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Impact of cognitive, functional, behavioral disorders and caregiver burden on the risk of nursing home placement

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SUMMARY

The caregiver burden and patient functional limitations contribute the most to the risk of nursing home placement in a real-life cohort of patients of a memory center, with subjective cognitive complaint, at any stage of cognitive impairment.

1 **Abstract**

2 **Objectives:** To estimate the attributable fraction of nursing home placement associated
3 with cognitive impairment, neuropsychiatric symptoms and behavioral disorders,
4 functional limitations and caregiver burden.

5 **Design:** Longitudinal study conducted on the “MEMORA cohort” linked with both
6 regional public health insurance and hospital discharge databases.

7 **Setting:** Memory center at the University Hospital of Lyon (France).

8 **Participants:** A sample of 2 456 outpatients attending the memory center between 2012
9 and 2017.

10 **Measures:** Cognitive impairment, functional limitations, neuropsychiatric
11 symptoms/behavioral disorders and caregiver burden were measured with the Mini-
12 Mental State Examination, the Instrumental activities of daily living scale, the
13 Neuropsychiatric Inventory (NPI) and a short version of the Zarit Burden Inventory,
14 respectively. Sociodemographics characteristics were collected during the first visit.
15 Comorbidities were gathered from the hospital discharge database. Dates of nursing
16 home placement were obtained from the public health insurance database.

17 **Results:** More than 38% of nursing home placements were attributable to caregiver
18 burden, and the attributable fraction associated with functional limitations exceeded 35%.
19 Between 20 and 25% of nursing home placements were due to cognitive impairment
20 while less than 16% were attributable to neuropsychiatric symptoms or behavioral
21 disorders. The associations between anxiety or agitation and the nursing home placement
22 were mediated by caregiver burden. Apathy or aberrant motor behaviors were associated
23 with a higher risk of nursing home placement independently of caregiver burden.

24 **Conclusions/implications:** Our findings suggest that a high proportion of nursing home

25 placements are attributable to caregiver burden and functional limitations in outpatients
26 attending a memory center. Cognitive impairment and neuropsychiatric symptoms or
27 behavioral disorders contribute less to nursing home placements. Interventions directed to
28 delay nursing home placement should emphasize actions towards reducing caregiver
29 burden and functional limitations of patients.

30 **INTRODUCTION**

31 Delaying nursing home placement of older adults is a major public health challenge. Up to
32 90% of patients with major neurocognitive disorders (NCD) would require nursing home
33 placement before death [1]. Nursing home placements represent high costs for the health
34 care system, the patient and their relatives. Nursing home placement costs 1.8 fold higher
35 than professional cares provided to patients with major NCD living at home i.e. an average
36 of 4,491 Euro per month in nursing home based on published data of 8 European countries
37 [2]. While the number of NCD cases worldwide is estimated at 47.5 million, this number is
38 expected to triple by 2050 due to population aging [3]. The burden of nursing home
39 placement as well as its overall cost is then likely to increase [4].

40 For patients and their relatives, nursing home placement has been described as a critical
41 life event [5]. Most of the patients would prefer remaining at home [6], and nursing home
42 placement is associated with several negative outcomes such as restricted quality of life [7]
43 [8], and increased mortality [9]. Although the placement could alleviate caregiver burden,
44 nursing home caregivers rate their health poorer than caregivers providing care at home
45 [10]. Many caregivers continue to assist with financial and legal affairs, make
46 arrangements for medical care, and provide emotional support and physical care after
47 nursing home placement [11 12]. In addition, many of them experience feeling of
48 disruption, sadness, guilt over placement, and uncertainty about the future [13] [14] [15].
49 In order to postpone nursing home placement, it is of crucial importance to identify its
50 putative risk factors, some of which could possibly be modified. In the past two decades,
51 a number of predictors of nursing home placement have been identified, including
52 cognitive impairment, functional limitations, some behavioral or neuropsychiatric
53 symptoms, as well as caregiver burden [6 14 16-21] [22]. Questions asked by healthcare

54 decision-makers now mostly relate to the magnitude of effects of these risk factors, and
55 the proportion of nursing home placements attributable to these, in order to prioritize and
56 plan public health interventions, as well as to implement adequate changes in clinical
57 practice. Previous studies have shown effects of different magnitude, possibly due to
58 methodological differences (follow-up time, study setting, measurements of outcome and
59 predictors, confounders taken into account). Furthermore, as emphasized by previous
60 authors, the differences in organization of cares provided to patients with cognitive
61 impairment between countries, as well as cultural differences may impact the role of
62 predictors of nursing home placement [23], thus illustrating the need for further research
63 aimed to enhance the understanding of factors implicated in the risk of nursing home
64 placement in different contexts.

65 Moreover, only few estimations of the fraction of nursing home placements attributable to
66 both patients symptoms due to NCD and caregiver burden are available, even if the
67 caregiver burden appears as the strongest risk factor accessible to interventions [19].

68 The objectives of this study were to estimate the association between a set of predictors
69 and nursing home placement and to estimate the fraction of nursing home placements
70 attributable to cognitive impairment, neuropsychiatric symptoms, functional limitations
71 and caregiver burden, in patients with cognitive complaint, at any stage of NCD.

