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Monetary costs of agitation in older adults with Alzheimer's disease in the UK: prospective cohort study

Stephen Morris,[1] Nishma Patel,[1] Gianluca Baio,[2] Lynsey Kelly,[3] Elanor Lewis-Holmes,[3] Rumana Z Omar,[2] Cornelius Katona,[3] Claudia Cooper,[3] Gill Livingston[3]

ABSTRACT

Objective: While nearly half of all people with Alzheimer's disease (AD) have agitation symptoms every month, little is known about the costs of agitation in AD. We calculated the monetary costs associated with agitation in older adults with AD in the UK from a National Health Service and personal social services perspective.

Design: Prospective cohort study.

Setting: London and the South East Region of the UK (LASER-AD study).

Participants: 224 people with AD recruited between July 2002 and January 2003 and followed up for 54 months.

Primary and secondary outcome measures: The primary outcome was health and social care costs, including accommodation costs and costs of contacts with health and social care services. Agitation was assessed using the Neuropsychiatric Inventory (NPI) agitation score.

Results: After adjustment, health and social care costs varied significantly by agitation, from £29 000 over a 1 year period with no agitation symptoms (NPI agitation score=0) to £57 000 at the most severe levels of agitation (NPI agitation score=12; p=0.01). The mean excess cost associated with agitation per person with AD was £4091 a year, accounting for 12% of the health and social care costs of AD in our data, and equating to £2 billion a year across all people with AD in the UK.

Conclusions: Agitation in people with AD represents a substantial monetary burden over and above the costs associated with cognitive impairment.

Strengths and limitations of this study

- This study used detailed, prospectively collected health and social care resource use data plus data on frequency and severity of agitation symptoms over a 54-month period to calculate the costs of agitation in people with Alzheimer's disease (AD).
- There is no previous evidence about the cost of agitation in AD, even though nearly half of all people with AD have agitation symptoms every month; this study calculated that the mean excess cost associated with agitation per person with AD was £4091 a year.
- A limitation of the study is that it is based on a relatively small data set of 224 people, recruited to be representative of those with AD between July 2002 and January 2003 and followed up to 54 months.
- We did not include the costs of informal care; these data were not collected and UK guidelines for undertaking economic evaluations recommend taking a health and social care perspective when measuring costs.

(AD) is the most common form of dementia, accounting for around 62% of cases.[2]

Nearly half of all people with AD have agitation symptoms every month.[3] These are positively correlated with institutionalisation,[4] pharmacological treatment and use of medical services,[3] but there is no evidence on the costs of agitation in people with AD.[5 6] The aim of this paper is to calculate the monetary costs associated with agitation in AD.

METHODS

Participants

We calculated National Health Service (NHS) and personal social services (PSS) costs associated with different levels of agitation using data from a naturalistic prospective cohort study of people with AD, covering

For numbered affiliations see end of article.

Correspondence to
Professor Stephen Morris;
steve.morris@ucl.ac.uk

INTRODUCTION

The monetary cost of dementia is huge, with an estimated global burden in 2010 of US $604 billion incurred by health (16% of the total) and social care (42%) services and informal care (42%).[1] Around 70% of worldwide costs occur in North America and Western Europe[1]; estimates for the UK show that the total monetary cost of dementia in 2014 was £26 billion.[2] Alzheimer's disease

the London and the South East Region of the UK (LASER-AD study).[3] [7–9] Two hundred and twenty-four people were recruited between July 2002 and January 2003 and followed up to 54 months. The cohort was purposively and prospectively recruited, using overall figures from a review of the epidemiology of AD, to be a representative sample of people with AD in terms of sex, living setting and severity of cognitive impairment in the community.[9] Participants and their carers were approached through local community mental health teams, dementia specialist nurses, the voluntary sector, memory clinics, nursing and residential homes, day hospitals, day centres and inpatient units. Written informed consent was obtained from all carers. Where the person with AD lacked capacity to consent, the study only proceeded if the carer consented and thought the person they cared for would have agreed to participate if they could. Measures were collected at baseline, and 18, 30, 42 and 54 months after baseline. Data were obtained from interviews with the patients with AD and their carers, carried out at a place of their choice. They were conducted by trained, experienced health professionals, and were terminated if the interviewee became distressed or appeared to want to stop.

