 (1.0%)                               | 0 (0.0%)                                      | 3 (1.1%)                                    | 0.5843   |
| CO5 Vasoprotectives                   | 0 (0.0%)                              | 4 (4.0%)                               | 4 (4.9%)                                      | 7 (2.6%)                                    | 0.2054   |
| C07 Beta blocking agents              | 29 (31.2%)                            | 26 (26.0%)                             | 21 (25.6%)                                    | 42 (15.8%)                                  | 0.0068   |
| C08 Calcium channel blockers          | 24 (25.8%)                            | 17 (17.0%)                             | 14 (17.1%)                                    | 28 (10.5%)                                  | 0.0047   |
| C09 Agents acting on the renin-angiotensin system | 51 (54.8%)                            | 45 (45.0%)                             | 37 (37.8%)                                    | 75 (28.2%)                                  | <0.0001  |
| C10 Lipid modifying agents           | 44 (47.3%)                            | 32 (32.0%)                             | 27 (32.9%)                                    | 74 (27.8%)                                  | 0.0077   |

Data were presented as mean ± SD or n (%). ATC: Anatomical Therapeutic Chemical Classification System; PAS-Cog: Psychogeriatric Assessment Scale–Cognitive Impairment.

of dementia showed that using any cardiovascular medications during the previous 12 months was associated with lower PAS-Cog scores (better cognitive function) and lower probability of dementia diagnosis (Table 4). When analysing subgroups of cardiovascular medications, cardiac therapy, diuretics, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system and lipid lowering agents were associated with both lower (better) PAS-Cog scores and a lower probability of dementia diagnosis (Table 4). There were no significant associations between antihypertensive use, peripheral vasodilators and vasoprotective agents with PAS-Cog scores or dementia diagnosis (Table 4).

Multivariable general linear regression models and multivariable logistic regression models controlling for age, gender, hypertension, angina, congestive cardiac failure, atrial fibrillation, ischaemic heart disease, stroke, deep vein thrombosis, diabetes mellitus, hypercholesterolaemia, depression, Parkinson’s disease and the use of antithrombotic agents and antihemorrhagics demonstrated associations that were largely consistent with the unadjusted variable regression models (Figure 1), with the exception of diuretic and lipid modifying agents. Following adjustment for these potential confounding factors, the use of diuretic, calcium channel blockers, and lipid modifying agents were associated with lower PAS-Cog scores but were not significantly associated with dementia diagnosis (Figure 1).

4 Discussion

We found that the use of cardiovascular system medica-
Table 3. Characteristics and comorbidities of study sample by dementia status.

| Characteristic                                      | Non-dementia (n = 185) | Dementia (n = 348) | P value |
|-----------------------------------------------------|------------------------|--------------------|---------|
| Age, yrs                                            | 86.0 ± 9.2             | 85.1 ± 8.1         | 0.2809  |
| Female                                              | 139 (75.1%)            | 256 (73.6%)        | 0.6933  |

Any ATC C-class Cardiovascular System Medication

| C01 Cardiac therapy                                 | 53 (28.7%)             | 44 (12.6%)         | < 0.0001 |
| C02 Antihypertensives                              | 5 (2.7%)               | 13 (3.7%)          | 0.6216   |
| C03 Diuretics                                      | 70 (37.8%)             | 87 (25.0%)         | 0.002    |
| C04 Peripheral vasodilators                        | 1 (0.5%)               | 3 (0.9%)           | 0.6882   |
| C05 Vasoprotectives                                | 7 (3.8%)               | 8 (2.3%)           | 0.3237   |
| C07 Beta blocking agents                           | 64 (34.5%)             | 52 (14.9%)         | < 0.0001 |
| C08 Calcium channel blockers                       | 40 (21.6%)             | 43 (12.4%)         | 0.005    |
| C09 Agents acting on the renin-angiotensin system  | 97 (52.4%)             | 102 (29.3%)        | < 0.0001 |
| C10 Lipid modifying agents                         | 74 (40.0%)             | 99 (28.5%)         | 0.0067   |

