Received: 31 October 2021 | Accepted: 20 April 2022

DOI: 10.1002/gps.5724

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry WILEY

Predictors of nursing home placement at 2 years in Alzheimer's disease: A follow-up survey from the THERAD study

Hélène Villars[1,2] | Virginie Gardette[1,2] | Pauline Frayssignes[1] | Eva Deperetti[1] | Amélie Perrin[1] | Christelle Cantet[2] | Maria Soto-Martin[1,2]

[1]Geriatric Department, Toulouse University Hospital, Toulouse, France

[2]Department of Epidemiology and Public Health, Inserm UMR 1295, Centre for Research in Population Health (CERPOP), Toulouse, France

Correspondence
Hélène Villars, Geriatric Department, Toulouse University Hospital, Toulouse, Cedex 9 31059, France.
Email: villars.h@chu-toulouse.fr

Funding information
Fondation Mederic Alzheimer; Ministère des Affaires sociales, de la Santé et des Droits des femmes

Abstract

Objectives: Nursing Home Placement (NHP) can prove to be the only solution to some dead-end situations in Alzheimer's disease (AD). The predictors of NHP are known and can be related to either the person with dementia or his/her caregiver. We aimed to identify predictors of NHP among people with AD over a 2-year follow-up period, with a particular interest in the modifiable predictors, notably those involving caregivers.

Methods: We studied data from the THERAD study, a French monocentric randomized controlled trial, involving 196 community-dwelling dyads, primarily assessing an educational intervention in AD. We performed a bivariate analysis followed by a multivariate Cox model, with a backward stepwise procedure.

Results: The mean age of the patients was 82 years old, 67.7% were women and 56.9% were living with a partner. The mean age of the caregivers was 65.8 years old, 64.6% were women and half were spouses of the patients with a moderate burden. During the follow-up, 23 patients died and 49 were institutionalized. The majority of NHPs occurred during the first year (35 NHP). The mean time to NHP was 27.77 months after the diagnosis. Five independent predictors of NHP were found: a higher patient education level (aHR 6.31; CI95% = 1.88–21.22), a high caregiver Burden (aHR 3.97; CI95% = 1.33–11.85), the caregiver being the offspring of the patient (aHR 2.92; CI95% = 1.43–5.95), loss of autonomy (aHR 2.75; CI95% = 1.13–6.65) and disinhibition as a behavioural and psychological symptoms of dementia (BPSD) (aHR 2.38; CI95% = 1.26–4.47).

Conclusions: Our data are in accordance with the literature in identifying loss of autonomy, burden and BPSD (disinhibition) as risk factors of NHP. We also found high patient education level and status of offspring caregiver as additional factors. It is essential to take into account the caregiver status when designing psycho-educational trials aiming to delay NHP. Further studies need to take into account both the modifiable risk factors related to the patient (productive BPSD) and the needs of offspring caregivers (work–life balance, mental load).

KEYWORDS
Alzheimer's disease, burden, dyadic approach, nursing home, offspring caregivers

Key points

- Nursing home placement (NHP) can be the only solution in some dead-end situations in Alzheimer's disease (AD). There is some evidence on the risk factors of NHP, related to both patients and caregivers (behavioural and psychological symptoms, loss of autonomy, and caregiver burden).
- We found these factors in our work on a sample of 196 dyads during a 2-year follow-up as part of the randomized controlled trial THERAD, where the primary endpoint was to assess the impact of an educational intervention on the quality of life of people with AD.
- We found two additional factors: high patient education level and the status of offspring caregiver.
- The needs of offspring caregivers differ from those of spousal caregivers in AD.
- Further trials should target subpopulations and take into account these predictors of NHP when testing interventions to delay such an occurrence.

1 | INTRODUCTION

In the last decade, the healthcare systems in Western countries have come under pressure from an increasingly aging population and the prevalence of neurodegenerative diseases. Initially, the main response to this issue was to institutionalize older adults in long-term care facilities or nursing homes. Over time, the care services provided in these institutions have improved, especially in terms of managing the behavioural and psychological symptoms of dementia (BPSD), a common reason for nursing home placement (NHP).[1]

Recently, in France—as well as in many European countries—the public health policies have been oriented towards "home care and support services" for older dependent people, in response to the wishes and needs of their families, and to ensure the sustainability of healthcare systems. The decision to be admitted to an NH, pertains to the person, as it is a significant life event for any individual. However, this decision is obviously most often made by the relatives[2] and is dictated by the beliefs, resources, and representations of these latter.[3] The decision of "aging in place" can introduce a significant burden for family members, negatively impacting their own health, especially in the case of BPSD. In this context, NHP appears as the only answer to some dead-end situations.

With the heavy price paid by older NH residents during the COVID pandemic, this topic has become a burning issue and increased research efforts are urgently required.