Measures

The Neuropsychiatric Inventory (NPI) uses responses from caregivers in a structured interview format to assess 10 behavioural domains (delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour);[10] two additional domains (night-time behavioural disturbance, appetite/weight changes) are commonly added, giving 12 domains in total.[11] Within each domain, behaviours are rated by caregivers in terms of frequency (1=occasionally—less than once per week, 2=often—about once per week, 3=frequently—several times per week but less than every day, 4=very frequently—once or more per day) and severity (1=mild, 2=moderate, 3=severe). A score for each domain is calculated as the product of the frequency and severity scores, giving nine possible values (0, 1, 2, 3, 4, 6, 8, 9, 12), including no symptoms (=0). A score >3 on any domain is usually regarded as clinically significant.[3] [12–14] A total NPI score is obtained by summing all the individual domain scores across the 12 domains, giving a range from 0 to 144. Agitation was assessed at each time point in the LASER-AD study using the agitation domain of the NPI, with higher values indicating more severe levels of agitation.

Resource use and costing

Resource use was measured using the Client Service Receipt Inventory, amended for use with older people[15] and collected from participant responses and caregiver reports for the previous 3 months at each time point. This incorporated information on where the person was living (at home, residential respite care, day respite care, residential care home (where staff typically do not have nursing qualifications), nursing care home, sheltered housing with a warden in the premises during the day, hospital awaiting placement), and their contacts with health and social care services (general practitioner (GP), practice nurse at the GP surgery, district nurse at the person's home, dietician, community psychiatric nurse, home help, meals on wheels, physiotherapist, chiropodist, optician, dentist, audiologist, psychologist, psychiatrist, day centre, hospital outpatient visits and inpatient stays). We did not include the costs of informal care—these data were not collected; we focused on health and social care costs, which is the costing perspective recommended in economic analyses in the UK.[16] We applied unit costs from routine sources[17] [18] in 2011 UK£ and calculated 3-month costs for each participant at each follow-up point. Three-month costs were multiplied by 4 to create 12-month figures.

Statistical analyses

We calculated unadjusted mean and median 12-month costs by NPI agitation score (≤3, >3) and examined between-group differences using one-way analysis of variance (ANOVA), and the Mann-Whitney two-sample test. We examined associations between NPI agitation score and demographic variables, coexisting conditions and cognitive impairment using χ^2 tests. We calculated descriptive statistics for caregivers, who assessed behaviours using the NPI and recorded resource use. We calculated unadjusted mean and median 12-month costs by individual NPI agitation score and tested for significant differences using one-way ANOVA with Bonferroni correction for multiple tests, and χ^2 tests on the equality of medians. Use of health and social services among people with AD who are agitated may be affected by the extent of cognitive decline, demographic factors and comorbidities; to isolate the costs associated with agitation, we ran analyses adjusting for these factors. To account for skewness of the cost data, we used a generalised linear model with γ family and log link,[19] adjusting for gender and age (using five 10-year bands) at baseline, marital status (6 categories), ethnic group (9 categories), highest level of education (5 categories), previous employment (9 categories), rurality (2 categories), coexisting conditions (diabetes, stroke, hypertension, heart disease), total NPI agitation score (in our data the range of scores was 0–82 with 66 unique values; we included categorical indicators for each score, including 66 categories in total), cognitive impairment (measured using the Mini-Mental State Examination;[20] 31 categories), and follow-up point (baseline, 18, 30, 42, 54 months). We also considered using log Normal, Gaussian, inverse Gaussian and negative binomial distributions, but the γ model gave the best fit in terms of residual plots and the Akaike Information Criterion. We adjusted for clustering for repeated measures by participant using clustered sandwich estimators for the SE that allowed for intragroup correlation within participants. We predicted 12-month health and social care mean

costs by NPI agitation score, controlling for the covariates. The differences in adjusted means were tested using Wald tests. In intervention studies, outcomes are sometimes measured in terms of change in NPI agitation scores, so we re-ran the analyses including NPI agitation scores as a linear term rather than categorical indicators.

Excess costs associated with agitation

We combined the adjusted annual costs per person at different levels of NPI agitation score with prevalence rates in the LASER-AD study to calculate the annual expected cost per person with AD based on the per cent with each NPI agitation score. From this, we subtracted the adjusted annual costs per person with no agitation symptoms (NPI score=0) to estimate the mean excess costs associated with agitation per person each year. We also calculated UK-specific excess costs of agitation based on the prevalence of AD in the UK.

RESULTS
Baseline characteristics of caregivers

The mean age of caregivers (SD) was 63 years (14 years). Most caregivers were female (69%), married (69%), had no children living at home (75%) and were living with the person with AD (56%; see online supplementary table S2). The modal relationship to the person with AD was 'Child' (35%).

