Neuropsychiatric symptoms in Alzheimer's disease

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associations with biomarkers

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CONTENTS

1

GENERAL INTRODUCTION

This thesis presents a collection of studies that were conducted to examine the ideopathogenesis of neuropsychiatric symptoms (NPS) across the Alzheimer's disease (AD) spectrum. This chapter serves as a general background to those studies. First, historical context of the AD construct is given to provide the reader with a general framework. Next, a case study is presented to illustrate the clinical presentation of AD and to provide direction for the research questions. A description of NPS in AD follows, and finally, the aims and outline of the thesis are described.

Dementia and Alzheimer's disease

Dementia has been posited as one of the global health priorities of our time, affecting 35.6 million people worldwide[1]. These figures are expected to double every twenty years to 115.4 million people in 2050[1]. Over the years, the view on dementia has evolved from dementia being part of normal aging, to dementia being viewed as a neuropsychiatric condition reflecting neuropathological changes[2]. Alzheimer's disease (AD), the most common form of dementia[3], has changed from a concept to a reliable disease definition due to increasing knowledge on etiology and pathogenesis. The biggest advances have been made with regard to *in vivo* technologies to study AD neuropathology. In addition, cohort and population studies have contributed to the understanding of risk factors associated with AD.

Historically, a diagnosis of AD dementia was based on clinical symptoms, with a definite diagnosis of AD requiring histopathological evidence. Nowadays, utilizing *in vivo* biomarkers, it is possible to identify individuals who are in early phases of the disease when clinical symptoms have not yet surpassed the threshold for dementia or have not yet presented themselves at all[4, 5]. AD is now viewed as a continuum (see Figure 1), where pathology starts decades before symptoms emerge (i.e. asymptomatic or preclinical phase), and where progression to a (prodromal) phase of mild cognitive impairment (MCI) is slow[5, 6]. Individuals with MCI experience cognitive problems without a significant decline in functioning as compared to previous levels. Around 34% of individuals with MCI eventually develop dementia[7], when the severity of cognitive impairments interferes with activities in daily living[8]. Arguably, the MCI stage is preceded by a phase of subjective cognitive decline (SCD), in which an individual experiences subtle cognitive decline which cannot be objectified with neuropsychological tests[9]. Identification and characterization of these early phases is thought to be crucial to target dementia prevention, and a great deal of energy and activity in the AD field is directed towards these preclinical and prodromal phases.

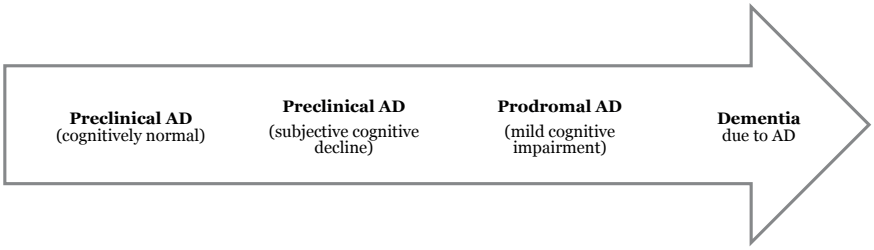

Figure 1. Proposed AD phases[a]

AD biomarkers

The primary neuropathological hallmarks of AD are the extracellular accumulation of amyloid-β peptides in plaques and the intracellular accumulation of hyperphosphorylated tau proteins in neurofibrillary tangles[10]. The ε4 allele of the apolipoprotein E (APOE) gene is thought to increase risk of AD by initiating and accelerating the accumulation of amyloid-β peptides, although the exact mechanisms are still not completely understood[11].

AD biomarkers can be used as proxies of neuropathology. For example, the presence of amyloid plaques and neurofibrillary tangles in the brain is thought to be reflected by low amyloid-β and high tau concentrations in the cerebrospinal fluid (CSF), which can be obtained via a lumbar puncture. Neuronal injury is reflected by neurodegeneration, i.e. atrophy on a structural magnetic resonance imaging (MRI) scan. Because the temporal ordering of the underlying mechanisms remains unclear[b], it was recently proposed to categorize these AD markers in categories for amyloid, tau and neuronal injury, each being rated as either positive or negative in the AT(N)-research framework[12].

The use of AD biomarkers serves several purposes. In the clinic, biomarkers allow for early diagnostics, giving patients and caregivers time to plan for the future and to decide upon financial matters or living arrangements. Additionally, they allow for the reliable differentiation from other pathologies. In research, biomarkers have improved the identification of individuals who are at the highest risk of developing AD, thereby opening windows to target treatments but also to determine factors that increase risk of disease progression.