Alzheimer's disease (AD) is an identified risk factor for NHP in older adults,[4–7] with an increasing risk as the disorder become more severe.[5] In this population, the components of the decision are numerous and complex, including the characteristics of the disease and the individual, his/her caregivers, and pre-existing relationships.[5] The more general sociocultural context also shapes the NHP decision (availability and use of home help and support services). Some of those factors weigh more heavily than others, and or are more easily modifiable if targeted by interventions.[8]

It is thus important to understand the components of this decision and to better identify the risk factors of NHP, in order to better target interventions aiming to fulfill the wishes of "aging in place". The aim of this paper was to determine the predictive factors of NHP among people with AD over a 2-year follow-up period, paying particular attention to modifiable or avoidable factors, notably those relating to the caregivers.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a prospective cohort study conducted over a 12-month open-label period during the THERAD trial. THERAD was a monocentric, randomized, single blind, controlled trial assessing the impact on quality of life (QOL) of a 2-month educational intervention called "Therapeutic Patient Education" (TPE) on the QOL of people with AD. The TPE was addressed to the dyad (patient/caregiver).

The *study protocol* has been detailed elsewhere,[9] and the results recently published.[10] The participants were 196 community-dwelling people with mild to moderately severe AD[11] and their caregivers (196 dyads, 98 in each group) recruited in the geriatric department of the Toulouse Hospital between 2013 and 2015. The intervention was composed of individual sessions (for patients and caregivers) and group sessions (caregivers only). Sessions aimed to develop the caregivers' understanding of the disease, and their abilities to manage crisis situations. Follow-up visits were offered at 2, 6, and

12 months. We did not found any significant difference in caregiver-reported patients' QOL at 2 months but a significant difference in self-reported patients' QOL at 2 and 6 months. No effect on caregivers's burden or QOL was reported.

2.2 | Data collected

The patient characteristics were collected at baseline: age, gender, marital status, educational level, dementia etiology, length of time elapsed since diagnosis, and comorbidities (Modified Cumulative Illness Rating Scale [CIRS, range: 0–56]).[12] Data on hearing impairments, gait, and balance disturbances (one leg balance[13]) were collected at baseline and during the follow-up.

The data collected at 2, 6, and 12 months included: cognitive impairment (Mini-Mental State Examination [MMSE] scale[11] score range 0–30, mild impairment [21–26], moderate [15; 20], moderately severe [11–15] and severe <11), functional impairment (Activities of Daily Living [ADL][14] score <6/6 [at least one incapacity], Instrumental Activities of Daily Living [IADL][15] score 0–8 and BPSD on the Neuro Psychiatric Inventory [NPI][16] [12 items]). Quality of life was proxy-reported and self-reported (QOL Logson scale[17]; scores ranging from 13 to 52).

Data on NHP events were collected during the first 12 months of the THERAD study at every visit and, at 24 months, through a phone call to the caregiver. If the caregiver proved unreachable, the patient's medical records or the French death registry were used. Close to the totality of observations were successfully collected (194/195).

The information on treatments came from caregiver reports and drug prescriptions (anti-dementia drugs, antipsychotics, anxiolytics and antidepressants [yes vs. no]). The following data on non-pharmacological strategies were also collected: physiotherapy, nurse, speech therapy, home help, and day care use.

The caregiver characteristics were measured at baseline: age, gender, educational level, marital status, relationship to the patient, living arrangements, length, and level of caregiving (hours per week), level of “burden” (Zarit Burden Inventory ZBI[18] score range: 0–88 [≤21: absent or low burden; 21–40: mild to moderate; 41–60: moderate to severe; 61–88: severe burden], depression (Mini Geriatric Depression Scale [GDS[19]]), and QOL based on the Nottingham health profile[20] (6-domain scale, score range 0–600). The last three characteristics were also collected during follow-up visits (M2, M6, M12).

2.3 | Statistical analysis

First, a bivariate analysis was performed to investigate the association between each of the patient and caregiver characteristics and the event (NHP) over 2 years of follow-up, using Cox proportional hazard models with hazard ratios (HR) and 95% confidence intervals (CI).

For each Cox model, time was used as a continuous variable and ‘time to event’ was defined as the time between the baseline date and the date of the event (NHP) or the date of the last follow-up for subjects with no events. Tests based on interaction with time were used to establish the proportional hazards assumption for the time-constant variables using a *p*-level of 0.05.

In the Cox models, the variables were considered as time-constant covariates when collected at baseline exclusively, and as time-dependent when measured at several endpoints, using the last measure available before the event.

Tests based on interaction with time were used to establish the proportional hazards assumption for time-constant variables using a *p*-level of 0.05.

For each qualitative time-constant variable, we calculated the incidence rate in % person-years, and its 95% CI, corresponding to the percentage of people presenting the event if 100 people are followed for 1 year.

In a second phase, we carried out multivariate Cox models, with a backward stepwise procedure. We included the variables that were significantly associated at the level of 0.20 in the bivariate analysis, keeping the intervention group in the model to control for any potential effect of the intervention on NHP (whatever its significance).

A multi-step approach was used: for the first step, two distinct models were performed, one including the patient characteristics, and the other the caregivers', using a *p*-level at 0.05. Secondarily, all the caregiver-related and patient-related variables that were significantly associated with NHP in the previous step, after the backward procedure (at the level of 0.05), were included in a last Cox model. The interactions between the independent variables in the final model were then tested (none were significant).

To avoid collinearity in the model, we did not include variables together that were highly correlated with each other, such as “marital status,” “caregiver age”, “living conditions,” and “caregiver status.”

A sensitivity analysis was conducted without this multi-step approach (including in the model all significant variables at the 20% threshold in the bivariate analysis).

All statistical analyses were performed using SAS 9.4 software (SAS Institute, Inc.).

