

Cognition and daily activities in a general population sample aged +55

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Abstract

Objective: We tested the association of individual cognitive domains measured with the Mini-Mental State Examination (MMSE) and disability.

Method: Cross-sectional study in a population-based cohort aged ≥ 55 years ($n = 4,803$). Sample was divided into two groups: individuals with cognition within the normal range (CNR) ($n = 4,057$) and those with cognitive impairment (CI) ($n = 746$). Main outcome measures: The MMSE, the Katz Index (Basic Activities of Daily Living, bADL), the Lawton and Brody Scale (Instrumental Activities of Daily Living, iADL), and the Geriatric Mental State (GMS-AGECAT).

Results: MMSE-orientation was associated with disability in bADL, iADL and a decrease in social participation, regardless of cognitive status. MMSE-attention was associated with disability in iADL, but only in CNR. MMSE-language was associated with disability in bADL, iADL and with reduced social participation, but only in CI. Conclusions: The associations observed between disability and orientation may have clinical and public health implications.

Keywords: cognition, Mini-Mental State Examination (MMSE), Activities of Daily Living, Disability, Aging

Introduction

There is evidence in the literature on the relationship between cognitive impairment (CI) and disability (Millán-Calenti et al., 2012), thus implying that successful interventions on cognitive performance could prevent disability. Global cognition, even within the normal range, has been shown to predict disability (St. John et al., 2015), and this may have special implications, particularly for the general population. To date, most studies have explored the association between disability and global CI, often using the Mini-Mental State Examination (MMSE) to document it (Millán-Calenti et al., 2012; Monaci & Morris, 2012; Overdorp et al., 2016; Razani et al., 2009). An association between disability and difficulties in executive function has also been documented (Martyr & Clare, 2012; Royall et al., 2007), although it was not as strong as the link with global cognition (Aretouli & Brandt, 2010; Martyr & Clare, 2012).

However, some authors have argued that the use of global cognitive scores constrains the assessment of specific cognitive domains that might have unique implications for disability (Razani et al., 2009). In this sense, some previous studies in clinical samples of patients with dementia have reported a significant association between disability and individual cognitive domains of the MMSE, specifically attention and orientation (Monaci & Morris, 2012; Razani et al., 2009). In agreement with these studies, we have previously confirmed this association in a heterogeneous clinical population of the elderly (Gracia-García et al., 2017). In addition, we found that orientation and attention MMSE subscores were more strongly associated with disability than MMSE global score and that the associations were independent of dementia diagnosis (Gracia-García et al., 2017). Furthermore, our previous results suggest that MMSE subtest might be differentially sensitive to disability in different functional domains (Gracia-García, 2017). In fact, we also found that language MMSE subscore was significantly associated with mild disability on bADL and with impairment on sADL (Gracia-García, 2017). To our knowledge, these findings have not been reported in community samples of elderly adults. The identification of difficulties in specific cognitive domains commonly assessed in clinical practice, other than classically defined executive functions (Lezak, 1982), may have clinical relevance.

This study aims to test for the first time in a large sample from the general population the following hypotheses derived from the previous clinical studies: 1) contrary to cognitive domains such as memory (registration and recall), low performance in orientation and attention, measured with the MMSE, would be associated with disability in different functional domains, specifically in instrumental (iADL), basic (bADL), and social (sADL) activities of daily living; 2) low performance in language MMSE subscore could be associated with disability on sADL; 3) these associations would also be observed in subjects with cognition within the normal range (CNR).

Method

Design overview and study population

The sample for this study was drawn from the Zaragoza Dementia and Depression Project (ZARADEMP) (Lobo et al., 2011, 2005), a longitudinal epidemiological study conducted in Zaragoza, Spain, conceived to determine the incidence and risk factors for dementia and depression—as well as their link to general morbidity—in the adult population aged 55 or older. Data from Wave I, the baseline, cross-sectional study has been used for this report. The principles of the Helsinki Convention on written informed consent, privacy, and confidentiality have been applied throughout the project. The Ethics Committee of the University of Zaragoza and the *Fondo de Investigación Sanitaria* (FIS) approved the project in accordance with Spanish law.

A random sample of community-dwelling elders, stratified by age and sex with proportional allocation, was drawn from the eligible individuals ($n = 157787$) in the Spanish official census list of 1991. The initial sample size was determined by the predictable mortality, migration, and refusals, taking into account the results of a previous study conducted in Zaragoza (Lobo et al., 1995), focused on the prevalence of dementia in the same population, as well as the first year of the fieldwork of the ZARADEMP Study. The refusal rate at enrollment was 20.5%, and 4,803 individuals were ultimately interviewed. Further details about the design and objectives of the ZARADEMP Study have been published previously (Lobo et al., 2005).

Clinical measurements

Several international instruments previously standardized in Spain by the same research group, and incorporated in the ZARADEMP Interview, have been used in this study.

- *Mini-Mental State Examination (MMSE)* (Folstein et al., 1975). The Spanish version was first validated in Spain in 1978 through an extensive process, and later revalidated (Lobo et al., 1999); the population norms of this version were very similar to those reported by Crum et al. in the American version (Crum et al., 1993). For the purposes of the present study, the MMSE total score was analyzed as a continuous variable with a maximum score of 30. MMSE items were also clustered into the following subscores, in line with procedures used by previous researchers (Razani et al., 2009; Tombaugh & McIntyre, 1992). 1) orientation: items evaluating orientation in time and place (maximum score = 10); 2) registration: items requiring the ability to register words, and to accurately repeat three items (maximum score = 3); 3) attention: items requiring attentional skills by performing serial 3s (maximum score = 5); 4) recall: measures short-term verbal memory and requires recalling three previously registered words (maximum score = 3); and 5) language: group of items that specifically assess nomination, articulation, verbal and written commands, and writing (maximum score = 8). Our group has

previously documented the validity coefficients for individual items in the MMSE (Lobo et al., 1999).

