



Relationship between mobility and cognitive impairment in patients with Alzheimer's disease



Paula Domenech-Cebrían^a, Mary Martinez-Martinez^b, Omar Cauli^{a,*}

^a Department of Nursing, University of Valencia, Valencia, Spain

^b Geroresidencias, La Saleta, Valencia, Spain

ARTICLE INFO

Keywords:

Mobility
Barthel index
Katz index
Cognitive impairment
Dementia
Institutionalization
Lipids

ABSTRACT

Objective: Alzheimer's disease (AD) is usually accompanied by impairments to mobility, performance of the basic activities of daily life (ADL), and progressive cognitive decline. We analyzed the relationship between cognitive performance and related cognitive subdomains and mobility.

Patients and Methods: All AD patients of the recruited individuals were living in nursing homes; they underwent a blood analysis, cognitive examination by using the Mini-Mental State Examination, functional evaluation of independence in the ADLs with Barthel score and Katz index, and mobility assessment with the elderly mobility scale.

Results: The mean sample age was 84 years and majority were women; more than 60% of the participants had severe cognitive impairment. Statistically significant relationships were found between the severity of cognitive impairment and functional capacity ($p < 0.01$) and their degree of mobility ($p < 0.05$). Among the different domains, memory impairment was not associated with impaired mobility or ability to perform the ADLs. Women had lower scores in the ADL and mobility assessments ($p < 0.05$) and an increased ratio of severe cognitive impairment (OR = 3.03 95% CI: [1.30, 7.05]) compared to men. Being overweight or obese and high blood levels of HDL cholesterol were directly ($p < 0.05$) and inversely ($p < 0.01$) associated with poor cognitive performance in individuals with mild to moderate cognitive dysfunction, respectively.

Conclusions: This study shows that better functional capacity and mobility are generally, but not exclusively, correlated with better cognitive function, depending on the severity of cognitive impairment. In contrast, lipid profile alterations might play a role in cognitive deficits in individuals with mild to moderate cognitive impairment who are overweight. Further longitudinal studies will be required to explore this possibility.

1. Introduction

Neurocognitive disorders (DMS-V) formerly called dementias, are a group of diseases which are of increasing public health concern because of their huge economic and social burden and the resulting poor quality of life they generate both for patients and their caregivers [1,2]. It is estimated that in the next few decades the number of people with neurocognitive disorders will reach 130 million worldwide [3]. A higher incidence of cognitive impairment is observed among older people who are institutionalized in nursing homes [4,5]. According to the RESYDEM study, a recent multicenter study of 852 residents of public, private, and state-assisted nursing homes throughout Spain, the prevalence of cognitive impairment because of neurodegenerative diseases in older institutionalized people is more than 60%. Alzheimer's disease (AD) the most prevalent acquired cognitive impairment [5,6]

and is more common among women, e.g. among Spanish institutionalized individuals, its prevalence is 23% in females and 5% in males [4].

Apart from deficits in cognition and behavior [7], deficits in mobility, balance, gait, and movement coordination are also found in people with cognitive impairment due to neurodegenerative diseases [8–11] and these lead to an increased disease burden and huge socio-economic costs. Individuals with cognitive impairment caused by dementias are less likely to participate in regular physical exercise compared to their counterparts with normal cognitive function because of lack of motivation [12]. Furthermore, physical inactivity can give rise to further decline in physical functioning [13]. These factors may partially explain the higher risk of falls and hip fractures in people with dementia compared with their peers without dementia [14]. An accurate level of mobility and the ability to perform any kind of physical

* Corresponding author at: University of Valencia, c/ Jaume Roig s/n, 46010, Valencia, Spain.

E-mail address: Omar.Cauli@uv.es (O. Cauli).

<https://doi.org/10.1016/j.clineuro.2019.02.015>

Received 30 June 2018; Received in revised form 5 February 2019; Accepted 16 February 2019

Available online 18 February 2019

0303-8467/ © 2019 Elsevier B.V. All rights reserved.

activity has both mental and physical beneficial effects [15–17] and so interventions and rehabilitation are important in the maintenance of mobility and for the performance of the activities of daily life (ADLs). It is also important to study their relationship in individuals with acquired cognitive impairment whose leading cause among older institutionalized individuals is AD.

According to one study, there is a significant association between the autonomy and independence of older adults and their impairment as a result of institutionalization [18]. In other words, institutionalization is harmful and is linked to an increased probability of suffering impaired mobility and autonomy from the time individuals are institutionalized. So far, no studies have directly analyzed the relationship between the severity of cognitive impairment, mobility, and the ability to perform the ADLs in institutionalized older individuals with AD [19,20]. Such analyses are crucial to be able to tailor different rehabilitative interventions, increase mobility, and the level of independence among individuals with cognitive impairment. Although cognitive impairment is irreversible, strengthening mobility and improving functional ability would help to slow down the progression of cognitive disorders. Indeed, responses in terms of the improved performance of the ADLs have been demonstrated among patients with different cognitive abilities in response to rehabilitation programs [21].

The main aim of our study was:

To determine the relationship between mobility status and functional ability in institutionalized individuals with AD.

Secondary aims were:

To evaluate mobility status and functional ability as a function of age, sex, the pathology causing cognitive impairment, poly medication, body mass index (BMI), and blood biochemical parameters.

To determine how these aforementioned associations relate to the basic cognitive subdomains e.g. orientation, fixation, memory, language, and concentration.

2. Material and methods

2.1. Sample

The study sample was recruited between 2015 and 2016 at four nursing homes in the Valencia province (Spain). In accordance with the requirements established by the Declaration of Helsinki, written consent was obtained from each person (or from their relatives when the patient was unable to understand), after having been informed in a clear and simple way of the purpose of the study and the procedures involved. The study protocol was approved by the Human Research Ethics Committee at the University of Valencia (Reference: H38417528).

2.1.1. Inclusion criteria

The following inclusion criteria were established: adults of both sexes, aged 65 and over, outpatients or people living in a nursing home; stable drug treatment for at least three months; and known diagnosis of AD. The severity of the cognitive impairment was assessed by the Lobo test (adapted Spanish version of the Mini-Mental State Examination [MMSE]). The exclusion criteria were: current or recent (< 3 months) hospitalization; diagnosis of cancer; or blindness.