3 | RESULTS

Figure 1 gives a flow chart of the study population.

During the 2-year follow-up, of the 195 participants included, 23 died (incidence rate = 6.28% person-years; CI95% = 3.71–8.85), and 49 were institutionalized (incidence rate = 15.73% person-years; CI95% = 11.33–20.14). In the Flowchart of the study population (Figure 1), the “censored observations” refer to participants whose follow-up was interrupted for a reason other than death or NHP.

The majority of these NHPs occurred during the first year, with 35 NHPs (incidence rate = 19.94% person-years; CI95% = 13.34–26.55).

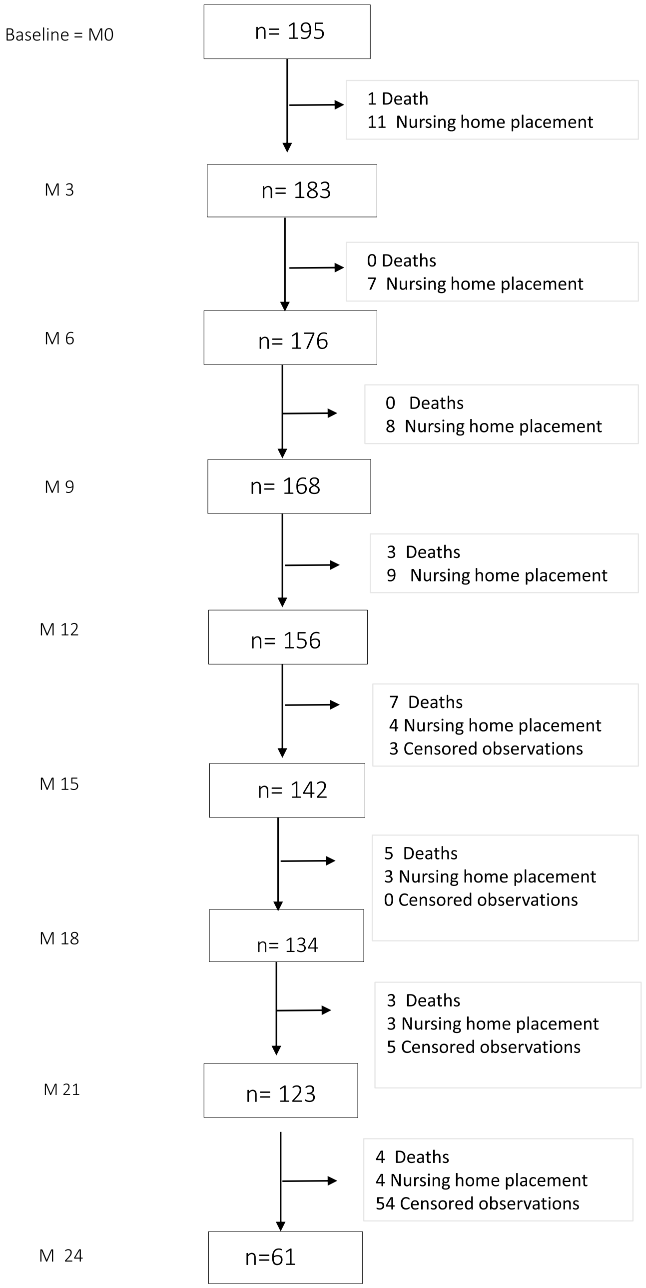

FIGURE 1 Flowchart of the THERAD Study population

The mean time to NHP after the baseline date was 9.35 ± 6.72 months. The mean time to NHP following diagnosis was 27.77 ± 22.47 months.

Table 1 presents the baseline characteristics of the population.

The mean age of the patients was 82 ± 6 years old, 67.7% were women, 56.9% were living with a partner and they had a relatively high educational level (88% had a professional activity in the past, 17% had a bachelor's degree or higher). The mean MMSE score was of 17.7 and the mean NPI score of 21.8 (NPI items in Table S1).

64.6% of the caregivers were women, more than half of them were the offspring of the patient, and their mean age was 65.8 years. Half of the caregivers were living with the patient, with a mean weekly caregiving duration of 21.7 ± 13.7 h, and presented a moderate burden (mean Zarit = 30.9).

Table 2 compares subjects with and without NHP. Several factors appeared significantly associated with NHP in the bivariate analysis. Among the patient factors these were: a greater age, unmarried patients, high educational level, low cognitive level, a later diagnosis, loss of autonomy, a poor proxy-rated QOL, some BPSD, and reliance on home help and day care centres. The significant caregiver factors were: younger carers, offspring caregivers, living apart from their relative, high educational level, and high burden.

Table 3 presents five independent predictors of NHP from the multivariate analysis: higher patient education level (aHR 6.31; CI95% = 1.88–21.22), high caregiver Burden (aHR 3.97; CI95% = 1.33–11.85), offspring caregiver status (aHR 2.92; CI95% = 1.43–5.95), loss of autonomy (aHR 2.75; CI95% = 1.13–6.65) and disinhibition as the only BPSD (aHR 2.38; CI95% = 1.26–4.47).

The belonging to the intervention group was not found as an independent risk factor of NHP (aHR 0.62; CI95% = 0.33–1.16).

The sensitivity analysis found the same results without applying the multi-step approach.

