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Original article

The association between adherence to a Mediterranean style diet and cognition in older people: The impact of medication

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SUMMARY

Background: Recent reviews indicate that adherence to a Mediterranean diet may be associated with better cognitive functioning. In assessing these relationships in older individuals, previous studies have not taken into account medication usage that may support or compromise cognitive functioning.
Objective: To investigate the association between adherence to a Mediterranean style diet, cognition and medication usage in cognitively healthy older individuals.
Design: Data were assessed from individuals aged 60–90 years (mean = 77.8 years, SD = 6.7) from 15 independent living aged care villages around Melbourne, Australia. Participants' diets were assessed using a food frequency questionnaire (FFQ). Cognition was assessed using reaction times from the Swinburne University Computerised Cognitive Assessment Battery (SUCCAB). Prescribed medications were recorded and analysed using binary measures. Cluster analyses were used to group participants in terms of cognitive measures and medications taken. Analyses controlled for age, gender, average daily kilojoule (kJ) intake and medication cluster.
Results: The relationship between cognitive speed clusters and medication clusters was significant (Chi-squared = 10.63, df = 3, $p = 0.014$). The odds ratio of 1.533 for average daily food intake suggested that for each additional kilojoule of average daily intake, the odds of belonging to the slower reaction time cluster increased by 53% and odds ratio of 0.573 for Mediterranean diet score suggested that for every additional unit, the odds of belonging to the slower reaction time cluster declined by 43%. The relationship between Mediterranean diet score and cognition was only significant when medication use was taken into account.
Conclusion: These data demonstrate that when medications are considered, a higher Mediterranean diet score is associated with a faster response on cognitive function tests. The present findings also indicate that it is pertinent to take into account medication use when investigating relationships between dietary status and cognitive performance.
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1. Introduction

Diet is considered to be one of the greatest contributors to overall health. The term 'Western diet' is used to describe a diet containing large amounts of red meat, refined sugars, grains, and high fat foods that is common in Western countries. The high levels of saturated fat and trans-fatty acids consumed in this diet have contributed to the obesity epidemic in these countries [1]. Obesity has been linked with impaired cognitive function and an elevated risk of late-onset dementia, such as Alzheimer's disease [2,3].

A Western diet and a sedentary lifestyle impacts general health, including increasing the rate of obesity, high blood pressure, high blood triglycerides, high levels of LDL and low levels of HDL cholesterol and insulin resistance. These comorbidities have resulted in an increased incidence of coronary artery disease, diabetes, chronic pain syndrome, inflammatory disease, cardiovascular disease, respiratory disease and end organ damage [4]. The comorbidities including high blood pressure, high cholesterol, insulin resistance and obesity are classified as the metabolic

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Abbreviations

ANOVA	analysis of variance
χ^2 test	chi-squared test
r	coefficient of correlation samplme
R	coefficient of multiple regression
CI	confidence intervals
DF	degrees of freedom
FFQ	food frequency questionnaire
kJ	kilojoules
MedDiet	Mediterranean diet
MedDietS	Mediterranean Diet Score
NS	not significant
n	number of observations
SD	standard deviation
SUCCAB	Swinburne University Computerised Cognitive Assessment Battery
F	variance ratio

syndrome, and can lead to cognitive impairment [5]. Metabolic syndrome may impair cognition in the elderly, especially in those with inflammation. Metabolic syndrome, particularly in ageing populations, is treated pharmacologically, to reduce blood pressure and cholesterol levels [6].

The Mediterranean diet (MedDiet) is considered a healthier alternative to the Western diet. The MedDiet is a diet with an abundance of plant foods in the form of fruits, vegetables, breads, other forms of cereals, beans, nuts, seeds, fish and olive oil as its main source of monounsaturated fats; while dairy foods, red meat and chicken are consumed in lower quantities, and red wine is consumed moderately with meals. These foods provide a high intake of β-carotene, vitamin C, tocopherols, omega-3 fatty acids, various minerals and other beneficial substances such as polyphenols and anthocyanins [7,8]. Adherence to the MedDiet was initially considered relevant to health when it was demonstrated that mortality was reduced within the populations located in the areas of Southern Europe [8,9].

Two recent systematic reviews have indicated that the MedDiet may be neuroprotective as well as cognition-enhancing in the shorter term [10,11]. Additionally this diet is likely to be protective against accelerated cognitive decline and the transition to mild cognitive impairment and dementia. Medications taken by older participants, and how medications may impact the protective effects of a MedDiet had not been assessed.

Within a Western society the use of medications is part of the primary armamentarium to reduce the impact of comorbidities, such as the metabolic syndrome. To this end, in Australia, as in the rest of the developed world, there has been a substantial increase in the use of blood pressure medications and statins to alleviate the effects of the metabolic syndrome. The use of medications and the impact of comorbidities may provide further understanding of the effects of cognitive changes within an ageing population [12].

The primary aim of this study was to investigate the association of adherence to a Mediterranean style of diet with respect to cognition, while taking into consideration the use of medications. This study utilised the baseline data from a randomised controlled trial investigating the effects of the MedDiet on cognition in cognitively healthy older people living independently within aged care facilities: the Lifestyle Intervention in Independent Living Aged Care (LIILAC) study [ACTRN12614001133628] [13].

2. Methods

2.1. Recruitment and approval

Participants were aged 60–90 years and living independently in 15 aged care and retirement villages in and around Melbourne, Australia. Recruitment took place between 1 April 2014 and 30 June 2015.

2.2. Eligibility criteria

Participants were fluent in written and spoken English. Participants had to obtain the approval of their medical practitioner to be involved in the trial.

2.3. Ineligibility criteria

Participants were unable to participate if they had a significant visual impairment, had a neurological or uncontrolled psychiatric disorder, were unable to walk independently and safely, or used illicit drugs or cognitive enhancing medications. Finally, those who had suspected cognitive impairment (defined as a score <24 on the Mini Mental State Examination) or depression (a score >9 on the Geriatric Depression Scale) were also excluded.

2.4. Ethical clearance

This study was approved by the Swinburne University Human Research Ethics Committee (project number 2013/057).

Selection criteria were followed in accordance with the published protocol [13].

