CHAPTER 3

Do instrumental activities of daily living predict dementia at one and two year follow-up? Findings from the DESCRIPA study

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ABSTRACT

Objectives: Problems in daily functioning are thought to be among the early symptoms of dementia. The aim of the current study is to investigate whether problems in instrumental activities of daily living (IADL) can predict a diagnosis of dementia at one and two year follow-up, above conventionally used clinical measurements. **Design:** Multicenter prospective cohort study (www.descripa.eu). **Setting:** Memory-clinics in Europe **Participants:** Non-demented subjects ≥55 years. **Measurements:** IADL was measured with pooled activities from five informant-based questionnaires. Structural Equation Modeling (SEM) was used to investigate the relation between IADL and dementia. Age, gender, education, depression and cognitive measures (mini-mental state examination and verbal memory) were included in the model **Results:** A total of 531 patients had a baseline and one year follow-up assessment. Of these patients, 69 (13.0%) developed dementia at one year follow-up. At two year follow-up, 481 patients were seen of whom 100 (20.8%) developed dementia. Patients with IADL disabilities at baseline had a higher conversion rate (24.4%) than patients without IADL disabilities (16.7%) (Chi-square=4.28, df=1, p=.039). The SEM model showed that IADL could predict dementia above the measured variables at one year follow-up, with an odds ratio of 2.20 (95% CI 1.51-1.3.13) and at two year follow-up with an odds ratio of 2.11 (95%CI 1.33-3.33). **Conclusion:** IADL is a useful addition to the diagnostic process in a memory clinic setting, as it as it indicates who is at higher risk of developing dementia at one and two year follow-up.

BACKGROUND

Dementia is one of the most common syndromes in later life. For diagnosing dementia, DSM-IV requires a decline from a previous level of functioning.[1] This decline is generally captured in scales developed to assess disabilities in activities of daily living (ADL).

Activities of daily living can be divided into Basic activities of daily living (BADL) and Instrumental activities of daily living (IADL). BADL involves self-maintenance skills such as bathing and toileting, whereas IADL includes more complex activities, such as preparing a meal, handling finances and shopping.[2,3]

The complex IADL activities are sensitive to cognitive decline in early stage dementia. BADL on the other hand, remains preserved until the later and more severe stages of the disease.[4-7] IADL assessment may therefore be important in screening for and diagnosing early dementia.[8-13]

Several studies investigated the diagnostic accuracy of IADL scales. Their findings range from no or moderate associations [14] to strong associations [13,15] between the level of IADL functioning and dementia. Other researchers suggest the diagnostic value of IADL is limited to specific IADL activities.[7,16,17] These results are difficult to compare, since the selection of items, patients and IADL measurement instruments differs between studies.

Another difficulty is that many studies are cross-sectional.[13,14,16] Since the diagnostic criteria require a decline in activities of daily living, a cross-sectional approach inevitably leads to a higher correlation between dementia and IADL. Longitudinal studies are necessary to obtain knowledge on the relation between IADL and dementia.

A longitudinal study in a community based sample showed a predictive value of IADL disability 10 years before the onset of dementia.[17] Other studies were also conducted in community based samples, with low prevalence rates of dementia.[7,11,13,15,16] Longitudinal studies in different settings with higher prevalence rates of dementia are needed to investigate the role of IADL in the prediction of dementia. A memory clinic might be a useful setting which is also clinically significant, as problems with IADL are often one of the first complaints of patients and their caregivers.[18]

In this prospective cohort study, we aimed to investigate whether interference in IADL can predict dementia at one year and two year follow up in a memory clinic setting.

METHODS

Subjects

Subjects were selected from the DESCRIPA study (www.descripa.eu). This is a multicenter study of the European Alzheimer's Disease Consortium with the aim to develop clinical criteria for the diagnosis of Alzheimer's disease at the predementia stage.[19] For this prospective cohort study subjects were recruited at 20 memory clinics across Europe between January 2003 and June 2005. Participants were included if they were 55 years of age or older and a new referral for the evaluation of cognitive complaints.

Patients with a diagnosis of dementia were excluded. Other exclusion criteria involved any somatic, psychiatric or neurological disorder that may have caused the cognitive impairment.