[a] In an area where things have changed so much over the last few years, there is almost no unique approach to define these categories. Displayed here are the diagnostic entities used throughout this thesis. For comparison purposes with other literature, note that "subjective cognitive decline" (SCD) is similar to "subjective cognitive impairment" (SCI) and the "worried-

[b] The well-known amyloid cascade hypothesis proposed by Jack et al. (in 2010, refined in 2013), assumes that tau pathology precedes Aβ deposition in time. Aβ pathology arises later (independently) from pre-existing tauopathy. Aβ then accelerates the existing tauopathy leading to neocortical spread of NFT. The linear causality of this model is somewhat controversial.

Case study

The following case serves to illustrate the clinical picture of AD and diagnostic procedures.

> Mr. G., a 76-year old man, presented at the memory clinic with short-term memory problems. Mr. G. was born and raised in Germany, and had fulfilled a high position at a large German bank. His job had required him to travel the world and live in many places, before he and Mrs. G. settled down in the south of the Netherlands. The couple does not have any children and both are retired. Mrs. G. observed her husband having increasingly word finding difficulties: he had started to replace Dutch words with the German equivalents. Whereas Mr. G. had had no problems settling in his new home-town back in the days, enjoying playing golf and participating in a social club, he has been avoiding such activities for the last two years. The fact that he preferred staying at home rather than going out was worrisome for his wife. Mrs. G. observed some other changes as well. For example, he had started worrying at lot about his failing memory - his good memory had always been his pride – , fearing it as the first sign of dementia. The worrying resulted in a low mood and it interfered with his sleep: he had difficulties falling asleep and when he woke up in the night, he could not fall asleep again. He started sleeping during the day, watching television and ignoring household chores, leading to the frustration of Mrs. G. However, Mr. G. was, when asked, able to conduct household chores without any difficulties.
>
> The neuropsychological testing showed some memory problems. On other cognitive domains his scores were, although below average, in the normal range[c]. It also showed a high level of intelligence, corresponding with his level of education and prior occupation. His daily functioning was mildly impaired and mild symptoms of depression were reported. A research nurse conducted a structured interview with Mrs. G.: symptoms of depression, apathy and agitation were present, causing high levels of burden for her[d]. Further, as part of additional diagnostic, laboratory assessment showed abnormal CSF-amyloid and the MRI scan showed some mild atrophy of the medial temporal lobe.

[c] Whether cognitive functioning is considered "normal" is based on normative data, i.e. adjusting for sex, age, and education levels.

[d] Several questionnaires are administered, among which the Geriatric Depression Scale (GDS-15), a self-report questionnaire that screens for symptoms of depression, and the Neuropsychiatric Inventory (NPI), an informant-based scale that screens for the presence, frequency, severity and burden of twelve neuropsychiatric domains.

Results of the neuropsychological, neuropsychiatric, laboratory assessment and the MRI-scan were discussed in a multidisciplinary meeting. It was concluded that Mr. G. suffered from prodromal AD, i.e. mild cognitive impairment due to AD.

In order to monitor his functioning over time, Mr. G. was invited at the memory clinic 1 year later. He reported increasing forgetfulness. Mrs. G. became very emotional when discussing the situation with the research nurse. It appeared that his reluctance to go out had also caused their social network to decrease substantially, and she felt she no longer could talk with anyone. Whereas last year Mrs. G. had been able to alleviate his low mood, this was no longer the case. The periods of low mood had become more severe and occurred more frequently. Although already showing reluctance, Mr. G. had still joined Mrs. G. for groceries last year. Now, he declined her requests harshly. Mrs. G. confirmed the decrease of his memory, which asked a lot of her patience. She admitted feeling guilty when she was not able to keep herself calm and started yelling at him. This in turn made Mr. G. increasingly agitated, almost in an aggressive manner. The depressive symptoms had increased, both on Mr. G.'s own and Mrs. G.'s report. He also increasingly needed help with daily tasks, such as planning and executing household chores. Repetition of the neuropsychological assessment showed decreases on domains of memory functioning, executive functioning and mental speed. The latter two were now also considered being "impaired" (i.e. scoring 1.5 standard deviations below average).

Both Mr. and Mrs. G. were offered help: Mrs. G. had individual sessions with a psychologist and Mr. G. took part in the local "MCI-group", a group-based psycho-education therapy.