Figure 1 outlines the recruitment profile of the 105 participants who entered the trial. Five participants left prior to initiation of any assessment. The 100 remaining participants, 28 males and 72 females, were assessed, of whom 93 responded to the question regarding their use of prescription medications. Among these 93 participants, 75% were prescribed more than two medications, 24% more than five medications, and 9% more than seven medications (mean 4.16, SD = 2.17).

2.5. Diet assessment

Diet was assessed using the Cancer Council of Victoria Dietary Questionnaire (Food Frequency Questionnaire [FFQ] for Epidemiological Studies Version 2 [DQES v2], November 2014) [14]. The output was utilised to produce a Mediterranean diet score (MedDietS) in accordance with Trichopoulou et al., 2003 [15]. The sex-specific median allows for a comparative cut-off to be made between genders on food consumption [15]. Beneficial foods, such as vegetables, legumes, fruits, nuts, cereals, and fish, were assigned a value of 0 if a person's consumption was below the median, and a score of 1 if it was equal to, or above, the median. Food components detrimental to health, such as meat, poultry, and dairy, consumption above the median was scored as 0, and intake below the median was scored as 1. For alcohol, a score of 1 was given provided consumption was within a specified range. When considering fat intake, the ratio of monounsaturated lipids to polyunsaturated lipids was evaluated, with a higher ratio being more acceptable and a score of 1 allocated accordingly. Kilojoules consumed was also reported within the FFQ. Thus, the total MedDietS ranged from 0 (minimal adherence to the traditional MedDiet) to 9 (maximal adherence) [15].

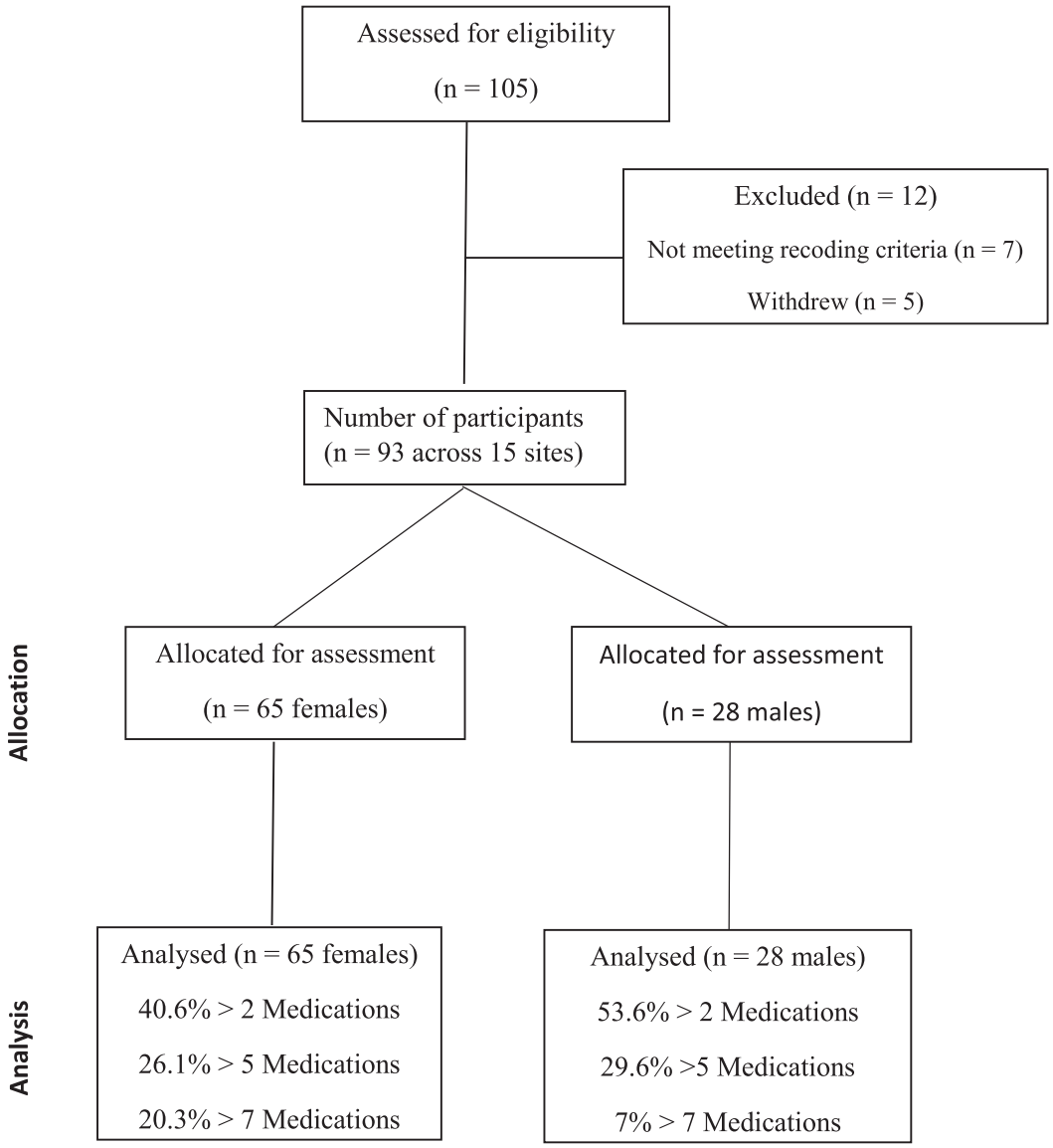

Fig. 1. Profile of participants.

2.6. Cognitive assessment

Assessment of cognitive performance utilised the Swinburne University Computerised Cognitive Assessment Battery (SUCCAB). The SUCCAB is a validated computer-based cognitive battery consisting of eight measures that focus on the cognitive domains that decline with increasing age and includes simple and choice reaction times, immediate and delayed recognition, congruent and incongruent Stroop colour-words, spatial working memory and contextual memory [16]. Speed of response to correctly performed trials was recorded for each of these measures. The analysis was focussed on response time to correctly performed trials; we have argued previously that response time is a particularly sensitive measure of cognitive ageing [16].

2.7. Medication assessment

All participants assessed at baseline had been evaluated as cognitively healthy, and during screening, usage of prescription and non-prescription medications was recorded. The medication data were recorded using a binary (Yes/No) measure.