ATC B-class Anticoagulant Medications

| B01 Antithrombotic agents                          | 47 (25.4%)             | 57 (16.4%)         | 0.0123   |
| B02 Antihemorrhagics                              | 2 (1.1%)               | 10 (2.9%)          | 0.2321   |

Comorbidities

| Number of comorbidities                            | 4.0 (1.3%)             | 3.5 (1.4%)         | < 0.0001 |
| Hypertension                                       | 109 (58.9%)            | 144 (41.4%)        | 0.0001   |
| Angina                                             | 14 (7.6%)              | 12 (3.5%)          | 0.0356   |
| Congestive Cardiac failure                         | 24 (13.0%)             | 18 (5.2%)          | 0.0015   |
| Atrial Fibrillation                                | 26 (14.1%)             | 26 (7.5%)          | 0.0148   |
| Ischaemic Heart Disease                            | 46 (24.9%)             | 60 (17.2%)         | 0.0358   |
| Stroke                                             | 49 (26.5%)             | 51 (14.5%)         | 0.0009   |
| Deep Vein Thrombosis                               | 3 (1.6%)               | 2 (0.57%)          | 0.3472   |
| Diabetes Mellitus                                  | 53 (28.7%)             | 59 (17.0%)         | 0.0016   |
| Hypercholesterolaemia                              | 48 (26.0%)             | 69 (19.8%)         | 0.1043   |
| Depression                                         | 88 (47.6%)             | 142 (40.8%)        | 0.1334   |
| Parkinson's Disease                                | 12 (6.5%)              | 13 (3.7%)          | 0.1527   |

Data were presented as mean ± SD or n (%). ATC: Anatomical Therapeutic Chemical Classification System.

Table 4. Unadjusted linear regression and logistic regression on PAS-Cog score and diagnosis of dementia.

| Medications on Cardiovascular System | PAS-Cog score | Dementia Diagnosis (Yes vs. No) |
|-------------------------------------|---------------|---------------------------------|
|                                     | Coefficient β (95% CI) | P value | Odds Ratio (95% CI) | P value |
| C Any Cardiovascular system medications | −4.8 (−6.2, −3.4) | < 0.0001 | 0.29 (0.18, −0.47) | < 0.0001 |
| C01 Cardiac therapy                 | −4.0 (−5.6, −2.3) | < 0.0001 | 0.41 (0.26, 0.64) | < 0.0001 |
| C02 Antihypertensives               | −3.7 (−7.5, 0.14) | 0.0588  | 1.20 (0.41, 3.5)  | 0.7432   |
| C03 Diuretics                       | −3.3 (−4.7, −1.9) | < 0.0001 | 0.53 (0.36, 0.77) | 0.0009   |
| C04 Peripheral vasodilators         | 2.9 (−4.6, 10.5)  | 0.4471  | 1.6 (0.17, 15.6)  | 0.6715   |
| C05 Vasoprotectives                 | −0.17 (−4.1, 3.8)  | 0.9333  | 0.46 (0.16, 1.3)  | 0.1339   |
| C07 Beta blocking agents            | −3.5 (−5.3, −1.9)  | < 0.0001 | 0.31 (0.20, 0.47) | < 0.0001 |
| C08 Calcium channel blockers        | −2.8 (−4.6, −1.0)  | 0.0021  | 0.55 (0.34, 0.89) | 0.0144   |
| C09 Agents acting on the renin-angiotensin system | −4.1 (−5.4, −2.8)  | < 0.0001 | 0.32 (0.22, 0.46) | < 0.0001 |
| C10 Lipid modifying agents          | −2.7 (−4.1, −1.3)  | 0.0001  | 0.56 (0.39, 0.82) | 0.0026   |

ATC: Anatomical Therapeutic Chemical Classification System, CI: confidence interval, PAS-Cog = Psychogeriatric Assessment Scale-Cognitive Impairment