4 | DISCUSSION

The main finding of this work is that the following are independent predictors of NHP among people with mild to moderate AD during a 2-year follow-up period: high educational level, increased loss of autonomy and existence of disinhibition for the patients; and increased burden and offspring status for the caregivers.

In THERAD, two potentially modifiable predictive factors of NHP were found: loss of autonomy and a BPSD of disinhibition. This is in accordance with the literature. Indeed, the first systematic review to be conducted on this topic also reported loss of autonomy as a predictive factor (as well as cognitive impairment, increased age and low self-rated health status).[7] A more recent review identified loss of autonomy,[5,21–23] and BPSD,[5,21–23] but also cognitive impairment,[5,21] widowhood,[24,25] and the fact of living alone.[4,21]

Productive and disturbing BPSD have long been identified as causes of NHP in people with dementia.[5,21–23] The most frequently cited are "aggression," "psychosis," "hallucinations," and "depression".[5] A French cohort[23] reported anxiety, apathy and aberrant motor behaviour as risk factors of NHP.[23] In our work, disinhibition was found to be significant. This symptom is one of the most challenging to address in AD.[26–28]

Among the other patient predictors, we identified the loss of autonomy factor, as documented by three of the four meta-analyses.[5,7,25] The degree of daily help required for basic activities such as dressing, bathing, etc., influences the ability of caregivers to fulfil their role over time—especially older caregivers - and has an impact in the decision of NHP.[5,7,25]

An unexpected result of ours is that a low level of education in the patient is not identified as a risk factor, instead we found those

TABLE 1 Characteristics of the dyads in the THERAD study population at baseline

A—Patient characteristics	Total population *n* = 195 mean (SD) or n (%)
Sociodemographic data	
Age (years)	82.03 (5.88)
1: <75 years	22 (11.28%)
2: [75–85] years	108 (55.38%)
3: ≥85 years	65 (33.33%)
Women	132 (67.69%)
Educational level	
Elementary or no formal	51 (26.15%)
Primary school certificate	60 (30.77%)
Secondary education/high school	51 (26.15%)
Bachelor's degree and higher	33 (16.92%)
Professional activity in the past	173 (88.72%)
Married or in a domestic partnership	111 (56.92%)
Diagnosis	
Alzheimer's disease	161 (82.56%)
Mixed dementia (AD and vascular)	34 (17.44%)
Stage of severity (MMSE)	17.65 (4.11)
[21–26]	51 (26.15%)
[15; 20]	77 (39.49%)
[11–15]	67 (34.36%)
Time elapsed since diagnosis (months), (*n* = 176)	14.57 (19.25)
Comorbidities (CIRS-G)	9.91 (3.85)
Functional autonomy	
ADL	5.33 (0.89)
score<6/6 (at least one incapacity)	101 (51.79%)
IADL (*n* = 192)	(1.23)
score 0–1 (≥4 incapacities) (*n* = 193)	102 (52.85%)
Gait and one leg balance <5 s (*n* = 184)	121 (65.76%)
Visual impairment	111 (56.92%)
Hearing impairment	40 (20.51%)
Quality of life hetero-assessed by caregivers (*n* = 185)	28.61 (5.24)
Quality of life self-assessed by patients (*n* = 145)	33.93 (6.03)
Behaviour (NPI total score) (*n* = 178)°	21.77 (18.40)
Pharmacological therapies	
Acetylcholinesterase inhibitors or NMDA receptor blocker	96 (49.23%)
Psychotropics	46 (23.59%)
Antipsychotics	5 (2.56%)
Anxiolytics	19 (9.74%)
Sedatives	8 (4.10%)
Antidepressants	26 (13.33%)

(Continues)

TABLE 1 (Continued)

A—Patient characteristics	**Total population *n* = 195 mean (SD) or n (%)**
Non-pharmacological therapies	
Physical therapy	27 (13.85%)
Occupational therapy	4 (2.05%)
Psychology	1 (0.51%)
Speech therapy	24 (12.31%)
Day care centre	12 (6.15%)
Domestic help (cleaning)	38 (19.49%)
Home help (daily living activities)	23 (11.79%)
Nurse	58 (29.74%)
Specialized nurse	6 (3.08%)
Home meal deliveries	2 (1.03%)
B Caregiver characteristics	**Total Population, *n* = 195 mean (SD) or *n* (%)**
Sociodemographic data	
Age (years)	65.75 (12.62)
≤65	106 (54.36%)
>65	89 (45.64%)
Women	126 (64.62%)
Educational level (*n* = 192)	
Primary school certificate or less	29 (15.10%)
Secondary education/high school	60 (31.25%)
Bachelor's degree and higher	103 (53.65%)
Professional activity (or in the past) (*n* = 191)	179 (93.72%)
Caregiver status	
Offspring	102 (52.31%)
Spouse	83 (42.56%)
Sibling	1 (0.51%)
Nephew/niece	3 (1.54%)
Daughter-in-law or son-in-law	6 (3.08%)
Married or in a domestic partnership	160 (82.05%)
Living arrangements	
Caregiver living at home with the patient	104 (53.33%)
Patient and caregiver living apart	91 (46.67%)
< 6.21 miles	53 (27.18%)
> 6.21 miles	38 (19.49%)
Length of caregiving (*n* = 193) years	
1: <1 year	53 (27.46%)
2: Between 1 and 3 years	84 (43.52%)
3: >3 years	56 (29.02%)
Hours of caregiving per week	21.67 (13.66)
Level of Bruden Zarit score (*n* = 194) mean	30.89 (15.77)
1: [0–20]	58 (29.90%)