2.8. Demographic and morphometric measures

Age, gender, education and smoking status were recorded as part of the study requirements. Height, weight, hip and waist circumference were measured and recorded.

2.9. Covariates and preliminary analysis

All food groups were calculated in grams per day and the total daily kilojoules consumed per day was also calculated. Age (in years) was calculated from self-reported birth date. Speed of response to each cognitive task was converted into a *Z*-score. Age, sex (gender), and daily energy intake were the control variables. Figure 2 shows the variable assessment process.

2.10. Statistical analysis

Cluster analyses were used to group 93 participants in terms of their cognitive measures and medications taken. Clustering allows the assignment of participants to groups with similar data patterns for the variables considered. Clustering enables structures to be

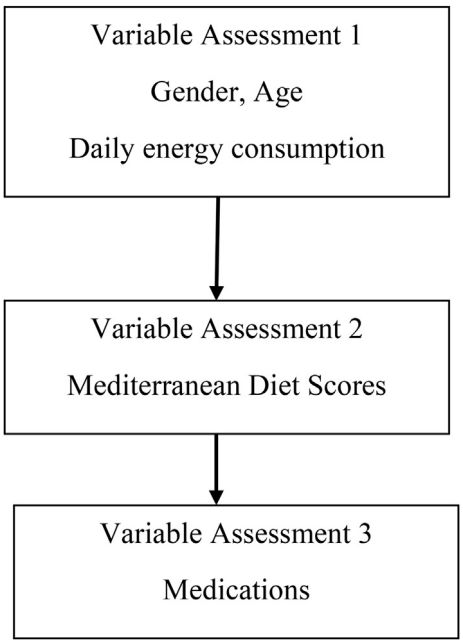

Fig. 2. The variable assessment stages.

identified within the data and relies on discriminant analysis to check if the group's differences are statistically significant and if all variables significantly discriminate between groups [17].

Participants were clustered in terms of their cognitive outcomes, as measured by the SUCCAB reaction time *Z*-scores for correctly performed trials, utilising Ward's method for hierarchical clustering. The resulting dendrogram suggested two clear SUCCAB cognitive clusters, which were compared in terms of average daily energy intake (kilojoules), MedDietS and age using ANOVA tests, while a comparison in terms of gender was carried out using a crosstab test.

Similarly, participants were clustered in terms of their prescribed medications, again using Ward's method but allowing for the binary nature of these data. The dendrogram suggested four clear clusters (see Fig. 3). The relationship between the medication and SUCCAB clusters was investigated using a crosstab test. Finally, hierarchical binary logistic regression analysis was used to determine the importance of MedDiet as a determinant of the cognition clusters, when controlling for medication cluster, age, gender, and average daily energy intake. All analyses were conducted using SPSS Statistics Version 23.

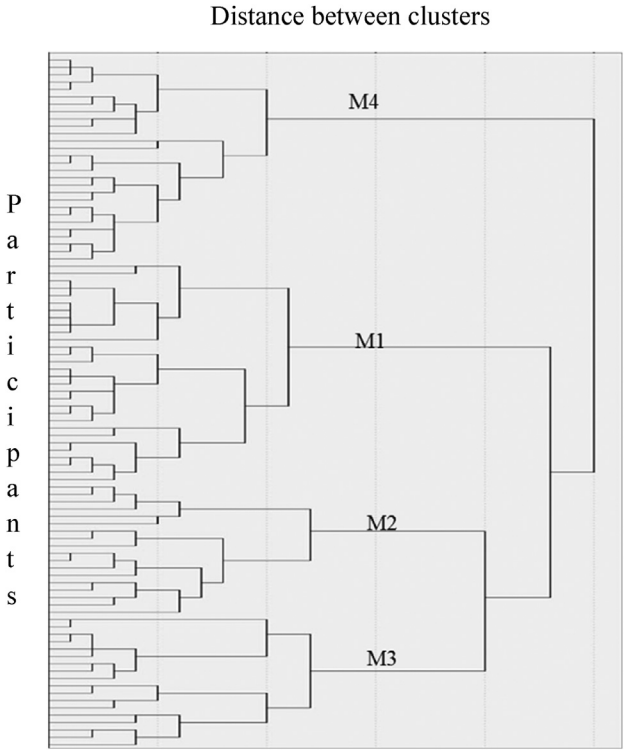

Fig. 3. Medication clustering. *M1 (Relatively healthy), M2 (Reflux concerns) M3 (Bone concerns) and M4 (Cardio-compromised) are the respective clusters.

3. Results

This study investigated the cognitive capabilities of an Australian cohort living in independent living aged care in relation to their adherence to a MedDiet and medication use.

Table 1 shows that the mean age of the combined group of participants was 78 years, with a relatively high mean BMI of 28.6, a high mean hip-to-waist ratio of 1.06, and a moderate level of consumption of alcohol and fats [18].

The cluster analysis for the SUCCAB measures suggested two clusters; the first containing 76 people with faster reaction times, while the second contained 17 people with relatively slow reaction times (see Appendix).

The cognitive assessments for the two SUCCAB clusters are depicted in Table 2. A significant difference was evident between the clusters for all the SUCCAB tasks. Mean performance accuracy is included in Table 2 for illustrative purposes.

Table 3 shows the comparison of the SUCCAB clusters in terms of age, total MedDietS, and average daily energy intake. These variables were used in subsequent analyses. Both clusters had a similar average age and there was no significant difference in MedDietS and daily energy intake (kJ) between the clusters. A cross tabulation test (Chi-squared = 4.65, df = 1, $p = 0.031$) showed a significantly higher percentage of females in the slower reaction time cluster (91%) than the faster reaction time cluster (67%).

Cluster analysis of medications prescribed, using binary data suggested four clusters (see Fig. 3). Fewer medications were taken by those in Cluster M1 than those in the other clusters ($t(89) = 7.82$, $p < 0.001$). Seventy-five percent of participants were using more than two medications, and 24% were taking more than five medications.

Details of the four clusters are explained in Table 4. The major medication groups within each group are shown as percentages.

Cluster M1 was a relatively healthy group, of whom 41.4% took blood pressure medication and 27.6% took omega-3 long chain fatty acids. With 13.8% on blood thinners and 3.4% taking cholesterol lowering drugs, it may suggest that general practitioners are taking precautionary measures for this group.

