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Neuropsychiatric Symptoms in Alzheimer's Disease: Associations with Beta Amyloid and Potential New Cutoff Points on Neuropsychiatric Assessment Scales

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Abstract

Neuropsychiatric Symptoms (NPS) have been shown to be associated with Alzheimer's disease (AD). They negatively affect disease outcome and could play a future role in the detection of prospective AD cases. In the present study we aimed at examining the relation between NPS and Amyloid beta (Ab) in both a cognitively healthy (N = 200) and cognitively impaired (N = 224) dataset from the Swedish BioFINDER study separately. Simple/multiple linear regressions, including covariates, were computed to estimate the strength of the association between NPS and Ab. ROC analyses were computed to calculate a new cutoff point on NPS scales based on positive/negative Ab status. The statistical analysis did not yield any significant results. The result in the cognitively healthy sample for Ab levels predicted by informant-rated apathy was borderline significant. Compared to reference cutoff points on NPS scales, the newly calculated cutoff points were lower. Future research on NPS in AD should employ longitudinal research designs and look at comorbidities with other neurodegenerative diseases. A better understanding of NPS in AD may establish NPS as an ’at- risk’ state for future AD and other dementias, increase the use of NPS in the clinical setting, and thus aid in identifying prospective AD cases.

Keywords: Alzheimer's disease, dementia, neuropsychiatric symptoms, apathy, cognitively healthy, cognitively impaired, ROC analysis

Introduction

The prevalence of Alzheimer's disease (AD) and other forms of dementia has been increasing steadily along with life expectancy. The total number of AD cases around the world has increased by more than 100% from 1990 to 2019 (Javaid et al., 2021). Moreover, according to the World Health Organization (WHO), AD was the seventh-leading cause of death worldwide, even surpassing the numbers of road injuries or diabetes (WHO, 2020). Fortunately, in recent years, great progress has been made in the development of potentially effective interventions for AD. Newly developed, disease-modifying therapies that work by altering the amyloid-ß metabolism in the brain (van Dyck et al., 2022) present a potential breakthrough in the future treatment of AD, but work best when started as early as possible in the disease process. While cognitive decline is strongly related to the onset of AD (American Psychiatric Association, 2013), Neuropsychiatric symptoms (NPS) have been closely associated with AD as well (Steinberg et al., 2008).

On Overview on Alzheimer's Disease

AD is a progressive brain disease characterized by cognitive decline. The hallmarks of the disease are worsening memory problems, particularly in the domain of episodic memory (Gaugler et al., 2022), thus memories regarding past events and experiences (Allen & Fortin, 2013). When talking about AD, it is important to demarcate it from dementia. The term dementia comprises a group of cognitive symptoms, such as memory problems and other forms of cognitive impairment, that interfere with the daily life of the sickened individual, caused by damage to the brain (American Psychiatric Association, 2013). AD, in turn, is one possible cause of dementia and makes for 60% to 80% of all dementia cases (Gaugler et al., 2022). The brain changes associated with AD lead to a variety of cognitive, behavioral, and emotional symptoms in the patients that include the main symptom of memory loss, confusion, deficiencies in problem-solving skills, disturbed sleep, anxiety/depression, social withdrawal, and more (Gaugler et al., 2022). AD does not only reduce the quality of lifes of

the patient itself, but also negatively affects the life of caregivers and family (Medrano et al., 2014). Worldwide estimates for the financial costs of dementia were US$604 billion in 2010 (Wimo et al., 2013). Considering the harm AD and other types of dementia are causing and the fact that this will become an even bigger problem in the future due to increased longevity, it should be evident that more research on this debilitating disease is necessary.

Neuropsychiatric Symptoms in AD

NPS are very common in dementia and thus represent a fundamental symptom category next to cognitive symptoms, as, according to Steinberg et al. (2008), 97% of dementia patients present with NPS. In a meta-analysis by Zhao et al. (2016), the prevalence of different NPS in AD has been described. Apathy was the most frequently observed NPS, with an overall prevalence of 49%, followed by depression, aggression, anxiety, and sleep disorder, with a prevalence of 42%, 40%, 39%, and 39%, respectively. NPS worsen during the course of preclinical and clinical dementia and typically develop in three phases: (1) Depression, irritability, and nighttime behavior; (2) Changes in appetite, apathy, and agitation (3) Hallucinations, delusions, disinhibition, and motor disturbances.

Furthermore, a variety of important disease outcomes, that affect both the caregivers and the patient itself have been associated with NPS. Peters et al. (2015) found evidence for an accelerated disease progression and subsequently early death in mild dementia patients with increased NPS. Moreover, impaired activities in daily living and decreased quality of life have been associated with increased NPS (González-Salvador et al., 2000; Lyketsos et al., 1997). Beyond that, caregiver burden has been shown, more than cognitive symptoms, to be strongly related to NPS. (Isik et al., 2019). Finally, NPS have shown to predict earlier institutionalization among AD patients better than cognitive symptoms (Steele et al., 1990), while more severe symptoms and anxiety seem to be especially important (Gibbons et al., 2002; Tun et al., 2007).

Biomarkers of AD

Current literature emphasizes the need for early intervention in the disease progression of AD. This can only be achieved by detecting future AD cases before cognitive symptoms surface (Rasmussen & Langerman, 2019). Therefore, researchers have focused on establishing biomarkers that may indicate if a person is at risk of developing AD. Most prominently, beta-amyloid (Ab) between neurons and tau (tau tangles) within neurons of the brain have been identified as possible driving forces for AD pathogenesis. In short, according to the Amyloid Hypothesis, a genetic mutation of the amyloid precursor protein (APP) alters the processing of Ab in a maladaptive way that, compared to the Ab fragment 40 (Ab 40), an increased number of the neurotoxic Ab fragment 42 (Ab42) is produced (Eratne et al., 2018). Moreover, the other suspect, tau, which is responsible for the formation of axons and dendrites, takes part in AD pathogenesis. According to Alonso et al. (2001), hyperphosphorylated tau accumulates as neurofibrillary tangles, leading to neuron loss and other pathological developments. The presence of an abnormally high quantity of these protein deposits is responsible for a range of detrimental changes to the brain, where disturbances of neuron-to-neuron communication and brain inflammation lead to gradual brain atrophy. Both Ab and tau can be detected in the cerebrospinal fluid (CSF) (Hajjo et al., 2022).

Concerning Ab in CSF as a biomarker of AD, two important measures are those of either Ab42 or the ratio of Ab42 and Ab40: the Ab42/Ab40 ratio. A decrease in Ab42 levels in CSF can be regarded as a consistent discriminant between future AD patients, normal controls, and patients with other neurodegenerative diseases (Zou et al., 2020).

Cognitive Decline as a Risk Marker for AD

Next to the advancement in neurobiology, the cognitive domain has been of major interest in the search for warning signs of AD. Several tests, like the well-known Mini-Mental State Exam (MMSE) (Folstein et al., 1975), are used to predict conversion to dementia. One

of the clinical constructs that is closely related to AD is Mild Cognitive Impairment (MCI). A lower MMSE can be an indication of MCI, a thorough neuropsychological assessment (including tests of episodic memory, executive functioning, etc.,) however, may be a more precise indication of MCI (Bondi et al., 2014). According to the DSM-V, MCI patients present with modest decline in performance in at least one cognitive domain (attention, executive function, memory, etc.). In contrast to AD however, their capacity to independently carry out everyday activities is preserved (American Psychiatric Association, 2013). In respect to AD, the subclass of amnestic MCI (aMCI), i.e., cognitive decline including memory impairment, has emerged as the typical prodromal stage of AD. The MCI construct is essential because it may represent a transitioning phase from normal, cognitively unimpaired (CU) aging to dementia and has therefore emerged successfully. It can help identify AD cases at an early stage of disease progression (Petersen, 2016). Beyond cognitive and neurobiological indicators for the onset of AD, researchers have focused on a third domain within finding early signs for AD: NPS

Neuropsychiatric Symptoms before the Onset of AD

Signs of developing NPS are present in many MCI cases, a preceding condition to AD or other dementias. According to a meta-analysis by Martin and Velayudhan (2020), the prevalence of NPS in people with MCI ranges between 35% and 85%. Comparable findings have been made for the prevalence of NPS in people with Subjective Cognitive Decline (SCD), a condition where the client reports cognitive impairment, which can, however, not be determined with objective measures (Sheikh et al., 2018).

Beyond cognitively impaired populations, several recently published papers indicate that NPS are present even in older CU populations and may predict conversion to MCI, AD, and other dementias. Masters et al. (2015) found a significantly earlier presence of NPS in CU who later scored > 0 on the Clinical Dementia Rating Scale (CDR) (Morris, 1993). Both apathy and anxiety have shown to predict subsequent cognitive decline in CU clients and

patients with MCI (Johansson et al., 2020; Roberto et al., 2021). Moreover, longitudinal studies suggest that NPS may be a good predictor of the onset of cognitive symptoms in cognitively healthy older adults. Burhanullah et al. (2020) followed cognitively healthy adults for a mean of 5.73 years and found an association between NPI symptoms and a faster decline in verbal memory and other cognitive domains. A cohort study with 12,452 cognitively healthy, older participants across the USA by Liew (2020) examined the predictive value of three different NPS sub-facets on different subtypes of dementia. Psychotic symptoms significantly predicted the onset of all dementia subtypes, whereas affective and agitation symptoms significantly predicted AD and partially other dementias, like vascular dementia. Additionally, mental illness in earlier stages of life has been shown to increase the risk for dementia and earlier onset of dementia in a longitudinal study with 1.7 million New Zealand citizens (Richmond-Rakerd et al., 2022).

Moreover, NPS seem to predict the conversion rate to dementia in people with cognitive decline (Peters et al., 2013), a finding that has been confirmed in a recently published meta-analysis by van Dalen et al. (2018), where a 2-fold risk for MCI patients to receive a dementia diagnosis later in life was found when they were showing symptoms of apathy. Similarly, Ma (2020) found out that MCI patients with depressive/anxiety/apathy symptoms have more severe cognitive deficits and a higher conversion rate to dementia. In conclusion,

there is strong evidence for the role of NPS as a precursor to cognitive decline, AD, and other dementias, which suggests their use as a screening tool for prospective AD cases.

AD Neuropathology and NPS

Beyond the link between NPS and cognitive symptoms, research has demonstrated NPS to be associated with AD neuropathology. Evidence suggests that the amygdala and other subcortical brain regions related to psychiatric symptoms could play an important role in the early neuropathological stages of AD (e.g., increased tau deposition in the amygdala during

the early AD stages) (Nelson et al., 2018; Rosenberg et al., 2015). Marshall et al. (2013) found apathy to be associated with higher a cortical amyloid burden in MCI patients. This effect remained significant even after controlling for the age of the participants. Moreover, MBI has been linked to impairment of brain structures critical for memory and learning. More specifically, there seems to be a correlation between MBI symptoms in CU patients and a higher tau-PET signal in the entorhinal cortex and hippocampus, brain regions strongly associated with AD-related memory loss, i.e., 'hippocampal memory loss' (Dubois et al., 2009; Johansson et al., 2021).