All subjects underwent a dementia assessment including clinical history, medical and neurological examination, functional evaluation with the clinical dementia rating scale, laboratory tests, rating scales for depression and neuropsychiatric symptoms, MMSE, a neuropsychological test battery and neuroimaging. The diagnosis of dementia was established using the DSM-IV clinical diagnostic criteria. Alzheimer's disease was diagnosed according to NINCDS-ADRDA criteria [20], vascular dementia according to NINCDS-AIREN criteria [21], Lewy Body dementia according to McKeith criteria [22] and fronto-temporal lobe dementia according to the Neary criteria [23].

The sample for the present study consisted of all subjects who completed the baseline assessment including an IADL assessment, one year and two year follow-up. Figure 1 shows the in- and exclusion of subjects. Of the sample who met the criteria at baseline (n=616), 531 completed the one year follow-up. Patients who did not complete the follow-up were older ($t(614)=3.11$, $p=.002$) and had lower MMSE scores ($z=-3.32$, $p<.001$). At two year follow-up, 481 patients were included. All patients provided written informed consent and the study was approved by the local medical ethics committee in each study center.

Measurement instruments

IADL

Variability between study centers existed in which informant-based IADL scale was administered (see Appendix I for an overview). Sixteen memory clinics used an IADL scale. Most memory clinics (9 centers) administered the Lawton IADL scale.[2] Three centers used the Blessed dementia rating scale (Blessed DRS) [24] and the Bayer ADL scale [25]. The Alzheimer's Disease Cooperative study ADL scale (ADCS-ADL) [26] and the Bristol ADL scale [27] were each administered in one center. Information on

the reliability and validity of the IADL scales can be found in appendix II. All IADL questionnaires were informant-based and completed by an informant of the patient.

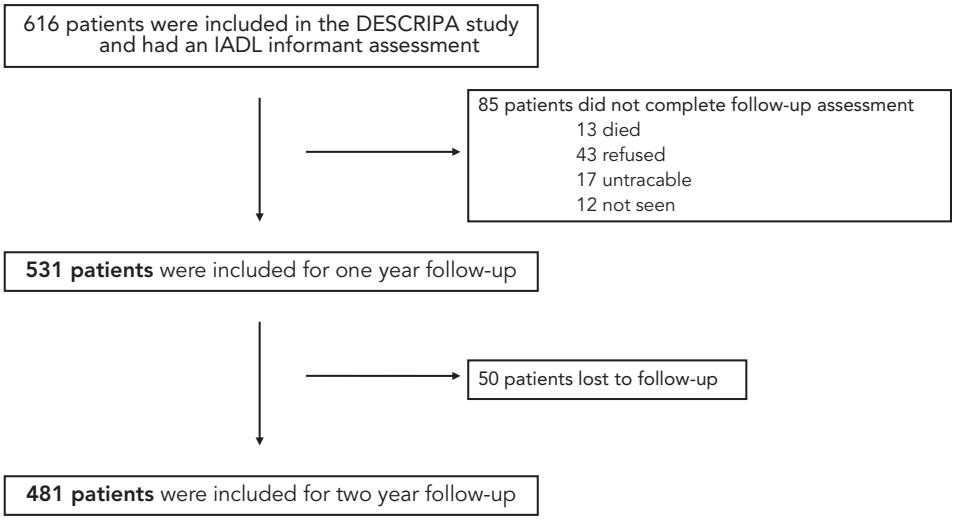

Figure 1. Flowchart of the inclusion and exclusion of patients in the DESCRIPA study.

Of all these IADL questionnaires, we selected the items with data from sufficient patients (n>50). Items aimed at IADL were selected, and items measuring orientation or memory were excluded. We then used the item content overlap of the different IADL scales to pool IADL activities. For example, all questionnaires had an item addressing housekeeping and these items were combined into a pooled 'housekeeping' item. We dichotomized the item responses of these pooled items into two responses: 'no problems' and 'slight to severe problems' (see appendix II). The most impaired score was used for the pooled item score when activities were represented by more than one item.

