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The prevalence, assessment, and management of neuropsychiatric symptoms in Alzheimer's disease

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Colophon

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More than Memory: The prevalence, assessment, and management of neuropsychiatric symptoms in Alzheimer's disease

Meer dan vergeetachtigheid: De prevalentie, diagnostiek en behandeling van neuropsychiatrische symptomen bij de ziekte van Alzheimer

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Voor Wim en Sientje Eikelboom, mijn lieve opa en oma

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Chapter 1

General introduction

Alzheimer's disease (AD) is often primary considered as a cognitive disorder, in which memory impairment is the most prominent clinical feature. Although memory deficits are the common clinical presentation of AD dementia,[1] AD is more than memory. In addition to cognitive impairment, nearly all individuals with AD exhibit neuropsychiatric symptoms (NPS) at some stage of the disease.[2-4] These symptoms cover a wide range of changes in mood, behavior, and perception, with apathy, depressive symptoms, aggression, anxiety, and sleep disturbances as most common NPS in AD dementia.[5] Patients and caregivers consider these symptoms as most troublesome and distressing symptoms of AD.[6-8] Box 1 illustrates some of the NPS that are commonly seen across the clinical stages of AD.

NPS have been traditionally associated with late-stage dementia,[9] but growing research emphasizes that NPS are also common in mild and moderate AD dementia,[10,11] in individuals with mild cognitive impairment (MCI, prodromal phase of AD),[12-14] as well as in individuals with subjective cognitive decline (SCD, preclinical phase of AD) who are at increased risk for developing AD dementia.[15-17]

Box 1. Examples of common neuropsychiatric symptoms in Alzheimer's disease

- Mr. Peters is 73 years old and received a diagnosis of mild cognitive impairment at a memory clinic last month. He solely reports experiencing increased forgetfulness and navigation difficulties. However, his wife also experiences that Mr. Peters does not initiate any household task anymore. She mentions that Mr. Peters sits on the couch all day, while he used to spend a lot of time in 'his shred' fixing bikes for friends and family members. His wife finds it very hard to see that Mr. Peters isn't the active husband that he used to be and that she has to motivate him for every activity, task, and social event.
- Ms. Green is 87 years old and received a diagnosis of Alzheimer's disease dementia two years ago. She finds it very difficult that she often doesn't know which date it is and that she has to spend all day looking for her stuff. Her daughter reports that Ms. Green often accuses her of stealing her clothing or jewelry. At these moments, she tries to convince Ms. Green that she must have placed her belongings somewhere she can't remember anymore, often leading to more suspicion and agitation. Her daughter experiences that her relationship with her mother worsens because of these accusations.
- Mr. Williams is a 68-year old male who was diagnosed with Alzheimer's disease dementia with prominent language impairments last year. He finds it very hard that he frequently has to look for specific words and that he has troubles following conversations, especially in groups. This makes him sad and annoyed, which results in withdrawal from social gatherings. His spouse reports that it is not completely new for Mr. Williams to feel sad or annoyed at times, but he is now less able to overcome these negative emotions and express his needs. His spouse feels helplessness, as he does not know how to support Mr. Williams.

All individuals described took part in the study reported in chapter 4.2. Personal details were adjusted to ensure anonymity.

Generally, cross-sectional studies show that NPS increase according to clinical AD stage.[10,11,14] Several longitudinal studies have suggested that specific NPS emerge during the course of AD starting with depressive symptoms, irritability, and sleep disturbances, followed by anxiety, agitation, and apathy, and lastly euphoria, hallucinations, delusions, and motor disturbances.[16,18] Yet, other longitudinal studies have not replicated such a pattern and have instead revealed substantial fluctuations in the course of NPS in AD dementia.[4,19,20]

Neuropsychiatric symptoms in diagnostic criteria for Alzheimer's disease

NPS such as hallucinations, apathy, and disinhibition are seen as the hallmark of non-AD dementias such as Dementia with Lewy Bodies (DLB) and the behavioral variant of Frontotemporal dementia (bvFTD) and are therefore core components of the diagnostic criteria proposed for these dementias.[21,22] However, this is not the case for AD dementia. Both the fifth edition of the Diagnostic and Statistical Manual (DSM-5) and the National Institute on Aging and the Alzheimer's Association (NIA-AA) provide a framework in which a diagnosis of a cognitive syndrome (e.g. MCI or dementia) is followed by a definition of its etiology (e.g. AD or vascular dementia [VaD]).[1,23,24] The DSM-5 diagnostic criteria include changes in social cognition for the diagnosis of all-cause dementia, while the NIA-AA criteria for all-cause dementia include changes in personality, behavior, or comportment. Although a diagnosis of all-cause dementia is required to fulfill the subsequent DSM-5 and NIA-AA criteria for AD dementia, NPS are not specified in the DSM-5 and NIA-AA criteria for dementia due to AD.[1,23] Moreover, NPS are not included in the NIA-AA criteria for MCI due to AD,[24] or the DSM-5 criteria for minor cognitive disorder (i.e. MCI).[23] The most recent NIA-AA research framework defines AD as a biological construct.[25] The clinical staging used within this framework is based on cognitive impairment and functional loss, but also acknowledges the coexistence of neurobehavioral changes in preclinical AD, prodromal AD, and AD dementia.[25] This shows that NPS are increasingly acknowledged in the diagnostic criteria for AD dementia.[26]

In addition to diagnostic criteria for AD dementia, specific criteria have been developed for neuropsychiatric syndromes in AD dementia including agitation,[27] apathy,[28] depression,[29] and psychosis.[30] In addition, the construct of mild behavioral impairment (MBI) has been proposed to identify individuals with late-onset NPS, but who have no or only mild cognitive deficits.[31] Individuals fulfill the criteria for MBI if there are late-onset changes in behavior or personality that persist for at least six months and produce impairment in social functioning or at the workplace.[31] Furthermore, the recent research criteria for the behavioral variant of AD (bvAD) describe individuals with early and predominant NPS that overlap the clinical syndrome of bvFTD in the context of AD pathology.[32]

Box 2. Terminologies used to describe changes in behavior and emotions in dementia
Changes in mood, behavior, and perception in dementia are difficult to demarcate and to define. Terms such as 'challenging behavior', 'difficult behavior', 'distressing behavior', or 'problem behavior' have been used as these changes often cause distress to patients, caregivers, and care staff.

In 1996, the International Psychogeriatric Association proposed the term 'behavioral and psychological symptoms of dementia' (BPSD) to gain more attention for non-cognitive symptoms in dementia both within the clinical setting and research community.[33] In addition, BPSD was proposed to replace the term 'challenging behavior' as this was viewed as prejudicial by many. Parallel to BPSD, the term 'neuropsychiatric disturbances' or 'neuropsychiatric symptoms' (NPS) was coined.[34] Around the same period, Tom Kitwood proposed that changes in behavior in dementia should be seen as an expression of unmet needs and are often valid responses to inappropriate external circumstances and changes in perception and communication related to dementia.[35] In line with the work by Kitwood, the National Institute for Health and Care Excellence (NICE) Guidelines used the term 'behaviors that challenge' to shift the focus from the patient towards the clinician who should find a solution or underlying cause for the behaviors expressed. In Dutch, the term *onbegrepen gedrag* [poorly understood behavior] is used to emphasize a similar idea.

During the past years, terms such as 'challenging behavior', 'difficult behavior', 'distressing behavior', and 'problem behavior' are not recommended to use due to the stigma attached to these terms. More recently, a movement has emerged that also criticize the use of the terms 'BPSD' and 'NPS'. The so-called #BanBPSD movement claims that labelling people with BPSD leads to medicalization and over-prescription of psychotropic drugs, thereby reducing the likelihood of perceiving these behaviors as normal human expressions. This movement addresses serious problems with over-prescription in dementia and stresses that not all behaviors observed in individuals with dementia directly arise from changes in the brain. However, in line with several other authors,[36,37] I think that it is important to recognize that not all behaviors are solely caused by psychosocial factors such as unmet needs. Also, although behaviors can be understood in the context of dementia, these behaviors are often quite abnormal and distressing for caregivers.[37] Therefore, throughout this thesis, I choose to use the term 'neuropsychiatric symptoms'. I preferred NPS over BPSD as BPSD is limited to dementia, while also individuals in preclinical and prodromal stages of dementia were studied in this thesis and, finally, the use of the term BPSD is discouraged if researchers want their papers to be cited.[38]

Impact of neuropsychiatric symptoms in Alzheimer's disease

NPS are one of the largest contributors to reduced quality of life in individuals with AD and their caregivers.[6,39,40] Furthermore, the presence of NPS has been related to accelerated cognitive decline in cognitively normal older adults,[41] and in individuals with MCI.[42,43] In line with these findings, NPS has been found to be an important risk factor for the progression to AD dementia in people with MCI,[44,45] and even in older adults without cognitive impairment.[46] Once a diagnosis of AD dementia is established,

the presence of NPS has been associated with a faster progression to severe dementia,[47,48] and earlier death.[48,49]

As NPS are related to increased burden and distress among caregivers,[50,51] NPS are among the most important predictors of crisis at home,[7] and early nursing home placement among community-dwelling individuals with AD dementia.[52,53] Thus, NPS have a major impact on the lives of people with AD and their caregivers.

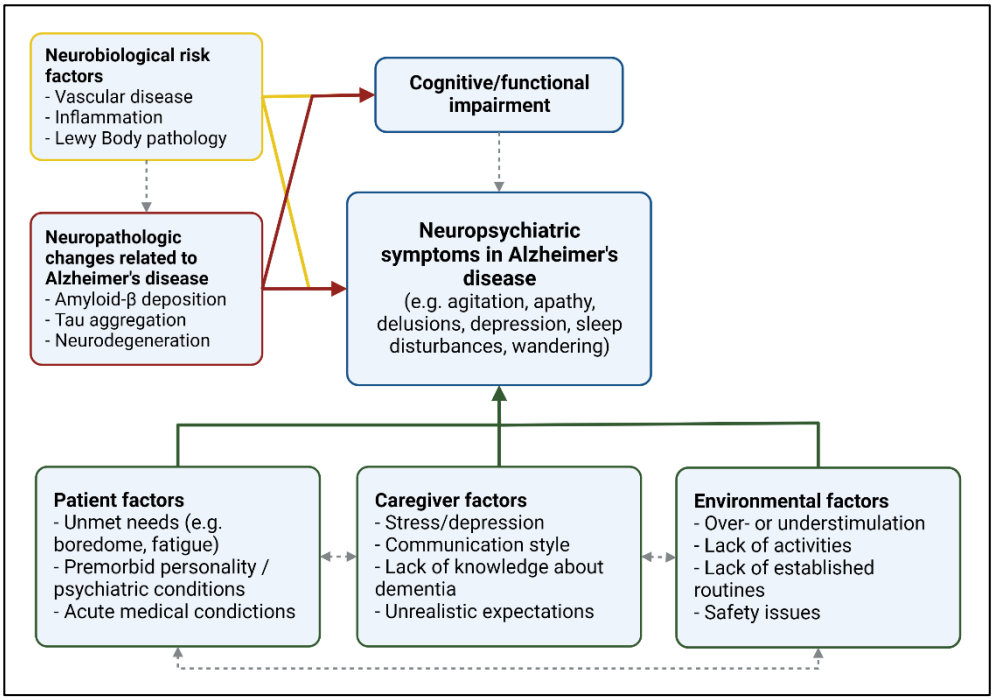
Etiology of neuropsychiatric symptoms in Alzheimer's disease

NPS in AD may arise from a complex interplay of neurobiological factors, medical conditions, and psychosocial factors relating to the person with dementia, their caregivers, and the environment. Kales, Gitlin, and Lyketsos have proposed a model incorporating all of these factors (Figure 1).[54] This model was used to guide the intervention that was described in chapters 4.1 and 4.2, with a special focus on the psychosocial factors presented. The sections below describe the most important and well-studied factors of this model.

Neurobiological factors

Several neurobiological theories have been proposed to explain the manifestation of NPS in AD. The *symptom hypothesis* postulates that AD-related pathophysiological processes cause both cognitive impairment and NPS.[55] The most important pathophysiological processes associated with AD include the abnormal deposition of amyloid-beta protein, aggregation of tau protein, and a loss of neurons and synapses.[25] The *symptom hypothesis* considers NPS as direct symptoms of these disease processes. Previous studies have shown associations between amyloid-beta and the presence of affective symptoms and apathy, especially in individuals without dementia.[e.g. 56,57] However, other studies have failed to find associations between amyloid-beta and NPS while providing evidence for a relationship between tau pathology and NPS in AD.[e.g. 58-60] Generally, neuroimaging studies have yielded mixed findings, with only a small number of relationships between specific brain regions or networks and NPS that have been replicated in AD dementia populations. Examples include associations between left frontal atrophy, hippocampal atrophy, and default mode network disruption and delusions,[61] parietal lobe atrophy and hallucinations,[61] atrophy in the anterior cingulate cortex and the orbitofrontal cortex and involvement of the cognitive control network and apathy,[62] and atrophy in the frontal cortex, cingulate cortex, insula, amygdala, and hippocampus and hypometabolism in the frontal and temporal cortices and agitation.[63] Several studies that have reviewed the existing literature emphasize that the relationship between AD-related pathophysiological processes and NPS is highly inconsistent.[44,64,65] Altogether, these findings suggest that the *symptom hypothesis* cannot explain the emergence of NPS in AD alone. In line with this, medications such as

Figure 1. Hypothetical model of factors relating to NPS in dementia adapted from Kales et al.[54] and Peters & Lyketsos[55]



Notes. The *symptom hypothesis* is illustrated by the red lines and the *risk factor hypothesis* is illustrated by the yellow lines. Psychosocial factors are highlighted by green lines, which are usually targeting by non-pharmacological interventions. These psychosocial factors were also of primary interest when conducting the Describe, Investigate, Create, Evaluate method™ described in chapters 4.1 and 4.2.

cholinesterase inhibitors and memantine that can have beneficial effects on cognitive and functional abilities in AD dementia, show no clear effects on NPS.[66]

An alternative neurobiological hypothesis is the *risk factor hypothesis* that states that NPS manifest from concurrent non-AD pathology.[55] Examples include the influence of inflammation and vascular disease on depressive symptoms,[67] and Lewy body disease co-pathology on psychotic symptoms.[61] However, NPS has been shown to be present in individuals with AD dementia in the absence of these co-pathologies as well.[e.g. 68,69]

Medical comorbidity

Acute medical conditions such as urinary tract infections, hyperglycemia, and anemia are common in older adults with dementia and have been found to trigger NPS.[70] Furthermore, pain has been associated with the emergence and worsening of several NPS in dementia, with the most evidence for an increase in depressive symptoms and agitation.[71] Sensory impairment in hearing and vision, and side effects of drugs may also

trigger or worsen NPS in AD dementia.[54] Note, in these cases, we refer to NPS in the absence of a delirium, although some of these medical conditions can lead to a delirium if left untreated which can further worsen NPS.[23]

Psychosocial factors

Person with dementia

The *need-driven dementia-compromised behavior model* states that NPS arise because people with dementia have difficulties expressing unmet needs such as physical discomfort, a need for company, boredom, or uncomfortable environmental conditions.[72] From this point of view, individuals with AD dementia try to express these needs through NPS. Other factors that have been related to the manifestation of NPS in dementia are pre-morbid neuroticism personality traits,[73] inadequate coping styles, and lifelong psychiatric conditions.[54]

Caregivers

Caring for someone with AD dementia who exhibits severe NPS can be stressful.[51] In turn, caregivers who experience distress and feel burdened tend to use dysfunctional management strategies leading to an increase of NPS,[74] suggesting a bilateral relationship between caregiver burden and NPS.[75] In addition, negative caregivers' communication styles consisting of anger, impatience, and criticism has been shown to trigger NPS.[76,77] Moreover, a lack of knowledge about dementia and its symptoms may give rise to NPS, e.g. assuming that individuals with AD dementia deliberately exhibit NPS.[78].

Environment

The *progressively lowered stress threshold model* provides an explanation for associations between environmental triggers and NPS in dementia.[79] This model posits that decreased abilities to process and manage external stimuli lead to a lowered threshold for stress increasing the likelihood for frustration, agitation, anxiety, or depressive symptoms. Environmental stressors may include changes in routine and the over- or understimulation of the physical and social environment. In addition, a lack of meaningful activities may also contribute to an increase in NPS.[54]

Assessment of neuropsychiatric symptoms in Alzheimer's disease

There are various ways to measure NPS in AD dementia. The most straight-forward way to assess NPS is to ask people with AD dementia about changes in their emotions and behavior. Yet, these assessments are limited by memory impairment and reduced illness-insight.[80] Therefore, NPS are generally measured using proxy-based instruments in AD dementia.[81,82] Such measures either assess specific NPS such as agitation,[83] or cover multiple NPS, with the Neuropsychiatric Inventory (NPI)[84] and the

Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)[85] as most commonly used scales.[86] However, researchers have raised concerns about the over-reliance on proxy reports for the assessment of NPS,[87] because these measures are shown to be affected by recall bias and caregiver's mood, distress, and cultural beliefs.[88,89] Therefore, additional clinician-based rating scales are advised. Usually, these scales establish NPS based on clinical judgment after collecting all available data from the patient and the caregiver. Examples include the Neuropsychiatric Inventory-Clinician rating scale (NPI-C)[88] and the Cornell Scale for Depression in Dementia (CSDD).[90]

Treatment of neuropsychiatric symptoms in Alzheimer's disease

Based on the data presented above that illustrate the substantial contribution of modifiable (psychosocial) factors to NPS in AD dementia, the national and international guidelines recommend non-pharmacological interventions as first-line treatment for NPS in AD dementia.[33,91,92] Examples of such interventions include psychoeducation, reminiscence therapy, art and music therapy, enhancing tailored activities, caregiver support, educating caregivers on specific skills to manage NPS, and improving the physical environment.[54,93] These interventions are shown to be effective in reducing NPS and improving NPS-related distress among caregivers,[94-97] with two recent network meta-analyses showing that non-pharmacological interventions are significantly more effective in reducing NPS in dementia than pharmacological treatments.[98,99] International guidelines show great overlap in their advice to assess and treat NPS in a multidisciplinary setting using a step-by-step approach examining causes and triggers of NPS to guide interventions.[100] In addition, these guidelines acknowledge that a 'one-size fits all' treatment approach does not exist for NPS given its multifactorial causes that are situation and person dependent.[101]

Currently, there are no medications approved by the FDA or EMA for treating NPS in dementia. Psychotropic drugs such as antipsychotics, antidepressants, and anxiolytics are shown to have at best modest effect in reducing NPS in dementia,[97,102] and are associated with serious side effects including an increased risk for cerebrovascular events, falls, and mortality.[103,104] Given these findings, the use of psychotropic drugs are generally only advised in case of a major depressive disorder and severe psychotic symptoms or aggressive behaviors with a safety risk.[92,100,105]

Despite the evidence available and international recommendations, current treatment of NPS in AD dementia is often limited to off-label pharmacological interventions, while non-pharmacological approaches are hardly implemented.[106,107] Physicians often treat NPS purely as medication targets ignoring psychosocial contributors and without taking time to conduct a comprehensive assessment of its manifestation and underlying causes.[106] The application of non-pharmacological interventions targeting NPS is further hindered by a lack of training and knowledge

among clinicians and the notion that non-pharmacological intervention are more time-consuming than pharmacological treatments.[54] This is a serious problem given the potential benefits of non-pharmacological interventions available and the notable side effects associated with psychotropic drug use in dementia.

Neuropsychiatric symptoms in early Alzheimer's disease at the memory clinic

Despite a growing interest in the manifestation and clinical impact of NPS in the early clinical stages of AD,[12,15,31,56] the majority of prior studies have been conducted in moderate to severe AD dementia.[5,97] At the start of this thesis, little was known about the manifestation and course of NPS in individuals in the early clinical stages of AD living at home.

A substantial proportion of the MCI and AD dementia diagnoses are established at hospital-based memory clinics, although exact numbers are lacking.[108] These outpatient clinics play an important role in timely diagnosis and in providing post-diagnostic support within a multidisciplinary setting.[109] The number of memory clinics is growing in the Nederlands, with 91 memory clinics in 2017 that diagnose around 24,000 patients annually.[108] At the start of this thesis, only few studies were conducted on the manifestation and treatment of NPS in AD dementia within this specific care setting.[e.g. 11,110-113]

The memory clinic may play a valuable role in the early detection and treatment of NPS, as these symptoms are common and distressing in the early clinical stages of AD. However, it was unknown how the current care for NPS was organized in this setting and whether challenges with underrecognition and undertreatment of NPS that have been reported in other care settings also occur at the memory clinic.[106,114] In addition, memory clinics offer outpatient care to patients living at home that convey specific challenges relating to the assessment and management of NPS that were understudied.

Thesis aims and outline

Given the knowledge gaps discussed above, the aims of this thesis were (1) to examine the prevalence and course of NPS in individuals in the early clinical stages of AD seen at the memory clinic, (2) to obtain insight in the way NPS are currently diagnosed and treated in AD dementia, with a special focus on the memory clinic setting, and (3) to investigate how the memory clinic could contribute to the timely assessment and non-pharmacological treatment of NPS in community-dwelling individuals with AD dementia. The outline of this thesis is provide below.

Box 3. The BEAT-IT study
This thesis is part of the *BEhavioral symptoms in Alzheimer's disease: Towards early Identification and Treatment* (BEAT-IT) study. This project is a joint effort from researchers based at the Erasmus MC University Medical Center, Amsterdam University Medical Centers, and University of California at San Francisco and was funded by an Alzheimer Nederland and ZonMw Memorabel grant. In addition to the research presented in this thesis, the BEAT-IT study entailed several projects led by dr. Ellen Singleton and dr. Rik Ossenkoppele who investigated the neuroanatomical and pathological underpinnings of the behavioral variant of Alzheimer's disease (bvAD)[115,116] and who provided research criteria for bvAD.[32]

Chapter 2: Prevalence and course of neuropsychiatric symptoms in Alzheimer's disease
In chapter 2.1, the prevalence and course of NPS is examined across the AD clinical continuum and associated with co-current cognitive symptoms and cognitive decline. Trajectories of biweekly NPI scores in a memory clinic population are described in chapter 2.2. Chapter 2.3 covers the existing literature on sex differences in the prevalence and severity of NPS in AD dementia.

Chapter 3: Current state of care for neuropsychiatric symptoms in Alzheimer's disease
In chapter 3.1, a case is reported to highlight the underrecognition of NPS as early manifestation of AD together with the serious negative clinical consequences related to this underrecognition. Chapter 3.2 describes the challenges physicians working at the memory clinic experience while assessing and managing NPS in AD dementia and examines their attitudes on the role of the memory clinic in the care for NPS in AD dementia. Chapter 3.3 describes how natural language processing (NLP) can be used to study the free-text documentation of NPS in electronic health records (EHRs) of individuals with AD dementia who visited the memory clinic. In chapter 3.4, EHRs were used to analyze the perception and responses towards NPS among residential aged care staff.

Chapter 4: Improving timely recognition and treatment of neuropsychiatric symptoms in Alzheimer's disease at the memory clinic
Chapter 4.1 presents the protocol of an intervention study aimed to improve the early recognition and adequate treatment of NPS in early AD dementia in the memory clinic setting using the Describe, Investigate, Create, Evaluate (DICE) method™ developed by Kales and colleagues.[100] In chapter 4.2, the outcomes of this intervention study are presented including quantitative, qualitative, and cost-effectiveness analyses.

Chapter 5: General discussion

In chapter 5, a summary of the key findings and their implications are discussed in light of the scientific literature. Next, methodological challenges related to the studies included in this thesis are presented together with recommendations for future research.

Chapter 2

Prevalence and course of neuropsychiatric symptoms in Alzheimer's disease

Chapter 2.1

Neuropsychiatric and cognitive symptoms across the Alzheimer's disease clinical spectrum: Cross-sectional and longitudinal associations

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Abstract

Background and Objectives

To investigate the prevalence and trajectories of neuropsychiatric symptoms (NPS) in relation to cognitive functioning in a cohort of β-amyloid–positive (A+) individuals across the Alzheimer disease (AD) clinical spectrum.

Methods

In this single-center observational study, we included all individuals who visited the Alzheimer Center Amsterdam and had a clinical diagnosis of subjective cognitive decline (SCD), mild cognitive impairment (MCI), or probable AD dementia and were A+. We measured NPS with the Neuropsychiatric Inventory (NPI), examining total scores and the presence of specific NPI domains. Cognition was assessed across 5 cognitive domains and with the Mini-Mental State Examination (MMSE). We examined trajectories including model-based trends for NPS and cognitive functioning over time. We used linear mixed models to relate baseline NPI scores to cognitive functioning at baseline (whole-sample) and longitudinal time points (subsample n = 520, mean 1.8 [SD 0.7] years follow-up).

Results

We included 1,524 A+ individuals from the Amsterdam Dementia Cohort with A+ SCD (n = 113), A+ MCI (n = 321), or A+ AD dementia (n = 1,090). NPS were prevalent across all clinical AD stages (≥1 NPS 81.4% in SCD, 81.2% in MCI, 88.7% in dementia; ≥1 clinically relevant NPS 54.0% in SCD, 50.5% in MCI, 66.0% in dementia). Cognitive functioning showed a uniform gradual decline; while in contrast, large intraindividual heterogeneity of NPS was observed over time across all AD groups. At baseline, we found associations between NPS and cognition in dementia that were most pronounced for NPI total scores and MMSE (range β = -0.18 to -0.11, false discovery rate [FDR]–adjusted $p < 0.05$), while there were no cross-sectional relationships in SCD and MCI (range β = -0.32 to 0.36, all FDR-adjusted $p > 0.05$). There were no associations between baseline NPS and cognitive functioning over time in any clinical stage (range β = -0.13 to 0.44, all FDR-adjusted $p > 0.05$).

Conclusions

NPS and cognitive symptoms are both prevalent across the AD clinical spectrum, but show a different evolution during the course of the disease.

Introduction

Alzheimer disease (AD) is characterized by a gradual decline in cognitive functions and activities of daily living.[1] As neuropsychiatric symptoms (NPS) are present in the majority of patients with AD dementia,[117] NPS are increasingly recognized as core clinical AD symptoms.[81] Previous studies have associated the presence of NPS with an increased ris*k* of progression to dementia and with worse cognitive performance and a faster cognitive decline in AD dementia.[118-120] These studies have emphasized the clinical relevance of NPS in AD by highlighting its prognostic value.

Several other studies have not found an association between NPS and cognitive functioning in AD dementia.[113,121,122] These discrepant results may have a number of causes, such as the fact that studies often used instruments that assess general cognitive functioning (i.e. Mini-Mental State Examination [MMSE]) and overall NPS burden (i.e. Neuropsychiatric Inventory [NPI] total score).[42,121] Furthermore, prior studies have often included patients based on clinical diagnostic criteria of AD without biomarker evidence,[41,113] thereby increasing the likelihood of including patients with non-AD primary etiologies.[25]

To address these challenges, the current study investigates (1) the prevalence and course of specific NPS and (2) associations between baseline NPS and performance on multiple cognitive domains at baseline and over time in a β-amyloid (Aβ)–positive (A+) sample ranging from normal cognition to dementia. This knowledge will provide a better understanding of the manifestation of NPS across the clinical stages of AD and its relationship with cognitive decline, which could aid patient management in clinical practice.

Methods

Participants

We included all patients who visited the Alzheimer Center Amsterdam between June 2002 and December 2017 and (1) had a clinical diagnosis of subjective cognitive decline (SCD), mild cognitive impairment (MCI), or probable AD dementia, (2) were A+, and (3) had NPI and neuropsychological assessment available at baseline. Individuals with possible AD dementia were excluded. All individuals underwent a standard diagnostic workup including medical history taking, neurologic examination, cognitive testing, lumbar puncture, and brain MRI.[123] A subsample of the individuals underwent Aβ PET for research purposes (n = 450). Clinical diagnoses were established using conventional diagnostic criteria at multidisciplinary meetings. Individuals had to meet the clinical criteria of SCD,[124] MCI,[24] or probable AD dementia,[1] in addition to Aβ positivity based on either CSF (i.e. $A\beta_{42}$ < 550 pg/mL or tau/$A\beta_{42}$ ratio > 0.52)[125] or visual rating of an Aβ PET scan with the radiotracers ^{18}F-florbetaben (n = 190), ^{11}C-Pittsburgh compound B (n = 133), ^{18}F-flutemetamol (n= 100), or 18F-florbetapir (n = 27).[126] In case of Aβ PET/CSF discordance, Aβ status was determined based on the visual rating of Aβ PET.

As all participants were Aβ-positive, SCD will be denoted as A+ SCD, MCI as A+ MCI, and AD dementia as A+ AD dementia.

Neuropsychiatric assessment

The NPI was used to assess NPS.[127] This 12-item informant based interview is a widely accepted measure of NPS in dementia.[81] Each NPS domain is rated according to its severity (0–3) and frequency (0–4). We multiplied the severity and frequency scores for each domain to obtain an NPI domain score (0–12). The presence of specific NPS was defined as a severity × frequency score of ≥ 1 for each NPI domain. Clinically relevant NPS was defined as a severity × frequency score of ≥ 4 for each NPI domain. We summed the severity × frequency scores of all 12 domains to obtain the NPI total score (0–144). The presence of any NPS was defined as an NPI total score of ≥ 1. At baseline, scores were missing for the following NPI domains: n = 8 for eating behaviors, n = 8 for nighttime behaviors, n = 2 for aberrant motor behaviors, n = 1 for apathy, and n = 1 for agitation.

Neuropsychological assessment

We used the MMSE to assess global cognitive functioning. In addition, a standardized neuropsychological test battery was used to measure performance across five cognitive domains. We used immediate recall scores of the Visual Association Test part A and the immediate recall and delayed recall of the Rey Auditory Verbal Learning Test to measure memory. For attention, the Digit Span forward, Stroop Color and Word Test color and word conditions, and the Trail-Making Test part A were administered. Executive functioning was assessed using Digit Span backward, Stroop Color and Word Test color word condition, Trail-Making Test part B, and the Frontal Assessment Battery. We used category fluency (animals) and the naming condition of the Visual Association Test to measure language. We measured visuospatial abilities using the number location, dot counting, and fragmented letters subtests of the Visual Object and Space Perception Battery.

Individuals who were not able to complete the Trail-Making Test or Stroop Color and Word Test due to cognitive difficulties were assigned the maximum score (i.e. higher scores reflect worse performance). We converted raw test scores into *Z* scores based on the mean and SD of an independent healthy reference group of 533 AD-biomarker negative individuals (mean [SD] age 59.7 [9.8], 54% female, mean [SD] MMSE score 28.9 [1.0]).[128] The *Z* scores of the Trail-Making Test and Stroop test were inverted to ensure that lower scores indicated worse performance. Next, *Z* scores were combined into cognitive domain scores by averaging cognitive scores if at least two tests within that domain were available for that individual. At baseline, cognitive domain scores were missing for 7–28%.

Standard protocol approvals, registrations, and patient consents

The Medical Ethics Review Committee of the Amsterdam University Medical Centers approved the study. Written informed consent was obtained from all participants.

Statistical analysis

We compared baseline clinical characteristics, NPS prevalence, and cognitive performance across the diagnostic groups using analysis of variance (with Tukey honestly significant difference post hoc test), Kruskal-Wallis tests, or χ^2 tests where appropriate.

We aimed to statistically analyze trajectories of NPI scores but the assumption of normality was not met for the longitudinal NPI domain scores given the substantial proportion of zeros, which remained unchanged after deploying several transformations. Therefore, we plotted individual trajectories of NPS and cognitive functioning over time according to disease stage and added model-based trends with 95% confidence intervals (CIs) to the graphs for descriptive purposes. In addition, we investigated the extent to which NPS and cognitive functioning changed over time within individuals (intraindividual variance) and between individuals (interindividual variance). To quantify the variation within and between individuals, we conducted multilevel null models to obtain the percentage variance explained by intravariance and intervariance for neuropsychiatric measures and cognitive measures over time. For these analyses, the continuous severity × frequency scores (0–12) of specific NPI domains were used.

To study associations between baseline NPS and cognitive functioning at baseline and over time, we performed linear mixed models (LMMs) including random intercepts and fixed slopes that were corrected for age, sex, and education. Determinants included the NPI total score and the presence of specific NPI domains. Outcomes were performance on the MMSE and the 5 predefined cognitive domains. LMMs were run separately for the clinical stages at baseline (i.e. SCD, MCI, AD dementia). We tested nonlinear associations using LMMs with quadratic and cubic splines and selected linear LMM for all models based on the likelihood ratio χ^2 test and Akaike information criterion. We checked assumptions by visual inspection of standardized residuals scatterplots and *Q-Q* plots. As normality of cognitive scores slightly deviated in language and visuospatial abilities most pronounced in A+ SCD, we conducted sensitivity analyses using a bootstrap procedure with 200 bootstrap samples to calculate CIs. This approach did not change the initial findings.

Level of significance was set at $p < 0.05$. The post hoc analyses on the NPS prevalence rates and the LMMs to study associations between NPS and cognitive performance were corrected for multiple testing using the Benjamini-Hochberg adjusted false discovery rate (FDR) of 0.05. Analyses were performed using SPSS version 26.0 and *R* version 4.0 (*lme4*, *splines*, *lmerTest*, *effectsize*, and *boot* packages).

Table 1. Demographic and clinical characteristics of the amyloid-β positive sample at baseline according to clinical AD stage

	A+ SCD (n=113)	A+ MCI (n=321)	A+ AD dementia (n=1,090)
Age, y, mean (SD)	65.8 (7.4)	67.7 (7.3)	65.9 (7.7)[a,b]
Sex, female, n (%)	52 (46.0%)	135 (42.1%)	571 (52.4%)[a]
Education level, median [IQR]*	6 [1]	5 [2]	5 [2][a,c]
APOE ε4, n(%) carriers†	65 (60.2%)	216 (70.8%)	704 (66.7%)
MMSE score, mean (SD)‡	28.0 (1.7)	26.3 (2.4)[d]	20.3 (5.1)[a,c]
Cognitive Z scores, mean (SD)§			
Memory	-0.39 (0.9)	-2.40 (1.7)[d]	-4.31 (2.1)[a,c]
Attention	-0.26 (0.9)	-0.68 (1.2)	-3.50 (4.0)[a,c]
Executive functioning	-0.22 (0.9)	-0.80 (1.0)[d]	-2.68 (1.7)[a,c]
Language	-0.11 (0.6)	-0.55 (0.7)[e]	-1.68 (1.6)[a]
Visuospatial abilities	-0.08 (0.7)	-0.39 (0.9)	-2.97 (3.8)[a,c]
NPI total score, mean (SD)‖	8.1 (9.2)	7.8 (9.0)	10.9 (10.6)[a,f]
No. of NPS present, mean (SD)‖	2.4 (1.9)	2.4 (1.9)	2.9 (2.1)[a]
Clinical FU available, n (%)	53 (46.9%)	142 (44.2%)	326 (29.9%)
No. FU assessments, mean (SD)	1.7 (0.8)	1.7 ± 0.7	1.6 ± 0.7
FU duration, y, mean (SD)	1.7 (0.8)	1.9 ± 0.7	1.7 ± 0.7
Progressed to MCI or dementia, n (%)	13 (24.5%)	61 (43.0%)	–

Notes. A+ = amyloid-β positive, AD = Alzheimer's disease, APOE = Apolipoprotein E, FU = follow-up, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, NPS = neuropsychiatric symptoms, SCD = subjective cognitive decline.

* Dutch education system categorized into (1) less than 6 years primary education [<6 years], (2) completed primary education [6 years], (3) more than 6 years of primary education, without a secondary school diploma [8 years], (4) lower vocational training [9 years], (5) advanced vocational training or lower professional education [10–11 years], (6) advanced professional training or upper secondary school [12–18 years], and (7) academic degree [>18 years]. Missing data for SCD n = 1, MCI n = 1, and dementia n = 12.

† Missing data for SCD n = 5, MCI n = 16, and dementia n = 34. ‡ Missing data for SCD n = 2 and dementia n = 16. § Missing data for Memory (SCD n = 3, MCI n = 26, dementia n = 221), Attention (SCD n = 3, MCI n = 13, dementia n = 101), Executive functioning (SCD n = 3, MCI n = 19, dementia n = 162), Language (SCD n = 4, MCI n = 24, dementia n = 142), Visuospatial abilities (SCD n = 23, MCI n = 84, dementia n = 326). ‖ Missing data for MCI n = 2 and dementia n = 9.

[a] $p < 0.001$; difference between A+ AD dementia and A+ MCI.
[b] $p < 0.05$; difference between A+ AD dementia and A+ SCD.
[c] $p < 0.001$; difference between A+ AD dementia and A+ SCD.
[d] $p < 0.01$; difference between A+ MCI and A+ SCD.
[e] $p < 0.05$; difference between A+ MCI and A+ SCD.
[f] $p < 0.01$; difference between A+ AD dementia and A+ SCD.

Data availability

Data not provided in the article and additional information on methods and materials can be shared upon reasonable request.

Results

Participants

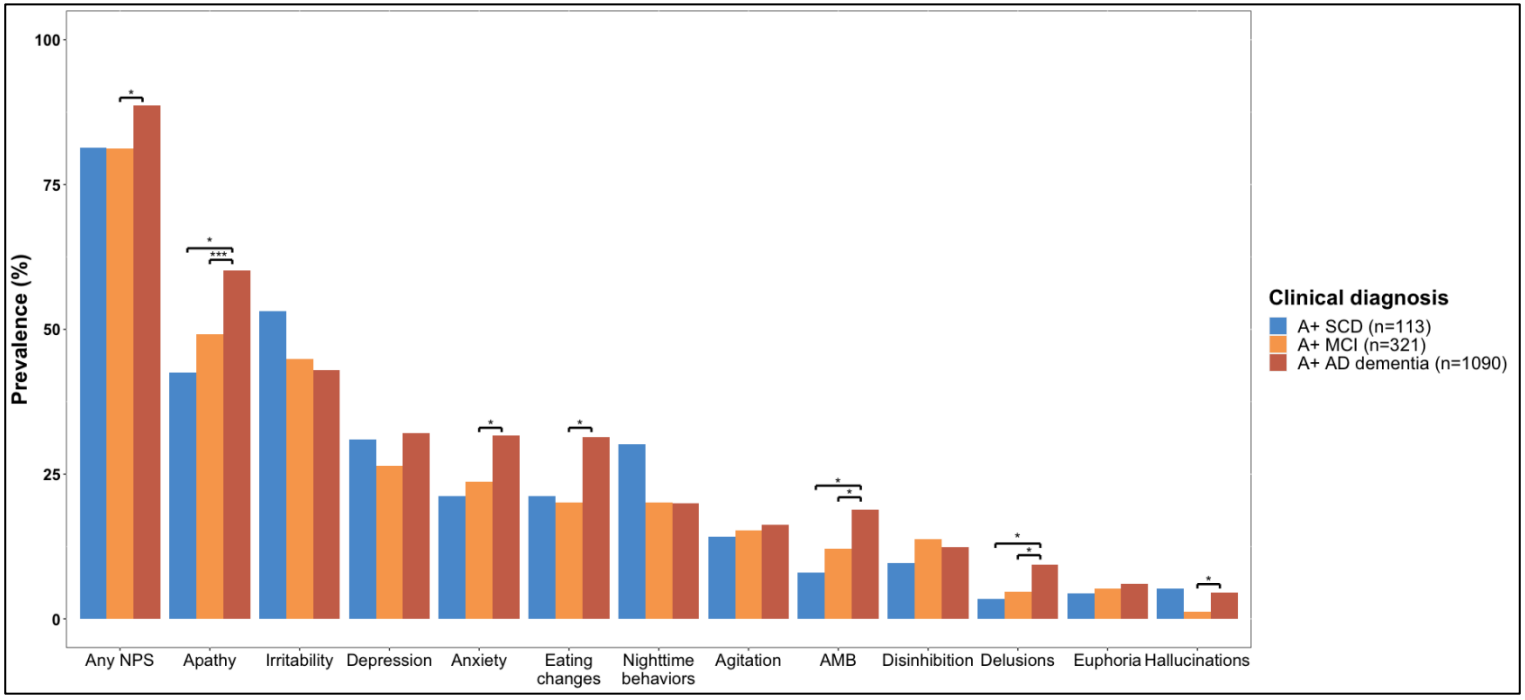
We included a total of 1,524 individuals of which 113 participants had a clinical diagnosis of A+ SCD, 321 participants with A+ MCI, and 1,090 participants with A+ AD dementia at baseline. Of the individuals with A+ AD dementia at baseline, the majority had mild dementia (87.2%, clinical dementia rating [CDR] score ≤ 1), while 12.4% had moderate dementia (CDR = 2), and 0.5% had severe dementia (CDR = 3). A subsample of the participants had follow-up assessments available: n = 53 (46.9%) with A+ SCD at baseline, n = 142 (44.2%) with A+ MCI at baseline, and n = 326 (29.9%) with A+ AD dementia at baseline. We found no differences in demographic and clinical characteristics between individuals with and without follow-up assessments for A+ SCD and A+ MCI. In A+ AD dementia, we did find lower cognitive functioning and higher NPS burden in individuals without follow up assessment compared to individuals with follow-up assessment (Supplemental Table 1). We conducted longitudinal analyses in patients who had follow up assessments available limited up to 3 years after baseline assessment, because < 10% of the 1,524 participants had more than 3 years of follow-up assessments available. Including these assessments may have resulted in underestimation of disease progression due to selective dropout.[129] For those with follow-up assessment available, mean follow-up duration was 1.7 years (SD 0.8) for A+ SCD, 1.9 years (SD 0.7) for A+ MCI, and 1.7 years (SD 0.7) for A+ AD dementia.

Baseline demographic and clinical characteristics of our sample of A+ individuals are shown in Table 1. Participants with A+ MCI were older than individuals with A+ AD dementia ($p < 0.001$) or A+ SCD ($p < 0.05$). Participants with A+ AD dementia had lower levels of education compared to those without dementia ($p < 0.001$). The proportion of female patients was higher in A+ AD dementia than A+ MCI ($p < 0.001$). Of the individuals without dementia at baseline who had follow-up assessment available, 24.5% (n = 13) of the individuals with A+ SCD progressed to MCI or dementia, and 43.0% (n = 61) of the participants with A+ MCI progressed to dementia. As expected, baseline MMSE and baseline cognitive domain scores differed according to clinical AD stage ($p < 0.001$; Table 1).

Prevalence of NPS at baseline across clinical stages

NPS were prevalent across all AD stages with at least one NPS present in 81.4% of the individuals with A+ SCD (54.0% rated as clinically relevant), 81.2% of the individuals with A+ MCI (50.5% rated as clinically relevant), and 88.7% of the individuals with A+ AD dementia (66.0% rated as clinically relevant). The NPI total score was higher for A+ AD dementia compared to A+ SCD ($p < 0.01$) and A+ MCI ($p < 0.001$), while we found no difference in NPI total score between A+ SCD and A+ MCI ($p = 0.97$; Table 1). The number of NPS present at baseline was higher for A+ AD dementia compared to A+ MCI

Figure 1. Prevalence of neuropsychiatric symptoms across a β-amyloid–positive sample according to clinical Alzheimer disease stage



Notes. AMB = aberrant motor behavior, MCI = mild cognitive impairment, SCD = subjective cognitive decline.
* $p < 0.05$ after correcting for false discovery rate.
** $p < 0.01$ after correcting for false discovery rate.
*** $p < 0.001$ after correcting for false discovery rate.

($p < 0.001$), with no difference between A+ SCD and the other clinical stages (all $p > 0.05$, Table 1). The prevalence rates of the specific NPI domains across the clinical AD stages are presented in Figure 1. The 3 most prevalent NPS were similar for all clinical stages and included apathy, irritability, and depression. The prevalence was higher at the more advanced clinical stage for the majority of NPI domains, especially for apathy, anxiety, eating behaviors, aberrant motor behaviors, and delusions. However, irritability, depression, nighttime behaviors, and hallucinations were more common in A+ SCD compared to A+ MCI or A+ AD dementia.

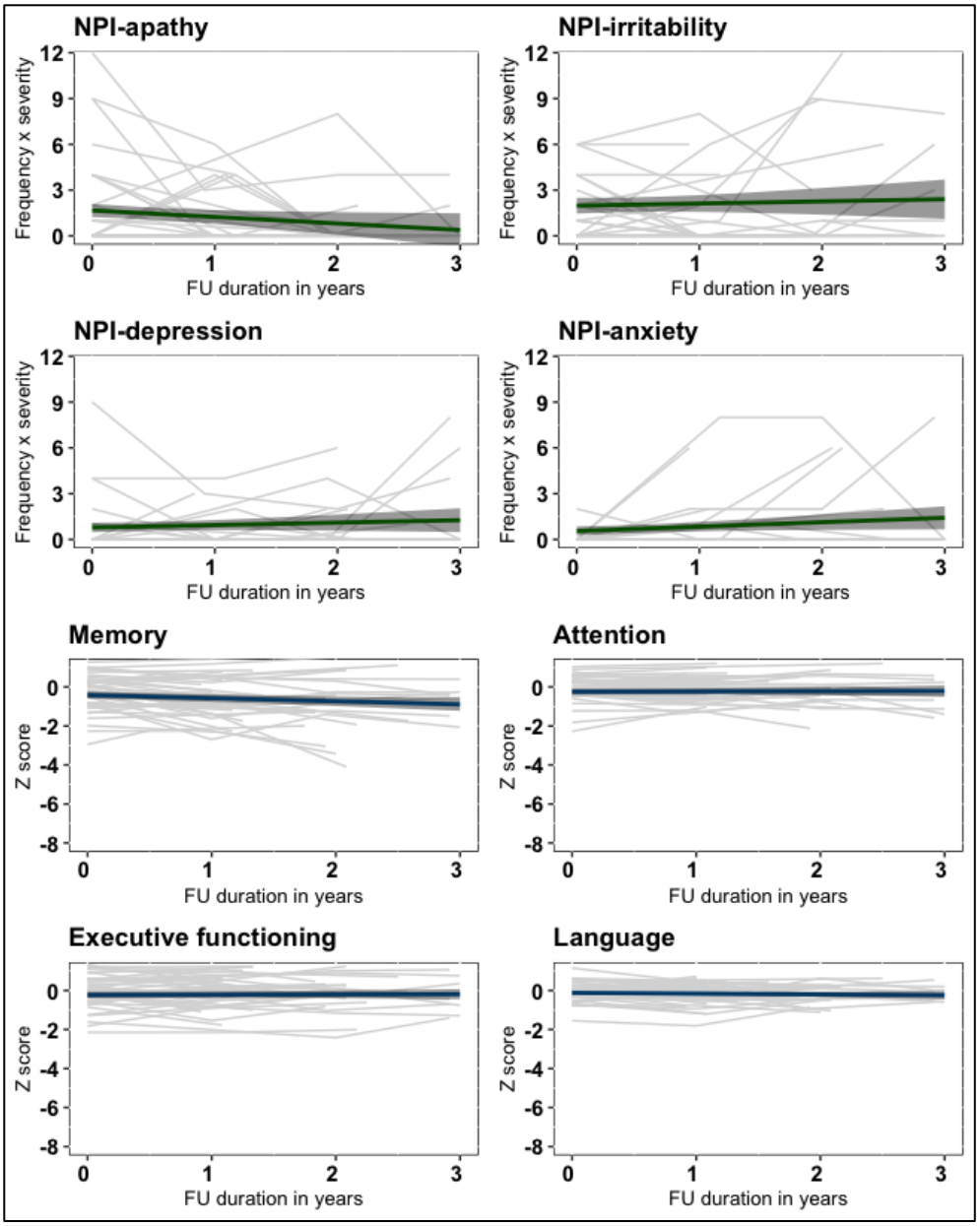
The NPI severity scores and frequency scores showed a similar pattern as the NPI prevalence rates, i.e. the highest severity and frequency scores were seen in A+ AD dementia with little differences between A+ SCD and A+ MCI (Supplemental Tables 2–3). Furthermore, the distribution of clinically relevant NPS (NPI domain scores ≥ 4) showed a similar pattern compared to the distribution of the presence of NPS (Supplemental Table 2).

Progression of NPS and cognition over time across clinical stages

We plotted trajectories of specific NPI domains and performance on specific cognitive domains over time for patients across the different clinical AD stages. In participants with A+ SCD at baseline, the trends of specific NPI domain scores remained stable over time with a decline in apathy and a subtle increase for depression, anxiety, and agitation (Figure 2, Supplemental Figure 1). Cognitive scores remained relatively stable over time for A+ SCD. In participants with A+ MCI at baseline, we observed a relatively stable trend of specific NPI domains over time, whereas a decline was observed in all cognitive domains (Figure 3, Supplemental Figure 2). In participants with A+ AD dementia, few changes were found in trends of specific NPI domains over time, with modest increases in irritability, aberrant motor behaviors, and nighttime behaviors and decrease in depression and anxiety (Figure 4, Supplemental Figure 3). Substantial decline was observed in all cognitive domains.