Furthermore, contemporary research advocates a link between NPS and CSF biomarkers. According to Masters et al. (2015), the NPS of preclinical AD individuals with positive CSF biomarkers exacerbate quicker than those without. Further, apathy and anxiety, but not depression, have been demonstrated to be related with cerebral Ab deposition (Johansson et al., 2020). Moreover, Johansson et al. (2022) found evidence that Ab does not only exacerbate symptoms of apathy but that this effect is mostly independent from cognitive decline. According to the authors, this finding could be explained by dysfunctions in functionally different brain networks. Correspondingly, apathy has been associated with lower connectivity in the frontoparietal control network but not with other brain networks (Munro et al., 2015). Further, important evidence stems from a meta-analysis by Ng et al. (2021) about the associations between AD neuropathology (tau, Ab, and neurodegeneration) and NPS in CU and preclinical AD cases. Moderately consistent, yet weak, cross-sectional associations between NPS and Ab were found. On the contrary, conflicting evidence could be observed for the link between NPS and tau, or neurodegeneration. The authors explain this finding with the Hypothetical Cascade Model of Dynamic Alzheimer's Biomarkers, according to which Ab deposits temporally precede tau abnormalities, neurodegeneration, and cognitive decline (Jack et al., 2010).

NPS in the (Clinical) Diagnosis/Definition of AD

According to the most recent criteria for a clinical diagnosis of AD from the International Working Group for the Diagnosis of Alzheimer Disease (IWG) biomarker evidence alone should not be enough to diagnose AD. Thus, the specific clinical phenotype of AD, gradually worsening episodic memory impairment that can be associated with cognitive and behavioural changes in AD, must occur together with biomarker evidence (Dubois et al., 2021). In the IWG criteria, several subtypes of AD are described, among them, the behavioral-dysexecutive variant of AD (bvAD). In contrast to the other AD subtypes, bvAD is characterized by behavioural deficits (strongly linked to NPS), changes in personality, and an earlier onset of the disease. While bvAD is recognized as an AD variant, research on it is scarce, and there are no criteria for its diagnosis available (Ossenkoppele et al., 2022). Most recently, Ossenkoppele et al. (2022) developed a new set of research criteria, emphasizing the need for the implementation of bvAD, but clinical diagnoses are still lacking. One of the most prominent clinical definitions of AD is the description provided by the DSM-V (American Psychiatric Association, 2013). Here, AD is described as a neurocognitive disorder where one or more cognitive domains must be impaired. According to the DSM-V, probable AD should be diagnosed if there is either genetic evidence for AD or if clear evidence for a decline in memory and learning occurs together with a steadily progressive decline in cognition. Only in the 'associated features' part of the AD diagnosis, behavioural and psychological changes are listed as depression, irritability, apathy, etc. The DSM framework, however, does not provide any instructions on how these associated features are to be operationalized.

Despite NPS being mentioned in the diagnostic criteria for AD, diminutive attention is given to them. Conversely, in the recently proposed NiA-AA criteria research framework (Jack et al., 2018), awareness for the importance of NPS in AD is raised. In this conceptualization, neurobehavioral changes are part of the AD definition through all six diesease stages. Interestingly, in this framework, neurobehavioral changes, like the onset of

NPS, may be the primary complaint of the potential AD patient and can exist without the presence of objective cognitive decline. This conceptualization, however, has been developed for scientific purposes only and does therefore not play a role in the clinical practice of diagnosing AD.

Although NPS are not neglected in the aforementioned definitions, their underrepresentation in the clinical diagnosis of AD is problematic since NPS have been demonstrated to be potential risk markers for cognitive decline and future AD as elaborated in the previous paragraphs (Johansson et al., 2022; Johansson et al., 2020; Masters et al., 2015; Ng et al., 2021; Wise et al., 2019).

Future of NPS as a Risk Marker for AD

As reviewed in the preceding paragraphs, the literature on AD and potential ways to forecast the onset of the disease as early as possible has been steadily growing in the last years and decades. Research on NPS as a marker for forthcoming AD, at an early stage of the disease process, is relatively young and has only been intensified most recently. Lanctôt et al. (2017) postulate an array of goals for the research on NPS that include, among others: (1) the development of standardized, accurate outcome measures of NPS that are clinically meaningful; and (2) the continuation of examining biomarkers of NPS. Research on NPS and AD biomarkers is particularly new but has already produced promising results, as can be seen by the associations of NPS with CSF biomarkers and their potential to predict future conversion to AD (Johansson et al., 2022; Johansson et al., 2020; Masters et al., 2015; Ng et al., 2021; Wise et al., 2019).

Moreover, additional research on NPS as a marker of future AD is needed because cognitive markers and biomarkers of AD have been shown to be insufficient for forecasting AD under some circumstances. First, single administrations of cognitive measures alone might not be enough to detect MCI patients who later convert to AD, as demonstrated by Arevalo-Rodriguez et al. (2015), but should be combined with MMSE subscales or extended

with longitudinal MMSE measures (Arevalo-Rodriguez et al., 2015; Choe et al., 2020). Another promising opportunity, however, could be to add NPS as an extra component to a prediction model to increase the certainty of conversion to AD forecasting, as NPS' potential power to predict conversion from MCI to AD has already been demonstrated (Ma, 2020; Velayudhan, 2023). Second, in regard to CU patients, cognitive measures are no adequate indicator for future AD. For that reason, biomarkers are used to detect clients who are in the very early stages of the AD disease process. Biomarker tests, like CSF Ab or CSF tau are still relatively difficult to conduct, as they are invasive and cost time and money (Shaw et al., 2007). Furthermore, if no genetic risk markers or family history of AD is available, it is unclear how clinicians are supposed to make out potential candidates to conduct the laborious biomarker testing with. Considering the fact that NPS seem to precede cognitive decline in the development of AD and MCI, NPS could play an important role in identifying prospective AD cases among CU, who can then further examined with respect to biomarkers (Wise et al., 2019).

Problems with Available NPS Assessment Scales

The Apathy Evaluation Scale (AES) (Marin et al., 1991) and the Hospital Anxiety and Depression Scale (HADS) (Bjelland et al., 2002) represent two of the most commonly utilized assessment scales for NPS in clinical practice. These assessment scales, however, have not been developed to identify prospective AD cases but for the diagnosis of clinically relevant psychiatric disorders. A range of recent scientific publications indicate that (neuro-) psychiatric symptoms in the elderly exhibit themselves on a lower/subsyndromal level. Subsyndromal depression and anxiety are more common in the elderly than in other age groups and have been linked to MCI (Jain et al., 2023; Oh et al., 2019; Polyakova et al., 2014). Clarke et al. (2007) were one of the first to try to develop new cutoff points on NPS scales based on a clinical dementia population. To our knowledge, however, no study has been executed were cutoff points on NPS scales were used to predict amyloid beta status. Currently

available NPS assessment scales might therefore fail to detect subsyndromal NPS, due to prospective cognitive decline. This constitutes a problem in both research on NPS as risk markers for AD and for future clinical applications.

Another issue in research on NPS in AD is the hesitation within the scientific community to further explore them as a clinical risk marker due to their low specificity to reliably predict cognitive decline. Concerns regarding the specificity of NPS in predicting cognitive decline have been discussed in a paper by Ismail et al. (2016), one of the pioneers in the development of the MBI construct. Accordingly, behavioural changes in older age could always be an expression of late-life personality change or symptoms of subsyndromal psychiatric disorders. Similarly, Canevelli et al. (2016) question the use of NPS constructs for the screening of potential dementia patients, as, according to them, many elderly may exhibit some form of subsyndromal behavioural deficiencies and may therefore meet criteria as potential dementia candidates. This, in turn, could lead to overdiagnosis and cause unnecessary stress for the clients and caregivers. The inference from these concerns should, however, not be the dismissal of NPS as potential clinical AD/dementia markers but the further research and improvement of the criteria (Ismail et al., 2016; Liew et al., 2018). Furthermore, since overdiagnosing has been an issue for primary psychiatric disorders for decades (Thombs et al., 2019), low specificity should not be taken as a dead-end argument against NPS. Beyond the concern that NPS due to AD could be confused with psychiatric disorders, there is the issue of their fluctuating nature. This makes them hard to quantify and thus hard to determine whether they represent an underlying pathology or just normal mood/behavioural variations (Chung & Cummings, 2000).

One solution for the problems at hand could be to establish new cutoff points for the existing NPS assessment scales that are optimized for identifying potential patients who are at risk for MCI/AD. By doing so, subsyndromal NPS could become visible to the

researchers/clinicians and the problem of low specificity could be resolved too.

The Study at Hand

This study aims at further increasing the insight into the relation between NPS and CSF biomarkers in AD. More precisely, first it will be examined whether scores on NPS assessment scales have an association with CSF biomarker status. In the next step, new cutoff points on NPS scales will be computed based on CSF biomarker status and then compared to the currently available cutoff points. Since NPS' potential as a risk marker for AD is presumably best in AD stages before the onset of cognitive decline, the statistical analyses will be done separately for a CU and a cognitively impaired sample. Furthermore, covariates will be added to the regression models to see how cognitive assessment (MMSE) and demographic variables perform in a model together with NPS.

Consequently, the present research question is: 'What is the association between NPS and Ab levels?' The following two hypotheses will be tested:

1. Scores on NPS scales will be associated with CSF biomarker status.
2. The sensitivity and specificity of the cutoff points based on CSF biomarker status will be higher than those of reference cutoff points.

Method

Participants

In the present study, a dataset from the Swedish BioFINDER study was utilized. BioFINDER is a longitudinal cohort study with the aim of finding markers associated with early AD pathology. Data collection started in September 2010. Approval to use the data was given by Professor Oskar Hansson, the leading researcher of the BioFINDER study, who is affiliated with Lund University. Cases in the dataset are split into two groups: (1) Nomas BioFINDER cohort = Cognitively healthy and (2) TiDiS BioFINDER cohort = Mild cognitive symptoms/impairment.

The Nomas BioFINDER cohort consists of 350 cognitively healthy elderly and was recruited from a longitudinal population-based community cohort study in Malmö, Sweden (Manjer et al., 2001) and included to the BioFINDER study between 2010 and 2014. The inclusion criteria included no cognitive symptoms as evaluated by a clinician, age ≥ 60 y., MMSE 27-30, No MCI or dementia diagnosis, and sufficient understanding of Swedish. Exclusion criteria included unstable illness or organ failure, alcohol or drug abuse, refusing MRI/lumbar puncture, and substantial neurological/psychiatric illness. (BioFINDER, 2023a)

The TiDiS BioFINDER cohort consists of 500 patients with mild cognitive impairment or subjective cognitive decline that have been recruited from either the Memory Clinic at Skåne University Hospital or Ängelholm's Hospital in Sweden. The inclusion criteria included having been referred to the memory clinic at Skåne University Hospital or Ängelholm hospital in Sweden due to cognitive symptoms, age 60-80 y., MMSE 24-30, no dementia diagnosis, and sufficient understanding of the Swedish. Exclusion criteria included unstable illness or organ failure, alcohol or drug abuse, refusing MRI/neuropsychological assessment and other available explanations for the cognitive impairment (like brain infection, epilepsy, severe depression, etc.) (BioFINDER, 2023b).