Cognitive examination

Mini Mental State Examination

The Mini-Mental State Examination (MMSE) was originally developed to differentiate organic from functional disorders.[28] Nowadays, it is widely used as a screening test for dementia.[29] The MMSE assesses several areas of cognition; orientation to time and place, registration of three words, attention and calculation, recall of three words, language and visual construction. MMSE scores range from 0 to 30, with lower scores indicating worse cognitive functioning.

Memory

All patients completed a memory test, but the tests varied among the centers. A primary test for verbal memory was selected for each center.[19] For the majority of patients (59.4%) this was the Rey Auditory Verbal Learning Test.[30] Alternative tests were selected for each primary test in case subjects had missing data for the primary test. Raw scores were converted to age-, education- and gender-corrected z-scores according to normative data of healthy control subjects.[19]

Depression

Depression severity scales differed between study centers. Scores were dichotomized for clinically significant depressive symptoms on each scale.[19]

Statistical Methods

Statistical analyses were performed with M-Plus version 6.1 [31] and SPSS (version 15.0 for Windows; SPSS inc, Chicago, USA).

We analyzed differences between demented and not demented subjects on demographic variables with independent t-tests or Chi-square tests as appropriate.

We used item response theory (IRT) to model the dimensional structure of IADL. We assumed that the IADL items measured an underlying construct, or 'latent trait'. In IRT, the latent trait is assumed to underlie and directly influence responses to items on a scale designed to measure that trait.[32] We used a commonly applied IRT model for binary items, the two-parameter logistic (2PL) model.[33,34] The estimation method used is the maximum likelihood and it is assumed that the distribution of the person parameter is standard normal. To investigate whether all items fitted the 2PL model, item goodness-of-fit was investigated using the item test of Stone.[35] Items were considered as misfitting if $p<0.01$. Reliability of summed items was calculated using a nonlinear SEM method for ordered categorical items.[36]

We modeled the relations between IADL, a diagnosis of dementia, depression, education, age, gender, MMSE and memory using structural equation modeling (SEM). SEM is a powerful statistical modeling technique, able to specify latent variable models that provide separate estimates of relations among latent constructs and their manifest indicators and the relations among constructs.[37]

The latent variable consisted of IADL as endogenous mediating variable. The measured variables were memory impairment and MMSE (as endogenous mediating variables); depression, education, age and gender (as exogenous variables); and diagnosis at one and two year follow up (as endogenous dependent variables). Education was scored as primary education (0), secondary education (1) or more than secondary education (2) and we assumed a linear relationship with the

endogenous variables. We investigated two models. The first model consisted of depression, education, age, gender, MMSE, IADL, memory and a diagnosis of dementia at one year follow-up. In the second model, we investigated whether these predictors were able to predict dementia after two years follow-up.

We started with a full model with all possible paths between the variables and removed non-significant paths in order to obtain a parsimonious model. Goodness-of-fit values of the final models were compared with the full model using a likelihood ratio (LR) Chi-square test. Associations between variables were presented as odds ratios (OR) with 95% confidence intervals (CI) or regression coefficients.

Statistical significance was set at $p<0.05$, unless indicated otherwise.

RESULTS

Baseline characteristics

The study sample consisted of 531 patients. At one year follow up, 69 (13.0%) patients developed dementia. The most common cause of dementia was Alzheimer's disease (n=59, 85.5%). A minority developed dementia with Lewy bodies (n=4, 5.8%), vascular dementia (n=2, 2.9%) or fronto-temporal dementia (n=3, 4.3%). Table 1 presents the baseline characteristics for the total study group and for the patients with and without a diagnosis of dementia at one year follow-up. Patients

Table 1. Baseline characteristics of the total study group and the comparison between demographic and baseline variables of the study groups.