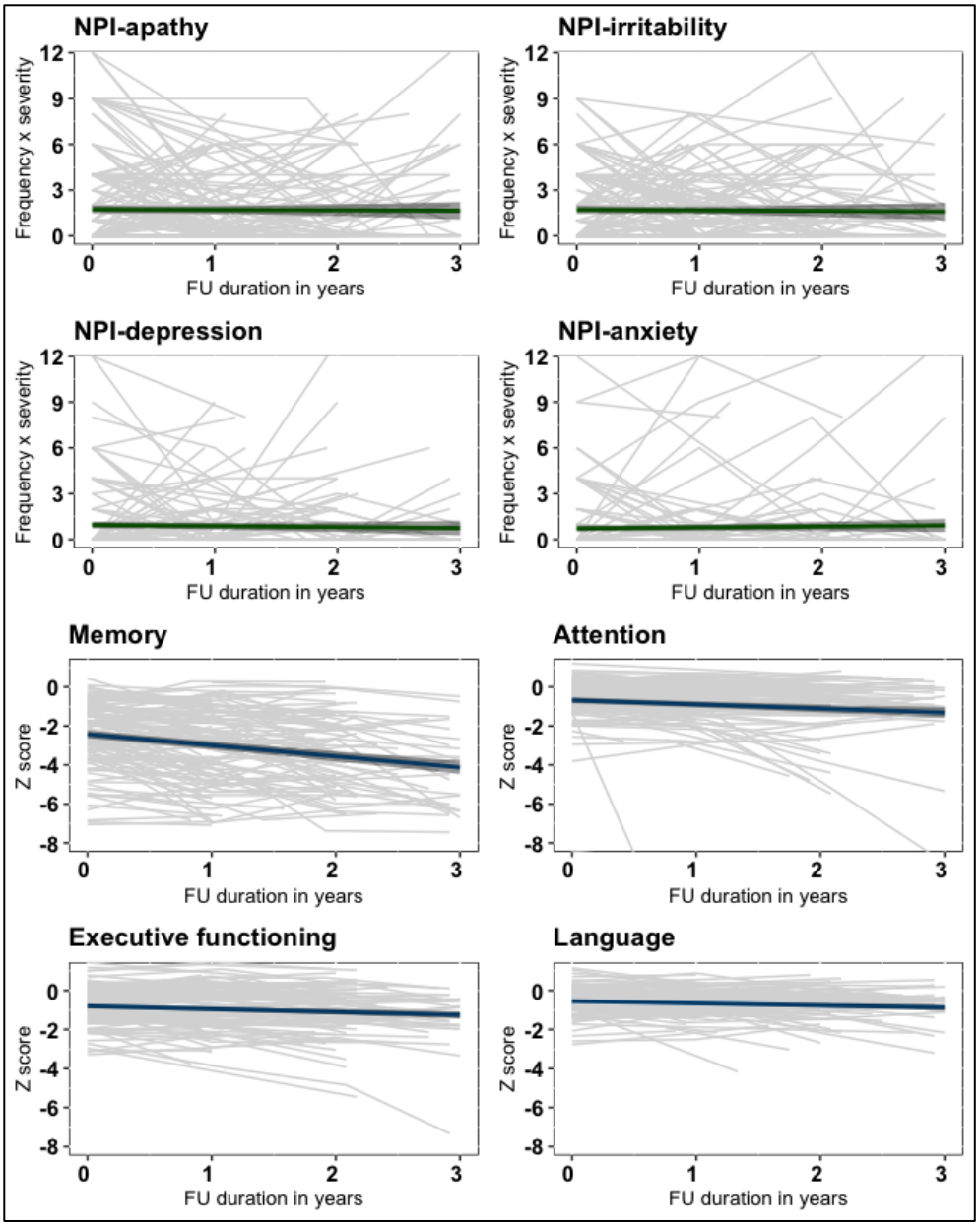
When looking at the trajectories of specific NPS and cognitive scores over time, we observed large variability in the course of specific NPS within and between individuals across all clinical stages (Figures 2–4, Supplemental Figures 2–3). To further quantify this intraindividual variability and interindividual variability, we performed multilevel null models for each measure according to clinical stage at baseline (Supplemental Table 4). Across all clinical AD stages, the intraindividual variance of NPS measures was higher (all mean % explained > 70%) compared to cognitive measures (all mean % explained < 45%). Hence, we observed larger changes on NPS measures over time within individuals than between individuals, while the opposite was the case for cognitive measures.

Figure 2. Longitudinal neuropsychiatric inventory domain scores and cognitive functioning for individuals with β-amyloid–positive SCD at baseline



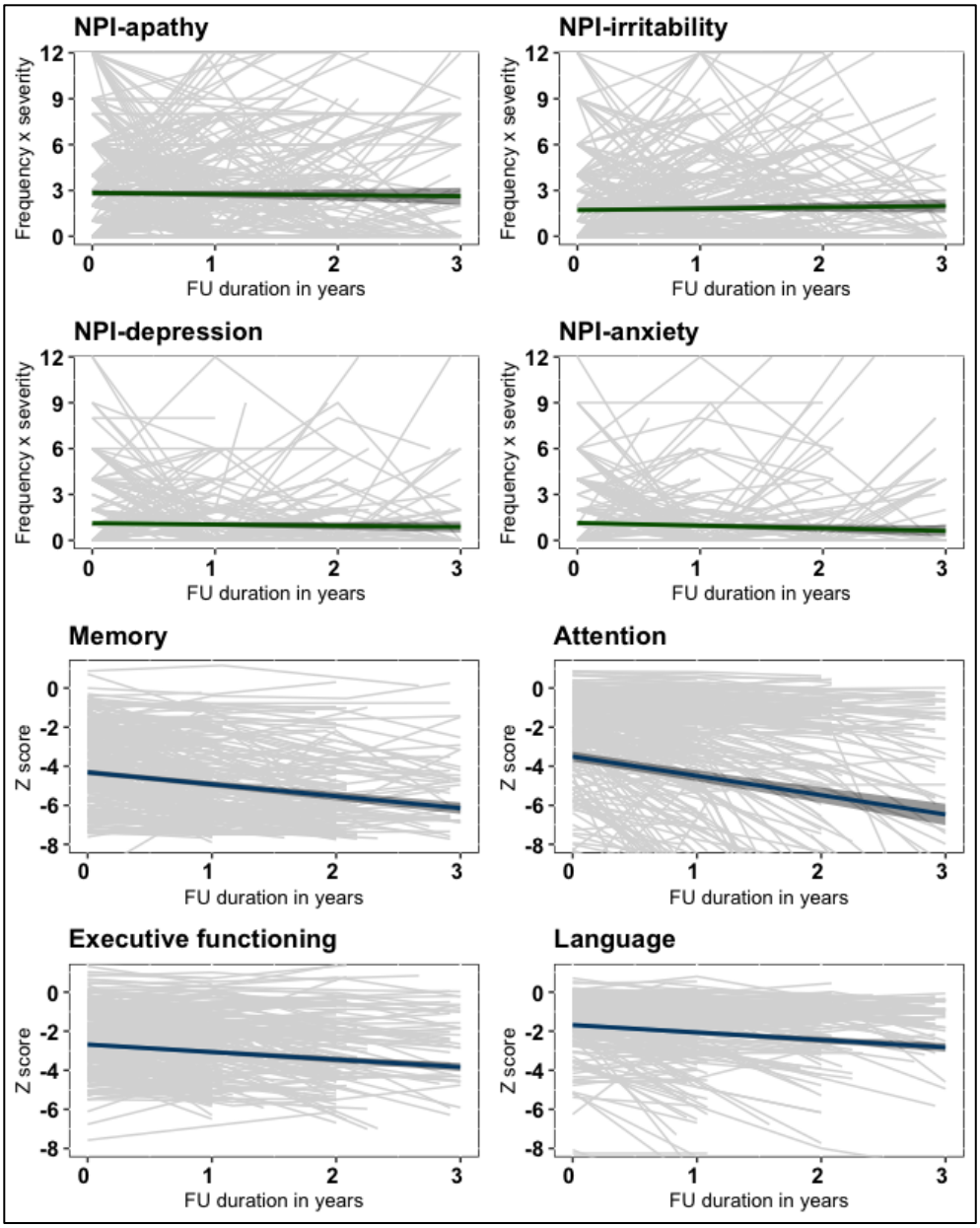
Notes. Individual trajectories are depicted with model based trends with 95% confidence intervals. Data show the four most prevalent neuropsychiatric symptoms at baseline and cognitive domains with most data available. See Supplemental Figure 1 for all data.

Figure 3. Longitudinal neuropsychiatric inventory domain scores and cognitive functioning for patients with β-amyloid–positive MCI at baseline



Notes. Individual trajectories are depicted with model based trends with 95% confidence intervals. Data show the four most prevalent neuropsychiatric symptoms at baseline and cognitive domains with most data available. See Supplemental Figure 2 for all data.

Figure 4. Longitudinal neuropsychiatric inventory domain scores and cognitive functioning for patients with β-amyloid–positive AD dementia at baseline



Notes. Individual trajectories are depicted with model based trends with 95% confidence intervals. Data show the four most prevalent neuropsychiatric symptoms at baseline and cognitive domains with most data available. See Supplemental Figure 3 for all data.

Cross-sectional associations between NPS and cognitive functioning at baseline

Age-, sex-, and education-corrected LMM in A+ AD dementia showed that higher baseline NPI total scores were associated with lower baseline MMSE scores (β = -0.08, 95% CI [-0.14, -0.02], FDR-adjusted $p < 0.001$) and lower performance on visuospatial abilities (β = -0.11, 95% CI [-0.18, -0.04], FDR-adjusted $p < 0.05$). Baseline NPI total scores were not related to cognitive functioning at baseline in A+ SCD and A+ MCI (all FDR-adjusted $p > 0.05$, Supplemental Table 5).

Next, age-, sex-, and education-corrected LMM assessing the associations between the presence of specific NPS and baseline cognitive performance showed that the presence of aberrant motor behaviors (β = -0.28 95% CI [-0.43, -0.13], FDR-adjusted $p < 0.05$), agitation (β = -0.27 95% CI [-0.43, -0.11], FDR-adjusted $p < 0.05$), euphoria (β = -0.27 95% CI [-0.41, -0.12], FDR-adjusted $p < 0.05$), and apathy (β = -0.18, 95% CI [-0.30, -0.06], FDR-adjusted $p < 0.05$) were associated with worse MMSE scores in A+ AD dementia. The presence of nighttime behaviors was related to worse performance in language in AD dementia (β = -0.29, 95% CI [-0.44, -0.13], FDR-adjusted $p < 0.05$). In A+ MCI, the presence of hallucinations was associated with worse performance in attention (β = -1.73, 95% CI [-2.68, -0.79], FDR-adjusted $p < 0.05$). We found no associations between the presence of specific NPS and cognitive functioning at baseline in A+ SCD (all FDR-adjusted $p > 0.05$, Supplemental Table 5).

Repeating age-, sex-, and education-corrected LMM for clinically relevant NPS (NPI domain score ≥ 4) yielded highly similar results (Supplemental Table 6).

Associations between baseline NPS and cognitive functioning over time

Using LMMs adjusted for age, sex, and education, baseline NPI total scores were not associated with changes in MMSE scores or cognitive domains over time in our cohort of A+ individuals ranging from SCD to AD dementia (all FDR-adjusted $p > 0.05$, Supplemental Table 7). With regard to specific NPS, baseline irritability was associated with less steep memory decline over time in individuals with A+ SCD at baseline (β = 0.44, 95% CI [0.26, 0.61], FDR-adjusted $p < 0.001$). None of the baseline NPI domain scores was associated with cognitive functioning over time in A+ MCI and A+ AD dementia (all FDR-adjusted $p > 0.05$, Supplemental Table 7).

Repeating these age-, sex-, and education-corrected LMM with the presence of clinically relevant NPS (NPI domain score ≥ 4) did not change our findings (Supplemental Table 8).

Discussion

The main findings in this A+ sample are (1) high prevalence rates of NPS across all clinical AD stages, (2) a substantial heterogeneity in trajectories of NPS over time, (3) cross-sectional associations between the presence and severity of NPS and worse cognitive functioning in dementia, and (4) absence of clear associations between

baseline NPS and performance on NPS were prevalent across the entire clinical AD spectrum and showed little relation with clinical severity.

Almost 90% of the patients with A+ AD dementia showed at least one NPS, which is in line with previous studies.[5,117] Furthermore, over 80% of the individuals in the predementia AD stages exhibited at least one NPS, which is remarkably higher compared to prior studies.[120,121] Although NPS prevalence and severity was higher in AD dementia compared to predementia AD stages, our findings suggest that NPS may precede cognitive impairment during the clinical course of AD. These findings support the construct of mild behavioral impairment (MBI) by recognizing that NPS can be an early manifestation of dementia.[31] We were not able to establish the prevalence of MBI in our study as we had no information on the duration and degree of impairment of the NPS in the predementia stages. We did not find many differences in NPS prevalence and severity between individuals with A+ SCD and individuals with A+ MCI, while some specific NPS were even more prevalent in A+ SCD compared to A+ MCI. NPS that were common in the A+ SCD stage included affective symptoms, irritability, and nighttime behaviors and might be a psychological response to the initial cognitive decline experienced and might be a reason to visit the memory clinic.23 Prior studies have indeed shown higher NPS prevalence rates in predementia memory clinic cohorts compared to population based studies.[10,117,130] Moreover, the high NPS prevalence observed across all clinical stages in our cohort may also be influenced by the fact that these individuals visited a tertiary academic memory clinic with an overrepresentation of early onset and atypical AD.

Our results indicate a different evolution over time for NPS compared to cognitive symptoms across the AD clinical spectrum. As expected, cognitive functioning showed a gradual decline that was most pronounced in the dementia stage.[131] In contrast, the course of NPS showed a less coherent pattern with a relatively stable trends across all clinical AD stages, which is in line with prior research.[18,19] Moreover, we found substantial heterogeneity within individuals in their course of NPS compared to the intraindividual variation of the course of cognitive functioning over time. Although previous studies have also suggested large variability in NPS prevalence and evolution between and within patients,[4,20,132] the fluctuations in NPS observed in our study may also be due to methodologic aspects of NPS measurements. For example, while cognitive functioning was assessed by an extensive neuropsychological assessment covering five cognitive domains with at least two cognitive tests for each domain, NPS were measured using a single caregiver rating scale that can be affected by caregiver distress and recall bias.[81] To obtain better insight in fluctuations in NPS in AD, future studies could assess NPS on short time intervals using a combination of informant-based scales, clinician-rating instruments, and self-report measures, e.g. by using an Ecological Momentary Assessments approach in which existing NPS scales are adjusted for daily assessments.[133]

At baseline, we found associations between the presence and severity of NPS and lower cognitive performance in patients with AD dementia that were most evident when looking at NPI total scores and MMSE performance. We found little evidence for a cross-sectional relationship between NPS and cognitive functioning in the predementia AD stages. Cross-sectional relationships between NPS and cognitive deficits as measured with the MMSE have previously been reported in AD dementia,[11,134] and associations between NPS and performance on specific cognitive domains have also rarely been found in AD dementia.[119,122,135,136] These differences in cross-sectional associations between clinical AD stages found in this study may be explained by the larger degree of cognitive variability among individuals with AD dementia compared to predementia stages. We found no clear associations between baseline NPS and cognitive functioning over time across clinical stages. Although prior studies have yielded similar results in different cohorts of patients with AD dementia,[113,135,136] our findings are in contrast to several other studies that have related the presence of NPS with accelerated cognitive decline in individuals with normal cognition,[41,46] MCI,[42] and AD dementia.[118,137] Previous studies have suggested that NPS are an integral part of AD and that the presence of NPS may be suggestive of underlying AD pathology.[138] The studies described above that have previously examined the relationship between NPS and cognitive functioning have primarily included samples without AD biomarker evidence. As a consequence, the presence of NPS in these samples may be suggestive of underlying AD pathology and has therefore been associated with cognitive decline. However, we already substantially increased the likelihood of underlying AD pathology as all individuals in our sample were A+. Consequently, the presence of NPS may have less predictive value in this sample of A+ individuals.

Our findings provide useful information for the management of care for patients with AD. While one can expect a gradual decline of cognitive functioning over time, it appears difficult to predict the progression of NPS given the large differences between and within individuals despite group trajectories showing generally little change over time. These findings emphasize a patient centered approach in the assessment and management of NPS across all clinical AD stages. Moreover, more future studies are needed that focus on identifying subgroups of individuals at ris*k* for developing NPS.

Cognitive symptoms have been related to pathophysiologic and neurodegenerative processes in AD, with generally weaker associations with Aβ as compared to brain atrophy and tau pathology.[139] Several theories have been proposed to explain the manifestation of NPS in AD.[55,81] While the symptom hypothesis states that NPS result from AD-related neuropathology that also contributes to cognitive impairment in AD, the ris*k* factor hypothesis suggests that NPS arise from concurrent non-AD pathology, e.g. vascular depression.[55,140] Recent studies have reported

inconsistent associations between NPS and AD pathology,[57,59,141] while providing some evidence for associations with non-AD biomarkers.[55,142,143] Our findings suggested substantial fluctuations over time with no coherent pattern of decline or increase in NPS as the disease progresses, leaving room open for other factors affecting NPS in AD. In addition to neurobiological causes, a variety of psychosocial factors have been proposed to play a role in the emergence and worsening of NPS in AD, including unmet needs, stress among caregivers, and environmental triggers.[54] Our findings show substantial fluctuations in NPS over time and no clear associations with cognitive symptoms, suggesting that the symptom hypothesis alone cannot explain the emergence of NPS in AD.

Strengths of this study include the large well-defined sample of individuals who were all A+ and underwent an extensive neuropsychological battery used to assess cognitive functioning. However, this study also has some limitations. First, although we took a unilateral perspective when examining the relationship between NPS and cognitive functioning, we acknowledge that cognitive impairments can also contribute to the presence and worsening of NPS in AD.[144] Second, we examined a relatively young cohort of participants (mean [SD] age 66.3 [7.7]) who visited a tertiary memory clinic and may be characterized by a relative absence of age-related comorbidities. This may limit the generalizability of our findings to cohorts with older individuals with AD. Furthermore, the number of individuals with A+ SCD or A+ MCI at baseline with follow up assessments was low, resulting in low power and increasing potential risk of bias for these analyses. Analyses of potential bias in loss to follow-up of individuals showed little bias in A+ SCD and A+ MCI, but did show that individuals without follow-up assessments had more severe A+ AD dementia and greater NPS burden. Future studies with larger sample sizes including individuals with severe AD dementia are therefore needed. In addition, we did not have information on the use of psychotropic drugs, cholinesterase inhibitors, and memantine. This is an important limitation as these medications may affect the prevalence and evolution of both cognitive and neuropsychiatric symptoms. Finally, we were not able to formally test NPS trajectories using LMM, as assumptions of normality and linearity were not met. This was caused by a substantial proportion of zero scores on the NPI, as well as the way NPI domain scores are calculated, i.e. by multiplying the severity score of 0–3 by the frequency score of 0–4 so that the values 5, 7, 10, and 11 cannot be observed.[145,146] Using symptom-specific instruments such as the Apathy Evaluation Scale (score range 18–71), Cohen-Mansfield Agitation Inventory (score range 29–203), and Geriatric Depression Scale (score range 0–30) may not only help to fully characterize specific NPS, but also enables the use of statistical modeling due to a larger variation in potential scores compared to the NPI.

To conclude, NPS were prevalent in a well-defined Aβ-positive sample ranging from normal cognition to dementia. We found little association between NPS and

cognitive symptoms at baseline and over time across the AD clinical spectrum. These findings suggest that NPS and cognitive symptoms are independent manifestations of AD that show a different evolution over the course of the disease.

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Author contributions

W.S.E., E.v.d.B., R.O., J.M.P. designed the study; W.S.E., S.J.B., analyzed the data; W.S.E. drafted the manuscript for intellectual content; E.v.d.B., E.S., R.O., J.M.P. interpreted the data; A.E.L. was involved in the acquisition of neuropsychological data; C.E.T., was involved in the acquisition of CSF biomarker data; B.N.M.v.B. was involved in the acquisition of PET data; P.S., W.M.v.d.F. contributed to the acquisition of patient data from the Amsterdam Dementia Cohort; E.v.d.B., E.S., S.J.B., M.C., A.E.L., C.E.T., B.N.M.v.B., Y.A.L., P.S., W.M.v.d.F., R.O., J.M.P. revised the manuscript for intellectual content; J.M.P. supervised the study. All authors read and approved the final version of the manuscript.

Supplemental materials

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Chapter 2.2

Biweekly fluctuations of neuropsychiatric symptoms according to the Neuropsychiatric Inventory: Erratic symptoms or scores?

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Abstract

Background and Objectives

This study investigates the stability of neuropsychiatric symptoms (NPS) assessed biweekly using the Neuropsychiatric Inventory (NPI) in a memory clinic population during a six week period.

Methods

Twenty-three spousal caregivers (mean [SD] age = 69.7[8.8], 82.6% female) of 23 patients (43.5% had dementia) completed all assessments. The NPI was assessed four times during six weeks. We examined whether NPI domains were present during all four assessments, studied within-person variation for each NPI domain, and calculated Spearman's correlations between subsequent time-points. Furthermore, we associated repeated NPI assessments with repeated measures of caregiver burden to examine the clinical impact of changes in NPI scores over time.

Results

The course of NPS was highly irregular according to the NPI, with only 35.8% of the NPI domains that were present at baseline persisted during all six weeks. We observed large within-person variation in the presence of individual NPI domains (61.3%, range 37.5–83.9%) and inconsistent correlations between NPI assessments (e.g. range r_s = 0.20–0.57 for agitation, range r_s= 0.29–0.59 for anxiety). Higher NPI total scores were related to higher caregiver burden (r_s = 0.60, p < 0.001), but changes in NPI total scores were unrelated to changes in caregiver burden (r_s = 0.16, p = 0.20).

Conclusions

We observed strong fluctuations in NPI scores within very short time windows raising the question whether this represents erratic symptoms and/or scores. Further studies are needed to investigate the origins of these fluctuations.

Introduction

Neuropsychiatric symptoms (NPS) such as depression, apathy, agitation, and sleep disturbances are frequently observed in individuals who visit the memory clinic.[130,147] These symptoms have a major impact on the lives of patients and their caregivers and are associated with increased caregiver burden.[50,148,149] The Neuropsychiatric Inventory (NPI) is considered the gold standard to assess NPS in neurocognitive disorders.[86]

Previous studies that examined the course of NPS using the NPI have shown large within-person variability in the progression of NPI scores when administering the NPI every 6 to 12 months.[20,132,147,150] It remains unclear whether there is also such within-person heterogeneity in longitudinal NPI scores when measured during shorter time intervals, e.g. within weeks instead of months.[20] Although several studies have administered the NPI twice within a timeframe of 2–3 weeks to establish the test-retest reliability of the NPI,[145] knowledge on short-term trajectories of NPS according to repeated NPI assessments is lacking.

Here, we describe the stability of NPI scores over a period of six weeks in a memory clinic population. During this six week period, the NPI was administered biweekly in order to compare our findings with previous test-retest studies that have assessed the NPI within a similar timeframe.[e.g. 151-153] Furthermore, we compared the trajectories of NPI scores with repeated measures of caregiver burden. NPS is a well-known contributor to caregiver burden.[50,148,149] Therefore, we included a measure of caregiver burden to examine the clinical impact of short-term changes in NPI scores. Based on previous test-retest studies,[145] we hypothesized stable NPI scores over time for apathy and psychotic symptoms, while we expected less stable NPI scores for affective symptoms, agitation-related behaviors, and sleep disturbances.

Methods

Study design and participants

We invited all caregivers of patients who visited the memory clinic of the Erasmus MC in Rotterdam, the Netherlands, between June 2020 and July 2020, and between November 2020 and January 2021, to participate in this study. We included participants regardless of clinical diagnosis and presence/severity of NPS at baseline, with the only requirement that caregivers had to live with the patient. All patients underwent a standard diagnostic workup including medical history taking, neurological examination, neuropsychological assessment, and brain MRI. Clinical diagnoses were established using conventional diagnostic criteria during a multidisciplinary meeting.

Measures

The Dutch NPI and Dutch Caregiver Strain Index (CSI)-Expanded were administered in person to caregivers during the initial the memory clinic visit.[127,154] During the six

weeks that followed, the NPI and CSI-Expanded assessments were repeated every two weeks by telephone. Caregivers evaluated the presence, frequency (0–4), severity (0–3), and distress (0–5) of NPS in the previous two weeks. NPI domain scores were calculated by multiplying the frequency and severity scores (0–12). The presence of specific NPI domains was defined as an NPI domain score of ≥1. We summed the 12 NPI domain scores to obtain the NPI total score (0–144).[127] The Dutch CSI-Expanded was used to assess caregiver burden. This instrument covers aspects of caregiver strain (13 items) and aspects of caregiving that may decrease burden (5 items), resulting in a total score ranging between -5 and 13.[154]

Data analysis

We examined the prevalence of specific NPI domains at baseline and its persistence. NPI domains were persistent if they were present on all four assessments. For each NPI domain, we described the between-person variation (i.e. how many individuals had an NPI domain score of ≥ 1 at least once) and the within-person variation (i.e. total number of assessments in which NPS were present in individuals who had an NPI domain score of ≥ 1 at least once, with both 0% and 100% indicating no variation).[132] For each NPI domain, we conducted Spearman's correlations to examine the relationship between NPI domain scores on subsequent time-points (baseline–t1, t1–t2, t2–t3). Individual trajectories of NPI domain scores over time were plotted for descriptive purposes, but not analyzed at group-level.

We correlated NPI total scores with CSI-Expanded total scores across all time-points. Next, we calculated delta scores for NPI total scores and CSI-Expanded total scores for each time-point and associated these delta scores using Spearman's correlations.

To examine the effects of cognitive status, we conducted exploratory analysis in which prevalence, persistence, between-person variation, within-person variation, and Spearman's correlations between NPI domain scores were performed for patients with dementia and patients with cognitive impairment no dementia (CIND) separately.

Ethics

This study received ethical approval from the Medical Ethics Committee of the Erasmus University Medical Center (MEC-2020-0341). All participants gave informed consent.

Results

Study participants

A total of 26 caregivers agreed to participate in this study. There were three drop-outs during the study due to perceived burden (n = 1), acute health problems of the caregiver (n = 1), and loss of contact (n = 1). All analyses were conducted in the 23 caregivers who

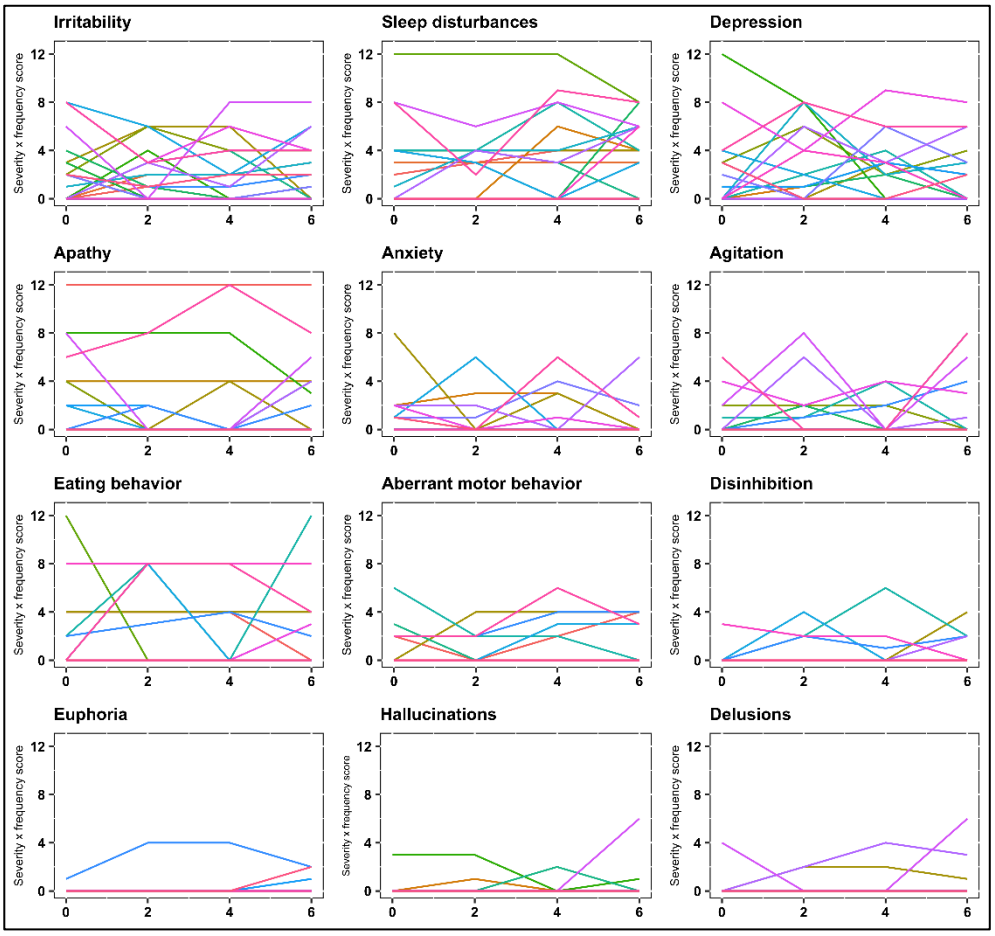
Table 1. Baseline characteristics of included sample

Caregivers (n = 23)	
Age, median (IQR)	71.0 (7.0)
Sex, N female (%)	18 (78.3%)
Education, median (IQR)	5.0 (2.0)
Relationship with patient, N(%)	
Spouse	23 (100.0%)
Patients (n = 23)	
Age, median (IQR)	74.0 (11.0)
Sex, N female (%)	5 (21.7%)
Education, median (IQR)	5.0 (2.0)
Clinical diagnosis, N (%)	
Dementia	10 (43.5%)
Alzheimer's disease dementia	6
Primary Progressive Aphasia	2
Behavioral variant Frontotemporal Dementia	1
Corticobasal Syndrome	1
Cognitive impairment no dementia, N(%)	8 (34.8%)
Mild cognitive impairment	6
Radiation-induced cognitive decline	1
Cognitive impairment due to epilepsy	1
No cognitive impairment, N (%)	4 (17.4)
Subjective cognitive decline	3
Major depressive episode	1
Could not be determined	1 (4.3%)
Months since clinical diagnosis, median (IQR) [a]	0.0 (0.0)
Mini-Mental State Examination score, median (IQR) [b]	26.0 (9.0)
Cognitive enhancer use at baseline, N (%)	0 (0.0%)
Cognitive enhancer started during study, N (%)	2 (8.7%)
Psychotropic drug use at baseline, N (%)	2 (8.7%)
Psychotropic drug started during study, N (%)	1 (4.3%)

Notes. IQR = interquartile range.
[a] Not applicable for n = 1.
[b] Missing data for n = 3.

completed all assessments (Table 1). Caregivers had a mean age of 69.7 (SD = 8.8), 82.6% were women, and all were spouses. The patients had a mean age of 72.8 (SD = 8.2) and 21.7% were women. Most patients were diagnosed with dementia (n=10,

Figure 1. Neuropsychiatric Inventory domain scores assessed biweekly



Notes. Each line represents the trajectories of the severity × frequency score (0–12) of each NPI domain for an individual participant assessed every two weeks during a six week period.

43.5%), eight individuals had CIND (34.8%), and four patients had no evidence of cognitive impairment (17.4%). A clinical diagnosis could not be determined in one individual (4.3%). Two patients (8.7%) were on a stable dose of psychotropic medications, while Escitalopram was prescribed during study period in only one patient (4.3%). A cognitive enhancer was prescribed during the six week period for two patients (8.7%).

Prevalence and course of NPS according to the NPI

At baseline, all caregivers indicated the presence of at least one NPS (mean number of NPI domains was 3.0 [range 1–6]), with a mean NPI total score of 12.3 (SD = 9.5). Irritability (56.5%), sleep disturbances (47.8%), and depression (42.3%) were most

Table 2. Prevalence, persistence, and between-person and within-person variation of the presence of specific NPI domains

NPI domain	Presence at baseline	Persistence[a]	Between-person variation[b]	Within-person variation[c]
Irritability	13 (56.5%)	7 (53.8%)	18 (78.3%)	70.8%
Sleep disturbances	11 (47.8%)	8 (72.7%)	14 (60.9%)	83.9%
Depression	10 (42.3%)	3 (30.0%)	16 (69.6%)	65.5%
Apathy	8 (34.8%)	4 (50.0%)	12 (52.2%)	60.4%
Anxiety	8 (34.8%)	1 (12.5%)	9 (39.1%)	55.6%
Eating behavior	6 (26.1%)	3 (50.0%)	10 (43.5%)	62.5%
Agitation	5 (21.7%)	1 (20.0%)	9 (39.1%)	61.1%
Aberrant motor behavior	5 (21.7%)	2 (40.0%)	7 (30.4%)	71.4%
Disinhibition	1 (4.3%)	0 (0.0%)	6 (26.1%)	50.0%
Euphoria	1 (4.3%)	1 (100.0%)	3 (13.0%)	50.0%
Hallucinations	1 (4.3%)	0 (0.0%)	4 (17.4%)	37.5%
Delusions	1 (4.3%)	0 (0.0%)	3 (13.0%)	66.7%

Notes.
[a] N (%) of individuals which showed NPS during all follow-up assessments when present at baseline.
[b] N (%) of individuals with NPS present at least at one time-point.
[c] For those with NPS at one time-point, % of assessments NPS was present.

common at baseline (table 2). Across all NPI domains, the within-person variation was 61.3% (range 37.5%-83.9%), indicating that NPI domains that were present once during the course of the study were observed at 61.3% of the four time-points (Table 2). Only 35.8% (range 0.0%–100.0%) of the NPI domains that were present at baseline persisted over all three follow-up assessments (Table 1). There were no substantial differences between patients with dementia and CIND in within-person variation across NPI domains (dementia: 63.5% [range 25.0–94.3%], CIND: 62.8% [range 25.0–79.2%]) and persistence of NPI domains (dementia: 37.2%, CIND: 35.8%) (see Supplemental Table 2).

Figure 1 shows considerable heterogeneity in course of NPI domain scores between individuals, but especially reveals substantial fluctuations within individuals. Spearman's correlations between NPI domain scores at two subsequent time-points (baseline–t1, t1–t2, t2–t3) varied greatly within NPI domains (see Supplemental Table 1). NPI total scores correlated significantly between time-points (range r_s = 0.55–0.67, $p < 0.01$), while low and inconsistent correlation coefficients were observed for specific NPI domains such as agitation (range r_s = 0.20–0.57), irritability (range r_s = 0.26–0.65), aberrant motor behavior (range r_s = 0.55–0.90), and anxiety (range r_s = 0.29–0.59). Spearman's correlations were slightly higher in patients with dementia compared to individuals with CIND for NPI total scores (dementia: range r_s=0.70–0.87, all $p < 0.05$, CIND range r_s = 0.56–0.83, 2/3 $p > 0.05$) and several NPI domain scores (Supplemental Table 3).

We considered the presence of sleep disturbances, irritability, and aberrant motor behavior to be most stable, while the presence of hallucinations, disinhibition, and anxiety were the least stable within persons (Table 2). When present, we considered the severity/frequency of apathy, sleep disturbances, and euphoria most stable, while depression, anxiety, hallucinations were the least stable (Figure 1 & Supplemental Table 1).

Associations between NPI scores and caregiver burden

Across all time-points, higher NPI total scores were related to higher caregiver burden (r_s = 0.60, $p < 0.001$). However, changes in NPI total scores were unrelated to changes in caregiver burden (r_s = 0.16, p = 0.20).

Discussion

This study shows that NPI scores at one time-point in a memory clinic sample are poorly related to NPI scores administered only two weeks later. Our findings provide further evidence for the large variability of NPI scores within individuals with neurocognitive disorders.[20,132,147,150] When looking at specific NPI domains, we found lowest stability over time for anxiety, hallucinations, depression, and disinhibition, which is in line with prior test-retest studies.[145,151-153] Our findings extend previous studies by looking at

trajectories over a period over several weeks compared to the commonly examined (bi)annual NPI assessments. [20,132,147,150]

The large within-person variation in NPI scores could reflect substantial fluctuations in the manifestation of NPS in patients visiting the memory clinic. Previous studies that have used diaries to daily assess NPS in dementia suggested a rather erratic nature of NPS.[155-157] This is in line with the growing body of evidence emphasizing the role of proximal causes of NPS including psychosocial factors (e.g. caregiver burden, caregiver communication style), environmental factors (e.g. light, temperature), and somatic conditions (e.g. pain, thirst).[54,156]

Alternatively, the irregular course of NPI scores could also arise from methodologic issues related to the NPI. Our finding that changes in NPI scores were unrelated to changes in caregiver burden could support this. Several factors could affect the NPI scores that are unrelated to the actual manifestation of NPS in our sample. First, caregivers tend to use different terminologies to describe NPS compared to the terms used in instruments such as the NPI.[158] They are also inclined to use broad terms covering multiple NPS that would generally be considered clinically distinct symptoms.[158] Consequently, caregivers may have endorsed different NPI domains during follow-up assessments, although similar NPS were present during the course of the study. Furthermore, although recall bias was reduced because caregivers were asked to evaluate the presence of NPS during the last two weeks instead of the commonly used four weeks, the recollection of NPS remains challenging.[89] Moreover, mood, fatigue, and distress among caregivers can affect the NPI administration.[75,89] To overcome these challenges, future studies could pair repeated NPI assessments with daily NPS measurements using an Ecological Momentary Assessments approach.[159]

Also, the variation in NPI scores could be an effect of unknown measurement error related to the NPI as little is known about what we should consider as actual change in NPI scores. Different statistical methods such as the standard error of measurement and the reliable change index have been developed to determine the minimal detectable change of clinical outcome scales.[160,161] These methods have been used to establish minimal detectable change for the individual domains of the nursing home version of the NPI after two weeks and the NPI total score after 52 weeks.[153,162] However, these psychometric indices that establish minimal detectable change do not determine minimally important change, i.e. clinically meaningful change.[160,161] Anchor-based approaches can be used to determine clinically meaningful change by which changes on an instrument are compared with minimally important changed defined by patients, caregiver, and/or clinicians. Future studies are needed that align NPI trajectories with anchor definitions of meaningful change in NPS to establish which changes in NPI scores we should consider as clinically meaningful.

Strengths and limitations

Strengths of this study are the inclusion of a representative tertiary memory clinic sample consisting of various clinical diagnoses and the low level of psychotropic medications used across patients. There are also some limitations to our study. First, the majority of the participants were still undergoing diagnostic workup and received a diagnosis at some point during the study. This may have affected the manifestation of NPS as receiving a diagnosis can have great psychological impact. Second, we included a small and clinically heterogeneous memory clinic population. The low sample size may affected the stability of correlation coefficients, especially the correlations below 0.50.[163] Furthermore, the proportion of female patients (22%) in our sample was lower than expected based on previous studies in Dutch academic memory clinics (40-55% females).[147,164,165] Although our within-person analysis reduces the potential impact of the clinical heterogeneity and underrepresentation of female patients, our results need to be replicated in larger samples including a higher proportion of females, especially since NPS may manifest differently in females than males.[166] Third, we found indications that NPI scores were somewhat more stable in individuals with dementia compared to individuals with CIND. This suggest that the NPI may be more appropriate to repeatedly assess NPS when used in individuals with dementia, which could be expected as the NPI was originally developed and validated to measure NPS in dementia.[84] Yet, future studies with larger samples are needed to examine the effects of demographic characteristics and clinical characteristics such as dementia type on the short term trajectories of NPI scores. Finally, no clear cutoffs exist for measures used in this study (e.g. within-person variation) making the comparison between NPI domains somewhat subjective.

Conclusion

This study suggest highly unstable NPI scores when assessed at two-week intervals. These findings question the reliability of NPI scores when administered at short-term intervals at the memory clinic, but also as outcome measure in trails that evaluate the effectiveness of (non)pharmacological interventions, especially for those who do not meet diagnostic criteria for dementia (i.e. CIND). Further studies are needed to investigate whether the large within-person variability of NPI scores reflect the erratic nature of NPS in neurocognitive disorders or arise from methodological issues. Although the origin of these fluctuations remains unclear, memory clinic clinicians should be aware that NPI scores at one time point are poorly related to future NPI scores within a timeframe of weeks.

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Author contributions

J.M.P., R.O. acquired funding for this study; W.S.E., E.v.d.B, J.M.P. designed the study; W.S.E., A.d.T., D.E.P., S.F., L.C.J., J.v.H. collected the data; W.S.E. analyzed the data and interpreted the data assisted by J.M.P., E.v.d.B.; W.S.E. drafted the manuscript for intellectual content; A.d.T., D.E.P., M.C., S.F., L.C.J., J.v.H., E.S., R.O., F.J.d.J., E.v.d.B., J.M.P. revised the manuscript for intellectual content; J.M.P., E.v.d.B. supervised the study; All authors read and approved the final version of the manuscript.

Supplemental materials

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Chapter 2.3

Sex differences in neuropsychiatric symptoms in Alzheimer's disease: A meta-analysis

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* shared first authorship.

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Abstract

Background and Objectives

Neuropsychiatric symptoms (NPS) are common in individuals with Alzheimer's disease (AD) dementia, but substantial heterogeneity exists in the manifestation of NPS. Sex differences may explain this clinical variability. We aimed to investigate the sex differences in the prevalence and severity of NPS in AD dementia.

Methods

Literature searches were conducted in Embase, MEDLINE/PubMed, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, PsycINFO, and Google Scholar from inception to February 2021. Study selection, data extraction, and quality assessment were conducted in duplicate. Effect sizes were calculated as odds ratios (OR) for NPS prevalence and Hedges' *g* for NPS severity. Data were pooled using random-effects models. Sources of heterogeneity were examined using meta-regression analyses.

Results

Sixty-two studies were eligible representing 21,554 patients (61.2% females). The majority of the included studies had an overall rating of fair quality (71.0%), with ten studies of good quality (16.1%) and eight studies of poor quality (12.9%). There was no sex difference in the presence of any NPS (k = 4, OR = 1.35 [95% confidence interval 0.78, 2.35]) and overall NPS severity (k = 13, g = 0.04 [− 0.04, 0.12]). Regarding specific symptoms, female sex was associated with more prevalent depressive symptoms (k = 20, OR = 1.60 [1.28, 1.98]), psychotic symptoms (general psychosis k = 4, OR = 1.62 [1.12, 2.33]; delusions k = 12, OR = 1.56 [1.28, 1.89]), and aberrant motor behavior (k = 6, OR = 1.47 [1.09, 1.98]). In addition, female sex was related to more severe depressive symptoms (k = 16, g = 0.24 [0.14, 0.34]), delusions (k = 10, g = 0.19 [0.04, 0.34]), and aberrant motor behavior (k = 9, g = 0.17 [0.08, 0.26]), while apathy was more severe among males compared to females (k = 11, g = − 0.10 [− 0.18, − 0.01]). There was no association between sex and the prevalence and severity of agitation, anxiety, disinhibition, eating behavior, euphoria, hallucinations, irritability, and sleep disturbances. Meta-regression analyses revealed no consistent association between the effect sizes across studies and method of NPS assessment and demographic and clinical characteristics.

Conclusions

Female sex was associated with a higher prevalence and greater severity of several specific NPS, while male sex was associated with more severe apathy. While more research is needed into factors underlying these sex differences, our findings may guide tailored treatment approaches of NPS in AD dementia.

Introduction

Neuropsychiatric symptoms (NPS) are highly prevalent in individuals with Alzheimer's disease (AD) dementia.[147] Although the majority of individuals with AD dementia exhibit NPS during the course of their disease, there is substantial heterogeneity among individuals regarding the manifestation and evolution of NPS.[20,147]

Emerging research has provided evidence for sex as an important, yet understudied factor that may play an important role in explaining clinical variability within AD dementia. Note that sex refers to the biological and physiological difference between females and males, while gender encompasses the social, environmental, and cultural influences on the biological factors in females and males.[167] Well-known sex differences in AD dementia include the disproportionate higher prevalence and lifetime ris*k* for developing AD dementia in females compared to males,[168] with previous studies showing that females are shown to be more vulnerable to AD pathology and AD ris*k* factors compared to males.[169-171] Furthermore, prior research has suggested more severe cognitive deficits and faster cognitive decline among females with AD dementia.[170,172,173]

Prior studies on sex differences in NPS in AD dementia have reported mixed findings. While several studies have suggested that females show a greater and a wider range of NPS,[174,175] others did not to find any sex differences in the prevalence and severity of NPS in AD dementia.[176,177]. When looking at specific NPS, female sex has been related to the presence of affective symptoms and psychotic symptoms,[178,179] whereas apathy and agitation were more prevalent in males.[179,180]. Determining sex differences in NPS prevalence and severity in individuals with AD has important clinical implications.[181] This knowledge may not only aid personalized assessment, but also guide interventions for NPS in AD. Furthermore, sex differences may have health policy and resource allocation implications for NPS screening and management.

To date, sex differences in NPS in AD dementia have not been systematically reviewed. Therefore, we aimed to review the existing literature on sex differences in specific NPS in AD using a meta-analytic approach. In addition, we examined the sources of heterogeneity across studies including study setting, methods of NPS assessment, and demographic and clinical characteristics.

Methods

This systematic review was preregistered with PROSPERO (CRD42020168064) and conducted conform to the PRISMA guidelines.[182]

Search strategy

In consultation with a research librarian, databases Embase, MEDLINE/PubMed, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, PsycINFO, and Google Scholar were searched from inception to February 2021 (see full search

queries in Supplemental Table 1). Studies included in the most recent meta-analysis summarizing the prevalence of NPS in AD dementia were also screened.[5]. Reference lists of identified studies were manually checked for potential studies of interest. Finally, experts on the author team were consulted to ensure that no relevant studies were missing.

Study selection

Articles were screened and selected based on the following criteria: (1) NPS prevalence (dichotomous data) and/or NPS severity (continuous data) for females and males separately. We included papers that referred to both sex differences and gender differences. Furthermore, sex differences had to be reported for either overall NPS burden or specific symptoms and not for clusters of NPS due to its limited comparability. (2) Clinical diagnosis of AD dementia based on either the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) classification systems or conventional consensus criteria.[1,183]. (3) NPS were assessed using a validated instrument such as the Neuropsychiatric Inventory (NPI)[84] or established using well-defined diagnostic criteria, e.g. depression in AD.[29] (4) Studies had to report sufficient information needed to perform a meta-analysis (e.g. means, standard deviations, frequency tables, and/or odds ratios [*OR*]). (5) Studies had a cross-sectional observational design. In case of longitudinal data, only baseline data were used. Articles containing small selectively sampled populations were excluded, e.g. sex- and age-matched samples. In cases in which the same cohort of patients was used in different studies, only the study with the largest N was selected.

Two independent reviewers (W.S.E., M.P.) screened titles and abstracts, and subsequently inspected full texts for eligibility. Discrepancies were discussed, and consensus was reached (with E.v.d.B.).

Data extraction

Data of each paper was extracted in duplicate (W.S.E., M.P.). In cases where statistical information was missing, an attempt was made to contact the study's principal investigator. This was unsuccessful in two studies.

Quality assessment

Two independent reviewers (W.S.E, M.P.) evaluated the quality of each study using an adjusted quality assessment tool for observational studies from the National Heart, Lung, and Blood Institute (Supplemental Table 2).[184,185] Originally, this tool includes 14 quality criteria covering the methodology and study population characteristics. Since we only included cross-sectional studies, we did not evaluate item 7 "Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?", item 10 "Was the exposure(s) assessed more than

once over time?", and item 13 "Was loss to follow-up after baseline 20% or less?". Furthermore, item 14 "Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?" was also omitted since studies were not required to include covariates in their analyses.

Data synthesis and statistical analysis

For this meta-analysis, we studied sex differences in NPS for studies reporting on NPS prevalence and NPS severity. We examined sex differences in studies that reported the prevalence of any NPS, total scores of NPS measures (e.g. NPI total score), and the prevalence and/or severity for specific NPS analogous to the twelve NPI domains: delusions, hallucinations, agitation/aggression, depressive symptoms, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime behaviors, and eating behaviors.[84] In addition, psychotic symptoms were also studied separately since studies used criteria for psychosis in AD,[186] psychosis domain score of the Behavioural Pathology in Alzheimer's Disease (BEHAVE-AD) Scale,[85] or NPI domains of hallucinations and delusions combined.[84] Note that instruments such as the NPI assess neuropsychiatric symptoms, while diagnostic criteria such as psychosis in AD or DSM diagnosis of a major depressive episode capture neuropsychiatric syndromes. In our analyses, these assessment methods will initially be combined and denoted as symptoms. Next, meta-regression analyses will be used to examine the differences in the outcomes between studies that used questionnaires (symptoms) and studies that used diagnostic criteria (syndromes).

For the studies that reported on NPS prevalence, *OR*s were calculated based on the 2 × 2 frequency tables based on the following formula:

$$OR = \frac{\text{NPSfemales/non} - \text{NPSfemales)}}{\text{(NPSmales/non} - \text{NPSmales)}}.$$

An *OR* = 1 represents that there is no sex difference in NPS, whereas an *OR* > 1 suggests that female sex is associated with higher odds of having NPS and an *OR* < 1 suggest that male sex is associated with higher odds of having NPS. For the studies that reported on NPS severity, means and standard deviations were converted into Hedges' g using the following formula:

$$g = \frac{M_1 - M_2}{SD_{pooled}},$$

where SD_{pooled} was calculated based on the following formula:

$$SD_{pooled} = \sqrt{\frac{SD_1^2 + SD_2^2}{2}}.$$

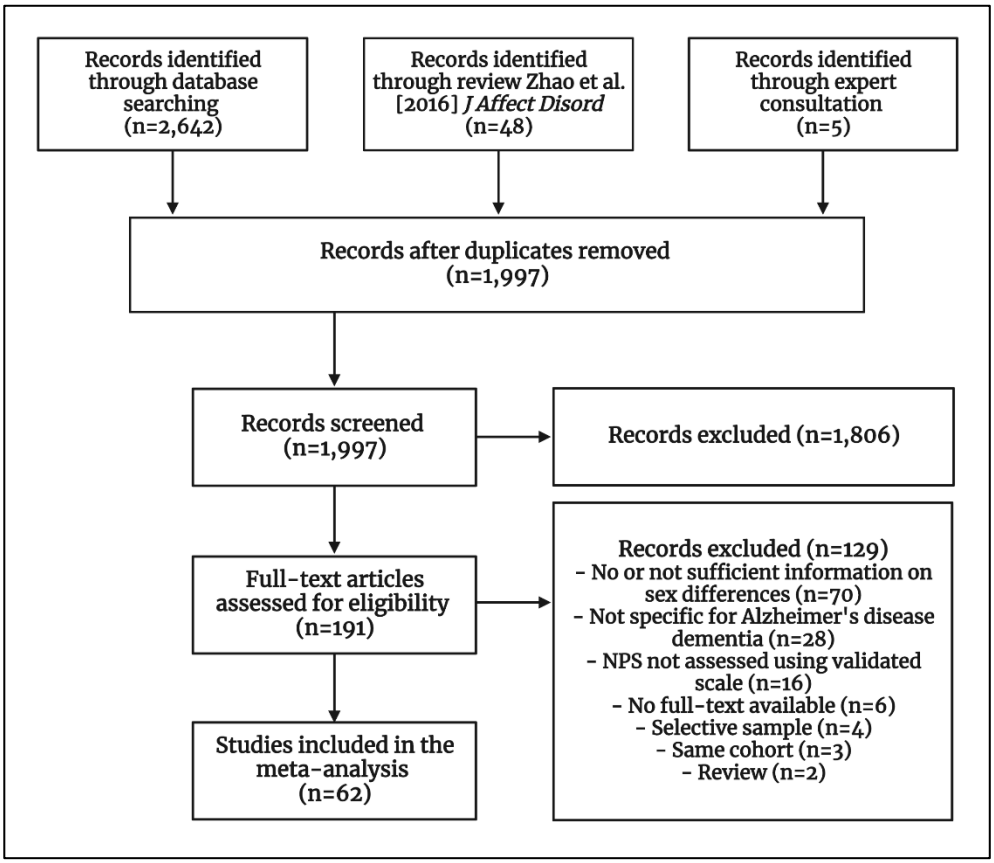
If studies did not report the means and standard deviations, reported effect sizes were converted to Hedges' g using conventional formulas.[187] A positive effect size indicates more severe NPS for women compared to men.