2.1.2. Sociodemographic variables

The sociodemographic variables recorded were sex, age, marital status, place of residence, BMI, and poly medication status.

2.1.3. Functional and cognitive evaluation

Each individual underwent a complete clinical, geriatric, and functional assessment. Four validated scales were used to evaluate the functional and cognitive areas: the Barthel Index [22], Katz index [23], elderly mobility scale [24], and the 'Mini-Examen Cognoscitivo' [25]. The Barthel Index assesses the ability to perform the ADLs (Cronbach's

alpha 0.90-0.92), and measures independence with 10 items, with a score range of 0–100. The items assessed are: feeding, bathing, grooming, dressing, urine and fecal continence, toilet use, transfers (bed to chair and back), mobility (on level surfaces), and ability to use stairs. The Barthel index represents the actual (not potential) functioning [22]. A lower score indicates greater dependence, while a higher score indicates greater independence, with 0 representing total dependence and 100 total independence.

Preservation of independence in functional abilities: independence in ADLs was assessed by nurse-reported difficulties with the basic activities of daily living (bathing, dressing, using the toilet, transfers, continence, and eating) over the previous 30 days [26]. The Katz Index (Cronbach's alpha 0.90-0.92), ranks the adequacy of the patient's performance and assigns a yes/no score for independence in each of the six ADL functions. The Katz test score can be categorized as follows: "No inability/mild inability" for groups A and B, "Moderate inability" for groups C and D, and "Severe inability" for groups E, F, and G.

Mobility was assessed using the EMS (Cronbach's alpha 0.90), a 20-point validated tool for assessing the frailty of elderly subjects [24]. The EMS assesses gait based on the type of assistance the patient requires to walk: maximum points are assigned if the individual can safely walk with no aid or if they use one walking stick. Those who use a frame, rollator, 2 walking sticks, or crutches receive lower scores. This differentiation is important because frame and rollator users have been shown to have weaker lower limbs (in terms of leg extensor power), and poorer functional performance in terms of walking speed, stair climbing, and chair raises [27]. Patients whose EMS score is under 10 are generally dependent on mobility maneuvers; require help with the basic ADLs such as transfers, using the toilet, and dressing; patients with EMS scores between 10 and 13 are usually borderline in terms of safe mobility and ADL independence i.e., they require some help with some mobility maneuvers; those with EMS scores over 14 can generally perform mobility maneuvers alone and safely and are independent in the basic ADLs.

The MEC is the Spanish version of MMSE and comprises 11 items that screen cognitive impairment by assessing 5 cognitive areas: orientation (temporal and spatial), attention and calculation, word recall, language, and visuospatial abilities. The maximum MEC score is 35 points and scores lower than 30 points suggest the presence of cognitive impairment. Specifically, normal cognitive function scores 30–35 points, borderline cognitive deficits score 29–25 points, mild cognitive impairment scores 24–20 points, moderate cognitive impairment scores 15–19 points, and severe cognitive impairment receive ≤ 14 points [25,28].

2.1.4. Blood analytical parameters

Blood samples were obtained from each patient between 7:30 a.m. and 10 a.m. after at least 8 h in fasting conditions; 10 mL of blood was collected from each patient into BD Vacutainer tubes (Becton Dickinson). After extraction, the blood samples were allowed to stand for 15 min and were centrifuged at 1500 rpm for 10 min at room temperature. Subsequently the serum supernatants were aliquoted and stored at -20°C until analysis. After thawing, the samples were centrifuged at 1500 rpm for 10 min at room temperature to completely remove all cells. For all other analytical determinations, residential center control blood extractions were used. Biochemical parameters (hemoglobin, glucose, urea, HDL cholesterol, LDL cholesterol, triglycerides, total proteins, creatinine, glutamic oxaloacetic transaminase [GOT], serum glutamic pyruvic transaminase [GPT], calcium, sodium, and potassium) were measured in clinical laboratories belonging to local public health centers. Serum analytic values were determined on a laboratory chemistry analyzer (Dimension Xpand Plus Integrated Chemistry System, Siemens, Erlangen, Germany).

2.1.5. Statistical analysis

The quantitative variables were subjected to a descriptive analysis

Table 1
Main characteristics of the sample.

Age	Mean ± SE: 83,8 ± 5.5 years (Minimum 64 –Maximum 95)	
Polypharmacy	Mean ± SE: 11.6 ± 4.7 (Minimum 4 –Maximum 23)	
BMI	Mean ± SE: 28.2 ± 5.6 years (Minimum 17 –Maximum 43)	
Gender		n (%)
	Man	21 (23.1%)
	Woman	70 (76.9%)

using central tendency and dispersion measures. Likewise, a descriptive analysis was also performed for the qualitative variables, based on frequency distributions. The Kolmogorov–Smirnov test was used to estimate the normal distribution of quantitative variables and thus, to define the type of test to be used (parametric or nonparametric). The differences between the means of two or more groups were analyzed using nonparametric tests (Mann–Whitney U or Kruskal–Wallis tests). The confidence level used for all the analyses was 95%, with a statistical significance of $p < 0.05$. The IBM SPSS statistical package (version 24.0) was used for all the statistical analyses.

3. Results

3.1. Characteristics of the sample

The main characteristics of the study sample ($N = 91$) are shown in Table 1. Male patients consumed a significantly higher number of drugs per day (8.3 ± 1.4 drugs) compared to women (6.4 ± 0.6 drugs, $p < 0.05$ Mann–Whitney U test). No significant differences were observed between men and women for age ($p = 0.18$, Mann–Whitney U test), or BMI ($p = 0.95$, Mann–Whitney U test). Regarding the BMI, 3.8% ($n = 3$) were underweight (BMI < 18.5), 30.8% ($n = 28$) had a normal weight (BMI 18.5–24.9), 30.8% ($n = 28$) were overweight (BMI 25–29.9), and 35.2% ($n = 28$) were obese (BMI > 30). There were no significant differences in the distribution of the BMI groups ($p = 0.90$, Chi-square test) or polypharmacy ($p = 0.39$, Kruskal–Wallis test) in terms of the diagnostic classes.