The use of cardiovascular system medications was associated with less cognitive impairment and a lower probability of having a dementia diagnosis in a population residing in a nursing home for at least one year, who had a high prevalence of cardiovascular diseases. Residents who had been using cardiovascular system medications over a 12-month period were 3.7 (β = −3.7) points lower in cognitive impairment compared to those not using such medications.
PAS-Cog score and 56% (OR = 0.44) less likely to be diagnosed with dementia than those who did not use any such medications. This association existed for cardiac therapy, beta-blockers, and agents acting on the renin-angiotensin system as classified by the ATC.

Similar associations between cardiovascular medication use and cognitive status have been reported in other studies. An association of reduced cardiovascular medications with dementia has been demonstrated in a community setting.\[27\] A similar, but smaller, association of cardiovascular medication use with better cognitive status within dementia patients has been shown in an analysis of a Swedish Registry data.\[28\] A three-year prospective cohort study from a Spanish register demonstrated that while total pharmaceutical consumption increased over the three-year period in people with dementia, the consumption of cardiovascular system drugs decreased.\[29\]

There are several possible explanations for the observed association. People living with cognitive impairment or dementia are likely to experience barriers to the access and prescription of medications for the management of cardiovascular disease and its risk factors. People living with cognitive impairment or dementia are less likely to be aware of or to effectively communicate their symptoms\[30\] and may also have a lower rate of presentation for investigation of symptoms or preventative health management.\[31,32\] Thus, this population may be less likely to receive management and prescriptions for non-symptomatic cardiovascular disease.

The balance of the benefits and harms of prescribing medications to manage cardiovascular risk factors are different in this population to a population without cognitive impairment. As dementia is a non-remitting progressive condition, associated with a reduced life expectancy for many, it may be reasonable that management of risk factors that are only likely to lead to a direct impact on health in the longer term is reduced.

However, in some people diagnosed with dementia or cognitive impairment there may be instances of under-treatment of cardiovascular symptoms.\[33\] In a Canadian study, it was demonstrated that patients with severe dementia were under-treated for stroke and hypertension.\[34,35\] Additionally, optimising prescribing and deprescribing medications for people with dementia is complicated by diminished decision making capacity and difficulties with comprehension and communication by the patient and the lack of clinical practice guidelines to guide deprescribing for healthcare practitioners; therefore these factors may affect the prescription or cessation of medications for management of cardiovascular risk factors.\[33\]

Limited life expectancy and cognitive impairment are important drivers of deprescribing amongst geriatricians.\[36\] Considering reducing or ceasing antihypertensive medications in frail elderly patients has been recommended, however patients in the palliative treatment stages of disease were excluded from the INSPIRED study.\[37,38\] Nevertheless, if there is inadequate management of cardiovascular disease risk factors in some individuals this could lead to greater...
comorbidities and potentially an increase in any vascular component to cognitive impairment.\textsuperscript{39} Hence, the decision to prescribe cardiovascular medications to residents of nursing homes must be balanced against the risk of increasing polypharmacy.\textsuperscript{40} In a registry study of people with dementia, there was higher use of drugs to control vascular risk factors at baseline in those with non-degenerative vascular dementia.\textsuperscript{59} Further, agents included in the antihypertensive class of medicines that includes these medications (anti-hypertensives, ATC code C02) in this analysis. However, the lack of association of the ‘antihypertensive’ group of medications may be because this class also includes anti-adrenergics. Anti-adrenergics are considered potentially inappropriate for prescription in older adults broadly, rather than specifically those with cognitive impairment.\textsuperscript{42}

It is also possible that the observed association is due to a lower prevalence of risk factors associated with cardiovascular disease in those with worsening cognition. A cohort study of nursing home residents in the United States of America found that those with more severe dementia had fewer comorbidities, less hypertension and diabetes than those with no cognitive impairment.\textsuperscript{41} Although the current analysis has adjusted for cardiovascular disease and risk factor history, our dataset does not capture all possible risk factors and it is possible that other confounders which were not measured and hence could not be adjusted for (such as Body Mass Index or smoking status) may explain the associations.