Table 1
Characteristics of the sample.

Participants	Mean (SD)
Age (years)	77.8 (6.73)
BMI (kg/cm)	28.6 (4.45)
Years of education	12.8 (3.52)
Blood pressure (sys/dias)	138/72 (16/10)
Alcohol g/day	116.78 (163)
Mono/saturated fats (g/day)	1.01 (0.13)

Table 2
Nonparametric (Mann–Whitney *U*) test comparison of scores for cognition clusters.

SUCCAB task	Mean reaction time *Z*-score (SD)			Mean performance accuracy, % (SD)		
	Faster reaction time ($N = 76$)	Slower reaction time ($N = 17$)	*Z*-test	Faster reaction time ($N = 76$)	Slower reaction time ($N = 17$)	*Z*-test
Simple reaction time	−0.24 (0.61)	1.09 (1.59)	−4.80***	100 (0)	100 (0)	0
Choice reaction time	−0.25 (0.59)	1.26 (1.42)	−5.01***	95.1 (5.3)	97.6 (4.1)	−2.10*
Immediate recognition	−0.36 (0.62)	1.12 (1.13)	−5.83***	76.1 (9.9)	75.7 (10.4)	−0.01
Delayed recognition	−0.23 (0.82)	0.84 (0.93)	−4.35***	71.3 (10.6)	73.1 (12.8)	−0.39
Congruent stroop	−0.23 (0.86)	1.00 (1.07)	−4.02***	97.3 (4.3)	98.2 (2.6)	−0.53
Incongruent stroop	−0.12 (0.77)	0.57 (1.71)	−2.321*	96.4 (5.6)	94.3 (11.4)	−0.56
Spatial working memory	−0.34 (0.71)	1.39 (0.99)	−5.73***	66.8 (9.6)	64.8 (7.9)	−0.92
Contextual memory	−0.19 (0.62)	0.74 (1.67)	−3.08**	79.9 (14.4)	75.0 (19.2)	−1.04

Note: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Table 3
Comparison of SUCCAB clusters.

	F stat	*p*-Value	Mean (SD) Faster reaction time ($N = 76$)	Mean (SD) Slower reaction time ($N = 17$)
Age	1.94	0.167	77.26 (7.25)	78.94 (6.02)
Total Mediterranean diet score	1.13	0.286	4.8 (1.53)	4.24 (1.79)
Energy intake, kJ (1000)/day	1.64	0.203	6.357 (1.876)	7.14 (2.91)

Table 4
Percentage of participants on each medication.

Medications	Medication clusters				
	Relatively healthy, $n = 29$	Reflux concerns, $n = 18$	Bone concerns, $n = 18$	Cardio-compromised, $n = 28$	Overall, $N = 93$
Angina	0.0	22.2	0.0	36.0	15
Antidepressants	10.3	0.0	5.6	25.0	11.8
Arrhythmias	0.0	27.8	22.2	10.7	12.9
Blood pressure	41.4	66.7	77.8	89.3	67.7
Blood thinners	13.8	27.8	33.3	53.6	32.2
Cholesterol drugs	3.4	38.9	33.3	96.4	44.1
Pain	6.9	72.2	11.1	2.1	19.4
Sleeping drugs	0.0	22.2	0.0	3.6	5.4
Ulcerations/reflux PPIs	13.8	83.3	16.7	17.9	29.0
Vitamin D	13.8	33.3	100.0	32.1	39.8
Vitamin B	6.9	38.9	16.7	0.0	12.9
Omega-3 fatty acids	27.6	16.7	44.4	0.0	20.4
Calcium	6.9	22.2	55.6	3.6	18.3
Glucosamine	6.9	5.6	33.3	3.6	10.8
CoQ10	0.0	0.0	16.7	3.6	4.3
Vitamin E	0.0	0.0	16.7	0.0	3.2
Magnesium	0.0	27.8	22.2	10.7	12.9
Women per group	19	15	16	15	65

Cluster M2, the group with reflux concerns had a moderate-to-high number of blood pressure medications, at 66.7%, pain medications, at 72.2%, and ulcer/reflux/protein pump inhibitors (83.3%). The high prescription of anti-ulcer drugs (H2 agonists) and protein pump inhibitors (PPIs) suggests that these patients are being treated for gastro-oesophageal reflux disease. This condition may lead to physical complications or symptoms that impact on well-being and quality of life; hence the substantial pain medication usage of 72.2%.

Cluster M3, the group with bone concerns. This group comprised mainly women, and had a moderate-to-high number of blood pressure medication (77.8%), omega-3 supplementation (44.4%), calcium supplements (55.6%), and vitamin D (100%). This was a very clear indication that they are being treated for osteopenia or osteoporosis.

Cluster M4, the cardio-compromised group, who had the highest number of blood pressure medication, at 89.3%, blood thinners, at 53.6%, and cholesterol lowering medication, at 96.4%, indicating that they are potentially being treated for coronary heart disease and/or metabolic syndrome. Although the medications taken by this cluster suggest that this group is cardio-compromised, Fig. 4 shows that they demonstrate a much faster cognitive reaction speed, which may be due in part to their medications potentially being cognitively protective.

The relationship between the cognitive speed clusters and medication clusters was found to be significant (Chi-squared = 10.63, df = 3, $p = 0.014$). As shown in Fig. 4, overall 18.3% of participants were assigned to the slow reaction time cluster, with the lowest percentage (3.6%) of these from the cardio-compromised medication cluster, a relatively low percentage (13.8%) from the relatively healthy medication cluster, rising to 27.8% for the reflux concern cluster and 38.9% for the bone concern medication cluster.