3.2. Analysis of functional mobility and cognitive impairment

The results of our evaluation of mobility using the EMS scale and ability to perform the ADLs using the Barthel index and Kats scale, as well as cognitive function and cognitive subdomain data are shown in Table 2. There was a significant difference between women and men in their ability to perform the ADLs (39.8 ± 3.7 women and 60.2 ± 5.4 men, $p < 0.05$, Mann–Whitney U test) and for the EMS (10.6 ± 0.8 women and 16.4 ± 0.8 men, $p < 0.001$, Mann–Whitney U test). No significant differences were observed between the sexes for the number of drugs administered daily for chronic conditions ($p = 0.07$, Mann–Whitney U test). Regarding the cognitive subdomains, compared to women, men showed significantly better overall scores ($p < 0.05$,

Table 2
Mobility, ability to perform basic daily activities and cognitive function.

EMS Scale	11.9 ± 6.9 (0-20)*	
Katz scale	A-B (mild inability)	20 (22.0%)
	C-D (moderate inability)	14 (15.4%)
	E-F-G (severe inability)	57 (62.6%)
Barthel index	44.5 ± 31.1 (0-100)	
Total cognitive score	10.2 ± 9.0 (0-28)	
Orientation score	2.4 ± 2.6 (0-10)	
Fixation score	1.9 ± 1.3 (0-3)	
Concentration score	1.3 ± 2.0 (0-7)	
Memory score	0.2 ± 0.4 (0-2)	
Language score	4.6 ± 3.9 (0-11)	

Mann–Whitney U test) and MMSE concentration subdimension scores ($p < 0.01$, Mann–Whitney U test).

3.3. Correlation between mobility, performance of daily activities, and cognitive function

There was a significant correlation between performance of the ADLs (Barthel index) and mobility (EMS scale; $Rho = 0.78$, $p < 0.001$, Spearman test; Fig. 1A). In addition, the different levels of independence in the ADLs were also significantly different (expressed as categories on the Katz scale) and Barthel index score ($p < 0.001$ Kruskal–Wallis test) or mobility (EMS scale; $p < 0.001$ Kruskal–Wallis test). Moreover, these correlations or group differences remained significant after controlling for covariables such age, sex, polypharmacy, and BMI ($p < 0.05$ in all cases). There was a significant positive correlation between cognitive function and ADL performance (Barthel index; $Rho = 0.52$, $p < 0.001$, Spearman test, Fig. 1B), and mobility (EMS scale; $Rho = 0.42$, $p < 0.001$, Spearman test, Fig. 1C). The different levels of independence in the ADLs (expressed as categorized variables based on the Katz scale) and cognitive function ($p < 0.01$ Kruskal–Wallis test) were also significantly different.

Analysis of the different cognitive subdomains revealed a significant correlation between the Barthel index and the orientation ($Rho = 0.52$, $p < 0.001$, Spearman test), fixation ($Rho = 0.51$, $p < 0.001$, Spearman test), concentration ($Rho = 0.49$, $p < 0.001$, Spearman test), and language scores ($Rho = 0.56$, $p < 0.001$, Spearman test). In contrast, no significant correlation was observed between the Barthel index score and memory score ($Rho = 0.09$, $p = 0.39$, Spearman test). Analysis of the different cognitive subdomains revealed a significant correlation between mobility (EMS scale) and the orientation ($Rho = 0.45$, $p < 0.001$, Spearman test), fixation ($Rho = 0.41$, $p < 0.001$, Spearman test), concentration ($Rho = 0.35$, $p < 0.001$, Spearman test), and language scores ($Rho = 0.46$, $p < 0.001$, Spearman test). In contrast, no significant correlation was observed between mobility (EMS scale) and the memory score ($Rho = 0.02$, $p = 0.82$, Spearman test). These associations remained significant or non-significant (memory score) after controlling for age, sex, polypharmacy, and BMI covariables (data not shown).

3.4. Analysis of individuals with mild to moderate cognitive impairment

Because 63.7% of the sample had severe cognitive impairment which was strongly correlated with low or absent mobility and a high level of dependence, next we analyzed the relationship between mobility, performance of the basic ADLs, and cognitive function in individuals with AD with mild to moderate cognitive impairment. In this analysis, there was no significant correlation between cognitive function and performance of the ADLs (Barthel index, $Rho = -0.09$, $p = 0.42$, Spearman test, Fig. 2A), and mobility (EMS scale, $Rho = -0.04$, $p = 1.0$, Spearman test). In contrast, there was an inverse and significant correlation between cognitive function and BMI in individuals with moderate cognitive impairment ($Rho = -0.31$, $p < 0.05$, Spearman test, Fig. 2B), but not with age ($Rho = -0.5$, $p = 0.75$, Spearman test) or polypharmacy ($Rho = 0.9$, $p = 0.58$, Spearman test), and there were no sex differences ($p = 0.09$ Mann–Whitney U test). Within the cognitive areas, the BMI index inversely correlated with orientation ($Rho = -0.33$, $p < 0.05$, Spearman test, Fig. 2C) and memory ($Rho = -0.30$, $p < 0.05$, Spearman test, Fig. 2D), although other cognitive subdomains were not significantly correlated with BMI ($Rho = 0.0$, $p = 1.0$ for the fixation score; $Rho = 0.40$, $p = 0.80$ for the concentration score; and $Rho = -0.16$, $p = 0.31$ for the language score). BMI was not significantly associated with mobility (EMS scale) or performance of the basic ADLs (Barthel index or Katz scale, data not shown).

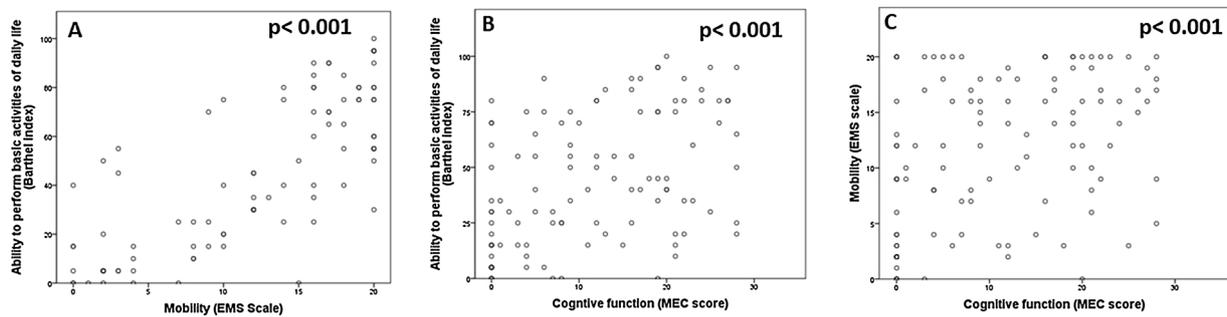


Fig. 1. Correlation between ability to perform basic activities of daily life (Barthel Index) and the (A) mobility (EMS scale), (B) cognitive function (MEC score) and (C) between cognitive function with mobility. The p value of Spearman correlation analysis are represented in each panel.