- Geriatric Mental State (GMS), a well-known semi-structured standardized clinical interview for assessing the mental state of elderly persons. The GMS-B, a shortened community version that may be used by lay-interviewers, has been selected in this study. The validity of the back-translated Spanish version of the GMS-B has been previously reported (Lobo et al., 1995). The GMS has a cognitive section (“Organic”) to assess memory and other neuropsychological items, and provides a threshold global score that differentiates between “non-cases”, “subcases”, and “cases” of dementia (Copeland et al., 1986). Although GMS categories do not match precisely onto the DSM or ICD, it was calibrated to detect disorders of clinical significance and has been used in several studies in dementia and cognitive impairment.
- History and Etiology Schedule (HAS), a standardized method of collecting history data from a caregiver, or directly from the respondent when he or she is judged to be reliable (Dewey & Copeland, 2001). It concentrates on those features expected to be relevant to psychiatric diagnosis in older people and is crucial to complete the GMS and facilitate a diagnostic process such as the one done in the present study. (Copeland et al., 1992).
- Disability in iADL was measured using the Lawton scale (Lawton & Brody, 1969) (where the maximum score of 8 equates to a maximum degree of disability), and disability in bADL was measured using the Katz index (Katz et al., 1970) (where the maximum score of 6 equates to a maximum degree of disability). Disability in sADL was scored by means of two direct questions addressed to the subject and/or informant: a) Have you (or has he/she) reduced or ceased your (his/her) participation in social or community events? And b) Have you (or has he/she) reduced or ceased your (his/her) participation in your (his/her) hobbies? The inter-rater reliability of this assessment has previously been verified in pilot trials. Both iADL and bADL were analyzed as continuous variables and disability in sADL, as reported previously (Gracia-García et al., 2017), was considered a dichotomic variable, differentiating between subjects with reduced/ceased participation in social events and/or hobbies and those with unchanged participation.
- Sociodemographic variables: Age was considered a continuous variable, and education an ordinal variable, categorized into two levels, taking basic (completed primary) studies as the cut-point: 0) primary school or lower; 1) secondary school or higher.
- Physical illness was assessed using the EURODEM risk factors questionnaire (Laurer et al., 1992), which includes information related to psychiatric (specifically depression) and medical diseases recognized as risk factors of dementia (such as cardiovascular and cerebrovascular diseases, Parkinson and diabetes), as well as information regarding general health status. This instrument may be used by trained interviewers. Each item in the interview has been operationally defined, according to previously

agreed EURODEM criteria. The variable “general health” was dichotomized for the purposes of this study, distinguishing between healthy subjects or with mild physical illness and subjects with a moderate-severe physical illness.

- The diagnosis of depression was based on the staged GMS-AGECAT approach (Copleand et al., 1986), which is valid for detecting “depression requiring clinical attention” in community samples (Copeland et al., 2004). The Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT) (Copleand et al., 1986) is a set of computer programs which analyze GMS data. Stage I of the AGECAT groups the items of the GMS into symptom components, gathered under eight diagnostic “clusters” (or “syndromes”). In Stage II, the computer program compares syndrome clusters (dementia, depression, anxiety, etc.) to reach a final diagnosis. Data about the validity of the Spanish version have also been reported (Lobo et al., 1990).

Diagnosis of cognitive impairment

The following categories have been considered for this report:

- “Probable case” of dementia (lay-interviewers): Individuals scoring 1+ in the GMS and/or <24 in the MMSE in Phase I of the study.
- “Sub-case” of dementia (research psychiatrists): Individuals scoring 1 in the GMS in Phase II of the study (and supported by HAS and ADL data).
- “Case” of dementia (research psychiatrists): Individuals scoring 2+ in the GMS in Phase II of the study (and supported by HAS and ADL data).

Procedure

A two-phase epidemiological case-finding process focused on dementia and depression. In phase I, well-trained and regularly supervised lay-interviewers conducted the 25-90-minute ZARADEMP interview at the participants’ residences. Institutionalized individuals were also interviewed. The participants were classified as “probable cases” of dementia based on previously agreed diagnostic criteria (see definitions above). In phase II, all probable cases of dementia were reassessed by a research psychiatrist using the same methods, which includes the MMSE, the GMS, the HAS, the disability questionnaires and the EURODEMP risk factor questionnaire. Medical reports and laboratory data, which are frequently available at most people’s homes in Spain, were also consulted when appropriate to complete the data. Outside caregivers were interviewed when the participant was considered to be unreliable. A brief, previously standardized, neurological examination was also completed; that included the “neurological-type” symptoms explored in the “observational items” of the GMS interview, supplemented by the Hachinski Scale (Hachinski, 1975) and a brief assessment following recommendations for psychiatrists (Obsiew, 1992). The research psychiatrist recorded a diagnosis of “case” of dementia, “sub-case” of dementia or “non-case” of dementia in all individuals examined in Phase II.