It is notable that Cluster M4, the group with the highest proportional use of blood pressure medications (angiotensin blocking drugs), and highest use of statins and blood thinners is well

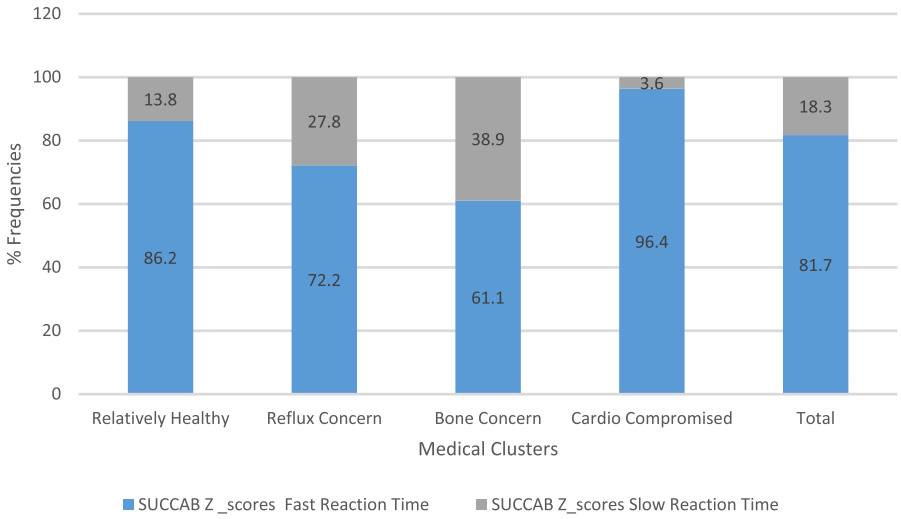

Fig. 4. Medication Cross tabulation clusters demonstrating reaction times.

represented in the fastest reaction time cluster (96.4%), while the relatively healthy cluster is less well represented in this cluster.

3.1. Binary logistic regression analysis for the SUCCAB clusters

The use of binary logistic regression is appropriate for predicting cognitive clusters as only two SUCCAB clusters were used, enabling us to explain the relationship between the SUCCAB clusters and the other variables of interest.

The assessment is staged. The control variables entered at Stage 1. The results given in Table 5 represent the control variables entered at Stage 1 and demonstrate no significant difference between the SUCCAB clusters in daily energy consumption, age and gender.

Stage 2 analyses are shown in Table 6, indicating that when the MedDietS is included, the average daily energy intake is significant with respect to the cognition clusters. The odds ratio of 1.33 suggests that for every additional kilojoule of average daily intake, the odds of belonging to the slower reaction time cluster increase by 33% on average when age, gender and MedDietS are controlled for. Although the MedDietS is trending to significance, average daily energy intake is the only significant predictor of SUCCAB cluster at Stage 2.

Stage 3 analysis included the medication clusters. Table 7 shows that when the medication clusters are included in the regression with the Cardio-Compromised (M4) cluster as the reference cluster, average daily energy intake and MedDietS are significant predictors for the SUCCAB clusters. In Table 7, Cluster M4 (the cardio-compromised cluster) is regarded as the reference category as this was the fastest reaction time group and it allowed for ease of interpretation. The odds ratio of 1.533 for average daily intake suggests that for every additional kilojoule, the odds of belonging to the slower reaction time cluster increase by 53% on average when age, gender, MedDietS and medication cluster are controlled for. The odds ratio of 0.573 for the MedDietS suggests that for every additional unit on the MedDietS the odds of belonging to the slower reaction time cluster decline by 43% on average when age, gender, average daily intake and medication cluster are controlled for. The odds ratio of 11.87 for the reflux concern cluster (M2) suggests that participants in this cluster are on average 11.87 times more likely than participants in the cardio-compromised cluster to fall into the

Table 5
Stage 1 binary logistic regression analysis.

Step 1 variables	*B*	SE	Wald (df = 1)	*p*-Value	Odds ratio for slower cluster, Exp(*B*)	95% CI for odds ratio	
						Lower limit	Upper limit
Daily energy intake (kJ × 10^3)	0.191	0.127	2.271	0.132	1.21	0.944	1.552
Age (years)	0.049	0.043	1.309	0.253	1.05	0.966	1.143
Male	−1.497	0.809	3.422	0.064	0.224	0.046	1.093
Constant	−6.297	3.562	3.126	0.077			

Note: no control variables are significant at stage 1.

Table 6
Stage 2 binary logistic regression analysis.

Step 2 variables	*B*	SE	Wald (df = 1)	*p*-Value	Odds ratio for slower cluster	95% CI for odds ratio	
						Lower limit	Upper limit
Average daily energy intake (kJ × 10^3)	0.285	0.14	4.168	0.041	1.33	1.011	1.749
Age	0.061	0.046	1.781	0.182	1.063	0.972	1.163
Male	−1.4	0.82	2.914	0.088	0.247	0.049	1.231
MedDiet score	−0.371	0.208	3.191	0.074	0.69	0.459	1.037
Constant	−6.227	3.715	2.808	0.094			

Table 7
Stage 3 binary logistics regression analysis.

Step 3 variables	*B*	SE	Wald (df = 1)	*p*-Value	Odds ratio for slower cluster	95% CI for odds ratio	
						Lower limit	Upper limit
Average daily energy intake (kJ × 10^3)	0.427	0.166	6.626	0.010	1.533	1.107	2.121
Age	0.051	0.049	1.1	0.294	1.053	0.957	1.158
Male	−0.837	0.893	0.879	0.349	0.433	0.075	2.492
Total Med score	−0.557	0.244	5.204	0.023	0.573	0.355	0.925
Relatively healthy (M1)	1.527	1.22	1.566	0.211	4.605	0.421	50.351
Reflux concerns (M2)	2.474	1.253	3.896	0.048	11.865	1.017	138.378
Bone concerns (M3)	3.504	1.255	7.801	0.005	33.248	2.844	388.743
Constant	−7.719	4.291	3.236	0.072	0.000		

slower reaction time cluster when age, gender, average daily intake and MedDietS are controlled for. Similarly, the odds ratio of 33.25 for the bone concern cluster (M3) suggests that participants in this cluster are on average 33.25 times more likely than participants in the cardio-compromised cluster (M4), to fall in the slower reaction time cluster when these variables are controlled for.

The summary of these results is shown in Table 8, suggesting that the effect of age and gender are not significant, while it appears that the effect of the MedDiet was suppressed until Stage 3 when medications were controlled for. Interestingly if the medication cluster is not taken into consideration, we do not see a significant effect of the MedDietS on cognitive outcomes.