3.5. Biochemical parameters

Biochemical parameters in blood are shown in Table 3. There were no significant associations between biochemical parameters (hemoglobin, glucose, urea, HDL or LDL cholesterol, triglycerides, total proteins, creatinine, GOT, GPT, calcium, sodium, or potassium) and mobility or cognitive impairment (data not shown). However, when considering individuals with moderate cognitive impairment, a significant correlation was found between the HDL cholesterol concentration and cognitive function ($Rho = 0.52, p < 0.01$, Fig. 3A) but not between LDL cholesterol and cognitive function ($Rho = 0.23, p = 0.21$, Fig. 3B). The other biochemical parameters were not correlated

with cognitive impairment in individuals with moderate cognitive impairment.

4. Discussion

New and significant findings in this study are that mobility and performance in the basic ADLs are associated with cognitive function in older institutionalized individuals with dementias, the leading cause of acquired cognitive impairment. This work does not replicate similar previous studies, because the specific features of our sample, i.e., very old (the mean sample age was 83 years) institutionalized individuals. The following main results were obtained: (1) the severity of

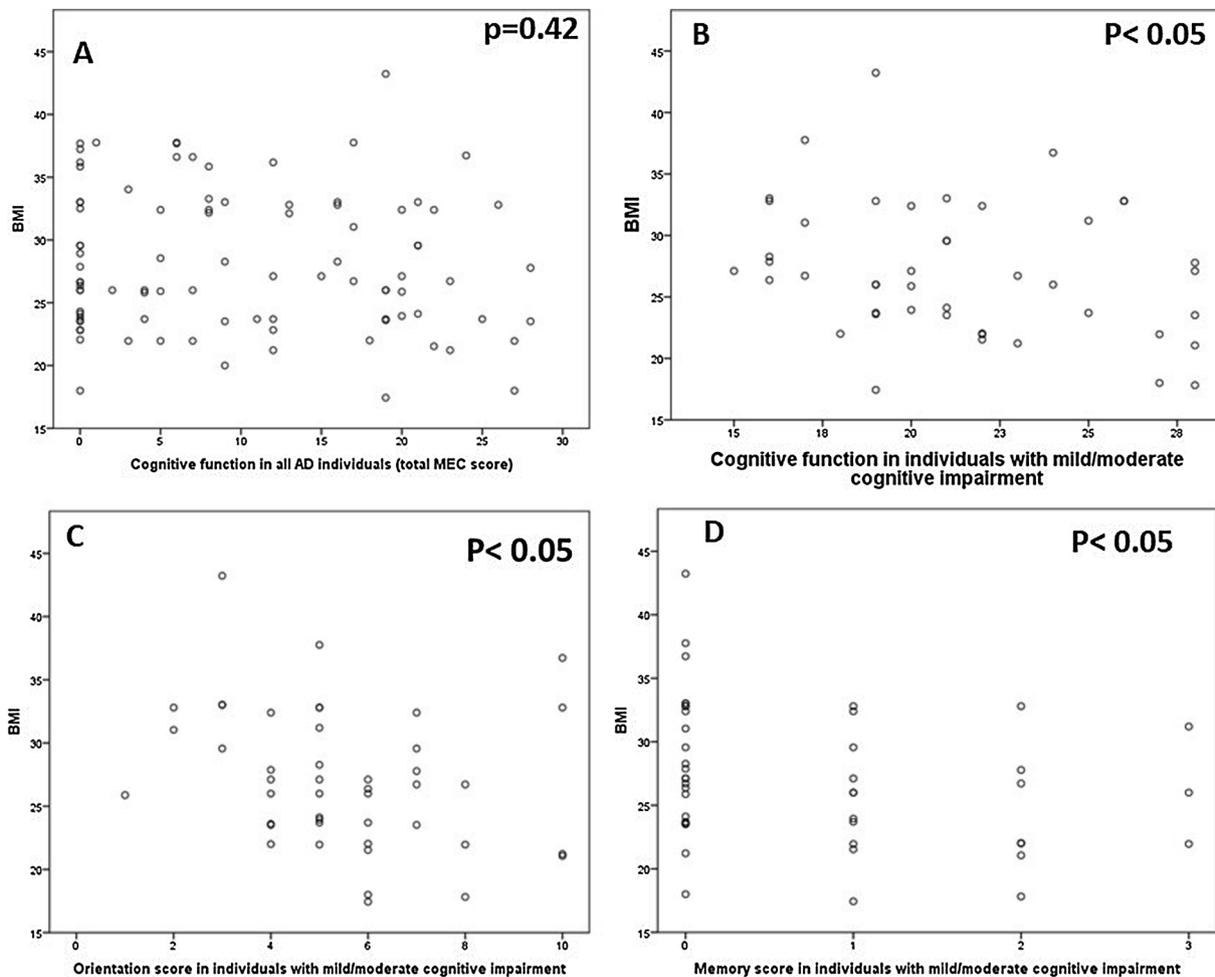


Fig. 2. Correlation between body mass index (BMI) and cognitive function in all AD individuals (A) and only in those AD individuals with mild/moderate cognitive impairment (B). Panels (C) and (D) represent the association between BMI and orientation and memory subdomains in those AD individuals with mild/moderate cognitive impairment. The p value of Spearman correlation analysis are represented in each panel.

Table 3

Mean values of biochemical parameters in blood. Mean and standard error of the mean, as measurements unit are reported. GOT: glutamic oxaloacetic transaminase; GPT: glutamic-pyruvate transaminase; HDL: high-density lipoproteins; LDL: low-density lipoproteins.

