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RESEARCH ARTICLE

Apathy in patients with Alzheimer's disease is a cost-driving factor

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Abstract

Background: Apathy is the most frequent neuropsychiatric symptom in patients with dementia of the Alzheimer's type (DAT). We analyzed the influence of apathy on the resource use of DAT patients and their caregivers.

Methods: Included were baseline data of 107 DAT patients from a randomized clinical trial on apathy treatment. The Resource Utilization in Dementia (RUD) instrument assessed costs over a 1-month period prior to baseline. Cost predictors were determined via a least absolute shrinkage and selection operator (LASSO).

Results: On average, total monthly costs were €3070, of which €2711 accounted for caregivers' and €359 for patients' costs. An increase of one point in the Apathy Evaluation Scale resulted in a 4.1% increase in total costs.

Discussion: Apathy is a significant cost driving factor for total costs in mild to moderate DAT. Effective treatment of apathy might be associated with reduced overall costs in DAT.

KEYWORDS
Alzheimer's disease, apathy, cost of illness, dementia, economics, resource use

1 | BACKGROUND

It is well established that dementia of the Alzheimer's type (DAT) and other forms of dementia add considerable financial cost to the family and to society. According to recent estimates, worldwide costs of dementia were US $818 billion in 2015, an rise of 35% compared to 2010.[1] Costs, including both direct costs[2–5] and informal care costs,[2–6] were increased for patients with progressed dementia severity compared to patients with milder stages as measured by the Mini-Mental State Examination (MMSE).[2–6] In line with this finding, longitudinal data showed that dementia-related resource use of the same patients increased over time.[3,6,7] Depending on disease severity, in Germany, the total monthly mean costs in a home-care setting were between €1312 and €2222 (mild) and €3336 and €3722 (severe), with informal care costs, which can be between €643 and €1057 (mild) and €1814 and €2376 (severe), accounting for the largest share.[5,8] For patients in long-term care institutions, the costs were even higher, ranging from €5109 (mild) to €5311 (severe).[8] Studies with data from statutory health insurance calculated dementia-related costs to range between €586 and €1129 per month.[9,10] Other European studies found that total costs were between €507 and €2411 (mild) and €881 and €4579 (severe).[5,8]

A recent study on the determinants of the societal costs (total costs for the society) of DAT listed the cost predictors from several studies,[11] to which we added the latest references (see Table S1 in supporting information). Age and functional status were identified as the cost-driving factors and were measured by activities of daily living (ADL) scales or the Disability Assessment for Dementia (DAD).[2,4–6,8,11–18] Less frequently, the influence of behavioral and psychological symptoms of dementia on resource use was examined. The Neuropsychiatric Inventory (NPI) is the most commonly used measure of such symptoms in dementia covering several domains, including apathy and depression.[2,4,6,8] Studies using the total NPI score showed both significant[6,8] and non-significant effects on costs.[2,4,8] Only a few studies analyzed the individual symptom domains of the NPI, of which a few found a significant correlation between apathy and total cost[19] as well as between apathy and informal care costs.[20]

Apathy is the most common neuropsychiatric symptom in DAT. It is broadly defined as a reduction of motivated behavior. It may occur in association with depressed mood or independently. A recent meta-analysis found apathy prevalence rates of 54% (95% confidence interval [CI] 45%–62%), 59% (95% CI 44%–73%), and 43% (95% CI 10%–75%) for mild, moderate, and severe dementia, respectively.[21] Apathy lowers quality of life, reduces the ability of ADLs, and increases caregiver burden.[22–25] Here, we examine the influence of moderate to severe apathy on resource use by DAT patients and their caregivers. We used a specific apathy scale and excluded DAT patients with coexisting clinically relevant depressed mood.

2 | PATIENTS AND METHODS

2.1 | Study design

This study is based on the baseline data of a 12-week multicenter, double-blind, placebo-controlled, randomized clinical trial that examined the use of bupropion for the treatment of apathy in 108 DAT patients (EU Clinical Trials Register Identifier: 2007-005352-17).[26] Patients were recruited in an outpatient setting in Germany between 2010 and 2014 and had mild to moderate probable DAT according to

the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.[27] All patients were living at home, not in institutions. Each patient had a family caregiver who served as a study partner. All patients and caregivers gave written informed consent before enrollment. In the case of limited ability to provide consent in a patient, a legal representative served as a substitute. The study was conducted in concordance with the Declaration of Helsinki and was approved by the ethics board of each participating center. Details of the study design and the results of the trial were previously published.[26]

2.2 | Inclusion and exclusion criteria

All patients fulfilled the NINCDS-ADRDA diagnostic criteria for probable AD,[27] here referred to as DAT, and were between 55 and 90 years of age with an MMSE score between 10 and 25 points. Patients with dementias other than DAT and individuals hospitalized within 6 months prior to the study were excluded.

