The association between specific neuropsychiatric disturbances in people with Alzheimer’s disease and dementia with Lewy bodies and carer distress.

Running head: Neuropsychiatric disturbances in dementia and carer distress

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Last but not least, we sincerely thank all participating patient and their carers, and the dedicated work of research staff in the DemWest study and Helse Vest.
ix. Abstract, keywords and key-points

Objective

Neuropsychiatric symptoms (NPSs) are identified as important care-recipient variables in terms of the impact on carer distress. The aim of this study was to determine whether specific neuropsychiatric disturbances in people with Alzheimer’s disease (AD) and dementia with Lewy bodies (DLB) differentially impact carer distress.

Methods

This was a cross-sectional study of people diagnosed with AD and DLB and their primary carers. The Relatives’ Stress Scale (RSS) was used to assess the level of reported distress in carers, and the Neuropsychiatric Inventory (NPI) was used to assess NPSs. The effect of NPSs on carer distress was analyzed using correlation analysis and partial least squares regression.

Results

This study included 159 participants diagnosed with AD (n=97) and DLB (n=62), and their primary carers (spouses and adult children). The majority of people diagnosed with dementia were women (64.2%), with a mean age of 75.9 (SD, 7.4) years and a mean Mini-Mental State Examination (MMSE) score of 23.5 (SD, 2.9). The main analysis identified apathy as the most important NPS contributing to carer distress. Compared to AD, the explained variance in the DLB group was higher ($r^2 = 37.3$ vs. $r^2 = 53.7$). In addition, more NPSs were considered clinically important in the DLB group.

Conclusion

The findings of this study identify apathy as the most important NPS contributing to carer distress among carers of people with AD and DLB. These findings help us identify the support needs of families dealing with dementia.
Keywords: Dementia, Neuropsychiatric symptoms, Neuropsychiatric Inventory (NPI), Carer distress, Alzheimer's disease, Dementia with Lewy bodies

Key points:

- Apathy is identified as the most important NPS contributing to carer distress among carers of people with AD and DLB.

- There appears to be little difference between the two diagnostic groups.

- Compared to AD, the explained variance is higher, and more NPSs are identified as clinically important, in the DLB group.
1.0 INTRODUCTION

Dementia is characterized by a progressive decline in cognition and the level of functioning, and deterioration in emotional control, social behavior, and/or motivation. Approximately forty-seven million people live with dementia worldwide. As the world’s populations age, this number is expected to increase, placing a significant burden on the economy, the care-system and informal carers.

Dementia care focuses on enabling people with dementia to continue living in their own homes, and on supporting and improving the lives of people with dementia and their carers. As the main providers of care, the immediate family of people with dementia (i.e., the spouse and/or adult children) often experience a significant care burden. Carer distress is associated with negative carer outcomes, such as a decline in general health, psychiatric morbidities, impaired quality of life, and shorter time to nursing home admission.

Although distress is a result of multifactorial influences, it is well established that summed scores of neuropsychiatric symptoms (NPSs) exert a negative impact on carer distress. Recently, attention has been given to the effect of individual NPSs associated with carer distress. Identifying specific aspects of dementia behavior associated with carer distress may help us tailor health-care services, and offer families dealing with dementia the support they need.

In a review conducted in 2012, Ornstein and Gaugler studied the effect of individual NPSs and NPS clusters on carer distress and depression. They found that no individual symptom or symptom cluster(s) was consistently identified as having a negative impact on either carer distress or depression. However, they identified aggression, depression, sleep disturbances and repetitive behaviors as the most frequently cited patient symptoms associated with carer distress. In 2016, Feast et al. responded to Ornstein and Gaugler’s recommendations, and systematically reviewed the relationship between individual NPSs and different measures of carer well-being. This was achieved by distinguishing between psychological constructs of negative carer outcomes, and by distinguishing
between how NPSs are measured (prevalence, frequency, and total intensity/sum score). In a meta-analysis of mean distress scores, depressive behaviors, agitation and apathy were identified as most distressing for carers. A second meta-analysis of only four studies reporting on correlation data found that irritability, aberrant motor behaviors and delusions were most strongly associated with distress. In 2017, we published a review on the association between individual NPSs as measured by the Neuropsychiatric Inventory (NPI) and carer distress. The principal finding of this review was that irritability, agitation, sleep disturbances, anxiety, apathy, and delusion were identified as important contributors to carer distress.