Health and social care costs associated with agitation

Of the 224 participants in the LASER-AD study, 111 had died by 54 months; our data set had 695 data points (person follow-ups). We applied unit costs to the resource use data in the LASER-AD study (see online supplementary table S1). Unadjusted mean (SD) per capita annual costs for participants with NPI agitation score ≤3 and >3 were £27 752 (£38 413) and £38 910 (£46 150; p<0.001, table 1). Median (IQR) values were £24 796 (£3512–£38 656) and £28 492 (£11 680–£40 164; p=0.001). Cost data were highly skewed (see online supplementary figure S1). The mode and median NPI agitation score were 0 and 1, respectively (table 2). Table 1 shows the per cent of the sample with different demographic variables, coexisting conditions and cognitive impairment by NPI agitation score. People with agitation scores >3 had a higher mean and median total NPI score, were more likely to be single and divorced and less likely to be married, less likely to be educated to secondary level and more likely to be educated to tertiary level, more likely to have heart disease, and more likely to have severe cognitive impairment (p<0.05).

Unadjusted mean and median costs increased with agitation score (p≤0.001; table 2).

After adjusting for demographic variables, coexisting conditions, cognitive impairment, follow-up and individual clustering for repeated measures, mean costs varied by NPI agitation scores, from £29 000 over a 12-month period

with no agitation symptoms (NPI agitation score=0) up to £57 000 at the most severe levels of agitation (NPI agitation score=12; p=0.01, table 2 and figure 1). Costs also varied significantly by age and gender, marital status, ethnic group, highest level of education, total NPI score and cognitive impairment (p<0.05, see online supplementary table S3).

When we reran the model including NPI agitation scores as a linear term rather than categorical indicators, we found that a one-unit increase in NPI agitation scores was associated with a £1736 increase in costs per patient over a 12-month period (95% CI £644 to £2807, p=0.001) in an unadjusted model, and £1064 (95% CI −£34 to £2162, p=0.058) when adjusting for the covariates.

Excess costs associated with agitation in the UK

The adjusted annual expected cost per person with AD based on the per cent with each NPI agitation score in our sample was £33 075 and the adjusted annual costs per person with no agitation symptoms was £28 983 (see online supplementary table S4). Hence, the excess cost associated with agitation per person with AD was £4091 a year. This suggests that on average agitation accounts for 12% (£4091/£33 075) of the health and social care costs of AD each year. In the UK, there are 800 000 people with dementia and around 62% of cases are accounted for by AD.[2] The expected excess cost associated with agitation in people with AD is therefore £2.0 billion a year (£4091×800 000×0.62).

DISCUSSION
Principal findings

Among people with AD, health and social care costs varied significantly by the level of agitation, from £29 000 over a 12-month period in people with no agitation symptoms up to around £57 000 at the most severe levels of agitation. On average, agitation symptoms account for 12% of the health and social care costs of AD. The excess cost associated with agitation was £2 billion a year across all people with AD in the UK.

Strengths and weaknesses

Our analysis is based on a unique data set containing very detailed information on frequency and severity of agitation symptoms and use of health and social care services over a 54-month time period. The data also include a range of demographic variables, coexisting conditions and cognitive impairment that can be included to isolate the costs associated with agitation.

With regard to limitations, the data set is relatively small, containing 224 people with AD. Given the large number of covariates included in our models, the fact that agitation is a significant predictor of costs suggests that the relationship is a strong one. Participants were recruited between July 2002 and January 2003 and followed up to 54 months; hence, the data are relatively old and the prevalence of agitations symptoms among

Table 1 Descriptive statistics of sample by agitation symptoms

	NPI agitation score ≤3 (N=493)	NPI agitation score >3 (N=202)	p Value
	Mean and median		
Per capita annual cost*			
Mean (SD)	27 752 (38 413)	38 910 (46 150)	<0.001
Median (IQR)	24 796 (3512–38 656)	28 492 (11 680–40 164)	0.001
Total NPI score			
Mean (SD)	14 (11)	32 (16)	<0.001
Median (IQR)	12 (6–19)	29 (21–42)	<0.001
Per cent			
Gender			
Male	27.8	28.7	0.80
Female	72.2	71.3	
Age category (years)			
50–59	1.4	1.5	
60–69	8.1	5.9	
70–79	33.7	45.5	0.06
80–89	46.9	37.6	
90–99	9.9	9.4	
Marital status			
Single	4.9	8.4	
Married	40.6	34.7	
Separated	1.4	0.5	0.01
Divorced	2.4	5.0	
Widower	50.5	49.5	
Other	0.2	2.0	
Ethnic group			
White British	78.5	75.3	
White Irish	7.1	8.9	
White other	9.5	8.9	
Greek	0.4	1.0	
Black Caribbean	2.6	3.0	0.65
Black other	0.4	1.5	
Indian	0.2	0.0	
Pakistani	0.4	0.0	
Other	0.8	1.5	
Highest level of education			
Primary	2.6	4.5	
Secondary	82.2	69.3	
Tertiary	9.9	13.9	0.002
Other	0.6	1.0	
Not known	4.7	11.4	
Previous employment			
Manager/administrator	6.7	4.0	
Professional	11.0	5.9	
Associate professional	1.8	2.0	
Clerical worker/secretary	18.9	17.8	
Skilled labourer	18.5	23.8	0.23
Services/sales	15.2	15.4	
Factory worker	11.2	8.9	
Other	15.6	20.3	
Don't know	0.2	0.0	
Rurality			
Urban	90.7	90.6	0.98
Rural	9.3	9.4	
Diabetes			
No	89.9	95.1	
Yes: IDDM	1.6	0.0	0.09
Yes: NIDDM—medically controlled	7.3	4.0	
Yes: NIDDM—diet controlled	1.2	1.0	