For the purposes of this study, since we were interested in the different patterns in the association between cognitive performance and disability based on cognitive status, subjects categorized as cases or sub-cases of dementia at baseline were considered to have “Cognitive Impairment” (CI) (n = 746), while the remaining subjects were considered to have “Cognition in Normal Range” (CNR) (n = 4,057). (see flow-chart in Figure 1).

Statistical analysis

Multivariate models were used to determine the association between MMSE scores and disability, both in the CI and the CNR group separately. Linear regression analysis were applied to explore the association between MMSE scores and Lawton (iADL) and Katz (bADL) scores; the two latter were the dependent variables in their respective analyses. Logistic regression analyses were used to examine the association between MMSE scores and impairment in sADL, with the latter being the dependent variable. MMSE global score and subscores (orientation, registration, attention, recall, and language) were introduced as independent variables in consecutive analysis for each of the functional domains (iADL, bADL, sADL). Multivariate models included terms for age, sex, education, physical health, and diagnosis of depression. The SPSS statistical software program was used for all analyses.

Results

Table 1 shows the baseline sample characteristics according to cognitive status. CNR subjects had a mean age of 72.1 years (SD 9.1), 54.9% were female, 17% had completed at least secondary school education, 5.6% had a moderate or severe physical illness, and 17.1% had clinically significant depression. The mean MMSE score for the CNR group was 27.2 (SD 2.5), the mean score on the Lawton scale was 0.2 (SD 0.8), the mean Katz index was 0.1 (SD 0.5), and 13.4% of the group had reduced or ceased their participation in sADL.

Subjects with CI had a mean age of 81.0 years (9.6), 72.7% were female, only 3.6% had completed at least secondary school education, 17% had a moderate or severe physical illness, and 17.1% had clinically significant depression. The mean MMSE score for the CI group was 16.2 (7.5), the mean score in the Lawton scale was 2.9 (SD 3.4), the mean Katz index was 1.6 (SD 2.3), and 53.6% had reduced or ceased their participation in sADL. All studied variables had differences statistically significant regarding the CNR group ($p = 0,000$). Table 2 shows the results from linear regression models used to determine the association between cognitive measures and disability in iADL (Lawton score) and bADL (Katz score).

The MMSE total score and orientation subscore were significantly associated with Lawton scores regardless of cognitive status. Similarly, Lawton scores presented significant associations with the attention subscore in CNR subjects, and the registration and language subscores in CI subjects (Table 2).

The association between cognitive variables and bADL shows a different profile. A statistically significant association between the Katz index and, firstly, total MMSE score and, secondly, orientation and language subscores was observed, regardless of cognitive status. Additionally, the recall subscore was significantly associated with the Katz index in CNR subjects, as did the registration subscore and the Katz index in CI subjects (Table 2).

Finally, Table 3 shows the odds ratios (OR) for the association between cognitive variables and disability in sADL.

In the CNR group, the association with a decrease on sADL was only significant for the orientation subscore. In the CI group, however, a significant association was also noted for total MMSE score and the language subscore.

Discussion

This study has found partial support for the hypotheses that lower performance in particular cognitive domains in the MMSE would be associated with disability in the older population; specifically, lower performance in orientation was associated with disability in all functional domains, regardless of cognitive status; attention was associated with disability, although this association was only significant in the case of iADL and restricted to CNR subjects; language was associated with disability on sADL, but only in CI individuals. To the best of our knowledge, this is the first study to reveal the association between different cognitive MMSE domains and disability in a large, representative sample of the general population of older adults including those institutionalized, and therefore the results may be generalizable. Moreover, our study, contrary to most previous reports, analyzed separately these associations in subjects with CNR and subjects with CI, and controlled for both depression and physical conditions, since both factors are known to contribute to disability in ADL (Den Ouden et al., 2013; Zivin et al., 2013), especially in CNR subjects (Rog, 2014).

In coincidence with some previous studies, we also found an association between low, global MMSE cognitive performance and disability. However, most of the previous studies were based on clinical samples of subjects with dementia (Monaci & Morris, 2012; Razaniet al., 2009). Both Millán-Calenti et al. (2012) and St. John et al. (2015) reported this association in a general population sample, but the former authors did not control for the effect of depression and St. John et al. (2015) used a depression rating scale, while we used the GMS-AGECAT interview, which is considered valid for the diagnosis of clinically significant depression. In addition, St. John et al. (St. John et al., 2015) assessed the subjects' physical health using "self-rated health", whereas we assessed general health status, but also used the EURODEM questionnaire to evaluate medical conditions considered to be risk factors of dementia, operationally defined according to previously agreed international criteria.

Some of the articles here reviewed, including our previous study (Gracia-García

etal., 2017), also documented the association of disability with low performance in specific cognitive domains such as orientation and attention (Monaci & Morris, 2012; Razani et al., 2009). However, all these studies were conducted in clinical samples. Moreover, with the exception of our previous study (Gracia-García et al., 2017), none of the previous reports documented specific associations with sADL. In fact, the association between cognitive measures and sADL has received very little attention (Plehn et al., 2004), even though social aspects are considered major domains in an individual's level of functioning (Üstün et al., 2010).

Furthermore, in contrast to our work, with the exception of the study by St. John et al. (2015), previous population studies did not analyze the association between disability and cognitive measures in CNR subjects. Our findings support our approach, as we found significant associations with both global cognitive measures and specific domains, in particular with orientation in CNR subjects.