The authors of all three reviews emphasize that the evidence is not conclusive as to whether individual NPSs differently impact carer distress, and they note several limitations and knowledge gaps within this field. For example, based on attribution theory, Ornstein and Gaugler argue that the etiology of dementia may influence the way carers experience the behavioral disturbances and psychiatric features of dementia and recommend testing these relationships across different diagnostic contexts. Alzheimer’s disease (AD) and dementia with Lewy bodies (DLB) are the two most common subtypes of neurodegenerative dementia, representing more than 80% of all dementia cases. We have previously demonstrated that severe NPSs are common in both AD and DLB at the time of diagnosis. However, compared to AD, people diagnosed with DLB have more numerous NPSs and more clinically significant NPSs in the early stages of the disease, and carers of people with DLB report significantly more distress. These differences, however, tend to decrease with increasing disease severity.

Another important limitation within this field, is that the majority of studies have used simple correlation analysis or lack controls for potentially confounding variables, partly due to small sample sizes. In our opinion, the use of multivariate methods would further our understanding of the relationship between individual NPSs and carer distress. To determine the relative effect of individual NPSs, further studies need to control for the full range of NPSs.
The primary aim of this study was to investigate multivariate associations between individual NPSs in people with mild dementia living at home and carer distress. Furthermore, we aimed to explore whether there are differences in the way individual NPSs are associated with carer distress in relation to diagnosis (AD versus DLB).

2.0 METHODS

A cross-sectional study of the association between individual NPSs in dementia and carer distress was conducted. Participants were recruited from a long-term dementia cohort study (DemVest, total n=223), including people with a first-time diagnosis of mild dementia (i.e., a Mini-Mental Examination (MMSE) score ≥ 20 or a Clinical Dementia rating-scale (CDR) global score = 1). For more details, see Aarsland et al.\textsuperscript{15}

Participants in the DemVest cohort were recruited by screening all referrals to outpatient clinics in western Norway between 2005 and 2007, followed by a recruitment phase to selectively identify people diagnosed with DLB and Parkinson's Disease Dementia (PDD) and their carers to the end of 2013. A diagnosis of dementia was made according to the Diagnostic and Statistical Manual for Mental Disorders (fourth edition) by an experienced clinician and licensed specialist in geriatric medicine or psychiatry. DLB was diagnosed according to the revised Consensus Guidelines for the Clinical Diagnosis of Probable and Possible Dementia With Lewy Bodies,\textsuperscript{20} and AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and the Stroke-Alzheimer’s Disease and Related Disorders Association.\textsuperscript{21} A pathological diagnosis is available for 56 patients in the DemVest cohort, showing a diagnostic accuracy of more than 80%.\textsuperscript{22}

2.1 Eligibility criteria
This study include people with mild dementia diagnosed with AD or DLB with a primary carer who was a spouse/partner or adult child. Patients with acute delirium or confusion, a terminal illness, those recently diagnosed with a major somatic illness, or those with a previous bipolar disorder or psychotic disorder were excluded.

2.2 Ethics

The Regional Ethics Committee for Medical Research Ethics in Western Norway (DemVest REK 2010/633) and the Norwegian authorities for the collection of medical data have approved the DemVest study. All participants, including those with dementia and their primary carer, provided written consent. The data were handled and kept in accordance with national health and data privacy protocols.

2.3 Measures

2.3.1 Neuropsychiatric symptoms (NPSs)

NPSs were assessed using the validated Norwegian version of the Neuropsychiatric Inventory (NPI).