Only participants with available data on the variables of interest (CSF Ab42 levels, apathy, depression, and anxiety assessment) were included in the study at hand.

Materials

Apathy, anxiety, and depression have been chosen as NPS because their association with CSF biomarkers has been documented in a variety of recent publications (Johansson et al., 2022; Johansson et al., 2020; Masters et al., 2015; Ng et al., 2021; Wise et al., 2019) and because their corresponding assessment scales are widely used in clinical practice and research (Bjelland et al., 2002; Radakovic et al., 2015).

The Apathy Evaluation Scale (AES) is a widely used tool in clinical and research practice to examine apathy in adult patients. Psychological constructs that are measured with

the AES include: general apathy, learning, interest in activities, lack of concern, and more. The questionnaire consists of 18 statements about the test subject that are rated on a 4-point Likert-type scale. Scores can range from 18 to 72; a lower score indicates the presence of apathic symptoms. An example of an item on the scale is 'S/he puts little effort into anything.' There are three different rater versions of the AES: clinician–rated, informant–rated, and self–rated (AES-C, AES_I, and AES-S, respectively) (Marin et al., 1991). In the study at hand, only the AES-S and the AES-I were used. A systematic review of the psychometric properties of the AES in neurodegenerative conditions by Radakovic et al. (2015) revealed adequate to excellent quality rating of the scale, with Cronbach's α values ranging from 0.69 to 0.95 in the included studies.

The Hospital Anxiety and Depression Scale (HADS) is a self-rated questionnaire that is widely used in clinical and research practice. It was developed to have a quick screening method to assess possible anxiety disorders and depression in nonpsychiatric hospital patients. The HADS consists of an anxiety subscale (HADS-A) and a depression subscale (HADS-D) with seven items for each construct. An example of an item on the HADS-A subscale is 'I get a sort of frightened feeling as if something awful is about to happen', and an example of an item on the HADS-D subscale is 'I still enjoy the things I used to enjoy'. The scoring on the items goes from zero to three, with a maximum of 21 points on each subscale; a higher score indicates the presence of anxiety or depressive symptoms (Zigmond & Snaith, 1983). A systematic review by Bjelland et al. (2002) found the HADS to perform well in the assessment of anxiety and depression in nonpsychiatric hospital populations.

The MMSE was used to evaluate participants' cognitive functioning. The MMSE is the most popular and commonly used testing tool for dementia. Typically, a cutoff of 24 is used to distinguish between cognitively normal functioning and dementia (Vyas et al., 2021). The MMSE has been shown to have good specificity and sensitivity across all educational and age groups (Hoops et al., 2009). Education level (in years) of the participants is ranked on a

scale ranging from 5 to 28.

CSF from the participants was acquired by means of lumbar puncturing. A common yet invasive technique that has been shown to cause minimal complications (Doherty & Forbes, 2014).

Reference Cutoffs on NPS Scales and CSF Ab42 Level

As one of the goals of this study is to test the effectiveness of new cutoff points on the AES and HADS to discriminate amyloid beta status on the AES and HADS, other cutoff points need to be used as a reference. For the AES scales, the cutoff points ≥ 41.5 and ≥ 36.5 for the AES-I and the AES-S, respectively, from the study of Clarke et al. (2007) will be used. As for the HADS scales, a cutoff point of ≥ 8 for both the HADS-A and HADS-D was used, as this cutoff indicates possible pathological levels of anxiety and depression and has been validated multiple times in both clinical and research practice. (Bjelland et al., 2002; Jerković et al., 2021).

The cutoff of the outcome variable CSF Ab42 level utilized in this study, was established during the BioFINDER study and is based on data from both the Nomas BioFINDER cohort and the TiDiS BioFINDER cohort. Individuals with a value < 502.2 on the biomarker CSF Ab42 are considered to have positive CSF Ab42 status, indicative of AD pathology.

Statistical Analyses

The statistical analyses of the data will consist of two main steps and will be performed separately for the Nomas and the TiDiS datasets.:

1. Linear regression models will be built to examine the relationship between the NPS scales and CSF Ab42 levels.
2. ROC analyses will be calculated to evaluate the performance of new cutoff points on NPS scales that are based on CSF Ab42 biomarker status.

To examine the relationship between the dependent variable of CSF Ab42 levels and the predictors AES-S score, AES-I score, HADS-A score, and HADS-D score, corresponding scatterplots will be created.

In the next step, four separate simple linear regression models with AES-S score, AES-I score, HADS-A score and HADS-D score as independent variables and CSF Ab42 levels as the outcome variable will be computed. Assumptions of simple linear regression (linearity, normality and homoscedasticity) will be checked. Further, simple linear regression models that produce a significant result will be extended to multiple linear regression with Age, Education level and MMSE added as covariates.

Receiver Operating Characteristics (ROC) analyses will be carried out to assess the power of scores on the NPS scales AES-S score, AES-I score, HADS-A score, and HADS-D to predict positive versus negative CSF Ab42 status. ROC analysis is a statistical procedure generally used to evaluate the predictive strength of a continuous variable to place a test subject in one category or another. In order to do so, a cutoff point on the continuous variable needs to be established (Pintea & Moldovan, 2009). The statistical procedure for the ROC analysis in the study at hand will go accordingly:

1. A logistic regression model will be built with the score on the NPS scale (e.g., AES-S score) as the independent variable and CSF Ab42 status as the outcome variable.
2. Predicted probabilities will be calculated based on the model of step 1 and added to the dataset.
3. A ROC analysis, including a ROC curve, will be computed with the predicted probabilities from step 2 as the predictor variable and CSF Ab42 status as the response variable. The ROC curve is a graph to illustrate the performance of the ROC analyses, with the Sensitivity (true positive rate) plotted on the Y-axis and the Specificity (true negative rate) plotted on the X-axis.

4. To retrieve the optimal cutoff on the NPS scale, the optimal threshold on the predicted probabilities will be extracted and then compared to the corresponding value on the NPS scale.
5. In a last step, the following model metrics will be computed: a) Sensitivity (true positive rate), Specificity (true negative rate), Area under the curve (AUC), Positive predictive value (proportion of positive predicted cases that are actually positive) (PPV), Negative predictive value (proportion of negative predicted cases that are actually negative) (NPV) (Pintea & Moldovan, 2009), and Youdens index (J) ((Sensitivity + Specifivity) – 1) (Fluss et al., 2005).
6. The Youdens index (J) of the newly calculated cutoffs and the reference cutoffs will be compared with each other.

Cutoff points will be judged based on their Sensitivity and Specificity; two statistical measures frequently used to evaluate the performance of a test. Sensitivity is defined as the probability of a positive test result in a truly positive case, whereas Specificity is the probability of a negative test result in a truly negative case (Monaghan et al., 2021). In the study at hand, the best cutoff point on a NPS scale will be defined as having the best combined sensitivity and specificity (Youdens Index (J).

All calculations and graphics were done with R Studio, R version 4.1.2 ‘Bird Hippie’ (RStudio-Team, 2020). For the ROC analyses the pROC package was used (Robin et al., 2011).

Ethics

The BioFINDER study has been ethically approved by the Swedish Ethical Review Authority (Etikprövningsmyndigheten, EPM), with decision number 2010/156. While the data contains sensitive medical information, the identity of the participants cannot be inferred due to anonymization.

Results

Demographics and characteristics of the Nomas and TiDiS datasets are displayed in Table 1 below. In this manuscript, non-significant results with $p > .1$ are labeled as 'trend level significant', and non-significant results near the $p = .05$ threshold are labeled as 'borderline significant'.

Table 1

Demographics and Records on the NPS Scales

Variable	Nomas	TiDiS
Sample size (*N*)	200	224
Age (years)	75.23±4.76	70.86±5.79
Gender (% men)	61.5%	51.3%
AES-S	28.03±5.70	32.56±8.81
AES-I	28.66±8.24	36.22±10.61
HADS-A	2.56±2.90	5.02±3.47
HADS-D	1.99±2.29	3.54±3.02
MMSE	28.9±0.97	27.64±1.74
Education level (years)	12.12±3.49	11.76±3.44
CSF Ab42 level (pg/ml)	574.63±215.03	537.48±243.58

Note. Numbers in the table indicate the mean and standard deviation (raw scores if not otherwise specified) for the corresponding variables for the Nomas and TiDiS datasets separately.

Simple/Multiple Linear Regressions

Assumptions for linear regressions were checked.

1. Assumption of linearity was partly violated as no clear linear relationship was displayed in the scatterplots.
2. Assumption of normality was not violated, as Quantile-Quantile (Q-Q) plot did not show any major deviations from the reference line.

3. Assumption of homoscedasticity was not violated, as the Breusch-Pagan test did not yield any significant results.

Four simple linear regression analyses were performed separately to predict CSF Ab42 levels based on AES-S score, AES-I score, HADS-A score, and HADS-D score. No significant regression equation was found for the TiDiS dataset. For the Nomas dataset, the regression coefficient for the AES-I score predicting CSF A42 levels was on a trend level significant (β = -4.21, p = .076). Table 2 and Table 3 show the results of the four simple regression analyses in the Nomas and TiDiS datasets, respectively.

Table 2

Summary of Simple Linear Regression Models Predicting CSF Ab42 Level in Nomas Dataset

Predictor	*β*	*SE*	*t(df)*	*p*
AES-S Score	-2.21	2.88	-0.77(173)	.443
AES-I Score	-4.21	2.35	-1.79(111)	.076*
HADS-A Score	0.06	5.64	0.01(181)	.991
HADS-D Score	-9.96	7.24	-1.38(180)	.170

Note. * p < .1. ** p < .05. *** p < .001. Table depicts four separately computed, simple linear regression results in the Nomas dataset.

Table 3

Summary of Simple Linear Regression Models Predicting CSF Ab42 Level in TiDiS Dataset

Predictor	*β*	*SE*	*t(df)*	*p*
AES-S Score	-0.01	2.02	-0.01(187)	.994
AES-I Score	2.51	1.79	1.40(166)	.164
HADS - A Score	1.83	4.91	.037(205)	.710
HADS - D Score	6.60	5.81	1.14(205)	.257

Note. * p < .1. ** p < .05. *** p < .001. Table depicts four separately computed, simple linear regression results in the TiDiS dataset.

Next, a multiple regression analysis was conducted with the trend level significant predictor AES-I Score in the Nomas and TiDiS datasets. MMSE, Education Level, and Age were added as predictors. While the multiple regression model in the Nomas dataset did not reach statistical significance [$F(4, 108) = 1.67$, $p > .05$, $R^2 = 0.02$], the coefficient AES-I Score reached borderline statistical significance ($\beta = -4.63$, $p = .052$), and the coefficient of the predictor MMSE was significant on a trend level ($\beta = -34.68$, $p = .093$). The coefficients of the model can be seen in Table 4. The multiple regression model in the TiDiS dataset did not reach statistical significance either [$F(4, 159) = 1.961$, $p > .05$, $R^2 = 0.02$], but the coefficient AES-I turned trend level significant ($\beta = 3.30$, $p = .076$). The coefficients of the model can be seen in Table 5.