All patients fulfilled the revised apathy criteria by Marin and Starkstein.[28] Patients who also fulfilled the depressed mood item for major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition were excluded. Additionally, all patients had to score at least 4 points on the apathy item of the NPI, while a maximum score of 3 points was allowed on the NPI-depression (dysphoria) item. Patients with apathy and depression were excluded from this trial to test the effects of the antidepressant bupropion specifically on apathy and to avoid potential confounding effects by improving depressed mood.

2.3 | Assessments

The German version of the Apathy Evaluation Scale-Clinician Version (AES-C) was used to assess apathy.[29] The instrument consists of 18 items with a range from 18 to 72, with higher scores reflecting greater apathy. A score of 41 or higher is considered to reflect clinically relevant apathy.[29] The NPI was used to measure additional domains of behavioral symptoms.[30] The distress scale of the NPI evaluated the impact of individual behavioral symptoms on the caregiver.[30] The Montgomery-Asberg Depression Rating Scale (MADRS) was used to monitor subthreshold depressive symptoms.[31] The Alzheimer's Disease Assessment Scale-Cognitive Subscale 12 (ADAS-Cog12) was used to measure cognition.[32] The MMSE was used to determine the global severity of cognitive impairment. The Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale was used to measure impairments in ADLs.[33] The Quality of Life-Alzheimer's Disease Scale (QoL-AD) was applied to measure patients' health-related quality of life.[34]

The Resource Utilization in Dementia (RUD) questionnaire, which served as an outcome, assesses formal and informal dementia care resource use across different settings.[35] The RUD covers both the patient's and the caregiver's resource use.[35] Resource use was calculated from a societal perspective, which refers to the perspective of the society including direct health-care costs and indirect costs. The unit costs correspond to the year 2016, which was the year the data (Table 1), became available. The RUD was missing in one patient, yielding a sample size of $N = 107$ for this analysis.

For direct costs, inpatient hospital cost was calculated in Euros per day and consisted of operating costs and capital costs.[36,37] Costs of emergency department admission dated from 2015 and were inflated to 2016.[38,39] Outpatient care was calculated using the average remuneration per hour (€32.61) and a fixed travel rate (€4.26).[40] The average remuneration cost per hour were obtained from 2018 and were deflated to their equivalent in 2016.[39] The cost of home support was calculated using the minimum wage plus wage labor costs. The cost of food delivery was based on the price of a local delivery service. Day care was calculated on the basis of the average remuneration in nursing homes and the investment costs for day care.[36,41,42] The costs of day care were from 2015 and were inflated to 2016 values based on the consumer price index.[39] Transportation costs consisted of two components: (1) the statutory fixed rate per kilometer (€0.3/km)[43] and the average distance of a patient to the hospital,[44] and (2) the cost of the driver, which was based on the minimum wage and the average travel time to the hospital.[44] Regarding ancillary therapy, costs per visit were calculated for physiotherapy and occupational therapy.[36] The cost of a social worker was calculated in Euros per hour based on the inflated specific average gross earnings from 2012.[39,45] Medication costs were based on the official 2016 German drug price list.[46] The cheapest preparation of

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors conducted a review of the literature in PubMed related to the costs incurred by patients with Alzheimer's disease (AD) and their caregivers as well as its cost-driving factors. While the influence of cognitive status, age, and functional status have been broadly examined, the influence of behavioral symptoms is less frequently evaluated. In particular, the influence of apathy on costs has not been adequately studied.
2. **Interpretation**: Our results showed that apathy significantly increases total costs, primarily by increasing caregiver costs, which are essentially caused by informal care. This relationship was observed in the absence of clinically relevant depression.
3. **Future Directions**: Future studies on AD-related resource use should consider apathy when analyzing the cost-driving factors in AD. Additionally, the impact of pharmacological and non-pharmacological treatment options on costs should be examined.