The NPI is a widely used carer-based assessment scale that evaluates 12 neuropsychiatric symptoms common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, sleep and night-time disturbances, and appetite/eating abnormalities. Each symptom is rated on a frequency scale (0-4) and a severity scale (0-3), with a higher score indicating more severe symptoms. The total score for each domain is calculated by multiplying the two scores (frequency x intensity).

Scores ≥4 on an individual item are regarded as clinically significant symptoms. This includes a frequency rating of at least “often” or “more frequently” and a severity rating of at least “moderate”.
The content validity, concurrent validity, inter-rater reliability, and test-retest reliability of the NPI have been established,\textsuperscript{24} as have the reliability and validity of the Norwegian version of the NPI.\textsuperscript{23}

2.3.2 Carer distress

Carer distress was assessed using the Relatives’ Stress Scale (RSS). The RSS is a self-administered questionnaire consisting of 15 items, designed to assess the degree of stress experienced by a relative caring for people with physical and/or behavioral debilities. The questionnaire covers various aspects of stress, such as subjective emotional responses, restrictions in the carer’s social life, and negative feelings associated with the patient and his or her behaviors. Each item in the RSS is assessed using a scale ranging from 0 to 4, with higher scores indicating more severe stress.\textsuperscript{27} According to Ulstein et al.,\textsuperscript{28} a score above 23 on the RSS indicates an increased risk of clinically significant psychological distress for the carers.

2.3.3 Other variables

In addition to a diagnosis of dementia, socio-demographic variables (patients sex and age), number of children, duration of symptoms prior to diagnosis (years), and family relations (spouse or adult children), cognitive functioning levels were assessed by means of the Mini Mental Status Evaluation (MMSE). The MMSE is a 30-point questionnaire that is used extensively in clinical and research settings to estimate the severity and progression of cognitive impairment.\textsuperscript{29}

The limitations of the patients in terms of daily activities were assessed using the Rapid Disability Rating Scale-2 (RDRS-2). This scale comprises items grouped into three domains: activities of daily living, degree of dependence and cognitive impairment.\textsuperscript{30} The items are ranked on a scale, with higher scores indicating poorer function. Because the RDRS-2 exists in both a 19-item version and a 21-item version, z-scores were applied.
2.4 Statistics

The characteristics of the entire sample (n = 159), the AD group (n = 97) and the DLB group (n = 62) are presented as proportions and mean values with standard deviations. The analytical approach was conducted in two steps. The Spearman rank test was used to display unadjusted correlations between the 12 NPSs (original scores) in the NPI and RSS total score, first in the entire sample and then separately in the AD and DLB groups. A Spearman rank coefficient (rho) of <0.1 was considered trivial, 0.1–0.29 was considered small, 0.3–0.49 was considered moderate and ≥0.5 was considered large. In the adjusted analysis, three separate partial least square (PLS) regression models (entire sample, AD and DLB) were used to study the associations between the 12 NPSs in the NPI and the RSS total score. PLS regression allows for multivariate modelling in samples with many variables related to observations. Due to the highly non-normal distribution of the NPI item scores, the NPI-items were recoded into binary variables (score <4 vs. ≥ 4). An NPI item score ≥4 is considered clinically important. Adjustments were made for carer status (spouse vs adult child) and the patient’s gender, age, duration of symptoms prior to diagnosis, number of children, MMSE total score, and RDRS-2, z-score. In a supplementary analysis, two additional PLS regression models (spouse and adult children) were applied to determine whether there were any differences in how NPSs are associated with carer distress in relation to carer status (spouse vs. adult child). Adjusted were made for patient age, sex, diagnosis (AD and DLB), number of children, MMSE total score, duration of symptoms prior to diagnosis, and RDRS-2, z-scores. See figures S1 and S2, available as supplementary material attached to the electronic version of this paper.