The summary of results in Table 8 demonstrates that when the medication use is taken into consideration, a higher MedDietS is associated with a faster response during the performance of cognitive tasks, particularly with respect to immediate recognition and spatial working memory, which are the major discriminating variables for the two cognitive clusters. In addition, it was found that the cardio-compromised participants in Cluster 4, who were taking higher levels of blood pressure and statin medications, are more likely to have faster response times than participants in medication clusters M2 and M3, the reflux concerns and bone concerns clusters, but similar response times to participants in cluster M1, the relatively healthy cluster. The Hosmer Lemeshow test indicates that the final model describes the data well (Chi-square = 4.44, df = 8, $p = 0.816$), confirming that medication cluster needs to be accounted for when considering the relationship between MedDietS and cognition.

4. Discussion

Previous research has suggested that adherence to a Mediterranean diet has the potential to improve cognition, reduce cognitive impairment and cognitive decline and reduce the incidence of dementia [19–23]. However, a high prevalence of medication use in older individuals may also act to enhance, and preserve cognitive function in the longer term. Conversely medications may undermine cognitive function and any benefits afforded by adherence to a healthier diet. Previous studies have not considered these potential confounding effects of medications on MedDiet–cognition relationships.

The aim of this study was to investigate the association between adherence to a Mediterranean style diet and cognition in cognitive intact older adults living independently, and to determine the impact of medication use on cognitive outcomes. Based on previous findings it was expected that those with higher adherence to a MedDiet would show faster reaction times on the cognitive tasks performed [23]. As the MedDietS values only showed a trend to significance, we further investigated, potential confounding influences of medication use. It was postulated that the medications taken by the participants may influence their MedDietS, and subsequently, their cognitive reaction time assessments. In fact, without taking into consideration the impact of medications, we were unable to demonstrate the association between adherence to a MedDiet and cognitive outcomes.

All the participants in the present study had been assessed as cognitively healthy and were living independently in aged care and retirement villages. At the time of assessment their potential underlying medical conditions had been managed by their medical practitioner and where required, prescribed particular medications to normalise their conditions in order to control the underlying identified comorbidities.

A large proportion of the participants in our trial had been prescribed various antihypertensive drugs such as, angiotensin–converting enzyme inhibitors (ACE), diuretics (D), beta-blockers (BB), and angiotensin receptor blockers (ARB). In the "cardio-compromised group," 89% of participants were using an ACE, ARB, D or BB medications. Interestingly, this cardio-compromised group had the fastest response times as compared with the other medication clusters and were comparatively similar to the "Relatively healthy" cluster. A recent network meta-analysis compared antihypertensive drugs with respect to the incidence of dementia and cognitive function, demonstrating that all antihypertensive drugs may to some extent be cognitively protective; in particular ARB's showed significant benefits to cognitive functioning compared with placebo [24]. Further studies need to be conducted to substantiate our current results with regard to antihypertensive drugs and cognitive performance.

High levels of midlife total cholesterol have been associated with compromised late life episodic memory, slower psychomotor speed [25–27] and a higher risk of Alzheimer's disease (AD) [28]. It would therefore be expected that the maintenance of lower cholesterol levels through statin use (44% overall and 96% in the cardio-compromised group), would also confer ongoing benefits to cognitive health [29,30]. However, a number of studies also indicate

Table 8
Summary of binary logistic regression analysis for the SUCCAB clusters.

Predictors	Odds ratios for slower reaction time cluster		
	Stage 1	Stage 2	Stage 3
Average daily energy intake (kJ × 10^3)	1.21	1.33**	1.53*
Age	1.05	1.06	1.05
Gender	0.22	0.25	0.43
Mediterranean diet score		0.69	0.57*
Cardio-compromised cluster (M4)			1.00
Relatively healthy cluster (M1)			4.61
Reflux concern cluster (M2)			11.87*
Bone concern cluster (M3)			33.25**

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

that statin medications may themselves impact adversely on cognition, possibly through side effects including increased physical and mental fatigue [31,32]. While prescribed medications are critical for ongoing patient medical care, these other factors may act to confound the understanding of diet–cognition relationships. Clearly more research is needed to better understand positive and negative impacts on cognitive health of both antihypertensive and statins medications; dosage, duration and different drug classes.

A relatively large proportion (25%) of participants in the cardio-compromised cluster were also taking antidepressant medications. Research suggests that these medications have a significant positive effect on psychomotor speed and delayed memory recall [33] and no adverse impact on the risk of cognitive decline leading to dementia [34]. Pain medication usage was high within the reflux group (72%) and may explain the slower reaction times observed in this cluster. Previous studies that have evaluated pain experiences, such as radicular or neuropathic pain, reported a basic slowing of reaction times. For example, slowing was observed in relation to incongruent and congruent Stroop stimuli trials, irrespective of other comorbidities and pain medication [35,36]. Research within this area is complex and further focused cognitive clinical research needs to be conducted to gain a clearer understanding of pain and related pain therapy and relationships with cognition [36].

Overall this study has found that when medication use was taken into consideration, that a higher adherence to a MedDiet is associated with faster cognitive reaction times. Interestingly the cardio-compromised group was the cluster with the fastest response times; suggesting that the medications also acted to normalise cognitive function. However, there may be other instances where medication use may have adversely affected cognition; this premise requires further investigation.

The participants in this study were screened as cognitively healthy – a key inclusion criterion for entry into the present study. Through analysis of medication clusters it has become apparent that cognitive status may also depend on medication use and that this is an important factor to take into account when considering the impact of diet on cognitive status. The alternative is to exclude all individuals that are taking medications from similar studies. As observed in our sample, there is a very high prevalence of medication use in older, independently living Australians. Excluding individuals taking medications would result in a sample that is not representative of the general population. Instead, we suggest that medication use be recorded and included in statistical analysis. Moreover, we suggest that previous studies in older cohorts that were not able to establish a relationship between MedDiet adherence and cognition may have been confounded by medication use.

4.1. Strengths and limitations

A key strength of this study is that the population of participants recruited were cognitively healthy and living in a homogenous environment, yet the profile of medications was diverse. All participants were tested within their own independent living facilities reducing potential confounding effects of travel time and assessment within an unfamiliar University setting. Age-sensitive computerised cognitive assessments were used to investigate dietary influences of a MedDiet, taking medications into account.

