

# The Progression of Dementia and Cognitive Decline in a Dutch 2-Year Cohort Study of People with Young-Onset Dementia

## Citation for published version (APA):

Gerritsen, A. A. J., Bakker, C., Verhey, F. R. J., Bor, H., Pijnenburg, Y. A. L., de Vugt, M. E., & Koopmans, R. T. C. M. (2018). The Progression of Dementia and Cognitive Decline in a Dutch 2-Year Cohort Study of People with Young-Onset Dementia. *Journal of Alzheimer's Disease*, 63(1), 343-351. <https://doi.org/10.3233/JAD-170859>

## Document status and date:

Published: 01/01/2018

## DOI:

[10.3233/JAD-170859](https://doi.org/10.3233/JAD-170859)

## Document Version:

Publisher's PDF, also known as Version of record

## Document license:

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# The Progression of Dementia and Cognitive Decline in a Dutch 2-Year Cohort Study of People with Young-Onset Dementia

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Accepted 31 January 2018

## Abstract.

**Background:** The progression of dementia in people with young-onset dementia (YOD) is relatively unknown.

**Objective:** To investigate the progression of dementia and cognitive decline in the three most common subtypes in YOD and to explore which factors are associated with this course.

**Methods:** The course of dementia was examined in 198 people with YOD. The primary outcomes were cognitive function, as assessed by the Mini-Mental State Examination (MMSE) and dementia severity, as assessed by the Global Deterioration Scale (GDS). Mixed-model analyses were used to explore factors associated with the course of dementia of the diagnostic sub-types.

**Results:** The mean overall two-year progression of dementia severity was 0.9 GDS points, this was a statistically significant change ( $p = 0.012$ ) and was not significantly different for the three dementia subtypes. The mean overall two-year decline in cognitive function was 1.6 points on the MMSE. The differences in cognitive decline were statistically significant ( $p = 0.046$ ) among the three diagnosis groups, AD participants showed the greatest decline, of 2.3 points. In addition to lower education ( $p = 0.010$ ), higher scores on the Neuropsychiatric Inventory (NPI) sub-syndromes psychosis ( $p < 0.001$ ) and hyperactivity ( $p = 0.002$ ) were associated with higher rates of cognitive decline. In contrast, higher scores on the NPI affect cluster were associated with lower levels of cognitive decline ( $p < 0.001$ ).

**Conclusion:** Different YOD subtypes show different rates of decline in cognitive functioning, and this decline seems less progressive compared to those observed in studies in late-onset AD. Further research is needed to evaluate whether managing neuropsychiatric symptoms can positively influence the decline of cognitive function.

Keywords: Cognitive decline, progression of dementia, young onset dementia

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## INTRODUCTION

The progression of dementia severity and cognitive decline are not well characterized in the three most common subtypes of young-onset dementia (YOD), which include Alzheimer's dementia (AD), vascular dementia (VaD) including mixed AD/VaD, and frontotemporal dementia (FTD). People with YOD, defined as dementia with symptom onset prior to age 65 years, and their families face an uncertain future because the progression of dementia in this group appears to be highly variable [1]. Due to this variability, clinicians experience difficulties with informing YOD families and with tailoring advanced care plans.

The progression of dementia severity involves increasing difficulties in cognition and concentration, work performance, social functioning, daily living activities, and psychomotor skills. The rate at which dementia progresses in YOD is unclear; however, some studies suggest a faster decline in younger versus older persons with AD [1, 2]. It remains uncertain if the hypothesis of faster decline is applicable for different subtypes of YOD. This information will aid the support of young people with dementia and their families and allow for advanced care planning.

Cognitive function is the main feature in dementia, and disease progression also reflects decline in cognitive function. The decline shows different patterns in the subtypes of YOD [3]. Factors associated with a more rapidly progressive course of dementia are: presence of neuropsychiatric symptoms (NPS), younger age of onset, presence of APOE  $\epsilon$ 4, higher education, higher Mini-Mental Stage Examination (MMSE) change prior to study inclusion and the use of antipsychotic medication [2, 4–8]. Items in the NPS that are associated with a more rapidly course of dementia are psychosis and agitation [9].