Continuous covariates were standardized to the same binary unit of measurement as the NPSs (0/1) using median split. To assess the robustness of the findings, all models were cross-validated, excluding every fourth subject. We report unstandardized regression coefficients with confidence intervals (CI). All CIs not including the value of zero were considered statistically significant. The clinical importance
of the results was judged by effect sizes, coefficients from the PLS-regression divided by the standard deviation of the RSS score for the entire sample. An effect size ≥0.2 was considered clinically meaningful.31,32

The PLS analysis and cross-validation were performed using Sirius v. 8.0 (Pattern Recognition Systems, Bergen, Norway), while other analyses were conducted using SPSS version 24.

3.0 RESULTS

3.1 Cohort characteristics

A total of 223 people diagnosed with mild dementia were recruited in the DemVest study. This study included 159 participants diagnosed with AD (n=97) and DLB (n=62) and their primary carers. The majority of patients were women (n=102; 64.2%), with a mean age of 75.9 (SD, 7.4) and a mean MMSE score of 23.5 (SD, 2.9). All patients were living at home at the time of inclusion, 62.3% with a spouse or partner. Spouses who were the main provider of care constitute 51.6% of the study group, while the remaining 48.4% of the carers were the adult children of the patient. For more details, see table 1.

3.2 The association between individual NPSs and carer distress

Correlation analysis revealed a moderate association between carer distress and apathy (ρ = 0.409) and aberrant motor behavior (ρ = 0.318). In the AD group, disinhibition (ρ = 0.373), apathy (ρ = 0.355), irritability (ρ = 0.338), agitation (ρ = 0.322) and aberrant motor behavior (ρ = 0.310) were all considered important contributors to carer distress, with a correlation coefficient ≥0.3. In the DLB group only apathy (ρ = 0.483), sleep and night-time disturbances (ρ = 0.366), and aberrant motor behavior (ρ = 0.328) were identified as important NPSs contributing to carer distress. For more details, see table 2.
The PLS regression models, adjusted for sociodemographic variables, number of children, carer status, cognitive functioning level, duration of symptoms prior to diagnosis and limitations in daily activity, identify apathy as the most important NPS contributing to distress in both diagnostic groups. Apathy is also the most prevalent NPS (≥4 n=59). Our findings further identify aberrant motor behavior, irritability, and appetite and eating abnormalities as important additional contributors to carer distress in all three samples, with an effect size ≥0.2.

According to the adjusted analysis, there are few differences between the two diagnostic groups. However, compared to AD ($r^2 = 37.3$), the explained variance in the DLB group is higher ($r^2 = 53.7$). Furthermore, in the DLB group, several more NPSs are identified as important contributors to carer distress: agitation, delusion, sleep and night-time disturbances, and depression. In contrast, these symptoms are considered trivial contributors to distress in the AD group with an effect size <0.2. For more details, see table 3.

In a supplementary analysis, two additional PLS regression models were applied to determine whether there were any differences in how NPSs were associated with carer distress in relation to family relation. The findings of this analysis revealed that the explained variance was considerably higher in the sample consisting of spouses ($r^2 = 61.3$) than in the sample of adult children ($r^2 = 31.8$). Furthermore, several more NPSs were identified as important contributors to carer distress among spouses, with an effect size <2. Apathy was the most important NPS contributing to carer distress in both samples, with a considerably higher effect size. For more details, see the supplementary online material, sFigure 1 and sFigure 2.

4.0 DISCUSSION

The principal finding of this study is that apathy, aberrant motor behavior, irritability, and appetite and eating abnormalities are important NPSs contributing to carer distress, all with an effect size ≥2.32,33. These findings correspond with a number of previous studies. Apathy,34–38 irritability,36–43 and aberrant
motor behaviors\textsuperscript{34,36,41,44,45} have all repeatedly been identified as important contributors to carer distress. In contrast to previous findings,\textsuperscript{12,13} depression was not identified as an important contributor to distress in our analysis.