Haemoglobin (g/dL)	12.5 ± 1.8
Glucose (mg/dL)	90 ± 13
Urea (mg/dL)	48 ± 7
GOT (U/L)	29 ± 3
GPT (U/L)	24 ± 3
HDL cholesterol (mg/dL)	38 ± 8
LDL cholesterol (mg/dL)	120 ± 9
Triglycerides (mg/dL)	124 ± 23
Total Proteins (g/dL)	6.5 ± 0.9
Creatinine (mg/dL)	0.92 ± 0.16
Calcium (mg/dL)	8.9 ± 1.2
Sodium (mEq/L)	138 ± 4.3
Potassium (mEq/L)	4.4 ± 0.7

impairment in mobility and the ADLs are closely associated with global cognitive impairment; (2) the results significantly differ according to the cognitive subdomains; (3) overweight individuals and those with low HDL blood cholesterol concentrations tend to have poorer cognitive performance than individuals with mild to moderate cognitive impairment. These findings are discussed in greater detail below.

Performance in the ADLs and mobility were significantly associated in this sample, indicating that these factors are dependent on patient mobility. Age, polymedication, or BMI did not modify the strength of this association, but the performance of the ADLs and mobility was significantly more impaired in women compared to men. Interestingly, this difference was not due to an increase in global disease burden in women, because the men in our sample were significantly more polymedicated than the women, thus indicating the presence of more pathologies among men. Several authors interpret the sex differences in terms of performing the ADLs and mobility in older individuals in the context of the prevalence of different disease types in men and women. Women live longer and older women outnumber older men, but they tend to develop more chronic diseases and conditions such as osteoarthritis, osteoporosis, anemia, and depression [29,30], which does not usually increase their mortality but does reduce their mobility and performance in the ADLs. Our study extends these findings to institutionalized individuals and, moreover, replicated findings from an elderly population admitted to internal medicine and geriatric wards in Italy in which the mean Barthel index scores obtained by women was significantly lower than for men [31]. Similarly, a study by the American Community Survey and the National Nursing Home Survey showed

that the rates of basic ADL disabilities among community-dwelling adults aged 65 and older is increased in women [32].

Compared to women, older males more frequently affected by chronic obstructive pulmonary and coronary artery diseases and malignancies, which likely result in increased recurrent hospital admissions and higher in-hospital and post-hospitalization mortality, even though these diseases do not tend to impair their ability to perform the ADLs. Both our study and that of Corrao et al. [31], showed that men were more impaired than women in terms of cumulative illness burden with respect to the number of comorbidities and thus, polymedication. Among males, disease frequency is obviously associated with sex differences in terms of risk-factor distribution; indeed, men are more often smokers and former smokers, in a context where such tobacco use strongly influences the appearance and outcomes of each of the abovementioned diseases. In contrast, the more chronic conditions which tend to affect women contribute to their more sedentary lifestyles and higher levels of discomfort [29,30,32,33] and, as we found in this present study, this leads to an age-related female profile characterized by a reduced capacity to perform the ADLs.

Even though many chronic diseases (such as neurological disease, rheumatoid arthritis, and cancer) are strongly associated with poor self-rated health, common symptoms (such as tiredness or weakness and musculoskeletal pains) as well as depression contribute more to these self-assessments of poor health [33]. Therefore, more preventive measures should be directed against these conditions, especially when they are not consequences of other diseases [33]. Regarding cognitive function, we observed a more severe impairment in global cognitive function in women compared to men, especially in the concentration subdomain. The reason for this is unknown, but it could be linked to comorbid depression whose prevalence is higher in female populations at every age [29,34] and which could contribute to the major decline in physical and functional impairment in older women, as seen in our study.

There was a correlation between cognitive function and mobility and performance of the ADLs; this could be explained by the fact that the more impaired the brain functions are, the more the motor ability and motivation for moving are reduced [35]. However, the same association was not present for the memory subdomain, indicating that it was not related to performance of the ADLs or mobility [35]. Others have reported that impaired visuospatial cognition decreases the ability to perform the basic ADLs [36]. We did not find a significant relationship between ADL and memory, which agrees with the results from a sample of AD patients in which short-term memory was not correlated with the ability to perform self-care ADLs [37]. When considering only the individuals with mild to moderate cognitive impairment, there were no significant associations between cognitive function

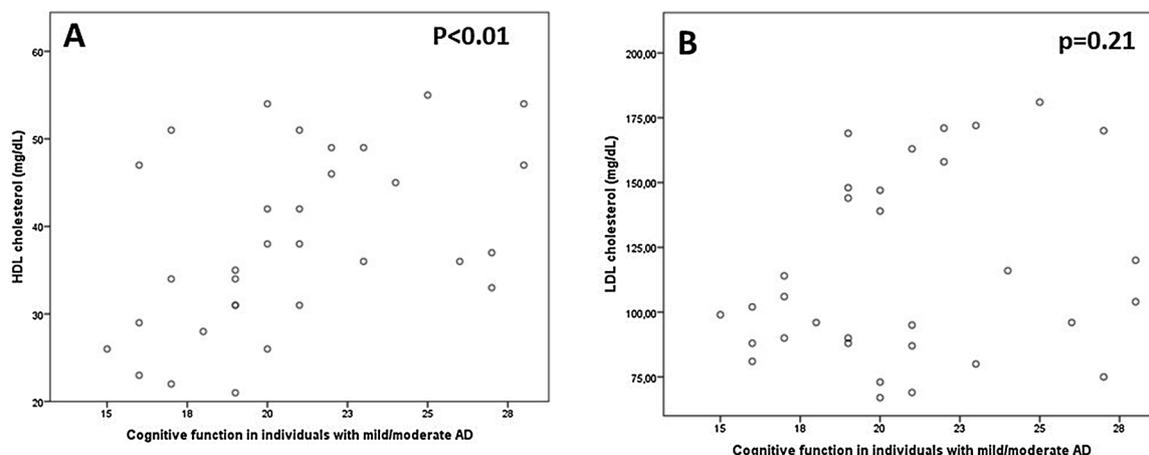


Fig. 3. Correlation between cognitive function in individuals with mild/moderate cognitive impairment and HDL cholesterol (A) and LDL-cholesterol. The rho and p value of Spearman correlation analysis (A and B) are represented in each panel.

and mobility or the performance of ADLs. All these results suggest that memory impairment does not affect ADL results and the ability to perform ADLs is maintainable until severe cognitive impairment occurs. The association between mobility or ADL performance and cognitive function is maintained after controlling for age, neurocognitive disease type, polymedication, and BMI. However, the BMI index was a significant factor associated with cognitive function in individuals with mild to moderate cognitive impairment.