Heterogeneity was assessed with the I^2 statistic and tested using Cochran's Q-test.[188] The I^2 statistic is an appraisal of the consistency of the effect sizes: > 25% suggests low, > 50% suggests moderate, and > 75% suggests high inconsistency across studies. In case of a significant Q statistic and moderate or high inconsistency across studies, we conducted outliers/influential study diagnostics. Influential studies were identified if one of the following was true: *DFFITS* value > $3\sqrt{(p/(k-p))}$ where p is the number of model coefficients and k is the number of studies, lower tail of a chi-square distribution of p degrees of freedom cutoff by the Cook's distance > 50%, hat value > $3(p/k)$, and/or the *DFBETAS* value > 1.[189] In case influential cases were identified, leave-1-out meta-analyses were conducted to examine how individual studies affected the summary statics. Based on these analyses and visual examination of the forest plots, we excluded one study in the meta-analysis for studies reporting on the prevalence of any NPS, one study in the meta-analysis on psychotic symptoms prevalence, one study in the meta-analysis on irritability prevalence, one study in the meta-analysis on agitation prevalence, and one study in the meta-analysis on aberrant motor behavior prevalence (Supplemental Table 8). For meta-analyses on NPS severity, one study was identified as an outlier in the meta-analyses on the total scores of NPS measures, agitation, aberrant motor behavior, anxiety, apathy, delusions, depressive symptoms, disinhibition, euphoria, and hallucinations (Supplemental Table 8).

The following meta-regression and subgroup analyses were selected a priori: study setting (community-based vs. clinic sample), clinical relevance (neuropsychiatric symptoms vs. a clinically relevant cutoff score or clinical criteria for NPS syndrome), method of NPS assessment (proxy vs. self-reported), NPI vs. non-NPI measures, mean age of patients, mean years of education of patients, mean Mini-Mental State Examination (MMSE) score, mean disease duration in years, percentage of APOE-ε4 carriers, and study quality (poor/fair/good). In addition, we ran subgroup analyses for studies reporting significant sex differences in age, MMSE score, proportion APOE-ε4 carriers, and/or disease duration compared to studies that did not find sex differences in these characteristics. We tested whether the heterogeneity across studies was explained by these moderators using omnibus Wald-type tests. We conducted meta-regression analyses including studies that were identified as outliers and only if a minimum of six studies was available for continuous moderators and at least four studies were available for each subgroup of categorical moderators.[190]

Funnel plot asymmetry was evaluated as an indication for publication bias. Begg's ran*k* tests and Egger's regression tests were used to test for funnel plot asymmetry. If any of these tests was indicative of funnel plot asymmetry, the trim-and-

Figure 1. PRISMA flowchart of included studies



fill method was used to estimate the number of missing studies and to recompute the summary statistics based on complete data.[191]

In order to aggregate studies that reported multiple independent outcomes, we used multilevel meta-analyses including a random factor for study. Multilevel meta-analyses were conducted for 18 outcomes across the 17 studies that reported the severity of depressive symptoms. Because substantial heterogeneity between studies was expected, random-effects models were applied for all analyses. All analyses were conducted using the metafor package in *R* v4.0.[192]

Results

Characteristics of included studies

A total of 1997 unique articles were obtained and screened for eligibility (Fig. 1). Next, the full texts of 191 records were reviewed, of which 62 met all the inclusion criteria (Supplemental Table 3).

The 62 studies included 21,554 individuals with AD dementia, including 13,201 (61%) females and 8,353 (39%) males. The majority of studies assessed NPS using a proxy instrument (k = 49, 79%), of which 31 used the NPI and four used its questionnaire form. Six studies additionally used self-report scales (10%). In eight studies (13%), clinicians established NPS based on a DSM diagnosis, an ICD-9 diagnosis, or criteria for depression in AD,[29] psychosis in AD,[186] or apathy in AD.[193] Information on the characteristics of the informant who rated NPS was reported in four studies,[194-197] of which two reported these characteristics for male and female patients separately.[195,196] The majority of the informants were the spouse [36,37,38,39], which was primarily the case for male patients (66–86% for male patients and 21–38% in female patients).[195,196] The majority of caregivers were female,[194-197] although to a lesser extent for female patients (90% for male patients and 61% for female patients).[195] Clinical AD diagnoses were supported by positive AD biomarkers in subsamples of only two studies. Information on APOE-ε4 status was reported in 13 studies, and percentage APOE-ε4 carriers ranged from 22% to 68% (Supplemental Table 3). Forty studies provided dichotomous NPS measures, while 17 studies reported continuous NPS measures and five studies reported both dichotomous and continuous outcomes. This resulted in 43 studies reporting on NPS prevalence and 22 studies reporting on NPS severity.

Study quality

The majority of the included studies had an overall rating of fair quality (n = 44, 71%), with ten studies of good quality (16%) and eight studies of poor quality (13%) (Supplemental Table 2).

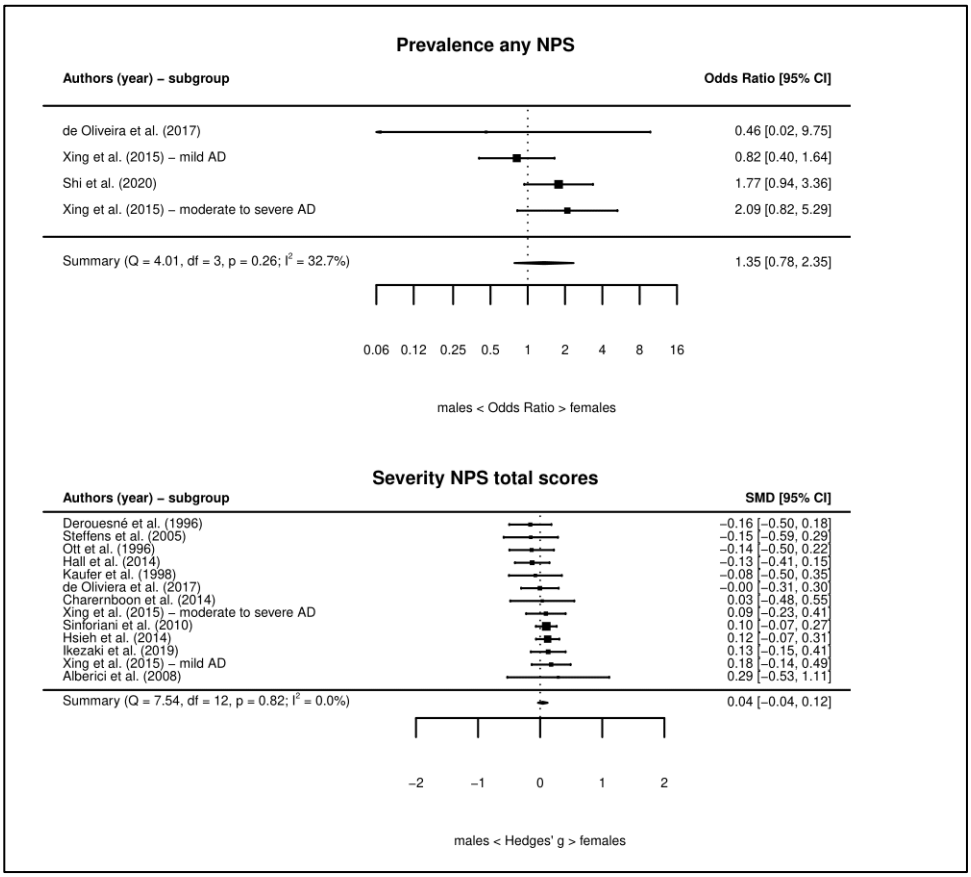
Sex differences in any NPS and total scores of NPS measures

There was no sex difference in the prevalence of any NPS (k = 4, OR = 1.35 [95% CI, 0.78, 2.35], p = 0.28), with low heterogeneity across studies (I^2 = 32.74%, Q = 4.01, p = 0.25) (Table 1 & Figure 2). We also found no relationship between sex and total severity scores of NPS instruments (k = 13, g = 0.04 [-0.04, 0.12], p = 0.31), with low heterogeneity across studies (I^2 = 0.00%, Q = 7.54, p = 0.82) (Table 2 & Figure 2).

Sex differences in the prevalence of specific NPS

We observed a higher prevalence among females compared to males for psychotic symptoms (k = 4, OR = 1.62 [1.12, 2.33], p = 0.01), depressive symptoms (k = 20, OR = 1.60 [1.28, 1.98], p < 0.001), delusions (k =12, OR = 1.56 [1.28, 1.89], p < 0.001), and aberrant motor behavior (k = 6, OR = 1.47 [1.09, 1.98], p = 0.01) (Figure 3). The heterogeneity across the studies included in these meta-analyses was moderate for depressive symptoms (I^2 = 58.19%, Q = 51.99, p < 0.001), but low for the meta-analyses on psychotic symptoms (I^2 = 0.00%, Q = 1.98, p = 0.58), delusions (I^2 = 0.00%, Q = 8.51,

Figure 2. Forest plots for the prevalence of any NPS and severity of NPS total scores



Notes. AD = Alzheimer's disease, NPS = neuropsychiatric symptoms.

p = 0.67), and aberrant motor behavior (I^2 = 0.00%, Q = 2.51, p = 0.78). There were no significant sex differences in the prevalence of the remaining NPS (Table 1 & Supplemental Figure 1).

Sex differences in the severity of specific NPS

The results showed that female sex was associated with more severe depressive symptoms (k = 16, g = 0.24 [0.14, 0.34], p < 0.001), delusions (k = 10, g = 0.19 [0.04, 0.43], p = 0.01), and aberrant motor behavior (k = 9, g = 0.17 [0.08, 0.26], p < 0.001). Furthermore, apathy was more severe among males compared to females (k = 11, g = -0.10 [-0.18, -0.01], p = 0.02) (Figure 4). We found moderate heterogeneity across studies including in the meta-analyses on delusions (I^2 = 58.78%, Q = 19.99, p = 0.02) and depressive symptoms (I^2 = 44.29%, Q = 30.15, p = 0.02), while heterogeneity was low for aberrant motor behavior (I^2 = 0.00%, Q = 3.25, p = 0.92) and apathy (I^2 = 0.00%,

Table 1. Sex differences in the prevalence of neuropsychiatric symptoms in Alzheimer's disease dementia

NPS	*k*	*OR* [95% CI][a]	*Z*	*P*	*Q*	*P Q*	I^2
Any NPS present (outlier excluded)	4	1.35 [0.78, 2.35]	1.07	0.28	4.01	0.25	32.74
Psychotic symptoms (outlier excluded)	4	1.62 [1.12, 2.33]	2.56	0.01	1.98	0.58	0.00
Depressive symptoms	20	1.60 [1.28, 1.98]	4.20	<0.001	51.99	<0.001	58.19
Delusions	12	1.56 [1.28, 1.89]	4.45	<0.001	8.51	0.67	0.00
Aberrant motor behaviors (outlier excluded)	6	1.47 [1.09, 1.98]	2.53	0.01	2.51	0.78	0.00
Anxiety	8	1.42 [0.74, 2.71]	1.05	0.29	23.37	0.002	78.49
Eating behavior	5	1.31 [0.97, 1.76]	1.78	0.08	5.40	0.25	22.00
Disinhibition	8	1.17 [0.80, 1.70]	0.81	0.42	13.54	0.06	42.07
Irritability (outlier excluded)	5	1.14 [0.83, 1.56]	0.80	0.43	6.11	0.19	0.00
Hallucinations	9	1.03 [0.79, 1.35]	0.24	0.81	9.89	0.27	14.23
Agitation (outlier excluded)	10	1.00 [0.75, 1.35]	0.01	0.99	16.63	0.06	46.06
Euphoria	6	0.98 [0.57, 1.68]	-0.08	0.93	6.56	0.26	14.77
Apathy	12	0.92 [0.73, 1.17]	-0.65	0.51	17.66	0.09	36.92
Sleep disturbances	8	0.86 [0.63, 1.16]	-0.99	0.32	14.49	0.04	62.49

Notes. k = number of studies, NPS=neuropsychiatric symptoms.

[a] OR = odds ratio (OR=1 no sex differences; OR > 1 female sex associated with NPS; OR < 1 male sex associated with NPS.

Table 2. Sex differences in the severity of neuropsychiatric symptoms in Alzheimer's disease dementia

NPS	*k*	*Hedges' g* [95% CI][a]	*Z*	*P*	*Q*	*P Q*	I^2
Total score NPS measure (outlier excluded)	13	0.04 [-0.04, 0.12]	1.03	0.31	7.54	0.82	0.00
Depressive symptoms (outlier excluded)	16	0.24 [0.14, 0.34]	4.59	<0.001	30.15	0.02	44.29
Delusions (outlier excluded)	10	0.19 [0.04, 0.34]	2.53	0.01	19.99	0.02	58.78
Aberrant motor behaviors (outlier excluded)	9	0.17 [0.08, 0.26]	3.56	<0.001	3.25	0.92	0.00
Anxiety (outlier excluded)	10	0.11 [0.00, 0.22]	1.98	0.05	13.27	0.01	25.15
Sleep disturbances	6	0.11 [-0.02, 0.24]	1.62	0.11	5.66	0.34	21.77
Disinhibition (outlier excluded)	10	0.08 [-0.05, 0.21]	1.16	0.25	17.01	0.05	46.48
Eating behavior	6	0.07 [-0.04, 0.18]	1.28	0.20	3.23	0.67	0.00
Hallucinations (outlier excluded)	10	0.07 [-0.13, 0.26]	0.65	0.51	36.63	<0.001	77.20
Agitation (outlier excluded)	11	0.01 [-0.07, 0.10]	0.26	0.79	12.53	0.25	3.12
Irritability	11	0.00 [-0.08, 0.07]	-0.10	0.92	14.91	0.14	0.00
Euphoria (outlier excluded)	10	0.00 [-0.10, 0.10]	-0.04	0.97	8.10	0.52	14.55
Apathy (outlier excluded)	11	-0.10 [-0.18, -0.01]	-2.25	0.02	5.00	0.89	0.00

Notes. k = number of studies, NPS=neuropsychiatric symptoms.
[a] Hedges' $g = 0$ no sex differences, Hedges' $g > 0$ female sex associated with NPS, Hedges' $g < 0$ male sex associated with NPS.

Figure 3. Forest plots for the prevalence of specific neuropsychiatric symptoms

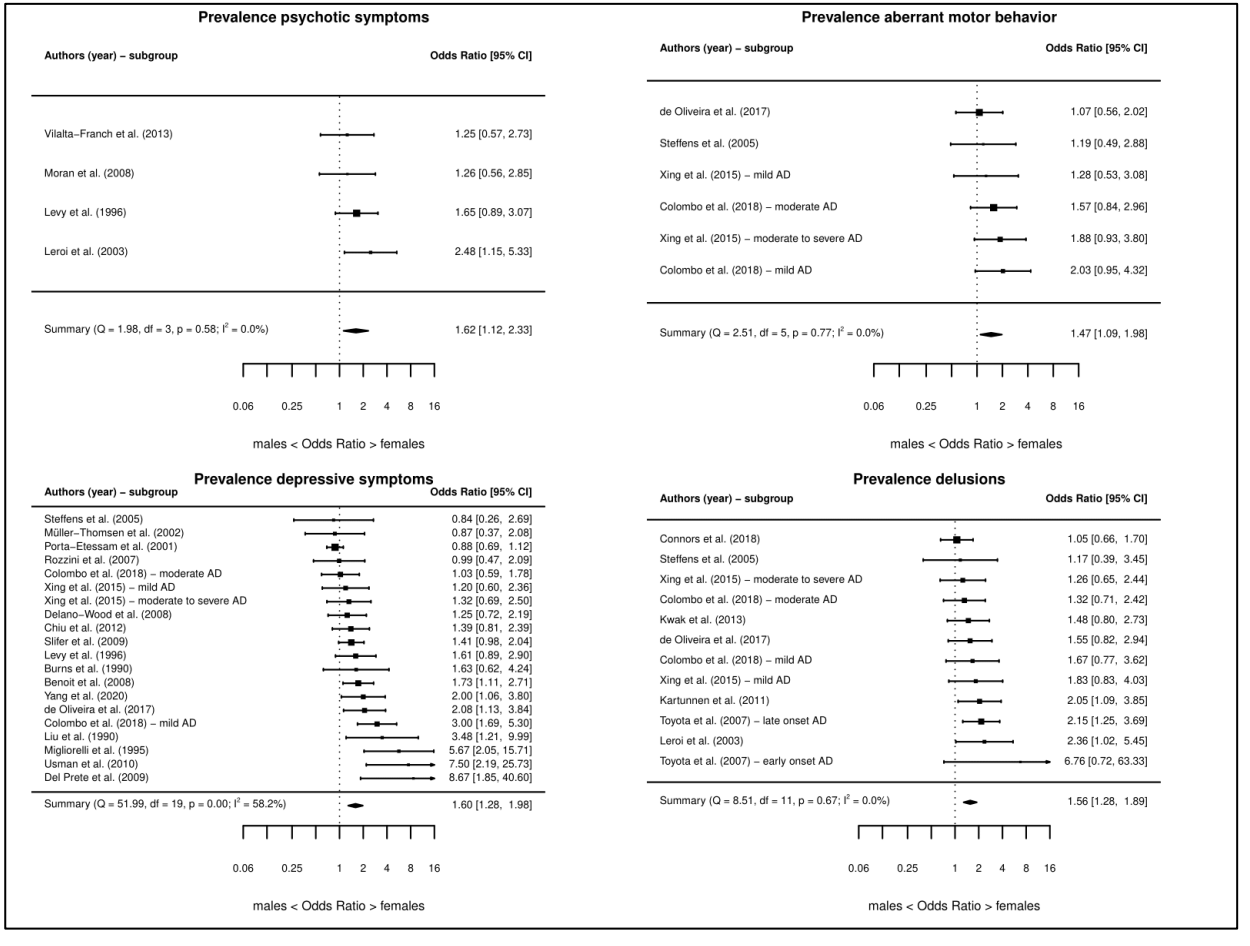
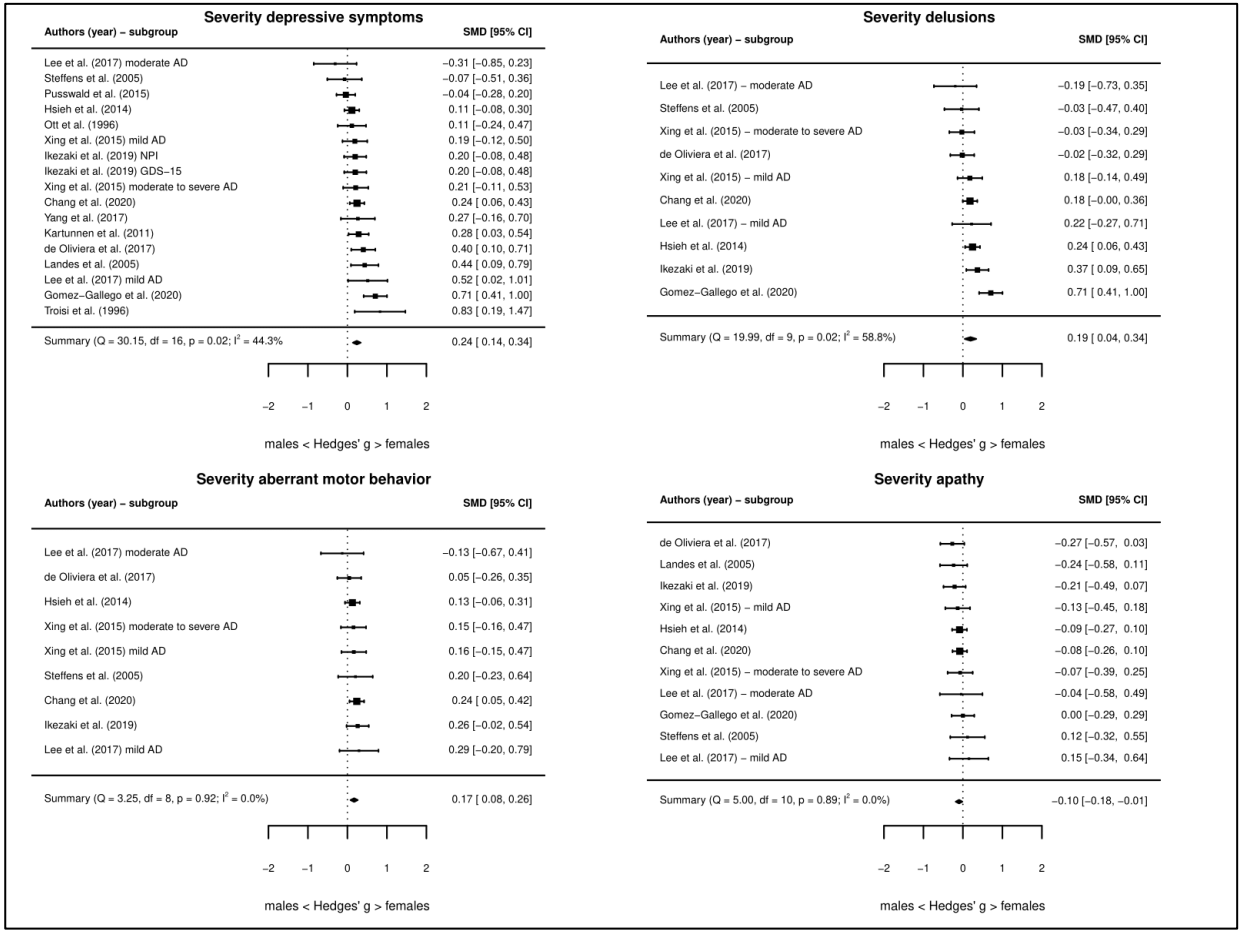


Figure 4. Forest plots for the severity of specific neuropsychiatric symptoms



Q = 5.00, p = 0.89). There were no significant sex differences in the severity of the remaining NPS (Table 2 & Supplemental Figure 2).

Meta-regression analyses

We did not find any consistent association between effect sizes across studies and clinical relevance (symptoms vs. syndromes), NPI vs. non-NPI measures, years of education, MMSE score, proportion APOE-ε4 carriers, and study quality (poor/fair/good) (Supplemental Table 4–5). Meta-regression analysis was not possible for study setting (community vs. clinic-based samples) because there was a paucity of studies with community samples available, and meta-regression for method of NPS assessment (proxy vs. self-report) was only possible for depressive symptoms but showed no difference.

Due to insufficient data, we were not able to compare the effect sizes on NPS prevalence of studies reporting significant sex differences in demographic or clinical characteristics with studies that did not. For all studies combined reporting on NPS severity, we found comparable effect sizes when comparing studies that reported significantly lower MMSE scores for females compared to males (k = 5, g = 0.39 [-0.19, 0.97]) with studies that reported no sex differences in MMSE scores (k = 10, g = 0.38 [-0.14, 0.89], Q_M = 0.00, p = 0.97). Of the 20 studies that tested the sex differences in age, only two reported older age among females and one study reported younger age in females compared to males. Nine studies tested the sex differences in APOE status, and three found a higher percentage of APOE-ε4 carriers among females. All five studies that compared disease duration between females and males found no sex difference.

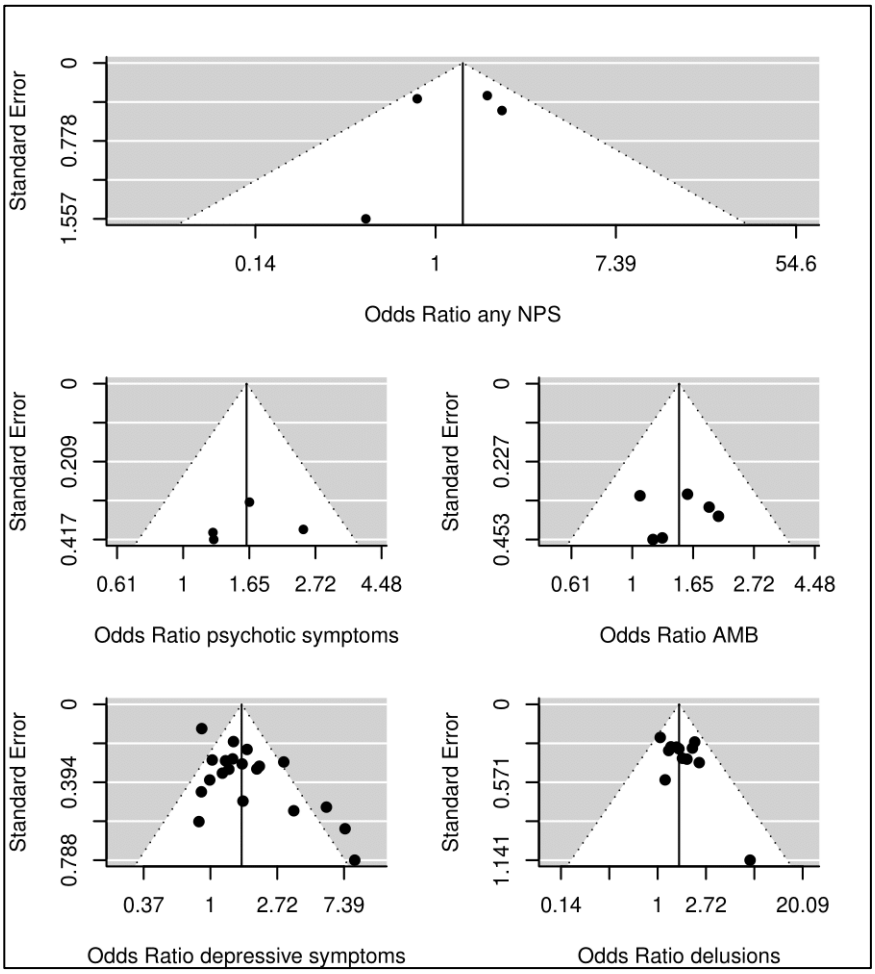
Publication bias

Begg's rank test and Egger's regression test indicated funnel plot asymmetry for the meta-analysis on the prevalence of depressive symptoms and the prevalence of agitation (Supplemental Table 6 & Supplemental Figure 3). However, publication bias was considered less likely as similar estimates were obtained when adjusting for potential publication bias using trim-and-fill method (Supplemental Table 7). We found no indication of publication bias for the remaining meta-analyses (Figures 4–5, Supplemental Figure 4).

Discussion

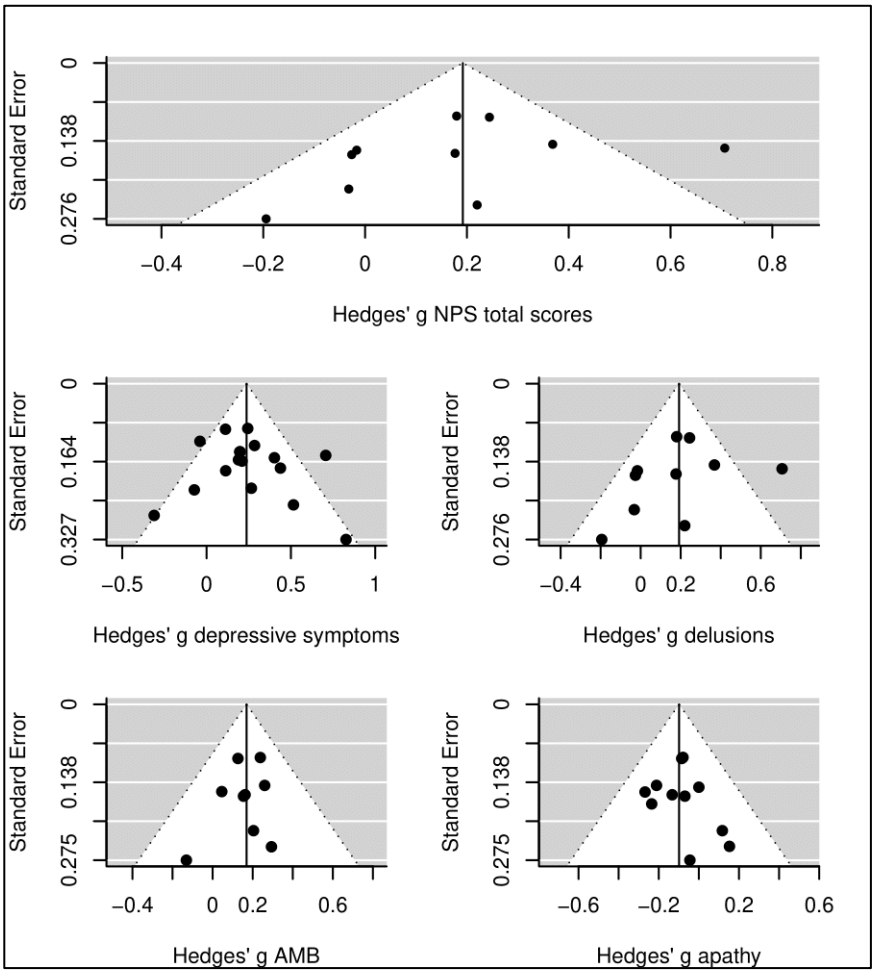
Our meta-analysis suggests that female sex is associated with a higher prevalence and greater severity of depressive symptoms, aberrant motor behavior, and psychotic symptoms in AD dementia, while male sex is related to increased severity of apathy in AD dementia. These associations were robust and generally not affected by characteristics relating to the study sample or the method of NPS measurement.

Figure 5. Funnel plots for the prevalence of specific neuropsychiatric symptoms



With this meta-analysis, we provide further evidence for greater NPS burden in females with AD dementia found in prior studies and increased severity of apathy among males with AD dementia.[174,175,178,179] However, we found no evidence for higher prevalence rates of agitation/aggression in males that have been reported previously.[180] Sex differences in affective symptoms in AD dementia are in line with higher prevalence rates of lifetime anxiety and mood disorders among females in the general population.[198] Studies on sex differences in psychotic symptoms in the general population have generally shown higher prevalence rates among males,[199] which is in contrast to the findings of our meta-analysis in AD dementia. The sex differences observed in this meta-analysis may be explained in part by a prior history of psychiatric illness, although we were not able to verify this as the included studies did not report

Figure 6. Funnel plots for the severity of specific neuropsychiatric symptoms



lifetime history of psychiatric illnesses. Yet, emergent psychiatric symptoms are common symptoms in AD[5,147] and cannot be fully explained by prior psychiatric disorders but are also related to neurobiological and psychosocial factors associated with AD.

Sex differences in genetics and neurodegenerative and pathophysiologic processes related to AD may partly explain the observed associations, as previous studies have indicated greater amyloid-β burden, tau pathology, and loss of brain volume in females compared to males.[169-171] In addition, sex differences in APOE status may also contribute to the differences found in NPS. However, prior studies have reported inconsistent associations between NPS and AD-related biomarkers and APOE-ε4 carriership,[e.g. 64,200] suggesting that neurobiological factors alone cannot explain these sex differences. Several other biological and medical factors including sex

hormones and cardiovascular disease have been related to sex differences in the risk for AD dementia and its clinical manifestation.[e.g. 201,202] Whether and how these factors may play a role in sex differences in NPS in AD dementia warrants further investigation.

Sex differences in NPS may also be explained by the differences in other clinical and demographic characteristics in AD dementia.[173,181] For example, females may exhibit more NPS as prior studies suggested that females may be diagnosed later in the disease process potentially leading to more symptoms at diagnosis.[203] Included samples in our study did not reveal sex differences in disease duration and we found comparable results when accounting for the sex differences in MMSE. Although a few studies have shown that associations between sex and NPS were independent of characteristics such as age, education level, cognitive functioning, and ethnicity,[e.g. 174,178] more studies are needed to examine how sex differences in the clinical and demographic characteristics contribute to sex differences in NPS in AD dementia. Moreover, as NPS were most often assessed using proxy instruments, it would also be interesting to compare informant characteristics for female and male patients. However, only two of the 62 included studies reported these characteristics for female and male patients separately making it impossible to examine whether informant characteristics affected our findings.

The findings of this study may have important implications. First, our findings suggest that sex is a differential factor explaining interindividual differences in the prevalence and severity of specific NPS. These findings may guide the early detection of specific NPS in AD dementia. Second, our results may provide a starting point in informing underlying mechanisms of NPS in AD dementia. More research is needed to study why females with AD are more prone to exhibit significant depressive symptoms, aberrant motor behavior, and psychotic symptoms, and why males are more prone to display severe apathy. Potentially, this research may provide insight into the sex-related differences in neurobiological mechanisms, medical conditions, and cultural factors including gender roles underlying the interindividual differences in the manifestation of NPS in AD dementia. In addition, both pharmacological and psychosocial treatment approaches for NPS in AD dementia are currently identical for females and males. Determining if the sex differences we observed in NPS are subserved by different underlying neurobiological and/or psychosocial mechanisms is critical to personalize treatment. If differences do exist, they could inform sex-specific pharmacological and non-pharmacological intervention that target NPS in AD dementia.[204,205]

This study has some limitations. First, we used meta-regression analyses in order to investigate sources of heterogeneity across studies. Although this approach is commonly used, meta-regression analyses should be interpreted with caution as these analyses may have low power and are prone to ecological bias, i.e. a relationship found at the sample level may not represent the individual level.[206] Second, in case of substantial heterogeneity across studies, we decided to exclude outliers or otherwise

influential studies, i.e. based on low number of participants or disproportionate males to females ratio (Supplemental Tables 8–9).[207] Although most researchers emphasize the importance of examining the potential outliers and influential studies when confronted with substantial heterogeneity across studies, outlier diagnostics remain under debate in the context of meta-analyses.[189] Third, the majority of the included samples were derived from memory clinics and day care centers, while nursing home populations were not available. Fourth, only two studies supported AD dementia diagnoses with AD biomarkers, whereas the remaining studies used solely a clinical diagnosis of AD dementia and thereby increasing the likelihood of including other etiologies than AD. Finally, the majority of the included studies primarily established NPS based on proxy-based instruments. To further support our findings, future studies are needed in which AD diagnoses are validated by AD biomarkers and the presence of NPS are based on updated diagnostic criteria.[27,28,208] Finally, it remains unclear whether the associations between sex and NPS in AD dementia change during the course of the disease as we investigated these relationships using cross-sectional data. Future longitudinal studies are needed to provide more insight into the effects of sex on NPS over the course of AD dementia.

Conclusion

In AD dementia, female sex is associated with greater prevalence and severity of depressive symptoms, psychotic symptoms, and aberrant motor behavior, while males exhibit more severe apathy compared to females. While more research is needed to identify factors underlying the sex differences in NPS in AD dementia, these findings may guide tailored treatment approaches of NPS in AD dementia.

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Author contributions

W.S.E., M.P., R.O., E.v.d.B., J.M.P. designed the study in consultation with M.C., J.R.G., Z.I., K.L.L., C.E.F., M.E.M.; W.S.E., M.P. conducted the literature search, study selection, and data extraction; W.S.E. analyzed the data and interpreted the data assisted by M.P., R.O., E.v.d.B., J.M.P.; W.S.E., M.P. drafted the manuscript for intellectual content. R.O., M.C., J.R.G., Z.I., K.L.L., C.E.F., M.E.M., E.v.d.B., J.M.P. revised the manuscript for intellectual content. J.M.P., E.v.d.B. supervised the study. J.M.P., R.O. acquired funding for this study. All authors read and approved the final version of the manuscript.

Supplemental materials

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Chapter 3

Current state of care for neuropsychiatric symptoms in Alzheimer's disease

Chapter 3.1

Neuropsychiatric symptoms complicating the diagnosis of Alzheimer's disease: A case report

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Abstract

Neuropsychiatric symptoms (NPS) are increasingly recognized as a core element of Alzheimer's disease (AD); however, clinicians still consider AD primarily as a cognitive disorder. We describe a case in which the underrecognition of NPS as part of AD resulted in substantial delay of an AD diagnosis, a wrong psychiatric diagnosis, and the organization of inappropriate care. The aim of this paper is to acknowledge NPS as an (early) manifestation of AD and to suggest features that may point toward underlying AD in older adults with late-life behavioral changes.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by a gradual decline in cognition and functional abilities.[1] In addition, neuropsychiatric symptoms (NPS) are increasingly seen as a third hallmark of AD,[9,81] as nearly all patients with AD develop NPS at some stage during the disease.[e.g. 2] To improve the recognition of NPS in AD, consensus criteria have been developed for apathy,[193] psychosis,[186] and depression in AD.[29] Furthermore, the concept of mild behavioral impairment (MBI) has recently been described to enhance awareness concerning NPS as an early manifestation of AD and other types of dementia.[31]

Despite the growing knowledge on the prevalence and diagnosis of NPS, AD is still primarily considered a cognitive disorder in clinical practice.[209] Consequently, AD is often not considered in cases in which psychiatric symptoms emerge in late-adulthood, resulting in misclassification of AD as psychiatric conditions.[210] Attention has already been drawn to this diagnostic challenge in other forms of dementia that are associated with NPS, such as the behavioral variant of frontotemporal dementia (bvFTD),[211] and dementia with Lewy bodies (DLB).[212] This misclassification can hamper the organization of appropriate patient care. This is important since pharmacological treatments often used in psychiatric conditions are shown to have a poorer risk-benefit ratio in AD (especially in the case of atypical antipsychotics for other NPS than psychosis or severe agitation).[93]

A timely diagnosis of NPS in AD greatly benefits both patients and caregivers, as psychoeducation and other (non)pharmacological interventions tailored for AD will delay institutionalization and enhance the quality of life of patients and their caregivers.[54] Tailored treatment can also include psychotropic medications with the largest effectivity for the use of antidepressants and atypical antipsychotics for NPS in dementia.[100,213] Moreover, targeting NPS is important since its presence is associated with steeper cognitive decline and increased risk of conversion from normal aging to mild cognitive impairment (MCI), MCI to AD, and earlier nursing home placement in patients with AD.[214]

In this case study, we illustrate how the classification of psychiatric symptoms emerging in later-life is challenging, and how its presence can hamper the diagnosis of AD. The aim of this paper is to stress that prominent behavioral symptoms can occur in the context of AD and to enhance awareness for this issue among clinicians. The patient described in this paper gave written informed consent.

Case description

Symptom presentation

We report on the case of a 54-year-old woman who was referred to our academic memory clinic with prominent behavioral changes. Approximately 2.5 years prior to referral, the patient started to show severe anxiety. Symptoms included a lack of

confidence, feelings of insecurity, and overwhelming fear. She often had panic attacks when being alone and urged her husband to accompany her in case she left the house. Furthermore, she was more apathetic, reflected by a loss of initiative to organize birthday parties, to visit friends, and to participate in conversations. In addition, she got lost more often, forgot where she stored her belongings, and used more notes to aid her memory.

There was no history of somatic or psychiatric diseases. Family history was positive for dementia (unknown etiology) with her mother being diagnosed at the age of 65 and her father being diagnosed with late-onset dementia (> 75 years old).

Disease course

Six months after symptom onset, she stopped working as a nurse because of the above-mentioned behavioral changes and problems with monitoring and planning her tasks (e.g. difficulties with handing out medication and adjusting to (digital) innovations at her workplace). Her general practitioner referred her to a psychiatric outpatient clinic, where she was diagnosed with a panic disorder with agoraphobia. The patient participated in group-psychotherapy but was advised to end this treatment after several months due to inactivity, reduced insight, and memory problems. Subsequently, she was prescribed a benzodiazepine and SSRI and tried different forms of psychological treatment and alternative medicine, all without any effect on NPS.

Because of the increasing memory complaints and the absence of improvement after various interventions, a neuropsychological assessment and MRI of the brain were carried out at the psychiatric outpatient clinic and a memory clinic. Although cognitive testing revealed deficits in multiple cognitive domains (memory, executive functions, visuoconstruction), they were interpreted as signs of a conversion disorder, since a symptom validity test suggested malingering and a brain MRI showed minimal (hippocampal) atrophy or vascular disease (Fig. 1A, B). Based on the absence of neuroimaging abnormalities, clinical suspicion for dementia was low, and the patient was prescribed with a SNRI and, given its limited effect, switched to a SSRI after two months. In addition, she received cognitive behavioral therapy that focused on graded activity and targeted avoidance behaviors. After several months, no improvements were observed, and the patient was therefore referred to the psychiatry department of our academic center. From here she was referred to our memory clinic.

Clinical assessment

During the outpatient visit at our memory clinic, the patient showed almost no spontaneous speech, was not able to reflect on her cognitive and functional abilities, but became emotional twice when her husband addressed her problems. Her husband reported that she became very apathetic and socially isolated. Moreover, she showed

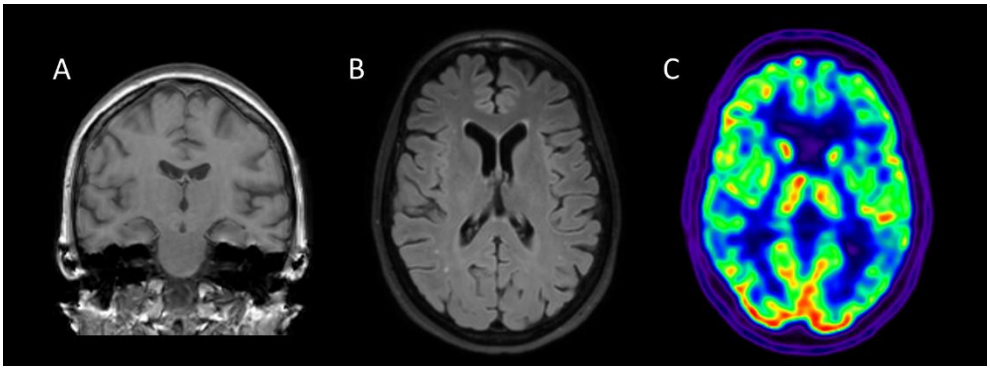
Table 1. Results neuropsychological assessment

Test	Raw score	Standardized score
Language		
Boston Naming Test	30/60*	-3
Attention & Executive functioning		
BADS – key search	4/16*	cutoff ≤ 7
Stroop Color and Word Test-word	74 s*	-3.2
Stroop Color and Word Test-color	41 s	1.8
Stroop Color and Word Test-word-color	*Unable to complete*	
VF phonemic (D, A, T)	19 in 180 s	-1.8
VF semantic (animals, professions)	7 in 120 s*	-3.7
WAIS-IV – digit span total score	8/48*	-3
WISC-III – mazes	*Unable to complete*	
Episodic memory		
Location Learning Test – recall	20*	-2.7
Visual Associations Test – recall	0/12*	-2.3
Visuospatial abilities		
CAMCOG – copy figures	1/3*	Cutoff ≤ 1
Clock drawing (Royall)	8/14*	Cutoff ≤ 9
Rey Complex Figure Test – copy	*Unable to complete*	
Gnosis & praxis		
Apraxia test	86/90*	Cutoff ≤ 86
Goldenberg ideomotor Apraxia Test	20/20	Cutoff ≤ 14
VOSP – dot counting	10/10	Cutoff ≤ 8
VOSP – incomplete letters	19/20	Cutoff ≤ 16

Notes. BADS = Behavioral Assessment of the Dysexecutive Syndrome, VF = verbal fluency, WAIS-IV = Wechsler Adult Intelligence Scale-IV, WISC-III = Wechsler Intelligence Scale for Children-III, CAMCOG = Cambridge Cognition Examination, VOSP = Visual Object and Space Perception.
Values are presented as raw test score/total score, or completion time in seconds. Standardized scores are age-, sex-, and education-adjusted *Z* scores.
* 2 SD below mean of age-, sex-, and education-adjusted norms or below cutoff score.

decreased activities of daily living as her husband had taken over grocery shopping and various other household chores. The patient showed no abnormalities on neurological examination but scored 17/30 on the Mini-Mental State Examination (MMSE, cutoff < 24) and 9/18 on the Frontal Assessment Battery (FAB, cutoff < 14). She scored within normal range on the self-administered Beck Depression Inventory (4/63) and Hospital Anxiety and Depression Scale (5/42). An extensive neuropsychological examination revealed severe impairments in almost all tested cognitive domains, including memory,

Figure 1. Neuroimaging findings



Notes. A) coronal T1-weighted MRI sequence showing limited hippocampal atrophy (MTA score 0). B) axial FLAIR MRI sequence demonstrating minimal vascular disease (Fazekas score = 1). C) ^{18}F-FDG PET scan showing (asymmetric) hypometabolism in the parietal lobe.

language, processing speed, visuoconstructive abilities, and executive functioning (Table 1). Symptom validity testing indicated no evidence for malingering. Differences with prior validity testing might be explained by the nature of the used tests. Prior testing with the Amsterdam Short-Term Memory test measured cognitive underperformance.[215] In our center, we administered a questionnaire tailored to capture over-reporting of psychiatric and neurological symptoms.[216] During cognitive testing, she gave up easily when confronted with cognitive demanding tasks, and had difficulties with comprehending questions and test instructions. Although the NPS were accompanied by evident cognitive deficits, our clinicians were uncertain about an AD diagnosis and therefore carried out additional pathophysiological AD biomarker diagnostics.

Since the previously performed brain MRI showed no abnormalities, an ^{18}F-FDG PET scan was conducted and analyzed semi-quantitatively using the vendor implemented methods for quantification, as well as visual rating by an experienced nuclear radiologist. The ^{18}F-FDG PET scan showed bilateral hypometabolism in the precuneus and hypometabolism in the parietal and temporal lobe (left more than right, Figure 1C). Additionally, there was subtle glucose hypometabolism in the prefrontal cortex. The results of the PET scan were rated as abnormal and the hypometabolic patterns were most indicative for AD.[217]

Analysis of cerebrospinal fluid (CSF) biomarkers revealed decreased amyloid-β_{42} levels (499 ng/L, cutoff > 697) together with increased levels in total tau (1,117 ng/L, cutoff < 375), and phosphorylated tau (135ng/L, cutoff < 52). This combination fits a typical AD profile (total tau/Aβ_{42} ratio of 2.24, cutoff > 0.52).[125]

Given the positive family history for (early-onset) dementia, a genetic analysis was carried out using whole-exome sequencing (WES). Screening of known dementia-

associated genes revealed no pathogenic mutations (see Supplemental Material for details).

According to the NIA-AA criteria,[1] a diagnosis of probable AD with high-likelihood of AD etiology (based on abnormal CSF biomarkers and hypometabolism on ^{18}F-FDG PET) was established by our multidisciplinary team. The patient was subsequently treated with Galantamine, with little clinical effect. The patient and her husband were supported by a care consultant specialized in patients with early-onset dementia. After one-year clinical follow-up, the MMSE score dropped from 17/30 to 9/30 showing further cognitive decline supporting the dementia diagnosis.

Discussion

We described a case of a 54-year-old woman with prominent late-life behavioral changes, including anxiety and apathy. Despite cognitive complaints and a positive family history for dementia, dementia was repeatedly ruled out by clinicians based on the presence and extent of NPS. This biomarker confirmed AD case illustrates how clinicians insufficiently acknowledge or recognize NPS as an (early) manifestation of AD.

Although the notable behavioral symptoms observed in this case are not observed in every patient with AD, NPS such as social withdrawal, apathy, and depression are very prevalent in early-stage AD, with prevalence estimates of nearly 80% in MCI and 90% in mild AD.[9,10,210]

This raises the question whether a subgroup of patients diagnosed with a late-onset psychiatric disorder could actually have underlying AD. Prior studies have supported this notion, showing overrepresented AD pathology in elderly who committed suicide, with only a small portion of the sample clinically being diagnosed with dementia.[218] This has serious ramifications since psychiatric symptoms in dementia require other (non)pharmacological interventions when compared to isolated psychiatric disorders.[54]

The described case would, prior to the assessments at our center, fulfill the ISTAART-AA criteria for MBI with changes in affective dysregulation and decreased motivation.[31] Cases of MBI have been reported previously,[219] showing retrospectively, the presence of MBI even in absence of any cognitive impairment prior to a diagnosis of dementia with different etiologies including frontotemporal lobar degeneration. In contrast to previous case reports, we specifically illustrate how NPS can hamper an AD diagnosis, elaborating more on the problems of underrecognition and undertreatment of NPS in AD.

While previous studies have reported on the diagnostics challenge of NPS in dementia,[220] these studies have mainly focused on differentiating late-onset psychiatric disorders and non-AD dementias, such as the bvFTD,[22] and DLB.[21] The appreciation of NPS in non-AD dementias has led to the incorporation of NPS in their diagnostic

criteria.[21,22] Although the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the new NIA-AA research framework of AD have acknowledged NPS as a part of AD,[25] behavioral symptoms are not mentioned in the clinical NIA-AA criteria of AD,[1] and are even an exclusion criterion for typical AD in the IWG-2 research criteria of AD.[221] The provisional criteria for psychosis, apathy, and depression in AD are important developments that facilitate research, early identification and tailored treatment of these syndromes.[29,186,193] In addition, the recent conceptualization of the behavioral variant of AD also contributes to these advances.[222] However, given the high prevalence of NPS across all stages of AD and the substantial impact of these symptoms on disease progression and the patient's well-being,[54] the incorporation of NPS in the clinical criteria of typical AD seems a crucial step as well, and would aid the awareness of clinicians.

This case demonstrates the additional diagnostic value of AD biomarkers in confirming AD. However, similar to the NIA-AA criteria,[1] we do not advocate for the use of these biomarkers in every older adult with late-onset behavioral symptoms. What is more important here is that clinicians in both memory and psychiatric clinics consider the possibility of underlying AD when confronted with late-onset psychiatry symptoms in middle- to older-age patients. In line with this notion, not only AD biomarkers, but also clinical features have been proposed that point toward an underlying neurodegenerative cause such as AD.[210] These features entail the concurrence of cognitive deficits, no psychiatric history, a gradual onset, a progressive deterioration over time, and a positive family history of dementia.[210,220,223] These factors were also present in the case described here and should be taken into consideration by clinicians.

In this case study, we have illustrated how late-onset psychiatric symptoms can hamper the diagnosis of AD, leading to inappropriate patient management. The improvement of recognition and diagnosis of NPS in early-stage AD is crucial, as it greatly benefits patients and caregivers through the effects of tailored interventions on quality of life, caregiver burden, and the delay of institutionalization. Therefore, raising awareness of NPS as an (early) manifestation of AD among clinicians in memory and psychiatric clinics, as well as general practitioners and community nurses is imperative.