72

73 **METHODS**

74 **The MEMORA cohort, health insurance and hospital databases**

75 The current study has been carried out on data of the MEMORA real-life cohort, which
76 aims to assess the determinants of functional decline, cognitive impairment and
77 neuropsychiatric symptoms and behavioral disorders of outpatients. The MEMORA

78 study is based on data from medical records as well as complementary information on
79 outpatients from the Clinical and Research Memory Centre of Lyon (Lyon Institute For
80 Elderly, University Hospital of Lyon, France). The MEMORA study data are also linked
81 with the public health insurance data available from the regional Primary Health Fund
82 and with the hospital data of the French hospital discharge database PMSI (Programme
83 de médicalisation des systèmes d'information).

84 The inclusion criteria in the MEMORA study are: attending a medical evaluation with a
85 neurologist or a geriatrician in the memory center (MC), whatever the cognitive stages
86 (cognitive complaint, either expressed by the patient or one of their relatives, at any stage
87 of the NCD), and living at home. The exclusion criteria are: living in nursing home, being
88 under guardianship or hearing or visual impairment preventing cognitive assessment.

89 In terms of ethical and legal considerations, information is individually provided to the
90 patients and their informal caregivers at inclusion, and they can oppose their participation in
91 the research. The authorization for handling personal data has been granted by the national data
92 protection commission: 06/08/2010.

93 The current study focused on a sample of outpatients included between 2012 and 2017
94 and for whom public health insurance data from the regional Primary Health Fund were
95 available.

96

97 **Measurements**

98 **Primary outcome: nursing home placement**

99 The dates of nursing home placement were extracted from the health insurance database of
100 the regional Primary Health Fund. For patients admitted in nursing home during follow-up,
101 the delay before admission was calculated as the time between the date of the first medical

102 examination at the MC and the date of nursing home placement. For patients without
103 nursing home placement, time was censored at 30 months or at death if it occurred
104 beforehand.

105 **Cognitive evaluation**

106 Global cognition was assessed with the Mini Mental State Examination (MMSE), a brief
107 cognitive screening instrument that included tests of memory, orientation, language,
108 praxis and attention [24]. This test yields a single cognitive function score ranging from
109 0 (severe cognitive impairment) to 30 (no impairment).

110 Diagnosis stage and etiologies were determined by a neurologist, a geriatrician, or a psychiatrist in
111 the MC. Patients with a subjective cognitive complaint with normal neuropsychological
112 performance were considered as having subjective cognitive disorders. Mild and major
113 neurocognitive disorders (NCD), which were previously known as mild cognitive impairment and
114 dementia, respectively, were identified using the Diagnosis and Statistical Manual of mental
115 disorders (DSM-V) nomenclature [25]. The etiologies were identified as follows:

116 Alzheimer's disease (AD), AD with cerebrovascular component, cognitive disorders of
117 vascular origin, Lewy body disease, frontotemporal degeneration, Parkinson's disease
118 and Parkinson's syndrome, psychiatric disorders, other disorders/undetermined, and
119 no trouble.

120 **Functional limitations**

121 The functional limitations were assessed using the summary score of the instrumental
122 activities of daily living scale (IADL) [26]. The IADL assesses patient's abilities in 8
123 instrumental activities: ability to make telephone calls, to go grocery shopping, to prepare
124 meals, to do housekeeping, to do laundry, to move and use transportation, to take
125 medications, and to handle finances. The IADL score ranges from 0 to 8. Usually, the

126 higher the IADL score, the higher the functional autonomy. Nevertheless, we have
127 considered the reverse score in order to determine the effect of functional limitations, a
128 score of 8 meaning a higher level of functional limitations in the current study.

129 **Neuropsychiatric symptoms**

130 Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI)
131 [27], including 12 neuropsychiatric symptoms or behavioral disorders: delusions,
132 hallucinations, depression, agitation, anxiety, apathy, disinhibition, irritability, elation,
133 aberrant motor behaviors, sleep disorders, and eating disorders. Both the frequency (4-
134 point scale) and the severity (3-point scale) of each item are evaluated, and the NPI is
135 summarized by a score ranging from 1 to 144, a higher score indicating a greater
136 number/severity of disorders. In the current study, we have considered the overall NPI score,
137 as well as 12 dummy variables indicating the presence of each neuropsychiatric symptom
138 or behavioral disorder.

139 **Sociodemographic characteristics**

140 The patients sociodemographic characteristics considered in the study were: age, sex,
141 marital status (single, married/in couple, divorced/separated, widowed, unspecified),
142 educational level (nil, primary, secondary, tertiary) and lifestyle (at home with spouse, at
143 home with relatives, at home alone with relatives in the neighborhood, at home alone
144 without relatives in the neighborhood, other lifestyle).

145 **Comorbidities**

146 The presence of comorbidities was obtained from the French hospital discharge database.
147 We focused on a set of comorbidities which were previously shown to increase the risk of
148 Alzheimer's disease [11 28]: hypertension, hypercholesterolemia, diabetes mellitus,
149 stroke and head trauma. In this study, we have considered the presence of each of these

150 comorbidities over the whole follow-up.

151 **Caregiver covariates**

152 The relationship between the patients and their caregivers was considered (spouse,
153 child/stepchild/grandchild, brother/sister/niece/nephew, other unspecified caregiver,
154 no caregiver). The subjective caregiver burden was assessed using the validated short
155 version of the Zarit Burden Inventory, which was previously developed for routine
156 medical care [29]. The score ranges from 0 (no burden) to 7 (higher burden). As
157 previously reported [30], the questionnaire included seven questions about the impact of
158 caregivers' help on their family or professional life, on their physical and mental health,
159 the problem of non-recognition, the fear for the parent's future, the wish to be helped and
160 the feeling of a global load.