TABLE 1 (Continued)

B Caregiver characteristics	Total Population, *n* = 195 mean (SD) or *n* (%)
2: [20–40]	81 (41.75%)
3: >40	55 (28.35%)
Quality of life (NHP score)	119.60 (112.00)

Note: The population size is presented in brackets in cases of missing data (n < 195). The detailed items of NPI at baseline are presented in Table S1.
Abbreviations: ADL, activities of daily living; CIRS-G, Cumulative Illness Rating Score-Geriatric; IADL, instrumental activities of daily living; MMSE, MiniMental State Examination; NHP, Nottingham Health Profile; NPI, Neuropsychiatric Inventory.

with a higher educational level to be more at risk (>primary school certificate or higher). The reasons behind this surprising factor are complex to analyse. It is influenced by the sociocultural context and representations towards institutions, but also reflects the financial possibilities of the family to access NH. This finding does not accord with the literature, where a "protective" effect of a high level of education[7,8] and an increased risk of NHP among people with low household incomes was found. These two factors are expected to be linked at a certain point.[29] Indeed a higher educational level may be related to the socioeconomic status of the family and their ability to pay for the institution.

Unlike previous findings, patient age was not identified as a predictor of NHP.[8] In our study, the time to NHP was shorter than previously reported in the literature.[25,28] This could be partly due to our recruitment in an outpatient geriatric department, with a mean age of 82 years, in contrast to cohorts of people with AD receiving care in neurological units. The effect of age was probably not identified because of the homogeneity of our sample population of older subjects.

The severity of the cognitive impairment, assessed on the MMSE, was not associated with NHP in our study despite this being identified in the literature as a risk factor for people with dementia.[5,21] To explain this result, we should emphasise that the mean MMSE in THERAD was of 17.4, which is relatively high compared to the severity of the participants' disease in previous studies focusing on this topic.

Lastly, regarding non-pharmacological treatment, a high or low (but not medium) level of reliance on adult day care service was not, as expected, associated with an increased risk of NHP.[5] Nor did we find any association between the reliance on day care and NHP. However, we did not quantify the level of reliance on day care centres or home help, which would have made it possible to compare our data with other reviews of the topic.[5,30]

As regards the caregiver factors, distress and burden were the most often cited.[5,21–23] In THERAD, we identified a moderate or high caregiver burden factor, with a trend for a dose effect relationship, as previously demonstrated in the literature.[5,22] For example, in a French cohort of 2456 outpatients attending a memory clinic between 2012 and 2017, 38% of the NHPs were attributable to caregiver burden[23] based on the ZBI.[18] This notion is sometimes expanded to include the concept of "caregiver distress".[5] The large "RightTimePlaceCare" study conducted in eight European countries demonstrates the impact of this caregiver burden.[22] This was shown to be especially significant for spouses, who more often stated reasons related to themselves compared to the offspring-caregivers. In this European study, the "caregiver factors" increasing the risk of NHP were "role captivity", "poorer general health", "higher stress", "a poorer caregiving relationship", and "lower attachment" to the person with dementia. The findings with regard to depression in caregivers were more equivocal.

We found the status of "offspring caregiver" to be a risk factor of NHP. The literature reports difficulties in life balance among adult offspring caregivers, especially with regards to work (work-family life balance).[31] In the group of offspring caregivers, the incidence of NHP is however similar independently of the patient's marital status. In the literature, it is widowhood of the patient that is reported as a risk factor of NHP[24,25] as well as the fact of living alone.[4] Being cared for by an "adult offspring caregiver" can be considered as a proxy report of "living alone" or "being widowed", and as such our finding is consistent with the literature.[31] Some evidence suggests that spouses regard caregiving as part of their marital duties, whereas for adult children, such caregiver tasks require an important change in their lifestyle.[32]

In terms of interventions, NHP has been shown to be delayed in people with dementia when a caregiver has received a psychoeducational intervention,[24,33] when the caregiver is a female adult offspring[24] or a spouse in a sample of 406 spousal caregivers over a 9.5-year period.[33] However, we did not report any effect of the THERAD intervention on NHP. This can be explained by several factors. First, on a methodological point of view, THERAD was not specifically designed in this purpose. Then, data from the literature are old (1996 and 2008). Since that period, the quality level of "usual care" of people with AD have improved that in nowadays caregivers counseling and support, notably on BPSD management or burden prevention, have become part of the "daily routine care". Consequently, demonstrating a positive impact of such interventions is not easy. Lastly, as reported, the results of the host trial THERAD are balanced, since our intervention did not demonstrate any impact on the caregiver's burden, a well-known NHP risk factor.