Studies on the course of cognitive functioning in older people with AD have shown a decline of 1–6 points on the MMSE per year, with a mean of approximately 3 points per year [10–12]. In YOD, a decline of 0.8–8.1 points per year has been found, mostly for people with AD [1, 3, 13–15]. However, the findings of cognitive decline in persons with young-onset AD (YO-AD; AD symptom onset prior to age 65 years) are not entirely consistent. There is little evidence that subtypes of YOD have different patterns of cognitive decline [3]. Most studies have found a more rapid decline in persons with YO-AD compared to those who have late-onset AD (LO-AD, AD symptom onset at or after age 65 years); however, one study found no difference [1, 13–16].

Knowledge about factors associated with dementia-related cognitive decline is almost exclusively derived from research in elderly populations [5, 7, 17]. Factors associated with a more progressive cognitive decline in people with late onset dementia are: the use of antipsychotic drugs, the presence of NPS, and a high rate of cognitive decline before inclusion in the study [5, 7, 11, 18–20]. In people with AD, other factors associated with rapid cognitive decline include the presence of genetic factors, such as one or more APOE  $\epsilon$ 4 alleles; cerebrospinal fluid biomarkers; a high total (phosphorylated) tau, low amyloid- $\beta$  1-42 or a high ratio of total tau to amyloid- $\beta$  1-42; early motor signs; younger age; diabetes mellitus; and (cerebro) vascular pathology [1–3, 10, 21, 22].

The use of antipsychotic drugs, frequently prescribed in people with YOD, is negatively associated with cognitive function [23]. Antipsychotic drugs block receptors for acetylcholine, muscarine, D2, 5HT2, or histamine. Blocking the acetylcholine receptor may cause a negative effect on cognitive function, given that an acetylcholine deficit is one of the causes of AD [12, 19, 24]. Blocking muscarine receptors can directly cause cognitive decline by forming amyloid- $\beta$  proteins (A $\beta$ ), which are components of neuritic plaques [18, 25]. However, studies on the relationship between antipsychotic drug use (APDU) and cognitive decline in LO-AD are conflicting, and the effect of APDU in YOD is uncertain [19, 24, 26]. In YOD antipsychotic drugs are frequently prescribed, therefore we expect a high risk of negative effects on cognitive functioning and the progression of the dementia [11].

NPS are common in persons with dementia, but the question remains whether these symptoms are a cause, an effect or only correlated to the decline in cognitive function. Some have suggested that chronic stress may contribute to the development of disorders such as dementia [27]. Also the natural course in elderly persons with AD may be affected due to NPS [2]. In YOD, where maybe as a result of a chronic stress condition, NPS frequently occur, there might be also a relationship with the decline of cognitive function.

Identifying younger individuals with dementia who are prone to a more rapidly progressive disease course might aid in informing them and their caregivers. The aim of this study is to investigate the progression of dementia and decline in cognitive function in people with YOD and to explore whether there is a relationship with dementia subtype,

the amount of neuropsychiatric symptoms and use of antipsychotic drugs.

## METHODS

### *Study design and selection of participants*

This longitudinal study is based on data from 215 YOD participants in the Needs in Young-onset Dementia (NeedYD) study, the design of which has been published previously [28]. Persons with dementia symptom onset prior to age 65 were included (age at inclusion could be over age 65). Participants were recruited from 1) the memory clinics of three Dutch Alzheimer centers located in Amsterdam, Nijmegen and Maastricht, 2) memory clinics of general hospitals, 3) mental health services in the south of the Netherlands, and 4) YOD specialized daycare facilities. At time of study-including, all of the participants were community dwelling. We selected only participants with the three most common subtypes of YOD: AD, VaD, and FTD.

### *Data collection and assessments*

The Medical Ethics Committee of the University Medical Center Maastricht and the local ethics committees of the participating institutions approved the protocol of the NeedYD study. The research project was performed according to the principles of the Declaration of Helsinki (version January 2004; <http://www.wma.net>) and in agreement with Dutch law regarding medical-scientific research in humans (WMO). Written informed consent was obtained from patients or their legal representatives prior to the study. Data collection started in 2007 and 2008 (baseline), followed by assessments every 6 months through 2 years of follow up.

### *Primary outcomes*

*Progression of dementia* was assessed via interviews using the Global Deterioration Scale (GDS), which rates dementia severity from no dementia (GDS stage 1) to advanced dementia (GDS stage 7) [29]. In addition to cognitive function, the scale considers functioning in daily living and behavior [29]. The GDS has been validated against behavioral, neuroanatomic, and neurophysiologic measures, with significant correlations found in each area.

