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Differences in neuropsychiatric symptoms between nursing home residents with young-onset dementia and late-onset dementia

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\textbf{ABSTRACT}

\textbf{Objective:} The aims of the current study are (1) to explore the differences in neuropsychiatric symptoms (NPS) between young-onset dementia (YOD) and late-onset dementia (LOD), and (2) to investigate whether the possible differences can be attributed to differences in dementia subtype, gender, psychotropic drug use (PDU), or dementia severity.

\textbf{Method:} Three hundred and eighty-six nursing home (NH) residents with YOD and 350 with LOD were included. Multilevel modeling was used to compare NPS between the groups. Furthermore, dementia subtype, gender, PDU, and dementia severity were added to the crude multilevel models to investigate whether the possible differences in NPS could be attributed to these characteristics.

\textbf{Results:} Higher levels of apathy were found in NH residents with YOD. After the characteristics were added to the models, also lower levels of verbally agitated behaviors were found in YOD.

\textbf{Conclusion:} We recommend that special attention be paid to interventions targeting apathy in YOD. Although no differences in other NPS were found, the PDU rates were higher in YOD, suggesting that the threshold for the use of PDU in the management of NPS is lower. This underscores the need for appropriate attention to non-pharmacological interventions for the management of NPS in YOD.

\textbf{Introduction}

Young-onset dementia (YOD) is defined as dementia with symptom onset before the age of 65. In YOD, neuropsychiatric symptoms (NPS), such as apathy, agitation, aggression, and hallucinations, are highly prevalent (Mulders et al., 2016; Mulders, Zuidema, Verhey, & Koopmans, 2014). A recent Dutch study showed that 90% of nursing home (NH) residents with YOD had one or more NPS (Mulders et al., 2016). Previous research in late-onset dementia (LOD) has shown that NPS often result in negative health outcomes such as a loss of quality of life (QoL), increased cost of care, and high workload for the NH staff (Mulders et al., 2016; Murman et al., 2002; Wetzel, Zuidema, de Jonghe, Verhey, & Koopmans, 2010; Zwijsen et al., 2014).

People with YOD may have a higher risk of developing NPS compared to people with LOD. For example, in the YOD NH population more than half of the residents are male, compared to 20% of the residents in the LOD NH population (Mulders et al., 2014; Wetzel, Zuidema, Jansen, Verhey, & Koopmans, 2010). Extreme NPS seem especially likely to occur in men below the age of 70 years, as these residents are stronger and more vital (Brodaty, Draper, & Low, 2003). Additionally, people with YOD are cared for at home for a longer period than people with LOD (Bakker et al., 2012). Therefore, dementia might be more advanced in NH residents with YOD compared to LOD at the time of institutionalization. Increased severity of dementia has been linked to more NPS (such as agitation, aggression, and apathy) in NH residents with YOD and LOD (Mulders et al., 2016; Zuidema, de Jonghe, Verhey, & Koopmans, 2009). In addition, frontotemporal dementia (FTD) is more common in YOD; higher levels of agitation, disinhibition, and irritability are found in people with FTD than in those with AD, at least in the community-dwelling population (de Vugt et al., 2006; Harvey, Skeleton-Robinson, & Rossor, 2003; Mulders et al., 2014; Ratnavalli, Brayne, Dawson, & Hodges, 2002).

To develop effective treatment and further enhance care for NH residents with YOD, it is important to gain more insight into the differences in NPS between NH residents with YOD and LOD and the specific characteristics of YOD that might give rise to these possible differences. This insight supports health care professionals to direct treatment and provide care that meets the specific care needs of younger nursing home residents.

There have been a few studies that directly compared rates of NPS between YOD and LOD. However, these studies did not take into account the possible influence of psychotropic drugs, which are often used in the treatment of NPS. Higher rates of psychotropic drug use (PDU) are found in nursing home residents with YOD (87%) than in those with LOD (rang-
Methods

Subjects

This retrospective cross-sectional study is part of the Behavior and Evolution of Young-Onset Dementia part 2 (Beyond-II) study, a multicenter intervention study aimed at improving the management of neuropsychiatric symptoms in institutionalized people with YOD (N = 203 YOD NH residents) (van Duijn-van den Usselt et al., 2017). Additional baseline data were used from two other longitudinal studies: the Beyond-I study (N = 185 YOD NH residents) and the ‘Grip on challenging behavior study’ (N = 362 LOD NH residents) (Mulders et al., 2014; Zwijsen et al., 2011). These studies used the same assessment instruments as the Beyond-II study.