A limitation of the study is the disproportionate sampling of women (70%) compared with men, a characteristic that is typical of independent living and aged care facilities in Australia [37]. Gender was considered as a control variable in our statistical analysis but did not significantly impact on relationships. Nevertheless, future studies should aim to achieve a gender balance in their cohorts. A further limitation of the current study is that medication dosage and duration was not assessed; only type of medication was recorded given that this was a secondary outcome of the study. Future studies may consider more specific aspects of medication usage, including the class of drug, dosage and length of medication use.

5. Summary and conclusion

This study of a random selection of participants living independently within aged care facilities has demonstrated that those who have a higher MedDietS perform faster on cognitive assessments only when medication use has been taken into account. Previous research has suggested that medications act to normalise health and potentially stabilize cognitive function, however, no previous studies have taken medications into account when considering the association between adherence to a MedDiet and cognitive performance. Larger cross sectional and longitudinal studies need to be conducted to properly evaluate this proposition.

Authors and contributors

All authors made a substantial contribution to the conception and design of this research, and all authors have been involved in critically revising the work for important intellectual content. The final approval of the version to be published has been agreed by all authors and an agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval and registration

Ethical approval was granted by Swinburne University of Technology Human Research Ethics Committee-SUHREC 2013/057. The trial was registered with the Australia and New Zealand Clinical Trials Registry [ACTRN12614001133628]. The Universal trial number is U1111-1161-5364.

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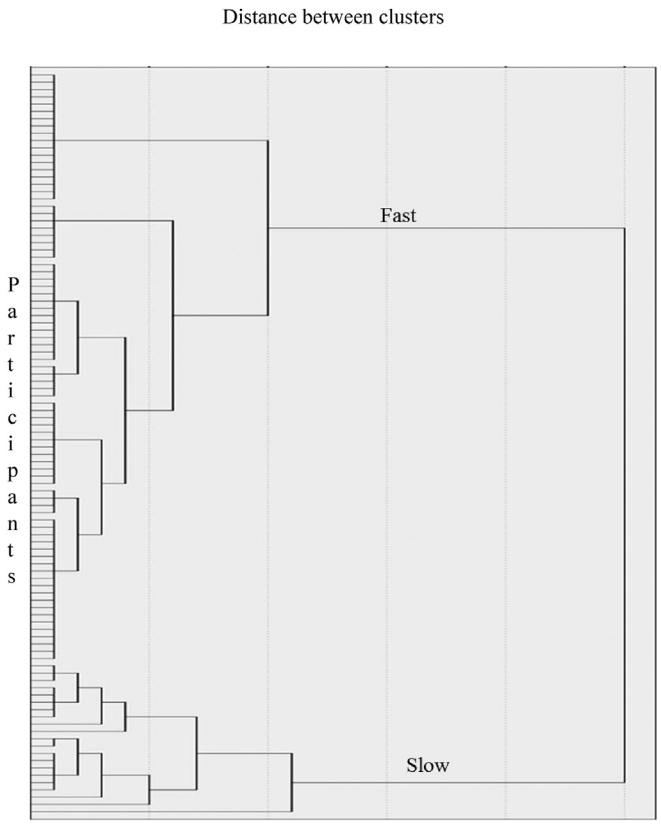
Appendix. Reaction time dendrogram for the SUCCAB showing two clear clusters



References

[1] Zobel EH, Hansen TW, Rossing P, von Scholten BJ. Global changes in food supply and the obesity epidemic. Curr Obes Rep 2016;5(4):449–55. https://doi.org/10.1007/s13679-016-0233-8.

[2] Gotsis E, Anagnostis P, Mariolis A, Vlachou A, Katsiki N, Karagiannis A. Health benefits of the Mediterranean diet: an update of research over the last 5 years. Angiology 2015;66(4):304–18. https://doi.org/10.1177/0003319714532169.

[3] Fitzpatrick AL, Kuller LH, Lopez OL, Diehr P, O'Meara ES, Longstreth WT, et al. Midlife and late-life obesity and the risk of dementia cardiovascular health study. Arch Neurol 2009;66(3):336–42.

[4] Mattson MP, Maudsley S, Martin B. A neural signaling triumvirate that influences ageing and age-related disease: insulin/IGF-1, BDNF and serotonin. Ageing Res Rev 2004;3(4):445–64. https://doi.org/10.1016/j.arr.2004.08.001.

[5] Babio N, Toledo E, Estruch R, Ros E, Martinez-Gonzalez MA, Castaner O, et al. Mediterranean diets and metabolic syndrome status in the PREDIMED randomized trial. Can Med Assoc J 2014;186(17):E649–57. https://doi.org/10.1503/cmaj.140764.

[6] Starr JM, McGurn B, Whiteman M, Pattie A, Whalley LJ, Deary IJ. Life long changes in cognitive ability are associated with prescribed medications in old age. Int J Geriatr Psychiatry 2004;19(4):327–32. https://doi.org/10.1002/gps.1093.

[7] Trichopoulou A, Kyrozis A, Rossi M, Katsoulis M, Trichopoulos D, La Vecchia C, et al. Mediterranean diet and cognitive decline over time in an elderly Mediterranean population. Eur J Nutr 2015;54(8):1311–21. https://doi.org/10.1007/s00394-014-0811-z.

[8] Feart C, Samieri C, Alles B, Barberger-Gateau P. Potential benefits of adherence to the Mediterranean diet on cognitive health. Proc Nutr Soc 2013;72(1):140–52. https://doi.org/10.1017/s0029665112002959.

[9] Keys A, Menotti A, Karvonen MJ, Aravanis C, Blackburn H, Buzina R, et al. The diet and 15-year death rate in the 7 countries study. Am J Epidemiol 1986;124(6):903–15.

[10] Hardman Roy J, Kennedy G, Macpherson Helen, Scholey Andrew B, Pipingas Andrew. Adherence to a Mediterranean-style diet and effects on cognition in adults: a qualitative evaluation and systematic review of longitudinal and prospective trials. Front Nutr 2016;3. https://doi.org/10.3389/fnut.2016.00022. Article 22.

[11] Petersson SD, Philippou E. Mediterranean diet, cognitive function, and dementia: a systematic review of the evidence. Adv Nutr 2016;7(5):889–904. https://doi.org/10.3945/an.116.012138.

[12] Crichton GE, Bryan J, Hodgson JM, Murphy KJ. Mediterranean diet adherence and self-reported psychological functioning in an Australian sample. Appetite 2013;70:53–9. https://doi.org/10.1016/j.appet.2013.06.088.