161 The potential predictors of nursing home placement were collected at baseline, except for
162 comorbidities that were identified throughout the patient pathway.

163

164 **Statistical analyses**

165 The MICE method (Multivariate Imputations by Chained Equations) was applied to
166 replace missing values for the following variables: marital status (5% of missing values),
167 education (15%), lifestyle (0.1%), relationship with the caregiver (1%), MMSE score
168 (9%), NPI score (18%), and MiniZARIT score (12%) [31]. This method has jointly
169 imputed the covariates and allowed to preserve the relationships between variables. The
170 nursing home placement and all the above cited factors were included in the imputation
171 model.

172 The patients' characteristics were described overall and according to the occurrence of
173 nursing home placement using means and 95% confident intervals (CI) or frequency

174 distributions as appropriate. The characteristics were compared between patients admitted
175 in nursing home and those who remained at home using Pearson's chi-square test, or
176 Fisher's exact test.

177 Cox proportional hazards models were performed to assess the relationship between
178 predictors and incident nursing home placement and to calculate crude and adjusted
179 Hazard Ratios (HRs) and 95%CI. The sample was truncated at 30 months to preserve
180 the proportional hazards assumption (105 patients were excluded). In the multivariate
181 analyses, two settings were analyzed: setting (*i*) with the NPI considered as a
182 continuous variable, and setting (*ii*) with each neuropsychiatric symptom or behavioral
183 disorder of the NPI individually taken into account. For each model, we examined
184 whether the relationship between the neuropsychiatric symptoms and the nursing home
185 placement was mediated by functional limitations (IADL limitation score) or caregiver
186 burden (MiniZARIT score).

187 An extension of population attributable fraction (PAF) for cohort studies was used to
188 assess the fraction of nursing home placement attributable to the risk factors [32].

189 A p-value <0.05 was considered as statistically significant. Analyses were performed
190 using R software (version 3.5.0; R Foundation for Statistical Computing, Vienna,
191 Austria).

192

193 **RESULTS**

194 The study included 2 456 patients, with a follow-up truncated at 30 months. Among them,
195 16.2% were admitted in nursing home at the end of the follow-up. The average delay
196 before the nursing home placement was 16.3 months (95% CI=[15.5-17.1]).

197 **Characteristics of the study sample**

198 Table 1 reports the characteristics of the study population according to the admission to a
199 nursing home. Patients admitted to a nursing home during the follow-up period were
200 older than those who remained at home (83.3 [82.7-83.9] vs 79.0 [78.7-79.4]).

201 Patients admitted in nursing home had poorer health compared to those remaining at
202 home: 59% of them had a MMSE score inferior to 20 (vs 43% of non-placed), the average
203 of IADL limitation score was 4.7 [4.1-4.9] (vs 3.6 [3.5-3.7]), and the average of the NPI
204 score was 22.7 [20.9-24.3] (vs 16.8 [16.1-17.5]). Almost all the neuropsychiatric
205 symptoms or behavioral disorders evaluated in the NPI were overrepresented in patients
206 admitted in a nursing home. Concerning the diagnosis stage, 55% of patients placed in
207 nursing home had major NCD vs 38% in the group of patients with no nursing home
208 placement. The caregiver burden was greater in patients admitted in nursing home: the
209 average of MiniZARIT score was 3.8 [3.6-4.0] vs 2.8 [2.7-2.9].

210 **Predictors of nursing home placement**

211 Table 2 reports the frequency of patients placed in nursing home according to the
212 potential predictors and the crude HRs estimated from a Cox regression. The proportion
213 of patients placed in a nursing home exceeded 30% in patients who had a head trauma or
214 head injury during their care pathway, and in patients with a diagnosis of probable AD
215 with a cerebrovascular component. Regarding the crude HRs, a one-point increase in
216 NPI, MMSE, IADL or MiniZARIT scores multiplied the risk of nursing home placement

217 by 1.02, 1.04, 1.20, and 1.28, respectively.

218 Table 3 and Table 4 present the adjusted HRs in settings (i) with the NPI score as
219 continuous, and (ii), with each neuropsychiatric symptom or behavioral disorder of the
220 NPI. In both settings, a first model (Model 1) without IADL limitation score and caregiver's
221 covariates was performed. In model 1, a dose-response relationship between MMSE and
222 nursing home placement was observed: the lower the MMSE, the higher the risk of nursing
223 home placement. When introducing the IADL limitation score in the settings (i) and (ii)
224 (see Model 2), this dose-response relationship remained in setting (ii). In setting (ii)
225 Model 2, a one-point increase in IADL limitation score multiplied the risk of nursing
226 home placement by 1.15 [1.09-1.21] (results were similar in setting (i)). A set of
227 neuropsychiatric symptoms and behavioral disorders was also significant in this Model 2.
228 Patients with apathy (HR=1.40 [1.09-1.80]), aberrant motor behaviors (HR=1.38 [1.09-
229 1.73]), agitation (HR=1.30 [1.00-1.68]), or anxiety (HR=1.31 [1.05-1.64]) had higher risk
230 of nursing home placement. The introduction of the caregiver's covariates in the models
231 (See Model 3) had little impact on the relationship between the MMSE and the nursing
232 home placement. The estimation associated with IADL limitation score was a little more
233 impacted since a one- point increase in the IADL limitation score multiplied the risk of
234 nursing home placement by 1.09 [1.03-1.15] in setting (ii). The estimations associated
235 with neuropsychiatric symptoms (setting (ii)) were more impacted, with agitation and
236 anxiety which did not remain significant. Only apathy and aberrant motor behaviors
237 remained associated with a higher risk of nursing home placement in setting (ii) Model 3.
238 Note that sleep disorders was associated with a lower risk of nursing home placement. A
239 one-point increase in the MiniZARIT score multiplied the risk of nursing home placement
240 by 1.17 [1.10-1.25].