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Author contributions

J.M.P., R.O. acquired funding for this study. W.S.E., E.v.d.B., R.O., J.M.P., H.S. designed the study; J.G.J.v.R. conducted the genetic analyses; W.S.E., J.G.J.v.R, H.S. analyzed the data and interpreted the data assisted by M.C., R.O., E.v.d.B., J.M.P.; W.S.E. drafted the manuscript for intellectual content. J.G.J.v.R., E.v.d.B., M.C., L.C.J., E.S., R.O., J.C.v.S., H.S., J.M.P. revised the manuscript for intellectual content. J.M.P. supervised the study. All authors read and approved the final version of the manuscript.

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Chapter 3.2

The recognition and management of neuropsychiatric symptoms in early Alzheimer's disease: A qualitative study among Dutch memory clinic physicians

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Abstract

Background and Objectives

Timely recognition and treatment of neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) dementia may improve quality of life, reduce caregiver burden, and delay disease progression. However, management of NPS in early AD dementia remains challenging. To date, little is known about the specific challenges of memory clinic-based physicians. The aims of this qualitative study were to obtain insights regarding the recognition and treatment of NPS in AD dementia in the memory clinic, to identify challenges experienced by physicians while managing NPS, and to examine the attitudes of memory clinic physicians on the role of the memory clinic in the care for NPS in early AD dementia.

Methods

*S*emi-structured interviews were conducted with thirteen physicians working at a memory clinic in the Netherlands (n = 7 neurologist, n = 6 geriatrician, 46% female). The data were analyzed by two independent researchers using thematic analysis.

Results

We observed large variation among Dutch memory clinic physicians regarding care practices, expertise, and attitudes on the role of the memory clinic considering NPS in AD dementia. The most prominent challenges that memory clinic physicians experienced while managing NPS included that the outpatient setting complicates the recognition and treatment of NPS, a lack of experience, knowledge, and/or resources to adequately apply non-pharmacological interventions, and a lack of consensus among physicians on the role of the memory clinic in NPS recognition and management.

Conclusions

We identified challenges that need to be addressed to improve the early recognition and adequate management of NPS in AD dementia at the memory clinic.

Introduction

Neuropsychiatric symptoms (NPS) include a wide range of symptoms including apathy, agitation, affective disturbances, and psychotic symptoms.[9] NPS are prevalent among individuals with early Alzheimer's disease (AD) dementia,[10,147] and put a large burden on people living with AD dementia and their caregivers.[40,50] Furthermore, the presence of NPS in early stage AD dementia is related to a faster cognitive decline and earlier institutionalization.[47,53]

International guidelines recommend non-pharmacological interventions as first-line treatment for NPS in dementia.[33,91] Examples of such non-pharmacological interventions include caregiver support, psychoeducation, and enhancing tailored activities and these interventions are shown to be effective in reducing NPS.[93,94] Pharmacological treatments have only limited effect on NPS in early dementia and may lead to serious side effects.[102,104]

Early identification and treatment of NPS seems imperative given the significant impact of NPS on the quality of life of patients and their caregivers,[40,50] and the associations with accelerated cognitive decline and institutionalization.[47,53,224] Memory clinics can play a role in the timely care for NPS in early AD dementia, as these multidisciplinary facilities offer a comprehensive diagnostic process and have the potential to offer post-diagnostic care and support.[109] In the Netherlands, patients present their cognitive complaints to their general practitioner. After general evaluation, the general practitioner may refer to the memory clinic, which is generally situated as part of the local hospital. General practitioner visits and referral to the memory clinic are covered by mandatory healthcare insurance in the Netherlands, making these facilities highly accessible. At the Dutch memory clinic, a multidisciplinary team that may include neurologists, geriatricians, psychologists, specialized nurses, and psychiatrists usually provide a standardized diagnostic work-up consisting of medical history taking, neurologic examination, neuropsychological assessment, laboratory testing, and neuroimaging.[108]

NPS are often underdiagnosed during the diagnostic stage of AD dementia and effective non-pharmacological interventions are hardly implemented in the care for NPS in individuals with AD dementia at the memory clinic.[106] Previous studies have identified several factors that contribute to the complexity of care for NPS, including the multifactorial cause of NPS,[54] its fluctuating nature,[20,147] and difficulties to distinguish NPS from primary psychiatric disorders.[210,225] Furthermore, the fact that the diagnosis of AD dementia strongly relies on cognitive and functional deficits further hampers the recognition of NPS in early AD dementia.[226]

In addition to the challenges mentioned above, there may be factors related to the specific care setting contributing to the complexity of care for NPS in AD dementia. Several qualitative studies among nursing home staff and general practitioners have indeed revealed unique challenges for these specific care settings such as a perceived

lack of time among nursing home staff and general practitioners, conflicting expectations on the treatment-plan between general practitioners and family members of patients, and a perceived priority of care tasks over personal interaction, or interaction among nursing home staff.[227-229] In addition to physicians working in primary care and nursing homes, we have indications that physicians also experience difficulties with assessing and managing NPS in the memory clinic setting.[209,225] However, there is a lack of knowledge on the current care for NPS in early AD dementia at the memory clinic and what kind of challenges physicians face in the care for NPS in AD within this specific setting.

A better understanding of the experiences and attitudes of memory clinic physicians on the current care for NPS is necessary to identify challenges that need to be overcome to improve timely diagnosis and treatment of NPS in early AD dementia. Therefore, the aims of the current study were to (1) obtain insight in the current assessment and management of NPS in early AD dementia in the memory clinic, (2) identify challenges experienced by physicians while managing NPS in early AD dementia in this specific care setting, and to (3) examine attitudes of memory clinic physicians on the role of the memory clinic in the care for NPS in early AD dementia.

Methods

Ethical approval was granted by the Medical Ethics Committee Erasmus MC of Rotterdam, The Netherlands (MEC-2020-0249). All participants gave informed consent. The Standards for Reporting Qualitative Research (SRQR) were followed for reporting this qualitative study.[230]

Sampling and recruitment

We included neurologists and geriatricians working at a memory clinic who regularly diagnose and treat patients with early AD dementia. In the Netherlands, memory clinics are primarily coordinated by geriatricians and neurologists.[108] These medical specialists are responsible for the diagnosis and treatment of patients, while referring to psychologists, psychiatrists, nurses, and/or social workers for additional diagnostic purposes or support. Therefore, we only included neurologists and geriatricians in this study. Participants were recruited via two strategies. A part of the participating physicians were already involved in an intervention study to improve the management of NPS in AD dementia in the memory clinic as part of the BEAT-IT project.[231] These physicians were interviewed during the first observational wave of the project, in which patients received care as usual and served as a control group (convenience sample). Furthermore, additional physicians were contacted to ensure maximum variation regarding profession (neurologist/geriatrician), type of hospital where they are employed (general/academic), and years of experience (purposive sampling). We continued inclusion until saturation was achieved.[232]

Semi-structured interviews

One researcher (W.S.E.) conducted the interviews either face-to-face or via telephone due to COVID-19 restrictions. All interviews were audio-taped after obtaining verbal informed consent.

The topic guide was developed prior to the start of the first interview, but was adapted halfway based on consensus among the researchers (see Supplemental Table 1). The semi-structured interviews revolved around the following topics: experiences of memory clinic physicians when managing NPS in early AD dementia; challenges they encounter in their daily clinical practice considering the management of NPS; attitudes on who is responsible for the care for NPS in community-dwelling patients with early AD dementia; and perspectives on the ideal care for NPS. Questions were asked in an open non-directive manner focusing on the participants' attitudes and experiences. Each question was explicitly related to AD to ensure that physicians addressed AD in their responses. When in doubt, the interviewer asked specifically whether the response was related to individuals with AD. Physicians were encouraged to discuss examples of cases they encountered in their daily clinical practice.

Analysis

The audiotapes of all interviews were transcribed verbatim and de-identified prior to data analysis. The data were analyzed by two independent researchers (W.S.E. & N.L.) following a thematic analysis approach.[233] The coding and analyses were an iterative process in parallel with the interviews allowing for adjustment of questions and topics. After familiarizing with the data, both researchers proposed a code book consisting of open codes that emerged from the data. These code books were discussed resulting in a final code book used to systematically code the data. The final coding consisted of open coding followed by axial coding and selective coding. Next, both researchers independently collided the codes into preliminary categories and themes. Finally, initial themes were redefined through discussion between all researchers resulting in the three key themes: (1) recognition of NPS, (2) management of NPS, and (3) role of the memory clinic in care for NPS in early AD dementia (Figure 1).

Results

Thirteen physicians of the fourteen physicians that were invited to be interviewed agreed to participate. One geriatrician declined to participate because of a lack of time due to additional COVID-19 care. Characteristics of the participants can be found in Table 1. Although physicians with a background in neurology and geriatric both had experience ranging from <10 years to >20 years, neurologists had more years of experience in the memory clinic (median [range] = 12.0 years [8–30]) than geriatricians (7.0 years [4–21]).

Table 1. Characteristics of the 13 memory clinic physicians included in this study

	N (%)
Sex	
Female	6 (46%)
Male	7 (54%)
Profession	
Neurologist	7 (54%)
Geriatrician	6 (46%)
Type of hospital employed	
General	8 (61%)
Academic	5 (38%)
Years of experience in the memory clinic	
< 10 years	6 (46%)
10–20 years	4 (31%)
> 20 years	3 (23%)

Recognition of NPS

Most memory clinic physicians (n=10/13) indicated that they frequently detect NPS such as apathy, irritability, depression, and anxiety in the patients they diagnose and treat with early AD dementia. Half of the physicians indicated that they always address NPS as part of their standard diagnostic work-up and they repeatedly emphasized the importance of these symptoms:

> *"I find it hard to imagine that you don't pay attention to NPS, because I think that this is something that caregivers struggle with the most. It is always about the behavior."* (Neurologist #7)

A neurologist suggested that not all physicians are aware that NPS are part of dementia and that therefore more education is needed:

> *"I think it's needed to highlight more often that dementia is more than cognitive impairment during our residency programs. And also to stress that especially these behavioural problems, these neuropsychiatric symptoms lead to major burden in patients, but also among family members."* (Neurologist #6)

Exemplary, three physicians included in our study considered NPS not as prominent symptoms in individuals in the early phase of AD dementia who they encounter at the memory clinic:

> *"I don't see that [NPS] much in the beginning of the disease, but later on in almost all patients. As the disease progresses, you see more of these symptoms."* (Neurologist #4)

These physicians reported that the evaluation of NPS is not part of their standard diagnostic work-up as their focus is on cognitive functioning to establish a dementia diagnosis.

There was consensus among the participants who frequently detect NPS that physicians need to actively address NPS in order to evaluate its presence and clinical relevance. Physicians suggested that patients and caregivers may feel hesitant to bring up NPS because of feelings of shame, difficulties describing these symptoms, and to avoid making the patient upset or angry. Furthermore, one neurologist pointed out that physicians may feel hesitant to address NPS as well because they have no subsequent strategy for managing these symptoms:

> *"I'm usually not inquiring about NPS as it is hard to treat, because you don't have a solution immediately. So, although I may detect it, I don't have a tailor-made solution ready."* (Neurologist #4)

Many physicians described that the setting of the outpatient memory clinic makes it difficult to recognize NPS as these symptoms mostly occur at home:

> *"The hardest of all with NPS observed at an outpatient clinic is that you see patients for only a very short period of time and within a very specific setting, although the problems arise very often within the interaction between patient and caregiver. (…) This setting is just not suited for finding a solution for NPS that occur at home."* (Geriatrician #3)

However, several physicians also gave examples of NPS that they observe when patients and caregivers visit the memory clinic together:

> *"The benefit of having both patient and caregiver in the doctor's office is that one can observe what also occurs at home. For example, if a patient says: 'that is totally untrue what you are saying.' and if the caregiver then also reacts in an agitated manner, I usually explain how the caregiver could better deal with this."* (Neurologist #1)

Half of the physicians worked at a memory clinic in which NPS assessment scales such as the Neuropsychiatric Inventory (NPI) and the Geriatric Depression Scale (GDS) are part of the standard diagnostic work-up. Another physician argued that merely using standardized screening tools might not be sufficient to fully capture NPS and may hamper an adequate response:

> *"I don't believe in this [using checklists to screen for NPS]. One should have a conversation with people and during this conversation, one should address these symptoms systematically. But just checking off these symptoms for the sake of it results in an awkward conversation that does not provide the correct information needed."* (Neurologist #6)

Management of NPS

Half of the group of physicians were aware of the existing Dutch guidelines for the treatment of NPS in dementia, but only one physician uses these guidelines regularly in daily clinical practice. Alternatively, physicians base their treatment on own clinical experience, peer consultation, literature research, and research findings presented at national conferences. One geriatrician acknowledged that the current guidelines for NPS are difficult to apply in the memory clinic setting:

> *"It makes it in particular difficult to use, because these guidelines for NPS are originated at the nursing home setting in which non-pharmacological interventions have way more potential benefit."* (Geriatrician #4)

Several physicians described that they sometimes experience a tension between the distress associated with NPS among caregivers and a lack of awareness of the presence of NPS and associated distress among patients. Two physicians experienced this even as an ethical dilemma as they wondered whether they should treat patients who do not experience any burden, while their caregivers do report severe NPS that causes substantial distress:

> *"Should one act if a patient who you are treating does not have any complaints, but the caregiver who you are not formally treating does have serious complaints? But caregivers are essential, so if they are in distress and experience severe burden, one should do something with these complaints right?"* (Geriatrician #4)
>
> *"You should always be aware that you are treating the patient and not the caregivers. I don't think you should treat a patient with medications in order to comfort caregivers. The patient should benefit from this too."* (Geriatrician #3)

Physicians differed substantially in the amount of experience they have with managing NPS and whether they feel competent while doing so. This was unrelated to the number of years that they worked at the memory clinic. The vast majority of the physicians treat NPS at a regular basis, while only three physicians indicated that they almost never treat NPS. Regardless of how often physicians treated NPS, many stated that they experience the care for NPS in early AD as challenging. Two physicians acknowledged that they lack specific knowledge considering NPS treatment:

> *"I think that it is also a lack of knowledge on how to deal with these symptoms and how to educate dyads on how to handle this."* (Neurologist #1)

Other physicians expressed that they have sufficient experience and expertise to manage NPS, but described other challenges:

> *"I don't find the symptoms in itself particularly difficult to manage, because I see that, when it works out well to really change things, patients and their caregivers are more relaxed. But it's really hard to get other care professionals involved and*

to create a treatment plan together. So it's more an organizational challenge than the symptoms per se." (Geriatrician #6)

Non-pharmacological interventions

The vast majority of the memory clinic physicians (n=10/13) preferred non-pharmacological approaches over pharmacological interventions to treat NPS, especially for specific symptoms including apathy, agitation, and sleep disturbances:

"I would say: 'The doctor as a medicine', because you don't have much more to rely on. So you have to explain and discuss it." (Neurologist #4)

Although non-pharmacological approaches were often mentioned and generally preferred over pharmacological interventions, a third of the physicians could not name specific non-pharmacological interventions and indicated that they rarely apply non-pharmacological interventions themselves:

"It's fine with me to be responsible for pharmacological treatments, but I think that supporting patients and caregivers to deal with these symptoms should take place in the community. (…). Cognitive Behavioural Therapy maybe? I don't have any experience with that and don't think that I would be able to provide that." (Neurologist #3)

These physicians also expressed the need for additional registered nurses at the memory clinic to support with non-pharmacological approaches:

"In an ideal world, I would like to have a registered nurse who has an appointment with the patient prior to my appointment. (…) Who also pays attention to non-cognitive complaints, non-pharmacological intervention and coaching in a way that the medical doctor has more time for the more persistent symptoms that may need a pharmacological treatment." (Neurologist #2)

Two-third of the physicians indicated that they regularly apply non-pharmacological strategies including the investigation of underlying triggers and causes, providing patients and caregivers psychoeducation, increasing meaningful activities, referring to a day care center, giving caregiver support, or enhancing physical exercise. The various psychosocial causes of NPS formed the main reason for physicians to apply non-pharmacological approaches to manage these symptoms. Examples that were described included a lack of knowledge among caregivers, caregiver burden, pre-existing personality traits of patients, difficulties coping with a dementia diagnosis, and negative communication styles among caregivers. As one geriatrician illustrated:

"Verbal or physical aggression often arises from the interaction between individuals. Paying attention to this really helps to remove the trigger and prevent further escalation." (Geriatrician #1)

Pharmacological interventions

All physicians gave examples of patients they treated with psychotropic medications who exhibited very severe and/or persistent NPS that were very distressing for caregivers, caused harm, or hampered homecare or other forms of healthcare. Furthermore, most physicians (n=11/13) felt competent and had experience with treating psychotic symptoms using pharmacological interventions. Yet, for other symptoms such as depression and anxiety, several physicians (n=3/13) mentioned that they felt less competent or had insufficient experience to use psychotropic drugs:

> *"We have less experience with the remaining [NPS]. Depressive disorders and anxiety disorders are treated by the psychiatrist (…) as we do this less often, so we don't recognize the side effects of these medications."* (Neurologist #2)

All physicians were aware of the limited effectiveness and associated negative side effects of pharmacological treatments when used to treat NPS. Several physicians (n=4/13) mentioned that concerns about the efficacy of pharmacological treatments for NPS and increased risk of serious side effects made them use non-pharmacological approaches for NPS instead:

> *"In general, I'm very hesitant with pharmacological interventions because you will have side effects very quickly and the effectiveness is questionable at best."* (Neurologist #6)

Almost all physicians stated that they prescribe psychotropic drugs to treat NPS, though large differences existed in how often physicians do so, with only a minority of physicians who prescribe very commonly. These physicians indicated that they sometimes feel powerless while managing NPS as they did not have much alternative treatments available:

> *"I think that it really doesn't matter much… (…) Nothing is safe or effective. It's really a matter of trial-and-error."* (Geriatrician #2)
>
> *"Every time that I'm attending a symposium or conferences on NPS, the conclusion is that nothing is effective. That is really demotivating."* (Geriatrician #5)

Two physicians expressed that they or their colleagues sometimes use pharmacological interventions because they lack the knowledge and experience with using non-pharmacological approaches:

> *"I think that, because one lacks knowledge [about non-pharmacological interventions] (…), one is also more inclined to use medications as a medical doctor. (…) You are just more likely to use medications if it's not going well at home, because it has to go well at home otherwise you have a problem."* (Neurologist #1).

In addition, pharmacological treatments were considered less time-consuming and part of care medical doctors are supposed to provide in a hospital setting:

> *"We, as medical doctors, sometimes have the tendency to 'think' solely in terms of pharmacological treatment options instead of non-pharmacological approaches. Everyone does consider non-pharmacological interventions as important, but I think that some medical doctors are just used to prescribe medications very quickly in clinical practice. (…) It's just so easy right?! Just one pill, that's all! (…) Maybe it's also because physicians feel that it's supposed to be that way in the hospital?"* (Neurologist #2)

The role of the memory clinic in the care for NPS

There was a substantial variation in the attitudes among physicians on the role of the memory clinic in the care for NPS in early AD. Several physicians (n=5/13) argued that the care for NPS belongs predominantly in the primary care setting, while memory clinics should purely focus on establishing a dementia diagnosis. These physicians stated that care provided in memory clinics is too expensive or that there is a risk of medicalization if community dwelling patients and caregivers regularly have to visit the memory clinic. Furthermore, physicians mentioned that in contrast to memory clinic physicians, primary care physicians such as general practitioners and community nurses commonly conduct home visits that enables them to observe NPS in the context in which they occur and can therefore intervene directly. Furthermore, some physicians suggested that clinicians working in other care settings are more experienced in managing NPS:

> *"I don't think that the memory clinic setting is suited to follow up on these kinds of issues. (…) I do think that the diagnostics belongs to us, but it's pretty much completed after that as we don't have anything more to offer. So then it's a kind of waste to keep following these patients within this highly specialized outpatient clinic. I think, in general, that others have more experience with these issues. For example, case managers or community mental healthcare services."* (Neurologist #5)

On the contrary, other physicians (n=6/13) felt that memory clinics should be actively involved in care for NPS in early AD. Some of them suggested that the memory clinic should limit this role to the detection and diagnosis of NPS, whereas others also expressed that the memory clinic should also be involved in the treatment of NPS.

> *"I don't think that the care for NPS should be primarily embedded within the primary care. (…) You don't only look at a diagnosis, but also at everything that comes along with that. (…) I can hardly imagine that you only focus on a part of dementia and leave the rest of it to others. That's just very hard to understand for me."* (Geriatrician #4)

Furthermore, two physicians expressed that the NPS diagnosis and treatment do not have to take place at the memory clinic, but that the memory clinic should play an active and coordinating role to ensure that at least some care provider is taking care of NPS:

> *"I would like to see memory clinics play a more active and coordinating role in the care [for NPS] at home, because I see dementia as a terminal illness that deserves excellent care. Imagine that we would to this to patients with cancer…"* (Geriatrician #6)

Although many physicians acknowledged that there are significant regional differences within the Netherlands in how the care for NPS in early AD dementia is organized, there was consensus among memory clinic physicians that the collaboration with primary care providers should be improved. Yet, many physicians mentioned that they experience that at least a part of the general practitioners and case managers they collaborate with lack knowledge and experience concerning both detecting and treating NPS. For some memory clinic physicians (n=3/13), this is a reason why they remain actively involved in the care for NPS.

We found no substantial difference between geriatricians and neurologists regarding care practice and attitudes on the role of the memory clinic. The only remarkable difference was found relating to the time available to address NPS. While the majority of the geriatricians reported that they feel that they have more time to adequately address NPS compared to general practitioners, the majority of neurologists indicated that they experience a lack of time to adequately manage NPS.

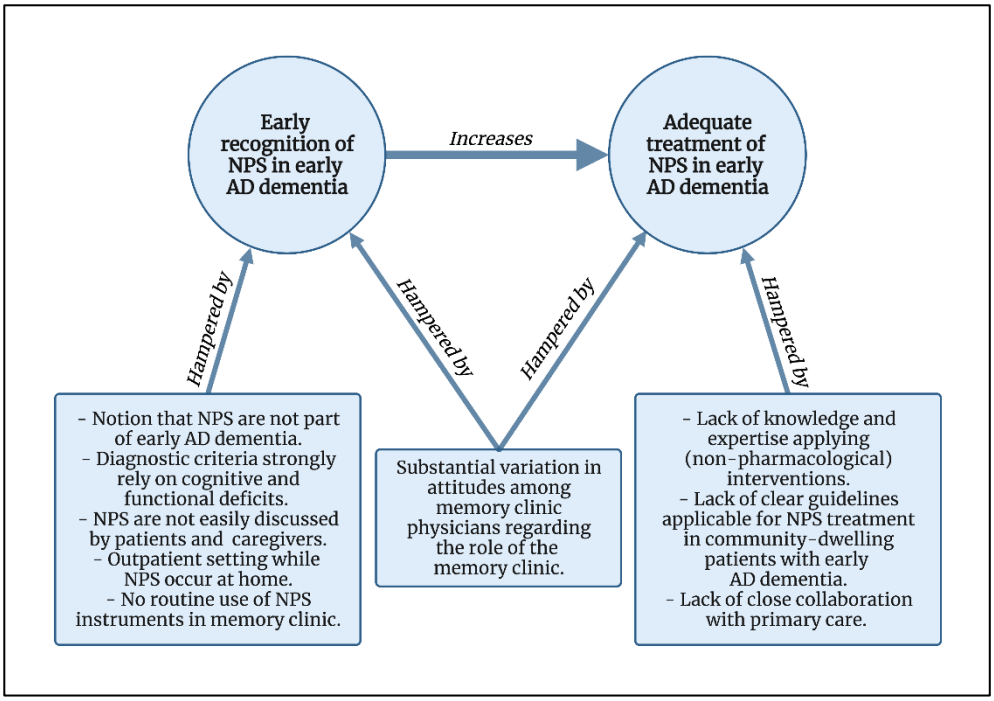
Discussion

This study examined the current state of care for NPS in early AD dementia at the memory clinic and the challenges physicians experience during the assessment and management of these symptoms. We observed substantial variation in the experiences, expertise, and attitudes of physicians working at the memory clinic related to the care for NPS in early AD dementia.

Moreover, we identified several challenges that memory clinic physicians experience while managing NPS including the memory clinic setting that makes it difficult to diagnose NPS, a lack of experience, knowledge, and/or resources to adequately apply non-pharmacological interventions, and a lack of consensus among physicians on the role of the memory clinic in care for NPS.

The majority of the physicians reported that they frequently observe NPS in individuals with AD dementia visiting the memory clinic, which is in line with prior studies showing that >85% of the individuals with AD dementia visiting the memory clinic exhibit at least one NPS according to standardized assessment scales such as the

Figure 1. The challenges identified that hamper early recognition and adequate treatment of NPS in early AD dementia



Notes. AD = Alzheimer's disease, NPS = neuropsychiatric symptoms.

Neuropsychiatric Inventory.[e.g. 10,147] Despite the high prevalence rates of NPS in early AD dementia, these symptoms are not always detected during the diagnostic stage of AD dementia.[106,114,209]

We identified several challenges that physicians experience when assessing NPS that may contribute to the underdiagnosis of NPS in early AD dementia. First, a minority of physicians stated that they do not consider NPS as a prominent symptom in the early phase of AD dementia, a view that is commonly shared among clinicians in dementia care.[9] It is important to make physicians aware of the fact that NPS occur frequently in early AD dementia, even as the first manifestation of the disease.[225] A good example of such an effort is the development of the concept of mild behavioural impairment (MBI), classifying individuals with NPS in the context of no or only mild cognitive impairment who are at risk for developing dementia.[31] Second, the majority of memory clinic physicians mentioned that the outpatient memory clinic is a difficult setting to detect NPS in early AD dementia as most of these symptoms occur at home. Therefore, physicians have to rely on retrospective information provided by patients and their caregivers to diagnose NPS, instead of witnessing it as it occurs. This results in a third challenge as physicians indicated that they find it challenging that they have to rely on information provided by patients and their caregivers as patients and their

caregivers do not always report NPS due to feelings of shame, difficulties describing NPS compared to cognitive symptoms, and because caregivers may try to avoid confronting patients with these symptoms. Results extend previous studies that have identified factors that hamper the assessment of NPS based on caregiver estimations such as that caregivers are often initially unaware that NPS are part of the disease,[8] and caregivers use different terminologies to describe NPS compared to physicians.[158] Altogether, these factors contribute to the observation that patients and caregivers may have difficulties bringing NPS up in the doctor's office and that physicians need to address and explain these symptoms. The majority of the physicians indicated the need for proactive screening of NPS in order to evaluate its presence and clinical relevance and half of the physicians indicated that NPS scales are part of the standard diagnostic work-up at their memory clinic, which is in line with a survey among Dutch memory clinics.[108] However, very few physicians reported that they used information from NPS scales to guide the assessment of NPS in AD highlighting that physicians fail to prioritize the standardized assessment of NPS. This has been reported previously and may hamper the early detection of NPS in AD dementia.[234]

The majority of the physicians indicated the effectiveness of non-pharmacological interventions over pharmacological treatments. Yet, we observed considerable differences among physicians in the amount of experience and expertise they have in applying non-pharmacological interventions for NPS in AD dementia. Despite these differences, all physicians indicated that they find the use of non-pharmacological treatments for NPS challenging. Although there is an overall increase in the routine use of psychosocial interventions over the last decades at memory clinics in the Netherlands,[108] some physicians in our study indicated that they rarely applied non-pharmacological interventions. These physicians reported that they lack specific knowledge and do not feel confident to apply these interventions. This has also been reported among general practitioners and nursing home staff.[228,229] A lack of experience and knowledge on the non-pharmacological treatment of NPS in AD dementia has serious consequences as our findings show that this can (1) lead to an underdiagnosis of NPS since physicians feel hesitant to address these symptoms and this (2) facilitates an increase in the prescription of psychotropic drugs. The physicians who do regularly apply non-pharmacological interventions reported that there is a lack of close collaboration with primary care providers and that they sometimes lack sufficient time to assess NPS, examine underlying causes, and follow-up on treatment advices.

Our findings reveal a lack of consensus among physicians included in our sample on the role of the memory clinic in the care for NPS in early AD dementia. While some physicians argued that the care for NPS should primarily take place in primary care, several others plead that the memory clinic should participate in the care for NPS in AD dementia. This lack of consensus clearly hampers the standardization of care for NPS in AD dementia. Therefore, it is important that memory clinics need to reach

consensus on their role in the care for NPS in AD dementia in order to make clear who is responsible for the diagnosis and treatment of these distressing symptoms, at least at a regional level. Important to note, although several physicians in our study claimed that the care for NPS in AD dementia should be organized in primary care, previous studies have shown that primary care providers such as general practitioners and home care staff are hesitant or inexperienced to apply non-pharmacological interventions and also do not always consider this their role.[229,235] So it should be important to include primary care providers in this discussion as well.

Strengths and limitations

The mixture of physicians in terms of sex, profession, years' experience, and hospital type is a strength of this study. Moreover, participants were included using both convenience sampling and purposive sampling and analyses were conducted in duplicate to increase validity and generalizability of our findings. However, although no new themes emerged during the final two interviews, the small number of physicians interview is a limitation of this study. In addition, we invited neurologists and geriatricians to participate in this study as these medical specialties coordinate the care provided at the memory clinic in the Netherlands, while care professionals such as psychiatrists are only consulted if needed.[108] However, psychiatrists are commonly part of the standard care provided at memory clinics in other countries.[236-238] Therefore, future studies in other countries are needed to study whether our findings also generalize to memory clinics worldwide. Furthermore, memory clinic physicians were interviewed about their attitudes on the role of the memory clinic in the care for NPS in early AD dementia and about their experiences with other care provides such as general practitioners. Yet, these care providers were not included in this study and future studies are needed to identify the attitudes and needs of primary care providers considering the care for NPS in early AD dementia.

Conclusion

Our results show large variation among memory clinic physicians regarding their care practices, knowledge, and attitudes on the role of the memory clinic relating to NPS in AD dementia. Hereby, our findings help to clarify the discrepancy between the recommendations of international guidelines and daily clinical practice observed in memory clinics. By doing so, we identified challenges that need to be addressed to improve the early recognition and adequate treatment of NPS in the early stages of AD dementia.

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Authors contributions

J.M.P., R.O. acquired funding for this study; W.S.E., E.v.d.B., J.M.P., designed the study; W.S.E., R.L.v.B.V., J.M.P. created the topic list; W.S.E., conducted the interviews, W.S.E., N.L. analyzed the data and interpreted the data assisted by M.C., R.O., E.v.d.B., J.M.P.; W.S.E. drafted the manuscript for intellectual content. N.L., R.L.v.B.V., F.U.S.M.R., M.C., R.O., E.v.d.B., J.M.P. revised the manuscript for intellectual content. J.M.P. supervised the study. All authors read and approved the final version of the manuscript.

Supplemental materials

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Chapter 3.3

The reporting of neuropsychiatric symptoms in electronic health records of individuals with Alzheimer's disease: A natural language processing study

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Abstract

Background and Objectives

Neuropsychiatric symptoms (NPS) are prevalent in the early clinical stages of Alzheimer's disease (AD) according to proxy-based instruments. Little is known about which NPS clinicians in the memory clinic report and whether their judgement aligns with the proxy-based instruments. We used natural language processing (NLP) to classify NPS in electronic health records (EHRs) to estimate the reporting of NPS in symptomatic AD at the memory clinic according to clinicians. Next, we compared NPS outcomes as reported in EHRs and NPS reported by caregivers on the Neuropsychiatric Inventory (NPI).

Methods

Two academic memory clinic cohorts were used: the Amsterdam UMC (n = 3,001) and the Erasmus MC (n = 646). Patients included in these cohorts had MCI, AD dementia, or mixed AD/VaD dementia. Ten raters annotated 13 types of NPS in a randomly selected training set of n = 500 EHRs from the Amsterdam UMC cohort and in a test set of n = 250 EHRs from the Erasmus MC cohort. For each NPS, a generalized linear classifier was trained and internally and externally validated. Prevalence estimates of NPS were adjusted for the imperfect sensitivity and specificity of each classifier. Intra-individual comparison of the NPS classified in EHRs and NPS reported on the NPI were conducted in a subsample (59%).

Results

Internal validation performance of the classifiers was excellent (AUC range: 0.81–0.91), but external validation performance generally decreased (AUC range: 0.51–0.93). NPS were prevalent in EHRs from the Amsterdam UMC, especially aberrant motor behavior (adjusted prevalence = 47.5%), apathy (adjusted prevalence = 69.4%), anxiety (adjusted prevalence = 53.7%, and depression (adjusted prevalence = 38.5%). The ranking of NPS was similar for EHRs from the Erasmus MC, although not all classifiers obtained valid prevalence estimates due to low specificity. There was minimal agreement between NPS classified in the EHRs and NPS reported on the NPI (all kappa coefficients < 0.28), with substantially more reports of NPS in EHRs than on NPI assessments.

Conclusions

NLP classifiers performed well in detecting a wide range of NPS in EHRs of patients with symptomatic AD visiting the memory clinic and showed that clinicians frequently reported NPS in these EHRs. Clinicians generally reported more NPS in EHRs than caregivers reported on the NPI.

Introduction

Over 80% of the individuals who visit the memory clinic in the early clinical stages of Alzheimer's disease (AD) experience neuropsychiatric symptoms (NPS) such as apathy, depressive symptoms, irritability, and sleep disturbances.[10,14,147] These symptoms are associated with poor clinical outcomes including reduced quality of life,[40] increased caregiver burden,[50] and a faster disease progression.[47]

Memory clinic physicians strongly rely on proxy-based instruments such as the Neuropsychiatric Inventory (NPI) to diagnose NPS in AD.[86,87,108] However, proxy-based NPS instruments are subject to recall bias and can be affected by the mood, fatigue, knowledge, and cultural beliefs of informal caregivers who usually provide the information.[88,89] Therefore, the perspective of clinicians on NPS may provide a valuable addition to the impression of caregivers.[88,239] However, little is known about how clinicians perceive and report NPS in the memory clinic setting. Electronic health records (EHRs) may provide a unique opportunity to address this question. Clinicians working at the memory clinic document symptoms, observations, outcomes of the diagnostic work-up, and differential diagnoses as free-text descriptions in EHRs. This unstructured format allows to report on complex clinical phenomena while taking the nuances of the individual patient into account,[240] and are increasingly used for research purposes to study clinical care practices, the manifestation of complex clinical symptoms, and the natural disease course.[241,242]

The advantages that free-text descriptions in EHRs offer simultaneously conveys a major challenge to structurally and systematically examine unstructured free text.[243] As the manual assessment of EHRs is very time-consuming, natural language processing (NLP) applications are increasingly used to automatically assign particular categories to phrases in free text. NLP algorithms can make free text machine-interpretable, for which they require a selection of EHRs to be manually rated by experts, i.e. annotated.[240,243] Based on these annotations, NLP algorithms are trained and validated in order to automatically classify the remaining EHRs.[243]

Recently, NLP applications have been used to detect NPS in EHRs of older adults with cognitive impairment.[244-246] These studies have shown that NLP applications can identify older adults at increased risk for dementia based on NPS presence,[245] estimate NPS prevalence based on EHRs in individuals with dementia,[244,246] and indicate potential underdiagnosis of NPS in dementia.[244] So far, NLP applications have not been used in the memory clinic setting. Previous studies have only focused on agitation, affective symptoms, and psychotic symptoms,[244-246] while neglecting other NPS that are also common in the early clinical stages of AD such as apathy, irritability, and sleeping behavior.[10,147] Furthermore, memory clinics establish NPS in AD by the impression of clinicians and u proxy-based instruments,[108] although no studies have examined whether these NPS outcomes overlap.

The aim of this study was to use NLP to estimate the reporting of a wide range of NPS reported by clinicians in EHRs of individuals with Mild Cognitive Impairment (MCI) or AD dementia at the memory clinic. In addition, we compared NPS reported in EHRs by clinicians and NPS reported by caregivers on the NPI.

Methods

This study was approved by the Medical Ethics Committees of the Erasmus MC (2018-1137) and the Amsterdam UMC (2021.0044).

Data

All EHRs were obtained from 3,001 individuals who visited the Alzheimer Center Amsterdam at the Amsterdam University Medical Centers between March 1993 and December 2020[123] and from 646 patients who visited the Alzheimer Center Erasmus MC at the Erasmus MC University Medical Center between January 2004 and April 2019. Patients were selected if they had a clinical diagnosis of MCI,[24] AD dementia,[1] or mixed AD/vascular dementia (VaD).[1] All individuals with MCI visiting the Alzheimer Center Amsterdam were amyloid-beta positive based on either cerebrospinal fluid analysis[125] or visual rating of an amyloid-beta PET scan,[126] while individuals with MCI visiting the Alzheimer Center Erasmus MC were only selected if they had AD as suspected primary etiology based on clinical impression, neuroimaging, and/or cerebrospinal fluid profile. In both samples, a subsample of the individuals with a clinical diagnosis of AD dementia had cerebrospinal fluid or amyloid-beta PET scan available indicating amyloid-beta positivity (65% in Alzheimer Center Amsterdam, 32% in the Alzheimer Center Erasmus MC).

EHRs from both hospitals contained free-text information on the referral, medical history, clinical impression, neurological examination, physical assessment, medication review, and psychiatric evaluation. There were also EHRs written by neuropsychologists describing their history taking, clinical impression, and neuropsychological test performances. EHRs from the Alzheimer Center Amsterdam were written by neurologists or neuropsychologists, while EHRs from the Alzheimer Center Erasmus MC were written by neurologists, geriatricians, or neuropsychologists. For each patient, the EHRs from these different clinicians created within a three-month period were clustered as this was the time usually needed to establish a clinical diagnosis. A random selection of 500 EHRs from the Alzheimer Center Amsterdam was used for the training set and internal validation, while a random sample of 250 EHRs from the Alzheimer Center Erasmus MC was used for external validation.

The NPI or its questionnaire form (NPI-Q) assessed as part of the diagnostic work-up were used.[84,247] For the head-to-head comparison, we denoted an NPI or NPI-Q domain score ≥ 1 as the presence of a specific NPS. For the intra-individual

comparison, we denoted an NPI or NPI-Q domain score ≥1 as the presence of a specific NPS.

Data annotation

Ten raters independently annotated the data. The raters consisted of four psychologists, two neurologists (in training), two psychiatrists (in training), one clinical neuropsychologist, and one geriatrician. The training set of 500 EHRs was divided into five sets of 100 EHRs that were independently annotated by two raters. Four of these raters also annotated the test set of 250 EHRs, divided into two sets of 125 EHRs each annotated by two raters. The pairs were selected such that they differed in terms of background and years of clinical experience.

In an iterative process, two raters (W.S.E., M.P.) developed a guideline for the annotation of 13 NPS categories of which 12 categories were analogous to the 12 NPI domains.[84] We added a 13th category for general terms that describe nonspecific NPS such as 'behavioral and psychological symptoms of dementia', 'changes in behavior', and 'challenging behavior'. Each of these categories were described in detail in the annotation guideline that was based on existing assessment scales, criteria for neuropsychiatric syndromes in dementia, and clinical experience. All ten raters tested the annotation guideline in 20 EHRs from the Alzheimer Center Amsterdam and 10 EHRs from the Alzheimer Center Erasmus MC that were not part of the training and test set. Hereafter, a consensus meeting was held with all raters discussing any disagreements. The final annotation guideline was established based on this discussion.

Annotations were made with the web-based annotation tool *brat*.[248] Raters were instructed to mark the word, phrase, or sentence that described an NPS and to label it with one of the 13 categories. After annotating the EHRs independently, each rater pair discussed the annotations where they initially disagreed and decided on a final consensus annotation. If needed, a third rater was consulted to reach consensus.

Text preprocessing

Different preprocessing steps were tested including stop word removal (using the Dutch stop word list in the R package stopwords), stemming (reducing words to their canonical form using the Dutch stemmer in R package SnowballC), and removal of phrases that indicated negations (e.g. "no depressive symptoms"). After preprocessing, the remaining free-text was divided into unigrams and bigrams, i.e. sequences of one or two words, which were used as features to train each classifier.[249]

Classifier training

We used NLP to assign categories to free text,[240] i.e. the classification of 13 NPS categories in EHRs. The annotations by the raters were used to train a classifier for each NPS category. We developed a binary classifier to determine the presence or absence of

that category in an EHR. Generalized linear classifiers (method glmnet in the R package caret) were trained and internally validated on the training set using tenfold cross-validation. The performance of the classifiers was externally validated on the test set.

Statistical analysis

Evaluation of annotations and classifier performance

Different inter-annotator agreement scores were derived from the annotations for each NPS category across all five pairs of raters, including accuracy (proportion of agreement) and the kappa coefficient (κ, proportion of agreement corrected for chance agreement).

The performance of each classifier was evaluated by comparing its automated classification of NPS with the manual annotations by the raters with the area under the receiver operating characteristic curve (AUC) on the training set using tenfold cross-validation and on the external test set. An AUC 0.70–0.80 was considered acceptable, an AUC 0.80–0.90 was considered excellent, and an AUC > 0.90 was considered outstanding.[250] For each classifier, sensitivity and specificity were calculated and a probability cutoff was selected by maximizing the Youden index.

Prevalence of NPS in EHRs

Only classifiers that had good diagnostic abilities (AUC ≥ 0.80) were included in subsequent analyses. The prevalence of each NPS category in the EHRs across patients was estimated for both cohorts separately using the classifiers. We estimated the prevalence and calculated confidence intervals taking the sensitivity and specificity of each classifier into account to correct for imperfect classifiers.[251]

Intra-individual comparison between EHRs and NPI

Intra-individual comparisons of the NPS classified in EHRs and NPS reported on the NPI were conducted in a subsample of individuals who had an NPI assessment available. For each NPS, we assessed the agreement between NPS reported in EHRs and NPS according to the NPI using the kappa coefficient. Of all the patients who had a particular NPS reported in their EHR, we calculated the proportion of patients with that NPS not endorsed on the NPI (EHR+NPI-). Similarly, of all the patients who had a particular NPS endorsed on the NPI, we calculated the proportion of patients with that NPS not reported in their EHR (EHR-NPI+).

Results

Patient characteristics

The majority of the patients included in both cohorts were diagnosed with AD dementia (78.4%), approximately half were female (52%), and the majority was White (90%) (Table 1). The patients from the Alzheimer Center Amsterdam were younger, a smaller

Table 1. Characteristics of the memory clinic cohorts

	Alzheimer Center Amsterdam	Alzheimer Center Erasmus MC
N patients	3,001	646
Age, mean (SD)[a]	67.2 (8.6)	71.1 (9.3)***
Sex, N (%) female	1,571 (52.4%)	323 (50.0%)
Education, median (IQR)[b]	5.0 (2.0)	5.0 (2.0)
Whites, N (%)[c]	189 (90.0%)	345 (89.1%)
MMSE, mean (SD)[d]	21.1 (6.4)	21.6 (5.5)
Diagnosis, N (%)		
Mild cognitive impairment	436 (14.5%)	157 (24.3%)***
AD dementia	2,438 (81.2%)	422 (65.3%)***
AD/VaD dementia	127 (4.2%)	67 (10.4%)***
Amyloid-beta positive, N (%)[e]	2,092 (69.7%)	184 (28.5%)***
NPI or NPI-Q available, N (%)	2,022 (67.4%)	133 (20.6%)***

Notes. AD = Alzheimer's disease, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, NPI-Q = Neuropsychiatric Inventory questionnaire, VaD = vascular dementia.
[a] data missing for n = 79 (Erasmus MC).
[b] Dutch education system categorized into (1) less than 6 years primary education [< 6 years], (2) completed primary education [6 years], (3) more than 6 years of primary education, without a secondary school diploma [8 years], (4) lower vocational training [9 years], (5) advanced vocational training or lower professional education [10-11 years], (6) advanced professional training or upper secondary school [12–18 years], and (7) academic degree [> 18 years]. Data missing for n = 261 (Amsterdam UMC) and n = 306 (Erasmus MC).
[c] data missing for n = 2792 (Amsterdam UMC) and n = 259 (Erasmus MC).
[d] data missing for n = 253 (Amsterdam UMC) and n = 125 (Erasmus MC).
[e] based on either cerebrospinal fluid (i.e., amyloid-beta$_{42}$ < 550 pg/mL or tau/amyloid-beta$_{42}$ ratio > 0.52) or visual rating of an amyloid-beta PET scan.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

proportion had MCI, and a higher proportion had an AD-biomarker confirmed diagnosis compared with the patients from the Alzheimer Center Erasmus MC (all $p < 0.001$, Table 1).

Annotations

For the training set, the median accuracy of the five pairs of raters across all NPS was 0.94 (range 0.92–0.96) and the median kappa coefficient across all NPS suggested moderate agreement (κ = 0.71, range κ = 0.49–0.74). There was low agreement between raters for aberrant motor behavior (median κ = 0.35), euphoria (median κ =0.49), disinhibition (median κ = 0.52), and agitation (median κ = 0.54), with highest agreement was obtained for hallucinations (median κ = 0.99) and general descriptions of NPS (median κ = 0.94) (Supplemental Table 1). For the external test set, the overall accuracy scores (0.94, 0.91) and the overall kappa coefficients (κ = 0.71, κ = 0.74) for

Table 2. Performance of the classifiers for the training and test set

	Training set				Test set			
NPS category	**AUC**	**Sensitivity**	**Specificity**	**Youden's Index**	**AUC**	**Sensitivity**	**Specificity**	**Youden's Index**
Eating behavior	0.91	0.85	0.81	0.66	0.83	0.59	0.94	0.52
Anxiety	0.90	0.78	0.89	0.66	0.84	0.60	0.92	0.52
Depression	0.90	0.71	0.97	0.68	0.88	0.79	0.85	0.64
Disinhibition	0.90	0.91	0.77	0.68	0.80	0.67	0.84	0.51
Irritability	0.89	0.83	0.83	0.66	0.84	0.76	0.84	0.61
Apathy	0.88	0.88	0.80	0.68	0.84	0.91	0.61	0.52
Delusions	0.88	0.79	0.87	0.67	0.75	0.69	0.78	0.47
Sleeping behavior	0.88	0.88	0.78	0.66	0.83	0.76	0.78	0.54
Agitation	0.87	0.87	0.83	0.70	0.81	0.63	0.90	0.53
Hallucinations	0.87	0.78	0.96	0.74	0.67	0.40	0.96	0.36
NPS general	0.87	0.80	0.92	0.72	0.93	0.85	0.90	0.75
AMB	0.81	0.91	0.61	0.52	0.51	0.61	0.51	0.12

Notes. AUC = area under the curve, AMB = aberrant motor behavior, NPS = neuropsychiatric symptoms.

the two pairs of raters were highly comparable to the training set (Supplemental Table 1). It was not possible to train a classifier for euphoria as this NPS was annotated in only five EHRs in the training set (1.0% of EHRs in training set).

Performance of classifiers

The cross-validated performance of the classifiers was excellent, with AUCs ranging from 0.81 to 0.91 (Table 2). The sensitivity and specificity of all classifiers were >0.70, except for the specificity of the classifier for aberrant motor behavior (0.61).

For the external test set, classifiers performance yielded AUCs ranging from 0.51 to 0.93. Although AUC values decreased compared to the training set (median AUC difference -0.06, range -0.30–+0.06), most AUCs remained excellent (AUC >0.80), except for delusions (AUC = 0.75), hallucinations (AUC = 0.67), and aberrant motor behavior (AUC = 0.51). Therefore, these three NPS were not included in subsequent analyses. The sensitivity of most classifiers was substantially lower, with a sensitivity >0.70 for only the classifiers of apathy, general descriptions of NPS, depressive symptoms, irritability, and sleeping behavior. The specificity of most classifiers was similar or higher in the external test set compared to the training set, except for aberrant motor behavior (training set 0.61 vs. test set 0.51) and apathy (0.80 vs. 0.61) (Table 2).

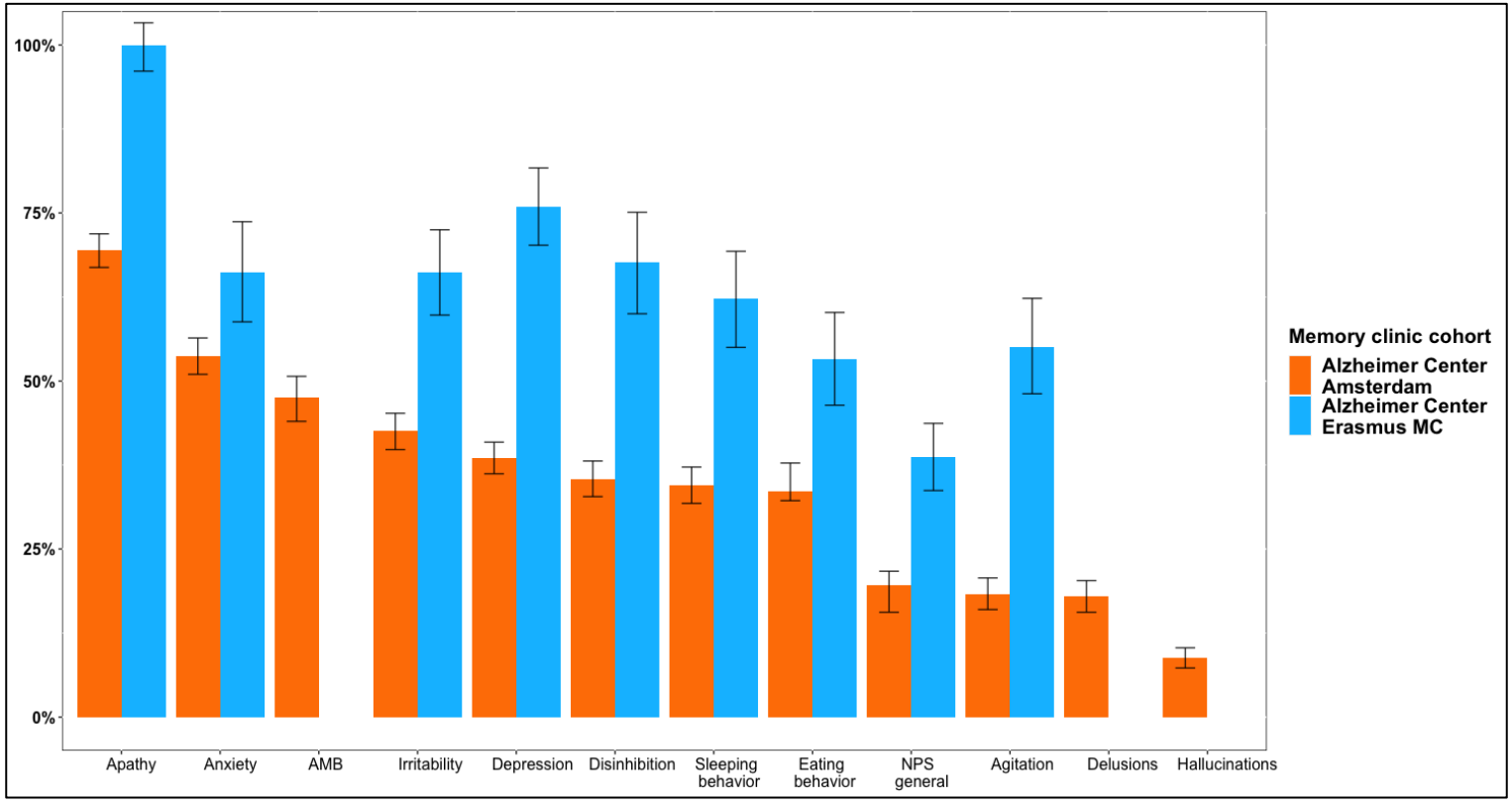
Prevalence of NPS in EHRs

The most prevalent NPS classified in the EHRs of patients who visited the Alzheimer Center Amsterdam were apathy (adjusted prevalence = 69.4%) and anxiety (adjusted prevalence = 53.7%), followed by aberrant motor behavior (adjusted prevalence = 47.5%), irritability (adjusted prevalence = 42.6%), and depressive symptoms (adjusted prevalence = 38.5%) (Figure 1). The majority of the prevalence estimates was lower when adjusted for the sensitivity and specificity of the classifiers, but did not change substantially (mean difference: -4.7 percentage point, range -16.2–+9.3%) (Supplemental Table 2).