Table 4

Multiple Linear Regression predicting CSF Ab42 Level in Nomas Dataset

Predictor	*β*	*SE*	*t*	*p*
Intercept	1471.48	706.122	2.08	.039**
AES-I Score	-4.63	2.36	-1.96	.052*
MMSE	-34.68	20.47	-1.69	.093*
Education Level	1.90	5.88	0.32	.747
Age	2.52	4.33	0.58	.562

Note. * $p < .10$. ** $p < .05$. *** $p < .001$. Table 4 depicts a Multiple Linear Regression Model predicting CSF Ab42 Level in the Nomas dataset. MMSE, Education Level and Age were added as Covariates to the independent variable AES I Score.

Table 5

Multiple Linear Regression predicting CSF Ab42 Level in TiDiS Dataset

Predictor	*β*	*SE*	*t*	*p*
Intercept	962.64	437.47	2.20	.029*
AES-I Score	3.30	1.85	1.78	.076*
MMSE	0.38	11.96	0.03	.974
Education Level	0.18	6.14	0.03	.977
Age	-7.80	3.47	-2.25	.026**

Note. * $p < .1$. ** $p < .05$. *** $p < .001$. Table 5 depicts a Multiple Linear Regression Model predicting CSF Ab42 Level in the TiDiS dataset. MMSE, Education Level and Age were added as Covariates to the independent variable AES I Score.

ROC analyses

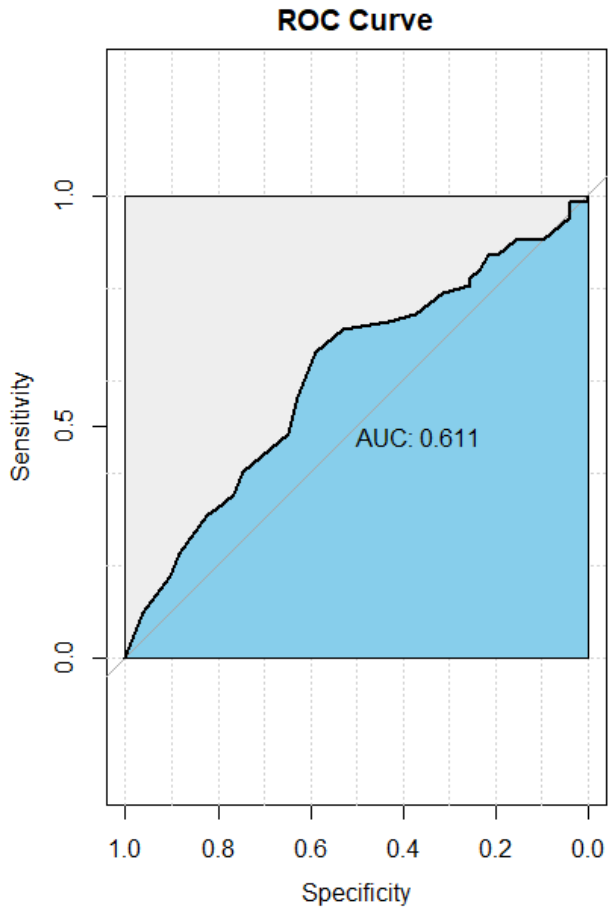
ROC analyses were performed for all four independent variables (AES-S score, AES-I score, HADS-A scorec and HADS-D score) and the categorical outcome variable (CSF Ab42 status) separately in the Nomas and TiDiS datasets. In the Nomas dataset, Youdens Index (J) of the new cutoffs were better for AES-S score (0.08 > 0.05), AES-I scores (0.25 > -0.06) and HADS-D score (0.12 > 0.07). Only for the HADS-A score (0.10 < 0.25), the reference cutoff performed better. The same pattern of results was observed for the TiDiS dataset with AES-S score (0.14 > 0.05), AES-I score (0.16 > 0.06), HADS-D score (0.14 > 0.05), and HADS-A score (0.05 < 0.13). Since only the AES-I score in the Nomas dataset predicted CSF AB42 levels significantly in the linear regression analyses, only the results of the corresponding ROC analysis will be depicted in detail here. Cutoff points, Sensitivity, Specificity, and model fit indices for the other ROC analyses can be found in tables in the Appendix.

The results of the ROC analysis in the Nomas dataset, with AES-I score as the predictor and the categorical outcome variable CSF Ab42 status, suggested that a threshold of ≥ 28 on the AES-I scale was the optimal cutoff point to classify subjects as having positive CSF Ab42 status. The sensitivity of the model was 0.66, and the specificity was 0.58. An

AUC of 0.61 and a J of 0.25 could be obtained. PPV and NPV were 0.41 and 0.34, respectively. The cutoff, of 42 obtained from Clarke et al. (2007) resulted in a sensitivity of 0.94 and a specificity of 0.06. The ROC curve of the model is depicted in Figure 1. Moreover, in the Nomas dataset, the ROC analysis with the HAD-A score reference cutoff point (HAD-A ≥ 8) as a predictor and CSF Ab42 status yielded a J of 0.25; sensitivity and specificity were 0.59 and 0.66, respectively. This J value was higher than all other J values except for the J obtained in ROC analysis with AES-I Score in the Nomas dataset described above.

Figure 1

ROC Curve of AES-I Score as a Classifier of CSF Ab42 Status



Note. Maximum values for both Sensitivity on the Y-axis and Specificity on X-axis are 1, resulting in maximus AUC of 1.

Discussion

The two main findings of this study are: 1.) NPS scales did not significantly predict CSF Ab42 levels; and 2.) On average, the newly calculated cutoff points based on CSF Ab42 levels performed badly, but better than the reference cutoff points.

In the CU sample, when implementing the AES-I score in a multiple regression model including covariates central to the topic, AES-I score predicted CSF Ab42 levels at a borderline significance level. ROC analyses revealed that AES-I score, in the CU sample seems to be the best among the NPS scales utilized in this study to discriminate between positive and negative CSF Ab 42 status. While there are a variety of studies that examine the association between NPS scales and CSF Ab 42 levels, to our knowledge, this is the first study that attempts to create cutoff points on NPS scales based on CSF Ab 42 positive/negative status.

The following discussion section will discuss non-significant yet trend/borderline significant results. While these results could be the product of chance, they should nevertheless be discussed, considering the magnitude of their effect sizes. The author acknowledges this mode of conduct is moving onto thin ice.

Findings on the Association between NPS scales and CSF AB42 levels

The Null findings of the study and the borderline significant result with the AES-I score in the CU sample are partially in line with the results of past research. The borderline significant result regarding the AES-I scale is in line with the findings of Vergallo et al. (2019) in a sample with probable AD. The authors found informant-rated apathy, measured with the NPI-Q, to be negatively associated with CSF Ab 42 levels. Furthermore, the results are partly in agreement with Johansson et al. (2020), who examined the association between the NPS apathy, anxiety and depression and Ab in a predementia sample. The AES-I score, and not AES-S score was associated with Ab deposition. Additionally, the results obtained in this study are further to a degree congruent with a longitudinal study by Johansson et al. (2022).

The authors in this study found baseline Ab pathology to be associated with increasing levels of informant-rated apathy over time.

Contrarily to the results regarding anxiety, Johansson et al. (2022) found a significant, yet weaker (compared to their results on informant-rated apathy), association between self-rated anxiety and baseline Ab pathology. These inconsistent results could be caused by the different research designs of the study. The study at hand is cross-sectional, with the mean age of the participants being 75.23 for the Nomas dataset and 70.86 for the TiDiS dataset. The participants in the study of Johansson et al. (2022) had a mean age of 73.8 at the time of the study but were 8 years older by the time of the final assessment. Therefore, it is possible that no significant effect could be found in this study because Ab deposition was lower in the present sample compared to the sample of Johansson et al. (2022), and Ab deposition is known to continuously increase during life (Rodrigue et al., 2012). More evidence inconclusive with the results regarding anxiety stems from a study by Krell-Roesch et al. (2018) from the Mayo Clinic Study of Ageing (MCSA) with 1039 CU subjects. The authors found Ab deposition to be weakly associated with symptoms of anxiety as measured on the Beck Anxiety Inventory (BAI) (Beck et al., 1988). Further, the authors found a marginal correlation with symptoms of depression on the Beck Depression Inventory (BDI) (Beck et al., 1961), as opposed to the results of the present study. A possible explanation for the discrepancy in the results on anxiety could be the different assessments of Ab levels between studies. Krell-Roesch et al. (2018) measured Ab deposition with positron-emission tomography (PET), while the present study assessed Ab42 levels in CSF.

In line with our Null findings on depression and anxiety is a cross-sectional study by Sun et al. (2008), who attempted to discriminate CSF Ab42/Ab40 ratios in CU individuals either with or without depression. Albeit the authors found weak associations between anxiety measured with the Beck Anxiety Inventory (Beck et al., 1988) and depression measured with the Beck Depression Inventory (BDI) (Beck et al., 1961), these associations were not

statistically significant. The authors explain their Null finding by the low anxiety and depression levels in their sample, an explanation that could apply to the present study as well. More evidence contrary to the findings on depression in this study are the results of a cohort study by Direk et al. (2013), who found a cross-sectional association between Ab levels and depressive symptoms in elderly people who later developed AD. According to the authors, their findings indicate that the association is due to prodromal AD, but since this association could not be found in the longitudinal analysis, the role of Ab during AD etiology varies along the disease process.

First, it must be noted that anxiety and depression were measured with the HADS, a self-administered questionnaire. In contrast to the findings on the AES-I, the results could therefore be compromised, as contemporary research suggests that cognitively impaired individuals might not have insight into their symptoms (Johansson et al., 2022). Moreover, differences in findings between studies could also be explained by the use of either CSF Ab42 levels or CSF Ab2/Ab40 ratio.

Furthermore, it is important to note that, even if the regression coefficient of AES-I was only borderline significant, AES-I performed better in predicting CSF Ab42 levels than MMSE. A potential explanation for this result is the supposed independence of apathy from cognitive impairment within the early stages of AD pathology, as suggested by Johansson et al. (2022). This finding is noteworthy since MCI is a well-respected risk marker for future AD (Petersen, 2016). Recent studies have, however, shown that brief cognitive tests like the MMSE might not be sufficient to establish an MCI diagnosis (Petrazzuoli et al., 2020). Finally, a conceivable explanation for the non-findings in this study is the violation of the assumption of linearity between independent and outcome variables.