Apathy is defined as a loss of motivation and manifests in behaviors such as diminished initiation, poor persistence, lack of interest, indifference, low social engagement, blunted emotional response, and lack of insight.\textsuperscript{46} The fact that people with apathy have increased reliance on carers to initiate and oversee activities, even when they are still capable of performing the activity, may explain why apathy is identified as an important contributor to distress. Carers also commonly misinterpret the loss of motivation and engagement as a sign of emotional disturbance or oppositional behavior, leading to additional strain on carers.\textsuperscript{46} However, even though the clinical distinction between apathy and depression, especially in more severe dementia, can be challenging, it is important to be aware that apathy is a distinct syndrome in dementia.

NPSs are an integrated part of dementia and require tailored and dynamic interventions throughout the disease course.\textsuperscript{16} Understanding the effect of individual NPSs on carer distress is of great clinical importance in terms of identifying carers at risk of stress-related health problems and identifying the support needs of families dealing with dementia. However, the lack of consistency in findings, across studies, and heterogeneity in measures and methodology, has made it difficult to draw conclusive interpretations regarding which NPSs impact carer well-being the most.\textsuperscript{12,14}

Carer distress is a result of multifactorial influences and their summation and interaction.\textsuperscript{3} Nevertheless, very few studies within this field include controls for potentially confounding variables, partly due to small sample sizes.\textsuperscript{12,14} In this study, adjustments were made for the diagnosis of dementia and the socio-demographic variables of the patient, in addition to duration of symptoms prior to diagnosis, family relations (spouse or adult children), cognitive functioning levels and the limitations of the patients in terms of daily activities. According to Ornstein and Gaugler, more research is needed to understand if and why certain NPSs affect certain carers more and how much of
this is attributable to, for example carer variability in response to NPSs, rather than the presence of NPSs themselves.12

In a supplementary analysis, we found that the explained variance in the sample of spouses ($r^2 = 61.3$) was considerably higher than in the sample of adult children ($r^2 = 31.8$). Furthermore, several more NPSs were identified as important contributors to carer distress among spouses, with an effect size <2.

To the best of our knowledge, no other studies have determined the effect of individual NPSs on carer distress in samples of spouses or adult children, and have simultaneously adjusted for other important covariates. Spouses differ significantly from children with regard to sociodemographic variables and provide more support. Adult children, in contrast, are more likely to have multiple demands and competing responsibilities.47 Thus, it is reasonable to believe that the carer experience is different for the two groups.

According to the adjusted analysis, there are few differences between the two diagnostic groups. However, compared to AD, the explained variance in the DLB group is higher. Furthermore, four additional NPSs were identified as important contributors to burden in the DLB group: agitation, delusion, sleep and night-time disturbances, and dysphoria/depression.

Ornstein and Gaugler12 refer to Winer (1986) and argue that according to attribution theory, carers who perceive patients as having less control over their behaviors have a lower emotional response and fewer negative effects. If the carer expects and/or sees NPSs as part of the disease based on their understanding of the specific dementia diagnosis, the carer is less likely to experience distress. The findings of this study cannot confirm or refute this suggestion. Based on the findings of this study, carers of people diagnosed with AD and DLB appear to have many of the same responses to NPSs. The differences between the two diagnostic groups seem to reflect the fact that carers of people diagnosed with DLB experience more distress6,18 and deal with more numerous and more clinically significant NPSs.16 For example, this study identifies sleep and night-time disturbances, which are core clinical features of DLB, as important contributors to distress in the DLB group, both in the PLS
regression model and in the correlation analysis. Sleep disturbances are not identified as an important contributor to distress in the AD group.