After 2 years, Mr. G. participated in the BB ACL follow-up study (see chapter 7). His cognitive functioning had remained somewhat stable, but the depression showed considerable fluctuations. Structuring of their daily routines had helped Mr. G. staying active, although their social network was still very limited.

Neuropsychiatric symptoms

For a long time, cognitive impairments were considered the hallmark of AD, and therefore received most attention from clinicians and researchers. The case study demonstrates that AD affects more than cognition alone. In fact, NPS occur almost universally over the course of dementia, including its prodromal phases, although type and prominence depend on disease stage[13]. For example, symptoms such as depression and irritability tend to be more prominent in early stages, whereas apathy tends to occur more often in later stages[14]. In addition, some NPS are more persistent than others. For example, apathy shows high persistence over time, whereas depression and anxiety tend to be more episodic in nature[15].

NPS have also been denoted as "behavioral and psychological symptoms of dementia", both terms referring to disturbances of mood, behavior, and perception in association with neurodegeneration[16]. The most common symptoms in MCI and AD dementia are depression, anxiety, apathy, agitation, irritability, and sleep disturbances[17-21]. NPS often dominate the clinical picture and frequently are the reason for helpseeking[13]. One can only imagine the distress and burden they cause, often said to be even greater than the cognitive problems. The case study illustrates how the presence of NPS lowers quality of life of both the person with AD (PwAD) and caregivers. NPS are associated with a number of other adverse outcomes as well, such as faster disease progression, earlier institutionalization, increased mortality, and higher health care costs[22-24].

NPS are now considered integral parts of the phenotype of AD (dementia) and were included in the 2011 NIAA-AA consensus recommendations for (all cause) dementia as a criterium for "changes in personality, behavior or comportment"[25]. The currently used MCI definitions, however, do not refer to NPS[26, 27]. This is remarkable given accumulating evidence that the presence of NPS in MCI is associated with increased risk for transitioning to dementia[28-31].

Several hypotheses have been posed to explain the presence of NPS in AD. In the "risk factor hypothesis", NPS are thought to cause a "wear-and-tear" on the brain, e.g. via chronic neuroendocrine axis activation which lowers brain reserve to cope with AD pathology. In this case, NPS and cognitive impairment are caused by different pathological processes which interact synergistically[32]. Another view is the "symptom hypothesis"[32], where NPS are considered prodromal symptoms of AD that result from and should be associated with underlying AD pathology[33]. Possibly, the association between AD pathology and NPS depends on global cognitive functioning. In other words, the explanation for the presence of NPS might differ per disease stage.

Note that these hypotheses are related to the PwAD, focusing on underlying neurobiology. Although beyond the scope of this thesis, it is important to realize that other factors might explain NPS (Figure 2). Thus, multiple internal and external, sometimes modifiable, interacting factors could play a role in the development of NPS.

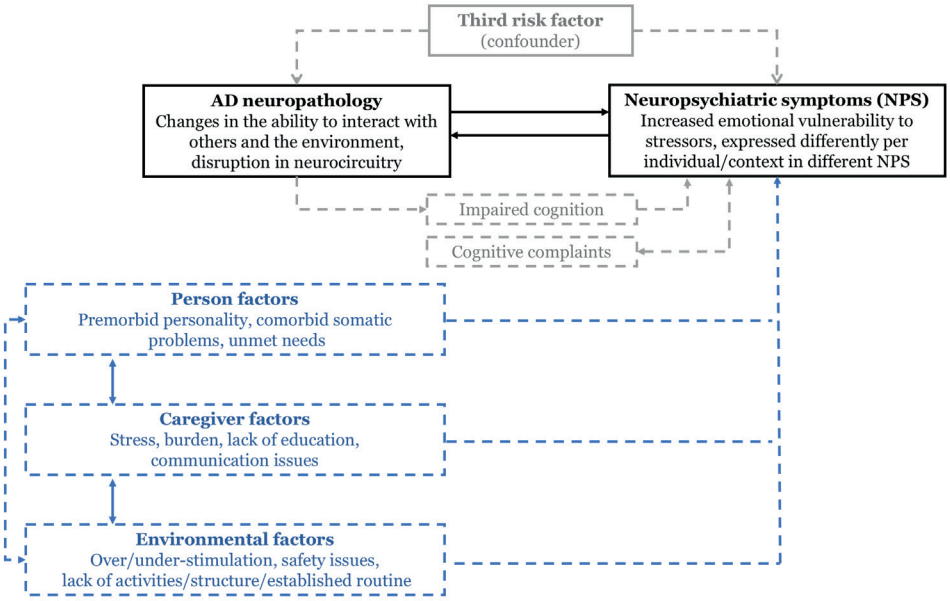

Figure 2. Factors associated with NPS, adapted from Kales et al.[13]

Note. The focus of this thesis is displayed in black

NPS are important targets for treatment given their impact on quality of life of patient and caregivers, prognostic outcomes, and care costs. However, the heterogeneity of NPS (in terms of phenomenology, between and within persons) contributes to complexity of prevention and effective management. Distinct symptoms might have different neurobiological causes, implicating future (pharmacological) interventions.