NPS as a Classifier of Ab42 Status

Generally, the Sensitivity and Specificity obtained in the ROC analyses can be considered small. The best Js were found for the new cutoff on AES-I and the reference cutoff

on HAD-A, both in the Nomas dataset. This finding on AES-I corresponds well with the result of the simple/multiple linear regression analysis, while the finding on HAD-A does not. The different results can most likely be explained by the different statistical approaches. A simple/multiple regression model is more sensitive to small variations in the data as the outcome variable is continuous, and hence the variability is maximized. In contrast, a categorical model (like a ROC) may not perform well if variation between datapoints is low since it is told to 'force' the datapoints in either category. An analysis with a larger sample could probably account for this.

Although the J values (0.25) are low, they must be evaluated in a broader context. NPS will certainly not be able to forecast possible AD (or other dementias) as a single predictor. Other established variables like cognitive decline, genetic testing, or biomarkers will most likely remain a better predictor of possible AD/dementia. Nevertheless, NPS in specific contexts, combined with other predictors, could contribute to a better classification of possible AD/dementia cases.

The newly calculated cutoff points for NPS based on CSF Ab42 levels scales are altogether lower than the reference cutoff points. Regarding AES-I, there is a notable 14-point difference (28 vs, 42). Concerning the scientific discussion about the problem of low specificity of NPS as a predictor of cognitive decline, this result is rather sobering. A lower cutoff point increases the chance of a false positive. The new cutoff points might nonetheless be used as a future reference point when estimating them with a larger sample with the addition of other predictors.

Different Findings in Nomas and TiDis Dataset

Overall, the NPS scales worked similarly well in predicting CSF Ab42 levels and CSF Ab42 status in the Nomas and TiDiS datasets. One apparent difference between the datasets is the borderline significant result of AES-I and thus the better Sensitivity/Specificity in the ROC analysis that could only be observed in the Nomas dataset. This result is in line with the

finding of (Johansson et al., 2020) who found the association between Ab deposition and informant-rated apathy to be statistically significant only in a CU sample, but not in an MCI sample. The most striking difference lies in the effect direction of the AES-I coefficient in the regression analyses. In the Nomas dataset, a negative relation between AES-I score CSF Ab42 levels was found, indicating a link between higher levels of apathy and neuropathological AD processes. Regarding the TiDiS dataset, however, the data hints at a negative association between higher apathy levels and neuropathological AD processes. While neither of the regression coefficients reached statistical significance, this finding is still worth discussion in regard to the moderately good effect sizes. A possible explanation could be the increased comorbidity of AD with other dementia or psychiatric diagnoses in the TiDiS dataset, as later AD stages are associated with more comorbidities (Santiago & Potashkin, 2021). Since the results in the TiDiS dataset suggest that higher levels of apathy are associated with higher CSF Ab42 levels (a smaller chance of prospective AD), these high levels of apathy could be caused by comorbid diseases like psychiatric illness or other types of dementia and are therefore less strongly associated with CSF Ab42 levels than with comorbid diseases. Another explanation could be the varying role in etiology of Ab in AD as proposed by (Direk et al., 2013). A prospective research design with only Ab42 positive cases could be useful in further investigating these inconclusive results.

Another interesting result constitutes the finding on MMSE between the Nomas and TiDiS datasets. While in the Nomas dataset, the effect size of MMSE was large, if only significant on a trend level, the effect of MMSE on CSF Ab42 levels in the TiDiS dataset was not observed. One reason for this discrepancy in results could have been the very high standard error of the MMSE regression coefficient in both datasets, which could have led to a distortion of the effect sizes. Contemporary research acknowledges the limitations of short cognitive assessment scales (like the MMSE) in the assessment of cognitive decline and advocates for a more comprehensive cognitive assessment (Arevalo-Rodriguez et al., 2015) or

neuropsychological assessment for increased accuracy (Bondi et al., 2014). In the future, such neuropsychological assessment could possibly be aided by the inclusion of NPS. One more finding that needs to be interpreted is the association of age with CSF Ab42 levels in the Nomas dataset, or rather, the non-finding of this association in the TiDiS dataset. An association of age with CSF Ab42 levels would be expected since Ab deposition is known to linearly increase during life, even in healthy individuals (Rodrigue et al., 2012). The non-finding in the Nomas dataset could thus be the consequence of overall lower CSF Ab42 levels, compared to the TiDiS data, that veiled the association between the two variables. This explanation, however, is not in line with the interpretations about other findings of this study and should therefore be considered with caution. Hence, this finding necessitates further investigation.

Inconclusiveness of Results

As can be seen in both the findings in the study at hand and in the discussed literature of the field, there is a great variation in the results on NPS and Ab biomarkers. The reasons for this inconsistency are plenty, and many of them are yet unknown. While it is not possible to provide a thorough explanation for this circumstance in this research paper, we want to mention a selection of possible difficulties within the research field that could account for this inconclusiveness:

1. ***Different Study Designs and Different Assessments:***

   A good example of this aspect is the incongruency between the results on informant-rated vs. self-rated apathy in predicting AB deposition. One possible explanation is given by Johansson et al. (2022), who argue that cognitively impaired individuals could lose insight into their symptoms and thus underreport apathy compared to informants. Another case is the difference between longitudinal and cross-sectional studies. Cross-sectional studies cannot account for variations in NPS over time, and moreover, the role of Ab in progressing AD is most likely to vary (Direk et al., 2013).

Further, different measures of Ab deposition (PET, Ab42, Ab42/Ab42 ratio, etc.) will presumably yield different results and can therefore not be compared with each other directly (Weise et al., 2015).

2. ***Overlap of Psychological Constructs***

Psychological and psychiatric constructs are known to overlap tremendously, as can be seen by the high numbers of comorbidities in the field (Kessler et al., 2005). Regarding NPS, it has been argued that the conceptual overlap between anxiety, depression, and apathy might account for the inconsistent results between studies (Johansson et al., 2020).

3. ***Comorbidity in AD***

Pure AD is uncommon, especially vascular dementia has been shown to concur with it. Many symptoms of the two diseases overlap, and they probably even share a similar etiology (Craft, 2009). As a result, prognostic models for Ab deposition are unstable since it is hard to trace back the underlying cause of a specific predictor, like NPS. Consequently, the cooccurrence of AD and other neurodegenerative diseases makes it difficult to identify the causes of effects.

4. ***NPS as a Product of Neuropathology or Behavioral Consequence of AD***

NPS can be a product of the behavioral reaction to AD, as a sickened individual will exhibit abnormal levels of psychiatric symptoms when confronted with cognitive impairment like severe memory loss (Cerejeira et al., 2012). On the other hand, it has been shown that neuropathological processes may alter brain chemistry in a way that directly produces NPS, as can be seen in the example of apathy (Mehak et al., 2023). Consequently, the interpretation of NPS in the association of AD is difficult since it may not be clear whether they are caused directly by neuropathology or constitute a behavioral reaction.

Overall, the findings of the present study reflect contemporary research on NPS and AD CSF biomarkers, as they fit well in a research field that is characterized by an inconclusiveness of results.

Limitations and Strengths

The results of this study must be interpreted in light of some limitations. A limitation of this study is the relatively small sample size, that resulted in the relinquishment of splitting the data into a training and test dataset for the ROC analyses. This procedure would have allowed for a more accurate estimation of the model performance in future datasets and should thus be carried out in prospective research. A strength of the study is the quality of the utilized data. Since the Swedish BioFINDER cohorts were assessed and evaluated by professional clinicians and researchers, it can be assumed that the standards regarding ethics and accuracy of data collection were high (BioFINDER, 2023a, 2023b). On the other hand, a further limitation constitutes the absence of longitudinal analyses in this study. As it can be seen in previous research on the topic at hand, findings may vary significantly depending on whether cross-sectional or longitudinal research designs were employed. Yet another strength of this study is the use of both linear regression analyses and ROC analyses to estimate the predictive power of NPS scales. A linear regression analysis considers all the available variance and therefore allows for a precise estimation of associations between variables. A ROC analysis on the other hand, while neglecting some of the available variance, forces cases into a particular category, which is necessary when assessing the strength of a predictor for a potential clinical setting.

Furthermore, participants in the BioFINDER study in both the Nomas and the TiDiS cohorts were treated according to ethical guidelines. Participants were informed that their participation was voluntary, and they could withdraw their consent at any time without consequences for their medical treatment.

Importance of the Study and Future Directions

Putting NPS in AD and other dementias into the focus of research is of great importance. There is a risk that in the current practice of allocating disease-modifying interventions for prospective AD, a large group of potential patients is neglected. As stated by Mortby et al. (2018), elderly individuals who present themselves with psychiatric but no cognitive symptoms are commonly labeled as psychiatric patients and therefore referred to a mental health professional. If the symptoms of those individuals, however, are the result of prospective AD, they don't get the treatment they need. Extending the knowledge on NPS in AD by establishing accurate cutoff points on NPS scales to predict future AD might eventually aid in increasing the awareness of clinicians about NPS as a potential precursor to future AD and thus help in solving this problem. Additionally, more insight into the association between NPS and AD could offset the underrepresentation of NPS in contemporary AD definitions like the IWG-3 criteria (Dubois, 2022) or the description provided by DSM-V (American Psychiatric Association, 2013).

Future studies on NPS in AD should make use of longitudinal study designs to detect the effect of NPS on Ab deposition and thereby AD, since previous studies have shown a great deal of divergence between the results of cross-sectional and longitudinal studies. Moreover, an important aspect that should be the focus of prospective studies is comorbidity. High comorbidity in AD cases makes it difficult, if not impossible, to disentangle cause and effect of NPS in AD. By controlling for, most importantly, other neurodegenerative diseases than AD, the association between NPS and Ab deposition can be isolated and interpreted more precisely. Another possible way that could resolve the problem of comorbidity is the employment of an Ab-positive only sample. Such a study design may also be able to examine the differences on other variables (like genetic variations, history of other illness, cognitive decline, etc.) between Ab positive individuals with NPS who later develop AD and those who do not. Finally, studies that combine NPS and cognitive decline as predictors for future AD/dementia, as done, e.g., by Liew, 2020 should be reinforced. Generally, efforts should be

made towards NPS as an ‘at- risk’ state for future AD. Other dementias or cognitive decline. On behalf of this case, a first step has been taken by Ismail et al. (2017) by developing the construct of Mild Behavioral Impairment (MBI), that accounts for NPS’ fluctuating nature (Lanctôt et al., 2017).

Conclusion

In the present study, inconclusive results have been found regarding the association between NPS scales and CSF Ab42 levels. The best effect was found for informant-rated apathy. Cutoffs on NPS scales have been computed based on positive/negative CSF Ab42 status. These cutoffs are lower compared to reference cutoff points. Future research on NPS in AD should employ longitudinal research designs and look at comorbidities with other neurodegenerative diseases. A better understanding of NPS in AD may establish NPS as an ’at- risk’ state for future AD and other dementias, increase the use of NPS in the clinical setting, and thus aid in identifying prospective AD cases.