We did not find the patient's gender to have any effect (whereas an increased risk in male participants once reported).[7] No gender-differentiated results were found for the caregivers either.[34] Measuring the impact of gender in THERAD was challenging because the majority of the caregivers were women (66%), as in France at the

TABLE 2 Predictors of NHP at 2 years in THERAD: bivariate analysis (Cox Model)

Patient characteristics					
Characteristics	**Population *n* = 195**	**Number of events *n* = 49**	**Incidence (pers per year) (CI 95%)**	**Hazard ratio (CI95%)**	***p*-value**
Group					
Intervention group	98	22	13.75 (8.01–19.50)	0.77 (0.44–1.36)	0.3721
Control group	97	27	17.82 (11.10–24.54)	1	
Gender					
Women	132	33	15.71 (10.35–21.07)	1.00 (0.55–1.82)	0.9892
Men	63	16	15.78 (8.05–23.51)	1	
Age at M0 (unit = +1 year)	195	49	-	1.07 (1.02–1.13)	0.0078
Married or in a domestic partnership					
Yes	111	22	11.71 (6.81–16.60)	0.54 (0.31–0.96)	0.0345
No	84	27	21.85 (13.61–30.09)	1	
Educational level					
Elementary or no formal	51	4	4.41 (0.09–8.73)	1	0.0161
Primary school certificate	60	18	19.64 (10.57–28.71)	4.36 (1.48–12.90)	0.0077
Secondary education/high school	51	17	22.12 (11.61–32.64)	4.92 (1.65–14.61)	0.0042
Bachelor's degree and higher	33	10	19.12 (7.27–30.97)	4.22 (1.32–13.46)	0.0149
Type of dementia					
Mixed dementia	34	11	22.61 (9.25–35.97)	1.53 (0.78–3.00)	0.2130
Alzheimer's disease	161	38	14.46 (9.86–19.05)	1	
MMSE[a] (unit = +1 point)	195	49	-	0.93 (0.88–0.99)	0.0314
Time since diagnosis (unit = +1 year)	195	49	-	1.16 (1.01–1.32)	0.0293
Hearing Impairment[a] (yes vs. no)	195	49	-	1.46 (0.78–2.76)	0.2406
CIRS-G at M0 (unit = +1 point)	195	49	-	1.06 (0.99–1.14)	0.0865
ADL[a]/6 < 6 versus = 6	195	49	-	5.16 (2.32–11.48)	<0.0001
Unit = +1 point	195	49	-	0.60 (0.50–0.73)	<0.0001
IADL[a]/5 ≥ 4 versus < 4 incapacities	195	49	-	2.85 (1.46–5.59)	0.0022
unit = +1 point	195	49	-	0.59 (0.44–0.79)	0.0004
One leg Balance[a] abnormal (<5 s) versus normal	194	48	-	1.61 (0.84–3.09)	0.1547
QoL-AD self-rated[a]/52 (unit = +1 point)	186	40	-	0.98 (0.93–1.04)	0.5367
QoL-AD proxy-rated[a]/52 (unit = +1 point)	190	44	-	0.90 (0.85–0.95)	0.0002
Behavioural and psychological symptoms of dementia[a] (NPI items):					
Delusions (yes vs no)	195	49	-	2.22 (1.23–4.01)	0.0079
Hallucinations (yes vs no)	194	48	-	1.76 (0.94–3.28)	0.0749
Agitation/aggression (yes vs no)	194	48	-	2.14 (1.15–3.99)	0.0165
Depression/dysphoria (yes vs no)	195	49	-	1.42 (0.80–2.55)	0.2331
Anxiety (yes vs no)	195	49	-	1.28 (0.69–2.39)	0.4302
Euphoria (yes vs no)	195	49	-	0.81 (0.38–1.72)	0.5797
Apathy (yes vs no)	195	49	-	1.70 (0.93–3.12)	0.0873
Disinhibition (yes vs no)	194	48	-	2.44 (1.38–4.31)	0.0021

TABLE 2 (Continued)

Patient characteristics					
Characteristics	**Population** ***n*** **= 195**	**Number of events** ***n*** **= 49**	**Incidence (pers per year) (CI 95%)**	**Hazard ratio (CI95%)**	***p*-value**
Irritability (yes vs no)	195	49	-	1.08 (0.60–1.95)	0.7948
Aberrant motor activity (yes vs no)	194	48	-	2.32 (1.28–4.19)	0.0056
Sleep disorders (yes vs no)	194	48	-	1.21 (0.68–2.14)	0.5235
Eating disorders (yes vs no)	194	48	-	1.43 (0.81–2.52)	0.2154
Pharmacological treatment[a]					
Antipsychotics (yes vs. no)	195	49	-	2.08 (0.74–5.79)	0.1631
Antidepressants (yes vs. no)	195	49	-	1.88 (1.00–3.54)	0.0517
Non-pharmacological therapies[a]					
Physical therapist (yes vs no)	195	49	-	1.52 (0.80–2.86)	0.2005
Day care centre (yes vs no)	195	49	-	2.67 (1.25–5.70)	0.0111
Home help (daily living activities) (yes vs no)	195	49	-	2.16 (1.14–4.08)	0.0174
Nurse (yes vs no)	195	49	-	1.59 (0.91–2.79)	0.1054