TABLE 1 Unit costs

Parameter	Amount	Unit	Year	Source
Ancillary therapy				
Occupational therapist	39.93	€/ visit	2016	36
Physiotherapist	18.09	€/ visit	2016	36
Multiplier ancillary therapy (private and statutory health insurance)	1.31	Percent	2016	36
Early retirement due to caring	121.74	€/ day	2016	59
Emergency department	120.60	€/ visit	2016	38
Hospital stay (inpatient)	692.77	€/ day	2016	36,37,52
Informal care (caregiver time)				
CG assisting ADLs	12.33	€/ hour	2016	36
CG assisting IADLs	12.33	€/ hour	2016	36
CG assisting supervision	12.33	€/ hour	2016	36
Medication			2016	46
Physicians				
General practitioner	19.53	€/ visit	2016	36
Geriatrician (using physician consultation average)	28.87	€/ visit	2016	36
Neurologist	66.62	€/ visit	2016	36
Psychiatrist	92.07	€/ visit	2016	36
Further physicians				
Dermatologist	21.89	€/ visit	2016	36
Ear, nose, and throat specialist	28.20	€/ visit	2016	36
Gynecologist	36.98	€/ visit	2016	36
Ophthalmologist	47.86	€/ visit	2016	36
Orthopedist/surgeon	41.15	€/ visit	2016	36
Radiologist	217.51	€/ visit	2016	36
Urologist	27.17	€/ visit	2016	36
Physician consultation average	28.87	€/ visit	2016	36
Multiplier outpatient medical sector (private and statutory health insurance)	3.72	Percent	2016	36,60
Professional services				
Day care	49.84	€/ day	2016	36
District nurse				
Compensation	32.61	€/ hour	2016	36
Travel flat rate	4.26	€/ visit	2016	36
Food delivery	6.50	€/ delivery		
Home aid orderly (minimum wage)	12.33	€/ hour	2016	36
Transportation	12.62	€/ travel	2016	43,44
Psychologist (using physician consultation average)	28.87	€/ visit	2016	36
Reduction of working time due to caring (based on 220 working days)	201.98	€/ day	2016	59
Social worker	12.59	€/ hour	2016	45
Sensitivity analysis (caregiver time)				
Lost production	22.98	€/ hour	2016	59
Lost leisure time	8.04	€/ hour	2016	59

Abbreviations: ADL, activities of daily living; CG, caregiver; IADL, instrumental activities of daily living.

the respective active compound was used in calculating medication costs.

For indirect costs, informal care costs contained the time of support provided by the caregiver in everyday life, including aspects of activities of daily living, instrumental activities of daily living, as well as supervision of the patient. The figures were calculated based on the minimum wage plus wage labor costs.[42] Two cost sensitivity analyses were conducted for informal care. In the first analysis, informal care by working caregivers was valued at the average gross wage. Informal care by non-working caregivers was calculated at 35% of the average gross wage. In the second analysis, the costs of the first sensitivity analysis were applied, but supervision was not valued with cost. Early retirement due to caregiving responsibilities was calculated according to the human capital approach.[47] For this, the number of days before the 65th birthday (age of retirement) within the study period was multiplied by the average gross wage in Germany (€121.74/day).

2.4 | Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics version 26.0.0.0[48] and R version 4.0.2 (R Core Team).[49] We examined the total, the caregiver's, and the patient's resource use. The distribution of the different cost categories showed positive skewness and positive kurtosis. The Kolmogorov–Smirnov and Shapiro–Wilk tests rejected the null hypothesis for all three distributions ($P < 0.001$). The relationship between costs (total, caregiver, and patient) and AES-C was estimated with Spearman's correlation. Bias-corrected and accelerated bootstrap 95% CIs (BCa 95% CI) with 1000 replications were calculated for total, patient, and caregiver costs.[50] As an additional exploratory measure, univariate analyses were carried out. For this purpose, the individual independent variables were grouped (sex, four age groups, tertiles for all other variables). Differences between two or more independent groups were tested with the nonparametric Mann–Whitney *U* test or the Kruskal-Wallis *H* test. To determine which independent variables were most important in explaining and predicting the total costs a least absolute shrinkage and selection operator (LASSO) approach[51] was performed, using the glmnet package[52] in R. The LASSO is used to select important covariates for the model without shrinking the estimated coefficients (post-LASSO, following Roider et al.[53]). The optimal penalty strength was obtained via a sophisticated cross-validation technique using the glmnet package. The independent variables that were the potential cost drivers were analyzed in a multiple regression model using a generalized linear model (GLM) with a gamma-distributed dependent variable and a log link function.[54] In addition, two regression sensitivity analyses were performed on the selection process. To test the sensitivity of our results regarding cognitive decline, we divided the sample into two groups based on the MMSE (MMSE ≤19 and MMSE ≥20) and determined the independent variables for predicting the total costs for both groups again using the LASSO approach. The second regression sensitivity analysis tested the robustness of the selection process. For each out of 1000 bootstrap samples the LASSO selected the predictors of cost.