Continued

Table 1 Continued

	NPI agitation score ≤3 (N=493)	NPI agitation score >3 (N=202)	p Value
Stroke			
No	90.7	92.1	0.55
Yes	9.3	7.9	
Hypertension			
No	63.5	69.8	0.11
Yes	36.5	30.2	
Heart disease			
No	95.9	91.6	0.02
Yes	4.1	8.4	
Cognitive impairment			
Mild (MMSE 21–30)	26.4	8.9	
Moderate (MMSE 10–20)	37.7	28.2	<0.001
Severe (MMSE ≤9)	35.9	62.9	

*2011 UK£.
IDDM, insulin-dependent diabetes mellitus; MMSE, Mini-Mental State Examination; NIDDM, non-insulin-dependent diabetes mellitus; NPI, Neuropsychiatric Inventory.

people with AD may have changed over time. In addition, management practices might have changed over time. For example, in 2006, the National Institute for Health and Care Excellence in England first published guidance on the use of medications and treatments for AD; this was amended in 2007 and 2009, and new updated guidance that recommended extending the use of drug treatment in AD was issued in 2011.[21] Prescribing practices have changed over time with a marked reduction in antipsychotic drug use in people with dementia: the mean prevalence of antipsychotic use on diagnosis of dementia fell in the UK from 19.9% in 1995 to 7.4% in 2011.[22] While participants were selected to be representative of patients with AD, they were recruited from one geographical area, potentially limiting generalisability. We did not include the costs of informal care, though these have been estimated to account for a substantial proportion of the total costs of dementia.[1 2 23] These data were not collected in the LASER-AD study. UK guidelines for undertaking economic evaluations recommend taking a health and social care perspective when measuring costs.[16]

Comparison with other studies

Several studies have evaluated the relationship between behavioural symptoms and costs of care associated with AD, but none have specifically evaluated the monetary cost of agitation in AD. The studies evaluating the impact of behavioural symptoms on costs of care have tended to find a positive relationship. For example, using data from the USA on 128 patients with AD Murman et al[24] found that after controlling for cognitive impairment and comorbidities behavioural symptoms measured using the NPI significantly increased total direct costs (healthcare costs plus informal care costs): a one-point increase in total NPI score was associated with an annual increase of between US$247 and US$409 in total direct costs, depending on the value of unpaid caregiving. Gustavsson et al found that in a sample of 1222 patients with AD from Spain, Sweden, the UK, and the USA, there was a significant relationship between behavioural symptoms measured using total NPI score and cost of health and social care among people living in the community after controlling for ability to perform activities of daily living and cognitive impairment: a one-

Table 2 Association between agitation symptoms and per capita annual cost*: unadjusted and adjusted analyses (N=695)

NPI agitation score	Number (%)	Mean (SD)	Median (IQR)	Adjusted mean (95% CI)†
0	314 (45.2)	28 218 (43 332)	13 962 (3048–36 444)	28 983 (24 364 to 33 603)
1	68 (9.8)	22 596 (24 266)	22 352 (2666–32 149)	43 910 (30 618 to 57 203)
2	60 (8.6)	29 544 (34 427)	27 328 (8546–39 088)	31 196 (22 903 to 39 490)
3	51 (7.1)	29 653 (23 081)	28 216 (9089–39 076)	35 120 (25 592 to 44 648)
4	60 (8.6)	27 909 (23 353)	27 566 (6796–38 728)	35 458 (26 843 to 44 074)
6	57 (8.2)	35 324 (40 889)	27 648 (9720–39 028)	25 138 (17 918 to 32 358)
8	45 (6.5)	42 289 (48 695)	31 076 (23 616–42 532)	36 568 (25 590 to 47 545)
9	12 (1.7)	46 589 (41 302)	39 388 (18 017–64 726)	38 568 (11 867 to 65 269)
12	28 (4.0)	61 064 (76 070)	36 794 (27 126–44 468)	57 023 (31 861 to 82 186)
p Value		0.001	<0.001	0.01