241 **Population Attributable Fraction (PAF)**

242 Figure 1 illustrates the adjusted attributable fractions of the MMSE, the NPI, the IADL
243 limitation and the MiniZARIT scores. Over the 30-months period, between 12 and 16%
244 of nursing home placements were attributable to neuropsychiatric symptoms or
245 behavioral disorders while between 20 and 25% were attributable to cognitive
246 impairment. The PAF associated with the IADL limitation score varied from 35 to 40%.
247 Between 38 and 43% of nursing home placements were attributable to caregiver
248 burden.

249

250

251 **DISCUSSION**

252 In this longitudinal study of outpatients of a memory center, the fraction of nursing home
253 placement attributable to either caregiver burden or functional limitations was estimated
254 between 35 and 43%. Between 20 and 25% of nursing home placements were due to
255 cognitive impairment while less than 16% were attributable to neuropsychiatric
256 symptoms or behavioral disorders. Higher cognitive impairment, functional limitations,
257 caregiver burden and age increase the risk of nursing home placement in these patients
258 with cognitive complaint or at any stage of NCD, which is consistent and complementary
259 with previous findings conducted in persons with major NCD already triggered [14] [18]
260 [21]. As expected, the major NCD stage which manifests itself by poorer cognition,
261 functional impairment and behavioral disorders, was associated with a higher risk of
262 nursing home placement.

263 Concerning neuropsychiatric symptoms, results of this study differ depending on the
264 adjustment for caregiver's covariates. The associations between the NPI score, symptoms
265 of anxiety or agitation and the nursing home placement were mediated by the caregiver
266 burden. On the other hand, patients with apathy or aberrant motor behaviors had a
267 higher risk of nursing home placement independent of caregiver burden. This contrasting
268 result on the role of the caregiver burden as a mediator in the relationships between
269 neuropsychiatric symptoms or behavioral disorders and nursing home placement is in line
270 with a previous study which also finds different effects of caregiver burden depending on
271 the behavior disturbances [33]. More precisely, our result on apathy as an independent
272 predictor of nursing home placement is consistent with Bakker et al. in community-
273 dwelling patients with dementia [34]. In another study, Scarmeas et al. suggested that
274 delusions and hallucinations increased the risk of nursing home placement while this

275 result is not observed in the present study [35]. However, similar to our results, in Gilley et
276 al. delusions were not associated with the risk of nursing home placement [36]. Another
277 observation is that depression was not associated with an increased risk of nursing home
278 placement in our study, in contrast to previous findings by Okura et al., Gilley et al., and
279 Dorenlot et al. [17 20] [17] [36]. One can note that in Dorentot et al., and Gilley et al. the
280 study has been conducted in community patients with major NCD and did not include
281 earlier stages of the NCD. Moreover Dorentot et al. considered major depression (25%),
282 whereas we considered the presence of depression assessed with the NPI (37%). The
283 possible explanation of the difference with Okura et al. is less obvious. Similar to our study, the
284 authors have also used the NPI to assess depression (prevalence of 25% to 36% depending of the
285 cognitive stages), and their study was conducted in elderly people at different stages of cognitive
286 impairment. The significant relationship between sleep disorders evaluated in the NPI and
287 lower risk of nursing home placement was not expected. The reason for this observation
288 remains unclear. Nevertheless, this last result has to be interpreted with caution since
289 sleep disorders were self-reported, and not based on measures with electroencephalogram
290 or polysomnography.

291 A strength of this study is to provide an estimation of attributable fractions that may help
292 decision-makers, for instance to prioritize prevention measures on the reduction of
293 caregiver burden. Another interesting characteristic is the large collection of data in a
294 real-life context of patients with cognitive complaint or any stages of NCD allowing to
295 reflect the current care practice, especially since the data were collected recently [37].
296 This context has allowed for an evaluation of risk factors for nursing home placement not
297 only among patients with major NCD, but also in patients with subjective cognitive
298 complaint or at early stage of NCD e.g. mild NCD, among whose interventions could be

299 implemented more earlier. Measurement biases are probably negligible in the present study
300 because reliable and international scales were used to measure cognitive impairment,
301 functional limitations, neuropsychiatric symptoms, and caregiver burden. In addition,
302 nursing home placement as well as comorbidities were issued from administrative data, a
303 source of data that is less likely to be biased than declarative variables [38].
304 Our study has several limitations that should be taken into account. As in all
305 observational studies, confounding and selection bias may have arisen. There is
306 probably a confounding bias due to the absence in the models of covariates reflecting the
307 use of health care services (nurse aides, home health aides, home care aides) [14]and
308 some comorbidities such as incontinence[6] [19]. Nevertheless the direction of the
309 bias remains unclear. The high prevalence of patients placed in a nursing home (16%)
310 may reflect the setting of the study in a MC. In the MC, the proportion of patients with
311 major NCD was higher (40.6%) than in the general population at similar age i.e the
312 prevalence of major NCD has been estimated at 7.4% in people aged between 75 and
313 79 years old and 12.9% in people aged between 80 and 84 years old in Western
314 Europe [39]. The reason of this difference may be that MCs in France are dedicated to
315 the care of patients with a cognitive impairment [40]. This study was conducted in
316 one center, in which the health care organization could differ from other memory
317 centers. The context of the present study should then be taken into account before the
318 generalization of these results.