*Cognitive function* was assessed using the MMSE, which ranges from 0–30 points. The MMSE is a

reliable and valid test of global cognitive function [30]. Lower scores indicate more severe cognitive impairment (0–17 severe, 18–23 mild and 24–30 no cognitive impairment) [31].

### *Covariates*

Dementia diagnoses were made according to the Diagnostic and Statistical manual of mental Disorders [32]. *The dementia subtypes* of AD (probable and possible), VaD and FTD were made according to the McKhann criteria, the ninds-airen criteria and the consensus on clinical dementia subtypes, respectively [33–35].

APDU data was retrieved from patients' medical charts and classified using the Anatomical Therapeutic Chemical Classification System [36]. At each assessment, we categorized the use of antipsychotics (psycholeptic categories ATC N05AA-N05AG) dichotomously (present or absent). Medication 'as needed' was not included in this study.

*NPS* were assessed with the Dutch version of the Neuropsychiatric Inventory (NPI) [37]. This instrument has a high inter-observer reliability and is a valid rating scale for neuropsychiatric symptoms in dementia [38]. The frequency (0–4) and severity scores (1–3) of the NPI items were multiplied, resulting in a score ranging from 0–12. We used the score of four neuropsychiatric sub-syndromes based on a study by the European Alzheimer Disease Consortium [39]. These sub-syndromes are psychosis (summed scores of delusions, hallucinations and nighttime behavioral disturbances; range 0–36), hyperactivity (summed scores of agitation, euphoria, disinhibition, irritability and aberrant motor behavior; range 0–60), affective (summed scores of depression and anxiety; range 0–24) and apathy (summed scores of apathy, sleep- and nighttime disturbances and appetite/eating disorder; range 0–36).

### *Demographic characteristics*

*Gender, date of birth and education* were collected through structured interviews with primary caregivers. *Disease duration* was calculated by subtracting the year of symptom onset from the year of baseline assessment. *Education* was collected and coded into 8 categories, ranging from 1 (elementary school) to 8 (university). The education categories were divided into "low" (categories 1 and 2), "middle" (categories 3, 4 and 5) and "high" (categories 6, 7 and 8).

### Statistical analysis

The analyses were performed using the Statistical Package for Social Sciences (SPSS), version 22.0.0.1 (2013). Proportions or means were calculated to describe participants' characteristics. Differences between groups (AD, VaD, FTD) were assessed using Analysis of Variance (ANOVA) with Bonferroni *post hoc* analysis, or Pearson Chi-Square ( $\chi^2$ ). Course analyses of MMSE and GDS were performed with a random intercept mixed-model analysis, which controls for the effect of repeated measures of the same person. All factors and interaction terms with measurement (time) were included at the start of the mixed model. In the final analysis all factors and the statistically significant interaction terms were used. GDS and MMSE were used as a linear outcome in the mixed-model analysis.

MMSE scores were analyzed with mixed-model analyses which can adequately deal with missing values. The missing values were mostly due to the result of non-cooperativeness, agitation, apathy, aphasia or difficulty understanding the items of the MMSE. Missing scores were imputed using the scores obtained before and after the missing value (when available) or using the individual course to impute to a maximum of two missing values of each individual. In total, 54 (5.5%) missing MMSE scores of a total of 990 measurements were imputed.

For all analyses, a *p*-value < 0.05 was the threshold for statistical significance.

## RESULTS

We included 198 of the 215 NeedYD study participants, including 122 people with AD, 34 with VaD and 42 with FTD [28]. The mean age at inclusion was 60.9 years, and the mean disease duration was 7.2 years (Table 1). The male to female ratio in all groups was approximately equal, with slightly more males (55%) in the AD group. Baseline assessment showed that dementia severity among participants with AD was more advanced compared with that among participants with VaD and FTD. In addition, participants with VaD and FTD had statistically significantly higher MMSE scores (+6.3 and +6.4 points, respectively) at baseline than did AD participants. Participants in the three groups did not differ in their level of education or APDU.