*2011 UK£.
†Controls are included for age, gender, marital status, ethnic group, highest level of education, previous employment, rurality, coexisting conditions (diabetes, stroke, hypertension, heart disease), total NPI score, cognitive impairment (MMSE) and follow-up.
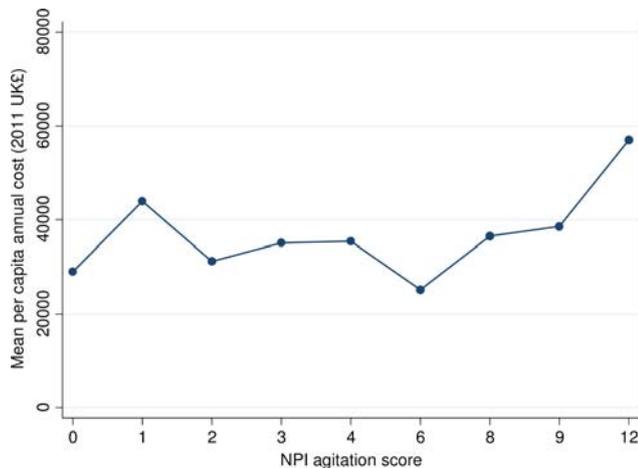MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory.

Figure 1 Adjusted[a] mean per capita annual cost[b] by agitation symptoms (N=695). [a]Controls are included for age, gender, marital status, ethnic group, highest level of education, previous employment, rurality, coexisting conditions (diabetes, stroke, hypertension, heart disease), total NPI score, cognitive impairment (MMSE) and follow-up. [b]2011 UK£. NPI, Neuropsychiatric Inventory; MMSE, Mini-Mental State Examination.

point increase in total NPI score was associated with a 1% increase in health and social care costs. Among people living in residential care, a one-point increase in total NPI score was associated with a 1.6% increase in costs of care in the USA only.[25] Using data for 272 patients with AD attending six memory clinics in Sweden, Denmark, Norway and Finland, Jönsson and Eriksdotter Jönhagen[26] found that total NPI score was significantly associated with health and social care plus informal care costs: after controlling for cognitive impairment, years since diagnosis of AD and comorbidities costs were calculated to increase by 8% for each one-point increase in total NPI score.

Implications for clinicians and policymakers

People with AD who are agitated are substantial users of health and social care services, suggesting that effective measures to reduce agitation would reduce the burden on these services, as well as providing health benefits to people with AD and their carers. Reducing agitation could be cost-effective and, in addition, bring considerable cost savings, which should be compared against the cost of interventions.

Further research

Health economic analyses of interventions for reducing agitation in AD incorporated into clinical trials are needed. Such analyses should evaluate the impact of interventions using final outcomes such as quality-adjusted life years, for example, using new approaches based on the DEMQOL system,[27 28] where cost-effectiveness thresholds have been identified.[16] They should also include comprehensive cost analyses, including health and social care costs associated with managing agitation as well as

intervention costs, and be conducted over sufficiently long time horizons to measure the full costs and benefits.

Author affiliations
[1]Department of Applied Health Research, University College London, London, UK
[2]Department of Statistical Science and PRIMENT Clinical Trials Unit, University College London, London, UK
[3]Division of Psychiatry, University College London, London, UK

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Online supplements

Table S1. Unit costs

Table S2. Baseline characteristics of caregivers (N=224)

Figure S1. Distribution of per capita annual cost (N=695)

Table S3. Association between agitation symptoms and per capita annual cost: adjusted analyses, full results (N=695)

Table S4. Calculation of excess costs associated with agitation in people with Alzheimer's disease

Table S1. Unit costs

Cost component	Unit cost[a]	Unit	Reference
General Practitioner (GP)	36	Per surgery consultation	[17]
Practice nurse/District nurse	60	Per hour	[17]
Dietician	35	Per hour	[17]
Community psychiatric nurse	50	Per hour	[17]
Occupational therapist	82	Per hour	[17]
Home help	27	Per hour	[17]
Meals on wheels	6.	Per meal	[17]
Physiotherapist	34	Per hour	[17]
Chiropodist	31	Per hour	[17]
Optician	57	Per contact	[18]
Dentist	92	Per contact	[18]
Audiologist	67	Per contact	[18]
Psychiatrist	418	Per contact	[17]
Psychologist	135	Per hour	[17]
Day centre	34	Per visit	[17]
Hospital outpatient visit	100	Per visit	[17]
Hospital inpatient stay	321	Per day	[17]
Residential respite care	105	Per overnight stay	[17]
Day respite care	96	Per day	[17]
Residential care home	519	Per week	[17]
Nursing care home	741	Per week	[17]
Sheltered housing	155	Per week	[17]
Hospital awaiting placement	321	Per day	[17]

[a] 2011 UK£.