A high proportion of carers of people with mild dementia experience moderate to high distress, and compared to AD, carer distress is higher among carers of people with DLB.\textsuperscript{5,18} Patterns of carer distress were found to differ between the two diagnostic groups. We have previously demonstrated that whereas the level of distress remains relatively stable across a three-year period in the DLB group, carer distress significantly increases from baseline and at both the two- and three-year follow-ups in the AD group.\textsuperscript{19} Apathy, which was identified in our findings as both the most prevalent NPS and the most important NPS contributing to carer distress, was notably more common in the DLB group. However, according to Vik-Mo et al., apathy increases over time in people diagnosed with AD, making the difference most pronounced in people with mild dementia.\textsuperscript{16} In our opinion, these findings highlight the need to consider both the disease stage and the diagnostic context, and thus emphasize the importance of these findings.

This study has some strengths and limitations. First, the participants in the DemVest study were selected from a large, clinically defined cohort, with rigorous diagnostic procedures, annual follow-up assessments, and low drop-out. Socio-demographic data on the carers were limited. This does not detract from our findings on the association between specific neuropsychiatric disturbances in people with AD and DLB and the burden of care placed upon their primary carer. It is, however, important to be aware that this limits our understanding of whether and why certain NPSs have a greater effect on care distress.

This study included 159 participants diagnosed with AD (n=97) and DLB (n=62). With regard to the two diagnostic groups, the number of predictors is fairly large compared to the number of observations. Hence, one strength of this study is that it uses PLS regression to study the associations between the 12 NPI items and the RSS total score. The PLS regression allows for multivariate modelling in samples with many variables relative to observations. To assess the robustness of the findings, all models were
cross-validated, excluding every fourth subject. Adjustments were made for carer status (spouse vs. adult child), number of children, and the patient’s gender, age, duration of symptoms prior to diagnosis, MMSE total score, and RDRS-2, z-score.

The majority of studies examining the association between individual NPSs and carer distress do not include samples from European countries. Hence, this study is an important contribution within this field. One limitation of the study is the cross-sectional study design, which limits the strength of the evidence for a causal inference.

5.0 CONCLUSION

The findings of this study identify apathy as the most important NPS contributing to carer distress. There appear to be few differences between the two diagnostic groups. However, compared to AD, the explained variance in the DLB group is higher. Furthermore, more NPSs were identified as important contributors to distress in carers of people diagnosed with DLB.

Dementia care focuses on enabling people with dementia to continue living in their own homes, and on supporting and improving the lives of people with dementia and their carers. The findings of this study help us better understand the complex and dynamic nature of the disease and how it affects the immediate family, highlight the need to address these symptoms in the early stages of the disease, and enable us to initiate tailored interventions.

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the Centre for Development of Institutional and Home Care Services (USHT), Sogn og Fjordane who all financially supported this study.

Last but not least, we sincerely thank all participating patients and their carers, and the dedicated work of the research staff in the DemWest study and Helse Vest.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Toril Marie Terum, John Roger Andersen and Ingelin Testad designed this study, conducted the statistical analysis and drafted the paper. Arvid Rongve, Ellen Svendsboe and Dag Aarsland critically revised the paper for important intellectual content. All authors approved the final version for submission. The manuscript contains original unpublished work and is not submitted for publication elsewhere.

DATA AVAILABILITY STATEMENT

The raw/processed data required to reproduce these findings cannot be shared at this time as the core research group is still actively analysing and reporting on the data, as per agreement with funder and ethical committee.

xi. References
REFERENCES


xii. Tables and footnotes

Table 1 Descriptive analysis of patient and carer variables

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<th>All (n=159)</th>
<th>AD (n=97)</th>
<th>DLB (n=62)</th>
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<td>23.7 (2.5)</td>
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<td>-0.19 (0.87)</td>
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<td>2.7 (1.9)</td>
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<td>NPI, total intensity mean (SD)</td>
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<td>RSS, total mean (SD)</td>
<td>16.7 (10.5)</td>
<td>15.6 (10.1)</td>
<td>18.4 (10.8)</td>
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Mean; SD, standard deviation; NPI, Neuropsychiatric Inventory; MMSE, Mini-Mental State Examination; RDRS-2, Rapid Disability Rating Scale-2; RSS Relative Stress Scale; †married or partner/divorced/widow(er) ‡prior to inclusion (years)
Table 2 The association between individual NPSs and carer distress, Spearman rank