Finally, as some cardiovascular medications may have a cognitive protective effect, those who are taking these agents may be less likely to develop dementia. We observed better cognitive status and a lower probability of dementia associated with taking agents acting on the renin-angiotensin system and these agents have been demonstrated to prevent cognitive impairment and dementia.\textsuperscript{15,17,44} Furthermore, calcium channel blockers were associated with better cognitive function in this analysis which is in line with the findings of a previous study which showed a longitudinal association between calcium channel blockers and a lower rate of cognitive decline in very old individuals.\textsuperscript{45} Treating vascular risk factors may offer a secondary prevention strategy towards disease progression in people with dementia.\textsuperscript{46} However, further evidence of this is needed before encouraging the use of cardiovascular medications in nursing homes as older people with dementia are already at risk of polypharmacy. In the current study, it is not possible to determine causation or to examine the direction of any effect.

The strengths of the current analysis were the access to detailed medication prescribing information for all subjects for 12 months from multiple sources. Therefore, the data on medication prescribing is considered highly accurate. Tests of cognitive function were conducted when no recent cognitive assessment was available and access to a diagnosis of dementia from medical records also suggests our measures of cognitive status for the individual participants are reliable. The participants were from 17 different nursing homes across four Australian states. The distributions of the age, gender, marital status and type of dementia were similar in the INSPIRED study sample to the latest available Australian population estimates (data not shown) and are therefore likely to be representative of Australians living in nursing homes nationwide.

The limitations of the current analysis are those inherent to the design of a cross-sectional study; it is not possible to know the direction of any effect, i.e. whether cognitive decline, dementia diagnosis, or prescription of cardiovascular medications occurred first, thus it is not possible to investigate causality. It is also possible confounders exist which have not been adjusted for but that may explain the association; although we have adjusted for history of cardiovascular diseases and risk factors for which data were available. As the captured pharmaceutical use data is retrospective, it represents medication use in nursing home residents that survived for 12 months or longer. Further, although the overall sample size for this analysis was relatively large, for some subgroups of medications the sample size was small which would decrease the statistical power to find associations with cognitive status.

In summary, this analysis has demonstrated consistent associations between the use of cardiovascular system medications and cognitive status among older adults living in nursing homes in Australia for 12 months or longer. The likely explanation for this cannot be determined, and warrants further investigation in longitudinal cohort studies. However, this finding may reflect a pattern of reduced access to or management of cardiovascular risk disease or its risk factors in nursing home residents with worse cognitive function.
Acknowledgements

This study was funded by the National Health and Medical Research Council (NHMRC) Partnership Centre on Dealing with Cognitive and Related Functional Decline in Older People (CDPC) (Grant No. GNT9100000). The contents of the published materials are solely the responsibility of the Administering Institution, Flinders University, and the individual authors identified, and do not reflect the views of the NHMRC or the Funding Partners.

The authors sincerely thank the INSPIRED study participants and their family members for their participation and interest in the study. The assistance of facility staff, careworker researchers, facility pharmacists and data collectors in each state is gratefully acknowledged for their efforts in data collection. Members of the study team Mrs Anne Whitehouse, Mrs Angela Basso, Ms Keren McKenna, Dr Wendy Shulver, Dr Lua Perimal-Lewis and Dr Rebecca Bilton are thanked for their input into study management, data collection and data coordination of the INSPIRED study.

The Australian Department of Human Services, are acknowledged as the data custodians for their respective data sets utilised as the source of some of the data collected for this study.