319

320 **CONCLUSION/RELEVANCE**

321 Our findings suggest that a high proportion of nursing home placement is attributable to
322 caregiver burden, and to functional limitations, and to a lesser extent to cognitive

323 impairment and neuropsychiatric symptoms and behavioral disorders in patients in MC.
324 This study supports the targeting of reduction of caregiver burden and functional
325 limitations among patients in MC at any stage of NCD, in order to delay the nursing
326 home placement [41].

327

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328

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Figure 1 Population Attributable Fraction (PAF)

legend: full line = Population Attributable Fraction (PAF) estimation ; dashed line = 95% CI

* we have considered here the reverse score MMSE (the higher the MMSE limitation score, the higher the cognitive disorders) so that the PAF's interpretation is the same for the 4 scores.

Table 1: Characteristics of study population according nursing home placement

	Total		Placed		Non placed		p value (Chi square test)
	n=2456	%	n=411	16.2%	n=2 045	83.8%	
Age (mean, 95% CI)	79.8	[79.4-80.1]	83.3	[82.7-83.9]	79.0	[78.7-79.4]	< 0.001
Sex							0.020
Male	953	38.8	138	33.6	815	39.9	
Female	1503	61.2	273	66.4	1230	60.2	
Marital status							< 0.001
Married/in couple	1358	55.3	177	43.1	1181	57.8	
Divorced/separated	211	8.6	38	9.3	173	8.5	
Widowed	733	29.9	164	39.9	569	27.8	
Single	103	4.2	25	6.1	78	3.8	
Unspecified	51	2.1	7	1.7	44	2.2	
Educational level							0.028
Nil	458	18.7	64	15.6	394	19.3	
Primary	830	33.8	164	39.9	666	32.6	
Secondary	815	33.2	130	31.6	685	33.5	
Tertiary	353	14.4	53	12.9	300	14.7	
Lifestyle at baseline							< 0.001
At home with its husband/spouse	1309	53.3	163	39.7	1146	56.0	
At home with relatives	165	6.7	24	5.8	141	6.9	
At home, alone, with relatives in the neighborhood	689	28.1	160	38.9	529	25.9	
At home, alone, without relatives in the neighborhood	211	8.6	40	9.7	171	8.4	
Other lifestyle	82	3.3	24	5.8	58	2.8	
MMSE							< 0.001
MMSE score (mean, 95% CI)	19.0	[18.8-19.3]	17.2	[16.5-17.8]	19.0	[19.1-19.7]	< 0.001
[0,10[371	15.1	69	16.8	302	14.8	
[10,20[751	30.6	174	42.3	577	28.2	
[20,26[781	31.8	128	31.1	653	31.9	
[26,30]	553	22.5	40	9.7	513	25.1	
IADL autonomy score (mean, 95% CI)	4.2	[4.1-4.3]	3.3	[3.1-3.5]	4.4	[4.3-4.5]	< 0.001
IADL limitation score (mean, 95% CI)	3.8	[3.7-3.9]	4.7	[4.1-4.9]	3.6	[3.5-3.7]	< 0.001
NPI score (mean, 95% CI)	17.8	[17.2-18.4]	22.7	[20.9-24.3]	16.8	[16.1-17.5]	< 0.001
Presence of (n=2078)							
<i>Delusions</i>	440	17.9	101	24.6	339	16.6	< 0.001
<i>Hallucinations</i>	188	7.7	45	11.0	143	7.0	< 0.001
<i>Agitation</i>	438	17.8	106	25.8	332	16.2	< 0.001
<i>Depression</i>	918	37.4	183	44.5	735	35.9	< 0.001
<i>Anxiety</i>	1073	43.7	216	52.6	857	41.9	< 0.001
<i>Elation</i>	135	5.5	28	6.8	107	5.2	< 0.001
<i>Apathy</i>	1333	54.3	286	69.6	1047	51.2	< 0.001