TABLE 2 Patient characteristics

Patients	N = 107	
	N	%
Females	41	38
	Mean	SD
Age	74.83	5.91
Education (years)	9.69	2.75
Disease duration (years)	4.12	2.62
AES-C	51.40	8.46
NPI total	16.14	9.35
NPI distress total	7.93	5.80
ADCS-ADL	51.95	16.81
ADAS-Cog12	35.40	12.12
MADRS	9.17	5.78
MMSE	19.31	4.15
QoL-AD	31.86	4.95

Abbreviations: AES-C, Apathy Evaluation Scale–Clinician version; ADAS-Cog12, Alzheimer's Disease Assessment Scale-Cognitive Subscale 12; ADCS-ADL, Alzheimer Disease Cooperative Study-Activities of Daily Living scale; MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; QoL-AD, Quality of life-Alzheimer's Disease Scale.

3 | RESULTS

Patient characteristics are listed in Table 2. Of the 107 patients, 41 (38%) were female. The patients were 74.8 ± 5.9 years old (range 52 to 87). The mean score of the AES-C was 51.40 ± 8.46 (range 29 to 67).[29]

3.1 | Resource use and associated costs

Table 3 describes the use of resources by patients and caregivers. The average total costs in the 1-month period before the baseline assessment were €3069 while the median total costs were €1552. The BCa 95% CI was €2421 to €3789. Thus, the extrapolated average annual total costs were €36,832. The caregiver's costs accounted for €2711 (88.3%) of the monthly average total costs. A large proportion of caregiving costs were associated with informal care at €2509 (81.7%). The average monthly patient-related costs of informal care were €359 (11.7%). Thus, the extrapolated annual average total cost related to the caregiver was €32,529, while the patient-related costs were €4303.

For caregiver-related costs, monthly average costs related to supervision of the patient were €1272 (41.4%). An average of €923 (30.1%) was attributed to assisting the patient in instrumental activities of daily living (IADLs), such as shopping, food preparation, and housekeeping. Furthermore, assistance with basic ADLs such as using the toilet, eating, and dressing incurred an average of €314 (10.2%) in monthly costs. In total, 87% of caregivers provided assistance. Among the indirect costs, the cost of productivity losses, such as early retirement and reduction of work experience due to caring, were €34 (1.1%) and €4

TABLE 3 Resource use per caregiver and patient in the 1-month period

	Overall patient population					
			BCa 95% CI**			
Parameter	*N* (%)*	Mean (€)	Lower	Upper	Median (€)	Total costs (%)
Caregiver						
Direct cost (caregiver health-care resource use)	86	165	72	283	41	5
Hospital	1	52	0	104	0	2
Emergency department	0	0	0	0	0	0
Physicians	60	45	32	59	20	1
General practitioner	40	12	9	16	0	0
Geriatrician	0	0	0	0	0	0
Neurologist	7	6	2	10	0	0
Psychiatrist	2	1	0	2	0	0
Further physicians	29	25	15	36	0	1
Ancillary therapy	10	7	3	11	0	0
Physiotherapist	10	7	3	11	0	0
Occupational therapist	0	0	0	0	0	0
Social worker	1	0	0	0	0	0
Psychologist	4	4	1	8	0	0
Medication	75	56	21	112	5	2
Indirect cost (caregiver work status)	87	2546	1987	3131	1110	83
Early retirement due to caring	1	34	0	68	0	1
Reduction of working time due to caring	2	3	0	8	0	0
Informal care (caregiver time)	87	2509	1966	3111	1110	82
CG assisting ADLs	50	314	230	400	0	10
CG assisting IADLs	85	923	765	1102	740	30
CG assisting supervision	37	1272	837	1730	0	41
Caregiver total cost	**99**	**2711**	**2127**	**3327**	**1158**	**88**
Patient						
Hospital	3	97	0	194	0	3
Emergency department	2	2	1	3	0	0
Physicians	56	34	25	43	20	1
General practitioner	45	16	11	22	0	1
Geriatrician	1	0	0	0	0	0
Neurologist	6	4	2	7	0	0
Psychiatrist	3	2	1	5	0	0
Further physicians	20	10	6	15	0	0
Ancillary therapy	7	8	3	13	0	0
Physiotherapist	2	1	0	3	0	0
Occupational therapist	6	6	2	12	0	0
Social worker	1	0	0	0	0	0
Psychologist	1	1	0	2	0	0