Table S2. Baseline characteristics of caregivers (N=224)

Characteristic	Baseline value (N=224)
Age (years)	
Mean (SD)	63 (14)
Gender (%)	
Male	31
Female	69
Marital status (%)	
Single/unmarried	9
Married	69
Co-habiting	2
Widowed	5
Separated/divorced	7
Not known	8
Number of children at home (%)	
0	75
1	8
2	7
3	2
4	1
Not known	7
Living with person with AD (%)	
Yes	56
No	43
Not known	1
Relationship to person with AD (%)	
Husband/partner	17
Wife/partner	20
Child	35
Friend	4
Other relative	9
Paid carer	14

Abbreviation: AD, Alzheimer's disease

Figure S1. Distribution of per capita annual cost (N=695)
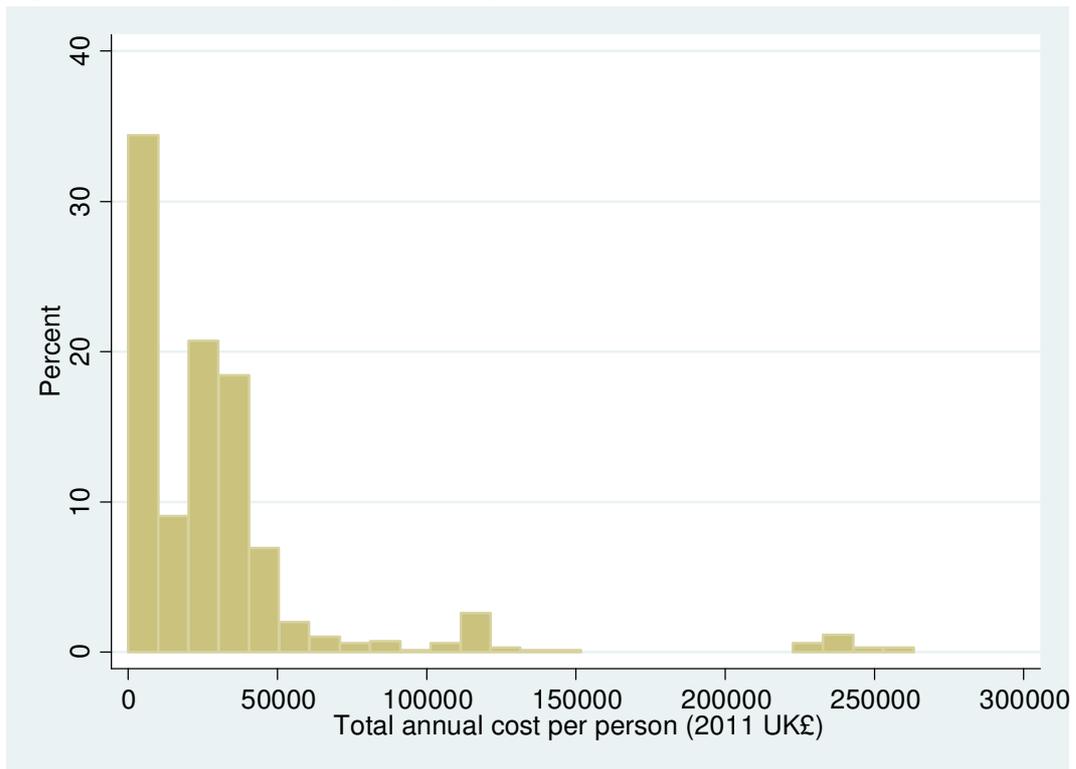
Tests for normality: Shapiro–Wilk normality test: P <0.01. Shapiro–Francia normality test: P <0.01.

Table S3. Association between agitation symptoms and per capita annual cost[a]: adjusted analyses, full results (N=695)