References

1 Burns A, Iliffe S. Dementia. BMJ 2009; 338: b75.
2 Martin Prince, Anders Wimo, Maëlenn Guerchet, et al. World Alzheimer Report 2015: the global impact of dementia. An analysis of prevalence, incidence, cost and trends; Alzheimer's Disease International: London, UK, 2015.
3 Martin Prince, Emiliano Albanese, Maëlenn Guerchet, et al. World Alzheimer Report 2014: dementia and risk reduction: an analysis of protective and modifiable factors. 2014, Alzheimer's Disease International: London, UK, 2014.
4 Sonnen JA, Larson EB, Crane PK, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol 2007; 62: 406–413.
5 Selnes OA, Vinters HV. Vascular cognitive impairment. Nat Clin Pract Neurol 2006; 2: 538–547.
6 Jellinger KA, Attems J. Prevalence and impact of cerebrovascular pathology in Alzheimer's disease and parkinsonism. Acta Neurol Scand 2006; 114: 38–46.
7 Heart disease may put you at risk for dementia. Neither disease is inevitable: risk can be modified. Heart Advis 2016; 19: 5, 7.
8 Rusanen M, Kivipelto M, Levalahti E, et al. Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study. J Alzheimers Dis 2014; 42: 183–191.
9 Justin BN, Turek M, Hakim AM. Heart disease as a risk factor for dementia. Clin Epidemiol 2013; 5: 135–145.
10 de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovasc Psychiatry Neurol 2012; 2012: 367516.
11 Bosel J, Amiri H. The utility of cardiovascular drugs in the treatment of cerebrovascular disease. Curr Opin Investig Drugs 2010; 11: 1015–1024.
12 Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. Lancet 1998; 352: 1347–1351.
13 Swiger KJ, Manalac RJ, Blumenthal RS, et al. Statins and cognition: a systematic review and meta-analysis of short- and long-term cognitive effects. Mayo Clin Proc 2013; 88: 1213–1221.
14 Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. Lancet Neurol 2008; 7: 683–689.
15 Li NC, Lee A, Whitmer RA, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. BMJ 2010; 340: b5465.
16 Maxwell CJ, Hogan DB. Antihypertensive agents and prevention of dementia. BMJ 2010; 340: b5409.
17 Gao Y, O’Caoimh R, Healy L, et al. Effects of centrally acting ACE inhibitors on the rate of cognitive decline in dementia. BMJ open 2013; 3: e002881.
18 Ligthart SA, Moll van Charante EP, Van Gool WA, et al. Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review. Vasc Health Risk Manag 2010; 6: 775–785.
19 Ahmed A, Ekundayo OJ. Cardiovascular disease care in the nursing home: the need for better evidence for outcomes of care and better quality for processes of care. J Am Med Dir Assoc 2009; 10: 1–3.
20 Cattel C, Gambassi G, Sgadari A, et al. Correlates of delayed referral for the diagnosis of dementia in an outpatient population. J Gerontol A Biol Sci Med Sci 2000; 55: M98–M102.
21 Brodaty H, Connors MH, Pond D, et al. Dementia. 14 essentials of assessment and care planning. Med Today 2013; 14: 18–27.
22 Lang L, Clifford A, Wei L, et al. Prevalence and determinants of undetected dementia in the community: a systematic literature review and a meta-analysis. BMJ open 2017; 7: e011146.
23 Jorm AF, Mackinnon A. Psychogeriatric assessment scales: user's guide; ANU/TECH Pty.: Canberra, Australia, 1994.
24 Federal Register of Legislation Aged Care Act 1997. Secondary Federal Register of Legislation Aged Care Act 1997. Australian government, the Federal Register of Legislation website: https://www.legislation.gov.au/Details/C2014C00810 (accessed Feb 1, 2017).
25 World Health Organization, Collaborating Center for Drug
Statistics Methodology. Guidelines for ATC classification and DDD assignment 2013. WHO Collaborating Center for Drug Statistics Methodology website: https://www.whocc.no/filearchive/publications/1_2013guidelines.pdf (assessed July 7, 2017)

26 Mellish L, Karanges EA, Litchfield MJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. *BMCR Res Notes* 2015; 8: 634.