<i>Disinhibition</i>	301	12.3	72	17.5	229	11.2	< 0.001
<i>Irritability</i>	979	39.9	192	46.7	787	38.5	< 0.001
Aberrant motor behaviors	538	21.9	130	31.6	408	20.0	< 0.001
<i>Sleep disorders</i>	401	16.3	61	14.8	340	16.6	< 0.001
<i>Eating disorders</i>	452	18.4	92	22.4	360	17.6	< 0.001
<i>Missing NPI</i>	378	15.4	33	8.0	345	16.9	< 0.001
Diagnosis stage							< 0.001*
Absence of trouble	19	0.8	1	0.2	18	0.9	
Subjective cognitive disorders	707	28.8	80	19.5	627	30.7	
Mild neurocognitive disorders, with amnesic component	173	7.0	24	5.8	149	7.3	
Other mild neurocognitive disorders	552	22.5	78	19.0	474	23.2	
Major neurocognitive disorders	996	40.6	227	55.2	769	37.6	
Other cases	9	0.4	1	0.2	8	0.4	
Diagnosis etiology							< 0.001*
Diagnosis not yet established	1141	46.5	169	41.1	972	47.5	
Alzheimer disease	588	23.9	143	34.8	445	21.8	
Alzheimer disease with cerebrovascular component	132	5.4	39	9.5	93	4.6	
Cognitive disorders of vascular origin	205	8.4	23	5.6	182	8.9	
Lewy body disease	41	1.7	9	2.2	32	1.6	
Fronto temporal dementia	11	0.5	1	0.2	10	0.5	
Parkinson's disease, and Parkinson's syndrome	52	2.1	8	2.0	44	2.2	
Psychiatric disorders	134	5.5	6	1.5	128	6.3	
Other disorders	86	3.5	10	2.4	76	3.7	
No trouble	66	2.7	3	0.7	63	3.1	
Mini ZARIT score (mean, 95% CI)	3.0	[2.9-3.0]	3.8	[3.6-4.0]	2.8	[2.7-2.9]	< 0.001
Relationship with caregiver							< 0.001
No caregiver	249	10.1	13	3.2	236	11.5	
Spouse	981	39.9	144	35.0	837	40.9	
Child/stepchild/grandchild	1052	42.8	218	53.0	834	40.8	
Brother/sister/niece/nephew	92	3.8	25	6.1	67	3.3	
Other unspecified	82	3.3	11	2.7	71	3.5	
Comorbidities n=2153 (presence of)							
<i>Hypertension</i>	1102	44.9	189	46.0	913	44.7	< 0.001
<i>Hypercholesterolemia</i>	385	15.7	79	19.2	306	15.0	< 0.001
<i>Diabetes</i>	395	16.1	57	13.9	338	16.5	< 0.001
<i>Stroke</i>	125	5.1	24	5.8	101	4.9	< 0.001
<i>Head trauma</i>	72	2.9	22	5.4	50	2.4	< 0.001

* p-value from a Fisher's exact test because of cells ≤ 5

Table 2: Crude Hazard ratios (HR) from Cox regressions

	% in nursing homes	HR	95% CI		p value
Age		1.09	1.07	1.10	< 0.001
Sex					
Male	14.5		Ref.		
Female	18.2	1.28	1.04	1.57	0.018
Marital status					
Married/in couple	13.0		Ref.		
Divorced/separated	18.0	1.42	1.00	2.01	0.051
Widowed	22.4	1.82	1.47	2.26	< 0.001
Single	24.3	1.96	1.29	2.98	0.002
Unspecified	13.7	1.11	0.52	2.36	0.787
Educational level					
Nil	14.0		Ref.		
Primary	19.8	1.46	1.09	1.95	0.010
Secondary	16.0	1.15	0.86	1.56	0.350
Tertiary	15.0	1.08	0.75	1.55	0.684
Lifestyle at baseline					
At home with its husband/spouse	12.5		Ref.		
At home with relatives	14.5	1.20	0.78	1.84	0.402
At home, alone, with relatives in the neighborhood	23.2	2.00	1.61	2.49	< 0.001
At home, alone, without relatives in the neighborhood	19.0	1.60	1.14	2.27	0.007
Other lifestyle	29.3	2.58	1.68	3.95	< 0.001
MMSE score		0.96	0.95	0.98	< 0.001
MMSE [0, 10[18.6	2.79	1.89	4.12	< 0.001
MMSE [10, 20[23.2	3.55	2.52	5.01	< 0.001
MMSE [20, 26[16.4	2.39	1.67	3.40	< 0.001
MMSE [26, 30]	7.2		Ref.		
IADL autonomy score		0.83	0.80	0.87	< 0.001
IADL limitation score		1.20	1.15	1.25	< 0.001
NPI score		1.02	1.01	1.02	< 0.001
Presence of (n=2182)					
Delusions	23.0	1.40	1.12	1.76	0.004
Hallucinations	23.9	1.42	1.04	1.94	0.026
Agitation	24.2	1.52	1.22	1.91	< 0.001
Depression	19.9	1.22	1.00	1.49	0.054
Anxiety	20.1	1.30	1.06	1.59	0.012
Elation	20.7	1.18	0.80	1.73	0.399
Apathy	21.5	1.84	1.45	2.32	< 0.001
Disinhibition	23.9	1.45	1.13	1.88	0.004
Irritability	19.6	1.18	0.97	1.45	0.105
Aberrant motor behaviors	24.2	1.60	1.29	1.98	< 0.001
Sleep disorders	15.2	0.80	0.60	1.05	0.101
Eating disorders	20.4	1.18	0.93	1.49	0.177