<table>
<thead>
<tr>
<th>NPI total severity (f x i)</th>
<th>All</th>
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<tr>
<td>Sleep and nighttime disturbances</td>
<td>.254</td>
<td>.130</td>
<td>.366</td>
</tr>
<tr>
<td>Appetite and eating abnormalities</td>
<td>.270</td>
<td>.295</td>
<td>.260</td>
</tr>
</tbody>
</table>

A Spearman rank coefficient (rho) <0.1 was considered trivial, 0.1-0.29 was considered small, 0.3-0.49 was considered moderate and ≥0.5 was considered large.
Table 3 The association between carer distress (RSS) and NPSs (NPI items, fxi) in carers of people with AD and DLB, PLS regression analysis

<table>
<thead>
<tr>
<th>NPI items</th>
<th>All (n=159) Mean difference (CI)</th>
<th>AD (n=97) Mean difference (CI)</th>
<th>DLB (n=62) Mean difference (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusion</td>
<td>1.74 (1.48-2.0)*</td>
<td>0.78 (0.46-1.10)*</td>
<td>2.73 (2.42-3.04)*</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0.85 (0.50-1.20)*</td>
<td>0.16 (-0.01-0.33)</td>
<td>1.13 (0.69-1.57)*</td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>1.76 (1.44-2.08)*</td>
<td>0.70 (0.49-0.92)*</td>
<td>3.08 (2.40-3.76)*</td>
</tr>
<tr>
<td>Dysphoria/depression</td>
<td>1.79 (1.14-2.44)*</td>
<td>1.31 (0.52-2.11)*</td>
<td>2.41 (2.19-2.63)*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.52 (1.47-1.57)*</td>
<td>1.79 (1.25-2.33)*</td>
<td>1.00 (-0.03-2.03)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0.14 (0.08-0.20)*</td>
<td>0.29 (0.16-0.42)*</td>
<td>NA</td>
</tr>
<tr>
<td>Apathy/indifference</td>
<td>4.92 (4.45-5.39)*</td>
<td>4.14 (3.57-4.71)*</td>
<td>5.51 (5.05-5.97)*</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>1.23 (0.98-1.48)*</td>
<td>1.61 (1.22-2.0)*</td>
<td>0.67 (0.09-1.25)*</td>
</tr>
<tr>
<td>Irritability/lability</td>
<td>2.64 (2.15-3.13)*</td>
<td>2.78 (2.36-3.2)*</td>
<td>2.79 (2.26-3.32)*</td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>3.08 (2.33-3.83)*</td>
<td>2.32 (1.68-2.96)*</td>
<td>3.75 (3.11-4.39)*</td>
</tr>
<tr>
<td>Sleep and night-time disturbances</td>
<td>1.84 (1.78-1.90)*</td>
<td>1.08 (0.64-1.53)*</td>
<td>2.48 (2.31-2.65)*</td>
</tr>
<tr>
<td>Appetite and eating abnormalities</td>
<td>2.62 (2.34-2.90)*</td>
<td>2.12 (1.88-2.36)*</td>
<td>3.28 (2.68-3.88)*</td>
</tr>
</tbody>
</table>

Adjusted for socio-demographic variables (patient sex and age), family relations (spouse or adult children) and number of children, in addition to MMSE (Mini Mental Status Evaluation), duration of symptoms prior to diagnosis (years), and RDRS-2, z-scores (limitations in daily activity). * CIs not including the value of zero were considered statistically significant. The results in bold are considered clinically important (effect size ≥ 0.2). The explained variance in the three samples: All $r^2 = 41.5$; AD $r^2 = 37.3$; DLB $r^2 = 53.7$. NA: Estimates is not available due to low number of patients with score greater than or equal to 4 on the NPI.