			Diagnosis at one year FU		
		Total study group (n=531)	Dementia (n=69)	No dementia (n=462)	p-value
Age in years		69.6 (7.5)	71.5 (7.8)	69.3 (7.4)	.021*
Gender (% female)		315 (59.3%)	46 (66.7%)	269 (58.2%)	.18†
Level of education §		201 / 201 / 129	27 / 25 / 17	174 / 176 / 112	.95†
MMSE ¶		28 (26-29)	27 (25-28)	28 (27-29)	<.001‡
Memory #	z-score	-1.08 (1.34)	-2.04 (1.08)	-0.94 (1.32)	<.001*
	<1.5 SD	258 (48.6%)	51 (73.9%)	207 (44.8%)	<.001†
Depression #,**		50 (10.0%)	3 (4.4%)	47 (10.8%)	.10*

Data are presented as mean (standard deviation), median (interquartile range) or n (percentage). * Comparison is made with the independent samples t-test. † Comparison is made with Pearson's Chi-square test. ‡ Comparison is made with Mann-Whitney U test. § Education is presented as primary / secondary / more than secondary education. ¶ Missing data for 2 patients. # Missing data for 30 patients. ** Depression according to cut-off score of depression scale.

who developed dementia were generally older (t(529)=-2.31, p=.021), had lower MMSE scores (z=-5.15, p<.001) and more memory impairments (Chi-square=20.07, df=1, p=<.001) at baseline. Comorbidity did not differ between patients who developed dementia and those who did not (data not shown). At two year follow-up, 481 patients were seen and 100 (20.8%) had developed dementia.

Problems in daily living

A high number of missing values and 'non applicable' answers was present for the Lawton IADL (at least one in 124 patients, 32.0%) and the Bayer ADL (at least one in 8 patients, 18.2%). The Bristol ADL and the Lawton IADL scores showed floor effects. Six patients (40%) who completed the Bristol ADL and 202 patients (76.5%) who completed the Lawton IADL had the lowest possible scores, indicating the least disability.

Predicting dementia using IADL

We selected nine pooled IADL items: shopping, telephone use, housekeeping, transport, finances, medication, food/drink preparation, laundry and handling money. The first eight items are all included in the Lawton IADL and Bayer ADL questionnaire.

These items consisted of a single factor, with the first factor explaining 60.2% of the variance. All items fitted the 2PL model. The item discrimination and item difficulty parameter estimates with item goodness-of-fit values are shown in Table 2. The nonlinear SEM reliability coefficient was .71.

Table 2. Percentage of patients without problems in IADL and item discrimination (α) and item difficulty (β) parameters of the 2PL Model with item goodness-of-fit p-values.

Item	N	% of patients without problems	α	β	Goodness-of-fit Stone (p-values)
Shopping	525	71.4	4.29	1.51	0.34
Telephone use	466	92.1	2.31	1.18	0.56
Housekeeping	465	82.6	1.78	1.97	0.53
Transport	462	91.6	0.85	1.23	0.51
Finances	438	86.5	2.60	1.96	0.53
Medication	411	92.2	2.35	1.72	0.32
Food / drink preparation	391	92.1	1.95	2.09	0.36
Laundry	291	95.2	3.39	1.20	0.49
Handling money	190	87.9	1.03	2.22	0.35

Pearson distribution standard normal.

Table 2 shows the percentage of patients without problems in IADL. The majority of patients had no or slight problems in IADL. The rate of conversion to dementia after one year in patients with at least one IADL problem was higher than in patients without IADL problems (15.9% versus 9.8%, Chi-square=4.42, df=1, p=.036). The rate of conversion to dementia after two years was also higher in patients with IADL disabilities at baseline than in patients without IADL disabilities (24.4% versus 16.7%, Chi-square=4.28, df=1, p=.039).

The structural model with IADL as latent variable and depression, education, age, gender, MMSE and memory as measured variables was tested. Several relations were removed from the model to obtain a parsimonious model. Gender was not associated with IADL, MMSE, memory or diagnosis and we therefore removed these paths from the model. Education, age and depression were also not associated with diagnosis and these paths were removed from the model. In addition, we removed the paths between gender, depression and education with IADL and Memory, as these were not associated. The final model with path coefficients is depicted in Figure 2. The fit of this final model was satisfactory (LR Chi-square=22.22, df=13, p=.052). IADL was able to predict dementia at one year follow-up, with an odds ratio of 2.20 (95% CI 1.51-3.13). This is an odds ratio for an increase of 1 standard deviation in IADL score.