All adjusted prevalence rates of NPS in EHRs of patients visiting the Alzheimer Center Erasmus MC were significantly higher compared to Alzheimer Center Amsterdam (all FDR-adjusted $p < 0.001$) (Figure 1). Still, the ranking of most common NPS in EHRs of the Alzheimer Center Erasmus MC was similar to the Alzheimer Center Amsterdam: apathy (adjusted prevalence = 100.0%), depressive symptoms (adjusted prevalence = 75.9%), anxiety (adjusted prevalence = 66.2%), and irritability (adjusted prevalence = 66.2%). Adjusting for the sensitivity and specificity of the classifiers when applied in the external test set substantially changed the prevalence estimates (mean difference: +12.3 percentage point range -0.3–+23.8%; Supplemental Table 2).

To evaluate the accuracy of the adjusted classifier estimates, estimates were compared with annotations for the training set and the external test set (Supplemental

Figure 1. Adjusted prevalence of neuropsychiatric symptoms classified in electronic health records



Notes. AMB = aberrant motor behavior, NPS = neuropsychiatric symptoms.
Prevalence estimates were adjusted for bias due to imperfect test.[310]
All adjusted prevalence rates were significantly higher in the Alzheimer Center Erasmus MC compared to Alzheimer Center Amsterdam (all FDR-adjusted $p < 0.001$).
Classifiers for aberrant motor behavior, delusions, and hallucinations were not used in the Erasmus MC data as AUC < 0.80.

Table 3). Generally, NPS prevalence rates based on adjusted classifiers were highly comparable to the annotations. However, several adjusted prevalence rates in the Alzheimer Center Erasmus MC data set were not valid probably due to low specificity (e.g. 100.0% [96.1–103.3%] for apathy).

Intra-individual comparison between EHRs and NPI assessments

A subsample of 2,022 individuals (67%) from the Alzheimer Center Amsterdam and 133 individuals (20.6%) from the Alzheimer Center Erasmus MC had an NPI assessment available. For both cohorts, the overall prevalence of NPS in EHRs was considerably higher than NPS reported on the NPI (Alzheimer Center Amsterdam median prevalence 52.5% vs. 20.1%; Alzheimer Center Erasmus MC 62.8% vs. 39.1%) (Figures 2 & 3).

Kappa coefficients indicated minimal to no agreement between NPS described in the EHRs by clinicians and NPS reported on the NPI by caregivers (Figures 2 & 3). Agreement was minimal for depressive symptoms in the Alzheimer Center Amsterdam ($\kappa = 0.28$) and agitation ($\kappa = 0.26$) in the Alzheimer Center Erasmus MC, while there was no agreement between all other NPS reported by clinicians and caregivers (all $\kappa < 0.18$). Kappa coefficients were highly similar across the two cohorts, except for a lower agreement for depressive symptoms ($\kappa = -0.04$) and anxiety ($\kappa = 0.01$) in the Alzheimer Center Erasmus MC compared to the Alzheimer Center Amsterdam (depression $\kappa = 0.28$, anxiety $\kappa = 0.15$).

Figures 2 and 3 show that the disagreements between NPS described in the EHRs by clinicians and NPS reported on the NPI by caregivers were mostly due to an lower NPS prevalence rates according to the NPI (i.e.. EHR+NPI-), as approximately 30% of the patients had a symptom solely reported in their EHR. Yet, NPS were solely reported on the NPI for almost 10% the patients (i.e. EHR-NPI+).

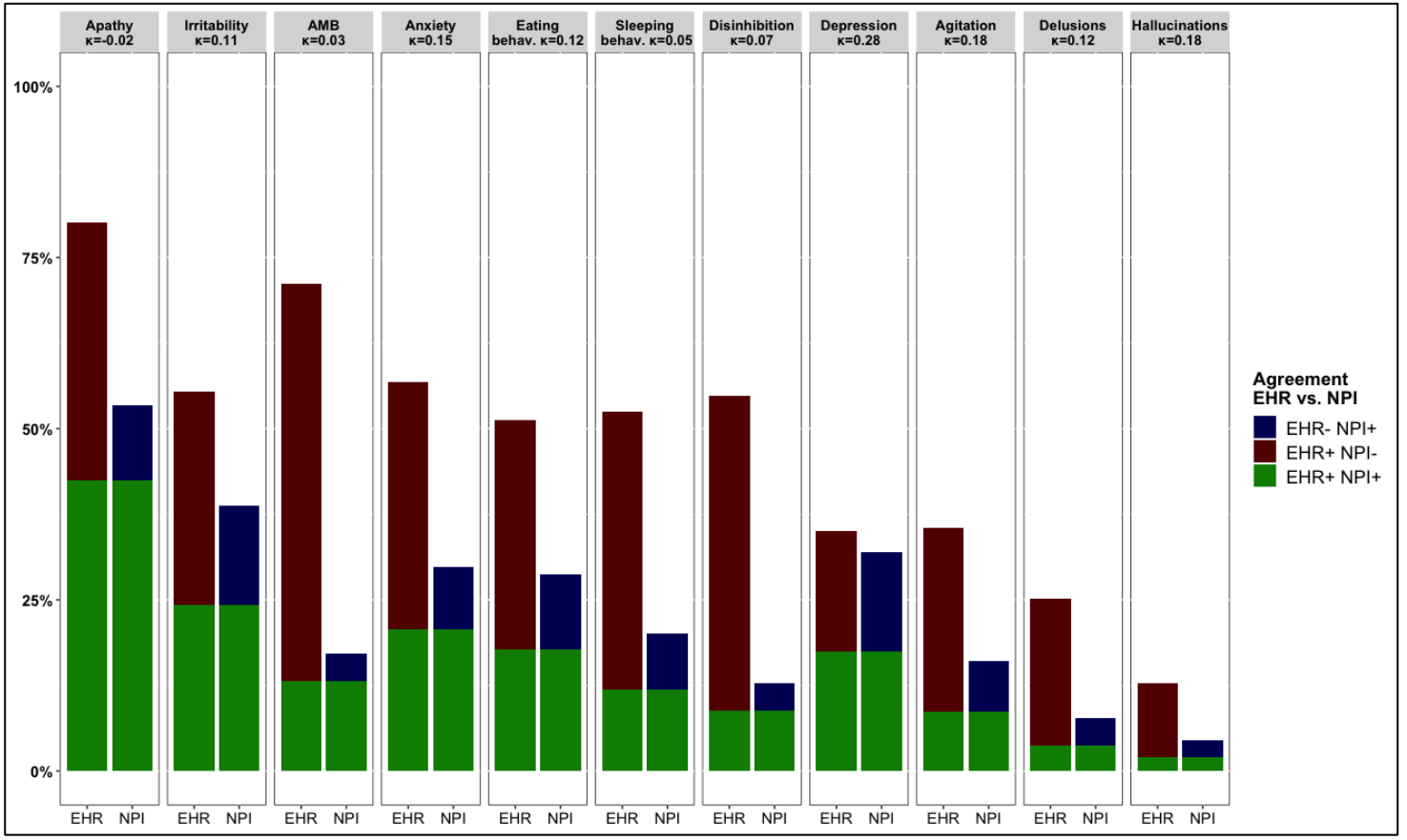
Discussion

Main findings of this study were that (1) NLP classifiers performed well in detecting a wide range of NPS in EHRs of patients with symptomatic AD visiting the memory clinic, although the generalizability of some NLP classifiers to detect NPS in EHRs in an external data set was limited; (2) clinicians frequently described NPS in EHRs of patients with symptomatic AD in both memory clinic cohorts; and (3) there was low agreement between NPS in EHRs reported by clinicians and NPS on NPI assessments reported by caregivers.

Performance of classifiers

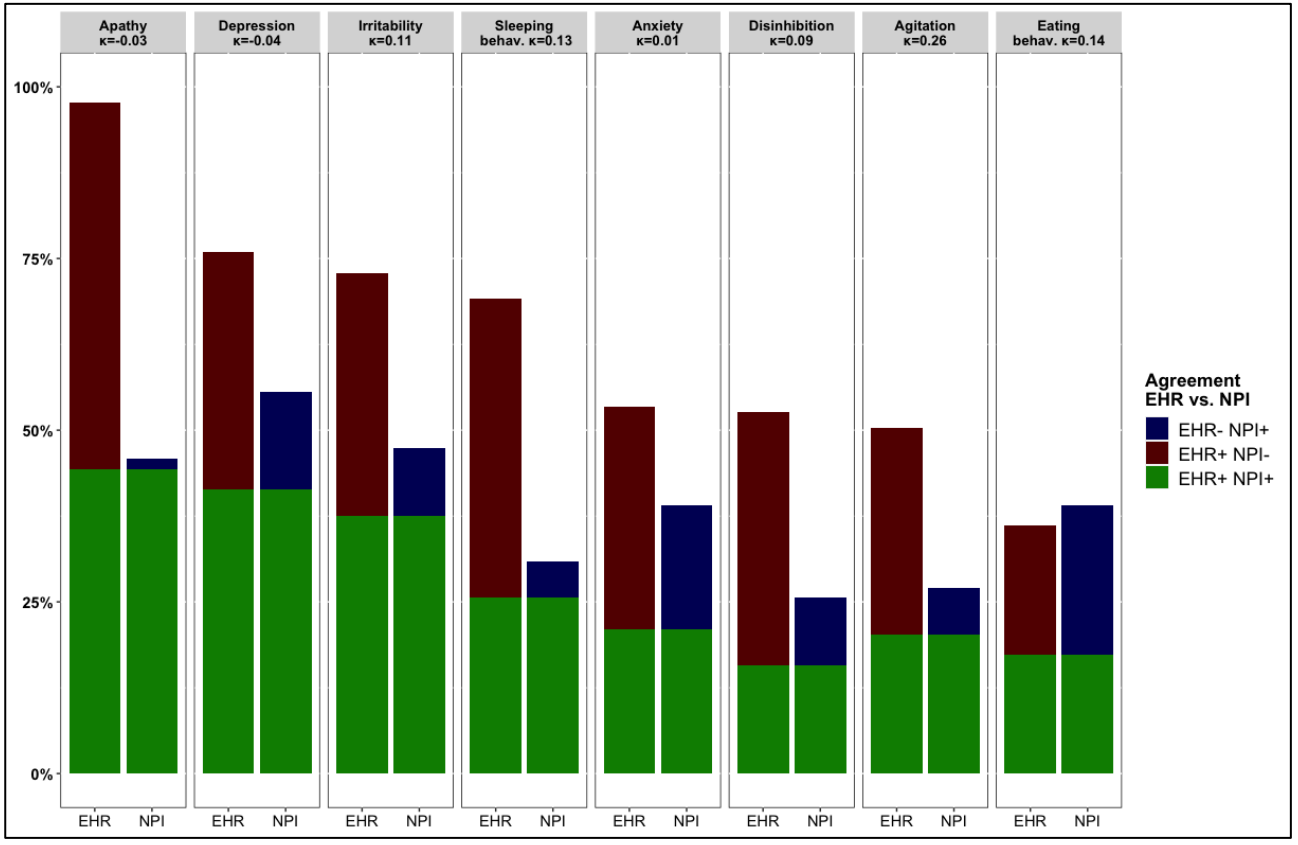
Based on the AUCs (range 0.81–0.91), performance of the classifiers was considered excellent in the training set and comparable to previous NLP studies in dementia.[252] External validation of classifiers showed good generalizability for the majority of NPS, except for hallucinations, delusions, and aberrant motor behavior. The few previous

Figure 2. Agreement between NPS described in EHRs and reported on NPI in Alzheimer Center Amsterdam cohort (n = 2,022)



Notes. AMB = aberrant motor behavior, EHR = electronic health record, EHR-NPI+ = NPS reported on NPI, but not described in EHR, EHR+NPI- = NPS described in EHR, but not reported on NPI, EHR+NPI+ = NPS reported on both EHR and NPI, κ = Kappa coefficient, NPI = Neuropsychiatric Inventory, NPS = neuropsychiatric symptoms.

Figure 3. Agreement between NPS described in EHRs and reported on NPI in Alzheimer Center Erasmus MC cohort (n = 133)



Notes. AMB = aberrant motor behavior, EHR = electronic health record, EHR-NPI+ = NPS reported on NPI, but not described in EHR, EHR+NPI- = NPS described in EHR, but not reported on NPI, EHR+NPI+ = NPS reported on both EHR and NPI, κ = Kappa coefficient, NPI = Neuropsychiatric Inventory, NPS = neuropsychiatric symptoms. Classifiers for aberrant motor behavior, delusions, and hallucinations were not included in these analyses as AUC<0.80.

studies that used NLP to detect NPS have not conducted external validation,[244-246] similar to the studies that used machine learning approaches recently reviewed in the field of geriatric psychiatry.[252] Hence, performing such analyses was considered a clear strength of this study as external validation is essential to establish the generalizability of classifiers.[240]

Prevalence of NPS in EHRs

Adjusting for imperfect sensitivity and specificity generally yielded accurate NPS prevalence rates when compared to annotated NPS. However, this resulted in extreme high values for some classifiers in the external data set (e.g. 100.0% [96.1–103.3%] for apathy), questioning the use of these classifiers in an external data set. A possible explanation is the moderate inter-rater agreement scores, probably due to substantial variation in terminologies used to denote NPS among clinicians.[158,253,254] Several researchers have raised concerns that divergent terminologies may hamper adequate recognition and treatment of NPS,[158,254] while it remains unknown to which degree this affects all NPS observed in AD. Our findings suggest that the clinicians' abilities to uniformly detect NPS was especially limited for aberrant motor behavior, euphoria, disinhibition, and agitation, while higher agreement was observed among clinicians for NPS such as hallucinations, delusions, and depressive symptoms. The implementation of the use of diagnostic criteria for NPS such as agitation may help to uniform the nomenclature used by clinicians working at the memory clinic.[27]

The adjusted prevalence estimates indicated that clinicians frequently reported NPS in EHRs of individuals with symptomatic AD visiting the memory clinic, especially apathy, anxiety, irritability, aberrant motor behavior, and depressive symptoms. These symptoms are commonly diagnosed in the early clinical stages of AD based on proxy-based measures, self-report instruments, and clinician rating scales.[10,11,14] The adjusted prevalence estimates of hallucinations, delusions, depressive symptoms, and agitation in our study were lower compared to prevalence rates in EHRs reported in two previous NLP studies.[244,246] These two studies clustered symptoms that were analyzed separately in our study (e.g. delusions and hallucinations). Furthermore, these studies also included EHRs of individuals with severe dementia living in nursing homes, which may explain the higher NPS prevalence rates reported. In addition, in contrast to previous studies,[244,246] our study adjusted for imperfect classification performances of the classifiers which generally reduced prevalence estimates.

We found a similar ranking of NPS reported in EHRs in both memory clinic cohorts included. Yet, we observed substantial higher prevalence estimates across all NPS in EHRs of patients who visited the Erasmus MC. This might be partly due to the limited classification abilities of the classifiers used in this external data set. However, NPS were also significantly higher according to the NPI (Supplemental Table 4). As the Alzheimer Center Erasmus MC is a frontotemporal dementia (FTD) center of expertise,

a large proportion of the patients referred to this center is suspected of having FTD. This may have resulted in a larger proportion of patients exhibiting NPS.

Comparison between EHRs and NPI assessments

We found at best minimal agreement between NPS that were described in EHRs by caregivers and NPS endorsed on the NPI by caregivers. It is important to note that NPS were spontaneously described or observed and reported in EHRs by clinicians, while NPS were assessed using a structured and standardized assessment tool in caregivers. Given these differences in NPS reports, we cannot directly compare the perspectives of clinicians and caregivers regarding their NPS impression, though these methods are both used to indicate the presence of specific NPS in the memory clinic.

Our findings do corroborate with prior studies showing large disagreement between clinicians and caregivers in standardized NPS instrument outcomes.[239,255-257] Discrepancies in NPS ratings might result from differences in the reference point based on which clinicians and caregivers consider certain behaviors abnormal. For instance, caregivers have to indicate whether behaviors are abnormal compared to pre-morbid functioning, while clinicians usually evaluate behaviors while referring to the general population and/or their personal clinical experience. In addition, prior research suggests substantial differences in nomenclature used to describe NPS between caregivers and clinicians.[158]

Clinicians generally reported more NPS in EHRs than caregivers reported on the NPI. Clinicians may be less biased by factors that are known to affect proxy-based NPS instruments such as mood, stress, fatigue, and recall bias.[89] In addition, NPS that were described in EHRs were not limited to specific wording and a timeframe of four weeks that is usually assessed with the NPI.[84] Finally, it should be noted that NPS were detected in EHRs based on imperfect classifiers with a tendency to overestimate the NPS prevalence. Although caregivers generally reported less NPS, a notable proportion of NPS that caregivers endorsed on the NPI were not mentioned in EHRs. A recent study by our group suggests that NPS may be underrecognized by memory clinic physicians as they experience difficulties diagnosing NPS that mainly occur at home and because some physicians do not perceive NPS as core feature of the early clinical stages of AD.[258]

No gold standard exists to establish the presence of NPS in AD. Therefore, we cannot make firm conclusions about the comparison between NPS reports by caregivers and clinicians. It is imperative to relate NPS ratings of clinicians and caregivers to alternative and possibly less subjective measures of NPS, e.g. using wearables such as actigraphy.[259]

Implications of findings

Our findings have important implications. First, although no gold standard exists, our findings may suggest that caregivers and clinicians report different NPS in community-

dwelling individuals with symptomatic AD. This has serious consequences as memory clinic clinicians strongly rely on proxy-based instruments to establish the presence of NPS and to evaluate the effectiveness of pharmacological and non-pharmacological interventions.[108] Moreover, proxy-based instruments are commonly used as outcome measure in clinical trials targeting NPS in AD.[87] Future studies should pair proxy-based NPS instruments with clinician-based instrument such as the NPI-C C.[88] Second, the developed classifiers might be used to study the manifestation of NPS in EHRs of populations without cognitive deficits as a growing body of research suggests that NPS may precede cognitive impairment during the course of AD.[17,147] Third, although the performance of a proportion of the classifiers was not considered sufficient to classify individual patients in the external test set at this stage, improving classification abilities holds promise for clinical practice. For example, these NLP applications might be used to identify patients in the early clinical stages of AD with significant NPS in other care settings than memory clinics, e.g. primary care. Hereby, these patients may be referred to a specialized memory clinic to receive adequate treatment as primary care providers have reported substantial difficulties in detecting and treating NPS.[229,235]

Strengths & limitations

Strengths of this study include (1) the large well-defined cohort of individuals with symptomatic AD, of which a large proportion had a clinical diagnosis supported by AD-biomarkers; (2) a large team of raters who independently annotated a wide range of NPS using a guideline; and (3) the external validation of the classifiers using an external memory clinic cohort. This study also has certain limitations that should be considered. First, the two cohorts studied were academic memory clinic populations with an overrepresentation of White and highly educated patients and young-onset and atypical variants of AD dementia. As considerable differences were already noted between these two cohorts in terms of NPS prevalence rates, future studies are needed to study the prevalence of NPS in EHRs of people in the early clinical stages of AD visiting memory clinics of general hospitals and other care settings. In addition, the limited performance of several classifiers might be explained by the low number of samples that were used to train the classifiers.[260] Finally, we were not able to take the severity and clinical relevance of NPS reported in EHRs into account. Instead, the mere presence of NPS in EHRs was annotated and used in all analyses. To align this with NPI assessments, we compared NPS reported in EHRs with NPI domain scores ≥ 1. However, this may have led to the inclusion of changes in behavior and emotions that may be trivial and of little clinical significance. Therefore, future studies are needed that take the severity of NPS reported by clinicians in EHRs into account, e.g. by examining the number of NPS reported in one EHR and/or by training separate classifiers for each NPS according to symptom severity.

Conclusion

Clinicians frequently report NPS in EHRs of individuals with symptomatic AD visiting the memory clinic. We found low agreement between which NPS clinicians described in EHRs and which NPS caregivers reported on the NPI, with substantially more NPS reported by clinicians than caregivers. More research is needed to determine whether this implies that caregivers underestimate NPS.

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Author contributions

R.O. and J.M.P. acquired funding for this study. W.S.E., E.H.S., E.v.d.B., M.C., R.O., J.A.K., and J.M.P. designed the study. J.C.v.S. contributed to the acquisition of patient data from the Alzheimer Center Erasmus MC. J.L.P.F., Y.A.L.P., and W.M.v.d.F. contributed to the acquisition of patient data from the Alzheimer Center Amsterdam. E.H.S., C.d.B., and R.O. contributed to the acquisition of EHR data from the Alzheimer Center Amsterdam. W.S.E. and J.M.P. contributed to the acquisition of EHR data from the Alzheimer Center Erasmus MC. F.G. was responsible for the acquisition of NPI data at the Alzheimer Center Amsterdam. W.S.E., E.H.S., E.v.d.B., M.C., J.A.G., E.G.B.V., M.P., C.G., M.O.M., R.O., and J.M.P. annotated the training and test set. J.A.K. anonymized the EHR data, trained and validated the classifiers, and provided the probability scores. W.S.E. analyzed data and interpreted the data assisted by E.v.d.B., M.C., R.O., J.A.K., and J.M.P.. W.S.E. drafted the first version of the manuscript, while E.H.S., E.v.d.B., C.d.B., M.C., J.A.G., E.G.B.V., M.P., C.G., M.O.M., F.G., J.L.P.F., Y.A.L.P., W.M.v.d.F., J.C.v.S., R.O., J.A.K., and J.M.P. critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

Supplemental Materials

Available online at: https://bit.ly/3A0f9ID.

Chapter 3.4

Residential aged care staff perceptions and responses towards neuropsychiatric symptoms: A mixed methods analysis of electronic healthcare records

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Abstract

Background and Objectives

To investigate electronic care notes to better understand reporting and management of neuropsychiatric symptoms (NPS) by residential aged care (RAC) staff.

Methods

We examined semi-structured care notes from electronic healthcare notes of 77 residents (67% female; aged 67–101; 79% with formal dementia diagnosis) across three RAC facilities. As part of standard clinical practice, staff documented the NPS presentation and subsequent management amongst residents. Using a mixed-method approach, we analyzed the type of NPS reported and explored care staff responses to NPS using inductive thematic analysis.

Results

465 electronic care notes were recorded during the 18-month period. Agitation-related behaviors were most frequently reported across residents (48.1%), while psychosis (15.6%), affective symptoms (14.3%), and apathy (1.3%) were less often reported. Only 27.5% of the notes contained information on potential causes underlying NPS. When faced with NPS, care staff responded by either providing emotional support, meeting resident's needs, removing identified triggers, or distracting.

Conclusions

Results suggest that RAC staff primarily detected and responded to those NPS they perceived as distressing. Findings highlight a potential under-recognition of specific NPS types, and lack of routine examination of NPS causes or systematic assessment and management of NPS. These observations are needed to inform the development and implementation of non-pharmacological interventions and care programs targeting NPS in RAC.

Introduction

Neuropsychiatric symptoms (NPS) include a broad range of symptoms such as agitation, delusions, apathy, wandering, and depression.[54] Previous studies have reported that 70–90% of the residents with dementia living in residential aged care (RAC) facilities show at least one NPS.[261,262] NPS are also common in residents with no or only mild cognitive impairment, with studies reporting 30–80% of these residents showing at least one NPS.[261,262] Although the manifestation of NPS is heterogeneous among RAC residents, apathy and agitation are generally the most prevalent symptoms observed.[263,264] NPS presence is associated with negative clinical outcomes including reduced resident quality of life and higher care staff workload, distress, and burnout.[265,266]

Although international guidelines recommend non-pharmacological strategies as first-line treatment approach for NPS,[33,91] these symptoms often trigger pharmacological interventions leading to high psychotropic drug use in RAC.[267] This is problematic since these medications often show limited efficacy with an increased risk for significant side effects when used to treat NPS.[104] Despite accumulating evidence of the efficacy of non-pharmacological interventions (e.g. staff training, recreational activities, and sensory stimulation) targeting NPS in RAC,[268] their adequate use and implementation remains insufficient.[269,270] Better understanding of how RAC staff perceive and respond to NPS is therefore essential. Identifying knowledge gaps and/or needs related to the care for NPS among RAC staff is important to help ensure that existing non-pharmacological interventions meet the needs and competences of RAC staff.

Research has provided some understanding of how care staff perceive and manage NPS in RAC. These studies have shown that staff (1) consider agitation as one of the most distressing NPS, while apathy causes less distress among care staff[265,271]; (2) experience that NPS can be triggered by environmental factors, or can be an expression of unmet needs[227,272]; and (3) sometimes feel powerless/overwhelmed when confronted with significant expressions of NPS.[227,273] In addition, these studies identified different management strategies that RAC staff apply when dealing with NPS such as creating a comforting environment, playing along instead of correcting residents, and distracting residents who exhibit NPS.[227,272]

Prior studies have traditionally used questionnaires, conducted interviews and/or focus groups with care staff. However, these methods can be subject to biases such as social desirability,[274] normative discourse,[275] recall bias,[276] and selection bias.[277] Furthermore, the extent to which clinicians are able to reflect on their own clinical practice can be impacted by limited feedback and confirmation bias.[278] The use of electronic healthcare records to study clinical care practices is a viable alternative to circumvent these biases and is increasingly used to gain insight into daily clinical

practice.[242] However, despite these advances, electronic healthcare records have rarely been used to study the management of NPS by care staff in RAC.[245]

This study analyzed electronic care notes retrieved from electronic healthcare records relating to the presentation and management of NPS to investigate (1) staff-reported NPS prevalence, (2) reported triggers/causes of NPS, and (3) interventions used to manage NPS.

Methods

The Standards for Reporting Qualitative Research (SRQR) were followed to report this study.[230] The SRQR checklist can be found in the Supplemental Materials.

Setting and participants

Electronic care notes generated during an 18-month period prior the commencement of participation in the BPSD^{PLUS} Program were analyzed. The BPSD^{PLUS} Program is a novel evidence-based person-centered care training and intervention program developed to provide RAC staff with specialized knowledge and understanding of dementia and NPS, together with a structured approach to aid the identification and management of NPS using non-pharmacological interventions. 77 residents and 70 RAC staff across three sites of one residential aged care provider in the Australian Capital Territory, Australia who participated in the BPSD^{PLUS} Program (used to describe the characteristics of the samples of this study). Site one consisted of both a general residential care unit and a dementia-specific unit, site two consisted of only a general residential care unit, and site three was solely a dementia-specific unit. Inclusion criteria for participation in the BPSD^{PLUS} Program required that care staff are engaged in the daily care of residents, and that residents to have been identified as having dementia, Mild Cognitive Impairment, or cognitive impairment according to their care records. Participating staff self-identified as follows: care worker, registered nurse, team leader, activities officer, care manager, physiotherapist aid, and activities coordinator.

Procedure

Electronic care notes retrieved from electronic healthcare records were examined. Standard procedures used in the participating facilities require care staff to document the occurrence of all behaviors in the electronic care notes; but detailed documentation is not required. Incident reports for major incidents are completed; however, we did not have access to these.

Supplemental Table 1 provides an example of the information collected in the electronic care notes (see Supplemental Materials). Care notes have a semi-structured format including multiple tick boxes for observed behaviors, their duration, and impact of interventions applied. Additionally, the care notes also included free text space

prompting staff to describe the observed NPS in more detail, to provide information on the context in which it occurred and to report potential triggers and strategies applied to manage the NPS. This study analyzed the information provided in the free text space and the data obtained from the tick boxes separately.

Data analysis

A mixed-method approach was used. First, the frequency, triggers and causes of NPS as reported were examined by classifying the NPS reported in the free text space into NPS categories to allowed for comparison with previous studies.[e.g. 263,264] Categories were based on (1) existing assessment scales,[e.g. 83,84] (2) diagnostic criteria of NPS-syndromes,[e.g. 29,279] and (3) consensus among the author team.

NPS in the open text fields were independently classified by two researchers (WSE and JK) achieving 85.2% of overall agreement. For NPS on which there was disagreement, the researchers discussed with a third researcher (clinician) to obtain total agreement. After consensus was reached, NPS were grouped into the following categories: (1) agitation/aggression, (2) wandering, (3) psychotic symptoms, (4) affective symptoms, (5) apathy, (6) sleep related behaviors, and (7) eating behaviors. Agitation/aggression-related behaviors included behaviors such as verbal agitation/aggression, physical agitation/aggression, (non)verbal repetitive behaviors, sexual inappropriate behaviors, and hoarding. Affective symptoms included anxiety and depressive symptoms. Psychotic symptoms consisted of delusions and visual and auditory hallucinations (Supplemental Table 2).

A qualitative approach using inductive thematic analysis was used to examine the management strategies applied by RAC staff in the open text fields.[233] This data-driven method allows meaningful fragments and themes to emerge from the data using inductive reasoning. A codebook with a list and definition of each code was developed prior to the coding process to ensure code reliability between two researchers (W.S.E., J.K.) (Supplemental Table 3). Codes were identified by the researchers by familiarizing themselves with the electronic care notes prior to completing the process of thorough analysis. After a consensus was reached for the code book, electronic care notes were independently analyzed by two researchers. The researchers systematically coded the data in an iterative process. Initial agreement between the two researchers (W.S.E., J.K.) for the codes classifying interventions was 83.3%. Disagreements were discussed until a consensus classification was reached. Next, both researchers collated the codes into preliminary categories and themes. Finally, initial themes were identified and named following a discussion between all authors. This resulted in the generation of key themes. All analyses were conducted using *ATLAS.ti* software version 8.3.4.

The two researchers (W.S.E., J.K.) who coded the data and conducted the thematic analysis had a background in psychology and health sciences. Both had

Table 1. Residents and care staff characteristics

Residents (n= 77)	
Sex, N female (%)[a]	51 (67.1%)
Age, mean (SD)	88.9 (6.3)
Continent of origin, N(%)[b]	
Australia	51 (69.9%)
Other	18 (30.1%)
Formal cognitive impairment/dementia diagnosis on record, (%)[a]	60 (78.9%)
Not specified	27 (45.0%)
Cognitive impairment, not specified	6 (10.0%)
Mild cognitive impairment	1 (1.7%)
Alzheimer's disease dementia	14 (23.3%)
Vascular dementia	5 (8.3%)
Mixed dementia	4 (6.7%)
Frontotemporal dementia	1 (1.7%)
Parkinson's disease dementia	1 (1.7%)
Lewy body dementia	1 (1.7%)
Care staff (n = 70)	
Sex, N female (%)[c]	52 (81.3%)
Age, mean (SD)	37.9 (11.8)
Continent of origin, N(%)[c]	
Australia/Oceania	22 (34.4%)
Asia	32 (50.0%)
Other	10 (15.6%)
Level of education, N(%)[b]	
High School/Certificate/Apprenticeship	27 (43.5%)
University or higher	35 (56.5%)
Months working in aged care, mean (SD)	57.5 (55.6)
Formal dementia training completed, N(%)[d]	27 (44.3 %)
Role, N(%)[c]	
Care worker	38 (59.4%)
Registered nurse	9 (14.1%)
Team leader	7 (10.9%)
Activities officer	4 (6.3%)
Care manager	3 (4.7%)
Physiotherapist aide	2 (3.1%)
Activities coordinator	1 (1.6%)

Notes.

[a] Missing information for n = 3.
[b] Missing information for n = 8.
[c] Missing information for n = 6.
[d] Missing information for n = 9.

experience with working with people living with dementia in the Netherlands and in Germany. The thematic analysis findings were discussed with the entire author team. The team included researchers with a broad range of experiences in clinical psychogeriatric nursing, geriatric psychiatry, and RAC and a number of researchers from Australia with experience of working with people living with dementia and clinical nursing.

Ethics

Written informed consent was obtained from residents, next-of-kin, and care staff. A capacity to provide informed consent assessment was conducted using the Evaluation to Sign Consent Measure.[280] For residents who were able to provide informed consent self-consent was used. For those not able to provide informed consent, an informant/power-of-attorney consent was obtained. Approval was obtained from the Human Ethics Committee of The Australian National University.

Results

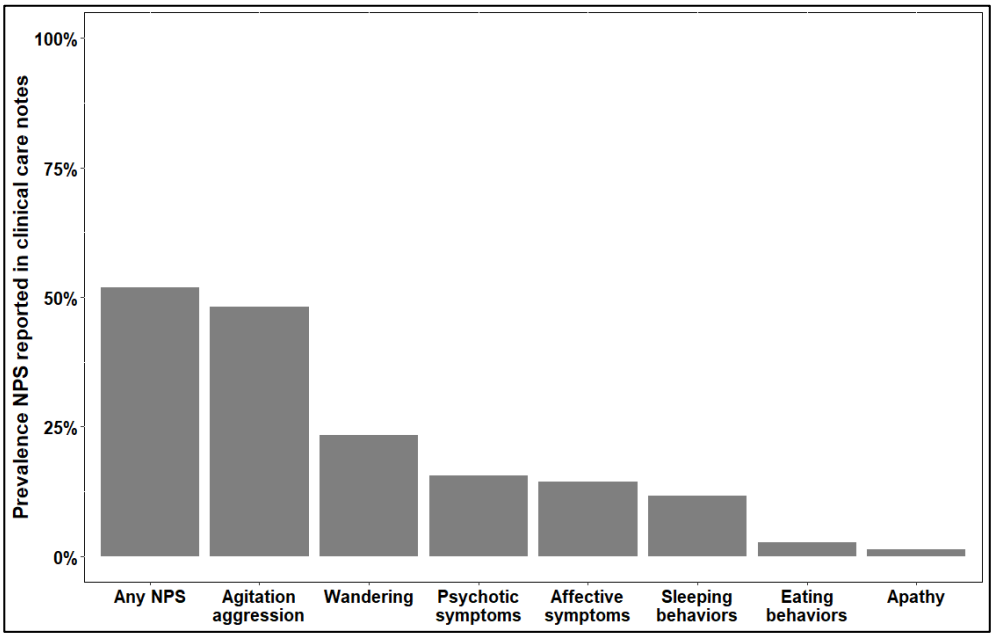
Residents and care staff characteristics

Characteristics of the residents and care staff can be found in Table 1. Residents had a mean age of 88.9 years (SD = 6.3) and 67.1% were female. All residents had cognitive deficits, with 78.9% having a formal diagnosis of (mild) cognitive impairment or dementia on record. The majority of the staff worked as care worker (i.e. carer, care assistant), 56.5% held an University degree or higher, and 44.3% had received prior formal dementia education.

Electronic care notes

A total of 465 electronic care notes were recorded within the 18-month period. Number of notes per resident ranged from 0–93, with no NPS-related notes having been recorded by staff for n = 31 residents (40.3%). For those with at least one electronic NPS related care note, the median number of notes per resident was 4.0 (IQR = 11.0).
For 36 care notes (7.7%), care staff did not provide any information in the free text spaces but only used the tick boxes. Nine notes (1.9%) did not contain any information on NPS in the free text space but contained information on cognitive problems (e.g. 'lost his wallet' or 'can't remember where his room is despite shown many times'). Terms like 'refusal of care' were observed in the free text space of 45 notes (9.7%). These terms were not categorized as a specific NPS when reported in isolation as it was unclear how these behaviors manifested, i.e. through agitation or withdrawal.

Figure 1. Prevalence rates of neuropsychiatric symptoms across 77 residents



Notes. NPS = neuropsychiatric symptoms.

Prevalence of NPS across residents

During the 18-month observation period, at least one NPS was reported in the free space of the electronic care notes of 40 residents (51.9% of the residents; Figure 1). Agitation-related behaviors were most often reported by care staff (48.1%) and included verbal agitation/aggression (32.4%), physical agitation/aggression (28.6%), verbal repetitive behaviors (20.8%), and sexual inappropriate behaviors (2.6%). Wandering was reported in 23.4% of residents' care notes. Other NPS reported were psychotic symptoms (15.6%)—including delusions (13.0%) and hallucinations (6.5%), affective symptoms (14.3%)—including depressive symptoms (10.4%) and anxiety (6.5%), sleep related behaviors (11.7%), eating behaviors (2.6%), and apathy (1.3%).

In general, NPS were more frequently reported in the tick boxes compared to the free space of the electronic care notes, although a similar distribution was observed (see Supplemental Table 4). Verbal agitation/aggression (49.4%) and physical agitation/aggression (45.5%) were reported most frequently across residents. Wandering was also frequently endorsed in the tick boxes (28.6%), while sexual inappropriate behaviors (3.9%) and paranoid ideation (14.3%) were not commonly observed. Although 'apathy' was not a tick box option, withdrawn behaviors (15.6%) and socially isolated behaviors (6.5%) were reported substantially more often reported in the tick boxes compared to the information provided in the free space data. There

were no tick box options for verbal repetitive behaviors, affective symptoms, hallucinations, sleep disturbances, and eating behaviors.

Triggers and causes of NPS

Of the 420 electronic care notes reporting NPS, 42.1% did not include any information on possible triggers or causes of NPS observed, and care staff indicated in 30.4% of the notes that triggers were unknown. The remaining 27.5% of the notes contained information on potential triggers or causes. Staff most frequently reported that assistance with activities of daily living were triggers of NPS (8.7%, e.g. 'Resident was hitting staff when they were removing her clothes for showering'.). Furthermore, care staff identified in 7.1% of the notes that cognitive deficits such as disorientation or memory impairments were related to reported NPS (e.g. '[resident name] couldn't find her room. [resident name] went into [other resident name] and was wandering in bathroom picking up towels and toilet paper'.). Less frequently reported triggers of NPS were an underlying somatic condition (1.6%), interactions with other residents (2.6%), or unmet needs such as boredom or pain (3.5%). Care staff at times also used an underlying diagnosis of 'dementia' as a suggested trigger (2.4%). In rare cases (< 2.0%) they mentioned specific recollections from the resident's past life as the cause of NPS (e.g. '[resident name] informed staff she doesn't like German people because of WWII'.).

Care staff responses to NPS

For the thematic analysis, 348 electronic care notes (74.8%) were analyzed that contained information on the management strategies used by RAC staff. This resulted in four themes (Table 2). These included responses to NPS through: (1) emotional support, (2) meeting the resident's needs, (3) removing direct triggers, and (4) distracting activities.

Emotional support

This approach was most frequently (59.7%) described in the electronic care notes and included strategies such as calming the resident down, reassuring and explaining the situation to the resident, or by offering a drink or food. Based on the information provided in the tick boxes, care staff indicated that these interventions were effective in 19.6% of cases.

> *"Resident wanted to go out with his wife to see family. Interventions: Reassured resident that family can visit him next week or later."* (R30)

> *"[name resident] kept coming in and out of [the] room, wandered in the dining hall. Interventions: Supplied with hot coffee, offered some casual conversations."* (R54)

Table 2. Themes on care staff response to neuropsychiatric symptoms

Theme	Categories/ Codes	Examples
Emotional support	Calming down Explaining Reassuring	*"Console him and speak slowly and politely to him"* *"Reassured resident that family can visit him next week or later"* *"1:1 staff provided"*
Distracting activities	Encouraging to join activities Diverting the residents mind	*"Resident was taken outside for a while to watch the bird"* *"Redirected her mind and talked about good day"*
Removing trigger	Removing objects Relocating residents	*"Removed cutlery and condiments/sugar"* *"I intervened and moved the other care recipient away"*
Meeting the resident's needs	Assisting Looking for somatic underlying causes Administering medication Giving space	*"Staff was trying to assist residents with toileting as asked by the resident"*

Meeting the resident's needs

Care staff approached this in a variety of ways such as assisting the resident in activities of daily

living tasks, looking for underlying pain or a somatic condition, or giving the resident space. Care staff reported this type of response in 21.2% of the care notes and indicated that 25.7% of these approaches were effective.

> *"[Resident was] constantly calling for help while was sitting on her wheelchair at the dining table. […] When staff asked what help she wants, she was unable to reply, after some time she asked for dental help. Interventions: […] Registered nurse reviewed if she is in any pain."* (R01)

> *"Resident was bashing on the glass in the care office yelling regarding her medications. […] She requested Mylanta for heart burn. [Once] it was administered she stormed off back to her room."* (R44)

Removing direct triggers

This included actions such as adapting the social and physical environment by moving other residents or objects away who triggered the resident's NPS. Additionally, staff removed objects/led other residents away to guarantee residents' safety. Care staff

reported using this type of response in 14.6% of reported care notes and indicated that these responses were effective in 21.8% of cases.

> *"Resident was pushing her wheelie walker into another resident who was sitting in his wheel chair minding his own business. Interventions: Moved other resident away from her when she is like this, for her own safety."* (R66)

> *"Resident was banging her knife on [the] dining table, [was] yelling at staff and residents, [was] throwing sugar sachets on the floor […], and resident [was] attempting to stab [staff name]. Interventions: Removed cutlery, condiments and sugar."* (R66)

Distracting activities

When confronted with NPS, care staff sometimes (4.6%) reported trying to divert the resident's attention through conversations or encouraged them to participate in other activities. Staff reported that 34.5% of these activities were effective.

> *"Resident [was] constantly yelling out: 'hey come here'. Interventions: Staff sat with resident talking and doing activities with her, she was still yelling out while staff is sitting next to her. […] Resident was taken outside for a while to watch the bird."* (R06)

> *"Resident observed to be sad and crying at medication round. She stated: 'why cannot she go. I miss my husband, he was a lovely man'. Interventions: Redirected her mind, talked about good day and reminded to attend dining area for breakfast."* (R17)

Discussion

Three important findings were made: (1) care staff primarily reported agitation-related behaviors, while apathy, affective symptoms, and psychosis were recorded relatively less often, (2) care staff did not routinely report on triggers and causes of NPS, and (3) care staff appeared not to systematically assess and manage NPS. These findings provide useful information to assist with the development and implementation of educational and care programs designed to support care staff in managing NPS.

In the 465 care notes that were retrieved during an 18-month period, care staff most frequently reported behaviors related to agitation and aggression, while apathy, affective symptoms, and psychosis were less frequently reported in electronic care notes. Based on prior studies which estimated NPS prevalence in RAC settings using questionnaires, higher NPS prevalence rates were expected.[e.g. 263,264] For example, a systematic review on the prevalence of NPS in RAC settings reported the weighted mean prevalence rates for apathy (36% [range 17–82%]), depressive symptoms (28% [range 9–66%]), delusions (22% [range 1–54%]), and hallucinations (14% [range 1–

39%]).[263] The differences in prevalence rates of specific NPS found in our study may have several explanations. First, previous studies have shown that RAC staff consider agitation, irritability, sleep disturbances, and delusions to be amongst the most distressing NPS, while symptoms like apathy usually cause less staff distress.[265] These distressing symptoms may impede the staff in their care delivery and also contain features that bring the resident to staff attention (e.g. intrusion into private spaces of other residents, repetitive attempts to try and leave). This may therefore have resulted in less frequent reporting of less distressing symptoms such as apathy, depression, and anxiety. Secondly, the manifestation of symptoms may provide a further explanation. Behavioral symptoms such as agitation and aggression may have a sudden onset and/or worsening, while symptoms such as apathy tend to be less acute or more consistent over time.[153] As a consequence, care staff may not have reported apathy in the electronic care notes during the 18-month period as this may be considered a 'chronic state'. The under-reporting and perhaps also underrecognition of NPS such as apathy, depression, and some forms of psychosis can be problematic as their presence is linked to greater dementia severity, poorer cognitive functioning and functional abilities, and higher levels of other NPS.[281,282]

In our study, care staff reported potential triggers or causes in only a small number of cases. In over 70% of the electronic care notes, care staff either indicated that the triggers or causes were unknown, or provided no information on potential triggers/causes of NPS, despite being prompted to do so. In cases in which care staff provided information in the free text space about triggers or causes, they primarily reported that assisting with activities of daily living triggered NPS. These results contrast with findings of previous studies in which care staff were interviewed on their attitudes towards NPS and identified different factors that may underpin NPS, e.g. pain, cognitive deficits, lack of stimulation, and feelings of frustration or shame.[227,272] We found that these reports were frequently solely generic descriptions of the context in which NPS occurred and did not entail concrete information on specific triggers or underlying causes that could serve as a starting point for non-pharmacological interventions. Yet, it is important to note that other studies have also shown that care staff often indicate that they have limited knowledge on the wide range of potential factors that may cause or trigger NPS.[228,283] Furthermore, care staff have also reported a lack of time needed to investigate underlying causes of NPS as a main limiting factor when confronted with NPS.[284,285]

When confronted with NPS, care staff indicated that they managed NPS by providing emotional support, distracting the resident, removing direct triggers, or meeting the resident's identifiable unmet needs including pain or boredom. Based on the care notes, we did not find indications that staff asked a general practitioner or other medical specialists for assistance. Moreover, care staff did not record the need to use medications to manage the behaviors. Several guidelines and international expert

groups recommend a multidisciplinary approach to manage NPS. This approach also includes a thorough characterization of NPS and the context in which they occur, a search for underlying and modifiable causes that provide a starting point for (non-)pharmacological interventions, and an evaluation of the efficacy and implementation of strategies used.[33,106,286] In line with these recommendations, several care programs have been developed which aim to structure and standardize these steps.[e.g. 100,287,288] However, the electronic care notes examined in this study suggested that care staff did not elaborately investigate the context in which NPS occur, or examine underlying causes. Moreover, care staff generally appeared not to respond to NPS in a systematic manner, instead attempting to reduce NPS as they occur (e.g. relocating or distracting the resident who exhibits NPS).

Several recommendations to improve the management of NPS in RAC can be made based on our findings. First, it seems important to provide targeted training to RAC staff on the full range of potential NPS and with a special focus on apathy, depression, and some psychotic symptom as less 'distressing' symptoms. RAC staff may be encouraged to use standardized assessment scales such as the Neuropsychiatric Inventory-Nursing Home version which has been specifically developed for NPS assessment within RAC settings. Ideally, this would typically occur at the staff level of the registered nurses in collaboration with a medical specialist. This type of approach may be helpful in raising awareness amongst care staff for all types of NPS.[100] Second, it is important to focus on potential determinants or causes of NPS in training programs for aged care staff. Prior research has identified a large number of determinants of NPS including biological factors (e.g. neurodegeneration), other dementia-related symptoms (e.g. cognitive deficits), medical problems (e.g. urinary tract infection), unmet needs (e.g. pain), factors relating to caregivers (e.g. communication issues), and factors associated with the environment (e.g. under-stimulation).[289] Improving care staff knowledge about such determinants of NPS is highly relevant as this identification forms the basis of effective non-pharmacological interventions. Yet, training alone might not suffice to change clinical practice and could be expanded with mentoring programs involving direct feedback loops in which the benefits of routinely assessment and systematic management are being experienced by care staff. Finally, in addition to staff training, aforementioned care programs that use a multidisciplinary step-wise approach to detect and treat NPS are advised to help structure and standardize the care for NPS in RAC settings. These programs have shown to be effective in mitigating NPS, reducing inappropriate psychotropic drug use, and improving confidence in the management of NPS among care staff.[290,291] RAC staff interviewed in a recent study after participating in a care program reported that the educational aspects of the program made them more aware of NPS and that a structured care program was helpful in knowing where to start when managing NPS.[292] On an organizational level, we acknowledge the extra time and costs required to carry out these targeted care

programs; however, there is a growing evidence for the cost-effectiveness of such interventions.[293]

Strengths and limitations

Strengths of this study include the use of electronic healthcare records to obtain unique insights into current care for NPS in the RAC setting that were examined using a mixed-methods approach. Moreover, this study was conducted across multiple RAC facility sites and included a diverse sample of care staff in terms of role, experience within aged care sector, cultural background, and age. However, several study limitations need to be considered. First, the information provided in the tick boxes may needs to be interpreted with caution as not all potential NPS were included as tick box options (e.g. no depression, anxiety, hallucinations). Furthermore, it was not always clear which NPS was truly being reported on when RAC staff selected some of the tick box options as these often reflected broad categories (e.g. does 'withdrawn behaviors' reflect apathy or depression?). Second, we acknowledge that electronic healthcare records probably cannot fully reflect the complete reasoning process behind the interventions that were applied and possibly do not contain all strategies implemented by staff to manage NPS (e.g. PRN psychotropic drug use, case conferencing, tailored activities). We included staff with different backgrounds, but we were not able to stratify analyses based on these roles as almost all care notes were recorded by care workers. In addition, although care staff were prompted to record all NPS and related triggers, we acknowledge that they have limited time to record all this information, making it likely that only the most serious events or the most obvious or persistent NPS are reported and considered in depth. Finally, by studying electronic care notes, we might have missed NPS that fluctuated quickly or persist at low intensity over time as this might not be observed and/or reported.

Conclusion

Our results highlight an under-reporting of apathy, affective symptoms, and psychosis in RAC electronic care notes. Furthermore, care staff often do not report underlying causes of NPS and appear not to apply systematic assessment and management strategies to respond to (causes of) NPS. These observations are informative for the development and implementation of non-pharmacological interventions and care programs targeting NPS in RAC settings.

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Author contributions

W.S.E., J.M.P., M.E.M. designed the study; W.S.E., J.K. analyzed the data; W.S.E., J.K., M.E.M. interpreted the data; W.S.E. drafted the manuscript for intellectual content; E.B., E.v.d.B., C.D., J.M.P., K.J.A., M.E.M. revised the manuscript for intellectual content; M.E.M., J.M.P. supervised the study. All authors read and approved the final version of the manuscript.