(Continues)

TABLE 3 (Continued)

Parameter	Overall patient population					
			BCa 95% CI**			
	N (%)*	Mean (€)	Lower	Upper	Median (€)	Total costs (%)
Professional services	28	149	70	244	0	5
District nurse	9	35	15	63	0	1
Home aid orderly	16	97	26	193	0	3
Food delivery	1	2	0	4	0	0
Day care	6	14	4	25	0	0
Transportation	2	1	0	3	0	0
Medication	98	68	53	88	48	2
Patient total cost (patient health-care resource use)	**98**	**359**	**224**	**510**	**102**	**12**
Total cost	**100**	**3069**	**2421**	**3789**	**1552**	**100**

*Percentage of patients for whom costs were incurred.
**95% bias corrected and accelerated bootstrap confidence interval.
Abbreviations: ADL, activities of daily living; BCa 95% CI, accelerated bootstrap 95% confidence interval; CG, caregiver; iADL, instrumental activities of daily living.

(0.1%), respectively. Of the direct costs, medication of €56 (1.8%), hospital stays of €52 (1.7%), and physician consultations of €45 (1.5%) were the highest.

For patient-related costs, professional services accounted for the largest proportion at an average of €149 (4.9%) per month. Home aid costs accounted for a substantial part of this (€97 [3.2%]). In addition, the costs were €35 (1.1%) for outpatient care and €14 (0.4%) for day care. Food delivery and transportation generally incurred minimal costs. In addition, hospitalization generated average costs of €97 (3.2%). In the 1-month period, 56% of patients consulted a physician. This generated mean costs of €34 (1.1%), of which €16 (0.5%) was related to general practitioner costs.

3.2 | Univariate analyses

There were significant differences in total costs between the tertile groups of the AES-C, NPI distress total score, ADCS-ADL, ADAS-Cog12, MMSE, MADRS, and QoL-AD. In all analyses, higher costs were associated with greater impairment and more advanced disease stages (detailed results of the univariate analyses for total, patient, and caregiver costs as well as the ranges for tertiles are presented in Tables S2–S4 in supporting information).

For patient-related costs, there were significant differences between the groups based on the AES-C where tertile 2 (49 to 55) showed lower average costs than tertile 3 (> 55) and tertile 1 (< 49). Furthermore, the tertile groups of ADCS-ADL, ADAS-Cog12, and MADRS showed significant differences.

For caregiver-related costs, there were significant differences between the tertile groups based on AES-C. The NPI distress total score, ADCS-ADL, ADAS-Cog12, MMSE, MADRS, and QoL-AD also showed significant differences.

Significant correlations were found between AES-C and total costs ($\rho = 0.505$, $P < 0.001$) and AES-C and caregiver-related costs ($\rho = 0.523$, $P < 0.001$; Figure 1). The relationship between AES-C and patient-related costs was also significant but lower ($\rho = 0.230$, $P = 0.017$).

3.3 | Multiple regression analyses

When including all covariates (sex, age, AES-C, NPI total, NPI caregiver distress total, ADAS-Cog12, MADRS, MMSE, QoL-AD, available number of physical comorbidities), the post-LASSO approach results in a sparse model including only the ADCS-ADL, with a negative impact on costs. While this makes it a very strong predictor, the ADL score can be interpreted as an aggregation of multiple domains. In addition, there was a significant Spearman correlation between AES-C and ADCS-ADL ($\rho = -0.625$, $P < 0.001$). Hence, we re-ran the process without the ADCS-ADL to gain insight into the remaining variables. The resulting model (Table 4) then includes estimated coefficients for age, AES-C, NPI-D, MMSE, and QoL-AD. Using the LASSO procedure, the AES-C was the first covariate to be added to the model and the coefficient of the MMSE had the biggest absolute standardized value. We therefore deem AES-C and MMSE to be the most important predictors. As discussed by Roider et al., the confidence intervals and *P*-values of the estimated coefficients should be treated with caution, as uncertainty from the selection process in the (post-) LASSO framework is ignored.[53] Further variable selection (e.g., by *P*-values) is not recommended as the model is optimized to predict new observations.