It is also worth noting that individual items such as orientation had a stronger association with disability than global cognition. Since the MMSE is basically a screening test using a global score, doubts might be raised about the validity of its individual items. In fact, the use of the orientation items in this study is supported by quite acceptable validity coefficients for the diagnosis of clinical dementia in a population sample (Lobo et al., 1999). The orientation subtest of the MMSE represents a multi-modal task because it requires interaction, interpretation, and memory of environmental information; its value in predicting disability might be related to this increased complexity (Razani et al., 2009). Impairment in orientation is a clinically significant symptom, and might be the harbinger of incipient dementia, but also of other neuropsychiatric disorders in people who have otherwise CNR. Notice that orientation, together with attention and recall, all of them associated with some disability in CNR subjects in this study, have been recognized as the first cognitive domains impaired in Alzheimer Disease (Henneges, 2016) and are among the most sensitive MMSE items for the diagnosis of dementia (Lobo et al., 1999). Some studies have previously demonstrated that subtle changes in cognition can precede some years a diagnosis of CI (Howieson, 2008).

The results in this study tend to confirm previous results in clinical samples about the association of disability with low performance in orientation, attention, and language (Razani et al., 2009; Gracia-García, 2017). Contrary to our expectation, we also found an association between memory tasks and bADL, in both CI and CNR. In our previous clinical sample, we did not observe associations between MMSE memory tasks and disability (Gracia-García, 2017); however, Razani et al. (2009) had previously reported an association between the MMSE recall subscore and some iADL in a sample of CI subjects.

The different results in the associations between CI and CNR individuals may be difficult to interpret. For example, both attention and recall were associated with disability in CNR, but not in CI individuals. However, this type of variability in the associations between cognitive items and disability according to cognitive status of

the sample has previously been reported (O'Connor et al., 2019). As these authors suggested, the variability may be due to the wide discrepancy between CI and CNR individuals regarding the frequency of poor performance in the different cognitive items. In our study, most CI patients, but only some CNR individuals, had low performance in attention and recall. A little variance in MMSE attention and recall subscores among CI subjects restricts the range for examining associations between these specific subscores and disability.

From a clinical perspective, the standard approach to the secondary prevention of disability may be an individualized intervention in subjects with early cognitive loss. However, if the association between cognitive measures and disability exists also among CNR subjects, as our study suggests, then the implication for public health is that broader, since population-based interventions targeted to improve the cognition might have the potential to reduce disability in older populations. Given the personal, family, and social burden of disability (Dartigues, 2009; Zivin et al., 2013), the study of variables related to disability should be considered relevant to public health, as these variables could eventually be used as predictors of functional outcomes and critical targets for prevention strategies. The findings in orientation may be particularly relevant, since this cognitive domain can be easily assessed in a primary care setting, and this may inform how the primary care doctor treats reduced orientation. Obviously, a cross-sectional study such as this one cannot draw conclusions about the direction of the reported associations. Nevertheless, the fact that disability was independently associated with cognitive measures, even in CNR subjects, suggests the importance of focusing on strengthening cognitive function as a means of improving functionality. Further studies should try to confirm the findings of St. John et al. (2015) in terms of global cognitive measures as disability predictors, but also should test the extent to which specific cognitive measures commonly used in clinical practice, such as the ones documented in this study, predict disability at follow-up.

Our study also contains some further limitations. We had a rather high refusal rate (20.5%), but it was expected by design and we have previously argued that it is an acceptable rate when compared with other large population studies (Lobo et al., 2011, 2005). In these previous reports of the ZARADEMP Study, we observed that the proportion of non-response due to refusals was significantly higher in women when compared with men (Lobo et al., 2005). However, since we have controlled our analysis by sex, we are confident this would not alter the main results in a significant way. Misclassification of some individuals in the screening process is inevitable. Since we were interested in being "sensitive" for the detection of CI in the baseline of the ZARADEMP Project, we selected for phase I a low threshold for the screening instruments, but "false positive" cases were corrected in phase II. On the contrary, some "false negative" cases may have been classified in the CNR group, but we trust this has not influenced seriously the main conclusions of the study. We also acknowledge that the ADL scales might not be sensitive enough to assess complex activities such as economic activities, everyday technology, and

driving, which have shown strong associations with MMSE scores in some studies (Vermeersch et al., 2015). In addition, the Lawton scale includes cultural elements that might influence the iADL scores (Lawton & Brody, 1969), particularly in a population with a low educational level such as the one in this study. It might be argued that a more detailed neuropsychological examination has advantages compared with the use of cognitive screening instruments such as the MMSE (Overdorp et al., 2016), which has a low sensitivity in the assessment of executive functions (Pendlebury et al., 2010), relevant in relation to disability (Royall et al., 2007). Still, it is noticeable that we were able to find associations between cognition and disability measured with a simple, cost-effective instrument used in routine clinical practice.

In conclusion, in a large, representative sample of subjects aged 55 years or over, we documented and quantified the association between low performance in specific cognitive domains measured with a simple instrument and disability in instrumental, basic, and social ADL, after controlling for conditions that contribute to disability such as physical illnesses and depression. This association with disability was documented even in CNR subjects. Our results suggest that orientation items may be valuable in predicting functional status more than global cognitive scores and more than other cognitive domains, even in CNR subjects. These results may have both clinical and public health implications with respect to predicting disability, although further, prospective studies should examine the extent to which the cognitive difficulties detected at baseline predict functional disability over time.