27 Schmader KE, Hanlon JT, Fillenbaum GG, et al. Medication use patterns among demented, cognitively impaired and cognitively intact community-dwelling elderly people. *Age Ageing* 1998; 27: 493–501.

28 Cermakova P, Fereshtehnejad SM, Johnell K, et al. Cardiovascular medication burden in dementia disorders: a nationwide study of 19,743 dementia patients in the Swedish Dementia Registry. *Alzheimer Res Ther* 2014; 6: 34.

29 Turro-Garriga O, Calvo-Perxas L, Albaladejo R, et al. Pharmaceutical consumption and cost in patients with dementia: A longitudinal study by the Registry of Dementias of Girona (RedeGi) in Catalonia (Spain). *Arch Gerontol Geriatr* 2015; 60: 448–452.

30 Machiels M, Metzelthin SF, Hamers JP, et al. Interventions to improve communication between people with dementia and nursing staff during daily nursing care: a systematic review. *Int J Nurs Stud* 2017; 66: 37–46.

31 Mitchell R, Harvey L, Brodaty H, et al. Hip fracture and the influence of dementia on health outcomes and access to hospital-based rehabilitation for older adults. *Disabil Rehabil* 2016; 38: 2286–2295.

32 Bunn F, Burn A-M, Goodman C, et al. Comorbidity and dementia: a scoping review of the literature. *BMCMed* 2014; 12: 192.

33 Reeve E, Bell JS, Hilmer SN. Barriers to optimising prescribing and deprescribing in older adults with dementia: a narrative review. *Curr Clin Pharmacol* 2015; 10: 168–177.

34 Harrison JK, Van Der Wardt V, Conroy SP, et al. New horizons: the management of hypertension in people with dementia. *Age Ageing* 2016; 45: 740–746.

35 Rockwood K, Eby E, Hachinski V, et al. Presence and treatment of vascular risk factors in patients with vascular cognitive impairment. *Arch Neurol* 1997; 54(1):33–39.

36 Ni Chroinin D, Ni Chroinin C, Beveridge A. Factors influencing deprescribing habits among geriatricians. *Age Ageing* 2015; 44: 704–708.

37 Primary Health Tasmania. A guide to deprescribing antihypertensive agents: Primary Health Tasmania, 2016.

38 Turner JP, McKinna RA, Bell JS. The management of polypharmacy in people with cancer and chronic conditions. In cancer and chronic conditions: addressing the problem of multimorbidity in cancer patients and survivors. Springer: Singapore, 2016: 261–286.

39 Norton S, Matthews FE, Barnes DE, et al. Potential for primary prevention of Alzheimer’s disease: an analysis of population-based data. *Lancet Neurol* 2014; 13: 788–794.

40 Fleg JL, Aronow WS, Frishman WH. Cardiovascular drug therapy in the elderly: benefits and challenges. Nat Rev Cardiol 2011; 8: 13–28.

41 Arsura EL, Brunner NG, Namba T, et al. Adverse cardiovascular effects of anticholinesterase medications. *Am J Cardiovasc* 1987; 293: 18–23.

42 American Geriatrics Society 2015. Updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2015; 63: 2227–2246.

43 LaMantia MA, Lane KA, Tu W, et al. Patterns of emergency department use among long-stay nursing home residents with differing levels of dementia severity. *J Am Med Dir Assoc* 2016; 17: 541–546.

44 Li EC, Heran BS, Wright JM. Angiotensin converting enzyme (ACE) inhibitors versus angiotensin receptor blockers for primary hypertension. *Cochrane Database Syst Rev* 2014: CD009096.

45 Peters R, Collerton J, Granic A, et al. Antihypertensive drug use and risk of cognitive decline in the very old: an observational study - the Newcastle 85+ Study. *J Hypertens* 2015; 33: 2156–2164.

46 Valenti R, Pantoni L, Markus HS. Treatment of vascular risk factors in patients with a diagnosis of Alzheimer’s disease: a systematic review. *BMCMed* 2014; 12: 160.