References

Allen, T. A., & Fortin, N. J. (2013). The Evolution of episodic memory. *Proceedings of the National Academy of Sciences*, *110*(supplement_2), 10379-10386. https://doi.org/doi:10.1073/pnas.1301199110

Alonso, A. d. C., Zaidi, T., Novak, M., Grundke-Iqbal, I., & Iqbal, K. (2001). Hyperphosphorylation induces self-assembly of τ into tangles of paired helical filaments/straight filaments. *Proceedings of the National Academy of Sciences*, *98*(12), 6923-6928. https://doi.org/10.1073/pnas.121119298

American Psychiatric Association, D. S. M. T. F. (2013). *Diagnostic and statistical manual of mental disorders : DSM-5*. American Psychiatric Association.

Arevalo-Rodriguez, I., Smailagic, N., Roqué, I. F. M., Ciapponi, A., Sanchez-Perez, E., Giannakou, A., Pedraza, O. L., Bonfill Cosp, X., & Cullum, S. (2015). Mini-Mental State Examination (MMSE)

for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI). *Cochrane Database Syst Rev*, *2015*(3), Cd010783. https://doi.org/10.1002/14651858.CD010783.pub2

Beck, A. T., Epstein, N., Brown, G., & Steer, R. (1988). Beck anxiety inventory. *Journal of Consulting and Clinical Psychology*, *56*(6), 893–897. https://doi.org/10.1037//0022-006x.56.6.893

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 561-571. https://doi.org/https://doi.org/10.1001/archpsyc.1961.01710120031004

BioFINDER. (2023a). *BioFINDER cohorts - Cognitively healthy eldery*. BioFINDER. Retrieved 12.08.2023 from https://biofinder.se/biofinder_cohorts/cognitively-healthy-elderly/

BioFINDER. (2023b). *BioFINDER cohorts - Mild cognitive symtoms*. BioFINDER. Retrieved 12.08.2023 from https://biofinder.se/biofinder_cohorts/mild-cognitive-symtoms/

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *Journal of psychosomatic research*, *52*(2), 69-77. https://doi.org/10.1016/s0022-3999(01)00296-3

Bondi, M. W., Edmonds, E. C., Jak, A. J., Clark, L. R., Delano-Wood, L., McDonald, C. R., Nation, D. A., Libon, D. J., Au, R., Galasko, D., & Salmon, D. P. (2014). Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. *Journal of Alzheimers Disease*, *42*(1), 275-289. https://doi.org/10.3233/jad-140276

Burhanullah, M. H., Tschanz, J. T., Peters, M. E., Leoutsakos, J. M., Matyi, J., Lyketsos, C. G., Nowrangi, M. A., & Rosenberg, P. B. (2020). Neuropsychiatric symptoms as risk factors for cognitive decline in clinically normal older adults: the cache county study. *American Journal of Geriatric Psychiatry 28*(1), 64-71. https://doi.org/10.1016/j.jagp.2019.03.023

Canevelli, M., Blasimme, A., Vanacore, N., Bruno, G., & Cesari, M. (2016). Mild behavioral impairment: Ethical, methodological and clinical reflections. *Neuroscience & Biobehavioral Reviews*, *69*, 402-403. https://doi.org/https://doi.org/10.1016/j.neubiorev.2016.08.025

Cerejeira, J., Lagarto, L., & Mukaetova-Ladinska, E. (2012). Behavioral and psychological symptoms of dementia [Review]. *Frontiers in Neurology*, *3*. https://doi.org/10.3389/fneur.2012.00073

Choe, Y. M., Lee, B. C., Choi, I. G., Suh, G. H., Lee, D. Y., & Kim, J. W. (2020). MMSE subscale ccores as useful predictors of AD conversion in mild cognitive impairment. *Neuropsychiatric Disease and Treatment*, *16*, 1767-1775. https://doi.org/10.2147/ndt.S263702

Chung, J. A., & Cummings, J. L. (2000). NEUROBEHAVIORAL AND NEUROPSYCHIATRIC SYMPTOMS IN ALZHEIMER'S DISEASE: Characteristics and Treatment. *Neurologic Clinics*, *18*(4), 829-846. https://doi.org/https://doi.org/10.1016/S0733-8619(05)70228-0

Clarke, D. E., Reekum, R., Simard, M., Streiner, D. L., Freedman, M., & Conn, D. (2007). Apathy in dementia: an examination of the psychometric properties of the apathy evaluation scale. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *19*(1), 57-64. https://doi.org/10.1176/jnp.2007.19.1.57

Craft, S. (2009). The role of metabolic disorders in alzheimer disease and vascular dementia: two roads converged. *Archives of Neurology*, *66*(3), 300-305. https://doi.org/10.1001/archneurol.2009.27

Direk, N., Schrijvers, E. M. C., de Bruijn, R. F. A. G., Mirza, S., Hofman, A., Ikram, M. A., & Tiemeier, H. (2013). Plasma amyloid β, depression, and dementia in community-dwelling elderly. *Journal of Psychiatric Research*, *47*(4), 479-485. https://doi.org/https://doi.org/10.1016/j.jpsychires.2012.12.008

Doherty, C. M., & Forbes, R. B. (2014). Diagnostic lumbar puncture. *The Ulster Medical Journal*, *83*(2), 93-102.

Dubois, B., Picard, G., & Sarazin, M. (2009). Early detection of alzheimer's disease: new diagnostic criteria. *Dialogues in Clinical Neuroscience*, *11*(2), 135-139. https://doi.org/10.31887/DCNS.2009.11.2/bdubois

Dubois, B., Villain, N., Frisoni, G. B., Rabinovici, G. D., Sabbagh, M., Cappa, S., Bejanin, A., Bombois, S., Epelbaum, S., Teichmann, M., Habert, M. O., Nordberg, A., Blennow, K., Galasko, D., Stern, Y., Rowe, C. C., Salloway, S., Schneider, L. S., Cummings, J. L., & Feldman, H. H. (2021). Clinical

diagnosis of alzheimer's disease: recommendations of the international working group. *The Lancet Neurology*, *20*(6), 484-496. https://doi.org/10.1016/s1474-4422(21)00066-1

Dubois, B. R. (2022). The rationale behind the IWG criteria for alzheimer's disease. *Alzheimer's & Dementia*, *18*(6), e060523. https://doi.org/https://doi.org/10.1002/alz.060523

Eratne, D., Loi, S. M., Farrand, S., Kelso, W., Velakoulis, D., & Looi, J. C. (2018). Alzheimer's disease: clinical update on epidemiology, pathophysiology and diagnosis. *Australasian psychiatry*, *26*(4), 347-357. https://doi.org/10.1177/1039856218762308

Fluss, R., Faraggi, D., & Reiser, B. (2005). Estimation of the Youden Index and its associated cutoff point. *Biometrical Journal: Journal of Mathematical Methods in Biosciences*, *47*(4), 458-472. https://doi.org/10.1002/bimj.200410135

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189-198. https://doi.org/10.1016/0022-3956(75)90026-6

Gaugler, J., James, B., Johnson, T., Reimer, J., Solis, M., Weuve, J., Buckley, R. F., & Hohman, T. J. (2022). Alzheimer's disease facts and figures. *Alzheimers & Dementia*, *18*(4), 700-789. https://doi.org/10.1002/alz.12638

Gibbons, L. E., Teri, L., Logsdon, R., McCurry, S. M., Kukull, W., Bowen, J., McCormick, W., & Larson, E. (2002). Anxiety symptoms as predictors of nursing home placement in patients with alzheimer's disease. *Journal of Clinical Geropsychology*, *8*(4), 335-342. https://doi.org/10.1023/A:1019635525375

González-Salvador, T., Lyketsos, C. G., Baker, A., Hovanec, L., Roques, C., Brandt, J., & Steele, C. (2000). Quality of life in dementia patients in long-term care. *International Journal of Geriatric Psychiatry*, *15*(2), 181-189. https://doi.org/10.1002/(sici)1099-1166(200002)15:2

Hajjo, R., Sabbah, D. A., Abusara, O. H., & Al Bawab, A. Q. (2022). A Review of the Recent Advances in Alzheimer's disease research and the utilization of network biology approaches for prioritizing diagnostics and therapeutics. *Diagnostics*, *12*(12), 2975. https://doi.org/10.3390/diagnostics12122975

Hoops, S., Nazem, S., Siderowf, A. D., Duda, J. E., Xie, S. X., Stern, M. B., & Weintraub, D. (2009). Validity of the MoCA and MMSE in the detection of MCI and dementia in parkinson disease. *Neurology*, *73*(21), 1738-1745. https://doi.org/10.1212/WNL.0b013e3181c34b47

Isik, A. T., Soysal, P., Solmi, M., & Veronese, N. (2019). Bidirectional relationship between caregiver burden and neuropsychiatric symptoms in patients with alzheimer's disease: a narrative review. *International Journal of Geriatric Psychiatry*, *34*(9), 1326-1334. https://doi.org/https://doi.org/10.1002/gps.4965

Ismail, Z., Agüera-Ortiz, L., Brodaty, H., Cieslak, A., Cummings, J., Fischer, C. E., Gauthier, S., Geda, Y. E., Herrmann, N., Kanji, J., Lanctôt, K. L., Miller, D. S., Mortby, M. E., Onyike, C. U., Rosenberg, P. B., Smith, E. E., Smith, G. S., Sultzer, D. L., & Lyketsos, C. (2017). The Mild Behavioral Impairment Checklist (MBI-C): a rating scale for neuropsychiatric symptoms in pre-dementia populations. *Journal of Alzheimer's Disease*, *56*(3), 929-938. https://doi.org/10.3233/jad-160979

Ismail, Z., Smith, E. E., Geda, Y., Sultzer, D., Brodaty, H., Smith, G., Agüera-Ortiz, L., Sweet, R., Miller, D., & Lyketsos, C. G. (2016). Neuropsychiatric symptoms as early manifestations of emergent dementia: Provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement*, *12*(2), 195-202. https://doi.org/10.1016/j.jalz.2015.05.017

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E., Snyder, H. M., & Sperling, R. (2018). NIA-AA Research Framework: toward a biological definition of alzheimer's disease. *Alzheimer's & Dementia*, *14*(4), 535-562. https://doi.org/10.1016/j.jalz.2018.02.018

Jack, C. R., Jr., Knopman, D. S., Jagust, W. J., Shaw, L. M., Aisen, P. S., Weiner, M. W., Petersen, R. C., & Trojanowski, J. Q. (2010). Hypothetical model of dynamic biomarkers of the alzheimer's pathological cascade. *The Lancet Neurology*, *9*(1), 119-128. https://doi.org/10.1016/s1474-4422(09)70299-6

Jain, N., Wang, Y., Zhang, Y., Jacobsen, E., Andreescu, C., Snitz, B. E., Chang, C.-C. H., & Ganguli, M. (2023). It goes both ways: the relationship between anxiety and mild cognitive impairment. *International Journal of Geriatric Psychiatry*, *38*(3), e5899. https://doi.org/https://doi.org/10.1002/gps.5899

Javaid, S., Giebel, C., Khan, M., & Hashim, M. (2021). Epidemiology of alzheimer's disease and other dementias: rising global burden and forecasted trends *F1000Research*, *10*(425). https://doi.org/10.12688/f1000research.50786.1