In the Netherlands, a large proportion of nursing homes have YOD special care units (YOD-SCUs) delivering specialized care for people with YOD. In the YOD group, only YOD-SCUs participated. Residents in the YOD group were included in this study if they had a dementia diagnosis with symptom onset before the age of 65 and had been residing in the YOD-SCU for at least one month before inclusion. The dementia diagnosis was established before inclusion in the study according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders, Text Revision (American Psychiatric Association, 2000). In the YOD group, internationally accepted criteria for diagnosing dementia subtypes were used (Gorno-Tempini et al., 2011; McKhann, 2006; McKhann, Folstein, Katzman, Price, & Standlan, 1984; Rascovsky et al., 2011; Roman et al., 1993). The diagnosis was retrieved from the medical file. The exclusion criteria were lack of informed consent, dementia caused by human immunodeficiency virus (HIV), traumatic brain injury, Down’s syndrome, Korsakov syndrome, Huntington’s disease, or alcohol-related dementia. In the Beyond-II study, informed consent was obtained from the residents’ legal representative and the informed consent rate was 88%. In the Beyond-I study, the residents or their legal representatives had the possibility to object to participation, resulting in a participation rate of 99%. Some YOD-SCUs participated in both the Beyond-I and Beyond-II studies. When residents had the same gender, date of birth, and diagnosis, one of them was randomly excluded from either the Beyond-I or Beyond-II sample used in this study to prevent duplicates.

In the LOD group, participating units for people with dementia (dementia special care units, DSCUs) were recruited from nursing homes that collaborate with the VU University Medical Center (Amsterdam) and the Radboud University Medical Center Nijmegen (Zwijsen et al., 2011). The same inclusion criteria (other than symptom onset before the age of 65) as in the YOD sample were applied in this study to obtain homogenous samples. Additionally, residents in the LOD group with an age of 70 years or younger were excluded to diminish the risk of YOD residents being part of the LOD group. Residents in the YOD group with an age of 70 years or older were not excluded, because they all had a symptom onset before the age of 65; therefore, there was no risk that they were part of the LOD group. In the LOD group, legal representatives of the residents had the possibility to object to participation, resulting in a participation rate of 99%.

Data collection and assessments

The Beyond-I and Beyond-II study protocols were approved by the Medical Ethics Committee region Arnhem/Nijmegen. The Grip on challenging behavior study protocol was approved by the Medical Ethics Review Committee of the VU University Medical Center. This research project was performed according to the principles of the Declaration of Helsinki (version November 2013, www.wma.net) and is in agreement with the law regarding medical-scientific research in humans (WMO). Trained researchers and research assistants collected the data through structured interviews with the nursing staff and from the resident’s medical files. Respondents were considered reliable if they were the vocational nurse specifically assigned to the resident or had regular contact with the resident in the past month.

Outcome measures

Neuropsychiatric symptoms (NPS) were assessed with the Dutch version of the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH). The NPI-NH has high interrater reliability and has been found to be a valid instrument for the assessment of a wide range of NPS in dementia (Kat et al., 2002; Kaufer et al., 2000). The NPI-NH consists of ten neuropsychiatric symptoms (delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria/elation, apathy/
indifference, disinhibition, irritability/lability, aberrant motor behavior) and two neurovegetative symptoms (nighttime behavior disturbances and appetite/eating disturbances). For each symptom, a screening question is used to determine whether the symptom is present. If the symptom is present, Frequency (F) and Severity (S) are rated on a four-point (ranging from 1 to 4) and three-point Likert-scale (ranging from 1 to 3), respectively, for each symptom. Scores for each symptom are calculated as F × S. We were interested in all NPS, including symptoms with a low frequency or severity and also when symptoms were not present. Therefore, we also included symptoms with a low frequency and severity in our analyses (instead of focusing on only clinical relevant behavior F × S ≥ 4) and chose to score F × S as 0 when a symptom was not present. A total score is calculated by summing the F × S scores (ranging from 0 to 144). Five NPI-NH factor scores were calculated by summing the symptom scores (F × S) included in each factor: (1) agitation/aggression, consisting of the agitation/agression, euphoria, disinhibition and irritability symptom scores; (2) depression, consisting of the depression and anxiety symptom scores; (3) psychosis, consisting of the delusion and hallucination symptom scores; (4) psychomotor agitation, consisting of the aberrant motor behavior and nighttime behavior symptom scores; and (5) apathy, consisting of the apathy and eating disorder symptom scores. These neuropsychiatric factors have been found to be relatively consistent in nursing home residents with dementia, across different stages of dementia (Zuidema, de Jonghe, Verhey, & Koopmans, 2007a).