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References

- Aretouli, E., & Brandt, J. (2010). PMC2987652; Everyday functioning in mild cognitive impairment and its relationship with executive cognition. *International Journal of Geriatric Psychiatry, 25*(3), 224–233. <https://doi.org/10.1002/gps.2325>
- Copeland, J. R., Beekman, A. T., Braam, A. W., Dewey, M. E., Delespaul, P., Fuhrer, R., Hooijer, C., Lawlor, B. A., Kivela, S. L., Lobo, A., Magnusson, H., Mann, A. H., Meller, I., Prince, M. J., Reischies, F., Roelands, M., Skoog, I., Turrina, C., deVries, M. W., & Wilson, K. C. (2004). Depression among older people in Europe: the EURODEP studies. *World psychiatry : official journal of the World Psychiatric Association (WPA), 3*(1), 45–49. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1414664/pdf/wpa010045.pdf>.
- Copeland, J. R. M., Davidson, I. A., & Dewey, M. E., et al. (1992). Alzheimer's disease, other dementias, depression and pseudodementia: prevalence, incidence and three-year outcome in liverpool. *British Journal of Psychiatry, 161*, 230–239.
- Copeland, J. R., Dewey, M. E., & Griffiths-Jones, H. M. (1986). A computerized psychiatric diagnostic system and case nomenclature for elderly subjects: GMS and AGE CAT. *Psychological Medicine, 16* (1), 89–99. <https://doi.org/10.1017/S0033291700057779>
- Crum, R. M., Anthony, J. C., Bassett, S. S., & Folstein, M. F. (1993). Population-based norms for the mini-mental state examination by age and educational level. *Jama, 269*(18), 2386–2391. <https://doi.org/10.1001/jama.1993.03500180078038>
- Dartigues, J. F. (2009). Alzheimer's disease: A global challenge for the 21st century. *The Lancet Neurology, 8*(12), 1082–1083. [https://doi.org/10.1016/S1474-4422\(09\)70298-4](https://doi.org/10.1016/S1474-4422(09)70298-4)
- den Ouden, M. E., Schuurmans, M. J., Mueller-Schotte, S., van der Schouw, & van der Schouw, Y. T. (2013). Identification of high-risk individuals for the development of disability in activities of daily living. A ten-year follow-up study. *Experimental Gerontology, 48*(4), 437–443. <https://doi.org/10.1016/j.exger.2013.02.002>
- Dewey, M. E., & Copeland, J. R. (2001). Diagnosis of dementia from the history and aetiology schedule. *International Journal of Geriatric Psychiatry, 16*(9), 912–917. [https://doi.org/10.1002/\(s\)1099-1166](https://doi.org/10.1002/(s)1099-1166)
- Farias, S. T., Harrell, E., Neumann, C., & Houtz, A. (2003). The relationship between neuropsychological performance and daily functioning in individuals with Alzheimer's disease: Ecological validity of neuropsychological tests. *Archives of Clinical Neuropsychology, 18*(6), 655–672. <https://doi.org/10.1093/arclin/18.6.655>
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12* (3), 189–198. <https://doi.org/10.1016/0022->

3956(75)90026-6

Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D., & Anderson, G. (2004). Untangling the concepts of disability, frailty, and comorbidity: Implications for improved targeting and care. *The Journals of*

- Gerontology Series A: Biological Sciences and Medical Sciences*, 59(3), 255–263.
<https://doi.org/10.1093/gerona/59.3.M255>
- Gracia-García, P., López-Antón, R., Santabárbara, J., de la Cámara, C., Saz, P., Larraga, L., Gonzalez-Torecillas, J. L., Fernandez-Braso, A. M., & Quintanilla, M. Á. (2017). Frequency and associations with low cognitive performance. *The European Journal of Psychiatry*, 31(2), 50–58. <https://doi.org/10.1016/j.ejpsy.2017.04.002>
- Hachinski, V. C., & Iliff, L. D., Zilhka E, Du Boulay G. H., McAllister V. L., Marshall J., Russell R. W., Symon L. (1975). Cerebral blood flow in dementia. *Archives of Neurology*, 32, 632–637
- Henneges, C., Reed, C., & Chen, Y. F., Dell'Agnello, G., & Lebec, J. (2016). Describing the Sequence of Cognitive Decline in Alzheimer's Disease Patients: Results from an Observational Study. *Journal of Alzheimer's disease : JAD*, 52(3),1065–1080. <https://doi.org/10.3233/JAD-150852>
- Howieson, D. B., Carlson, N. E., Moore, M. M., Wasserman, D., Abendroth, C. D., Payne-Murphy, J., & Kaye, JA. (2008). Trajectory of mild cognitive impairment onset. *Journal of the International Neuropsychological Society*, 14(2), 192–198. doi: 10.1017/S1355617708080375
- Katz, S., Downs, T. D., Cash, H. R., & Grotz, R. C. (1970). Progress in development of the index of ADL. *Gerontologist*, 10(1), 20–30. https://doi.org/10.1093/geront/10.1_Part_1.20
- Launer, L. J., Brayne, C., & Breteler, M. M. (1992). Epidemiologic approach to the study of dementing diseases: A nested case-control study in European incidence studies of dementia. *Neuroepidemiology*, 11(Suppl 1), 114–118. <https://doi.org/10.1159/000111005>
- Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist*, 9(3), 179–186. https://doi.org/10.1093/geront/9.3_Part_1.179
- Lezak, M. D. (1982). The problem of assessing executive functions. *International Journal of Psychology*, 17(2–3), 281–297. doi: 10.1080/00207598208247445
- Lobo, A., Lopez-Anton, R., Santabárbara, J., de-la-Cámara, C., Ventura, T., Quintanilla, M. A., Roy, J. F., Campayo, A. J., Lobo, E., Palomo, T., Rodriguez-Jimenez, R., Saz, P., & Marcos, G. (2011). Incidence and lifetime risk of dementia and Alzheimer's disease in a southern European population. *Acta Psychiatrica Scandinavica*, 124(5), 372–383. <https://doi.org/10.1111/j.1600-0447.2011.01754.x>
- Lobo, A., Saz, P., & DÍa, J. L. (1990). The AGE-CAT organic section as a screening instrument for minor cognitive deficits. *Psychiatric Journal of the University of Ottawa : Revue De Psychiatrie De l'Universite d'Ottawa*, 15(4), 212–215. <https://www.ncbi.nlm.nih.gov/pubmed/2284373>
- Lobo A, Saz P, Marcos G, DÍa JL, De-la-Cámara C, Ventura T, Montañés JA, Lobo-Escolar A, Aznar S. (2005). The ZARADEMP project on the incidence, prevalence and risk factors of dementia (and Depression) in the elderly community II: Methods and first results. *European Journal of Psychiatry*, 19(1), 40–54. <https://doi.org/10.4321/s0213-61632005000100004>.
- Lobo, A., Saz, P., Marcos, G., DÍa, J. L., de, L. C., Ventura, T., Morales Asín, F., Fernando