	Adjusted mean (95% CI)			
NPI agitation scores				
0	28 983	(24 364	to	33 603)
1	43 910	(30 618	to	57203)
2	31 196	(22 903	to	39 490)
3	35 120	(25 592	to	44 648)
4	35 458	(26 843	to	44 074)
6	25 138	(17 918	to	32 358)
8	36 568	(25 590	to	47 545)
9	38 568	(11 867	to	65 269)
12	57 023	(31 861	to	82 186)
P value	0.01			
Gender*age category (years)	.			
Male*60-69	106 172	(22 527	to	189 816)
Male*70-79	20 838	(14 560	to	27 116)
Male*80-89	27 740	(18 508	to	36 971)
Male*90-99	37 134	(9778	to	64 490)
Female*50-59	58 633	(-23 297	to	140 563)
Female*60-69	20 663	(8848	to	32 477)
Female*70-79	30 443	(22 400	to	38 487)
Female*80-89	43 813	(34 943	to	52 683)
Female*90-99	36 165	(23 067	to	49 264)
P value	<0.001			
Marital status				
Single	61 977	(32 527	to	91 427)
Married	22 821	(18 359	to	27 283)
Separated	33 384	(6357	to	60 411)
Divorced	28 087	(13 377	to	42 797)
Widower	36 598	(30 183	to	43 013)
Other	72 443	(14 808	to	130 077)
P value	0.002			
Ethnic group				
White British	31 901	(27 905	to	35 896)
White Irish	28 072	(16 285	to	39 859)
White other	37 326	(23 133	to	51 518)
Greek	2763	(-960	to	6486)
Black Caribbean	59 761	(25 301	to	94 220)
Black other	35 488	(-912	to	71 888)
Indian	4226	(166	to	8286)
Pakistani	63 600	(23 645	to	103 556)
Other	39 098	(14 420	to	63 776)
P value	<0.001			
Highest level of education				
Primary	32 855	(3512	to	62 198)
Secondary	33 992	(29 155	to	38 829)
Tertiary	36 291	(16 018	to	56 565)
Other	3136	(1207	to	5065)
Not known	22 863	(17 604	to	28 122)
P value	<0.001			
Previous employment				
Manager/Administrator	39 121	(20 144	to	58 098)
Professional	21 740	(12 042	to	31 438)
Associate professional	28 380	(9253	to	47 507)
Clerical worker/Secretary	33 826	(25 944	to	41 708)
Skilled labourer	31 487	(23 055	to	39 918)

Services/Sales	38 584	(	28 147	to	49 020	)
Factory worker	27 280	(	17 251	to	37 310	)
Other	35 395	(	21 644	to	49 146	)
Don't know	40 168	(	7614	to	72 723	)
P value	0.37				
Rurality					
Urban	33 298	(	29 453	to	37 143	)
Rural	22 908	(	13 076	to	32 739	)
P value	0.10				
Diabetes					
No	32 531	(	28 909	to	36 152	)
Yes: IDDM	31 176	(	10 046	to	52 307	)
Yes: NIDDM – medically controlled	30 498	(	17 161	to	43 835	)
Yes: NIDDM – diet controlled	62 095	(	19 912	to	104 278	)
P value	0.26				
Stroke					
No	32 006	(	28 266	to	35 747	)
Yes	38 756	(	25 394	to	52 118	)
P value	0.30				
Hypertension					
No	33 479	(	28 254	to	38 704	)
Yes	30 746	(	24 510	to	36 982	)
P value	0.55				
Heart disease					
No	32 346	(	28 739	to	35 953	)
Yes	36 216	(	19 148	to	53 285	)
P value	0.64				
Total NPI score					
0	23 593	(	13 823	to	33 363	)
1	15 907	(	8882	to	22 932	)
2	22 190	(	11 085	to	33 294	)
3	24 164	(	12 457	to	35 871	)
4	46 735	(	28 502	to	64 969	)
5	30 567	(	14 160	to	46 974	)
6	22 628	(	10 565	to	34 690	)
7	40 133	(	16 714	to	63 552	)
8	35 762	(	24 854	to	46 671	)
9	27 722	(	18 587	to	36 857	)
10	50 437	(	27 556	to	73 318	)
11	43 285	(	20 729	to	65 841	)
12	35 797	(	25 150	to	46 444	)
13	39 215	(	20 201	to	58 229	)
14	37 723	(	21 893	to	53 554	)
15	23 841	(	17 017	to	30 665	)
16	34 838	(	22 421	to	47 255	)
17	21 277	(	9213	to	33 341	)
18	31 299	(	17 852	to	44 745	)
19	23 970	(	16 782	to	31 157	)
20	55 337	(	20 991	to	89 682	)
21	28 149	(	17 217	to	39 081	)
22	40 379	(	22 795	to	57 964	)
23	56 096	(	30 241	to	81 951	)
24	13 821	(	7610	to	20 032	)
25	18 446	(	10 328	to	26 563	)
26	18 959	(	2224	to	35 693	)
27	40 681	(	5711	to	75 651	)
28	29 549	(	13 015	to	46 083	)
29	43 221	(	20 283	to	66 159	)