	% in nursing homes	HR	95% CI	p value
Diagnosis stage				
Absence of trouble	5.3	0.44	0.06 3.20	0.421
Subjective cognitive disorders	11.3		Ref.	
Mild neurocognitive disorders, with amnesic component	13.9	1.23	0.78 1.93	0.382
Other mild neurocognitive disorders	14.1	1.27	0.93 1.73	0.134
Major neurocognitive disorders	22.8	2.19	1.69 2.82	< 0.001
Other cases	11.1	1.03	0.14 7.39	0.978
Diagnosis etiology				
Diagnosis not yet established	14.8	0.58	0.46 0.72	< 0.001
Alzheimer disease	24.3		Ref.	
Alzheimer disease with cerebrovascular component	29.5	1.25	0.88 1.79	0.212
Cognitive disorders of vascular origin	11.2	0.43	0.28 0.67	< 0.001
Lewy body disease	22.0	0.91	0.46 1.79	0.785
Fronto temporal dementia	9.1	0.35	0.05 2.52	0.298
Parkinson's disease, and Parkinson's syndrome	15.4	0.63	0.31 1.29	0.207
Psychiatric disorders	4.5	0.16	0.07 0.37	< 0.001
Other disorders/unknown	11.6	0.45	0.23 0.85	0.014
No trouble	4.5	0.16	0.05 0.52	0.002
Mini ZARIT score				
		1.28	1.21 1.34	< 0.001
Relationship with caregiver				
Spouse	5.2		Ref.	
Child/stepchild/grandchild	14.7	1.48	1.20 1.82	< 0.001
Brother/sister/niece/nephew	20.7	2.05	1.34 3.13	0.001
Other unspecified	27.2	0.91	0.49 1.68	0.757
No caregiver	13.4	0.34	0.19 0.60	< 0.001
Comorbidities (from PMSI data)				
Hypertension	17.2	0.87	0.72 1.06	0.180
Hypercholesterolemia	20.5	1.15	0.90 1.48	0.258
Diabetes mellitus	14.4	0.74	0.56 0.98	0.033
Stroke	19.2	1.08	0.71 1.63	0.719
Head trauma	30.6	1.89	1.23 2.91	0.004

Table 3: Multivariate Cox models with NPI considered as continuous (setting (i))

	Model 1				Model 2 = Model 1 + IADL limitation				Model 3 = Model 2 + caregiver covariates			
	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value
Age	1.07	1.05	1.09	< 0.001	1.06	1.04	1.08	< 0.001	1.06	1.05	1.08	< 0.001
Sex												
Male		Ref.				Ref.				Ref.		
Female	0.93	0.74	1.18	0.576	1.07	0.84	1.36	0.581	1.09	0.85	1.39	0.487
Educational level												
Nil		Ref.				Ref.				Ref.		
Primary	1.65	1.23	2.23	< 0.001	1.68	1.25	2.27	< 0.001	1.66	1.23	2.24	0.001
Secondary	1.65	1.21	2.26	< 0.001	1.72	1.25	2.36	< 0.001	1.66	1.20	2.28	0.002
Tertiary	2.13	1.45	3.14	< 0.001	2.22	1.51	3.27	< 0.001	2.17	1.46	3.21	< 0.001
Lifestyle at baseline												
At home with its husband/spouse		Ref.				Ref.				Ref.		
At home with relatives	0.92	0.59	1.43	0.714	0.86	0.55	1.34	0.511	1.20	0.72	1.99	0.492
At home, alone, with relatives in the neighborhood	1.70	1.33	2.18	< 0.001	1.88	1.47	2.42	< 0.001	2.54	1.77	3.63	< 0.001
At home, alone, without relatives in the neighborhood	1.59	1.10	2.29	0.014	1.87	1.29	2.71	0.001	2.71	1.72	4.28	< 0.001
Other lifestyle	2.51	1.62	3.90	< 0.001	2.60	1.68	4.02	< 0.001	4.02	2.44	6.63	< 0.001
MMSE												
MMSE [0,10[2.90	1.93	4.34	< 0.001	2.10	1.37	3.21	0.001	2.04	1.34	3.13	< 0.001
MMSE [10,20[2.84	1.98	4.08	< 0.001	2.13	1.46	3.10	< 0.001	1.95	1.34	2.83	< 0.001
MMSE [20,26[2.03	1.41	2.91	< 0.001	1.78	1.23	2.56	0.002	1.70	1.18	2.44	< 0.001
MMSE [26,30]		Ref.				Ref.				Ref.		
NPI score	1.02	1.01	1.02	< 0.001	1.01	1.01	1.02	< 0.001	1.01	1.00	1.01	0.012
Comorbidities (from PMSI data)												
<i>Hypertension</i>	0.76	0.61	0.93	0.010	0.75	0.61	0.93	0.008	0.75	0.61	0.93	0.009
<i>Hypercholesterolemia</i>	1.54	1.18	2.00	< 0.001	1.60	1.23	2.08	0.001	1.68	1.29	2.19	< 0.001
<i>Head trauma</i>	1.54	1.00	2.38	0.049	1.46	0.94	2.25	0.090	1.40	0.91	2.17	0.127
<i>Missing</i>	0.34	0.21	0.55	< 0.001	0.34	0.21	0.55	0.000	0.33	0.21	0.54	< 0.001
IADL limitation score					1.15	1.10	1.22	< 0.001	1.09	1.03	1.15	0.003
Relationship with caregiver												
Spouse										Ref.		
Child/stepchild/grandchild									0.62	0.44	0.88	0.008
Brother/sister/niece/nephew									0.80	0.47	1.36	0.407
Other unspecified									0.44	0.22	0.87	0.018

No caregiver

MiniZARIT score

0.31	0.16	0.60	0.000
1.16	1.09	1.24	0.000

Table 4: Multivariate Cox models with the different behaviors that composed the NPI (setting *(ii)*)