- Pascual, L., Montañés, J. A., & Aznar, S. (1999). Revalidation and standardization of the cognition mini-exam (First Spanish Version of the Mini-Mental Status Examination) in the general geriatric population]. *Medicina Clinica*, 112(20), 767–774. <http://www.ncbi.nlm.nih.gov/pubmed/10422057>
- Lobo, A., Saz, P., Marcos, G., D a, J. L., & De-la-C amara, C. (1995). The prevalence of dementia and depression in the elderly community in a Southern European population. The Zaragoza study. *Archives of General Psychiatry*, 52(6), 497–506. <https://doi.org/10.1001/archpsyc.1995.03950180083011>
- Martyr, A., & Clare, L. (2012). Executive function and activities of daily living in Alzheimer’s disease: A correlational meta-analysis. *Dementia and Geriatric Cognitive Disorders*, 33(2–3), 189–203. <https://doi.org/10.1159/000338233>
- Mill an-Calenti, J. C., Tub o, J., Pita-Fern andez, S., Rochette, S., Lorenzo, T., & Maseda, A. (2012). Cognitive impairment as predictor of functional dependence in an elderly sample. *Archives of Gerontology and Geriatrics*, 54(1), 197–201. <https://doi.org/10.1016/j.archger.2011.02.010>
- Monaci, L., & Morris, R. G. (2012). Neuropsychological screening performance and the association with activities of daily living and instrumental activities of daily living in dementia: Baseline and 18- to 24-month follow-up. *International Journal of Geriatric Psychiatry*, 27(2), 197–204. <https://doi.org/10.1002/gps.2709>