[13] Hardman RJ, Kennedy G, Macpherson H, Scholey AB, Pipingas A. A randomised controlled trial investigating the effects of Mediterranean diet and aerobic exercise on cognition in cognitively healthy older people living independently within aged care facilities: the Lifestyle Intervention in Independent Living Aged Care (LIILAC) study protocol [ACTRN12614001133628]. Nutr J 2015:14. https://doi.org/10.1186/s12937-015-0042-z.

[14] Victoria CCo. Internet: http://www.cancervic.org.au/research/epidemiology/nutritional_assessment_services1.

[15] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med 2003;348(26):2599–608. https://doi.org/10.1056/NEJMoa025039.

[16] Pipingas A, Harris E, Tournier E, King R, Kras M, Stough CK. Assessing the efficacy of nutraceutical interventions on cognitive functioning in the elderly. Curr Top Nutraceutical Res 2010;8(2–3):79–87.

[17] Murtagh F, Legendre P. Ward's hierarchical agglomerative clustering method: which algorithms implement ward's criterion? J Classif 2014;31(3):274–95. https://doi.org/10.1007/s00357-014-9161-z.

[18] Magarey AM, Daniels LA, Boulton TJC. Prevalence of overweight and obesity in Australian children and adolescents: reassessment of 1985 and 1995 data against new standard international definitions. Med J Aust 2001;174(11):561–4.

[19] Tsivgoulis G, Judd S, Letter AJ, Alexandrov AV, Howard G, Nahab F, et al. Adherence to a Mediterranean diet and risk of incident cognitive impairment. Neurology 2013;80(18):1684–92.

[20] Ye X, Scott T, Gao X, Maras JE, Bakun PJ, Tucker KL. Mediterranean diet, healthy eating index 2005, and cognitive function in middle-aged and older Puerto Rican adults. J Acad Nutr Dietetics 2013;113(2):276–81.

[21] Gardener SL, Rainey-Smith SR, Barnes MB, Sohrabi HR, Weinborn M, Lim YY, et al. Dietary patterns and cognitive decline in an Australian study of ageing. Mol Psychiatry 2015;20(7):860–6. https://doi.org/10.1038/mp.2014.79.

[22] Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martinez-Gonzalez MA, et al. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern Med 2015;175(7):1094–103. https://doi.org/10.1001/jamainternmed.2015.1668.

[23] Hardman RJ, Kennedy G, Macpherson H, Scholey AB, Pipingas A. Adherence to a Mediterranean-style diet and effects on cognition in adults: a qualitative evaluation and systematic review of longitudinal and prospective trials. Front Nutr 2016;3(22). https://doi.org/10.3389/fnut.2016.00022.

[24] Marpillat NL, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. J Hypertens 2013;31(6):1073–82. https://doi.org/10.1097/HJH.0b013e3283603f53.

[25] Solomon A, Kareholt I, Ngandu T, Wolozin B, MacDonald SWS, Winblad B, et al. Serum total cholesterol, statins and cognition in non-demented elderly. Neurobiol Aging 2009;30(6):1006–9. https://doi.org/10.1016/j.neurobiolaging.2007.09.012.

[26] Fratiglioni L, Mangialasche F, Qiu C. Brain aging: lessons from community studies. Nutr Rev 2010;68(12):S119–27. https://doi.org/10.1111/j.1753-4887.2010.00353.x.

[27] Ma CR, Yin ZX, Zhu PF, Luo JS, Shi XM, Gao X. Blood cholesterol in late-life and cognitive decline: a longitudinal study of the Chinese elderly. Mol Neurodegener 2017:12. https://doi.org/10.1186/s13024-017-0167-y.

[28] Rantanen KK, Strandberg AY, Pitkala K, Tilvis R, Salomaa V, Strandberg TE. Cholesterol in midlife increases the risk of Alzheimer's disease during an up to 43-year follow-up. Eur Geriatr Med 2014;5(6):390–3. https://doi.org/10.1016/j.eurger.2014.05.002.

[29] Barone E, Di Domenico F, Butterfield DA. Statins more than cholesterol lowering agents in Alzheimer disease: their pleiotropic functions as potential therapeutic targets. Biochem Pharmacol 2014;88(4):605–16. https://doi.org/10.1016/j.bcp.2013.10.030.

[30] Samaras K, Brodaty H, Sachdev PS. Does statin use cause memory decline in the elderly? Trends Cardiovasc Med 2016;26(6):550–65. https://doi.org/10.1016/j.tcm.2016.03.009.

[31] Gnjidic D, Naganathan V, Ben Freedman S, Beer CE, McLachlan AJ, Figtree GA, et al. Statin therapy and cognition in older people: what is the evidence? Curr Clin Pharmacol 2015;10(3):185–93. https://doi.org/10.2174/1574884710031508201522249.

[32] Chatterjee S, Krishnamoorthy P, Ranjan P, Roy A, Chakraborty A, Sabharwal MS, et al. Statins and cognitive function: an updated review. Curr Cardiol Rep 2015;17(2). https://doi.org/10.1007/s11886-014-0559-3.

[33] Rosenblat JD, Kakar R, McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int J Neuropsychopharmacol 2016;19(2). https://doi.org/10.1093/ijnp/pyv082.

[34] Bali V, Holmes HM, Johnson ML, Chen H, Fleming ML, Aparasu RR. Comparative effectiveness of second-generation antidepressants in reducing the risk

of dementia in elderly nursing home residents with depression. Pharmacotherapy 2016;36(1):38–48. https://doi.org/10.1002/phar.1680.
[35] Hu KS, Fan ZW, He SC. Uncovering the interaction between empathetic pain and cognition. Psychol Res Psychol Forsch 2015;79(6):1054–63. https://doi.org/10.1007/s00426-014-0634-9.
[36] Ferreira KD, Oliver GZ, Thomaz DC, Teixeira CT, Foss MP. Cognitive deficits in chronic pain patients, in a brief screening test, are independent of comorbidities and medication use. Arq Neuropsiquiatr 2016;74(5):361–6. https://doi.org/10.1590/0004-282x20160071.
[37] Australian Bureau of Statistics AG.