Caregiver characteristics					
Characteristics	**Population n = 195**	**Number of events n = 49**	**Incidence (pers per year) (CI 95%)**	**Hazard ratio (CI 95%)**	***p*-value**
Gender					
Women	126	33	16.56 (10.91–22.21)	1.15 (0.64–2.10)	0.6372
Men	69	16	14.26 (7.27–21.25)	1	
Age at M0					
≤65	106	34	21.52 (14.29–28.75)	1	
>65	89	15	9.77 (4.83–14.72)	0.46 (0.25–0.84)	0.0123
Caregiver status at M0					
Spouse	83	13	8.86 (4.05–13.68)	1	
Offspring	111	36	22.11 (14.89–29.33)	2.44 (1.29–4.61)	0.0059
Living condition at M0					
Together	104	18	10.08 (5.42–14.73)	1	
Apart	91	31	23.34 (15.12–31.55)	2.26 (1.27–4.05)	0.0059
Length of time caregiving at M0					
<1 year	53	10	11.15 (4.24–18.06)	1	0.0956
Between 1 and 3 years	84	19	14.10 (7.76–20.44)	1.27 (0.59–2.73)	0.5442
>3 years	56	20	24.02 (13.49–34.55)	2.12 (0.99–4.52)	0.0531
Educational level					
Less than bachelor's degree	89	14	9.25 (4.40–14.09)	1	
Bachelor's degree and higher	103	35	22.65 (15.14–30.15)	2.43 (1.31–4.52)	0.0050
Depression[a] (mini GDS: ≥1 vs. 0)	195	49	-	1.77 (0.97–3.22)	0.0608
Burden[a] (Zarit)	195	49		1	0.0006
[20–40]versus [0–20]			-	2.53 (1.02–6.31)	0.0461
>40 versus [0–20]			-	4.83 (1.97–11.86)	0.0006

Abbreviations: ADL, activities of daily living; CIRS-G, Cumulative Illness Rating Score-Geriatric; GDS, Geriatric Depression Scale; IADL, instrumental activities of daily living; MMSE, MiniMental State Examination; NHP, Nottingham Health Profile; NPI, Neuropsychiatric QOL, quality of life.

[a] Time-dependent covariates were based on the last measure available before the event.

TABLE 3 Factors associated with Nursing Home Placement at 2 years in THERAD: data from the multivariate analysis

Dependent variable: nursing home placement at 2 years	**Final model, *N* = 182 Patient-related variables Step 1**			**Final model, *N* = 182 Patient and caregiver-related variables Step 2**		
Yes (n = 42) versus No (n = 140)	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Intervention group (therapeutic patient education vs. control group)	0.64	0.35–1.20	0.1642	0.62	0.33–1.16	0.1371
Patient age V1 = M0 (years)	-	-	-			
Patient educational level (≥Primary school certificate vs. < primary school certificate)	5.30	1.61–17.42	0.0060	6.31	1.88–21.22	0.0029
Time elapsed since the diagnosis of AD V1 = M0 (years)	-	-	-			
Total MMS[a]	-	-	-			
Total ADL[a] (<6 vs. = 6)	3.74	1.56–8.96	0.0031	2.75	1.13–6.65	0.0251
Total IADL[a]/5 (≥4 vs. < 4 incapacities)	-	-	-			
One leg balance[a] (abnormal vs. normal)	-	-	-			
NPI 1-delusions[a] (yes vs. no)	-	-	-			
NPI 2-hallucinations[a] (yes vs. no)	-	-	-			
NPI 3-agitation/aggression[a] (yes vs. no)	-	-	-			
NPI 7-apathy[a] (yes vs. no)	-	-	-			
NPI 8-disinhibition[a] (yes vs. no)	2.17	1.18–4.01	0.0132	2.38	1.26–4.47	0.0072
NPI 10- aberrant motor behaviour[a] (yes vs. no)	2.02	1.07–3.82	0.0297	-	-	-
Antipsychotics[a] (yes vs. no)	-	-	-			
Antidepressant[a] (yes vs. no)	-	-	-			
Day care centre[a] (yes vs. no)	-	-	-			
Home help (daily living activities)[a] (yes vs. no)	-	-	-			
Nurse[a] (yes vs. no)	-	-	-			
Comorbidities CIRS-G score/60 V1 = M0	-	-	-			
Patient quality of life proxy-reported by caregiver[a]	-	-	-			

Dependent variable: Nursing home placement at 2 years	**Final model, *N* = 182 Caregiver-related variables Step 1**					
Yes (n = 42) versus no (n = 140)	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**
Intervention group (therapeutic patient education vs. control group)	0.84	0.45–1.56	0.5819			
Caregiver educational level (> bachelor degree vs. < bachelor degree)	-	-	-			
Caregiver status at M0 (offspring vs. spouse)	2.34	1.18–4.61	0.0145	2.92	1.43–5.95	0.0031
Length of time in caregiving at M0 1: <1 year 2: Between 1 and 3 years 3: >3 years	-	-	-			
Total GDS[a] (≥1 vs. = 0)	-	-	-			
Total Zarit[a]	-	-	0.0018			0.0370
1: [0–20]	1	-	-	1	-	-
2: [20–40]	3.14	1.06–9.29	0.0387	2.46	0.82–7.32	0.1068
3: >40	6.33	2.15–18.62	0.0008	3.97	1.33–11.85	0.0136

TABLE 3 (Continued)

Dependent variable: Nursing home placement at 2 years Yes (n = 42) versus no (n = 140)	Final model, *N* = 182 Caregiver-related variables Step 1					
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
-	Variable not introduced in the initial model					
-	Variable introduced in the initial model but deleted with the backward stepwise procedure					

Abbreviations: GDS, Geriatric depression scale; NPI, neuropsychiatric inventory.