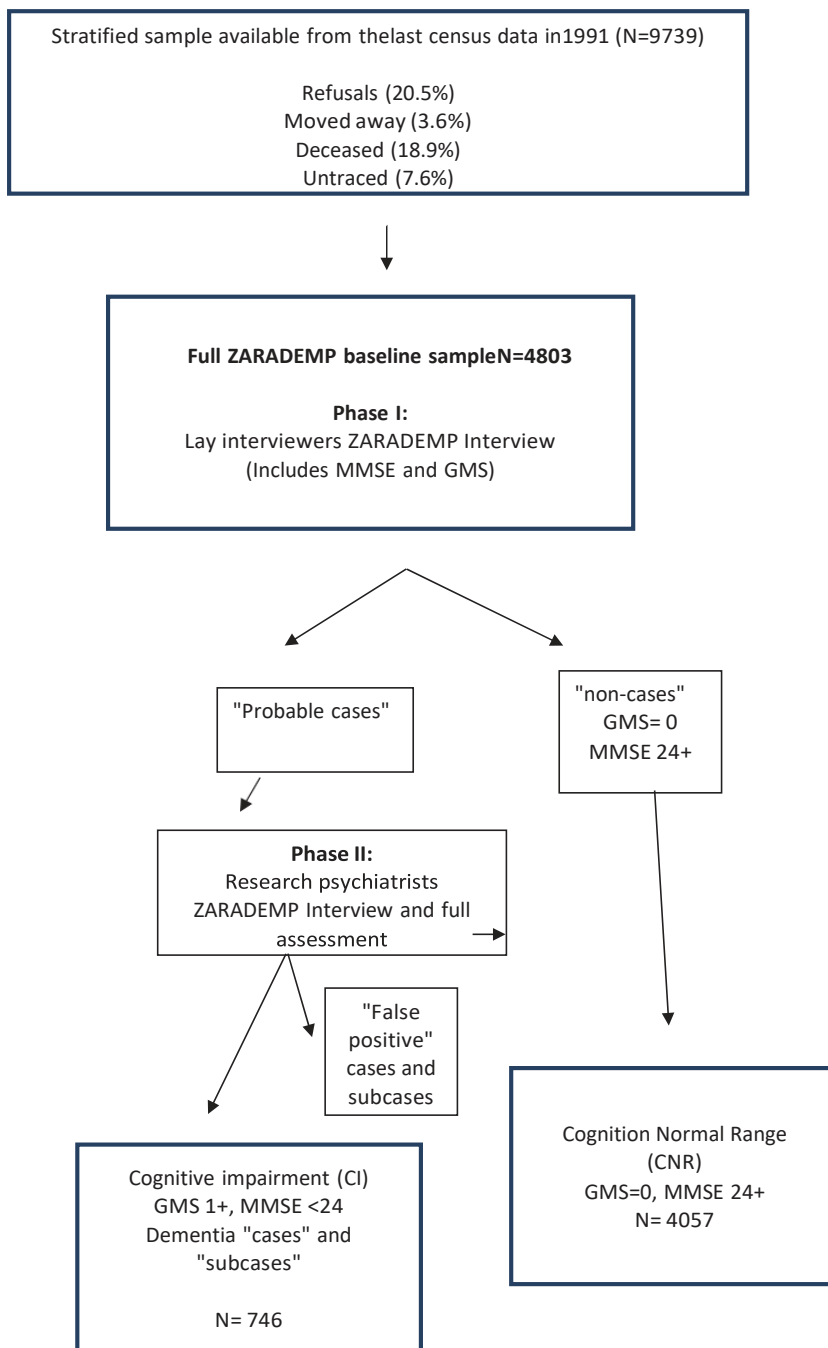
- O'Connor, M. G., Duncanson, H., & Hollis, A. M. (2019). Use of MMSE in prediction of driving fitness: Relevance of specific subtest. *Journal of the American Geriatrics Society*, *67*(4), 790–793. <https://doi.org/10.1111/jgs.15772>
- Obsiew, F. (1992). Bedside neuropsychiatry eliciting the clinical phenomena of neuropsychiatric illness. In S. C. Yudofsky & R. E. Hales (Eds.), *Textbook of Neuropsychiatry* (pp. 89–126). AmericanPsychiatry Press.
- Overdorp, E. J., Kessels, R. P., Claassen, J. A., & Oosterman, J. M. (2016). The combined effect of neuropsychological and neuropathological deficits on instrumental activities of daily living in older adults: A systematic review. *Neuropsychology Review*, *26*(1), 92–106. <https://doi.org/10.1007/s11065-015-9312-y>
- Pendlebury, S. T., Cuthbertson, F. C., Welch, S. J. V., Mehta, Z., & Rothwell, P. M. (2010). Underestimation of cognitive impairment by mini-mental state examination versus the montreal cognitive assessment in patients with transient ischemic attack and stroke. A population-based study. *Stroke*, *41*(6), 1290–1293. <https://doi.org/10.1161/STROKEAHA.110.579888>
- Plehn, K., Marcopulos, B. A., & McLain, C. A. (2004). The relationship between neuropsychological test performance, social functioning, and instrumental activities of daily living in a sample of rural older adults. *The Clinical Neuropsychologist*, *18*(1), 101–113. <https://doi.org/10.1080/13854040490507190>
- Razani, J., Wong, J. T., Dafaeeboini, N., Edwards-Lee, T., Lu, P., Alessi, C., & Josephson, K. (2009). Predicting everyday functional abilities of dementia patients with the mini-mental state exam-ination. *Journal of Geriatric Psychiatry and Neurology*, *22*(1), 62–70. <https://doi.org/10.1177/0891988708328217>
- Rog, L. A., Park, L. Q., Harvey, D. J., Huang, C. J., Mackin, S., & Farias, S. T. (2014). The independent contributions of cognitive impairment and neuropsychiatric symptoms to everyday function in older adults. *The Clinical Neuropsychologist*, *28*(2), 215–236. doi:10.1080/13854046.2013.876101. Royall, D. R., Lauterbach, E. C., Kaufer, D., Malloy, P., Coburn, K. L., & Black, K. J. & Association, Committee on Research of the American Neuropsychiatric. (2007). The cognitive correlates of functional status: A review from the committee on research of the American neuropsychiatric association. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *19*(3), 249–265. <https://doi.org/10.1176/jnp.2007.19.3.249>.
- St. John, P. D., Tyas, S. L., & Montgomery, P. R. (2015). Cognition, even in the normal range, predicts disability: Cross-sectional and prospective analyses of a population based sample. *International Journal of Geriatric Psychiatry*, *30*(10), 1008–1016. <https://doi.org/10.1002/gps.v30.10>
- Tombaugh, T. N., & McIntyre, N. J. (1992). The mini-mental state examination: A comprehensive review. *Journal of the American Geriatrics Society*, *40*(9), 922–935. <https://doi.org/10.1111/jgs.1992.40.issue-9>
- Üstün, T. B., Chatterji, S., Kostanjsek, N., Rehm, J., Kennedy, C., Epping-Jordan, J., Saxena, S., von Korff, M., & Pull, C. (2010). WHO/NIH joint project. Developing the world health organization disability assessment schedule 2.0. . *Bulletin of the World Health Organization*, *88*(11), 815–823. <https://doi.org/10.2471/BLT.09.067231>
- Vermeersch, S., Gorus, E., Cornelis, E., & De Vriendt, P. (2015). An explorative study of the

relationship between functional and cognitive decline in older persons with mild cognitive impairment and Alzheimer's disease. *British Journal of Occupational Therapy*, 78(3), 166–174. <https://doi.org/10.1177/0308022614565114>

World Health Organization. "Mental health and older adults", [WHO Web Site]; 2013. Retrieved 12 December 2017, from: <https://www.who.int/news-room/fact-sheets/detail/mental-health-of-older-adults>.