Supplemental materials

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Chapter 4

Improving timely recognition and treatment of neuropsychiatric symptoms in Alzheimer's disease at the memory clinic

Chapter 4.1

Early recognition of neuropsychiatric symptoms to improve quality of life in early Alzheimer's disease: Protocol of the BEAT-IT study

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Abstract

Background and Objectives

Neuropsychiatric symptoms (NPS) are very common in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia and are associated with various disadvantageous clinical outcomes including a negative impact on quality of life, caregiver burden, and accelerated disease progression. Despite growing evidence of the efficacy of (non)pharmacological interventions to reduce these symptoms, NPS remain underrecognized and undertreated in memory clinics. The BEhavioural symptoms in Alzheimer's disease Towards early Identification and Treatment (BEAT-IT) study is developed to (1) investigate the neurobiological etiology of NPS in AD and (2) study the effectiveness of the Describe, Investigate, Create, Evaluate (DICE) approach to structure and standardize the current care of NPS in AD. By means of the DICE method, we aim to improve the quality of life of AD patients with NPS and their caregivers who visit the memory clinic. This paper describes the protocol for the intervention study that incorporates the latter aim.

Methods

We aim to enroll a total of 150 community-dwelling patients with MCI or AD and their caregivers in two waves. First, we will recruit a control group who will receive care as usual. Next, the second wave of participants will undergo the DICE method. This approach consists of the following steps: (1) describe the context in which NPS occur, (2) investigate the possible causes, (3) create and implement a treatment plan, and (4) evaluate whether these interventions are effective. Primary outcomes are the quality of life of patients and their caregivers. Secondary outcomes include NPS change, caregiver burden, caregivers' confidence managing NPS, psychotropic medication use, the experiences of patients and caregivers who underwent the DICE method, and the cost-effectiveness of the intervention.

Conclusions

This paper describes the protocol of an intervention study that is part of the BEAT-IT study and aims to improve current recognition and treatment of NPS in AD by structuring and standardizing the detection and treatment of NPS in AD using the DICE approach.

The trial was registered on the Netherlands Trial Registry (NTR7459); registered 6 September 2018.

Introduction

Background and rationale

The majority of patients with Alzheimer's disease (AD) experience neuropsychiatric symptoms (NPS) during the course of their disease.[9,81] NPS include behaviors such as apathy, agitation, and psychosis, and are already highly prevalent in patients in the early stages of AD including those with mild cognitive impairment (MCI).[294] NPS have a large impact on the quality of life (QoL) of patients and their caregivers,[295] leading to extensive healthcare costs.[296] In addition, NPS are related to accelerated progression of the disease and earlier institutionalization.[4,53]

Although NPS are increasingly recognized as core features of AD,[9] NPS are currently underrecognized during the diagnostic phase in memory clinics. This notion arises from our local experience, but one that has also been raised previously by several international research groups.[100,106,114,244] While cognitive testing and instrumental activities of daily living (IADL) questionnaires are typically administered during standard clinical work-up, assessment of NPS (e.g. using the Neuropsychiatric Inventory [NPI]) is often not.[234] The failure of clinicians to prioritize the assessment of NPS leads to undertreatment and a variety of associated suboptimal outcomes.[210,225] This is clearly a missed opportunity since there is growing evidence for the efficacy of psychosocial and pharmacological interventions to reduce NPS and improve QoL in patients with AD.[297-300]

NPS are often considered as medication targets in cases where NPS are appropriately detected by clinicians.[106] This leads to high rates of (off-label) psychotropic medication prescriptions that are only modestly effective in dementia.[301] In addition, this symptomatic treatment does not do justice to the multiple contributors causing NPS, including factors relating to the patient (e.g. personality), caregiver (e.g. communication style), and environment (e.g. safety).[54,106,302] Therefore, a patient-centered care (PCC) approach is preferred that considers all these individual factors when managing NPS.[81,298,303]

After a comprehensive assessment of NPS, non-pharmacological interventions are the first choice to treat NPS in dementia as recommended by the national and international guidelines on the diagnosis and treatment of dementia.[33,91,92] Although several psychosocial interventions have been developed and proven to be effective,[e.g. 304-306] these programs have rarely been implemented into standard care in memory clinics.[100] Previous studies have suggested various barriers to implementing these guidelines, including a lack of training and knowledge among clinicians regarding the efficacy, dosing, and timing of non-pharmacological interventions.[54,95] Non-pharmacological strategies are also considered to be more time-consuming compared to psychotropic medication. Furthermore, there are only limited evidence-based interventions suitable for patients with early-stage dementia and their caregivers given the focus of previous research on institutionalized patients with severe dementia.[307] To

overcome these barriers, there is a need for a tool that translates the current guidelines into clinical practice and integrates a comprehensive assessment into the standard work-up at memory clinics in order to improve early recognition and tailored treatment of NPS in AD.

Recently, a multidisciplinary expert panel proposed such a tool that integrates current models and theories on the causes of NPS to structure the assessment and management of these symptoms following four steps: Describe, Investigate, Create, Evaluate, i.e. the DICE method.[100] This framework identifies NPS, examines possible underlying causes, and consequently integrates pharmacological and non-pharmacological interventions to treat these symptoms following a PCC approach.

Similar approaches to the DICE method have been developed to address NPS in dementia, e.g. 'Grip on Challenging Behaviour',[291] '4D Approach',[308] 'Act in Case of Depression',[309] 'STA OP!'.[310] However, studies in community-dwelling patients are lacking, as the majority of these methods have been carried out in the nursing home setting. A recent pilot study showed that the use of the DICE method reduced caregiver distress in caregivers of community-dwelling patients with dementia and supports the use of this approach in the outpatient setting.[311] Moreover, the DICE method has been suggested as the most promising non-pharmacological approach to manage NPS in dementia.[286] Besides the evidence on its effectiveness, demonstrating the cost-effectiveness of the DICE method is crucial before this approach can be part of the standard care.[299,312]

The BEhavioral symptoms in Alzheimer's disease Towards early Identification and Treatment (BEAT-IT) study is developed to increase our understanding of NPS across the spectrum of AD. This project aims to (1) investigate the etiology of the behavioral variant of AD (bvAD)[222] as a model of the neurobiological mechanisms of NPS in AD and (2) study the effectiveness of the DICE method for the management of NPS in patients with MCI and AD. This paper describes the protocol of an intervention study that focuses on the latter aim.

Objectives

The aim of this study is to use the DICE method to structure and standardize the recognition of NPS in AD in the memory clinic, implement current guidelines for the treatment of NPS in MCI and AD, and to investigate the effects of the treatment on QoL. Note that we will not evaluate the treatments itself (e.g. the efficacy of psychosocial interventions or antidepressants) since those are already evidence-based interventions recommended by current guidelines, but rather examine the benefits of structuring these interventions in the context of the memory clinic. We will do this by investigating the effectiveness and cost-effectiveness of the DICE method in community-dwelling patients with AD or MCI visiting the memory clinic and compare this group to a control group who will receive care as usual (CAU). We hypothesize that the structuring and

standardization of the care of NPS with the use of the DICE approach will improve the QoL of both caregivers and patients at the early stages of AD. In addition, implementing the DICE method is expected to allow early recognition of NPS and reduce NPS, caregiver burden, and psychotropic drug use, and is aimed to be cost-effective. By doing so, this study may contribute to the improvement of early identification and management of NPS in AD in memory clinics.

Methods

The Standard Protocol Items: Recommendations for Interventions Trials (SPIRIT) guidelines were followed for this protocol.[313]

Study design

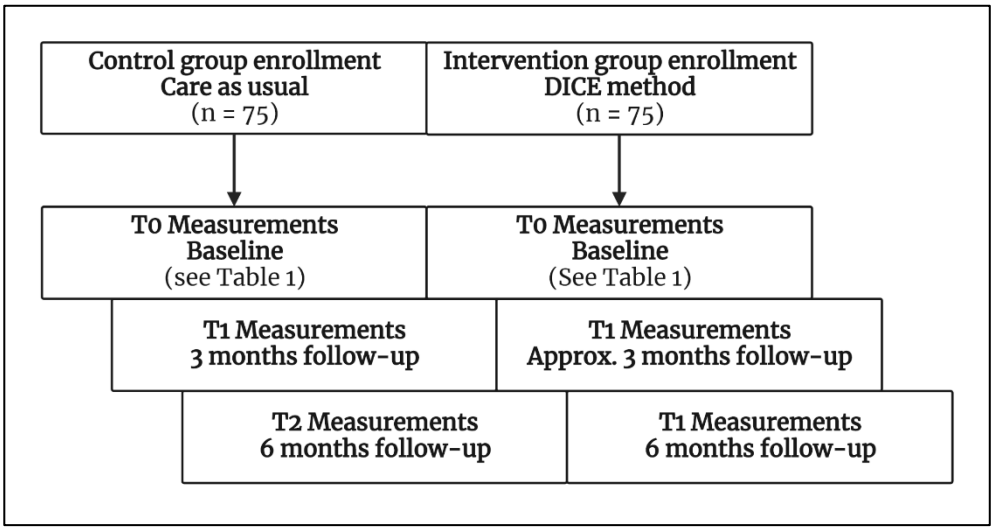
This study is a prospective multicenter study with a quasi-experimental design (see Figure 1). In the first part of the study, a control group will be recruited who will receive CAU. After 1 year, we will enroll the second wave of participants who will receive a structured and standardized assessment and treatment of NPS based on the principles of the DICE method. Hence, the enrollment of the control group will be completed before the start of the inclusion of the intervention group. This design has the advantage that it reduces the risk of contamination and crossover between the two groups. Moreover, a crossover design is not possible given the progressive nature of AD. Furthermore, cluster randomization of hospitals is not feasible because of the differences in CAU between the sites. Since patients of both waves will be enrolled in the same sites, we assume that the waves will not show meaningful differences in demographic and clinical characteristics. Also, no substantial changes are expected in the upcoming years regarding current CAU in the memory clinics based on the view of collaborating experts and the organization of care in the last years.

Subjects will be followed for 6 months while undergoing three assessments during this period. The primary outcome will be the QoL of patients and their caregivers. Secondary outcomes include changes in the prevalence and severity of NPS, caregiver burden, caregivers' confidence managing NPS, psychotropic medication use, the experiences of patients and caregivers who underwent the DICE method, and the cost-effectiveness of the intervention.

Eligibility criteria

In order to be eligible to participate in this study, patients must meet all of the following criteria (see Table 1): (1) a clinical diagnosis of probable AD (NIA-AA criteria by McKhann et al.[1]) or MCI due to AD (NIA-AA criteria by Albert et al.[24]) with at least intermediate probability of AD etiology based on: patient history, neuropsychological assessment,[164] and neuroimaging (magnetic resonance imaging (MRI) or positron-emission tomography (PET)). The clinical diagnosis needs

Figure 1. Design of the BEAT-IT study



Notes. Note that only the assessments are depicted since intervention visits will vary across subjects in the intervention group due to personalized approach.

to be established within the last 2 years so that patients with a diagnosis who visit the memory clinic for clinical follow-up might also participate; (2) presence of NPS established with the Neuropsychiatric Inventory Questionnaire (NPI-Q, presence of ≥ 1 symptoms) administered within the last month [247]; (3) a Mini-Mental State Examination (MMSE) score > 15 so that patients are able to reflect on their QoL [314]; (4) patients need to be community-dwelling; and (5) availability of a reliable informant who is considered to be the primary caregiver.

A potential subject who meets any of the following criteria will be excluded from participation in this study: (1) patients meet the (additional) criteria of any non-AD neurodegenerative disease, except vascular co-pathology; (2) legally incapable (as judged by the attending physician and therefore unable to give a written consent; (3) evidence of current delirium or previous delirium in the past 6 months; (4) primary (premorbid) psychiatric disorders such as schizophrenia or bipolar disorder that could better explain the manifestation of NPS, or current abuse of alcohol or drugs; and (5) currently participating in a clinical trial. Patients are allowed to be on medication (e.g. acetylcholinesterase inhibitors or psychotropic drugs) prior to inclusion since no differences between the two waves are expected regarding the medication use at baseline, and this will be carefully documented in a case report form (CRF).

Recruitment

Patients will be recruited from six different memory clinics in and around Rotterdam in the Netherlands (Erasmus MC University Medical Center, Franciscus Gasthuis

Table 1. Eligibility criteria

Inclusion criteria	Exclusion criteria
Diagnosis of MCI due to AD or AD dementia based on patient history, neuropsychological assessment, and neuro-imaging within last two years	Meeting additional criteria of a non-AD neurodegenerative disease (vascular co-pathology is permitted)
Presence of NPS; ≥1 symptoms on NPI-Q	Legally incapable to give informed consent
MMSE score > 15	Evidence of current delirium or previous delirium
Patients need to be community-dwelling	Primary (premorbid) psychiatric disorders that could better explain the manifestation of NPS
Availability of a reliable informant	Participating in a clinical (medication) trial

Notes. AD = Alzheimer's disease, MCI = Mild Cognitive Impairment, MMSE = Mini-Mental State Examination, NPI-Q = Neuropsychiatric Inventory Questionnaire, NPS = neuropsychiatric symptoms.

& Vlietland, Het Van Weel-Bethesda Ziekenhuis, Maasstad Hospital, and Spijkenisse Medical Center) to facilitate patient enrollment and guarantee a good mixture of patients from both academic and general hospitals. After a diagnosis of MCI or AD dementia is established at one of the memory clinics, study eligibility will be evaluated based on the in- and exclusion criteria by the local attending physician. Alternatively, patients already diagnosed with MCI or AD dementia who visit the memory clinic for clinical follow-up will also be identified based on these criteria.

Interventions

Control group

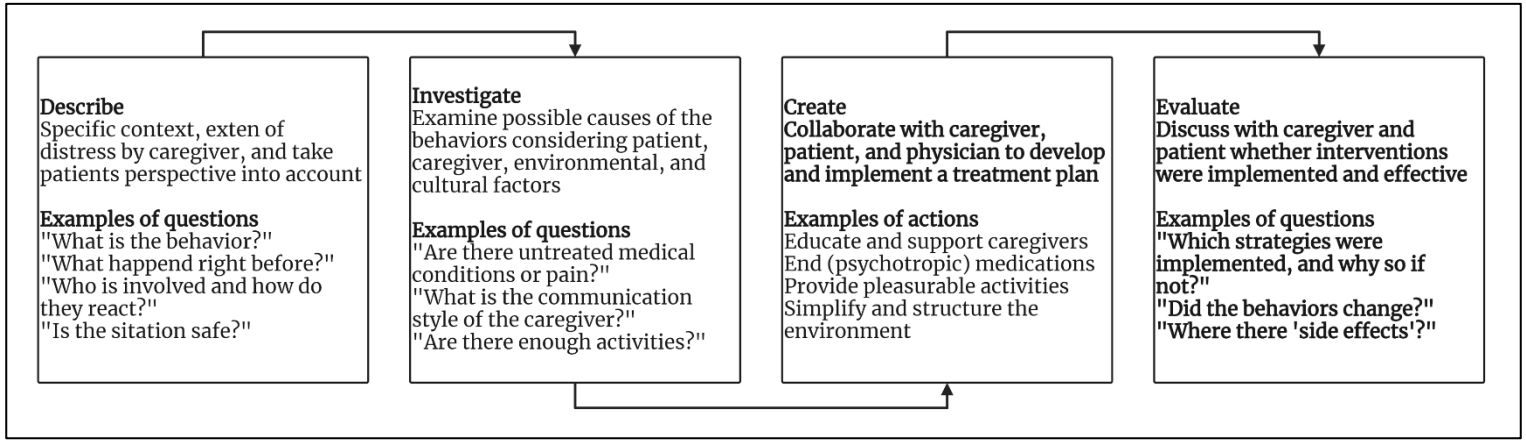
Participants in the control group will receive CAU at their local hospital. We expect that the CAU will be quite heterogeneous over sites and may consist of psychoeducation about dementia by a nurse or consultant specialized in dementia, the prescription of psychotropic drugs, and/or the referral to a psychiatric outpatient clinic for specialized treatment in patients with severe NPS.[315] Because of these differences, we will carefully keep track of the procedures undertaken by clinicians for patients in the CAU group. Based on recommendations for assessing usual care in clinical trial,[316] we will develop a study-specific CRF that will be filled out at the time of enrolment and will be updated at each follow-up visit.

Intervention group

All participants in the second wave will be enrolled in the intervention group. In this group, we will apply the DICE method to structure and standardize the assessment and management of NPS. Participants who withdraw from study participation after being informed by their physician and/or the researchers will receive CAU at their hospital

as described above. The DICE method will take place at the Neurology Department of the Erasmus MC and will be carried out by a psychiatrist (M.C.) and neuropsychologists (E.v.d.B., W.S.E., J.M.P.) who are all involved in the memory clinic of this department.
The steps of the DICE method are depicted in Figure 2. More detailed information on the development and background of the DICE method can be found elsewhere.[100] During the first visit, the patient and caregiver will undergo a consultation by an experienced psychiatrist to establish clinically relevant NPS (Describe). Factors related to the patient, caregiver, and environment will be examined following the DICE method[54,93] and the DICE manual.[317] For factors related to the patient, we will record the chronic somatic conditions using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) semi-structured interview,[318] followed by a clinical examination to explore the medication changes, pain, sleep hygiene, and sensory changes. If necessary, a lab evaluation will be conducted to screen for infections, thyroid problems, and metabolic disorders. Other patient-related factors including unmet needs, boredom, and emotional well-being will be assessed using the Checklist of Factors to Consider to Identify Potential Causes of Behavioral Symptoms developed by Gitlin et al.[93] Caregiver-related factors will be screened by using the Relationship Closeness Scale,[319] Center for Epidemiologic Studies Depression Scale,[320] and the CareQol-7D.[321] This will be extended by history taking on family and cultural expectations, knowledge about dementia, and the availability of support. Environmental factors will be assessed to the patient and caregiver by the Informal Assessment: Brief Questions to Guide Describing Behavioral Symptoms.[93] A full and accurate description of specific behavior will provide more insight about the 'who, when, where, and what' about the situations in which the behavior is occurring, while taking safety risks and the level of physical and social stimulation into account (Investigate). Thereafter, a multidisciplinary meeting will take place in which a personalized treatment advice is formulated based on the current guidelines on the diagnosis and assessment of NPS in dementia (Create).[33,91,92] During the second visit, this treatment advice is discussed and adjusted to the needs, values, and characteristics of the patient and caregiver following a PCC approach. Given the large heterogeneity in symptoms, interventions will vary for each individual and can include psychoeducation, psychosocial interventions, caregiver support, and/or pharmacological treatment based on the current (inter)national guidelines.[33,91,92,322-324] Notably, the interventions and strategies that will be used to reduce NPS and enhance the QoL are all evidence-based treatment strategies that are or should be carried out in the current clinical practice. Finally, we will monitor treatment progression 1 month after the last visit by telephone (Evaluate). Patients and their caregivers are then invited for an extra visit if necessary. In such cases, alternative interventions will be discussed if planned interventions were not implemented or effective. Additional diagnostic procedures or interventions will be monitored in the CRF.

Figure 2. The DICE method with examples of questions and actions



Notes. Adapted from Kales et al.[100] and Gitlin et al.[93]

Outcome measures

For the control group, measurements will take place at baseline (T0), with follow-up testing at 3 months (T1) and 6 months (T2). For the intervention group, measurements will take place at baseline (T0), directly after treatment (T1), and follow-up at 6 months (T2). The T1 measurements will be planned after finishing the (psychosocial) intervention and/or when medication is stabilized and thus may vary between subjects in the intervention group. We will gather all relevant clinical and intervention-related information which enables us to study post hoc whether this variation in T1 assessments may have resulted in bias. All measurements will take place at the local hospitals or at the patients' homes, see Table 2 for an overview of all outcome measures.

Primary outcomes

The QoL of the patient will be measured by the Quality of Life in Alzheimer's Disease (QoL-AD) questionnaire [67].[325] This is one of the most widely used QoL questionnaires in AD and has good psychometric properties.[326] Patients are questioned via a 13-item interview format. The proxy version of the QoL-AD is also used and filled out by the caregiver since previous studies have shown that the caregivers' perspective on the patients' QoL might be a more valid indicator of treatment success.[40]

The CarerQol-7D will be used to measure the care-related QoL in caregivers.[321] The instrument includes six burden dimensions and a subjective valuation scale for happiness.

Secondary outcomes

Changes in NPS will be assessed with the NPI-Q,[247] a general screening questionnaire including 12 distinct NPS. For each item, caregivers have to indicate the presence, the severity, and the extent of emotional distress that each symptom causes. Similar to Gitlin et al.,[327] we will add a frequency score and will ask caregivers how confident they are in managing a certain symptom on a 5-point Likert scale (0 = not confident to 4 = extremely confident).

A two-step approach will be used to further assess NPS: if certain symptoms are present, as indicated by an NPI-Q frequency score ≥ 1, specific questionnaires will be used to assess these symptoms in more detail. All instruments will be administered to the caregiver. To measure the depressive symptoms, the Dutch version of the Cornell Scale for Depression in Dementia (CSDD) will be used.[90] The CSSD consists of 19 items covering mood, behavioral changes, and circadian changes related to depression and is validated in patients with dementia.[90] Anxiety symptoms will be measured by the Rating Anxiety in Dementia (RAID) scale, an 18-item inventory that includes specific fears and somatic symptoms related to anxiety.[328] Agitation, irritability, aggression, and motor disturbances will be measured by the Dutch version of the Cohen-Mansfield Agitation Inventory (CMAI-D).[329] Hallucinations will be assessed by the subscale B of

the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) [78],[85] and delusions will be assessed by the subscale A of the BEHAVE-AD.[85] Apathy is assessed with the informant-reported Apathy Evaluation Scale (AES-I) [75] and comprises of 18 items.[330] Sleep disturbances will be measured by the 8-item Sleep Disorder Inventory (SDI),[331] an expanded version of the sleep disturbances item of the NPI. Similar to the NPI, caregivers have to score each symptom of the SDI on frequency, severity, and caregiver distress.

Caregiver burden will be measured with the perseverance time, a one-item questionnaire that assesses caregiver burden by asking the period of time (in months) that the informal caregiver thinks he or she is able to maintain the care if the current situation remains stable [68].[332] This questionnaire is a good predictor for institutionalization.[333]

The Clinical Dementia Rating Scale (CDR), MMSE, and a neuropsychological assessment will be administered during the diagnostic procedure at the local memory clinic prior to inclusion. The CDR includes six domains covering cognitive function and IADL associated with dementia.[334] Disease severity will be determined based on clinical diagnosis and CDR global score with MCI due to AD (CDR score 0.5), mild AD dementia (CDR score 1), and moderate to severe AD dementia (CDR score 2–3). Global cognitive function will be measured with the MMSE.[335] The neuropsychological assessment will be carried out according to the Dutch Parelsnoer Institute for Neurodegenerative Diseases and covers the major cognitive domains including memory, attention, processing speed, language, visuospatial abilities, and executive functioning.[164]

The Amsterdam Instrumental Activities of Daily Living Questionnaire (A-IADL-Q) is a proxy measure to detect problems in IADL in patients with dementia.[336] This tool is a reliable and valid instrument to detect changes in IADL over time.

Physical health and comorbidities of the patient will be assessed using the CIRS-G.[318] The severity of 14 common medical problems in the geriatric population (e.g. heart, liver, vascular diseases) will be judged by one of the researchers during a short interview with the patient and caregiver.

Psychotropic medication use will be documented in the CRF. The total number of medications used will be registered and classified according to the ATC coding: antidepressants, antipsychotics, hypnotics and sedatives, anxiolytics, and anti-dementia medications.[301]

Cost-effectiveness

For the cost-effectiveness evaluation, patients will complete the EQ-5D-5L, the most commonly used health-related QoL instrument,[337] and the ICEpop CAPability measure for Older people (ICECAP-O), a 5-item well-being scale,[338] and caregivers will fill out the CarerQol-7D. In addition, the Institute for Medical Technology Assessment Valuation of

Table 2. Outcome measures

Outcome	Measure	Purpose	Respondent	Time of assessment
Demographic characteristics	E.g. age, education, sex, ethnicity, relation to caregiver	Descriptive, covariate, moderator	Patient & caregiver	T0
Clinical characteristics	E.g. diagnosis, AD biomarkers, disease duration	Descriptive, moderator	Patient & caregiver	T0*
Disease severity	CDR[334]	Descriptive, moderator	Patient	T0*, T2
Cognitive status	MMSE[335]	Descriptive, moderator	Patient	T0*, T2
Cognitive functioning	Standardized cognitive test battery[164]: RAVLT,[339] VAT,[340] DS,[341] VF,[342] LDST,[343] SCWT,[344] TMT[345]	Descriptive, moderator	Patient	T0*
Functional abilities	A-IADL-Q[336]	Descriptive, moderator	Caregiver	T0, T2
Psychotropic medications	Brown bag review[301]	Descriptive, secondary outcome	Caregiver	T0, T1, T2
Comorbidities	CIRS-G[318]	Descriptive	Patient	T0, T2
Quality of life patient	QoL-AD[325]	Primary outcome	Patient & caregiver	T0, T1, T2
Quality of life caregiver	CarerQol-7D	Primary outcome	Caregiver	T0, T1, T2
Caregiver burden	Perseverance time[332]	Secondary outcome	Caregiver	T0, T1, T2
Caregiver competence managing NPS	Additional NPI-Q item[327]	Secondary outcome	Caregiver	T0, T1, T2
Cost-effectiveness	EQ-5D-5L,[337] ICECAP-O,[338] iMTA iVICQ,[346] iMTA MCQ[347]	Secondary outcome	Patient Caregiver	T0, T1, T2
NPS prevalence, severity, and distress	NPI-Q[247]	Secondary outcome	Caregiver	T0*, T1, T2

Table 2. *continued*

Outcome	Measure	Purpose	Respondent	Time of assessment
If NPI-Q frequency score ≥ 1 on:				
Agitation, motor disturbances, irritability, disinhibition	Cohen-Mansfield Agitation Inventory[83]	Secondary outcome	Caregiver	T0, T1, T2
Apathy	Apathy Evaluation Scale-I[330]	Secondary outcome	Caregiver	T0, T1, T2
Depression, anxiety, euphoria	CSDD,[90] RAID[328]	Secondary outcome	Caregiver	T0, T1, T2
Hallucinations, delusions	BEHAVE-AD subscales psychosis, delusions[85]	Secondary outcome	Caregiver	T0, T1, T2
Nighttime behaviors	Sleep Disorder Inventory[331]	Secondary outcome	Caregiver	T0, T1, T2

Notes. AD = Alzheimer's disease, A-IADL-Q = Amsterdam Instrumental Activity of Daily Living Questionnaire, BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale, CDR = Clinical Dementia Rating, CIRS-G = Cumulative Illness Rating Scale for Geriatrics, CSDD = Cornell Scale for Depression in Dementia, DS = Digit Span, iMTA iVIQ = iMTA Valuation of Informal Care Questionnaire, iMTA MCQ = iMTA Medical Costs Questionnaire, LDST = Letter Digit Substitution Test, MMSE = Mini-Mental State Examination, NPI-Q = Neuropsychiatric Inventory Questionnaire, QoL-AD = Quality of Life in Alzheimer's disease, RAID = Rating Anxiety In Dementia, RAVLT = Rey Auditory Verbal Learning Test, SCWT = Stroop Color Word Test, TMT = Trail Making Test, VAT = Visual Association Test, VF = Verbal Fluency (animals).
* will be carried out during the diagnostic procedure at local hospitals.

Informal Care Questionnaire (iMTA iVICQ) will be used to assesses the amount, costs, and appraisal of the care provided by the caregivers.[346] The iMTA Medical Consumption Questionnaire (iMTA MCQ) consists of 31 questions regarding healthcare utilization and incorporates direct healthcare use of the patient.[347] Both the iMTA MCQ and the iMTA iVICQ will be sent to the caregivers and can be completed at home.

Qualitative endpoint data
A random selection of one out of four of the dyads in the intervention group will be invited to participate in the qualitative part of this study, accounting for the site and disease stage. Semi-structured interviews will be conducted in order to achieve more insight into the experiences of participants who underwent the DICE method and what they considered as helpful elements. The interviews will be conducted face-to-face, will be audio-taped, and will last approximately 60 min. Interviews will be performed until saturation is reached, i.e. until no new concepts and themes are obtained,[232] which we estimate to reach after we interviewed 15–20 patients with their caregivers.[209,348,349] Questions will be asked in an open non-directive manner, focusing on the subjects' thoughts, feelings, and experiences. Topics include the subjects' experience of the intervention, and which elements were considered to be effective and which not, with the aim to examine the efficacy of and experiences with the DICE method from the perspective of patients and caregivers.

Sample size
In order to reach sufficient power to detect reliable and clinically relevant changes, we performed a power calculation using *G*Power*. The power calculation is based on the results of a recent meta-analysis by Kim and Park,[298] on the effectiveness of PCC in a mix of institutionalized and community-dwelling patients, and the results of a pilot study on the effectiveness of the DICE method in community-dwelling patients and caregivers.[311] Both studies showed a moderate effect size for the effects of PCC interventions on QoL in patients with AD and their caregivers when compared to CAU. Since there are limited validated sample size calculation methods for the mixed model approach we aim to use,[350] our calculation is based on a repeated measures ANOVA. Using *G*Power*, the required sample sizes were n = 86 and n = 46 for between-group and within-group analyses, respectively, based on a power of 0.80 and an alpha of 0.05. After enquiry, the 6 recruitment centers suggested that at least 25 patients receive a MCI or AD diagnosis annually at each site. Though there are a high number of patients available at all 6 study sites, the participation of eligible dyads is expected to be 150 since not all patients will fulfill our criteria or will be willing to participate (based on an estimated inclusion rate of 40%[351]). We will carefully keep track of the reasons why eligible subjects refuse to participate. We will recruit a total of 150 patients during the total inclusion period of approximately 3 years (n = 75 in the control group and n = 75

in the intervention group), which exceeds the estimated needed sample size, even when accounting for dropout/loss to follow-up.

Statistical methods

T-tests or Chi-square tests will be used to identify the differences in baseline characteristics (e.g. age, education level, disease severity) between the control group and the intervention group. For the primary and secondary study outcomes, we will use an intention-to-treat approach including all subjects irrespective of the adherence to our intervention.[352] Thereafter, we will perform per-protocol analyses with only the subjects who completed the intervention (underwent all DICE steps). We will correct for multiple testing.

We will use the Little's Missing Completely at Random Test to examine whether the data are missing at random or missing completely at random. The mixed model analyses will be able to handle the data when the missing data is completely at random. Multiple imputation will be used in cases when data is missing at random.

Linear mixed models will be used for the primary and secondary outcomes for the T0, T1, and T2 time points. These statistics are preferred when using longitudinal data because of its advantage in handling missing data and its capacity to deal with nested data and variance in follow-up duration between and within the groups. Changes in the trajectories of the primary and secondary outcomes are compared between the two groups. Subject, hospital, and time are considered as random effects, and baseline measure, group, and disease severity are accounted as fixed effects.

We will perform a cost-utility analysis of the intervention group versus the control group in accordance with the Dutch guidelines for economic evaluations on the basis of questionnaires.[353]

Quality and length of life will be combined into quality-adjusted life years (QALYs) using a Markov model to extrapolate lifetime outcomes based on the data from this study combined with literature data. The EQ-5D-5L, ICECAP-O, and CarerQol-7D data will be transformed into QALYs for patients and caregivers (well-being years for ICECAP-O), using published tariffs obtained from general reference populations.[353,354]

With the simple Markov model, we will calculate the incremental effectiveness of the DICE method versus the control group in QALYs, incremental costs, and the incremental cost-effectiveness ratios. We will also perform one-way, two-way, and probabilistic sensitivity analyses to determine the effect of uncertainty in all input parameters. Using a non-parametric bootstrapping (randomly drawing 5000 observations with replacement from the patient sample), the degree of uncertainty for costs and health effects and the cost-utility ratio will be depicted. In addition, an acceptability curve will be drawn, which indicates the probability that the intervention studied has lower incremental costs per QALY gained than various thresholds.

A budget impact analysis will be performed that includes relevant features and tariffs of the Dutch healthcare system; anticipated uptake of the new intervention as well as usual care will be considered. The budget impact per year of implementing the new intervention will be estimated. All elements of medical costs for the intervention group and the control group will be considered and calculated.

Qualitative analyses

The audiotapes of all interviews will be transcribed verbatim. This data will be analyzed by two independent researchers with *ATLAS.ti* software according to the thick analysis approach.[355] This approach endorses multiple triangulations, i.e. the use of multiple interpreters and techniques to analyze the data, to enhance validity.

The coding and analyses will be an iterative process simultaneously with the interviews, allowing adjustment of questions and topics. We will make use of open coding, thematic coding, and causal coding.[356] Open coding is an explorative process in which all elements of the data are coded. Thematic coding is a more deductive technique that included the coding of themes and categories that are proposed by the researchers prior to the analysis or emerge from the material and are considered to be of importance by the researchers. Causal coding will help us to get more insight into the working elements of the DICE approach as proposed by the participants. Characteristics of patients and their caregivers (age, sex, relationship, disease severity) will be used for descriptive purposes.

Discussion

The current paper describes the protocol of the BEAT-IT study, a multicenter study designed to investigate the effectiveness of a comprehensive assessment and personalized treatment of NPS in AD, following the DICE method to improve the QoL in patients with MCI and AD in the memory clinic. We hypothesize that early recognition and tailored treatment of NPS will benefit the QoL of patients and their caregivers; will reduce NPS, caregiver burden, and psychotropic drug use; and will lead to cost-effective care.

The novelty of this study lies in the inclusion of the whole spectrum of NPS, the enrollment of both patients with MCI and AD, and the evaluation of an approach that integrates both non-pharmacological and pharmacological interventions in the memory clinic setting. Besides standardized quantitative measures, a qualitative approach will be used to examine its efficacy and feasibility from the perspective of caregivers and patients. Also, important additional information will be obtained from studying the first wave of participants, enabling us to examine 'naturalistic' progression of NPS and its relationship with other clinical measures. Insight in the current CAU of NPS will aid us in the formulation of recommendations to improve the daily clinical practice regarding the care of NPS in AD. After establishing the effectivity of the DICE

method in the memory clinic setting, a next step would be to examine the implementation of this approach at other sites by taking already suggested and unique local barriers into account.

At the time of writing, recruitment is ongoing and is expected to be completed in December 2019 for the control group. Hereafter, the intervention group will be enrolled until the beginning of 2021, and follow-up measures will be completed in autumn 2021. Results will be available in late 2021.

There are a few possible threats to this study. Firstly, the use of the NPI-Q to screen for eligible patients might introduce an observer bias since this measure is not part of the regular diagnostic workup at some sites. Consequently, NPS may be detected more often, resulting in care that may not fully reflect the current CAU, i.e. underestimating the expected underrecognition and undertreatment of NPS in AD. Second, the current guidelines consider psychosocial interventions as the first-line treatment but mainly suggest interventions that may be more suitable for institutionalized patients with severe dementia, e.g. reminiscence therapy, aromatherapy, or 'snoezelen'.[33,92] Although various non-pharmacological interventions have been shown to be effective in community-dwelling patients,[299] these strategies are rarely mentioned in the guidelines and therefore not integrated in clinical practice.[357] For our interventions, we will select non-pharmacological strategies based on prior studies[e.g. 93] and our clinical expertise. Third, our outcome measures are mainly based on self-reported questionnaires that may not fully capture all effective aspects of the intervention.[358,359] Moreover, patients with dementia may have difficulties completing the QoL questionnaires (EQ-5D-5L, ICECAP-O) due to cognitive problems.[360] To circumvent some of these problems, we will also use qualitative research methods which enables us to better understand and measure the QoL of patients and to give participants the opportunity to express their experiences with the DICE method in an unrestricted manner. Fourth, the substantial differences across sites in CAU might be a challenge to this study, as patients visiting certain sites may receive more and different treatments compared to other centers. We will therefore aim to record all valuable information through our CRF, which enables us to perform post hoc sensitivity analyses, and verify whether this heterogeneity might affect the results. A final issue might be that patients are included based on clinical diagnostic criteria, without the use of AD pathophysiological biomarkers (e.g. abnormal levels of Aβ or tau proteins in CSF or on PET). Despite the fact that an MRI or (FDG-) PET scan of the brain is required, this may lead to the inclusion of patients who do not have underlying AD pathology, especially in those with MCI. However, the applied diagnostic criteria resemble those that are used in clinical practice where AD pathophysiological biomarkers are not part of the standard diagnostic workup. In addition, since this is a clinical study targeting clinical symptoms rather than the underlying disease process, we argue that the effects might be similar in patients with other underlying etiologies. We will however perform

a sensitivity analysis in a subgroup of patients with positive AD biomarkers in order to study whether the effects are similar in this subgroup compared to the whole study group.

To conclude, the BEAT-IT study as a whole will increase our knowledge of the underlying neurobiology of NPS in AD, which may enable us to identify potential targets for therapeutic agents. The intervention study might provide evidence on how to structure and standardize the care of NPS in AD to improve the QoL of both caregivers and patients. Moreover, the findings of the intervention study will result in recommendations to improve the early detection and treatment of NPS in AD in the memory clinic.

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Author contributions

R.O. and J.M.P. acquired funding for the BEAT-IT study. W.S.E., E.S., J.C.v.S., R.O., and J.M.P. designed the study in consultation with F.M.R., R.L.B., J.A.G., F.J.J.d., T.H., J.J.M.D., L.J.H.M.V., E.C.T., and S.E.H. who also contributed to the 'Methods' section of this manuscript. W.S.E. coordinates the intervention study under the supervision of J.M.P., R.O., and J.C.v.S.. W.SE., F.M.R., R.L.B., J.A.G., F.J.d.J., T.H., J.J.M.D., L.J.H.M.V., E.C.T., S.E.H., and J.C.v.S. will be responsible for patient inclusion. W.S.E., E.v.d.B., M.C., and J.M.P. will carry out the DICE method. E.S. coordinates the prospective cohort of bvAD patients under the supervision of R.O., J.M.P., Y.A.L.P., and P.S.. W.S.E., R.O., and J.M.P. wrote the first version of the manuscript. E.S., A.A.D., M.K., E.v.d.B., M.C., and S.U.Z. critically reviewed the paper. All authors read and approved the final version of the manuscript.

Chapter 4.2

Effects of the DICE method to improve timely recognition and treatment of neuropsychiatric symptoms in early Alzheimer's disease at the memory clinic: The BEAT-IT study

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Submitted

Abstract

Background and Objectives

Neuropsychiatric symptoms (NPS) are highly prevalent in Alzheimer's disease (AD) dementia and are associated with poor clinical outcomes. Therefore, timely detection and treatment of NPS have potential clinical benefits for people with AD dementia and their caregivers. However, NPS are currently underrecognized at the memory clinic and non-pharmacological interventions are scarcely implemented. This study evaluates the effectiveness of the Describe, Investigate, Create, Evaluate (DICE) method™ to structure and standardize the care for NPS in early AD dementia at the memory clinic.

Methods

Community-dwelling people with MCI or AD dementia and NPS and their caregivers were enrolled in two consecutive waves between 2018 and 2021. The first wave underwent care as usual (control group) and the second wave underwent the DICE method (intervention group). Primary outcomes were quality of life (QoL) of the patient and caregiver. Secondary outcomes included caregiver burden, NPS severity, NPS-related distress, competence managing NPS, and psychotropic drug use. Linear mixed models were used to study changes in outcomes between groups. Reliable change index was calculated to identify those who benefited the most of the intervention. Furthermore, a cost-effectiveness analysis was performed and semi-structured interviews were conducted with a subsample of participants who completed the intervention (n = 12).

Results

We included 36 participants in the control group and 24 participants in the intervention group. The DICE method did not improve QoL (range β =-0.12–0.39) or secondary outcomes over time (all FDR-corrected $p > 0.05$). A proportion of the participants of the intervention group showed reliable improvement in QoL (52%). At baseline, more NPS, NPS-related distress and less cognitive deficits were related to treatment benefits. Interviews revealed substantial heterogeneity among participants regarding NPS-related distress among caregivers, caregiver burden, and availability of social support. The intervention did not lead to significant gains in quality-adjusted life years and well-being years nor clear savings in health care and societal costs.

Conclusions

Results show no benefits of the DICE method in early AD at group-level, but suggest that individuals with high levels of NPS, NPS-related distress, and in the early stage of AD dementia might benefit from this approach.

The trial was registered on the Netherlands Trial Registry (NTR7459).

Introduction

Neuropsychiatric symptoms (NPS) are highly prevalent in the early clinical stages of Alzheimer's disease (AD).[10,147] These symptoms are related to negative clinical outcomes such as accelerated disease progression,[47] lowered quality of life (QoL),[40] increased caregiver burden,[50] and earlier nursing home placement.[53] NPS are also associated with increased formal healthcare utilization and informal care leading to major healthcare costs.[296,361]

The etiology of NPS in AD is multifactorial and consists of potential modifiable psychosocial causes such as unmet needs, negative communication style of caregivers, and environmental stressors.[54,289] Therefore, international guidelines recommend non-pharmacological interventions as first-line-treatment for NPS.[33,91,92] Examples of such interventions include skill training for caregivers, psychoeducation programs, and enhancing meaningful activities.[94,95] These interventions are effective in reducing NPS severity, NPS-related distress among caregivers, and psychotropic drug use.[94,95,362] Moreover, investing in non-pharmacological interventions for NPS is shown to be cost-effective.[293]

Given the clinical relevance of NPS and the availability of evidence-based interventions, timely detection and treatment of NPS has potential clinical benefits for people with AD dementia and their caregivers.[114,224] The memory clinic may be a suitable setting for early assessment and management of NPS in early AD dementia, as these multidisciplinary facilities offer a comprehensive diagnostic work-up and have the potential to offer post-diagnostic care.[108] However, NPS are currently underdiagnosed and non-pharmacological interventions are hardly implemented in individuals who visit the memory clinic with early AD dementia.[225,258] Instead, NPS are often considered as medication targets,[106] leading to high rates of off-label prescription of psychotropic drugs that are at best only modestly effective in dementia and are associated with serious side effects.[102,103]

Hence, there is a need for a tool that translates the current international guidelines into clinical practice and integrates a comprehensive assessment of NPS into the standard work-up at the memory clinic in order to improve early recognition and tailored treatment of NPS in AD. The Describe, Investigate, Create, Evaluate (DICE) method™ provides such a tool.[100] This person-centered framework uses a step-by-step approach to describe NPS in the context in which they occur, investigate possible underlying causes and triggers, create interventions targeting the underlying causes and triggers that have been identified, and subsequently evaluate the implementation and effectiveness of these interventions. Recent studies have shown that the DICE method reduces NPS-related distress and improves confidence in managing NPS in caregivers and care professionals of individuals with dementia living at home.[311,363] Although the DICE method has been suggested as the most promising non-pharmacological intervention to diagnose and treat NPS in dementia,[286] no studies have

been conducted that have evaluated the use of this method in people with AD dementia visiting the memory clinic.

The aim of the current study was to evaluate the effectiveness of the DICE method used to structure and standardize the care for NPS in early AD at the memory clinic as part of the BEhavioral symptoms in Alzheimer's disease Towards early Identification and Treatment (BEAT-IT) study.[231] We hypothesized that improving early assessment and adequate management of NPS would improve the QoL of patients with early AD dementia and their caregivers.

Methods

This trial was registered on the Netherlands Trial Registry (NTR7459). Detailed information on the design and the intervention components was described prior to starting the intervention.[231] This study was conducted and reported following the CONSORT guideline (Supplemental Materials).

Study design

This was a multicenter study with a quasi-experimental design. Participants were recruited from the following six memory clinics located in the greater Rotterdam area, the Netherlands: Erasmus MC University Medical Center, Franciscus Gasthuis, Franciscus Vlietland, Het Van Weel-Bethesda Ziekenhuis, Maasstad Hospital, and Spijkenisse Medical Center. Patients were enrolled together with their primary caregiver in two waves. The first wave of participants was offered care as usual at their local hospital and served as a control group. As the enrollment of the first wave was completed, a second wave of participants was recruited at the same hospitals and all underwent the DICE method at the Erasmus MC University Medical Center in additional to care as usual.

Participants

Participants were eligible to participate if they met all of the following criteria: (1) a clinical diagnosis of MCI with AD as the primary suspected etiology,[24] AD dementia,[1] or suspected mixed AD dementia/vascular dementia (VaD) that was established in the memory clinic within the last two years and was based on a neuropsychological assessment and neuroimaging; (2) the presence of NPS as indicated by the Neuropsychiatric Inventory-Questionnaire (NPI-Q) total score ≥ 1 [364]; (3) a Mini-Mental State Examination (MMSE) score > 15 at baseline; (4) patients had to be community-dwelling; and (5) a reliable informal caregiver needed to be available who was considered the primary caregiver. Patients were excluded if they (1) met the criteria of any non-AD neurodegenerative disease, except vascular co-pathology; (2) were legally incapable; (3) showed evidence of current delirium or previous delirium in the past six months; (4) were diagnosed with a primary (premorbid) psychiatric disorder such as

schizophrenia or bipolar disorder that could better explain the manifestation of NPS, or current abuse of alcohol or drugs; or (5) were participating in a clinical trial.

Procedure

For both waves, potential participants were informed by their attending physician at their local hospital. When both patient and caregiver agreed to participate, they were contacted by a researcher for additional information and screening of the eligibility criteria. We registered reasons for declining participations and monitored reasons for drop-out.

This study was conducted during the COVID-19 pandemic, which affected the enrollment of participants. During the first lockdown in the Netherlands (March 2020–July 2020), we had to stop the recruitment of participants in the control group earlier than planned. Follow-up assessments of participants who were already enrolled were conducted via telephone and questionnaires were send through mail and discussed via telephone. We started the enrollment of the second wave of participants three months after COVID-19 restrictions ended as it took time until the care at the memory clinics normalized, and also in order to minimize the effects of COVID-19 restrictions on study outcomes.

Control group

Participants in the control group received care as usual at their local hospital. We recorded the care received including clinical follow-up visits, prescription of psychotropic drugs, and referral to case management, mental healthcare, or day care center.

At baseline, 13 participants (38%) in the control group had a case manager, while eight (24%) were on the waiting list. Furthermore, two participants (6%) went to an adult day care center, while two participants (6%) were on the waiting list. Six participants (17%) used psychotropic medications, and 19 participants (48%) received cognitive enhancers at baseline.

During the six-month study period, 20 participants (59%) visited their local memory clinic for a clinical follow-up visit. No participants were referred to a psychiatrist working at the local memory clinic, while two participants (6%) were referred to external mental healthcare. During the study period, four participants (12%) were referred to a case manager and four participants (12%) were referred to adult day care. Local physicians prescribed new psychotropic medications for two participants (6%) during the six-month study period.

Intervention group

All participants included in the second wave underwent the DICE method to structure and standardize the assessment and management of NPS in addition to the care as usual

received at their local hospital.[100] In short, participants were invited for a first visit, in which NPS were *described* and possible causes of NPS related to the patient, caregiver, and their environment were *investigated*. Thereafter, participants were discussed during a multidisciplinary meeting consisting of neuropsychologists, a psychiatrist, and a geriatrician to *create* a treatment plan based on current guidelines on the diagnosis and treatment of NPS in dementia. During a second visit, the treatment plan was discussed with the participants and adjusted to their wishes. Next, participants were provided with advice on how to manage NPS with a focus on psychoeducation, caregiver support, and increasing meaningful activities. After one month, implementation of strategies was *evaluated* by telephone and adjusted if needed. The intervention itself was carried out by a neuropsychologist (W.S.E.) together with either a psychiatrist (M.C.) or a licensed clinical neuropsychologist (E.v.d.B.). Figure 1 illustrates the use of the DICE method for one participant in which personal details were adjusted to ensure anonymization.

The interventions were delivered as planned for all but two participants. For these two participants, the second visit was replaced by a telephone call with the caregiver as in one participant no NPS were identified after thorough assessment, and in the other participant, the first visit resulted in too much distress for the patient that it was decided to perform the *create* with the partner only.

Outcome measures

Participants underwent a baseline assessment, a follow-up assessment after three months, and a follow-up assessment after six months. Visits took place at the patients' home or at the local hospital. As a consequence of the lockdowns during the COVID-19 pandemic, a part of the assessments were conducted via telephone.

Primary outcomes

QoL of the patient was measured using the Quality of Life in Alzheimer's Disease (QoL-AD) questionnaire.[314] Patients were questioned via an interview format (score range 13–52), while the proxy version was filled out by the caregiver (score range 13–52).

The CarerQol-7D was used to asses care-related QoL in caregivers.[321] The CarerQol-7D includes six burden dimensions and a subjective visual analog scale (VAS) for happiness (score range 0–10). The scores on the six burden dimensions were transformed into a utility score (score range 0–100) by adding up the relative utility weights for each item derived from the Dutch population.[365]

Change in QoL measures after three months follow-up were primary outcomes, while we also studied whether effects maintained after six months.

Figure 1. Anonymized case illustrating the Describe, Investigate, Create, Evaluate (DICE) method™

	Person with dementia Male, 73 years old, moderate AD dementia	**Caregiver** Female, 72 years old, spouse	**Environment**
DESCRIBE	Patient describes feeling sad when he experiences that he is getting forgetful. During such moments, he feels sad, but also annoyed because of his memory problems.	Caregivers recognizes that her husband can feel down and also becomes agitated. Also, caregiver observes the patient wandering around the house looking for his stuff. During these situations, the caregiver tries to help the patient, but also wants to be honest about his memory problems.	These behaviors occur when the patient forgets groceries or when he makes mistakes during administrative tasks. Wandering tends to occur more often when the couple is alone at home during evening times.
INVESTIGATE	Patient wears glasses, but reports difficulties with vision. Neuropsychological assessment conducted at local hospital revealed severe cognitive impairment, most pronounced in memory, language, and spatial navigation.	Caregiver describes that she corrects patient when he makes mistakes like she is used to do. Caregiver reports feeling overwhelmed and stressed since she has to take over instrumental activities of daily living.	Patient liked to read, but that is now too difficult due to cognitive impairment and visual problems. Patient liked to do different sports, but is not able to go to the sport facilities alone as he gets lost.
CREATE	Patient was explained that it is normal that he sometimes feels down because of the situation. Patient was instructed to use non-verbal cues to aid the communication when feeling sad and/or annoyed. Patient was advised to go an optician to follow-up on visual impairment.	Caregiver was advised to avoid confronting patient with his cognitive problems and advised to simplify tasks to prevent having to experience memory problems. Caregiver was advised to seek for mental support to improve own well-being.	Patient and caregiver were advised to improve lighting in the house, because of poor vision and wandering. Also, they were instructed to ask children to assist in going to the sport facilities. Ways were discussed to improve physical activity during the day.
EVALUATE	Patient went to the optician, but needed extra help with creating pictures to aid communication.	Caregiver went to her GP who referred her to a psychologist to receive mental support for her own well-being	Caregiver indicated that she found it difficult to ask for help, so additional advice was given on how to ask for help.