[a] Time-dependent covariates were based on the last measure available before the event.

time we conducted THERAD and in the literature.[35] In the light of the closing gender gap in life expectancy, men are likely to be providing more direct care to their partners, with an unknown potential impact on NHP.[34,36] A recent review underlines the increasing attention on gender analyses in this literature and identifies gaps in current research.[35]

THERAD has several limitations. First, as previously mentioned, the decision leading to NHP is complex. It depends on the sociocultural context, and the national policies and health care system, which can be taken into account but not "modified" by a medical intervention. Information on some other important factors such as family representation, financial resources, caregiver comorbidities or distance to NH was not available. Secondly, the study was primarily designed to assess the impact of an educational intervention on the QOL of people with AD and not to study time to their NHP.[9] However, since we observed numerous NHPs in the first year of follow-up, we then decided to collect more data to this effect by following our cohort for one more year.

The main strengths of the study are the large population comprising 196 dyads, a regularly updated data collection, with low attrition and an innovative dyadic approach. From a methodological point of view, the Cox modelling using time-dependent covariables appears to be robust. Lastly, our results could have some implementations in clinical practice.

Indeed, interventions targeting modifiable caregiver risk factors (burden) and patient risk factors (autonomy, BPSD) should first aim to pursue the dyad's goal to "stay at home".

Clinicians must be aware of the risk factors of "high caregiver burden": gender (female), low educational level, higher amount of time spent caregiving, depression and social isolation.[37,38] This subpopulation of caregivers is at higher risk of shouldering a high burden, which is itself a risk factor of NHP, as found in the literature mentioned above and in our work. Specific interventions targeting this subpopulation could be envisaged using psychosocial interventions that have already been proven to be effective.[37,38] It is crucial to provide timely support for caregivers at the time of diagnosis, and refer them to appropriate services such as national organisations, local agencies, family associations, and respite care,[38] notably through online resources. Besides the responsibility to recognize a real caregiver burden, the physician must also understand its implication on the health and well-being of the person with AD and implement strategies to alleviate this.

In terms of interventions for people with AD, actions to promote autonomy have been tested in trials. These have shown, for example, that physical activity is very effective in maintaining autonomy in basic activities of daily living (ADL) in older adults with dementia.[39] There is thus a need to design trials aiming to maintain the level of autonomy in both instrumental and basic ADL in people with AD, in order to support the decision to "stay at home".

Lastly, the disturbing symptom of disinhibition is a particularly difficult target of pharmacological and non-pharmacological interventions and the management of productive BPSD remains a major issue.[40] The caregiver burden can be alleviated by BPSD management, such as training, which has proved to be effective in the literature, especially when implemented early.[40]

The status of offspring caregiver needs to be taken into account when designing interventions to delay NHP, by tailoring actions to the specific needs of this subgroup (life-work balance, mental load).

Interventions targeting the "transition" (from home to NH) are also needed since the circumstances of NHP sometimes influence the person's acceptance and the emotional reaction of his or her caregiver (abrupt abandonment of the caregiver role, culpability).[41]

Further studies tailored to the specific needs of subpopulations of caregivers (offspring caregivers and exhausted caregivers) and of people with AD (dependent and with BPSD) are needed.

5 | CONCLUSION

In our study, a high educational level, a great loss of autonomy and the presence of disinhibition, in people with AD, but also a high level of caregiver burden and the caregiver status (offspring) were independent predictors of NHP among people with mild to moderate AD during a 2-year follow-up period.

Interventions targeting caregivers in order to better identify those at risk of high burden, but also to alleviate this burden, are known in the literature but not always implemented in routine clinical practice. In general, interventions aiming to support the decision to "stay at home" need to take into account the modifiable risk factors of NHP and encompass the entire bio-psycho-social sphere of the dyad.[42]

ACKNOWLEDGMENTS

We would like to thank the pluriprofessional team of the THERAD study, particularly Audrey Zueras, Marie-Pierre Bautrait and Corine Bonnafous; the French Ministry of Health's DGOS for their funding; the Toulouse University Hospital research and innovation team, Marie-Elise Llau and Fatiha Boudouh-Ponsard; all participants (patients and caregivers); and the Mederic Alzheimer Foundation for the research scholarship. This study was funded by the French Ministry of Health (DGOS; Grant PREQHOS 2011: Afssaps: 2012-A00301–42). The author received a national research scholarship (PhD 2018) from the Mederic Alzheimer Foundation (financial support for the communication and dissemination of results once the study was completed; *clinicaltrials.gov/ct2/show/NCT01796314*).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Toulouse University Hospital, France at DOI: 10.1002/gps.5724.

ETHICAL STATEMENT

The study protocol was approved by the French agencies at the French Ministry of Health (CNIL and ANSM [2012-A00301–42]). It was also approved by the institutional review board (IRB) of South-West France, the *Comité de Protection des Personnes (CPP) Sud-Ouest*.

ORCID

Hélène Villars https://orcid.org/0000-0001-7668-1808

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Villars H, Gardette V, Frayssignes P, et al. Predictors of nursing home placement at 2 years in Alzheimer's disease: a follow-up survey from the THERAD study. *Int J Geriatr Psychiatry*. 2022;1-13. https://doi.org/10.1002/gps.5724