Zivin, K., Wharton, T., & Rostant, O. (2013). PMC4024243; the economic, public health, and caregiver burden of late-life depression. *Psychiatric Clinics of North America*, 36(4), 631–649. <https://doi.org/10.1016/j.psc.2013.08.008>

Figure 1. Study flowchart. Characterization of study groups.



MMSE: Mini-Mental Status Examination; GMS-B: Geriatric Mental State B.

Table 1. Baseline characteristics of the sample according to cognitive status.

	Cognition within the Normal Range(CNR)	Cognitive Impairment (CI)	p
	(n = 4,057)	(n = 746)	
	n (%)	n (%)	
Sex (female)	2,229 (54.9)	542 (72.7)	0,000
Secondary school or higher education	690 (17.0)	27 (3.6)	0,000
Current moderate-severe physical illness	225 (5.6)	127 (17)	0,000
Current depression	693 (17.1)	132 (17.7)	0,000
	mean (SD)	mean (SD)	p
Age	72.1 (9.1)	81.0 (9.6)	0,000
MMSE	27.2 (2.5)	16.2 (7.5)	0,000
MMSE-orientation	9.7 (0.7)	6.0 (3.2)	0,000
MMSE-registration	3 (0.8)	2.7 (0.8)	0,000
MMSE-attention	4.4 (1.1)	1.4 (1.7)	0,000
MMSE-recall	1.8 (1.1)	0.5 (0.8)	0,000
MMSE-language	7.7 (0.5)	6.1 (2.2)	0,000
Lawton scale (disability in iADL)	0.2 (0.8)	2.9 (3.4)	0,000
Katz index (disability in bADL)	0.1 (0.5)	1.6 (2.3)	0,000
	n (%)	n (%)	p
Reduced participation in sADL	521 (13.4)	383 (53.6)	0,000

MMSE: Mini-Mental State Examination; ADL: activities of daily living; iADL: instrumental activities of daily living; bADL: basic activities of daily living; sADL: social activities of daily living; SD: standard deviation. p-value < 0,05 = statistically significant differences between groups.

Table 2. Multivariate linear regression models. Association between cognitive measures and ADL.

	iADL (Lawton score)					
	CNR sample (n = 2,643*)			CI sample (n = 363*)		
	B	SE	p	B	SE	p-value
MMSE	-0.04	0.01	0.000	-0.29	0.02	0.000
MMSE-orientation	-0.07	0.02	0.008	-0.57	0.05	0.000
MMSE-registration	0.16	0.21	0.441	-2.26	0.21	0.000
MMSE-attention	-0.03	0.01	0.012	-0.08	0.09	0.356
MMSE-recall	-0.00	0.01	0.864	-0.16	0.15	0.264
MMSE-language	-0.02	0.02	0.365	-0.75	0.08	0.000
	bADL (Katz index)					
	CNR sample (n = 4,057)			CI sample (n = 746)		
	B	SE	p-value	B	SE	p-value
MMSE	-0.01	0.00	0.000	-0.17	0.01	0.000
MMSE-orientation	-0.06	0.01	0.000	-0.33	0.03	0.000
MMSE-registration	0.01	0.11	0.942	-1.33	0.15	0.000
MMSE-attention	-0.01	0.01	0.283	-0.09	0.05	0.083
MMSE-recall	0.02	0.01	0.011	0.02	0.09	0.789
MMSE-language	-0.03	0.01	0.023	-0.51	0.04	0.000

CNR: Cognition within the Normal Range. CI: Cognitive Impairment. ADL: activities of daily living; bADL: basic activities of daily living; iADL: instrumental activities of daily living; B: coefficient of association; SE: standard error; P: significance level. Values in bold: statistically significant association. Multivariate models include socio-demographic and clinical variables (physical morbidity and depression). Katz index = number of bADL for which subject is dependent (continuous variable). Lawton score = number of iADL for which the subject is dependent (continuous variable). * Missing values on Lawton total score are due to missing values for some individual iADL because of cultural factors.

Table 3. Multivariate logistic regression models. Association between cognitive variables and sADL.

	CNR sample (n = 3,890*)			CI sample (n = 715*)		
	OR	CI95%	p-value	OR	CI95%	p-value

MMSE	0.98	0.94–1.02	0.393		0.83	0.78–0.89	0.000
MMSE-orientation	0.78	0.67–0.90	0.001		0.65	0.58–0.78	0.000
MMSE-registration	0.36	0.09–1.43	0.148		0.00	0.00-	0.998
MMSE-attention	1.03	0.94–1.13	0.513		0.95	0.80–1.13	0.578
MMSE-recall	1.10	1.00–1.22	0.057		1.10	0.80–1.52	0.554
MMSE-language	0.94	0.77–1.14	0.520		0.49	0.35–0.70	0.000

Cognition within the Normal Range. CI: Cognitive Impairment. ADL: activities of daily living; sADL: social activities of daily living; OR: odds ratio; CI: confidence interval; P: significance level. Values in bold: statistically significant association. Multivariate models include socio-demographic and clinical variables (physical morbidity, depression). *Some values are missing due to a lack of information on social activities.