Secondary outcomes

The perseverance time question was used to measure caregiver burden.[332] Caregivers were asked to indicate the time they felt able to maintain care under a hypothetical stable situation using the following categories: < 1 week, 1 week–1 month, 1–6 months, 6 months–1 year, 1–2 years, and > 2 years. Across all measurements, the lower four categories were combined as only very few caregivers endorsed these categories: <1 week (0%), 1 week–1 month (5%), 1–6 months (13%), 6 months–1 year (14%). This resulted in three categories: < 1 year, 1–2 years, > 2 years.

The presence and severity of NPS were assessed using the Dutch NPI-Q.[364] An additional item was added for which caregivers had to rate how confident they feel in managing this symptom (score range 0=not confident to 4=extremely confident).[327] We summed the severity × frequency scores of all 12 NPS to obtain the NPI-Q total score (score range 0–144). In addition, average NPS-related emotional distress (score range 0–5) and average confidence while managing NPS (score range 0–4) were calculated by adding up the emotional distress scores for each item and the confident scores of each item divided by the number of NPS endorsed on the NPI-Q.

The Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) was administered to the caregiver.[85] This semi-structured interview assesses NPS that are observed in AD covering 25 symptoms grouped into the following seven categories: delusions, hallucinations, activity disturbances, aggression, sleep disturbances, depressive symptoms, and anxiety. Each symptom is rated on its severity (score range 0–3), with all severity scores summed resulting in the BEHAVE-AD total score (score range 0–75).

A two-step approach was used to further assess specific NPS: when specific NPS were endorsed on the NPI-Q at baseline, additional instruments were used to assess these symptoms in more detail at baseline and all subsequent follow-up assessments. All these instruments were administered to the caregiver. In case depressive symptoms and/or anxiety were present on the NPI-Q, the Dutch version of the Cornell Scale for Depression in Dementia (CSDD) was used to measure depressive symptoms (score range 0–38),[90] and anxiety symptoms were assessed using the Rating Anxiety in Dementia (RAID) scale (score range 0–54).[328] In case apathy was present on the NPI-Q, the Dutch version of the informant-reported Apathy Evaluation Scale (AES-I) was administered (score range 18–72).[330] In case delusions and/or hallucinations were present on the NPI-Q, the subscales A and B of the BEHAVE-AD were used and combined (score range 0-36).[85] In case agitation, irritability, and/or aberrant motor behavior were endorsed on the NPI-Q, the Dutch version of the Cohen-Mansfield Agitation Inventory (CMAI-D) was administered (score range 29–203).[329] In case sleep disturbances were reported on the NPI-Q, the Sleep Disorder Inventory (SDI) was assessed and severity × frequency scores of all eight items were summed to obtain a

total score (score range 0–96).[331] The original English versions of the BEHAVE-AD, RAID, and SDI were translated into Dutch using forward-backward translation.

Psychotropic medication use was documented during each assessment and were classified as follows: antidepressants, antipsychotics, hypnotics and sedatives, anxiolytics, and cognitive enhancers.[301]

At baseline and after six months follow-up, the Clinical Dementia Rating Scale (CDR)[334] and the MMSE[335] were administered to measure disease severity and global cognitive functioning respectively.

Qualitative outcomes

All participants of the intervention group were invited to participate in a semi-structured interview after completing the study. These interviews were conducted face-to-face by a researcher (N.L.) who was not involved in the assessments or intervention. All interviews were audio-taped after obtaining verbal informed consent. Topics included NPS-related self-efficacy, knowledge about NPS in dementia, caregiver burden, and experiences with the DICE method. Topics were discussed from both the perspective of patients and caregivers.

Cost-effectiveness analysis

Patients completed the EQ-5D-5-L to measure health-related QoL,[366] and the ICEpop CAPability measure for Older people (ICECAP-O) to assess well-being.[338] In addition, the Institute for Medical Technology Assessment Valuation of Informal Care Questionnaire (iMTA iVICQ) was used to establish the amount, costs, and appraisal of informal care provided by the caregiver who participated in the study.[346] Also, the iMTA Medical Consumption Questionnaire (iMTA MCQ) was administered to assess the healthcare use of the patient in the past three months.[347]

Statistical analysis

Differences in demographic variables and baseline clinical characteristics between the two groups were examined using analysis of variance, Mann-Whitney U tests, or χ^2 tests where appropriate.

Quantitative outcomes

We used linear mixed models (LMM) including random intercepts for participant and hospital to investigate differences between the two groups in the outcomes over time. Interaction between group and time after three months and six months were examined, with three months follow-up as primary endpoint. All LMMs were corrected for age of the patient, sex of the patient, and disease stage (MCI/dementia). Nonlinear associations were tested using LMMS using quadratic and cubic splines. We selected linear models for all analyses based on the Akaike information criterion and likelihood

ratio χ^2 tests. For all LMMs, assumptions were checked by visual inspection of scatterplots of standardized residuals and Q-Q plots. For CarerQol-7D VAS scores, NPI-Q total scores, NPI-Q competence scores, CMAI total scores, SDI total scores, normality slightly deviated. Subsequent sensitivity analyses using bootstrap procedure with 200 bootstrap samples to calculate confidence intervals did not change our findings.

To study individual effects of the intervention on the primary outcomes, reliable change index (RCI) was calculated for each participant in the intervention group. The RCI can be used to establish whether a delta score (post-test – pre-test) of an individual participant is statistically significant taking measurement error, test-retest reliability, and treatment-nonspecific changes in the control group into account.[367] The RCI was calculated for the self-reported QoL-AD total score, proxy rated QoL-AD total score, CarerQol-7D utility score, and the CarerQol-7D VAS score across all time points (T1–baseline and T2–baseline). In addition, we conducted sensitivity analyses using a regression-based approach to take regression to the mean into account. Multiple linear regression analyses were performed to predict follow-up scores based on baseline performance and examine potential moderating variables that may affect change over time including age and sex of the patient, relationship to patient (partner/child), and disease severity (dementia/MCI). As none of these predictors were associated with follow-up scores (all $p < 0.05$), simple linear regression analyses were used to predict follow-up scores. An RCI or residual score of >1.645 (one-tailed $\alpha = 0.05$) indicates a significant improvement. Participants in the intervention group who showed significant improvement on any of the primary outcomes after three months and/or six months follow-up were referred to as 'responders'. To examine whether specific baseline characteristics were related to treatment benefits, we compared baseline clinical and demographic characteristics between responders and non-responders using Mann-Whitney tests or χ^2 tests.

LMMs were corrected for multiple testing using the Benjamini-Hochberg adjusted false discovery rate (FDR) of 0.05. Remaining analyses were considered exploratory and were therefore uncorrected for multiple testing. Analyses were conducted using SPSS version 26.0 and *R* version 4.0 (*lme4*, *splines*, *lmerTest*, and *boot* packages).

Qualitative outcomes

The interviews were analyzed using a thematic analysis approach by two independent researchers (W.S.E., N.L.).[233] These researchers independently proposed a code book consisting of open codes that emerged from the data. Next, these codes were discussed resulting in a final code book, and two researchers systematically coded the data using a combination of open coding, axial coding, and selective coding. Codes were collided into preliminary categories and themes that were redefined following consensus among researchers.

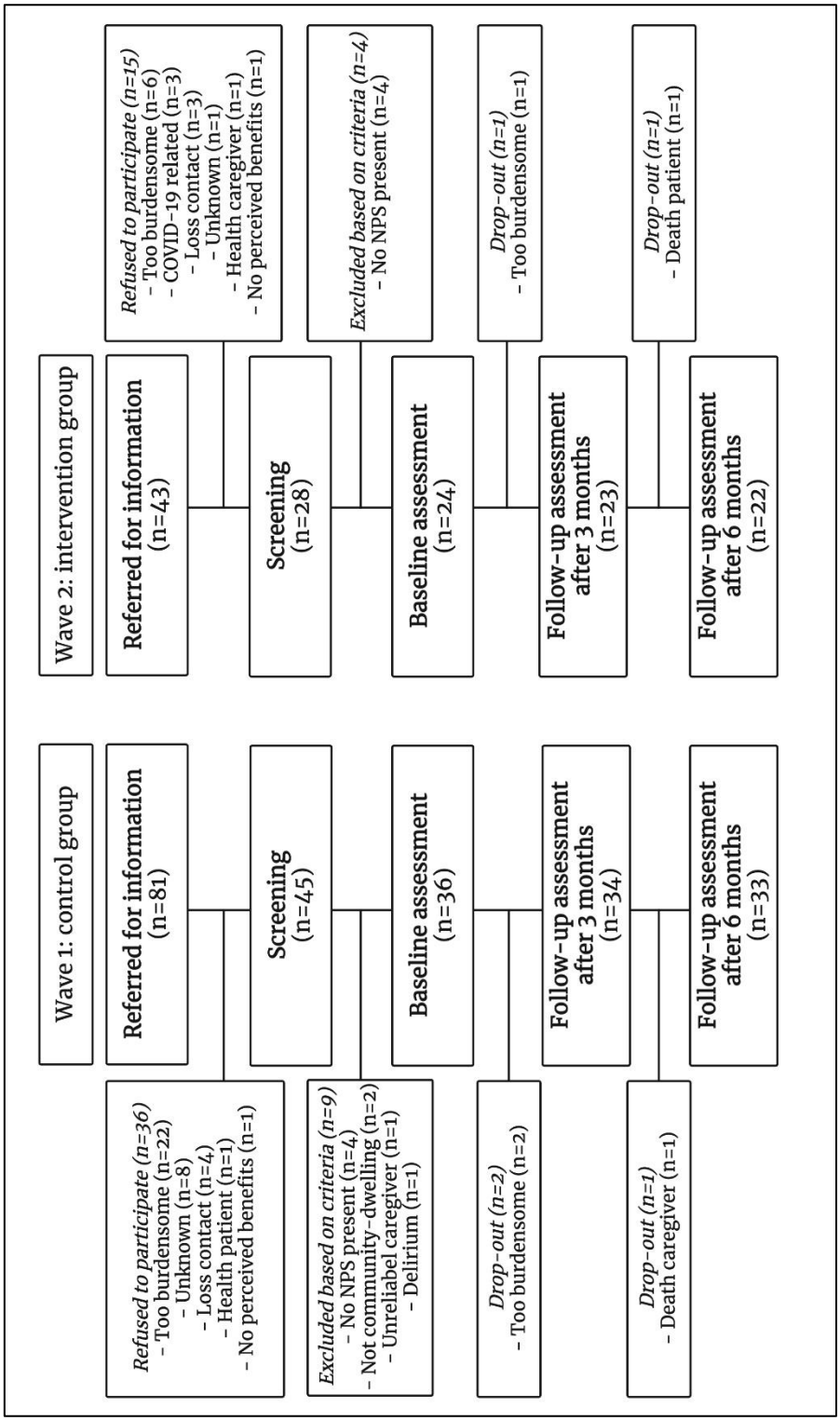


Figure 2. Flow chart of included participants

Cost-effectiveness

For each patient, the number of quality-adjusted life years (QALYs) and well-being years during the six-month follow-up was calculated as an area under the curve, taking account of the values of the three measurements. To prevent bias in estimates of QALYs and wellbeing years, we adjusted for small imbalances between the groups in baseline values using Manca's regression-based method.[368] Health care costs and costs of informal care were calculated as the multiplication of reported utilization and costs per unit in Euro's for 2019.[369-371] The costs of the DICE intervention performed in daily practice (excluding research protocol costs) was calculated based on invested time, personnel cost, and overhead. For the cost-effectiveness calculation, it was assumed that the DICE intervention will be applied once during the first year of patient follow up. The uncertainty for costs, QALYs, and well-being years was assessed by means of non-parametric bootstrapping (5000 observations).

Ethics

This study was approved by the Medical Ethics Committee of the Erasmus Medical Center in the Netherlands (MEC-2018-1443). Written informed consent was obtained from all participants before study inclusion.

Results

Recruitment

The procedure of recruitment is depicted in Figure 2. Physicians reported no substantial barriers for enrollment. Only one physician reported that not all patients underwent comprehensive neuropsychological assessment making it not possible to fulfill the eligibility criteria.

Eighty-one patients were referred by collaborating physicians for participating in the control group. After additional information was provided by the researchers, 36 patients and their caregivers declined participation, of which experiencing participation as too burdensome due to a lack of time and/or being too busy with organizing care was most often reported as reason (Figure 1). After additional screening, nine patients were excluded because they did not meet the inclusion criteria resulting in a total of 36 patients and their caregivers included in the control group (44% of the referred patients).

Forty-three patients were referred by collaborating physicians for participating in the intervention group. After discussing additional information, 15 patients and their caregivers declined participation of which experiencing participation as too burdensome was most often reported as reason. Three caregivers did not want to participate as they considered a COVID-19 contamination risk. Four patients were excluded from study participation after screening as their caregivers did not report any NPS on the NPI-Q. After screening, 24 patients were included in the intervention group

together with their caregivers (56% of the referred patients). Collaborating physicians reported that a high workload, which was partly due to additional involvement in COVID-19 care, made it hard to refer patients for the intervention group.

Participants

We included 36 participants in the control group and 24 participants in the intervention group resulting in a total of 60 participants. The majority of participants had AD dementia (77%), while 11 participants had MCI (18%) and three participants (5%) were diagnosed with mixed AD/VaD dementia. Participants were enrolled shortly following diagnosis (median 1.6 months). Of the individuals with dementia, the majority had mild dementia (mean [SD] MMSE score = 23.0 [3.8], 90% CDR score ≤1). Cerebrospinal fluid analysis or amyloid-beta PET scan were conducted in 18 participants (30%) and indicated an AD-like biomarker profile in accordance with the clinical diagnosis. One patient was a known APP-mutation carrier. The majority of the patients were born and raised in the Netherlands (93%), while four patients (7%) had a diverse background (n = 2 Suriname, n = 1 Indonesia, n = 1 Germany). All but two caregivers (n = 1 Netherlands Antilles, n = 1 Germany) were born in the Netherlands and three caregivers (5%) were descendant of a first-generation immigrant. At baseline, we found no differences in demographic and clinical characteristics between the two groups (Table 1).

Three participants (8%) dropped out of the control group because two caregivers experienced participating as too burdensome, and one caregiver deceased during the study leading to a nursing home admission of the patient. Two participants (8%) dropped out the intervention group as one caregiver experienced participating as too burdensome and one patient deceased. We found no substantial differences in baseline characteristics between participants who dropped out of the study and those who completed the study (Supplemental Table 1).

Quantitative outcomes

Primary outcomes

We found no effect of the intervention compared to care as usual on changes in self-reported QoL-AD scores (β = 0.20, p = 0.37) and proxy QoL-AD scores (β = 0.14, p = 0.43) over three months follow-up (Figure 3). Furthermore, the intervention group did not differ in trajectories of CarerQol-7D utility scores (β = -0.12, p = 0.54) and CarerQol-7D VAS scores (β = 0.30, p = 0.16) over three months compared to the control group. Effects did not change after six months (all p > 0.05) (Table 2).

Secondary outcomes

Compared to the control group, the intervention group showed a significant increase in

Table 1. Clinical and demographic characteristics at baseline according to group

	Control group (n=36)	Intervention group (n=24)
Department included, N (%)		
Neurology	23 (63.9%)	15 (62.5%)
Geriatrics	13 (36.1%)	9 (37.5%)
Characteristics patients		
Age, mean (SD)	73.1 (7.7)	72.5 (6.9)
Female, N (%)	16 (44.4%)	12 (50.0%)
Education, median (IQR)[a]	4.5 (1.0)	5.0 (1.0)
Clinical diagnosis, N (%)		
MCI	9 (25.0%)	2 (8.3%)
AD dementia	24 (66.7%)	22 (91.7%)
Mixed AD dementia/VaD	3 (8.3%)	0 (0.0%)
Months after diagnosis, median (IQR)	1.6 (3.6)	1.6 (1.5)
CDR score		
0.5 (very mild)	17 (47.2%)	7 (29.2%)
1 (mild)	16 (44.4%)	15 (62.5%)
≥2 (moderate to severe)	3 (8.3%)	2 (8.3%)
AD-biomarker signature, N (%)[b]	9 (25.0%)	9 (37.5%)
MMSE score, mean (SD)	23.8 (3.8)	23.5 (3.9)
NPI-Q total score, median (IQR)[c]	14.0 (15.0)	11.5 (26.0)
No. NPS on NPI-Q, median (IQR)[c]	5.0 (4.0)	3.5 (5.0)
Cognitive enhancers, N (%)	19 (47.8%)	11 (45.8%)
Cholinesterase inhibitor	17 (42.2%)	11 (45.8%)
Memantine	2 (5.6%)	0 (0.0%)
Psychotropic drugs, N (%)	6 (16.7%)	5 (20.8%)
Antidepressant	5 (13.9%)	5 (20.8%)
Sedative-hypnotic	1 (2.8%)	1 (4.2%)
Antipsychotic	0 (0.0%)	0 (0.0%)
Mood stabilizer	0 (0.0%)	0 (0.0%)
Characteristics caregivers		
Age, mean (SD)	65.9 (11.0)	64.9 (13.0)
Female, N (%)	26 (72.2%)	14 (58.3%)
Education, median (IQR)[a]	5.0 (1.0)	5.0 (1.0)
Relationship to patient, N (%)		
Spouse or partner	28 (77.8%)	19 (79.2%)

Table 1. *continued*

	Control group (n=36)	Intervention group (n=24)
Child	8 (22.2%)	5 (20.8%)
Lives together with patient, N (%)	27 (75.0%)	19 (79.2%)

Notes. AD = Alzheimer's disease, CDR = clinical dementia rating scale, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, NPI-Q = Neuropsychiatric Inventory-Questionnaire, NPS = neuropsychiatric symptoms, VaD = vascular dementia.
[a] Dutch education system categorized into (1) less than 6 years primary education [<6 years], (2) completed primary education [6 years], (3) more than 6 years of primary education, without a secondary school diploma [8 years], (4) lower vocational training [9 years], (5) advanced vocational training or lower professional education [10-11 years], (6) advanced professional training or upper secondary school [12-18 years], and (7) academic degree [>18 years].
[b] Established based on either cerebrospinal fluid analysis (amyloid-beta$_{42}$ < 550 pf/mL or tau/amyloid-beta$_{42}$ ratio > 0.52) or visual inspection of an amyloid-beta PET scan.
[c] missing score for n=1.
* $p < 0.05$ difference between control group and intervention group based on analysis of variance, Mann-Whitney tests, or χ^2 tests.

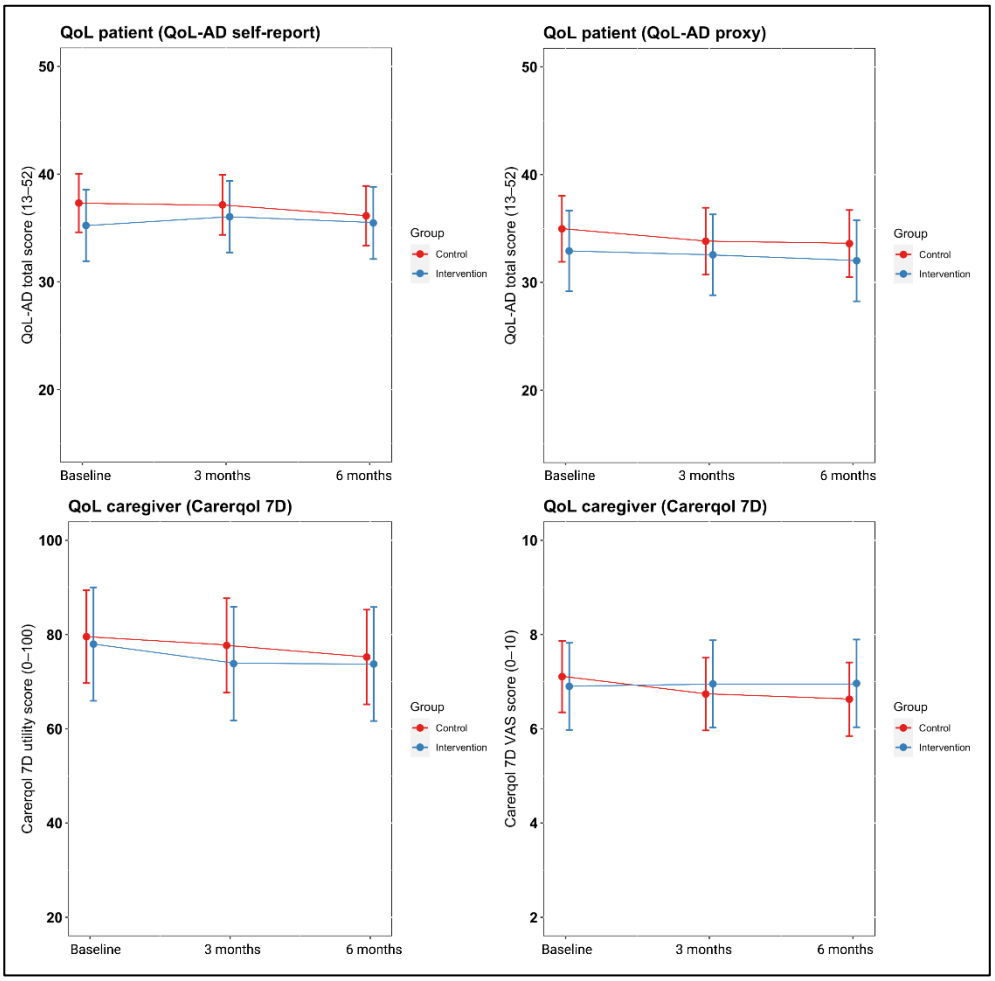
competence while managing NPS as measured using the NPI-Q over three months follow-up (β = 0.67, p = 0.04). This effect did not survive correcting for multiple comparisons (FDR-corrected > 0.05), and diminished after six months (β = 0.34, p = 0.31). The intervention did not have an effect on the course of NPI-Q total scores and NPS-related distress (all $p > 0.05$). In addition, there were no differences between the intervention group and the control group in trajectories of perseverance time and psychotropic drug use over six months follow-up (all $p > 0.05$) (Table 2).

We found a significant increase in CMAI total scores (β = 0.41, p = 0.01) and RAID total scores in the intervention group compared to the control group after six months (β = 0.82, p = 0.02), which did not survive correcting for FDR (all FDR-corrected $p > 0.05$) (Supplemental Table 2). We found no differences between the two groups regarding trajectories of AES-I total scores, CSDD total scores, BEHAVE-AD psychosis scores, SDI total scores, and the presence of specific NPI items (all $p > 0.05$) (Supplemental Table 2).

Reliable change index

Eleven participants of the intervention group (52%) showed reliable improvement on at least one of the primary outcomes after three months and/or six months follow-up and were therefore classified as 'responders' (Table 3). We found no differences between responders and non-responders in demographic characteristics at baseline. Responders showed a higher degree of NPS-related distress as measured using the NPI-Q (median [IQR] = 2.3 [1.0]) compared to non-responders (median [IQR] = 2.0 [1.0], p = 0.02). We observed higher NPI-Q total scores at baseline among responders (median [IQR] = 25.0 [21.0]) compared to non-responders (median [IQR] = 9.5 [25.0]), although not statistically significant (p = 0.28). Also, responders tended to have a lower disease

Figure 3. Primary outcomes over time according to group



Notes. QoL = quality of life.

severity (46% CDR score = 0.5) compared to non-responders (8% CDR score = 0.5), although not statistically significant (p = 0.19). A smaller proportion of responders used cognitive enhancers at baseline (27%) compared to non-responders (67%, p = 0.04). Responders showed a higher prevalence of apathy (91%) as measured with the NPI-Q at baseline compared to non-responders (42%, p = 0.01). Several other NPI-Q domains were endorsed more prevalent among responders compared to non-responders, although not statistically significant, including sleep disturbances (36% vs. 8%, p = 0.10), anxiety (46% vs. 25%, p = 0.30), euphoria (18% vs. 0%, p = 0.12), and depressive symptoms (82% vs. 67%, p = 0.41). In contrast, non-responders showed higher prevalence compared to responders on NPI-Q domains including disinhibition (25% vs. 0%, p = 0.08), aberrant motor behavior (42% vs. 18%, p = 0.22), agitation (33% vs. 18%,

Table 2. Primary and secondary outcomes for the intervention group compared to the control group after three and six months follow-up

	3 months follow-up		6 months follow-up	
Measure	**Standardized estimate [95% CI]**	**P value**	**Standardized estimate [95% CI]**	**P value**
QoL-AD self-report	0.20 [-0.23, 0.62]	0.37	0.28 [-0.15, 0.71]	0.2
QoL-AD proxy	0.14 [-0.21, 0.50]	0.43	0.08 [-0.28, 0.44]	0.65
Carerqol 7D utility score	-0.12 [-0.51, 0.26]	0.54	0.01 [-0.39, 0.40]	0.98
Carerqol 7D VAS scale	0.30 [-0.11, 0.72]	0.16	0.39 [-0.04, 0.81]	0.08
Perseverance time[a]	2.12 [0.13, 34.23]	0.6	3.10 [0.20, 48.13]	0.42
NPI-Q total score[b]	-0.15 [-0.61, 0.30]	0.51	-0.17 [-0.64, 0.29]	0.46
NPI-Q average distress[b]	0.01 [-0.58, 0.60]	0.96	0.07 [-0.52, 0.66]	0.81
NPI-Q average competence	0.67 [0.02, 1.32]	0.04*	0.34 [-0.32, 1.00]	0.31
BEHAVE-AD total score[b]	-0.09 [-0.45, 0.27]	0.63	0.01 [-0.35, 0.37]	0.97
Psychotropic drug use[b]	0.68 [0.01, 110.61]	0.88	2.64 [0.02, 398.46]	0.71

Notes. Estimates are standardized beta coefficients (β) for continuous outcomes and odds ratios (OR) for discrete outcomes derived from linear mixed models corrected for age, sex, disease severity (mild cognitive impairment/dementia), and hospital.
BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale, NPI-Q = Neuropsychiatric Inventory-Questionnaire, QoL-AD = Quality of Life in Alzheimer's Disease.
[a] Perseverance time categories: >2 years, 1-2 years, <1 year.
[b] Scores were inverted so that positive estimates indicate a positive effect of the intervention (e.g. decrease of NPI-Q total score, NPI-Q average distress, BEHAVE-AD total score, and psychotropic drug use).
* $p < 0.05$.
** FDR-corrected $p < 0.05$.

Table 3. Baseline demographic and clinical characteristics of responders and non-responders in the intervention group

	Responders (n=11)	Non-responders (n=12)
Characteristics caregivers		
Age, mean (SD)	68.0 (18.0)	73.0 (21.0)
Female, N (%)	8 (72.7%)	6 (50.0%)
Education, median (IQR)[a]	5.0 (1.0)	5.0 (1.0)
Relationship to patient, N (%)		
Spouse or partner	8 (72.7%)	10 (83.3%)
Child	3 (27.3%)	2 (16.7%)
Lives together with patient, N (%)	8 (72.7%)	10 (83.3)
Perseverance time, N (%)		
>2 year	8 (72.7%)	10 (83.3%)
1-2 years	0 (0.0%)	1 (8.3%)
<1 year	3 (27.3%)	1 (8.3%)
Characteristics patients		
Age, median (IQR)	77.0 (10.0)	75.0 (8.0)
Female, N (%)	5 (45.0%)	6 (50.0%)
Education, median (IQR)[a]	5.0 (2.0)	5.0 (1.0)
Clinical diagnosis, N (%)		
MCI	2 (18.2%)	0 (0.0%)
AD dementia	9 (81.8%)	12 (100.0%)
CDR score		
0.5 (very mild)	5 (45.5%)	1 (8.3%)
1 (mild)	5 (45.5%)	10 (83.3%)
≥2 (moderate to severe)	1 (9.1%)	1 (8.3%)
MMSE score, median (IQR)	25.0 (6.0)	23.0 (6.0)
Cognitive enhancers, N (%)	3 (27.3%)	8 (66.7%)*
Psychotropic drugs, N (%)	3 (27.3%)	2 (16.7%)
BEHAVE-AD total score, median (IQR)	5.0 (7.0)	4.5 (7.0)
NPI-Q total score, median (IQR)	25.0 (21.0)	9.5 (25.0)
No. NPS on NPI-Q, median (IQR)	4.0 (4.0)	2.5 (6.0)
NPI-Q average distress, median (IQR)	2.3 (1.0)	2.0 (1.0)*
NPI-Q average competence, median (IQR)	2.0 (0.9)	2.6 (1.4)
NPI-Q delusions, N (%)	3 (27.3%)	3 (25.0%)
NPI-Q hallucinations, N (%)	2 (18.2%)	3 (25.0%)
NPI-Q agitation, N (%)	2 (18.2%	4 (33.3%)

Table 3. *continued*

	Responders (n=11)	Non-responders (n=12)
NPI-Q depression, N (%)	9 (81.8%)	8 (66.7%)
NPI-Q anxiety, N (%)	5 (45.5%)	3 (25.0%)
NPI-Q euphoria, N (%)	2 (18.2%)	0 (0.0%)
NPI-Q apathy, N (%)	10 (90.9%)	5 (41.7%)*
NPI-Q disinhibition, N (%)	0 (0.0%)	3 (25.0%)
NPI-Q irritability, N (%)	7 (63.6%)	7 (58.3%)
NPI-Q aberrant motor behavior, N (%)	2 (18.2%)	5 (41.7%)
NPI-Q sleep disturbances, N (%)	4 (36.4%)	1 (8.3%)
NPI-Q eating behavior, N (%)	3 (27.3%)	5 (41.7%)

Notes. AD = Alzheimer's disease, CDR = clinical dementia rating scale, MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination, NPI-Q = Neuropsychiatric Inventory-Questionnaire, NPS = neuropsychiatric symptoms.

[a] Dutch education system categorized into (1) less than 6 years primary education [<6 years], (2) completed primary education [6 years], (3) more than 6 years of primary education, without a secondary school diploma [8 years], (4) lower vocational training [9 years], (5) advanced vocational training or lower professional education [10-11 years], (6) advanced professional training or upper secondary school [12-18 years], and (7) academic degree [>18 years].

* $p<0.05$ difference between responders and non-responders based on Mann-Whitney tests or χ^2 tests.

$p = 0.41$), although not statistically significant.

Qualitative outcomes

Twelve patients and their caregivers of the intervention group (50%) agreed to participate in a semi-structured interview after the last follow-up assessment was completed. Identified themes were: (1) substantial heterogeneity among participants, and (2) experiences with the intervention.

There was considerable heterogeneity among participants regarding the symptoms that caused most distress. While the majority of patients and caregivers reported NPS including apathy, irritability, and/or psychotic symptoms as most distressing, four participants reported solely difficulties due to cognitive problems, such as memory or language deficits. Furthermore, there was substantial variation in the degree of caregiver burden among caregivers. Several participants experienced serious burden while caring for the patient in terms of emotional distress and/or having to assist in daily activities:

> *"He sees things that are not real and, every morning, I have to assist him with dressing up and showering. It feels like a constant battle. … Sometimes it's OK, but we have fights over twenty times a day."* (participant #09, spouse of male with dementia).

However, five spouses did not consider themselves a caregiver:

> *"I visit a peer support group for dementia caregivers, but actually, I don't see myself as a caregiver at all. For example, last month, I went on a four-day city trip with a friend of mine, while my husband stayed at home alone, which was absolutely fine for the both of us."* (participant #01, spouse of male with dementia)

In line with this, there were differences among participants to which extent they felt supported by family and friends and had to ask them for help.

A few participants spontaneously mentioned benefits of the intervention. Some of these experiences were related to the management of NPS (e.g. dealing with negative emotions), while other experiences were not specific for NPS (e.g. disclosing the diagnosis to family and friends). One caregiver reported that the intervention was too short and another caregiver indicated that the intervention would have been more effective if it was delivered sooner because of the extent of cognitive impairment and NPS at this stage. There were no clear differences between responders and non-responders regarding causes of distress, caregiver burden, and the availability of social support.

Cost-effectiveness

Average health care costs for six months per patient did not significantly differ between the intervention group (€2,751) and in the control group (€2,417, p = 0.88) (Table 4). The non-significant difference observed was very close to the average cost of the DICE intervention (€327). After six months, the intervention group did not differ from the control group in the number of QALYs (p = 0.72) and well-being years (p = 0.75) (Table 4). The cost-effectiveness analysis showed that switching from care as usual to the intervention led to an increase in health care costs and societal costs, while QALYs and well-being years remained relatively stable (Table 5). This resulted in negative incremental costs per QALY. The probability that the intervention produces more QALYs and well-being years than care as usual ranged between 37–52%, while the probability that the intervention saves health care and societal costs ranged between 45–46%.

Discussion

Main findings of the present study were that (1) the DICE method did not improve QoL in patients with early AD dementia and their caregivers visiting the memory clinic, (2) there was a trend of increase in the intervention group in confidence managing NPS and severity of agitation and anxiety compared to the control group, and (3) in exploratory analysis, treatment-related benefits in QoL were related to higher levels of baseline NPS-related distress among caregivers, higher baseline prevalence of apathy, and less cognitive deficits at baseline.

Table 4. Average costs per group and cost-effectiveness analysis after six months

	Intervention group (n=24)	Control group (n=36)
Average costs per patient per group		
Health care perspective		
Hospital care	€371	€378
Semi-mural care	€615	€343
Extramural care	€1,376	€1,639
Anti-dementia/ psychotropic drug use	€63	€57
Intervention costs	€327	€0
Total health care costs, mean (SD)	€2,752 (€4,179)	€2,417 (€4,227)
Societal perspective		
Informal costs	€3,553	€3,507
Total costs, mean (SD)	€6,305 (€6,246)	€5,924 (€6,260)
Cost-effectiveness of the intervention		
QALYs per patient	0.81	0.82
Well-being years per patient	0.86	0.86
Incremental health care costs per patient	+€343	
Incremental societal costs per patient	+€435	
Incremental QALYs per patient	-0.02	
Incremental well-being years per patient	+0.01	
Health care perspective		
Incremental costs per QALY gained	-€20.70	
Incremental costs per well-being year gained	+€55.83	
Societal perspective		
Incremental costs per QALY gained	+€26.26	
Incremental costs per well-being year gained	+70,829	

Notes. Incremental costs are presented over a 12-month period.

We found no effects of the intervention on QoL of patients and caregivers. Positive effects on QoL have rarely been reported for care programs similar to the DICE method, as QoL have rarely been used as outcome measure and studies that did include such measures did not find an effect.[372,373] Furthermore, baseline QoL measures were high in our sample (Figure 3), compared to previous European studies among community-dwelling patients with mild AD dementia.[6,374-377] In addition, QoL measures remained relatively stable over time in the control group. Therefore, there might be little room for improving QoL measures in this sample. Another explanation might be that we enrolled a clinically divers population in the intervention group in terms of NPS presence, NPS severity, and cognitive impairment at baseline (Table 1), which reflects

the memory clinic population.[147,164] The heterogeneity was also further emphasized by the outcomes of the semi-structured interviews. These showed that several caregivers do not experience any NPS-related distress, while others experience major burden due to NPS. Furthermore, some caregivers do not consider themselves as a caregiver, while other caregivers did as they have to assist in a variety of activities of daily living. As this could be expected based on our liberal inclusion criteria, we conducted an RCI analysis to examine whether specific subgroups of participants did benefit from the intervention.[367] These exploratory analyses revealed reliable improvement in QoL among caregivers with high levels of baseline NPS-related distress, and in patients with higher prevalence rates of apathy and in the mild stages of AD dementia. The finding that responders had higher levels of NPS burden might inform future studies to include participants who have clinically relevant and/or distressing NPS established either by using clinically relevant cutoff scores or by a clinician. The finding that participants in the mild clinical stages of AD benefited most from the DICE method may be due to the interventions provided. Interventions such as psychoeducation were provided to both patients and caregivers, and patients with less cognitive impairments may have benefited more from these interventions compared to patients with severe memory deficits.

We found a significant improvement of confidence in managing NPS after three months follow-up among caregivers in the intervention group compared to the control group. Although this association was not statistically significant after correcting for multiple testing and diminished after six months follow-up, large effects sizes were found for three months follow-up and six months follow-up (Table 2). An increase in confidence while managing NPS has also been found in two previous studies that evaluated the effectiveness of the DICE method to improve the assessment and management of NPS in caregivers and care professionals.[311,363] In addition, we also found an increase in the severity of agitation and anxiety symptoms after six months follow-up. This might result from an increase of awareness of NPS among caregivers due to the intervention, as caregivers may not have been aware that NPS are an integral part of AD dementia before.[8] Also, the intervention group was recruited during COVID-19 pandemic and was faced with lockdowns during participation. A recent meta-analysis showed an increase in NPS among patients with dementia and MCI during COVID-19 lockdowns, especially in depression, anxiety, agitation, irritability, and apathy.[378] Therefore, the increase in agitation and anxiety observed in the intervention group could be unrelated to the intervention.

There were no significant gains in QALYs and well-being years following the intervention resulting in large uncertainties regarding positive or negative effects and additional costs or savings. Health related QoL and well-being was relatively high for the patients in the study, which may be partly due to the inclusion of MCI and mild AD dementia. Due to the small sample size, results should be viewed only as explorative.

The small difference in health care costs in the intervention group was almost identical to the costs of the intervention itself suggesting that other health care costs were highly similar for both groups. Optimizing the intervention and repeating this study in a larger sample with a longer follow up might be an option to get better information for physicians, patients, and policy makers on the cost-effectiveness of this intervention.

Strengths and limitations

Strengths of the current study include addressing the whole spectrum of NPS in AD that represents the memory clinic population and using a combination of quantitative and qualitative outcome measures. However, this study also has some limitations. First, this study was conducted during the COVID-19 pandemic, which has affected the enrollment of participants resulting in a lower number of participants than was anticipated on.[147] Consequently, the power to detect an effect was limited. As standardized estimates indicated large effects for caregiver burden and competence managing NPS, future studies that include larger sample sizes are expected to find significant improvement on the clinical outcomes included. Yet, the COVID-19 pandemic may have affected our outcomes as some assessments were conducted through telephone and the COVID-19 related restrictions may have impacted the QoL and NPS of the participants. We recorded the mode and location of administration (home/hospital/telephone) for each assessment and did not find any effect of this on the primary and secondary outcomes across all participants (all $p > 0.05$). However, as discussed above, we were not able to rule out the potential effects of COVID-19 lockdowns on the severity and manifestation of NPS.[378] Second, this study examined the efficacy of the DICE method in a research setting and can thus be classified as a stage II study (pure 'efficacy') according to the NIH Stage Model for Behavioral Intervention Development.[379] Therefore, future studies are needed that study the implementation of the DICE method in the memory clinic setting. A recent study by our group suggests several challenges that need to be overcome prior to implementing care programs such as the DICE method in the memory clinic.[258] For example, there is currently no consensus among memory clinic physicians on whether the care for NPS in early AD dementia should be located at the memory clinic at all, with a substantial proportion of the Dutch memory clinic physicians arguing that this should primarily be located within primary care instead.[258] Addressing challenges like these seem imperative prior to implementation of the DICE method. Finally, only a third of the included participants had their clinical diagnosis of MCI or AD dementia supported by AD-biomarkers. This may have led to in the inclusion of non-AD pathologies, although patients with substantial vascular pathology and those that met additional criteria for non-AD neurodegenerative diseases were excluded. A priori, we intended sensitivity analyses in patients with positive AD biomarkers,[231] this was not possible given the low sample size (n = 9 per group).

Conclusion

This study shows no benefits for QoL of the DICE method in individuals who visit the memory clinic with early AD. However, findings do suggest that patients with substantial NPS burden and mild AD dementia and caregivers with high levels of NPS-related distress might benefit from a structured care program addressing NPS, which might contribute to the early assessment and adequate management of NPS in early AD.

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Author's contributions

R.O. and J.M.P. acquired funding for this study. W.S.E., E.v.d.B., M.C., E.S., R.O., and J.M.P. designed the study in consultation with J.A.G., M.K., R.L.v.B.V., J.J.M.D., T.d.H., S.H., F.J.d.J., F.M.R., E.C.T., S.V., L.J.H.M.V., S.U.Z., and J.C.v.S. W.S.E. coordinated the intervention study under the supervision of E.v.d.B., R.O., and J.M.P.. W.S.E., Ev.d.B., J.A.G., R.L.v.B.V., J.J.M.D., T.d.H., S.H., F.J.d.J., F.M.R., E.C.T., S.V., L.J.H.M.V., and J.C.v.S. contributed to the enrollment of participants. W.S.E., E.v.d.B., M.C., J.A.G., and J.M.P. conducted the DICE method. M.K. conducted the cost-effectiveness analyses and wrote these sections of this manuscript. N.L. conducted the semi-structured interviews and assisted in the qualitative analysis. W.S.E. analyzed the quantitative and qualitative data and interpreted the data assisted by E.v.d.B., M.C., R.O., and J.M.P.. W.S.E. drafted the first version of the manuscript, while E.v.d.B., M.C., J.A.G., M.K., N.L., R.L.v.B.V., J.J.M.D., T.d.H., S.H., F.J.d.J., F.M.R., E.C.T., S.V., L.J.H.M.V., S.U..Z., E.H.S., J.C.v.S., R.O., and J.M.P. and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

Supplemental materials

Available online at: https://bit.ly/3Apfs0W.

Chapter 5

General discussion

NPS are common in AD and have a major impact on the lives of patients and their caregivers. This thesis aimed (1) to study the prevalence and course of NPS in individuals in the early clinical stages of AD visiting the memory clinic, (2) to obtain insight in the current care provided for NPS in early AD dementia, with a special focus on the memory clinic setting, and (3) to examine ways to improve timely recognition of NPS and the use of non-pharmacological treatments in AD dementia in the memory clinic setting. This chapter provides a summary of the key findings of this thesis. Thereafter, methodological challenges related to this thesis are discussed based on which I provide recommendations for future research.

Key findings

Neuropsychiatric symptoms are a core feature of early Alzheimer's disease

NPS are traditionally associated with severe AD dementia.[9] Chapter 2.1 shows indeed that NPS are most prevalent in the severe stages of AD dementia. However, chapters 2.1 and 3.3 also highlight that NPS are common in mild AD dementia as well, with caregivers and clinicians reporting at least one NPS in nearly 90% of the individuals who visit the memory clinic with mild AD dementia. More strikingly, amyloid-beta positive individuals with no or only mild cognitive impairment also frequently exhibit NPS (chapter 2.1). Together with the case study presented in chapter 3.1, our findings point out that NPS may precede cognitive impairment during the course of AD.

While NPS were related to disease severity with most prevalent and severe NPS in the advanced clinical stages of AD (chapter 2.1 3), we found no robust associations between specific NPS and cognitive decline across five cognitive domains in an amyloid-beta positive sample ranging from normal cognition to dementia (chapter 2.1). More importantly, NPS and cognitive symptoms showed a different evolution over time. While a gradual decline was observed in cognitive functioning, the progression of specific NPS was less coherent and unrelated to cognitive functioning (chapter 2.1). These findings may indicate that neuropsychiatric and cognitive symptoms have different underlying mechanisms in AD. In line with this, cognitive symptoms have been related to neurodegeneration, amyloid-beta, and tau pathology,[139,380] while these associations are less consistent for NPS.[64,65]

Research on the manifestation of NPS in AD dementia is shifting from severe dementia to the early clinical stages including the preclinical and prodromal phases of AD. In accordance to our findings, recent studies have shown that NPS are prevalent in older adults with MCI,[12-14] and in individuals with normal cognitive functioning who are at risk for developing dementia.[15-17] We found little evidence for associations between NPS and cognitive decline in amyloid-positive individuals without dementia (chapter 2.1), suggesting that NPS seem to have less predictive value on cognitive decline in an amyloid-positive sample. However, a large body of research has shown that NPS are related to a faster progression to dementia.[46,282,381] This led several researchers to

suggest that NPS might be a modifiable risk factor to prevent (further) cognitive decline in older adults with normal cognitive functioning or MCI.[224,282,382] However, these claims assume that NPS may have a causal effect on brain functioning relating to AD symptoms. To date, research has failed to provide solid evidence for this hypothesis. Therefore, the relationship between NPS and accelerated cognitive decline might be explained by other mechanisms.[55,81] For example, the presence of NPS may be a first manifestation of the disease or reflect a more aggressive form of the disease or a different phenotype, e.g. bvAD.[32] Alternatively, both NPS and other AD-related symptoms such as cognitive deficits may share a similar confounding factor such as genetic status,[e.g. 383,384] or vascular and Lewy body co-pathologies.[e.g. 385-387] Although the presence and severity of late-onset NPS is a well-established risk factor for cognitive decline in older adults the mechanisms underlying this relationship remain unknown and warrant further investigation.

To conclude, although it is less likely that all NPS observed in AD directly arise from AD-related pathophysiological processes, it is important to recognize NPS as a core feature of the early clinical stages of AD given its prevalence and clinical impact. NPS are not mentioned in the clinical diagnostic criteria for probable AD dementia developed by Mckhann et al.[1] This may have led to the notion among clinicians that late-onset NPS are not part of mild AD dementia or even rules out the possibility of an AD dementia diagnosis. Chapter 3.1 highlights that this notion can lead to a diagnostic delay, wrong psychiatric diagnoses, and inappropriate care. The incorporation of NPS in the clinical diagnostic criteria for AD dementia contributes to the awareness of NPS as an (early) manifestation of AD and potential treatment target.[26,114]

There is limited group-to-individual generalizability regarding the course of neuropsychiatric symptoms in Alzheimer's disease

NPS in AD are heterogeneous in type, severity, and evolution.[3,5,18,20] This thesis shows that this heterogeneity is also visible when looking at the individual course of specific NPI domains across the AD clinical spectrum (chapter 2.1). In line with prior research,[4,19] chapter 2.1 shows that the course of specific NPS is generally stable when looking at group-level, but highly unstable when looking at individual patients. Moreover, we found remarkable fluctuations in the course of specific NPI domains when assessed at shorter time intervals than the commonly (bi)annual assessments (chapter 2.2). Our findings are in line with the growing body of evidence emphasizing that the variance of longitudinal data can be two to four times larger within individuals than within groups questioning the accuracy of aggregated estimates at group-level in social and medical sciences.[388,389]

The large intraindividual variation in NPS observed in chapters 2.1 and 2.2 spark the discussion around whether these fluctuations capture the fluctuating nature of NPS in AD dementia or reflect the inability of NPS scales such as the NPI to reliably

assess NPS longitudinally. Support for the former idea comes from caregivers and patients who we encounter at the memory clinic reporting that symptoms greatly vary from day to day and from studies that showed daily fluctuations in NPS based on daily assessments of NPS.[155-157] On the other hand, fluctuations in scores may also be affected by recall bias and distress among caregivers.[75,88,89] Moreover, little is known about what we should consider as relevant change in NPI scores rather than noise due to measurement error.[160]

To conclude, group-level estimates of NPS trajectories provide little information about the course of NPS for the individual patient. Further studies are needed to investigate the origins of the large intraindividual heterogeneity in the evolution of NPS in AD.

There are important sex and gender differences in the manifestation of neuropsychiatric symptoms in Alzheimer's disease

There is a great need for factors explaining the heterogeneity in the manifestation of NPS observed in AD dementia. Sex and gender differences may explain a part of this clinical variability. Our meta-analysis revealed that the prevalence and severity of depressive symptoms, psychotic symptoms, and aberrant motor behavior was higher among females, while apathy was more severe among males (chapter 2.3). Our results align with the growing body of research showing important sex and gender differences in the clinical manifestation of AD.[181,390,391] However, the underlying mechanisms of the sex and gender differences in NPS in AD remain unclear. There are indications that females may be diagnosed at a later disease stage because of a verbal memory test advantage leading to more severe symptoms at diagnosis.[203] Alternatively, the higher lifetime prevalence of mood disorders among females and externalizing and substance disorders among males,[198] and the effects of inequalities in discrimination, occupation, and access to education[390] could also contribute to the sex differences observed in NPS in AD dementia.

Note that studies included in our meta-analysis used sex and gender interchangeably, ignoring the fact that these labels reflect different constructs.[167] Moreover, these findings are based on the binary classification of sex (male or female), while neglecting nonbinary and intersex populations, and the biological correlates of gender identities.[390] Future studies are needed that study the effects of sex and gender on NPS manifestation in AD dementia separately, while taking the continuum of gender identities into account ascertained by self-report.

To conclude, there are important sex and gender differences in het manifestation of NPS in AD dementia. These findings may aid timely diagnosis of NPS in AD dementia as it indicates that especially females are at an increased risk for exhibiting specific NPS in AD dementia. In addition to timely diagnosis, paying attention to the adequate treatment of NPS is also especially important in females with AD

dementia as community-dwelling females with AD dementia are more likely to receive inappropriate psychotropic drugs than males with AD dementia,[392] even after adjusting for NPS severity.[393]

There is low agreement between clinician's and caregiver's perception of neuropsychiatric symptoms

Comparing NPS described by clinicians in EHRs and NPS reported by caregivers according to the NPI revealed little agreement between clinicians and caregivers (chapter 3.3). This resembles our experience while conducting the DICE intervention as caregivers tended to report different NPS on the NPI-Q at baseline than ultimately diagnosed by the researchers after a thorough assessment of NPS (chapter 4.2).

Our results are in line with previous studies that revealed significant discrepancies between NPI assessments by clinicians and caregivers of individuals with dementia.[239,255,257] Chapter 3.3 showed that clinicians described significantly more NPS in EHRs compared to NPI assessments by caregivers. This contradicted our hypotheses as we expected that caregivers would report more NPS than clinicians based on prior research.[239,255]

There are several explanations that might explain these findings. First, clinicians may be less biased by factors that are known to affect proxy-based NPS instruments such as mood, stress, fatigue, and recall bias.[89] Second, there might be differences in the reference-point based on which clinicians and caregivers consider certain behaviors abnormal. For instance, caregivers have to indicate whether behaviors are abnormal compared to pre-morbid functioning, while clinicians usually evaluate behaviors while referring to the general population and/or their personal clinical experience. Also, caregivers do not always consider NPS as part of early AD dementia,[8] and use different terminologies do describe NPS than clinicians.[158] In addition, NPS may be more frequently reported in EHRs compared to the NPI as EHRs are not limited to specific wording and a specific timeframe,[84] and, finally, because NPS were classified in EHRs using imperfect classifiers with a tendency to overestimate the NPS prevalence.