The number of obese and overweight people is reaching epidemic proportions worldwide, including among older individuals living in nursing homes [38,39]. Among the adverse consequences of such high BMIs, the relationships between obesity and cognitive function, as well as the risk of dementias such as AD, have more recently come to attention [40,41]. The association between BMI and cognitive function (e.g. orientation and memory) in individuals with mild to moderate cognitive impairment agree with clinical and experimental evidence which indicates that obesity and/or high fat diets are associated with deficits in learning, memory, and executive functioning [42–45]. On the one hand, inflammation has been proposed as an important pathophysiological mechanism underlying cognitive impairment [46,47] and has also been implicated in the neuropathological hallmarks of AD (i.e., the presence and formation of amyloid plaques and neurofibrillary tangles) [48]. On the other hand, obesity is associated with low-grade inflammation in peripheral tissues and interestingly, interventions to treat obesity and central inflammation, such as calorie restriction, exercise, and bariatric surgery are already showing promise in improving some aspects of cognitive function [44,49,50].

While many genetic and environmental factors contribute to a healthy aging process, recent studies indicate that HDL may play a significant role in maintaining cognitive function during aging. Different studies have shown that plasma HDL levels are strongly positively correlated with cognitive function [51]. Moreover, the Leiden 85-plus study which included 561 subjects also reported that low HDL levels were associated with cognitive impairment, independent of atherosclerotic disease [52]. A population-based study, the Longitudinal Aging Study Amsterdam, further associated high HDL with better memory performance in people aged 65 years and older [53]. Moreover, low HDL levels were associated with poor memory and a decline in memory in middle-aged adults and cognitively-normal elderly individuals in the Whitehall II study and the Sydney Memory and Aging study, respectively [54,55]. These findings underscore the protective effects of increased plasma HDL and its role in maintaining superior cognition, both during biological aging and in dementias. In addition, HDL cholesterol was found to have a protective effect on hippocampal volume [56], dementia risk [52,57], and cognitive functioning [52,58,59].

In conclusion, these results have important clinical consequences for health-care programs because they indicate that interventions such as physical activity programs which could benefit people with mild to moderate cognitive impairment should be encouraged [50–62]. Such programs will likely help patients control weight increases and would have positive physical, functional, and psychological effects in older institutionalized people.

Acknowledgements

This work was supported by Grant GV/043 (2015) from the Conselleria de Educació, Generalitat Valenciana (Valencia, Spain) and a Grant for developing countries for Young Researchers 2017 (Programa de Cooperación 0'7) from the University of Valencia.