We then investigated whether IADL could also predict a dementia diagnosis at two year follow-up. Several relations were removed from the model, leading to the final model (Figure 3) with a satisfactory fit (LR Chi-square=19.09, df=11, p=.071).

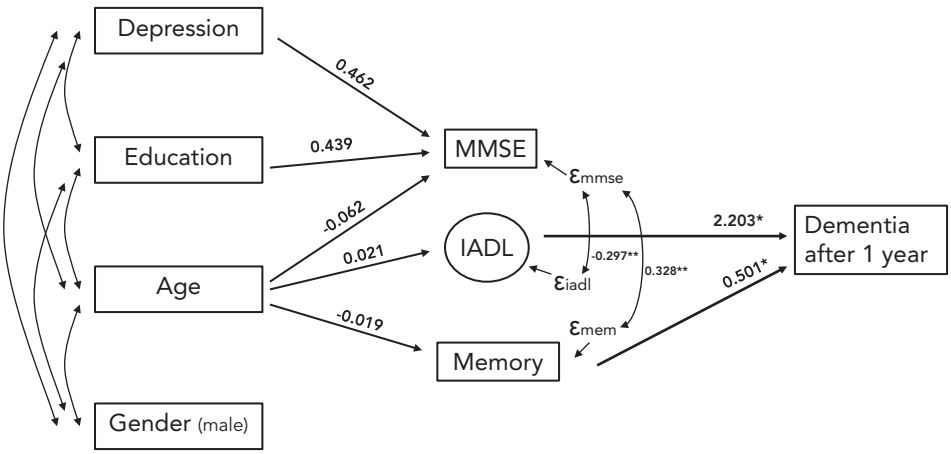

Figure 2. Final SEM model for dementia after one year with estimated path coefficients. Path coefficients to dementia are presented as odds ratios (*). Path coefficients between residual terms (ε) are presented as correlations (**).The circle represents the latent variable, squares represent measured variables. Indicators (items) for IADL are not shown. All shown path coefficients are p<.05.

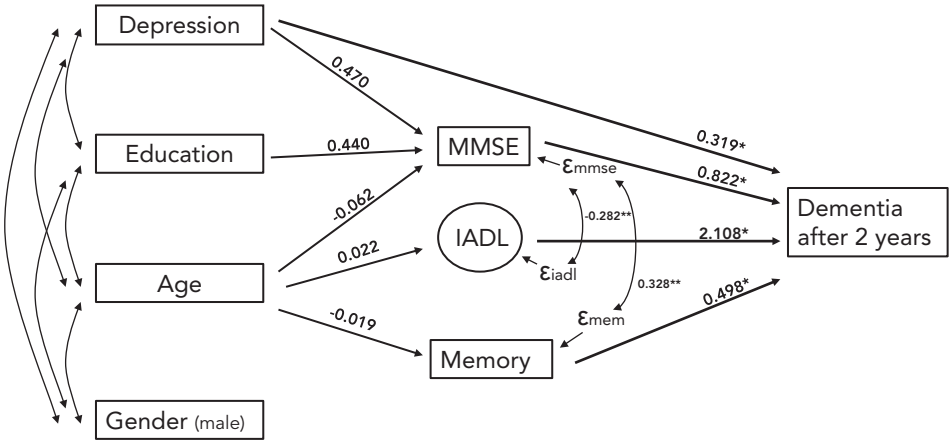

Figure 3. Final SEM model for dementia after two years with estimated path coefficients. Path coefficients to dementia are presented as odds ratios (*).Path coefficients between residual terms (ε) are presented as correlations (**). The circle represents the latent variable, squares represent measured variables. Indicators (items) for IADL are not shown. All shown path coefficients are p<.05.

Depression, MMSE, memory and IADL scores all contributed to a diagnosis of dementia at two year follow-up. The odds ratio of IADL was 2.11 (95%CI 1.33-3.33).

DISCUSSION

This study showed that IADL disability contributes to predicting dementia at one and two year follow-up, over commonly used clinical measures such as MMSE and memory. A minority of the memory-clinic patients experienced major problems in IADL at baseline, but a substantial part of the patients had slight problems in at least one IADL activity. These patients had a higher risk of developing dementia at follow-up than the patients who did not have IADL disabilities.