30	20 897	(	9537	to	32 256	)
31	46 870	(	-868	to	94 608	)
32	24 717	(	15 551	to	33 884	)
33	23 252	(	4477	to	42 027	)
34	32 839	(	862	to	64 816	)
35	18 022	(	2413	to	33 632	)
36	45 720	(	-12 125	to	103 564	)
37	14 944	(	5308	to	24 579	)
38	36 810	(	23 078	to	50 542	)
39	20 524	(	6476	to	34 572	)
40	22 872	(	14 496	to	31 248	)
41	12 418	(	1653	to	23 183	)
42	42 246	(	7638	to	76 854	)
43	38 972	(	4391	to	73 552	)
44	91 489	(	50 078	to	132 900	)
45	35 315	(	11 478	to	59 153	)
46	86 883	(	7744	to	166 022	)
47	32 128	(	-5314	to	69 569	)
48	27 034	(	10 312	to	43 757	)
49	25 890	(	7565	to	44 215	)
50	36 616	(	40	to	73 192	)
51	15 263	(	6986	to	23 540	)
52	24 059	(	1751	to	46 368	)
53	21 026	(	5762	to	36 291	)
54	14 641	(	5653	to	23 629	)
57	169 936	(	-24 228	to	364 099	)
59	54 625	(	28 475	to	80 775	)
60	29 625	(	16 477	to	42 773	)
61	30 444	(	-27 798	to	88 685	)
64	1673	(	672	to	2674	)
65	1725	(	531	to	2918	)
66	24 912	(	9101	to	40 722	)
67	52 075	(	13 525	to	90 626	)
69	47 684	(	-5887	to	101 256	)
79	7651	(	1391	to	13 910	)
82	7435	(	1774	to	13 096	)
P value	<0.001					
MMSE score						
0	70 323	(	54 271	to	86 375	)
1	39 663	(	26 441	to	52 885	)
2	36 960	(	20 551	to	53 370	)
3	45 878	(	25 791	to	65 964	)
4	30 985	(	14 793	to	47 177	)
5	53 935	(	25 859	to	82 010	)
6	39 690	(	16 784	to	62 596	)
7	22 396	(	15 634	to	29 158	)
8	64 027	(	35 175	to	92 878	)
9	35 884	(	16 215	to	55 553	)
10	15 640	(	5322	to	25 958	)
11	23 619	(	13 114	to	34 124	)
12	30 401	(	18 028	to	42 775	)
13	20 569	(	12 682	to	28 456	)
14	14 157	(	6889	to	21 424	)
15	27 900	(	16 776	to	39 024	)
16	24 417	(	14 756	to	34 078	)
17	20 616	(	13 845	to	27 387	)
18	31 333	(	19 682	to	42 984	)
19	11 466	(	5544	to	17 388	)

20	18 803	(	10 219	to	27 388	)
21	15 315	(	9553	to	21 078	)
22	15 672	(	9053	to	22 291	)
23	6427	(	3235	to	9618	)
24	9784	(	5026	to	14 542	)
25	7937	(	3633	to	12 242	)
26	6250	(	3165	to	9334	)
27	2901	(	1308	to	4493	)
28	9377	(	4141	to	14 612	)
29	11 295	(	3436	to	19 155	)
30	2931	(	1413	to	4449	)
P value	<0.001					
Follow-up						
Baseline	35 161	(	28 575	to	41 748	)
18 months	34 223	(	28 028	to	40 418	)
30 months	31 898	(	26 252	to	37 544	)
42 months	31 045	(	25 696	to	36 395	)
54 months	29 432	(	23 358	to	35 507	)
P value	0.78					

Abbreviations: NPI, Neuropsychiatric Inventory; IDDM, insulin dependent diabetes mellitus; NIDDM, non-insulin dependent diabetes mellitus; MMSE, mini–mental state examination; CI, confidence interval. [a] 2011 UK£.

Table S4. Calculation of excess costs associated with agitation in people with Alzheimer's disease

NPI agitation score	Percent observations across N=695	Adjustment mean per capita annual cost[a]
0	45.2	28 983
1	9.8	43 910
2	8.6	31 196
3	7.3	35 120
4	8.6	35 458
6	8.2	25 138
8	6.5	36 568
9	1.7	38 568
12	4.0	57 023

Abbreviations: NPI, Neuropsychiatric Inventory. [a] 2011 UK£.

Annual expected cost per person with AD based on percent with each NPI agitation score = 45.2%*£28 983 + 9.8%*£43 910 + 8.6%*£31 196 + 7.3%*£35 120 + 8.6%*£35 458 + 8.2%*£25 138 + 6.5%*£36 568 + 1.7%*£38 568 + 4.0%*£57 023 = £33 075

Annual cost per person with AD with no agitation symptoms (NPI agitation score =0) = £28 983.

Mean excess cost associated with agitation per person with AD each year = £33 075 - £28 983 = £4091.

Number of people with dementia in the UK = 800 000; around 62% (= 496 000) are accounted for by AD.

Excess cost associated with agitation in people with AD in the UK each year = £3265*800 000*0.62 = £2.0 billion.