The Dutch version of the Cohen-Mansfield Agitation Inventory (CMAI-D) was used to assess agitation and aggression (Cohen-Mansfield & Billig, 1986; de Jonghe & Kat, 1996). The CMAI has well-established validity and reliability and assesses 29 agitated or aggressive behaviors (de Jonghe & Kat, 1996). The frequency of each symptom is rated on a seven-point scale (range 1–7) ranging from never to several times an hour. The total CMAI score ranges from 29 to 203. We used CMAI factors based on a previous study in which three CMAI factors in a large NH sample were found: physically non-aggressive behaviors (range 7–49), physically aggressive behaviors (range 8–56), and verbally agitated behaviors (range 4–28) (Zuidema, de Jonghe, Verhey, & Koopmans, 2007b).

Other measures

Dementia severity was assessed with the Global Deterioration Scale (GDS) (Reisberg, Ferris, de Leon, & Crook, 1982). The GDS describes seven different stages of dementia on a seven-point scale (1–7), ranging from ‘subjectively and objectively normal cognition’ to ‘severe cognitive decline.’ The GDS has been validated against behavioral, neuro-anatomical and neurophysiological measures, for which significant correlations were found (Reisberg et al., 1982).

In addition, data on dementia subtype, age, gender and length of stay at the YOD-SCU or DSCU were collected from resident’s medical files. Psychotropic drug use (PDU) was derived from the nursing homes pharmacists’ electronic files and was classified according to the Anatomical Therapeutic Chemical (ATC) classification system (World Health Organisation Collaborating Centre for Drug Statistics Methodology, 1997) into antipsychotics, anxiolytics, hypnotics, antidepressants, anti-epileptics, anti-dementia drugs, and any psychotropic medication.

Statistical analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22. Before analysis, the data were checked for missing values. If the proportion of missing values in the CMAI total and factor scores was 20% or less, the missing items were replaced with the mean of the remaining items. It was not possible to use mean imputation on the NPI-NH factor scores, GDS, or PDU, as these scores consisted of less than 5 items, and even a single missing value would constitute more than 20% of the items. Therefore, residents with missing items on the NPI-NH symptom scores, GDS, and PDU were excluded from analysis.

Demographic variables for both groups (LOD and YOD) were described by calculating means or proportions. Multilevel modeling (random intercept linear mixed models) was used to compare the mean CMAI total, CMAI factor (physically aggressive behaviors, physically nonaggressive behaviors, verbally agitated behaviors), NPI-NH total, and NPI-NH factor (agitation, depression, psychosis, psychomotor agitation, apathy) scores as dependent variables, with group (YOD versus LOD) as an independent variable. Multilevel modeling allows correction for the clustering of residents in different health care organizations and therefore also for possible differences in cohorts as each health care organization was part of a specific cohort. Furthermore, to investigate whether the possible differences could be attributed to differences in dementia subtype (Alzheimer’s dementia, vascular dementia, or other subtypes including FTD), gender, psychotropic drug use (using dichotomous categories: present or absent), or dementia severity (GDS: mild, moderate, severe), we added these variables to the crude multilevel models.

Results

Resident characteristics

A total of 736 residents were included, of whom 386 residents had YOD and 350 had LOD. In the YOD group, the ratio of males to females was approximately equal (49.5% female), in contrast to the LOD group, in which a large majority of subjects were female (73.7%). In both the YOD and LOD group, most residents had Alzheimer’s dementia (43.3% in YOD and 48.6% in LOD). The second most prevalent dementia subtype was vascular dementia (35.1%) in the LOD group and frontotemporal dementia (FTD) (25.1%) in the YOD group. In both YOD and LOD, most residents had advanced dementia (62.7% in YOD and 76.8% in LOD). Furthermore, psychotropic drug use (PDU) seemed more common in the YOD group (76.9% in YOD versus 55.1% in LOD) (Table 1).

Differences in NPS between YOD and LOD

The unadjusted multilevel models showed that residents with YOD had higher mean NPI-NH apathy factor scores than residents with LOD (p < .001, B = 2.612) (Table 2, model 1). No other statistically significant differences were found on either the NPI-NH or the CMAI factor scores. After entry of PDU, gender, dementia severity and dementia subtype into the multilevel models, significant differences in both the apathy score (p < .001 B = 2.794) and the mean CMAI verbally agitated behaviors factor score were found (p = .023, B = −1.403) (Table 2, model 2). Residents with YOD had lower mean CMAI...
verbally agitated behaviors factor scores compared to residents with LOD.