Given the inclusion criteria of the DESCRIPA study, one would expect minimal IADL problems at baseline. Problems in IADL are considered as the border between preclinical stages of dementia (indicated as mild cognitive impairment (MCI)) and dementia.[38] In MCI, IADL functioning should be essentially normal.[39] A previous study in a memory clinic population, found IADL scores in the upper ranges of the scale, indicating no to slight problems in daily functioning.[14] However, several recent studies have indicated that patients with MCI have more IADL problems than healthy controls.[40-44] Our findings are in line with these studies and support the view that slight problems in IADL are already present in patients at risk of developing dementia.

We found IADL to be helpful for predicting dementia, a finding which is in concordance with previous studies in community-based samples.[15,17,45] However, other studies did not find a contribution of IADL to the prediction of dementia.[7,11,14] Possible explanations for these differences are the method of measuring IADL in the latter studies, either by a limited number of items or based on self-report, which could have influenced the results.

Depression was not found to be a risk factor for dementia, which is in line with a previous study on affective symptoms as predictor for Alzheimer's disease in MCI patients.[46] However, it must be noted that patients with a severe depression were not included in the DESCRIPA study and that the depression parameter in the current study was based on screening questionnaires. Our findings on the contribution of IADL disability, memory and MMSE to a diagnosis of dementia at two year follow-up support the idea that cognitive and functional disabilities are independently associated with dementia. This emphasizes the need for an assessment of complex daily functioning in patients at risk for dementia.

Strengths of our study include the sample size and the prospective design. The latter allowed us to minimize the incorporation bias usually present in studies examining the diagnostic or predictive value of IADL. Our results are therefore very valuable for the prediction of outcome at follow-up of non-demented patients in a memory clinic.

Another strength of this study is the use of SEM modeling. This method is able to deal with skewed answer patterns and missing data, to a larger extent than for example logistic regression. As both of these aspects were present in our study, and probably also in comparable studies, our results may provide a better estimation of the relations between the different clinical variables.

The DESCRIPA study is a large European multicenter study, which has several limitations because of differences between countries and study centers. Differences in the diagnostic process might have caused some misclassifications in diagnoses. These differences are probably limited, since the main diagnostic tools were identical across the different study centers. Another difference is that in some countries or regions patients might visit the memory clinic later in the disease course. However, the conversion rate to dementia in the present study was comparable conversion rates in other studies [47], suggesting generalizability of our results. Another limitation is that age and MMSE differed between patients who completed the follow-up and patients who did not. We included age and MMSE in our model to correct for their possible influences on the relation between IADL and dementia.

Another possible disadvantage is our method with pooled IADL items. Items might not be completely comparable across questionnaires, as the formulation of items

might have influenced the responses.[48] Even though items were pooled when the content was highly comparable, our findings should be interpreted as a general indication of the contribution of IADL to dementia.

As a consequence of the item pooling, it is difficult to make recommendations on which IADL questionnaire should be used in clinical practice. However, the majority of the items were part of the Lawton IADL and the Bayer ADL, suggesting that these questionnaires contribute to a diagnosis of dementia. It is important to note though that the psychometric properties of IADL questionnaires need improvement, as argued in a recent review.[49] The clinical utility of IADL questionnaires has been questioned.[45] We found a large amount of missing items on many scales, indicating limited usefulness in clinical practice. In addition, the majority of these scales has not been developed for diagnostic purposes but for evaluation over time, which might have led to an underestimation of the true diagnostic value of IADL. To optimize the use of IADL, improvements in IADL scales are necessary.

We focused in IADL in this study, corrected for generally used clinical variables. We did not include biomarkers in our model, but these are increasingly used in memory clinics. Future studies might include biomarkers and obtain a broader prediction model of dementia. Detailed investigation into the difficulty of specific IADL activities might be useful for clinical practice.

In conclusion, non-demented subjects who visit a memory clinic may already have slight problems in complex daily functioning. As those patients are at a higher risk of developing dementia, they should be closely followed. IADL is a useful addition to other commonly used clinical measurements for predicting dementia.

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