Jerković, A., Proroković, A., Matijaca, M., Vuko, J., Poljičanin, A., Mastelić, A., Ćurković Katić, A., Košta, V., Kustura, L., Dolić, K., Đogaš, Z., & Rogić Vidaković, M. (2021). Psychometric properties of the HADS measure of anxiety and depression among multiple sclerosis ptients in croatia. *Frontiers in Psychology*, *12*, 794353. https://doi.org/10.3389/fpsyg.2021.794353

Johansson, M., Stomrud, E., Insel, P. S., Leuzy, A., Johansson, P. M., Smith, R., Ismail, Z., Janelidze, S., Palmqvist, S., van Westen, D., Mattsson-Carlgren, N., & Hansson, O. (2021). Mild behavioral impairment and its relation to tau pathology in preclinical alzheimer's disease. *Translational Psychiatry*, *11*(1), 76. https://doi.org/10.1038/s41398-021-01206-z

Johansson, M., Stomrud, E., Johansson, P. M., Svenningsson, A., Palmqvist, S., Janelidze, S., van Westen, D., Mattsson-Carlgren, N., & Hansson, O. (2022). Development of apathy, anxiety, and depression in cognitively unimpaired older adults: effects of alzheimer's disease pathology and cognitive decline. *Biological Psychiatry 92*(1), 34-43. https://doi.org/10.1016/j.biopsych.2022.01.012

Johansson, M., Stomrud, E., Lindberg, O., Westman, E., Johansson, P. M., van Westen, D., Mattsson, N., & Hansson, O. (2020). Apathy and anxiety are early markers of Alzheimer's disease. *Neurobiology of Aging*, *85*, 74-82. https://doi.org/10.1016/j.neurobiolaging.2019.10.008

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 617-627. https://doi.org/10.1001/archpsyc.62.6.617

Krell-Roesch, J., Lowe, V. J., Neureiter, J., Pink, A., Roberts, R. O., Mielke, M. M., Vemuri, P., Stokin, G. B., Christianson, T. J., Jack, C. R., Knopman, D. S., Boeve, B. F., Kremers, W. K., Petersen, R. C., & Geda, Y. E. (2018). Depressive and anxiety symptoms and cortical amyloid deposition among cognitively normal elderly persons: the Mayo Clinic Study of Aging. *International Psychogeriatrics*, *30*(2), 245-251. https://doi.org/10.1017/s1041610217002368

Lanctôt, K. L., Amatniek, J., Ancoli-Israel, S., Arnold, S. E., Ballard, C., Cohen-Mansfield, J., Ismail, Z., Lyketsos, C., Miller, D. S., Musiek, E., Osorio, R. S., Rosenberg, P. B., Satlin, A., Steffens, D., Tariot, P., Bain, L. J., Carrillo, M. C., Hendrix, J. A., Jurgens, H., & Boot, B. (2017). Neuropsychiatric signs and symptoms of Alzheimer's disease: new treatment paradigms. *Alzheimer's & Dementia*, *3*(3), 440-449. https://doi.org/10.1016/j.trci.2017.07.001

Liew, T. M. (2020). Neuropsychiatric symptoms in cognitively normal older persons, and the association with alzheimer's and non-alzheimer's dementia. *Alzheimer's Research & Therapy*, *12*(1), 35. https://doi.org/10.1186/s13195-020-00604-7

Liew, T. M., Yu, J., Mahendran, R., Ng, T.-P., Kua, E.-H., & Feng, L. (2018). Neuropsychiatric and Cognitive Subtypes among Community-Dwelling Older Persons and the Association with DSM-5 Mild Neurocognitive Disorder: Latent Class Analysis. *Journal of Alzheimer's Disease*, *62*, 675-686. https://doi.org/10.3233/JAD-170947

Lyketsos, C. G., Steele, C., Baker, L., Galik, E., Kopunek, S., Steinberg, M., & Warren, A. (1997). Major and minor depression in alzheimer's disease: prevalence and impact. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *9*(4), 556-561. https://doi.org/10.1176/jnp.9.4.556

Ma, L. (2020). Depression, Anxiety, and Apathy in Mild Cognitive Impairment: Current Perspectives. *Frontiers in Aging Neuroscience*, *12*, 9. https://doi.org/10.3389/fnagi.2020.00009

Manjer, J., Carlsson, S., Elmståhl, S., Gullberg, B., Janzon, L., Lindström, M., Mattisson, I., & Berglund, G. (2001). The Malmö Diet and Cancer Study: representativity, cancer incidence and mortality in participants and non-participants. *European Journal of Cancer Prevention*, *10*(6), 489-499. https://doi.org/10.1097/00008469-200112000-00003

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the apathy evaluation scale. *Psychiatry Research*, *38*(2), 143-162. https://doi.org/https://doi.org/10.1016/0165-1781(91)90040-V

Marshall, G. A., Donovan, N. J., Lorius, N., Gidicsin, C. M., Maye, J., Pepin, L. C., Becker, J. A., Amariglio, R. E., Rentz, D. M., Sperling, R. A., & Johnson, K. A. (2013). Apathy is associated with increased amyloid burden in mild cognitive impairment. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *25*(4), 302-307. https://doi.org/10.1176/appi.neuropsych.12060156

Martin, E., & Velayudhan, L. (2020). Neuropsychiatric symptoms in mild cognitive impairment: a literature review. *Dementia and Geriatric Cognitive Disorders*, *49*(2), 146-155. https://doi.org/10.1159/000507078

Masters, M. C., Morris, J. C., & Roe, C. M. (2015). "Noncognitive" symptoms of early alzheimer disease: a longitudinal analysis. *Neurology*, *84*(6), 617-622. https://doi.org/10.1212/wnl.0000000000001238

Medrano, M., Rosario, R. L., Payano, A. N., & Capellán, N. R. (2014). Burden, anxiety and depression in caregivers of Alzheimer patients in the Dominican Republic. *Dementia & Neuropsychologia*, *8*(4), 384-388. https://doi.org/10.1590/s1980-57642014dn84000013

Mehak, S. F., Shivakumar, A. B., Saraf, V., Johansson, M., & Gangadharan, G. (2023). Apathy in alzheimer's disease: a neurocircuitry based perspective. *Ageing Research Reviews*, *87*, 101891. https://doi.org/https://doi.org/10.1016/j.arr.2023.101891

Monaghan, T. F., Rahman, S. N., Agudelo, C. W., Wein, A. J., Lazar, J. M., Everaert, K., & Dmochowski, R. R. (2021). Foundational Statistical Principles in Medical Research: Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value. *Medicina (Kaunas)*, *57*(5). https://doi.org/10.3390/medicina57050503

Morris, J. C. (1993). The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology*, *43*(11), 2412-2414. https://doi.org/10.1212/WNL.43.11.2412-a

Mortby, M. E., Black, S. E., Gauthier, S., Miller, D., Porsteinsson, A., Smith, E. E., & Ismail, Z. (2018). Dementia clinical trial implications of mild behavioral impairment. *International Psychogeriatrics*, *30*(2), 171-175. https://doi.org/10.1017/S1041610218000042

Munro, C. E., Donovan, N. J., Guercio, B. J., Wigman, S. E., Schultz, A. P., Amariglio, R. E., Rentz, D. M., Johnson, K. A., Sperling, R. A., & Marshall, G. A. (2015). Neuropsychiatric aymptoms and functional connectivity in mild cognitive impairment. *Journal of Alzheimer's Disease*, *46*(3), 727-735. https://doi.org/10.3233/jad-150017

Nelson, P. T., Abner, E. L., Patel, E., Anderson, S., Wilcock, D. M., Kryscio, R. J., Van Eldik, L. J., Jicha, G. A., Gal, Z., Nelson, R. S., Nelson, B. G., Gal, J., Azam, M. T., Fardo, D. W., & Cykowski, M. D. (2018). The amygdala as a locus of pathologic misfolding in neurodegenerative diseases. *J Neuropathol Exp Neurol*, *77*(1), 2-20. https://doi.org/10.1093/jnen/nlx099

Ng, K. P., Chiew, H., Rosa-Neto, P., Kandiah, N., Ismail, Z., & Gauthier, S. (2021). Associations of AT(N) biomarkers with neuropsychiatric symptoms in preclinical alzheimer's disease and cognitively unimpaired individuals. *Translational Neurodegeneration*, *10*(1), 11. https://doi.org/10.1186/s40035-021-00236-3

Oh, D. J., Han, J. W., Kim, T. H., Kwak, K. P., Kim, B. J., Kim, S. G., Kim, J. L., Moon, S. W., Park, J. H., Ryu, S.-H., Youn, J. C., Lee, D. Y., Lee, D. W., Lee, S. B., Lee, J. J., Jhoo, J. H., & Kim, K. W. (2019). Epidemiological characteristics of subsyndromal depression in late life. *Australian & New Zealand Journal of Psychiatry*, *54*(2), 150-158. https://doi.org/10.1177/0004867419879242

Ossenkoppele, R., Singleton, E. H., Groot, C., Dijkstra, A. A., Eikelboom, W. S., Seeley, W. W., Miller, B., Laforce, R. J., Scheltens, P., Papma, J. M., Rabinovici, G. D., & Pijnenburg, Y. A. L. (2022). Research criteria for the behavioral Variant of alzheimer disease: a systematic review and meta-analysis. *Journal of the American Medical Association neurology*, *79*(1), 48-60. https://doi.org/10.1001/jamaneurol.2021.4417

Peters, M. E., Rosenberg, P. B., Steinberg, M., Norton, M. C., Welsh-Bohmer, K. A., Hayden, K. M., Breitner, J., Tschanz, J. T., & Lyketsos, C. G. (2013). Neuropsychiatric symptoms as risk factors

for progression from CIND to dementia: the Cache County Study. *The American Journal of Geriatric Psychiatry 21*(11), 1116-1124. https://doi.org/10.1016/j.jagp.2013.01.049

Peters, M. E., Schwartz, S., Han, D., Rabins, P. V., Steinberg, M., Tschanz, J. T., & Lyketsos, C. G. (2015). Neuropsychiatric symptoms as predictors of progression to severe alzheimer's dementia and death: the Cache County Dementia Progression Study. *The American Journal of Psychiatry*, *172*(5), 460-465. https://doi.org/10.1176/appi.ajp.2014.14040480

Petersen, R. C. (2016). Mild Cognitive Impairment. *Continuum: Lifelong Learning in Neurology*, *22*(2), 404-418. https://doi.org/10.1212/con.0000000000000313

Petrazzuoli, F., Vestberg, S., Midlöv, P., Thulesius, H., Stomrud, E., & Palmqvist, S. (2020). Brief cognitive tests used in primary care cannot accurately differentiate mild cognitive impairment from subjective cognitive decline. *Joural of Alzheimer's Disease*, *75*(4), 1191-1201. https://doi.org/10.3233/jad-191191

Pintea, S., & Moldovan, R. (2009). The receiver-operating characteristic (ROC) analysis: Fundamentals and applications in clinical psychology. *Journal of Evidence-Based Psychotherapies*, *9*(1), 49.