**Discussion**

In this study, the differences in NPS between heterogeneous samples of nursing home (NH) residents with YOD and LOD were investigated. Higher levels of apathy were found in NH residents with YOD compared to LOD. Furthermore, after corrections were applied for gender, PDU, GDS, and dementia subtype, higher levels of verbally agitated behaviors were found in LOD than in YOD.

In line with our findings, Cohen-Mansfield and Libin (2005) found that higher levels of verbal agitation were associated with older age. An explanation could be that with advanced age, more physical impairments are likely to occur, hindering activities in daily life. This likely results in feelings of frustration and a consequent increase in verbally agitated behaviors in response to the high levels of physical impairment. Higher rates of verbal aggression in LOD were only found in our study after taking into account the influence of possible confounders (gender, PDU, dementia subtype, dementia severity).

An explanation could be the higher prevalence of residents with less advanced dementia in the YOD group, as verbally agitated behavior is less prevalent in advanced dementia (Mulders et al., 2016). Furthermore, we did not find differences in the CMAI total or other factor scores, which supports the notion that agitation is a multidimensional construct consisting of different aspects that should be taken into account in further research in order to prevent loss of information.

### Table 1. Demographic and clinical characteristics of the YOD and LOD group.

<table>
<thead>
<tr>
<th></th>
<th>YOD</th>
<th>LOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resident age at inclusion Mean (SD)</td>
<td>62.4 (6.9)</td>
<td>84.43 (6.3)</td>
</tr>
<tr>
<td>(Range)</td>
<td>(39–78)</td>
<td>(71–102)</td>
</tr>
<tr>
<td>Resident gender Male n (%)</td>
<td>195 (50.5)</td>
<td>92 (26.3)</td>
</tr>
<tr>
<td>Dementia severity (GDS) n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild (2,3,4)</td>
<td>62 (16.1)</td>
<td>13 (3.7)</td>
</tr>
<tr>
<td>Moderate (5)</td>
<td>81 (21.0)</td>
<td>66 (18.9)</td>
</tr>
<tr>
<td>Severe (6,7)</td>
<td>242 (62.7)</td>
<td>267 (76.3)</td>
</tr>
<tr>
<td>Dementia subtype     n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>167 (43.3)</td>
<td>170 (48.6)</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>56 (14.5)</td>
<td>123 (35.1)</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>97 (25.1)</td>
<td>7 (2.0)</td>
</tr>
<tr>
<td>Other</td>
<td>66 (17.1)</td>
<td>50 (14.3)</td>
</tr>
<tr>
<td>PDU (at least one) n (%)</td>
<td>297 (76.9)</td>
<td>193 (55.1)</td>
</tr>
<tr>
<td>CMAI total score Mean (SD)</td>
<td>49.60 (18.37)</td>
<td>50.55 (18.21)</td>
</tr>
<tr>
<td>CMAI factor scores Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physically aggressive behaviors</td>
<td>–1.316</td>
<td>.900</td>
</tr>
<tr>
<td>Physically nonaggressive behaviors</td>
<td>–2.366</td>
<td>.766</td>
</tr>
<tr>
<td>Verbally agitated behaviors</td>
<td>–1.833</td>
<td>1.361</td>
</tr>
<tr>
<td>NPI-NH total score Mean (SD)</td>
<td>22.84 (17.77)</td>
<td>21.22 (17.80)</td>
</tr>
<tr>
<td>NPI-NH factor scores Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>5.95 (5.97)</td>
<td>3.46 (4.96)</td>
</tr>
</tbody>
</table>

* SD = standard deviation.
  b GDS = Global Deterioration Scale.
  c 1 missing in YOD group, 4 missing in LOD group.
  d PDU = Psychotropic drug use.
  e 8 missing in LOD group.
  f CMAI = Cohen-Mansfield Agitation Inventory.
  g 1 missing in YOD group, 6 missing in LOD group.
  h NPI-NH = Neuropsychiatric Inventory-nursing home version.

### Table 2. Multilevel models with differences between groups (YOD/LOD) on NPS with no correction (Model 1), and correction for gender, PDU, dementia severity, and dementia subtype (Model 2).