References

- [1] A. Deb, J.D. Thornton, U. Sambamoorthi, K. Innes, Direct and indirect cost of managing alzheimer's disease and related dementias in the United States, *Expert Rev. Pharmacoecon. Outcomes Res.* 17 (2017) 189–202.
- [2] S. Schaller, J. Mauskopf, C. Kriza, P. Wahlster, P.L. Kolominsky-Rabas, The main cost drivers in dementia: a systematic review, *Int. J. Geriatr. Psychiatry* 30 (2015) 111–129.
- [3] Alzheimer's Disease International, *The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends*, World Alzheimer Report, (2015).
- [4] R. López, J.A. Mongil, López Trigo, F.J. Castrodeza Sanz, S. Tamames Gómez, T. León Colombo, Grupo de Trabajo de Atención Sanitaria en Residencias de Ancianos de la Sociedad Española de Geriátria y Gerontología, Prevalence of dementia in institutionalized patients. The RESYDEM study, *Rev. Esp. Geriatr. Gerontol.* 44 (2009) 5–11.
- [5] M. Luppa, T. Luck, S. Weyerer, H.H. König, E. Brähler, S.G. Riedel-Heller, Prediction of institutionalization in the elderly. A systematic review, *Age Ageing* 39 (2010) 31–38.
- [6] S. Björk, C. Juthberg, M. Lindkvist, A. Wimo, P.O. Sandman, B. Winblad, D. Edvardsson, Exploring the prevalence and variance of cognitive impairment, pain, neuropsychiatric symptoms and ADL dependency among persons living in nursing homes; a cross-sectional study, *BMC Geriatr.* 16 (2016) 154.
- [7] H. Lövheim, P.O. Sandman, S. Karlsson, Y. Gustafson, Behavioral and psychological symptoms of dementia in relation to level of cognitive impairment, *Int. Psychogeriatr.* 20 (2008) 777–789.
- [8] E.H. Franssen, L.E. Souren, C.L. Torossian, B. Reisberg, Equilibrium and limb coordination in mild cognitive impairment and mild Alzheimer's disease, *J. Am. Geriatr. Soc.* 47 (1999) 463–469.
- [9] F.E. Shaw, Falls in cognitive impairment and dementia, *Clin. Geriatr. Med.* 18 (2002) 159–174.
- [10] P. Pérez-Ros, F.M. Martínez-Arnao, R.M. Orti-Lucas, F.J. Tarazona-Santabalbina, A predictive model of isolated and recurrent falls in functionally independent community-dwelling older adults, *Braz. J. Phys. Ther.* 8 (June(17)) (2018) pii:S1413-3555 30197-1.
- [11] L.Z. Rubenstein, K.R. Josephson, A.S. Robbins, Falls in the nursing home, *Ann. Intern. Med.* 121 (1994) 442–451.
- [12] L.C.W. Lam, C.W.C. Tam, V.W.C. Lui, W.C. Chan, S.S. Chan, S. Wong, et al., Prevalence of very mild and mild dementia in community-dwelling older Chinese people in Hong Kong, *Int. Psychogeriatr.* 20 (2008) 135–148.
- [13] C.P. Ferri, M. Prince, C. Brayne, H. Brodaty, L. Fratiglioni, M. Ganguli, et al., Global prevalence of dementia: a Delphi consensus study, *Lancet* 366 (2005) 2112–2117.
- [14] N.L. Baker, M.N. Cook, H.M. Arrighi, R. Bullock, Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988–2007, *Age Ageing* 40 (2011) 49–54.
- [15] S. Machado, A.S.S. Filho, M. Wilbert, G. Barbieri, V. Almeida, A. Gurgel, C.V. Rosa, V. Lins, A. Paixão, K. Santana, G. Ramos, G.M. Neto, F. Paes, N. Rocha, E. Murillo-Rodríguez, Physical exercise as stabilizer for Alzheimer's disease cognitive decline: current status, *Clin. Pract. Epidemiol. Ment. Health* 13 (2017) 181–184.
- [16] C. Rendeiro, J.S. Rhodes, A new perspective of the hippocampus in the origin of exercise-brain interactions, *Brain Struct. Funct.* (2018), <https://doi.org/10.1007/s00429-018-1665-6>.
- [17] D.E. Warburton, C.W. Nicol, S.S. Bredin, Health benefits of physical activity: the evidence, *CMAJ* 174 (2006) 801–809.
- [18] Y. Pinillos Patiño, E. Prieto Suárez, Funcionalidad física de personas mayores institucionalizadas en Barranquilla, Colombia, *Rev. Salud Pública* 14 (2012) 438–447.
- [19] J.D. Chandler, J.E. Chandler, The prevalence of neuropsychiatric disorders in a nursing home population, *J. Geriatr. Psychiatry Neurol.* 1 (1988) 71–76.
- [20] O. Danila, J.P. Hirdes, C.J. Maxwell, R.A. Marrie, S. Patten, T. Pringsheim, N. Jetté, Prevalence of neurological conditions across the continuum of care based on in-terrai assessments, *BMC Health Serv. Res.* 22 (2014) 14–29.
- [21] L. Poynter, J. Kwan, M. Vassallo, How does cognitive impairment impact on functional improvement following the rehabilitation of elderly patients? *Int. J. Clin. Pract.* 67 (2013) 811–815.
- [22] F.I. Mahoney, D.W. Barthel, Functional evaluation: the Barthel index, *Md State Med. J.* 14 (1965) 61–65.
- [23] S. Katz, T.D. Down, H.R. Cash, R.C. Grotz, Progress in the development of the index of ADL, *Gerontologist* 10 (1970) 20–30.
- [24] R. Smith, Validation and reliability of the elderly mobility scale, *Physiotherapy* 80 (1994) 744–747.
- [25] A. Lobo, J. Ezquerro, F. Gómez, J.M. Sala, A. Seva, El Mini Examen Cognoscitivo: un test sencillo, práctico, para detectar alteraciones intelectivas en pacientes médicos, *Actas Luso Esp Neurol Psiquiatr Cienc Afines* 3 (1979) 189–202.
- [26] S. Katz, T.D. Down, H.R. Cash, R.C. Grotz, Progress in development of the index of ADL, *Gerontologist* 10 (1963) 20–30.
- [27] E.J. Bassey, M.A. Fiatarone, E.F. O'Neill, M. Kelly, W.J. Evans, L.A. Lipsitz, Leg extensor power and functional performance in very old men and women, *Clin. Sci. (Lond)* 82 (1992) 321–327.
- [28] M.F. Folstein, S.E. Folstein, P.R. McHugh, "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician, *J. Psychiatr. Res.* 12 (1975) 189–198.
- [29] C. Buigues, C. Padilla-Sánchez, J.F. Garrido, R. Navarro-Martínez, V. Ruiz-Ros, O. Cauli, The relationship between depression and frailty syndrome: a systematic review, *Aging Ment. Health* 19 (2015) 762–772.
- [30] M.A. Tenkorang, B. Snyder, R.L. Cunningham, Sex-related differences in oxidative stress and neurodegeneration, *Steroids* 133 (2018) 21–27.
- [31] S. Corrao, P. Santalucia, C. Argano, C.D. Djade, E. Barone, M. Tettamanti, L. Pasina, C. Franchi, T. Kamal Eldin, A. Marengoni, F. Salerno, M. Maruccci, P.M. Mannucci, A. Nobili, REPOSI Investigators, Gender-differences in disease distribution and outcome in hospitalized elderly: data from the REPOSI study, *Eur. J. Intern. Med.* 25 (2014) 617–623.