Thesis aims and outline

This introduction shows that AD is no longer considered a purely cognitive disorder. The gradual but progressive nature of AD and the burden of affective symptoms across the AD spectrum was illustrated in the case study. With this thesis we aim to gain insight in the relationship between AD biomarkers and NPS that occur across the AD spectrum. This thesis consists of several chapters, which are of different natures but have the following in common:

(1) a focus on affective symptoms, such depression, anxiety, apathy, agitation, irritability and sleep disturbances. These are the most common NPS in MCI and AD dementia[17-21].

(2) the association between these NPS and AD pathology is studied in participants across the AD spectrum, in outpatient multicenter cohorts. Study cohorts that are included in this thesis are:

The **BioBank Alzheimer Center Limburg** (BB-ACL) study, which is an ongoing prospective cohort study that aims to examine determinants, risk factors, course of, and consequences of cognitive impairments (**chapter 7**). The ACL is embedded in the memory clinic of the Maastricht University Medical Center + (MUMC+), the Netherlands. Since 2009, 855 patients have been included, with up to 10 years of follow-up data available.

The Dutch **Clinical Course of Cognition and Comorbidity in Mild Cognitive Impairment** (4C-MCI) study, which is a longitudinal, multicenter study focusing on the course of cognitive decline in non-demented memory clinic visitors[34]. Between January 2010 and May 2011, 315 memory clinic visitors from the MUMC+, Radboud University Medical Center, and Vrije Universiteit Medical Centre were included with up to three year follow-up data.

The Dutch **Parelsnoer Institute – Neurodegenerative Diseases** (PSI-NDZ) study, which is a collaboration of the eight Dutch University Medical Centers (UMCs) designed to harmonize the collection of clinical data and biomaterials from patients with chronic diseases, among which neurodegenerative diseases[35]. Since 2009, 1,206 patients were included with up to five year follow-up data.

The **Alzheimer's Disease Neuroimaging Initiative** (ADNI) database, which comprises longitudinal data from 59 participating sites in the US (adni-info.org). Its primary aim is to define the progression of AD, by developing and validating imaging, genetic, and biochemical biomarkers. Since 2004, 2,392 individuals with up to 11 year follow-up data were included.

The **Uniform Data Set** (UDS) of the **National Alzheimer's Coordinating Centre** (NACC), which reflects total enrollment from 39 past and present Alzheimer's Disease Centers (ADCs) across the US[36]. This dataset consists of 28,717 individuals, with up to 14 year of follow-up data (enrollment since 2005, data freeze as of March 2019).

Specifically, the chapters address the following research questions:

Is underlying AD pathology associated with affective symptoms in individuals across the AD spectrum? Does disease severity have an influence on this relationship?

In the first part of this thesis we provide an up-to-date overview of the literature regarding the association between AD biomarkers and affective symptoms in MCI and AD dementia. In **Chapter 2,** the association between the most important genetic risk factor for AD, APOE ε4 genotype, and affective symptoms is summarized in a systematic literature review and meta-analysis. In **Chapter 3**, a systematic review is presented that summarizes findings on the relationship between biomarkers and affective symptoms utilizing the AT(N) research

framework. Both chapters systematically examine factors that could possibly explain contrasting prior results. In **Chapter 4,** the cross-sectional association of CSF biomarkers and hippocampal atrophy with affective symptoms is studied in individuals across the AD spectrum. We also examined whether disease severity would explain under what conditions AD biomarkers are related to affective symptoms.

How do symptoms such as depression and apathy develop over time? Is AD pathology associated with such trajectories?

Chapter 5 aims to identify whether different trajectories of depression and apathy exist in individuals across the AD spectrum and whether these trajectories are predicted by baseline biomarkers.

What is the impact of NPS, somatic comorbidities, and cognitive functioning on patient health-related quality of life (HRQoL)?