	Model 1				Model 2 = Model 1 + IADL dependence				Model 3 = Model 2 + caregiver covariates			
	HR	95% CI		p value	HR	95% CI		p value	HR	95% CI		p value
Age	1.07	1.05	1.08	< 0.001	1.06	1.04	1.07	< 0.001	1.06	1.04	1.08	< 0.001
Sex												
Male		Ref.				Ref.				Ref.		
Female	0.97	0.76	1.22	0.770	1.08	0.85	1.38	0.51	1.12	0.88	1.44	0.364
Educational level												
Nil		Ref.				Ref.				Ref.		
Primary	1.70	1.26	2.29	0.001	1.71	1.27	2.32	0.001	1.67	1.23	2.26	0.001
Secondary	1.71	1.25	2.35	0.001	1.75	1.28	2.41	0.001	1.67	1.21	2.30	0.002
Tertiary	2.29	1.55	3.38	< 0.001	2.33	1.58	3.44	< 0.001	2.22	1.49	3.29	< 0.001
Lifestyle at baseline												
At home with its husband/spouse		Ref.				Ref.				Ref.		
At home with relatives	1.00	0.64	1.56	0.995	0.94	0.60	1.48	0.795	1.33	0.79	2.23	0.281
At home, alone, with relatives in the neighborhood	1.84	1.43	2.37	< 0.001	2.02	1.56	2.61	< 0.001	2.82	1.96	4.07	< 0.001
At home, alone, without relatives in the neighborhood	1.78	1.22	2.58	0.003	2.06	1.41	3.01	0.000	3.02	1.90	4.80	< 0.001
Other lifestyle	2.98	1.91	4.65	< 0.001	3.04	1.95	4.75	< 0.001	4.65	2.79	7.75	< 0.001
MMSE score												
MMSE [0,10[2.93	1.94	4.43	< 0.001	2.17	1.41	3.35	0.000	2.11	1.37	3.25	0.001
MMSE [10,20[2.55	1.77	3.66	< 0.001	1.99	1.36	2.89	0.000	1.87	1.28	2.72	0.001
MMSE [20,26[1.86	1.29	2.67	0.001	1.66	1.15	2.39	0.007	1.62	1.12	2.33	0.010
MMSE [26,30]		Ref.				Ref.				Ref.		
NPI detailed												
<i>Delusions</i>	0.96	0.75	1.24	0.761	0.97	0.76	1.26	0.843	0.95	0.74	1.22	0.680
<i>Hallucinations</i>	1.06	0.76	1.47	0.735	0.94	0.67	1.30	0.691	0.90	0.65	1.25	0.522
<i>Agitation</i>	1.35	1.04	1.74	0.022	1.30	1.00	1.68	0.047	1.21	0.94	1.56	0.146
<i>Depression</i>	0.94	0.76	1.18	0.604	0.97	0.78	1.21	0.778	0.93	0.74	1.16	0.526
<i>Anxiety</i>	1.29	1.03	1.61	0.025	1.31	1.05	1.64	0.017	1.25	1.00	1.56	0.051
<i>Elation</i>	1.09	0.73	1.64	0.664	1.03	0.69	1.55	0.876	1.00	0.67	1.51	0.982
<i>Apathy</i>	1.62	1.27	2.08	< 0.001	1.40	1.09	1.80	0.009	1.31	1.01	1.69	0.040
<i>Disinhibition</i>	1.09	0.82	1.44	0.565	1.06	0.80	1.40	0.682	1.05	0.80	1.40	0.712
<i>Irritability</i>	0.98	0.78	1.23	0.872	0.97	0.78	1.22	0.811	0.93	0.74	1.16	0.502
<i>Aberrant motor behaviors</i>	1.41	1.12	1.78	0.003	1.38	1.09	1.73	0.006	1.30	1.03	1.64	0.026
<i>Sleep disorders</i>	0.71	0.53	0.94	0.017	0.68	0.51	0.90	0.008	0.66	0.50	0.88	0.005

	Eating disorders	0.93	0.72	1.19	0.545	0.88	0.68	1.13	0.303	0.82	0.63	1.05	0.111	
	<i>Missing NPI</i>	0.79	0.51	1.22	0.294	0.76	0.50	1.18	0.226	0.76	0.48	1.19	0.232	
Comorbidities (from PMSI data)														
	Hypertension	0.77	0.62	0.94	0.013	0.76	0.61	0.94	0.010	0.76	0.61	0.93	0.009	
	Hypercholesterolemia	1.50	1.16	1.96	0.002	1.58	1.21	2.06	0.001	1.67	1.28	2.17	<0.001	
	Head trauma	1.63	1.05	2.51	0.028	1.54	1.00	2.38	0.052	1.49	0.96	2.31	0.077	
	<i>Missing</i>	0.32	0.20	0.52	<0.001	0.33	0.20	0.52	<0.001	0.33	0.20	0.52	<0.001	
IADL limitation score						1.15	1.09	1.21	<0.001	1.09	1.03	1.15	0.003	
Relationship with caregiver														
Spouse											Ref.			
Child/stepchild/grandchild											0.60	0.42	0.86	0.006
Brother/sister/niece/nephew											0.75	0.44	1.28	0.288
Other unspecified											0.44	0.22	0.87	0.019
No caregiver											0.35	0.18	0.69	0.002
MiniZARIT score											1.17	1.10	1.25	<0.001