Table 1  
Baseline characteristics of the study population

|                                    | Total                | Alzheimer's dementia | Vascular dementia <sup>(1)</sup> | Frontotemporal dementia | Test, <i>p</i> -value <sup>(2)</sup> |
|------------------------------------|----------------------|----------------------|----------------------------------|-------------------------|--------------------------------------|
| Participants, N                    | 198                  | 122                  | 34                               | 42                      |                                      |
| Male, N (%)                        | 105 (53.0)           | 67 (54.9)            | 17 (50)                          | 21 (50)                 | $\chi^2$ (2) 0.455 <i>p</i> = 0.797  |
| Mean age baseline (SD) [range]     | 60.9 (5.6) [43–74]   | 60.9 (5.0) [48–73]   | 60.7 (5.3) [46–69]               | 61.0 (7.2) [43–74]      | F (df2, 2.525) <i>p</i> = 0.979      |
| Disease duration, y (SD) [range] N | 7.2 (4.2) [1–30] 193 | 6.7 (3.7) [1–21] 118 | 7.9 (5.2) [2–30] 34              | 8.2 (4.5) [1–24] 41     | F (df2, 2.525) <i>p</i> = 0.083      |
| MMSE baseline (SD) N               | 20.2 (7.8) 153       | 17.6 (7.2) 90        | 23.9 (5.3) 30                    | 24.0 (8.4) 33           | F (df2, 57.809) <i>p</i> < 0.001     |
| GDS baseline (SD) N                | 4.4 (1.1) 187        | 4.7 (1.0) 118        | 3.9 (1.0) 31                     | 4.1 (1.3) 38            | F (df2, 9.437) <i>p</i> < 0.001      |
| Low/mid/high education % N         | 45.6/32.1/22.3 193   | 47.5/30.0/22.5 120   | 37.5/40.6/21.9 32                | 46.3/31.7/22.0 41       | $\chi^2$ (4) 1.458 <i>p</i> = 0.834  |
| Antipsychotic use % at baseline N  | 21.3 197             | 18.0 122             | 23.5 34                          | 29.3 41                 | $\chi^2$ (2) 2.429 <i>p</i> = 0.297  |

MMSE, Mini-Mental State Examination; GDS, Global Deterioration Scale. (1) Including mixed vascular/Alzheimer's dementia. (2) Comparison among Alzheimer's dementia, vascular dementia and frontotemporal dementia. Tests:  $\chi^2$ , Pearson Chi-Square; F, F-test (ANOVA).

Table 2  
Global Deterioration Scale and Mini-Mental State Examination findings

| Diagnosis [N]      | All [198]        | Alzheimer's dementia [122] | Vascular dementia <sup>(1)</sup> [34] | Frontotemporal dementia [42] |
|--------------------|------------------|----------------------------|---------------------------------------|------------------------------|
| Mean MMSE (SD) [N] |                  |                            |                                       |                              |
| Baseline           | 20.2 (7.8) [153] | 17.6 (7.2) [90]            | 23.9 (5.3) [30]                       | 24.0 (8.4) [33]              |
| 0.5 y              | 19.9 (8.0) [135] | 17.2 (7.8) [76]            | 22.6 (6.4) [30]                       | 24.1 (7.4) [29]              |
| 1 y                | 19.2 (8.5) [133] | 16.2 (7.9) [75]            | 23.1 (6.6) [30]                       | 23.3 (8.6) [28]              |
| 1.5 y              | 18.2 (9.0) [131] | 15.2 (8.3) [73]            | 21.9 (7.1) [30]                       | 22.1 (10.1) [28]             |
| 2 y                | 18.6 (9.4) [112] | 15.3 (8.7) [59]            | 22.5 (6.5) [26]                       | 22.3 (10.7) [27]             |
| GDS (SD) [N]       |                  |                            |                                       |                              |
| Baseline           | 4.4 (1.1) [187]  | 4.7 (1.0) [118]            | 3.9 (1.0) [31]                        | 4.1 (1.3) [38]               |
| 0.5 y              | 4.8 (1.1) [180]  | 5.1 (1.0) [111]            | 4.4 (0.9) [32]                        | 4.5 (1.3) [37]               |
| 1 y                | 5.1 (1.1) [176]  | 5.3 (1.0) [112]            | 4.6 (0.9) [31]                        | 4.6 (1.3) [33]               |
| 1.5 y              | 5.2 (1.1) [165]  | 5.4 (1.1) [102]            | 4.5 (1.1) [31]                        | 4.9 (1.1) [32]               |
| 2 y                | 5.3 (1.2) [149]  | 5.6 (1.1) [90]             | 4.7 (1.0) [24]                        | 4.7 (1.4) [35]               |

MMSE, Mini-Mental State Examination; GDS, Global Deterioration Scale. (1) Including mixed vascular/Alzheimer's dementia.