Important to mention, no golden standard exists when comparing NPS ratings by clinicians and caregivers. As a consequence, differences between raters may indicate both an underestimation or overestimation of particular NPS. To assess NPS less subjectively, there is a shift towards the use of sensors and wearables to measure behavioral and physiological correlates related to NPS in dementia.[259,394] For example, recent studies have shown that actigraphy can be used to detect agitation[395], wandering,[396] apathy,[397] and sleep disturbances.[156,398] Future studies should relate NPS ratings by clinicians and caregivers to such measures to provide more insight in the potential underdiagnosis of particular NPS among either clinicians or caregivers. However, despite the added value of these 'objective' measures of NPS, the assessment

of NPS should not solely be based on these measures as interviews with the DICE intervention participants indicated that caregivers greatly vary in their capabilities to cope with NPS and experience related emotional distress in the context of similar symptom severity(chapter 4.2). This indicates that subjective proxy-based measures of NPS are useful in identifying patients and caregivers at increased risk for burden due to NPS and those who might benefit from care programs such as the DICE method.

Also relevant to mention are the differences in nomenclature used to describe NPS. Besides considerable differences in nomenclature between clinicians and caregivers,[158] there is also substantial variety in terminologies used to denote NPS among clinicians.[254,399] This is further illustrated by the low agreement between clinicians who annotated NPS such as aberrant motor behavior, anxiety, euphoria, disinhibition, and agitation in EHRs (chapter 3.3). Complex groups of symptoms are often grouped under syndromes or clusters such as psychosis, agitation, and apathy that are difficult to demarcate. Diagnostic criteria for these syndromes can contribute to the uniform use among clinicians.[27-30]

To conclude, clinicians and caregivers hold a clearly different perspective on NPS in AD. While this should be interpreted in light of a lack of golden standard to establish NPS and a lack of consensus on the nomenclature used to describe NPS among clinicians, our findings stress that it is essential to include the perspectives of both caregivers and clinicians to accurately capture NPS in AD at the memory clinic.

Neuropsychiatric symptoms are currently underrecognized in Alzheimer's disease

Chapters 3.1 and 3.2 suggest an underrecognition of NPS in AD dementia at the memory clinic; yet, manifesting in various ways. First, some memory clinic physicians do not consider NPS as prominent symptoms in mild AD dementia (chapter 3.2). This notion may lead to a limited awareness for NPS resulting in an underdiagnosis of NPS, which is supported by the observation that these physicians report observing very few NPS in individuals they diagnosis with mild AD dementia. Alternatively, although other clinicians may detect NPS, the case study shows that the notion that NPS are not part of early AD dementia can lead to a delay of an AD dementia diagnosis and inappropriate care (chapter 3.1). In contrast, other physicians acknowledged the importance of NPS in mild AD dementia, but mentioned that they probably fail to detect all NPS in the patients they diagnose with mild AD dementia at the memory clinic, because the outpatient memory clinic makes it difficult to detect NPS that occur at home and due to difficulties establishing NPS based on caregiver reports (chapter 3.2). Although chapter 3.3 revealed that NPS were generally underreported by caregivers based on lower NPI scores than EHRs reports of NPS, a notable proportion of NPS reported by caregivers were not mentioned in EHRs suggesting that clinicians also underdiagnose particular NPS including depressive symptoms, anxiety, irritability, apathy, and eating behavior. Also, a proportion of the memory clinic physicians acknowledged that the assessment

of NPS is not always part of their standard diagnostic work-up as they do not have sufficient experience and knowledge on the subsequent (non-pharmacological) treatment of NPS in AD dementia (chapter 3.2). Finally, several physicians stated that they do not systematically assess NPS as they do not regard the diagnosis and treatment of NPS situated at the memory clinic (chapter 3.2).

Chapter 3.4 shows that the underrecognition of NPS is not unique to the memory clinic setting. The sporadic notions of particular NPS such as apathy, affective symptoms, and psychotic symptoms in EHRs in this setting illustrate that these symptoms remain undetected by residential aged care staff as we know that these symptoms do occur frequently in this population.[263]

To conclude, this thesis provides further evidence for the underrecognition of NPS in the early clinical stages of AD. This does not only entail that clinicians may not notice the presence of NPS in AD, but also that NPS are detected but not recognized as part of AD and/or that NPS are detected but not acted upon.

Adequate treatment of neuropsychiatric symptoms is hampered by substantial variation in expertise, knowledge, and attitudes among clinicians

The underrecognition of NPS described above results in an undertreatment of these symptoms in AD dementia. Chapters 3.2 and 3.4 suggest more factors that may contribute to an undertreatment or inappropriate treatment of NPS, e.g. overprescription of psychotropic drugs. First, chapter 3.4 shows how a lack of knowledge on potential triggers and causes of NPS among residential aged care staff led to inappropriate and ineffective interventions. Memory clinic physicians did mention several psychosocial triggers and causes of NPS, but some acknowledged having little experience and knowledge on the subsequent application of non-pharmacological strategies to manage NPS, which sometimes leads to an increased use of psychotropic drugs. A lack of knowledge and expertise regarding non-pharmacological interventions for NPS have been reported previously among general practitioners and residential aged care staff.[228,229]

In addition, we revealed a lack of consensus among memory clinic physicians regarding their attitudes on the role of the memory clinic in the care for NPS in AD dementia (chapter 3.2). While several physicians plead that memory clinics should play a proactive role in the care for NPS in AD dementia, others argued that this should be primarily designated to primary care providers such as general practitioners and case managers. In support of the latter, the outpatient setting makes it hard to assess and treat symptoms that occur at home and patients seen at Dutch memory clinics are regularly referred back to the referring physician once a diagnosis is established.[108] On the other hand, memory clinics have great potential for contributing to the timely diagnosis and treatment of NPS in AD dementia as these facilities conduct a comprehensive diagnostic assessment and have recourses available to offer post-

diagnostic care in various ways. In addition, a proportion of the memory clinic physicians have raised concerns about the time and expertise primary care providers have to adequately detect and manage NPS in AD dementia. Literature has indeed shown that general practitioners experience difficulties managing NPS and not always consider the management of NPS as their responsibility.[229,400] Furthermore, we conducted a study among Dutch home care nurses and formal caregivers and found that there was also a great need for training and educational programs to increase knowledge and skills related to the recognition, nomenclature, and management of NPS in dementia among these care providers.[401]

To conclude, in addition to the underrecognition of NPS in AD, insufficient experience and knowledge about non-pharmacological strategies to manage NPS and a lack of consensus on the role of the memory clinic in the care for NPS clearly hampers the care for NPS in community-dwelling individuals in the early clinical stages of AD.

Electronic health records provide a unique insight in the care for neuropsychiatric symptoms in dementia

Chapters 3.3 and 3.4 describe studies that used EHRs to investigate the current care for NPS in memory clinics and residential aged care facilities. This enabled us to study how clinicians perceive, describe, and respond to NPS while limiting biases that research methods such as interviews and focus groups are subject to including social desirability,[274] normative discourse,[275] recall bias,[276] and selection bias.[277] As shown in the sections above, the findings of both chapters clearly extend prior research on the current care for NPS in dementia among residential aged care staff based on questionnaires and interviews,[227,272,402] and the qualitative study among memory clinic physicians described in chapter 3.2. This emphasizes the way EHRs can contribute to a better understanding of the current care for NPS in AD dementia in order to improve early recognition and adequate treatment of NPS in AD dementia.

Chapter 3.3 shows the feasibility of NLP applications to assist in the processing of unstructured text that EHRs mainly consist of. These applications enable the analysis of large datasets with unstructured data,[240,243] and are increasingly used in dementia research.[252] The use of EHRs has clear advantages as these data are not primary collected for research purposes and therefore offer an unique insight in daily clinical practice. In addition, the unstructured format provides the opportunity to describe subtle changes in behavior and emotions using terminologies that are not limited to the terminologies used in structured NPS assessment scales. However, several challenges and limitations related to the use of EHRs and NLP applications to study the current care for NPS must also be noted. For example, although the existing biobank of the Alzheimer Center Erasmus MC and the Amsterdam Dementia Cohort facilitated the selection of eligible patients, there were no pipelines available for the extraction and anonymization of EHRs making it a very time-consuming process. In addition, the use

of EHR data was new for our local medical ethical committees, which hampered the process. Therefore, new pipelines and guidelines developed in collaboration between researchers, data managers, EHR system developers, and ethical committee members are needed to facilitate the use of EHRs for research purposes. Furthermore, it should be stressed that EHRs do not reflect the full clinical reasoning process. Finally, NLP classifiers performed generally well in detecting NPS in EHRs. However, as with most machine learning algorithms, it is not apparent why particular EHRs were classified as containing specific NPS and others were not. In addition, the performance of the classifiers depended on a relatively small selection of NPS that were annotated in the training set, while we know that clinicians use a tremendous number of terminologies to describe NPS.[158,254,399] Despite these limitation, the use of EHRs for research purposes offers great opportunities for future research on NPS in AD.

The DICE method is not effective when applied to all patients with early AD dementia at the memory clinic

Chapters 4.1 and 4.2 describe the design and outcomes of a care program used to structure and standardize the assessment and management of NPS in individuals in the early clinical stages of AD visiting the memory clinic. Several care programs have been developed to structure the care for NPS in dementia.[291,309,310] We choose to apply and evaluate the DICE method as this care program was especially designed for individuals with dementia living at home,[100] and experts in the field suggested this method as most promising non-pharmacological intervention to manage NPS in dementia.[286] Recent studies showed that the DICE method significantly reduces NPS-related distress and improves confidence in managing NPS in caregivers and care professionals,[311,363] but no studies were conducted in the memory clinic setting at the start of this thesis.

We applied the DICE method in a small sample of memory clinic visitors with MCI or mild AD dementia who exhibited at least one NPS. Apathy, depressive symptoms, and irritability were most commonly addressed with psychoeducation about the origins of NPS, providing caregiver support, and increasing meaningful and tailored activities for patients (Box 4). Our findings showed no improvement in QoL and in any of the secondary outcomes following the DICE method compared to care as usual (chapter 4.2). The majority of previous studies also found little to no effect of similar care programs on NPS, QoL, and psychotropic medication use when applied in residential aged care.[373,403,404] While low treatment fidelity often threatens the efficacy of these care programs in the residential aged care setting,[373] this would not explain the null findings of our study as the intervention was conducted by the researchers. Rather, the high levels of QoL at baseline and the considerable proportion of participants who were interviewed and indicated low levels of (distressing) NPS and minimal caregiver burden might better explain these findings (chapter 4.2). Despite that participating physicians were inclined to assist in this study highlighting its relevance, enrollment of

Box 4. Commonly used strategies targeting neuropsychiatric symptoms following the DICE approach

Generalized strategies

- Explain that behaviors are not intentional, but rater arise from unmet needs, a lowered stress threshold, cognitive impairment, and/or brain disease.
- Enhance tailored activities, while taking preserved capabilities and previous interests into account.
- Encourage to utilize a support network to initiate activities with patients, assist in instrumental daily activities of daily living, and to ensure well-being of caregivers.

Targeted strategies

- Apathy: explain that the problem lies in initiating activities, while individuals often do enjoy activities once initiated. Encourage caregivers to assist in initiating activities and
- Irritability/agitation: avoid confrontation with impairments. Create a soothing environment including structured daily routines.
- Depression/worrying: convey that worrying is often normal given the challenges patients have to deal with. Encourage caregivers to aid in non-language forms of self-expression and distraction (e.g. music, physical activity).
- Delusions/hallucinations: educate caregivers to avoid trying to convince that perceptions are incorrect. Instead, distract with tailored activities and notify physician if symptoms cause significant distress or safety threat.
- Sleep disturbances: evaluate sleep hygiene. Use a nightlight to prevent wandering at night.

study participants was hampered by the low number of eligible participants referred. Consequently, the power to detect an effect was limited, which is a common problem in studies evaluating non-pharmacological interventions in dementia,[405]

Given the substantial heterogeneity in QoL, NPS, cognitive impairment, and caregiver burden observed among participants of the intervention, we calculated reliable change indexes to examine who benefited most from the intervention. These analyses suggested that caregivers with high levels of baseline NPS-related distress, and patients with severe apathy and less cognitive impairment at baseline showed a higher proportion of reliable change in QoL following the intervention (chapter 4.2). Greater treatment benefits among individuals with higher levels of NPS has been reported previously,[406] and emphasize the need for proper screening of NPS prior to participating in care programs such as the DICE.

To conclude, the DICE method was not effective and unlikely to be cost-effective when applied at the memory clinic in its current format. Future studies should examine the effectiveness of the DICE when evaluated only in individuals who show clinically relevant NPS after completing the first step of this method.

Methodological considerations

Clinical diagnosis of AD dementia

All prospective studies and almost all studies in the meta-analysis included in this thesis enrolled patients based on a clinical diagnosis of AD dementia without access to AD-biomarker information.[1] This does not align with the movement towards a biological definition of AD and may have led to the inclusion of patients with non-AD pathologies such as vascular disease, Frontotemporal lobar degeneration, or Lewy bodies.[25] However, besides the ethical concerns related to this reconceptualization of AD,[407] the majority of the Dutch physicians still refer to AD as dementia.[408] In line with this, only a third of the all participants included in our intervention study had a clinical AD diagnosis supported by AD-biomarkers (chapter 4.2).

While this thesis has a special focus on AD as NPS are less appreciated compared to non-AD dementias, much of its findings are probably not limited to individuals with dementia due to AD pathology. For example, the high prevalence and large intraindividual variation in the manifestation of NPS has also been reported for DLB, bvFTD, VaD, and Parkinson's disease dementia.[19,409,410] Furthermore, a diagnostic delay due to severe NPS and misdiagnoses of psychiatric conditions are commonly seen in DLB and bvFTD.[410,411] Finally, effects of the intervention described in chapter 4.2 are assumed to be similar for individuals with non-AD dementias, as the majority of prior studies have evaluated non-pharmacological interventions in all-cause dementia populations.[94,95,98,99] To note, pure AD pathology is the exception rather than the rule, especially in older adults.[412]

Assessment of neuropsychiatric symptoms in early clinical stages of Alzheimer's disease

The assessment of NPS in the early clinical stages of AD is hampered by several challenges. First, we found that not all commonly used NPS instruments are sensitive to capture NPS when administered to caregivers of community-dwelling individuals in the early clinical stages of AD. For example, a large number of the items of the Cohen-Mansfield Agitation Inventory (CMAI) were not endorsed by the caregivers of the patients enrolled in the intervention study either because these behaviors were not observed in MCI or mild dementia (e.g. biting, scratching, eating/drinking inappropriate substances) or were not considered abnormal by informal caregivers (e.g. making verbal sexual advances). Therefore, the majority of participants showed floor effects on the CMAI, despite knowing that agitated-like behaviors such as irritability are very common in mild AD dementia (chapter 2.1). New instruments are needed that are sensitive to capture the subtle changes in emotions and behavior observed in the early clinical stages of AD. While doing so, it is important to include caregivers in the process given the different terminologies used to denote NPS by caregivers than clinicians.[158] The Mild Behavioral Impairment Checklist (MBI-C) might

be a suitable instrument because it is developed to assess late-onset NPS in pre-dementia stages.[413] Yet, the use of the MBI-C in mild AD dementia has not been studied and warrants further investigation.

Moreover, the majority of the studies included in this thesis investigated the *presence* of specific NPS. However, mild NPS may be present without an immediate need to intervene (e.g. mild worrying about memory problems), while the mere presence of other symptoms may be considered clinically relevant (e.g. psychotic symptoms). For the NPI, the golden standard of NPS assessment in dementia,[86] a domain score ≥ 4 is often to denote clinically relevant NPS.[18,110,132] However, this cutoff has not been properly validated,[84] so future studies are needed to establish the clinical relevance of this cutoff score. The use of diagnostic criteria for NPS such as apathy, agitation, and psychosis in neurocognitive disorders and an MBI diagnosis is encouraged to establish clinically relevant NPS.[27-31]

Establishing the effectiveness of non-pharmacological interventions targeting neuropsychiatric symptoms in dementia

Outcome measures

The evaluation of the efficacy of non-pharmacological interventions for NPS in dementia relies strongly on valid and reliable outcome measures. We selected QoL as primary outcome for the study described in chapter 4.1 given the substantial impact of NPS on QoL of people with AD dementia and their caregivers.[6,39,40] However, while conducting the intervention study, we experienced that the DICE approach did not directly address QoL dimensions assessed such as physical health, relationship with family, and financial problems.[314,321] Instead, the non-pharmacological strategies applied mainly revolved around educating patients and caregivers on the origins of NPS, enhancing skills to manage NPS among caregivers, and encouraging patients and caregivers to assemble family and friends to assist and support them. The quantitative outcomes presented in chapter 4.2 align with this experience showing no significant improvement in QoL following the DICE method, while we found a trend towards significant improvement in confidence managing NPS among caregivers who followed the intervention. Future studies should therefore focus less on measures of QoL, but instead include measures of dementia knowledge and self-efficacy to better cohere to the content of the interventions evaluated.

Design of the intervention

There were several challenges related to the content of the intervention described in chapters 4.1 and 4.2. First, we aimed to address all potential NPS observed in the early clinical stages of AD dementia. This led to the inclusion of a heterogeneous group of individual who exhibited NPS that ranged from subtle to very severe symptoms and consisted of affective symptoms, agitation-related behaviors, and psychotic symptoms

(chapter 4.2). Consequently, the strategies provided were also very heterogeneous and required creativity to ensure that strategies were adequately adjusted to individual preferences and context. However, this creative process of brainstorming solutions lies at the very core of managing NPS in dementia.[100] Moreover, allowing the inclusion of all NPS regardless of severity and type enabled us to study the effects of the DICE method when applied in a representative memory clinic population.

The intervention consisted of two sessions in which NPS were described, underlying causes were investigated, and targeted strategies were discussed (chapter 4.1). Based on our own experience and that of the participants, the number of visits was considered sufficient to assess and address mild NPS, while the number of visits was considered insufficient to address severe NPS (e.g. aggression or psychotic symptoms), NPS that occurred in the context of pre-existing relationship problems or pre-morbid personality disorders, or NPS with co-occurring very severe cognitive impairment. This shows the need to identify patients based on the severity of NPS and the context in which they occur to provide them with additional support. Furthermore, the implementation of strategies was difficult for all NPS as researchers experienced that the evaluation step mainly consisted of repeating strategies that were advised during the initial visits. This emphasizes the need to provide ongoing help to facilitate the implementation of strategies provided. The web-based tool *WeCareAdvisor* developed by the researchers who created the DICE method might offer such support.[327]

Future directions

Moving from neuropsychiatric symptoms to syndromes

NPS is an umbrella term covering a wide range of specific symptoms. These specific symptoms presumably have different underlying mechanisms and therefore need different treatment approaches.[289] Physicians working at the memory clinic indicated that they indeed guide their interventions for NPS based on this notion (chapter 3.2). However, current theories and models on the etiology of NPS do not explicitly differentiate between specific symptoms.[54,55] Therefore, new theories and models are needed that allow individual symptoms to have a unique set of determinants.[414] An example of such a model is provided by Massimo and colleagues who present an integrative theoretically informed model of apathy in dementia showing the unique set of its contributory factors that provide great starting points for interventions.[415]

One step further, the complexity of individual symptoms are generally neglected when using scales such as the NPI. For example, apathy, agitation, and depression are considered symptoms when assessed using the NPI,[84] while research suggests that these are rather syndromes of symptoms consisting of different dimensions (e.g. cognitive, affective, and behavioral apathy).[27-29] Future research should therefore shift to the use of either symptom-specific scales or diagnostic criteria

for NPS syndromes to studying the prevalence, course, and treatment of NPS in AD dementia.

Studying the evolution of neuropsychiatric symptoms from a complex systems perspective

Chapters 2.1 and 2.2 spark the discussion around whether the substantial within-person variation in NPS instruments arise from methodological issues related to the scales used or reflect the fluctuating nature of NPS in AD dementia. This discussion cannot be resolved based on the data provided in this thesis. However, the *complex systems approach* to psychopathology might provide avenues for future research. This approach postulates that psychiatric symptoms and mental disorders should not be seen as a fixed condition with a root cause, but rather as a temporal dynamic state that arise from the interaction between biological, psychosocial, and socio-cultural processes.[416,417] Because the exact configuration of such interactions will be completely person-specific, a complex systems approach assumes that psychosocial states are highly individual and context specific. However, universal patterns may be found in the dynamics of psychological phenomena requiring individual time series data. Most of these dynamics are found to change in a nonlinear and irregular manner and complex systems approaches focus on these changes.[418] More importantly, while fluctuations are usually considered noise in regression-based approaches, fluctuations are of main interest in a complex systems approach and thought to precede phase transitions between dynamic states thereby providing valuable clinical information.[417,419] The complex systems theoretical model and its associated research methods are increasingly used in the social and medical sciences, e.g. to study the onset of psychiatric conditions,[420,421] and to predict clinical improvement following psychosocial interventions.[422,423] To date, this approach has received little attention in dementia research

Regarding the evolution of NPS in AD, complex systems theory can be used to gain more insight in the degree to which fluctuations in proxy-based measures of NPS reflect measurement error or have clinical meaning. These analyses require time series with many time points that can be collected using daily ecological momentary assessments (EMA).[424] Testing whether time series are dependent on past values can inform the degree to which fluctuations are random and therefore arise from measurement error.[425] Also, particular states and transitions between dynamic states can be identified in time series of individual patients. Examples of such states include weeks or days with severe NPS or little NPS, but also weeks or days with highly fluctuating NPS or stable NPS. These states can then be linked to co-current factors related to the patient (e.g. discomfort), caregiver (e.g. stress), or environment (e.g. activities) to provide insight in contributory factors of NPS. Note that these analyses are

conducted at the level of individual patients as a dynamic systems approach assumes physiological states to be highly individual and non-stationary.[416]

Challenges to be overcome in order to improve care for neuropsychiatric symptoms at the memory clinic

Clinicians have reported challenges while diagnosing and treating NPS in AD across different care settings.[227,229,292] This thesis extends this knowledge by identifying several unique challenges related to the memory clinic setting. These challenges are to be addressed in order to improve the care for NPS at the memory clinic.

First, memory clinic physicians should be informed about the prevalence and clinical relevance of NPS in prodromal AD and mild AD dementia. This includes educating physicians on the various ways NPS can manifest in the early clinical stages of AD and making them aware of the current diagnostic criteria for neuropsychiatric syndromes in dementia to improve agreement in terminologies used to describe NPS.[27-30]

Second, the lack of consensus among physicians on the role of the memory clinic in the care for NPS clearly hampers the diagnosis and treatment of these symptoms in the early clinical stages of AD. While a part of the memory clinic physicians argue that the memory clinic should be actively involved in the care for NPS in AD dementia, others claim that this should be designated to primary care providers such as general practitioners and case managers. It is imperative that care providers from memory clinics and primary care reach consensus on their role in the care for NPS in AD dementia in order to make clear who is responsible for the diagnosis and treatment of these distressing symptoms, at least at a regional level. Professional societies for neurologists, geriatricians, psychologists, and nurses and interdisciplinary organizations such as the *Nederlands Geheugenpoli Netwerk* [Dutch Memory Clinic Association] could provide a platform to discuss this issue.

In case of active involvement of the memory clinic in the care for NPS in AD, several actions are needed. First, a proactive screening of NPS is imperative in which self-reports, proxy-based instruments, and clinical judgments by clinicians are combined. Currently, NPS screening is often conducted for differential diagnostic purposes during the diagnostic phase of AD. However, these assessment should also be conducted once an AD diagnosis is established. Second, a proportion of the memory clinic physicians indicated a lack of knowledge regarding the application of non-pharmacological interventions to target NPS. Therefore, educational programs on non-pharmacological interventions for physicians are needed, possibly complemented with the involvement of psychologists, social workers, and/or geriatric nurses. Interventions such as the DICE method can be used as a framework to standardize and structure the non-pharmacological management of NPS in AD. In addition, several physicians

Box 5. Recommendations for memory clinic clinicians based on the findings of this thesis:

- Be aware that late-onset NPS can be an early or even first manifestation of AD. The gradual onset of symptoms, co-occurrence of cognitive deficits, a progressive deterioration over time, a positive family history of dementia, and no history of psychiatric conditions may point towards underlying AD.
- The prevalence of NPS based on proxy-based measures such as the NPI poorly correlate to future assessments within a timeframe of weeks.
- Be aware of sex and gender differences in the manifestation of NPS in AD dementia: females tend to exhibit more depressive symptoms, aberrant motor behavior, and psychotic symptoms, while males show more severe apathy.
- It is important to actively address NPS as patients and caregivers may feel hesitant to bring up NPS due to feelings of shame or guilt, difficulties describing NPS, or to prevent confronting the patient.
- It is advised to complement proxy-based NPS scales such as the NPI with clinician-based judgement to obtain an accurate picture of NPS in AD dementia.
- Caregivers who report high levels of NPS-related distress may benefit from a multidisciplinary stepwise care program to guide the assessment and management of NPS in AD.

emphasized the benefits of involving old-age psychiatrists while diagnosing and treating NPS in AD at the memory clinic (chapter 3.2), which should be payed attention to as the number of psychiatrists involved in memory clinics is declining in the Netherlands.[108]

Important to note that in case of designating the NPS care to primary care providers, additional educational and care programs are also needed as Dutch general practitioners, home care nurses, and case managers report a lack of knowledge and confidence managing NPS in AD.[400,401] In addition, the involvement of the memory clinic in the care for NPS in AD is not all black and white and regional differences may exists. For example, many memory clinic physicians indicated that the care for NPS greatly benefits from a close collaboration between hospital-based physicians and primary care providers (chapter 3.2). Most important here is that there is a care provider who is responsible for the care for NPS in AD who feels confident enough to manage these symptoms.

Conclusion

With this thesis, I tried to raise awareness for NPS in the early clinical stages of AD by highlighting its prevalence and clinical impact. Also, I have identified unique challenges related to the diagnosis and treatment of NPS in AD at the memory clinic. Based on these findings, I have suggested several avenues that warrant future research. All in all, I provided further evidence that AD entails more than memory deficits as NPS should be considered as one of the core features of early AD as well. Hereby, I hope to contribute to the timely recognition and adequate treatment of these distressing symptoms in AD, thereby improving the lives of people with AD dementia and their caregivers.

Chapter 6

Thesis summaries

English summary

Alzheimer's disease (AD) is often primarily perceived as a memory disorder. Although memory deficits form the clinical hallmark of AD, AD is more than memory as neuropsychiatric symptoms (NPS) are also nearly universal in individuals with AD. These symptoms cover a wide range of changes in mood, behavior, and perception including apathy, depressive symptoms, aggression, anxiety, and sleep disturbances. Individuals with AD and their caregivers consider these symptoms as most troublesome and distressing symptoms in AD.

At the start of this thesis, little was known about (1) the prevalence and course of NPS in the early clinical stages of AD, (2) the way NPS in AD are currently diagnosed and treated at the memory clinic, and (3) how the timely recognition and non-pharmacological treatment of NPS in AD could be improved in the memory clinic setting. This thesis addresses all of these knowledge gaps.

Chapter 2 focuses on the prevalence and course of NPS across the clinical stages of AD. Chapter 2.1 shows that NPS are common across the entire AD clinical spectrum ranging from normal cognition to dementia. Although NPS and cognitive symptoms are both prevalent, little cross-sectional and longitudinal associations were found between these symptoms suggesting that NPS and cognitive symptoms are independent manifestations of AD. Chapters 2.1 and 2.2 point out that the course of specific NPS is generally stable when looking at group-level, while individual patients show substantial fluctuations in NPS when assessed annually and even biweekly as well. These findings spark the discussion around whether these fluctuations reflect the fluctuating nature of NPS in AD or arise from the inability of NPS instruments to reliably assess NPS longitudinally. Furthermore, we conducted a systematic review to examine whether sex and gender differences could explain the heterogeneity observed in the manifestation of NPS in AD dementia (chapter 2.3). Depressive symptoms, psychotic symptoms, and aberrant motor behavior are more prevalent and severe among females with AD dementia, while apathy is more severe in males with AD dementia. These findings provide new hypotheses on the etiology of NPS in AD dementia and emphasize the need for tailored treatment.

Chapter 2 underline that NPS should be considered as a core feature of early AD. In addition, it shows that group-to-individual generalizability is limited regarding the course of NPS and highlights the importance of sex and gender differences in the manifestation of NPS in AD.

Chapter 3 provides an overview of the current state of care for NPS in AD. Chapter 3.1 reports on a case of a patient with severe NPS leading to a significant delay of an AD diagnosis and inappropriate care. This indicates that NPS are currently underrecognized as early manifestation of AD at the memory clinic. To further examine

the current care for NPS in AD at the memory clinic, we interviewed physicians working at the memory clinic (chapter 3.2). These physicians reported experiencing substantial challenges relating to the care for NPS in AD. Most prominent challenges were that the outpatient setting hampers adequate recognition and treatment of NPS, a lack of experience, knowledge, and/or resources to apply non-pharmacological interventions, and that there is no consensus among physicians on the role of the memory clinic in the care for NPS in AD. Chapters 3.3 and 3.4 report on studies that used electronic health records (EHRs) to obtain a unique insight in how clinicians currently perceive, diagnose, and treat NPS in memory clinics and residential aged care. Chapter 3.3 shows that natural language processing applications can be used to classify NPS in EHRs of individuals with AD who visited the memory clinic. NPS were frequently described in EHRs, while there was at best minimal agreement between NPS classified in the EHRs and NPS reported by caregivers. Chapter 3.4 revealed that residential aged care staff primarily detected and responded to those NPS they perceived as distressing, while less distressing NPS were underreported in EHRs. In addition, EHRs showed a lack of routine examination of causes and no systematic assessment and management of NPS.

Chapters 3 highlights that NPS are currently underrecognized in AD, which does not only entail that clinicians may not notice the presence of NPS in AD, but also that NPS are detected but not always recognized as part of early AD, and that NPS are detected but not always acted upon leading to undertreatment. In addition, inadequate treatment of NPS arises from a substantial variation in expertise, knowledge, and attitudes among clinicians. Finally, clinicians and caregivers hold a different perspective on NPS in AD.

Chapter 4 describes the protocol and outcomes of an intervention study that evaluated the Describe, Investigate, Create, Evaluate (DICE) method to improve early recognition and adequate treatment of NPS in early AD at the memory clinic setting. The DICE method was not effective and unlikely to be cost-effective when applied at the memory clinic in its current format. Future studies should examine the effectiveness of the DICE when evaluated only in individuals who show clinically relevant NPS.

Key findings, methodological considerations, and future directions are discussed in chapter 5. Main challenge for future researchers and clinicians is to develop new ways to assess NPS in the early clinical stages of AD, shift from neuropsychiatric *symptoms* to *syndromes*, better take intraindividual fluctuations of NPS into account, and to reach consensus about the role of the memory clinic in the care for NPS in the early clinical stages of AD.

With this thesis, I provided further evidence that AD entails more than memory deficits as NPS should be considered one of the core features of early AD as well. Hereby, I hope to contribute to the timely recognition and adequate treatment of these distressing symptoms in AD, thereby improving the lives of people with AD dementia and their caregivers.

Nederlandse samenvatting

Bij de ziekte van Alzheimer denkt men overwegend aan vergeetachtigheid. Alhoewel geheugenproblemen kenmerkend zijn voor de ziekte van Alzheimer, zijn er meer klachten die voorkomen bij deze vorm van dementie. Zo zien we bij nagenoeg alle mensen met de ziekte van Alzheimer ook neuropsychiatrische symptomen. Deze symptomen beslaan een divers spectrum aan veranderingen in emoties, gedrag en waarneming. Veelvoorkomende voorbeelden zijn initiatiefverlies, somberheid, prikkelbaarheid, achterdocht en slaapproblemen. Het zijn juist deze veranderingen die patiënten en hun naasten het meest lastig vinden om mee om te gaan.

Aan het begin van dit promotieonderzoek was er nog weinig bekend over (1) de prevalentie en het beloop van neuropsychiatrische symptomen in de beginfase van de ziekte van Alzheimer, (2) de manier waarop neuropsychiatrische symptomen momenteel worden gediagnosticeerd en behandeld bij mensen met de ziekte van Alzheimer, en (3) hoe de vroegtijdige herkenning en niet-medicamenteuze behandeling van neuropsychiatrische symptomen bij de ziekte van Alzheimer kunnen worden verbeterd. Dit proefschrift gaat in op al deze punten en in het bijzonder vanuit de geheugenpolikliniek. Bijna elk ziekenhuis in Nederland heeft een geheugenpolikliniek waar een team van neurologen, geriaters, psychologen, verpleegkundigen en psychiaters samen onderzoeken of er bij mensen met geheugenklachten sprake is van dementie.

Hoofdstuk 2 gaat over de prevalentie en het beloop van neuropsychiatrische symptomen tijdens de verschillende fases van de ziekte van Alzheimer. Hoofdstuk 2.1 laat zien dat neuropsychiatrische symptomen vaak voorkomen in alle fases van de ziekte van Alzheimer: van mensen met (nog) geen cognitieve stoornissen tot mensen met ernstige dementie. Alhoewel neuropsychiatrische symptomen en cognitieve stoornissen vaak voorkomen hangt de aanwezigheid van neuropsychiatrische symptomen niet samen met ernstigere cognitieve stoornissen. Dit suggereert dat neuropsychiatrische en cognitieve symptomen onafhankelijke uitingen zijn van de ziekte van Alzheimer. Hoofdstukken 2.1 en 2.2 laten zien dat het beloop van neuropsychiatrische symptomen doorgaans gelijk blijft is als men naar het groepsgemiddelde kijkt, terwijl individuele patiënten duidelijke schommelingen laten zien in symptomen wanneer deze jaarlijks of zelfs om de twee weken worden gemeten. Het blijft onduidelijk of deze bevindingen laten zien dat de symptomen zelf sterk fluctueren over tijd of dat dit ligt aan de manier waarop neuropsychiatrische symptomen momenteel worden gemeten. Ten slotte voerden wij een literatuuronderzoek uit om te achterhalen in hoeverre sekseverschillen een deel van de grote variatie in neuropsychiatrische symptomen tussen mensen met de ziekte van Alzheimer kunnen verklaren (hoofdstuk 2.3). Wij vonden dat doelloos repetitief gedrag (bijv. ijsberen), depressieve symptomen (bijv. somberheid) en psychotische

symptomen (bijv. achterdocht) vaker en in ernstigere mate voorkomen bij vrouwen met de ziekte van Alzheimer, terwijl apathie meer ernstig lijkt te zijn onder mannen met de ziekte van Alzheimer. Deze bevindingen vormen een boeiend startpunt voor nieuwe hypotheses over de oorzaken van neuropsychiatrische symptomen bij de ziekte van Alzheimer en pleitten voor een persoonsgerichte aanpak van deze symptomen.

Hoofdstuk 2 benadrukt dat neuropsychiatrische symptomen moeten worden erkend als een integraal onderdeel van de vroege fase van de ziekte van Alzheimer. Daarnaast laat het zien dat het beloop van neuropsychiatrische symptomen op groepsniveau weinig informatief is voor de individuele patiënt en onderstreept dit hoofdstuk het belang van sekseverschillen in het onderzoek naar neuropsychiatrische symptomen bij de ziekte van Alzheimer.

Hoofdstuk 3 geeft een overzicht van de stand van zaken omtrent de huidige zorg voor neuropsychiatrische symptomen bij de ziekte van Alzheimer. Hoofdstuk 3.1 presenteert een casus van een patiënt met ernstige neuropsychiatrische symptomen waardoor het lang duurde voordat de Alzheimerdementie diagnose werd gesteld. Dit laat zien dat het momenteel onvoldoende bekend is dat neuropsychiatrische symptomen een eerste uiting kunnen zijn van de ziekte van Alzheimer. Interviews met artsen werkzaam op verschillende geheugenpoliklinieken in Nederland lieten zien dat de zorg voor neuropsychiatrische symptomen bij de ziekte van Alzheimer erg lastig kan zijn vanwege uiteenlopende redenen (hoofdstuk 3.2). Hiervan waren de volgende redenen het meest belangrijk: het werken in het ziekenhuis terwijl neuropsychiatrische symptomen veelal thuis voorkomen, artsen ervaren een gebrek aan kennis, ervaring en/of faciliteiten om niet-medicamenteuze behandelingen toe te kunnen passen en er is geen consensus onder artsen over de rol van de geheugenpolikliniek binnen de zorg voor neuropsychiatrische symptomen bij de ziekte van Alzheimer. Hoofdstukken 3.3 en 3.4 beschrijven studies die gebruik maakten van elektronisch patiëntendossiers om een unieke inkijk te krijgen in de manier waarop zorgprofessionals momenteel neuropsychiatrische symptomen waarnemen, diagnosticeren en behandelen. Hoofdstuk 3.3 laat zien dat machine learning toepassingen kunnen worden gebruikt om neuropsychiatrische symptomen te classificeren in patiëntendossiers van mensen die met de ziekte van Alzheimer de geheugenpolikliniek bezoeken. Neuropsychiatrische symptomen worden vaak beschreven in deze patiëntendossiers, maar er is nauwelijks overlap tussen de symptomen die zorgprofessionals beschrijven in het patiëntendossier en de symptomen die naasten van dezelfde patiënten rapporteren op een gestructureerd interview. Hoofdstuk 3.4 toont dat het zorgprofessionals werkzaam in verpleeghuizen voornamelijk neuropsychiatrische symptomen in patiëntendossiers beschrijven die voor hen als belastend worden ervaren (bijv. agressie en dwalen) terwijl er een onderrapportage lijkt van minder belastende symptomen (bijv. intiatiefverlies en somberheid). Verder blijkt uit de patiëntendossiers dat er doorgaans

geen sprake is van een aanbevolen gestructureerde analyse van neuropsychiatrische symptomen en onderliggende oorzaken.

Hoofdstuk 3 brengt aan het licht dat er momenteel sprake is van een onder (h)erkenning van neuropsychiatrische symptomen bij de ziekte van Alzheimer. Dit betekent niet alleen dat neuropsychiatrische symptomen soms worden gemist door zorgprofessionals, maar ook dat deze symptomen niet altijd worden erkend als integraal onderdeel van de vroege fase van de ziekte van Alzheimer en dat neuropsychiatrische symptomen wel worden herkend, maar hier vervolgens niet op wordt geanticipeerd wat tot een onderbehandeling leidt. Verder belemmeren de grote variatie in expertise, kennis en visies op de rol van de geheugenpolikliniek de zorg voor neuropsychiatrische symptomen bij de ziekte van Alzheimer.

Hoofdstuk 4 beschrijft het protocol en de uitkomsten van een interventie studie dat onderzocht of de *Describe, Investigate, Create, Evaluate* (DICE) methode kan bijdragen aan vroegtijdige herkenning en evidence-based behandeling van neuropsychiatrische symptomen bij de ziekte van Alzheimer op de geheugenpolikliniek. De DICE methode liet geen duidelijke meerwaarde zien en is waarschijnlijk niet kosteneffectief in de vorm waarin deze methode werd aangeboden. Toekomstig onderzoek moet uitwijzen of mensen met aanzienlijke neuropsychiatrische symptomen wel baat hebben bij de DICE methode.

De belangrijkste uitkomsten, methodologische overwegingen en visie op toekomstig onderzoek worden besproken in hoofdstuk 5. Voor onderzoekers en zorgprofessionals is het noodzaak om nieuwe manieren te ontwikkelen om neuropsychiatrische symptomen op een passende manier te meten binnen de vroege fase van de ziekte van Alzheimer, om de focus van neuropsychiatrische *symptomen* te verleggen naar *syndromen*, om rekening te houden met de individuele schommelingen in neuropsychiatrische symptomen en om overeenstemming te bereiken over welke rol de geheugenpolikliniek zou moeten spelen in de zorg voor neuropsychiatrische symptomen bij mensen in de vroege fase van de ziekte van Alzheimer.

Met dit promotieonderzoek heb ik duidelijk willen maken dat de ziekte van Alzheimer meer is dan vergeetachtigheid aangezien ook neuropsychiatrische symptomen integraal onderdeel vormen van deze aandoening. Hiermee heb ik een bijdrage willen leveren aan de vroegtijdige herkenning en behandeling van deze belastende symptomen om zo de levens van mensen met de ziekte van Alzheimer en hun naasten te verbeteren.

Meer informatie mediaberichten over de bevindingen van dit proefschrift zijn te vinden op: https://linktr.ee/presswillemeikelboom

About the author

Willem Sake Eikelboom was born on January 17th 1994 in Leeuwarden. Willem completed his high school in Zwolle in 2012, after which he moved to Nijmegen to start his bachelor in Psychology at the Radboud University. During his bachelor, Willem participated in the Honors Program, which provided him the opportunity to do clinical internships at the Vincent Van Gogh Institute for Psychiatry and a research internship at the Radboudumc studying cognitive reserve in young-stroke. These experiences sparked his fascination for the various ways people cope with brain damage of different kind. After a short intermezzo of several months as clinical intern at the Center for Autism at the University Medical Center of Dresden in Germany, Willem started the master Healthcare Psychology at the Radboud University in February 2016. He was a clinical intern at the Department of Neuropsychology at the Erasmus MC until the beginning of 2017, while simultaneously writing this master thesis on a new language screenings instrument for Primary Progressive Aphasia. After completing his Master's degree cum laude, Willem moved back to Nijmegen to work as a research assistant at the Department of Geriatrics of the Radboudumc.

In January 2018, he started his PhD on neuropsychiatric symptoms in Alzheimer's disease at the Alzheimer Center Erasmus MC in Rotterdam under the supervision of dr. Janne Papma, dr. Esther van den Berg, and dr. Rik Ossenkoppele. During his PhD, Willem visited the lab of dr. Moyra Mortby at the Neuroscience Research Australia institute in Sydney. Also, he was board member of the Science Café Rotterdam and the Neuropsychiatric Syndromes Professional Interest Area of the Alzheimer's Association. He completed his PhD in the summer of 2022.

In September 2022, he started his post-doctoral training to become a licensed healthcare psychologists [GZ-psycholoog] at the Consortium Psychologische Vervolgopleidingen Venray e.o., which he combines with a position as post-doc researcher at the Center of Excellence for Korsakoff and Alcohol-Related Cognitive Disorders at the Vincent Van Gogh Institute for Psychiatry. Currently, Willem lives in Nijmegen enjoying having friends, his band *blikwinkel*, and nature around.

PhD Portfolio

	Year	ECTS
Courses		
Basic course on Endnote (Erasmus MC)	2018	0.1
BROK cursus (NFU)	2018	1.5
Preventing Failed Interventions in Behavioral Research (NIHES)	2018	1.4
Analysis of Qualitative Data (Evers Research & Training)	2018	0.6
Patient Oriented Research: design, conduct, and analysis (CPO)	2018	0.3
PhD Day (Erasmus MC)	2018	0.2
Basic Course on R (MolMed)	2018	1.0
Personal Leadership & Communication (MolMed)	2019	1.0
Academic Writing (MolMed)	2019	2.0
Research Integrity (Erasmus MC)	2020	0.3
Total		9.2
Teaching activities		
Lectures 4 Alzheimercafes Gorinchem, Rotterdam, Vlaardingen	2018–2021	1.2
Workshop Vrijwilligersdag Alzheimer Nederland	2018	0.3
Lecture Dankavond Vrijwilligers Alzheimer Nederland	2019	0.3
Lecture for geriatricians and geriatricians in training Erasmus MC	2019	0.3
Workshop Deltaplan Dementie Jaarevent	2019	0.3
Lectures Neuropsychological Assessment bachelor Medicine Erasmus MC	2020–2021	0.6
Lecture Symposium Young Onset Dementia ConForte	2020	0.3
Workshop ZonMw Post diagnostic Care for Dementia	2020	0.3
Lecture Webinar Alzheimer Center Erasmus MC	2021	0.3
Supervision thesis of 8 master students Medicine/Psychology	2018–2022	16.0
Total		19.9
Conferences		
Dementie Update (attendance)	2018	0.3
Symposium Psychosociale Innovaties bij Dementie (attendance)	2018	0.3
Alzheimer's Association International Conference (poster presentation)	2018	2.5
Nederlandse Vereniging voor Neuropsychologie (attendance)	2018	0.3
Nederlands Geheugenpoli Netwerk (poster presentation)	2018	0.5
Jaarevent Deltaplan Dementie (attendance)	2018	0.3
ACE Alzheimer Day Erasmus MC (poster presentation)	2019	0.5
Australian Dementia Forum (oral presentation)	2019	1.0
Alzheimer's Association International Conference (oral presentation)	2019	2.5
Alzheimer Europe (poster presentation)	2019	1.5
Nederlandse Vereniging voor Neuropsychologie (attendance)	2019	0.3
Alzheimer's Association International Conference (poster presentation)	2020	2.5
International Psychogeriatric Association (oral presentation)	2020	1.0
Nederlandse Vereniging voor Neuropsychologie (attendance)	2020	0.3

Geriatriedagen (poster presentation)	2021	0.5
Alzheimer's Association International Conference (poster presentation)	2021	2.5
Nederlandse Vereniging voor Neuropsychologie (attendance)	2022	0.6
Alzheimer's Association International Conference (oral presentation)	2022	2.5
Total		19.9

Board membership

Science Café Rotterdam – board member (chair 2019-2021)	2018–2021	3.0
Neuropsychiatric Syndromes PIA ISTAART–committee member	2019–2022	2.0
Total		5.0

Grants

Travel grants for conference visits	2018–2020	€2k
Alzheimer Nederland/Erasmus Trustfonds		
Fellowship grant for international research NeuRA Sydney	2019	€3k
Alzheimer Nederland		
Fellowship grant international research NeuRA Sydney	2019	€750,-
Erasmus Trustfonds		
Co-PI: Knelpuntenanalyse Onbegrepen gedrag in de thuissituatie	2021–2022	€50k
ZonMw		

Other activities

Weekly research meetings Alzheimer Center Erasmus MC	2018–2022
Book reviewer *Tijdschrift voor Neuropsychologie*	2019–2022
Peer reviewer panel member	2019–2022

Alzheimer's & Dementia, Annals of Clinical and Translational Neurology, Brain and Behavior, Journal of Alzheimer's Disease, Journal of Geriatric Psychiatry and Neurology, Journal of Medical Internet Research, Journal of Neuropsychological Society, Neurobiology of Aging, Neuropharmacology, Neuropsychological Review.

List of publications

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Eikelboom WS, Spikman JM. Sociale Cognitie en Emotie. In: Kessels RPC, van den Berg E, Ponds R, Spikman J, van Zandvoort M, eds. *Klinische Neuropsychologie*. Meppel: Uitgeverij Boom; 2022: 259-282.

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Abbreviations

A+ = β-amyloid–positive
AA = Alzheimer's Association
AD= Alzheimer's disease
AES-I = Apathy Evaluation Scale Informant version
A-IADL-Q = Amsterdam Instrumental Activities of Daily Living Questionnaire
AMB = aberrant motor behavior
AUC = area under the curve
Aβ = amyloid-beta
BEAT-IT = BEhavioural symptoms in Alzheimer's disease Towards early Identification and Treatment
BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale
BPSD = behavioral and psychological symptoms of dementia
bvAD = behavioral variant of Alzheimer's disease
bvFTD = behavioral variant of frontotemporal dementia
CAU = care as usual
CDR = Clinical Dementia Rating Scale
CI = confidence interval
CIRS-G = Cumulative Illness Rating Scale for Geriatrics
CMAI = Cohen-Mansfield Agitation Inventory
CMAI-D = Dutch version of Cohen-Mansfield Agitation Inventory
CRF = case report form
CSDD = Cornell Scale for Depression in Dementia
CSF = cerebrospinal fluid
DICE = Describe, Investigate, Create, Evaluate
DLB = dementia with Lewy Bodies
DSM = Diagnostic and Statistical Manual
EHR = electronic health record
FDG-PET = fluorodeoxyglucose positron-emission tomography
FDR = false discovery rate
IADL = instrumental activity of daily living
ICD = International Classification of Diseases
ICECAP-O = ICEpop CAPability measure for Older people
iMTA iVICQ = Institute for Medical Technology Assessment Valuation of Informal Care Questionnaire
iMTA MCQ = Institute for Medical Technology Assessment Medical Consumption Questionnaire
LLM = linear mixed model
MBI = mild behavioral impairment
MCI = mild cognitive impairment
MMSE = Mini-Mental State Examination
MRI = magnetic resonance imaging
NIA = National Institute on Aging
NICE = National Institute for Health and Care Excellence
NLP = Natural Language Processing
NPI = Neuropsychiatric Inventory
NPI-C = Neuropsychiatric Inventory-Clinician rating scale
NPI-Q = Neuropsychiatric Inventory questionnaire
NPS = neuropsychiatric symptoms
OR = odds ratio
PCC = patient-centered care
PET= positron-emission tomography
QALY = quality-adjusted life years
QoL = quality of life
QoL-AD= Quality of Life in Alzheimer's Disease questionnaire
RAC = residential aged care
RAID = Rating Anxiety in Dementia
SCD = subjective cognitive decline
SDI = Sleep Disorder Inventory
SRQR = Standards for Reporting Qualitative Research

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more than memory

Alzheimer's disease is often perceived as a memory disorder. However, Alzheimer's disease is more than memory deficits as nearly all individuals with Alzheimer's disease show neuropsychiatric symptoms such as apathy, depressive symptoms, aggression, anxiety, and sleep disturbances. Individuals with Alzheimer's disease and their caregivers consider these symptoms as most troublesome and distressing.

This thesis shows that neuropsychiatric symptoms are already prevalent in early Alzheimer's disease. Although neuropsychiatric symptoms are common, this thesis emphasizes that there is a large heterogeneity between and within individuals regarding the course of these symptoms over time. Furthermore, this thesis highlights that neuropsychiatric symptoms are currently underrecognized in Alzheimer's disease and reveals that there is no consensus among physicians on the role of memory clinic in the care for neuropsychiatric symptoms in Alzheimer's disease. Finally, this thesis presents a person-centered intervention that can be used to timely diagnose and manage neuropsychiatric symptoms in Alzheimer's disease at the memory clinic.

This thesis provides further evidence that Alzheimer's disease entails more than memory deficits as neuropsychiatric symptoms should be considered one of the core features of early Alzheimer's disease as well. Doing so, this thesis hopes to contribute to the timely recognition and adequate treatment of these distressing symptoms, thereby improving the lives of people with Alzheimer's disease and their caregivers.