Polyakova, M., Sonnabend, N., Sander, C., Mergl, R., Schroeter, M. L., Schroeder, J., & Schönknecht, P. (2014). Prevalence of minor depression in elderly persons with and without mild cognitive impairment: a systematic review. *Journal of Affective Disorders*, *152-154*, 28-38. https://doi.org/https://doi.org/10.1016/j.jad.2013.09.016

Radakovic, R., Harley, C., Abrahams, S., & Starr, J. M. (2015). A systematic review of the validity and reliability of apathy scales in neurodegenerative conditions. *International Psychogeriatrics*, *27*(6), 903-923. https://doi.org/10.1017/s1041610214002221

Rasmussen, J., & Langerman, H. (2019). Alzheimer's disease - why we need early diagnosis. *Degenerative Neurological and Neuromuscular Disease.*, *9*, 123-130. https://doi.org/10.2147/dnnd.S228939

Richmond-Rakerd, L. S., D'Souza, S., Milne, B. J., Caspi, A., & Moffitt, T. E. (2022). Longitudinal associations of mental disorders with dementia: 30-year analysis of 1.7 million new zealand

citizens. *Journal of the American Medical Association Psychiatry*, *79*(4), 333-340. https://doi.org/10.1001/jamapsychiatry.2021.4377

Roberto, N., Portella, M. J., Marquié, M., Alegret, M., Hernández, I., Mauleón, A., Rosende-Roca, M., Abdelnour, C., de Antonio, E. E., Gil, S., Tartari, J. P., Vargas, L., Espinosa, A., Ortega, G., Pérez-Cordón, A., Sanabria, Á., Orellana, A., de Rojas, I., Moreno-Grau, S., . . . Valero, S. (2021). Neuropsychiatric profiles and conversion to dementia in mild cognitive impairment, a latent class analysis. *Scientific reports*, *11*(1), 6448. https://doi.org/10.1038/s41598-021-83126-y

Robin, X., Turck, N., Hainard, A., Tiberti, N., Lisacek, F., Sanchez, J.-C., & Müller, M. (2011). pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC bioinformatics*, *12*(1), 1-8. https://doi.org/10.1186/1471-2105-12-77

Rodrigue, K. M., Kennedy, K. M., Devous, M. D., Sr., Rieck, J. R., Hebrank, A. C., Diaz-Arrastia, R., Mathews, D., & Park, D. C. (2012). β-Amyloid burden in healthy aging: regional distribution and cognitive consequences. *Neurology*, *78*(6), 387-395. https://doi.org/10.1212/WNL.0b013e318245d295

Rosenberg, P. B., Nowrangi, M. A., & Lyketsos, C. G. (2015). Neuropsychiatric symptoms in alzheimer's disease: what might be associated brain circuits? *Molecular aspects of Medicine*, *43-44*, 25-37. https://doi.org/10.1016/j.mam.2015.05.005

RStudio-Team. (2020). *RStudio: Integrated Development for R*. In *Studio: Integrated Development for R. RStudio*

Santiago, J. A., & Potashkin, J. A. (2021). The impact of disease comorbidities in alzheimer's disease. *Front in Aging Neuroscience*, *13*, 631770. https://doi.org/10.3389/fnagi.2021.631770

Shaw, L. M., Korecka, M., Clark, C. M., Lee, V. M., & Trojanowski, J. Q. (2007). Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nat Reviews. Drug Discovery.*, *6*(4), 295-303. https://doi.org/10.1038/nrd2176

Sheikh, F., Ismail, Z., Mortby, M. E., Barber, P., Cieslak, A., Fischer, K., Granger, R., Hogan, D. B., Mackie, A., Maxwell, C. J., Menon, B., Mueller, P., Patry, D., Pearson, D., Quickfall, J., Sajobi, T., Tse, E., Wang, M., & Smith, E. E. (2018). Prevalence of mild behavioral impairment in mild cognitive

impairment and subjective cognitive decline, and its association with caregiver burden. *International Psychogeriatrics*, *30*(2), 233-244. https://doi.org/10.1017/S104161021700151X

Steele, C., Rovner, B., Chase, G. A., & Folstein, M. (1990). Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. *The American Journal of Psychiatry*, *147*, 1049-1051. https://doi.org/10.1176/ajp.147.8.1049

Steinberg, M., Shao, H., Zandi, P., Lyketsos, C. G., Welsh-Bohmer, K. A., Norton, M. C., Breitner, J. C. S., Steffens, D. C., & Tschanz, J. T. (2008). Point and 5-year period prevalence of neuropsychiatric symptoms in dementia: the Cache County Study. *International Journal of Geriatric Psychiatry*, *23*(2), 170-177. https://doi.org/https://doi.org/10.1002/gps.1858

Sun, X., Steffens, D. C., Au, R., Folstein, M., Summergrad, P., Yee, J., Rosenberg, I., Mwamburi, M., & Qiu, W. Q. (2008). Amyloid-associated depression: A prodromal depression of Alzheimer disease? *Archives of General Psychiatry*, *65*(5), 542-550. https://doi.org/10.1001/archpsyc.65.5.542

Thombs, B., Turner, Kimberly A., & Shrier, I. (2019). Defining and Evaluating Overdiagnosis in Mental Health: A Meta-Research Review. *Psychotherapy and Psychosomatics*, *88*(4), 193-202. https://doi.org/10.1159/000501647

Tun, S.-M., Murman, D. L., Long, H. L., Colenda, C. C., & von Eye, A. (2007). Predictive validity of neuropsychiatric subgroups on nursing home placement and survival in patients with alzheimer disease. *The American Journal of Geriatric Psychiatry*, *15*(4), 314-327. https://doi.org/https://doi.org/10.1097/01.JGP.0000239263.52621.97

van Dalen, J. W., van Wanrooij, L. L., Moll van Charante, E. P., Brayne, C., van Gool, W. A., & Richard, E. (2018). Association of apathy with risk of incident dementia: a systematic review and meta-analysis. *Journal of the American Medical Association Psychiatry*, *75*(10), 1012-1021. https://doi.org/10.1001/jamapsychiatry.2018.1877

van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., Cohen, S., Froelich, L., Katayama, S., Sabbagh, M., Vellas, B., Watson, D., Dhadda, S., Irizarry, M., Kramer, L. D., & Iwatsubo, T. (2022). Lecanemab in early alzheimer's

disease. *New England Journal of Medicine*, *388*(1), 9-21. https://doi.org/10.1056/NEJMoa2212948

Velayudhan, L. (2023). Apathy and depression as risk factors for dementia conversion in mild cognitive impairment. *International Psychogeriatrics*, 1-7. https://doi.org/10.1017/s1041610223000042

Vergallo, A., Giampietri, L., Pagni, C., Giorgi, F. S., Nicoletti, V., Miccoli, M., Libertini, P., Petrozzi, L., Bonuccelli, U., & Tognoni, G. (2019). Association between CSF beta-amyloid and apathy in early-stage alzheimer disease [Article]. *Journal of Geriatric Psychiatry and Neurology*, *32*(3), 164-169-169. https://doi.org/10.1177/0891988719838627

Vyas, A., Aisopos, F., Vidal, M.-E., Garrard, P., & Paliouras, G. (2021). Calibrating Mini-Mental State Examination scores to predict misdiagnosed fementia patients. *Applied Sciences*, *11*(17), 8055. https://www.mdpi.com/2076-3417/11/17/8055

Weise, D., Tiepolt, S., Awissus, C., Hoffmann, K. T., Lobsien, D., Kaiser, T., Barthel, H., Sabri, O., & Gertz, H. J. (2015). Critical comparison of different biomarkers for alzheimer's disease in a clinical setting. *Journal of Alzheimer's Disease*, *48*(2), 425-432. https://doi.org/10.3233/jad-150229

WHO. (2020). *Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region. 2000-2019*.

Wimo, A., Jönsson, L., Bond, J., Prince, M., Winblad, B., & International, A. D. (2013). The worldwide economic impact of dementia 2010. *Alzheimer's & Dementia*, *9*(1), 1-11. e13.

Wise, E. A., Rosenberg, P. B., Lyketsos, C. G., & Leoutsakos, J. M. (2019). Time course of neuropsychiatric symptoms and cognitive diagnosis in National Alzheimer's Coordinating Centers volunteers. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *11*, 333-339. https://doi.org/10.1016/j.dadm.2019.02.006

Zhao, Q.-F., Tan, L., Wang, H.-F., Jiang, T., Tan, M.-S., Tan, L., Xu, W., Li, J.-Q., Wang, J., Lai, T.-J., & Yu, J.-T. (2016). The prevalence of neuropsychiatric symptoms in alzheimer's disease: systematic

review and meta-analysis. *Journal of Affective Disorders*, *190*, 264-271. https://doi.org/https://doi.org/10.1016/j.jad.2015.09.069

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361-370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Zou, K., Abdullah, M., & Michikawa, M. (2020). Current biomarkers for alzheimer's disease: from CSF to blood. *Journal of Personalized Medicine*, *10*(3). https://doi.org/10.3390/jpm10030085

Appendix

Tables with ROC Analyses for the Nomas and the TiDiS dataset

Table A

Performance Indices of ROC Analyses in Nomas Dataset

NPS scale		Cutoff	*SE*	*SP*	*J*	*AUC*	*PPV*	*NPV*
AES-S	new	34	0.87	0.22	0.09	0.53	0.47	0.38
	ref.	36.5	0.93	0.12	0.05			
AES-I	new	28	0.66	0.59	0.25	0.61	0.41	0.34
	ref.	42	0.94	0.06	-0.01			
HAD-A	new	2	0.54	0.56	0.10	0.54	0.57	0.36
	ref.	8	0.66	0.59	0.25			
HAD-D	new	2	0.60	0.52	0.12	0.56	0.54	0.34
	ref.	8	0.87	0.20	0.07			

Note. 'New' = newly calculated cutoff based on Ab 42 status, 'ref.' = reference cutoff point. SE = Sensitivity, SP = Specificity, J = Youden's Index, AUC = Area under the Curve, PPV = Positive Predictive Values, NPV = Negative Predictive Values.

Table B

Performance Indices of ROC Analyses in TiDiS Dataset

NPS scale		Cutoff	*SE*	*SP*	*J*	*AUC*	*PPV*	*NPV*
AES-S	new	18	0.14	0.90	0.14	0.52	0	0.50
	ref.	37	0.33	0.72	0.05			
AES-I	new	18	0.60	0.57	0.17	0.58	0	0.48
	ref.	42	0.34	0.72	0.06			
HAD-A	new	4	0.54	0.51	0.05	0.50	0.51	0.50
	ref.	8	0.54	0.59	0.13			
HAD-D	new	3	0.49	0.66	0.14	0.56	0.47	0.40
	ref.	8	0.09	0.96	0.05			

Note. 'New' = newly calculated cutoff based on Ab42 status, 'ref.' = reference cutoff point. SE = Sensitivity, SP = Specificity, J = Youden's Index, AUC = Area under the Curve, PPV = Positive Predictive Values, NPV = Negative Predictive Values.