Table 4 shows the results of the regression analyses of the remaining variables for total costs. Worsening results in AES-C, NPI caregiver distress total, MMSE, and QoL-AD as well as increasing age were estimated to increase the costs, while AES-C and MMSE showed significance.

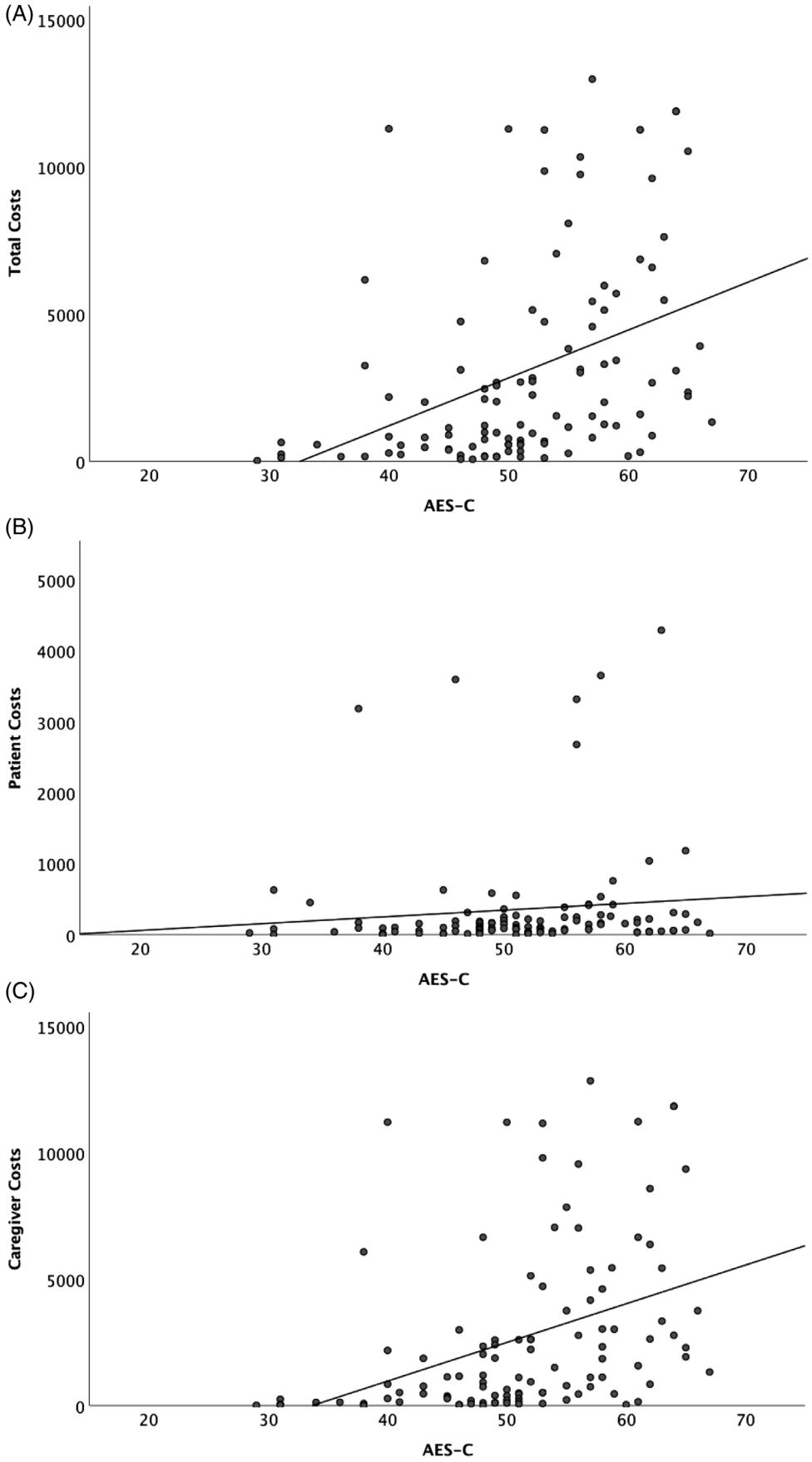

FIGURE 1 Association between costs and Apathy Evaluation Scale–Clinician version (AES-C) including the regression line for (A) total costs and AES-c, (B) patient costs and AES-C, and (C) caregiver costs and AES-C