### Progression of dementia and decline in cognitive function

The mean overall two-year progression of dementia severity was 0.9 GDS points, a statistically significant change ( $p=0.012$ ). The baseline difference in dementia severity (VaD participants  $-0.8$  and FTD participants  $-0.6$  compared with AD participants) was statistically significant and was present (Bonferroni 45.41,  $df=2$ ,  $p<0.001$ ) during the two-year course (Table 2). A mixed-model analysis using dementia severity as the dependent variable showed a statistically significant change over the two years. However, we found no significant interaction between diagnosis and time, indicating that the progression of dementia severity was similar for the three dementia subtypes.

The mean overall two-year decline in cognitive function was 1.6 points on the MMSE ( $p=0.046$ ). Participants with AD showed the greatest decline of 2.3 points after two years (Table 2). A mixed-model analysis with cognitive function as the dependent variable showed a significant interaction between diagnosis and time (Table 3), indicating that the decline in cognitive function differs among the three diagnosis groups.

### Factors associated with the progression of dementia and cognitive decline

A mixed-model analysis revealed a significant relationship between dementia severity and age, with younger participants showing a more rapid decline (Table 3). Neither dementia severity nor the progression of dementia severity was related to gender, APDU, disease duration or any of the NPI sub-syndromes.

In addition, the analysis showed a significant association between decline in cognitive function and the three NPI sub-syndromes (Table 3). Higher psychosis and hyperactivity NPI scores were related to a steeper cognitive decline ( $p<0.001$  and  $p=0.002$  resp.), whereas higher affective NPI scores were associated with a slower course ( $p<0.001$ ). Additionally, participants who had low education levels showed more rapid cognitive decline than did participants who had higher levels of education ( $p=0.010$ ). Furthermore, diagnosis was associated with cognitive decline, with a more rapid decline observed in AD participants. No significant relationship was found between cognitive decline and gender, APDU, age or disease duration.

## DISCUSSION

To our knowledge, this is the first longitudinal study to describe and compare the progression of dementia and the decline in cognitive function in people with the three most common subtypes of YOD. In addition, the association of NPI sub-syndrome scores or APDU concerning the course of dementia was examined. The results showed no relationship between dementia subtype and dementia progression. However, participants with AD had a more progressive decline in cognitive function compared with those with VaD or FTD. The decline in cognitive function was negatively associated with both the psychosis NPI sub-syndrome score and the hyperactivity score, and it was positively associated with the affective sub-syndrome score. We suggest that differences in cognitive decline compared to disease progression emphasize the distinction between cognitive functioning and performing self-care tasks. We did not