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>95% CI</th>
<th>Model 2</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>P</td>
<td>Lower bound</td>
<td>Upper bound</td>
</tr>
<tr>
<td>CMAI factor scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physically aggressive behaviors</td>
<td>–2.366</td>
<td>.766</td>
<td>–1.833</td>
<td>1.361</td>
</tr>
<tr>
<td>Physically nonaggressive behaviors</td>
<td>.761</td>
<td>.440</td>
<td>–1.22</td>
<td>2.743</td>
</tr>
<tr>
<td>Verbally agitated behaviors</td>
<td>–827</td>
<td>.115</td>
<td>–1.865</td>
<td>.211</td>
</tr>
<tr>
<td>NPI-NH total score</td>
<td>2.047</td>
<td>.342</td>
<td>–2.271</td>
<td>6.364</td>
</tr>
<tr>
<td>NPI-NH factor scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation/aggression</td>
<td>.061</td>
<td>.943</td>
<td>–1.658</td>
<td>1.780</td>
</tr>
<tr>
<td>Depression</td>
<td>-.972</td>
<td>.117</td>
<td>–2.201</td>
<td>.258</td>
</tr>
<tr>
<td>Psychosis</td>
<td>–.419</td>
<td>.387</td>
<td>–1.393</td>
<td>.555</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>.988</td>
<td>.143</td>
<td>–3.49</td>
<td>2.324</td>
</tr>
<tr>
<td>Apathy</td>
<td>2.612</td>
<td>.000**</td>
<td>1.251</td>
<td>3.972</td>
</tr>
</tbody>
</table>

Note: CMAI = Cohen-Mansfield Agitation Inventory; NPI-NH = Neuropsychiatric Inventory-nursing home version.

* PDU = Psychotropic drug use.
  ** .001.
We found higher levels of apathy in NH residents with YOD than in those with LOD. This might be partly explained by the high prevalence in YOD of FTD, in which higher rates of apathy have been found compared to AD (de Vugt et al., 2006). However, these differences were still strongly significant after dementia subtype was corrected for, suggesting that higher rates of apathy exist in NH residents with YOD, irrespectively of dementia subtype. Another explanation might be that the frequency and severity of the NPS (including apathy) were rated by nursing staff members. Nurses might observe apathy in LOD less often because they might perceive the inactivity as part of older age. Although apathy is often not experienced as disturbing by nursing staff, the higher rates found in NH residents with YOD still raise concern because of the strong negative association between apathy and quality of life in NH residents with YOD (Appelhof et al., 2017; Zwijsen et al., 2014). Therefore, special attention needs to be directed to interventions targeting apathy in NH residents with YOD.

Although we did not find any additional differences in NPS between the two groups, the PDU rates in YOD seemed higher than those of the LOD group (77% in YOD versus 55% in LOD). This suggests that the threshold for the use of psychotropic drugs in the management of NPS is lower in YOD. An explanation for the higher levels of PDU in YOD could be that the same behaviors in younger individuals are perceived as more threatening or distressing by the nursing staff. Consequently, physicians might be more inclined to prescribe psychotropic drugs in YOD than in LOD (Zuidema, de Jonghe, Verhey, & Koopmans, 2011). In future studies, further testing is needed on differences in distress experienced by YOD and LOD nursing staff in response to residents’ NPS.

Several limitations of this study should be considered. We chose to use factor scores instead of symptom scores on the NPI-NH in order to reduce the number of tests in the analyses and thereby diminish the risk of a Type 1 error. Additionally, we used factor scores of the CMAI instead of the total score to provide clarity regarding the possible differences in specific aspects of aggression and thereby prevent a loss of information. However, the factor structure of both the NPI-NH and CMAI was evaluated in older NH residents with dementia and has not yet been established in YOD (Zuidema et al., 2007a, 2007b). Furthermore, part of the YOD group was drawn from an older cohort. There is a possibility that there are differences within these cohorts (for example, due to changes in the health care system), for which we partly corrected with the use of the multi-level models. At last, we cannot confirm that the international accepted criteria for diagnosing dementia subtypes were used in all residents part of the LOD group.

**Conclusion**

This study provides important insight into the differences in NPS between NH residents with YOD and LOD. The higher rates of apathy found in NH residents with YOD raise concern because of the strong negative association between apathy and quality of life (Appelhof et al., 2017). Therefore, in order to improve care, we recommend that special attention be paid to interventions targeting apathy in NH residents with YOD. For example, especially for nursing home residents with YOD, it might be important to provide a stimulating socio-therapeutic environment and approach to facilitate social engagement and activities of daily living. Further research is needed to gain insight into possible biological or psychosocial influences underlying the differences in apathy between nursing home residents with YOD and LOD.

Although NH residents with YOD were no more likely than those with LOD to develop NPS other than apathy, residents with YOD still received psychotropic drugs more often in the treatment of NPS. This underscores the need for appropriate attention to effective non-pharmacological interventions for the management of NPS in YOD.

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**Disclosure statement**

No potential conflict of interest was reported by the authors.

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