TABLE 4 Multiple regression analysis of potential cost-driving factors

	Total costs				
		95% CI*			
Parameter	β**	Lower	Upper	P	exp(β)***
Intercept	**4.948**	**0.337**	**9.559**	**0.035**	
Age	0.038	−0.001	0.078	0.055	1.039
AES-C	**0.040**	**0.010**	**0.070**	**0.008**	**1.041**
NPI distress	0.028	−0.008	0.065	0.131	1.029
MMSE	**−0.085**	**−0.136**	**−0.033**	**0.001**	**0.919**
QoL-AD	−0.020	−0.078	0.038	0.496	0.980

*95% Wald confidence interval for β.
**Regression coefficient, where a value of 0 indicates no influence and a value > 0 (< 0) indicates positive (negative) influence.
***Factor by which the predicted costs are influenced if the parameter is increased by 1 and the other parameters remain unchanged.
Abbreviations: AES-C, Apathy Evaluation Scale–Clinician version; MMSE, Mini-Mental State Examination; NPI distress total, Neuropsychiatric Inventory caregiver distress scale; QoL-AD, Quality of Life-Alheimer's Disease Scale.
Values of significant parameters (p<0.05) are marked in bold.

TABLE 5 Sensitivity analyses of informal care

			BCa 95% CI**	
Parameter	Mean (€)	Lower	Upper	Median (€)
Sensitivity analysis I				
Informal care (caregiver time)	1742	1386	2132	965
CG assisting ADLs	233	172	304	0
CG assisting IADLs	670	570	784	482
CG assisting supervision	840	548	1170	0
Sensitivity analysis II				
Informal care (caregiver time)	903	767	1051	603
CG assisting ADLs	233	172	304	0
CG assisting IADLs	670	570	784	482

Abbreviations: ADL, activities of daily living; BCa 95% CI, accelerated bootstrap 95% confidence interval; CG, caregiver; iADL, instrumental activities of daily living.

The regression coefficient of AES-C was 0.040 in the total cost model. Accordingly, an increase in the AES-C by 1 point, with all other parameters constant, leads to an increase in the total costs by approximately 4.1% (exp[0.040]≈1.041).

3.4 | Cost sensitivity analysis

Table 5 shows the results of the cost sensitivity analysis. The costs for informal care were lower than those of the initial approach. Within the cost sensitivity analysis I (informal care by non-working caregivers at 35% of the average gross wage), informal care costs were €1742, with a lower BCa 95% CI of €1386 and an upper of €2132. The lower costs mainly stemmed from the fact that only 18 of the 107 caregivers were working. The cost sensitivity analysis II (initial approach but supervision was not valued) showed average costs of €903, with a lower BCa 95% CI of €767 and an upper of €1051. In addition to the few caregivers working, the costs of informal care were lower because supervision was excluded.

3.5 | Regression sensitivity analysis

In addition, two regression sensitivity analyses were carried out. The first examined the sensitivity of variable selection with respect to cognitive status. Table S5 in supporting information showed that in

patients with more and less cognitive impairment, as expressed by the MMSE, the AES-C is selected as a cost predictor by the LASSO approach in both cases. Furthermore, from a total of 1000 bootstrap samples, the AES-C was selected in all cases (1000/1000; Table S6 in supporting information). Age (977/1000), NPI distress total (997/1000), MMSE (982/1000), and QoL-AD (978/1000) also showed high robustness within variable selection.

4 | DISCUSSION

The goal of this study was to analyze the impact of apathy without dysphoria on the cost of care for DAT patients and their caregivers. The data showed that apathy increases overall resource use, especially of caregivers. Patients' resource use did not show an association with apathy.

Previous studies have reported that costs in DAT are primarily a function of cognitive impairment. We also observed this association in our results. Depending on the MMSE, the costs ranged from €947 to €3900 per month (Table S4). Comparable studies for the German health-care system showed similar total costs of between €1312 and €3722[5] or €2222 and €3336,[8] respectively. In line with our results, informal care in these two studies also accounted for the largest share of costs. However, in most of the published literature, only informal care costs were reported as part of caregiver costs. Caregiver health-care resource use and caregiver work status were usually not analyzed.[2,4,6,8] To our knowledge, only Wimo et al. presented caregiver health-care costs, which ranged from €104 to €221 per month in Germany, €67 to €151 in France, and €61 to €152 in the UK depending on Alzheimer's disease severity.[5] Caregiver costs in our study included the caregiver health-care resource use (€165), the effects on caregiver work status (€37), and the caregiver time devoted to supporting the patient (€2509). Compared to informal care costs, however, the former were of minor importance to caregiver costs.