Table 3  
Mixed Model Analysis

|  | Mini Mental State Examination         |  | Global Deterioration Scale            |  |
|--|---------------------------------------|--|---------------------------------------|--|
|  | Estimates [95% CI] ( <i>p</i> -value) | Overall <i>p</i> -value <sup>(4)</sup> | Estimates [95% CI] ( <i>p</i> -value) | Overall <i>p</i> -value <sup>(4)</sup> |
| Intercept                              | 11.07 [-14.27 – 36.42]                | 0.386                                  | 10.34 [6.54 – 14.15]                  | <0.001                                 |
| Time                                   |                                       | 0.059                                  |                                       | 0.012                                  |
| Baseline                               | -5.77 [-13.76 – 2.21] (0.151)         |  | -7.32 [-11.55 – -3.09] (0.001)        |  |
| 0.5 y                                  | 0.06 [-7.27 – 7.40] (0.986)           |  | -5.97 [-9.80 – -2.13] (0.003)         |  |
| 1 y                                    | -2.88 [-10.98 – 5.22] (0.475)         |  | -5.15 [-9.23 – -1.07] (0.014)         |  |
| 1.5 y                                  | -1.17 [-7.26 – 4.93] (0.699)          |  | -4.37 [-7.84 – -0.89] (0.014)         |  |
| 2 y <sup>(1)</sup>                     |                                       |  |                                       |  |
| Sex, male                              | 0.92 [-3.49 – 5.33]                   | 0.678                                  | 0.02 [-0.45 – 0.49]                   | 0.943                                  |
| Diagnosis <sup>(2)</sup>               |                                       | 0.053                                  |                                       | 0.018                                  |
| Alzheimer's dementia                   | -6.61 [-14.22 – 1.01] (0.088)         |  | 0.50 [-0.06 – 1.07] (0.078)           |  |
| Vascular dementia                      | -3.70 [-11.27 – 3.87] (0.334)         |  | 0.31 [-0.95 – 0.33] (0.334)           |  |
| Frontotemporal dementia <sup>(1)</sup> |                                       |  |                                       |  |
| Antipsychotic use                      | 0.71 [-1.38 – 2.80]                   | 0.494                                  | 0.07 [-0.22 – 0.36]                   | 0.620                                  |
| Age at baseline <sup>(2)</sup>         | 0.20 [-0.19 – 0.58]                   | 0.310                                  | 0.09 [-0.15 – -0.03]                  | 0.003                                  |
| Disease duration at baseline           | -0.16 [-0.71 – 0.40]                  | 0.575                                  | 0.01 [-0.04 – 0.07]                   | 0.620                                  |
| Education <sup>(3)</sup>               | -5.90 [-12.98 – 1.17] (0.101) /       | 0.434                                  | 0.22 [-0.8 – 0.82] (0.464) /          | 0.741                                  |
| Low/Middle/High <sup>(1)</sup>         | 0.40 [-7.06 – 7.86] (0.916)           |  | 0.22 [-0.44 – 0.89] (0.507)           |  |
| NPI psychosis <sup>(3)</sup>           | -0.37 [-0.70 – -0.03]                 | 0.032                                  | -0.01 [-0.03 – 0.02]                  | 0.534                                  |
| NPI hyperactivity <sup>(3)</sup>       | -0.30 [-0.66 – 0.05]                  | 0.090                                  | 0.01 [-0.01 – 0.02]                   | 0.238                                  |
| NPI affective <sup>(3)</sup>           | 1.13 [0.40 – 1.85]                    | 0.003                                  | -0.02 [-0.05 – 0.01]                  | 0.167                                  |
| NPI apathy                             | 0.14 [0.001 – 0.27]                   | 0.048                                  | -0.01 [-0.03 – 0.01]                  | 0.433                                  |

NPI, Neuropsychiatric Inventory. (1) Reference. (2) Remained in the final model of interaction with time of the Global deterioration scale. (3) Remained in the final model of interaction with time of the Mini mental state examination model. (4) 2-year value.

find any relationship between decline in cognitive function and disease severity or APDU. Younger age at baseline and low levels of education were associated with a more rapidly progressive course of dementia.

We found no YOD studies to compare our findings on the progression of dementia, but the results are in line with findings on LO-AD, where a younger age is related to a more progressive course [1, 2, 8, 40]. In contrast to our findings on dementia severity, we found an association between YOD subtypes and decline in cognitive function (Table 3). This is in line with the study of Smits, et al. [3], who found that the annual decline in MMSE scores differed among dementia subtypes, although not exclusively YOD. The AD participants in that study also showed a faster decline in their MMSE scores compared with VaD participants. However, participants with the behavioral variant of FTD had the most progressive decline, which is in line with an earlier study on FTD subtypes by Brodaty et al. [41].

The maximum two-year decline in cognitive function that we found, 2.3 points on the MMSE in AD participants, suggests that the hypothesis of a faster cognitive decline in persons with YO-AD, compared with LO-AD, is not supported. The 2.3 decline is less than found in a meta-analysis of 3.492 AD participants, where a mean decline of 3.3 MMSE points per

year was reported [10]. One study exclusively on YO-AD showed a 6-month decline of 0.5 MMSE points, which is in line with our findings [41].

The relationship that we found between the NPI sub-syndrome psychosis score and a more progressive cognitive decline is supported by studies with persons suffering from AD [5, 7, 12]. We found no studies concerning the possible relationship between the NPI hyperactivity sub-syndrome score and a more progressive decline in cognitive function. Psychotic symptoms and hyperactivity may be considered chronic stress conditions, which might offer an explanation for our findings. It has been suggested that chronic stress conditions cause dysfunction of the hippocampus and prefrontal cortex by structural degeneration and can lead to dementia [27]. Some studies have suggested a correlation between depression, part of the affective NPI sub-syndrome, and AD [42, 43]. However, these studies also suggested that some neuropathological brain changes, which are correlated with depression, can lead to AD [44]. On the contrary, we found a less progressive decline in cognitive function in participants with higher scores on the affective NPI sub-syndrome. It is unlikely that medication, such as selective serotonin reuptake inhibitors, frequently prescribed for mood disorders in persons with dementia, contribute to this less progressive cognitive decline. A review on this topic

showed no effect on cognition between placebo and treated groups [45].