- [32] E. Fuller-Thomson, B. Yu, A. Nuru-Jeter, J.M. Guralnik, M. Minkler, Basic ADL disability and functional limitation rates among older AMERICANS from 2000–2005: the end of the decline? *J. Gerontol. A Biol. Sci. Med. Sci.* 64 (2009) 1333–1336.
- [33] A. Molarius, S. Janson, Self-rated health, chronic diseases, and symptoms among middle-aged and elderly men and women, *J. Clin. Epidemiol.* 55 (2002) 364–370.
- [34] M.M. Mielke, P. Vemuri, W.A. Rocca, Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences, *Clin. Epidemiol.* 6 (2014) 37–48.
- [35] A. Morais, S. Santos, P. Lebre, Psychomotor, functional, and cognitive profiles in older people with and without dementia: what connections? *Dementia* (2017), <https://doi.org/10.1177/1471301217719624>.
- [36] M. Kamiya, A. Osawa, I. Kondo, T. Sakurai, Factors associated with cognitive function that cause a decline in the level of activities of daily living in Alzheimer's disease, *Geriatr. Gerontol. Int.* 18 (2018) 50–56.
- [37] R.J. Perry, J.R. Hodges, Relationship between functional and neuropsychological performance in early Alzheimer disease, *Alzheimer Dis. Assoc. Disord.* 14 (2000) 1–10.
- [38] J.A. Harris, N.G. Castle, Obesity and nursing home care in the United States: a systematic review, *Gerontologist* (2017), <https://doi.org/10.1093/geront/gnx128>.
- [39] R. Zarzeczny, A. Nawrat-Szoltysik, A. Polak, A. Manasar, J. Maliszewski, A. Kieltyka, B. Matyja, M. Dudek, J. Zborowska, A. Wajdman, The relationship between selected body fatness indices and level of blood interleukin-6 in female nursing home residents aged 80+ years without inflammation: a pilot study, *Exp. Gerontol.* 108 (2018) 240–246.
- [40] S. Alford, D. Patel, N. Perakakis, C.S. Mantzoros, Obesity as a risk factor for Alzheimer's disease: weighing the evidence, *Obes. Rev.* 19 (2018) 269–280.
- [41] J.N. Mazon, A.H. de Mello, G.K. Ferreira, G.T. Rezin, The impact of obesity on neurodegenerative diseases, *Life Sci.* 182 (2017) 22–28.
- [42] M.F. Elias, P.K. Elias, L.M. Sullivan, P.A. Wolf, R.B. D'Agostino, Obesity, diabetes and cognitive deficit: the Framingham Heart Study, *Neurobiol. Aging* 26 (2005) 11–16.
- [43] M. Cournot, J.C. Marquié, D. Ansia, C. Martinaud, H. Fonds, J. Ferrières, J.B. Ruidavets, Relationship between body mass index and cognitive function in healthy middle-aged men and women, *Neurology* 67 (2006) 1208–1214.
- [44] A.A. Miller, S.J. Spencer, Obesity and neuroinflammation: a pathway to cognitive impairment, *Brain Behav. Immun.* 42 (2014) 10–21.
- [45] S. Sabia, M. Kivimaki, M.J. Shiplet, M.G. Marmot, A. Singh-Manoux, Body mass index over the adult life course and cognition in late midlife: the Whitehall II Cohort Study, *Am. J. Clin. Nutr.* 89 (2009) 601–607.
- [46] R.M. Barrientos, M.G. Frank, N.Y. Crysdakem, T.R. Chapman, J.T. Ahrendsen, H.E. Day, S. Campeau, L.R. Watkins, S.L. Patterson, S.F. Maier, Little exercise, bid effects: reversing aging and infection-induced memory deficits, and underlying processes, *J. Neurosci.* 31 (2011) 11578–11586.
- [47] A.M. Stranahan, B. Martin, S. Maudsley, Anti-inflammatory effects of physical activity in relationship to improved cognitive status in humans and mouse models of Alzheimer's disease, *Curr. Alzheimer Res.* 9 (2012) 86–92.
- [48] P.B. Gorelick, Role of inflammation in cognitive impairment: results of observational epidemiological studies and clinical trials, *Ann. N. Y. Acad. Sci.* 1207 (2010) 155–162.
- [49] M.L. Alosco, R. Galio, M.B. Spitznagel, G. Strain, M. Devlin, R. Cohen, R.D. Crosby, J.E. Mitchell, J. Gunstad, Cognitive function after bariatric surgery: evidence for improvement 3 years after surgery, *Am. J. Surg.* 207 (2014) 870–876.
- [50] M.L. Alosco, M.B. Spitznagel, G. Strain, M. Devlin, R. Cohen, R. Paul, R.D. Crosby, J.E. Mitchell, J. Gunstad, Improved memory function two years after bariatric surgery, *Obesity (Silver Spring)*. 22 (2014) 32–38.
- [51] N. Barzilai, G. Atzmon, C.A. Derby, J.M. Bauman, R.B. Lipton, A genotype of exceptional longevity is associated with preservation of cognitive function, *Neurology* 67 (2006) 2170–2175.
- [52] E. van Exel, A.J. de Craen, J. Gussekloo, P. Hou, A. Bootsma-van der Wiel, P.W. Macfarlane, G.J. Blauw, R.G. Westendorp, Association between high-density lipoprotein and cognitive impairment in the oldest old, *Ann. Neurol.* 51 (2002) 716–721.
- [53] T.N. van den Kommer, M.G. Dik, H.C. Comijs, C. Jonker, D.J. Deeg, Role of lipoproteins and inflammation in cognitive decline: do they interact? *Neurobiol. Aging* 33 (2012) e1–12 196.
- [54] A. Songh-Manoux, D. Gimeno, M. Kivimaki, E. Brunner, M.G. Marmot, Low HDL cholesterol is a risk factor for deficit and decline in memory in midlife: the Whitehall II study, *Arterioscler. Thromb. Vasc. Biol.* 28 (2008) 1556–1562.
- [55] J. Song, C. Zhong, M.A. Bonaguidi, G.J. Sun, D. Hsu, Y. Gu, K. Meletis, Z.J. Huang, S. Ge, G. Enikolopov, K. Deisseroth, B. Luscher, K.M. Christian, G.L. Ming, H. Song, Neuronal circuitry mechanism regulating adult quiescent neural stem-cell fate decision, *Nature* 489 (2012) 150–154.
- [56] H. Wolf, A. Hensel, T. Arendt, M. Kivipelto, B. Winblad, H.J. Gertz, Serum lipids and hippocampal volume: the link to Alzheimer's disease? *Ann. Neurol.* 56 (2004) 745–748.
- [57] M. Bonarek, P. Barberger-Gateau, L. Letenneur, V. Deschamps, A. Iron, B. Dubroca, J.F. Dartigues, Relationships between cholesterol, apolipoprotein E polymorphism and dementia: a cross-sectional analysis from the PAQUID study, *Neuroepidemiology* 19 (2000) 141–148.
- [58] D.A. Hottman, D. Chernick, S. Cheng, Z. Wang, L. Li, HDL and cognition in neurodegenerative disorders, *Neurobiol. Dis.* 72 (2014) 22–36.
- [59] A. Merched, Y. Xia, S. Visvikis, J.M. Serot, G. Siest, Decreased high-density lipoprotein cholesterol and serum apolipoprotein AI concentrations are highly correlated with the severity of Alzheimer's disease, *Neurobiol. Aging* 21 (2000) 27–30.
- [60] C.V. Teixeira, T.J. Rezende, M. Weiler, M.H. Nogueira, B.M. Campos, L.F. Pegoraro, J.E. Vicentini, G. Scriptori, F. Cendes, M.L. Balthazar, Relation between aerobic fitness and brain structures in amnesic mild cognitive impairment elderly, *Age* 38 (2016) 51.
- [61] S.C. Marshall, K. Berg, Cessation of exercise in the institutionalized elderly: effects on physical function, *Physiother. Can.* 62 (2010) 254–260.
- [62] C. Piedras-Jorde, J.C. Meléndez-Moral, J.M. Tomás-Miguel, Benefits of physical activity in nursing home residents, *Rev. Esp. Geriatr. Gerontol.* 45 (2010) 131–135.