The results of the statistical analysis confirmed the cost-driving influence of apathy on total costs. In our model, age, AES-C, NPI-D, MMSE, and QoL-AD were selected by the LASSO procedure. Previous studies examining apathy as a subdomain of the NPI were consistent with our findings. Similarly, these studies showed a significant correlation between apathy and total costs[19] and between apathy and informal care costs.[20]The relevant literature showed varying results with respect to the association of age with costs in dementia. While some authors found the same significant relationship in terms of higher age being associated with higher costs,[2,55] this could not be confirmed by others.[4] QoL AD has not been assessed as a predictor of cost in the relevant literature (Table S1). The significant correlation between costs and MMSE has been previously demonstrated.[2,6,8] Hence, costs increased with cognitive decline. In some studies, ADLs also had a significant impact on costs.[4,6,8] In our case, the LASSO procedure supports this finding. However, due to the fact that ADL mpairment is correlated with cognitive and non-cognitive symptoms and was found to be a very strong predictor resulting in a very sparse model, we chose to exclude the ADCS-ADL from the LASSO approach. The NPI-D was selected by LASSO while the NPI total was not selected. Other studies focusing on the NPI total found varying results with significant correlations in some,[6,8] but not all, studies.[2,4,8] In our study, the univariate analyses showed that the costs of the two lower tertiles (< 11 and 11–18) of the NPI total did not differ, while there was an increase in costs in the third tertile (> 18).

Our study has limitations. The RUD only covers a 1-month period. The inclusion of DAT patients with moderate to severe apathy and exclusion of clinically significant depression is helpful to isolating the specific impact of apathy on costs. However, patients often have both apathy and depression, and the combined impact on costs cannot be assessed with our design. Furthermore, due to the nature of the study, we did not include a group without apathy or patients with severe DAT for comparison of costs. Because specific study magnetic resonance image of the brain was not required, we cannot systematically analyze the impact of vascular lesions on apathy and on costs in our study. The patients also all lived in their private homes and received informal care by family caregivers. These points limit the overall generalizability of the results. Additionally, future research should examine whether treatment of apathy[56] reduces costs. Initial data provide evidence for efficacy of methylphenidate and non-pharmacological therapies (such as information and communication approaches or occupational therapy).[57,58]

To conclude, this study showed that there is a significant correlation between moderate to severe levels of apathy in DAT patients and resource use specifically caused by informal care of caregivers. Because apathy is frequent in DAT, this association contributes to the overall societal costs related to DAT. In this regard, more effective treatment options of apathy may reduce these costs.

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CONFLICTS OF INTEREST

Dr. Buerger reported receiving personal fees from Biogen Idec outside the submitted work. Dr. Dodel reported receiving personal fees from Abbott/AbbVie, AXON Neuroscience, Bayer Vital GmbH, BB-Biotec, Bial, Biogen, GE Healthcare, UCB, ESAI, Novartis, and Wilhelm Schwabe GmbH outside the submitted work. Dr. Frolich reported receiving personal fees from Lundbeck, Avanir, Roche, Biogen, AXON Neuroscience, Boehringer Ingelheim, Eisai, Functional Neuromodulation, and Merck, Sharpe & Dohme GmbH outside the submitted work. Dr. Hausner reported receiving personal fees from ZI Mannheim during the conduct of the study. Dr. Priller reported receiving personal fees from DZNE and grants from UK DRI during the conduct of the study. Dr. Teipel reported receiving speaking fees from and serving on advisory boards for Roche Pharma AG, Biogen, and Merck, Sharpe & Dohme GmbH outside the submitted work. Dr. von Arnim reported receiving personal fees from Roche, Willhelm Schwabe GmbH, KG, and Biogen outside the submitted work. Dr. Wiltfang reported receiving personal fees from Abbott, Boehringer-Ingelheim, Immungenetics, Lilly, Roche

Pharma, Actelion, Amgen, Janssen Cilag, Pfizer, Med Update GmbH, and, Merck, Sharpe & Dohme GmbH outside the submitted work; in addition, Dr. Wiltfang had a patent to PCT/EP 2011001724 issued and a patent to PCT/EP 2015052945 issued. Dr. Jessen reported receiving personal fees from Biogen, Roche, GE Healthcare, Esai, AC Immune, Nutricia, and Janssen Cliag outside the submitted work. No other disclosures were reported. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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

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