Contrary to our expectations, APDU was not a significant factor in either the progression of dementia or cognitive decline, as found in other studies concerning elderly persons with dementia [19, 46]. In this explorative study, we did not find an explanation for this finding, but younger persons may experience fewer side effects from these drugs. For extrapyramidal side effects, an age-related effect has been found, but age-related effects on the progression of dementia or cognitive decline remain to be explained [47]. Furthermore, not all studies reported negative effects of APDU on the progression of cognitive decline in LO-AD [26].

Low education was associated with a faster decline in cognition. We know that low education is a risk factor in AD, but our result contrasts that of Rasmusson et al., who found a more rapidly cognitive decline in elderly people with higher education [8, 48].

### *Limitations*

Although we studied a relatively large cohort of people with YOD, some limitations should be considered. First, inherent to the use of the MMSE in a cohort study on dementia, we had to address missing values. Doing so is often ignored in research, but it is preferable to use imputation methods that provide less biased outcomes because all valuable information is used [49, 50]. Using imputation, we were able to adequately address the problem of missing data without resorting to case-wise deletion. Second, the MMSE is validated in elderly people, and a younger population with higher scores might affect the outcome [31]. However, we used this instrument not to compare younger versus older persons, but to examine individual differences over time. Therefore, the age-related effect will not have influenced our outcomes. Third, we only investigated APDU at evaluation time points and did not consider defined daily doses of APDU or continuous exposure. However, this influenced both users and nonusers at the evaluation. Therefore, we think that chronic users registered more “yes” scores in their evaluations, and do have their effect in our analysis. Fourth, the MMSE is widely used in dementia research and therefore allows for comparison of our study findings with the results of previous studies. However, the MMSE was not developed for people with YOD specifically, and might for instance not be appropriate for the assessment of cognitive functioning in people with FTD [21]. However, as it is a

frequently used instrument, it is useful to compare with outcomes in the elderly. Adding the GDS as outcome measurement in our study, tackles the difficulty of the interpretation of the MMSE on FTD participants. Fifth, in this study we did not investigate whether the familial variant of AD or FTD influenced the outcomes of the course of cognitive decline or disease progression, knowing that the progression is frequently more rapid. At baseline, this information was not always available. As these familial forms are rare, with suggested prevalence rates in AD and FTD of 1–3 and 20–40% it is most unlikely that this limitation biased the outcomes. On the contrary, more disease progression and decline of cognitive function should be expected in the FTD group when this familial variant dominated the study population [51, 52].

### *Conclusion*

This longitudinal study on the progression of dementia and decline in cognitive function in YOD showed an overall mean two-year progression of 0.9 GDS points and a decrease of 1.6 points on the MMSE scale.

The NPI sub-syndromes of psychosis and hyperactivity were negatively correlated with the decline in cognitive function in YOD, whereas the affective NPI sub-syndrome was positively correlated with cognitive function. Therefore, the challenge is to see whether preventing and adequately managing psychosis and hyperactivity could decrease the decline of cognitive functioning. The first choice in managing these symptoms are psychosocial interventions. However, we found no negative effect of antipsychotic medication on either the progression of dementia or the decline of cognitive functioning; therefore, the use of this medication might be considered. This must be closely monitored and considered with respect to any potential (side) effects [53]. Furthermore, it is challenging to find out why persons with affective symptoms showed a more favorable course of cognitive functioning.

The decline in cognitive function was highest in AD participants, whereas the progression of dementia severity showed no statistically significant differences in the three dementia subtypes. When advising persons with YOD and their families about prognoses, the different courses of cognitive decline should be considered.

More research is needed to clarify if and why younger people with YOD have a more rapidly



progressive course of dementia compared with elderly YOD persons.

## ACKNOWLEDGMENTS

Yvette Daniels and Deliane v Vliet participated in data collection. This research was supported with grants from the Dutch Alzheimer's Foundation, Bunnik, the Wever Care Group, Tilburg, and of the Florence Care Group, the Hague, all of them in the Netherlands.

Authors' disclosures available online (<https://www.j-alz.com/manuscript-disclosures/17-0859r2>).

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