Chapter 6 focuses on the impact of NPS, somatic comorbidities (medical illnesses), and cognitive functioning on HRQoL over time in memory clinic patients without dementia. To this end, we utilized data from the 4C-MCI study.

How to investigate the natural course of cognitive functioning and its associated factors in a memory clinic population?

In **Chapter 7** we describe the general cohort profile of the BB ACL study.

Finally, **chapter 8** provides a summary, general discussion and implications of the main findings of this thesis.

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2

APOLIPOPROTEIN E AND AFFECTIVE SYMPTOMS IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE-TYPE DEMENTIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: APOE status has been associated to affective symptoms in cognitively impaired subjects, with conflicting results.

Methods: Databases CINAHL, Embase, PsychINFO and PubMed were searched for studies evaluating APOE genotype with affective symptoms in MCI and AD dementia. Symptoms were meta-analyzed separately and possible sources of heterogeneity were examined.

Results: Fifty-three abstracts fulfilled the eligibility criteria. No association was found between the individual symptoms and APOE ε4 carriership or zygosity. For depression and anxiety, only pooled unadjusted estimates showed positive associations with between-study heterogeneity, which could be explained by variation in study design, setting and way of symptom assessment

Discussion: There is no evidence that APOE ε4 carriership or zygosity is associated with the presence of depression, anxiety, apathy, agitation, irritability or sleep disturbances in cognitively impaired subjects. Future research should shift its focus from this single polymorphism to a more integrated view of other biological factors.

1. INTRODUCTION

Affective symptoms are considered a core feature of Alzheimer's disease (AD) dementia as they are highly prevalent and occur in nearly all patients over the disease course, including in its prodromal phase (i.e. mild cognitive impairment, MCI)[1-5]. Heterogeneity in the expression of affective symptoms in cognitively impaired subjects is thought to be associated with genetic variability. Apolipoprotein E (APOE) is the most important and well-documented genetic risk factor for late onset AD[6] and additionally, might impact disease phenotypes, such as manifestations of affective symptomatology.

The APOE gene is polymorphic, having three common alleles (ε2, ε3 and ε4) that alter APOE structure and function, which has implications for all AD related biochemical disturbances[7]. Whereas the prevalence of ε4-carriers in the general population is estimated around 14%, among amyloid-beta positive subjects with MCI and AD dementia it is as high as 65%[8,9]. Carrying the ε4-allele increases the risk to develop AD dementia, with ε4-heterozygotes having a two-to-four fold high risk and ε4-homozygotes having a 12-fold higher risk compared to non-carriers[10].

The most common symptoms in subjects with MCI and AD dementia are, albeit in a different order per disease stage, depression, anxiety, agitation, apathy, irritability and sleep disturbances[3-5,11,12]. These affective symptoms accelerate disease progression[13], are considered to be risk factors for neurocognitive disorders[14-17], and some have been associated with AD biomarkers[18]. Their presence has a huge impact on both patients' and caregivers' quality of life[19], results in higher institutionalization rates[20] and increased health care costs[21]. This underlines the importance of determining mechanisms implicated in affective symptomatology, thereby possibly opening a way for earlier and more personalized treatment options.

APOE genotype has been related to affective symptoms in subjects with MCI and AD dementia, however, results are equivocal. Two previous reviews attributed this to differences in study design, study setting, subject characteristics, the use of different instruments to assess affect or different definitions (symptom vs. disorder)[22, 23]. Additionally, whereas some studies evaluated associations dichotomously (i.e. non-carrier vs. carrier of at least one APOE ε4 allele), others have examined dose effect of APOE ε4 alleles (i.e. hetero- and homozygosity). However, these reviews did not perform a systematic search of the literature and did not address the suggested methodological differences in a quantitative manner[22, 23].

2. METHODS

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[24]. The literature search was conducted in databases CINAHL, Embase, PsychINFO and PubMed that were searched to October 2017. The search string consisted of population related terms (e.g. cognitive impaired, dementia, AD), predictor related terms (APOE ε4 genotype), of outcome-related terms (affective symptoms) and of specific limitations (e.g. humans, language restrictions). A full description of the search strategy is provided in Appendix 1.

The symptoms depression, anxiety, apathy, agitation, irritability, sleep disturbances were chosen as these are the most common symptoms in MCI and AD dementia[3-5, 11, 12]. Further, these symptoms have most often been grouped together in factor analyses, e.g. "agitation, depression, anxiety and irritability", or "depression, anxiety, apathy and irritability"[25].

To be eligible for inclusion, publications fulfilled the following criteria: a) is population or clinically based and explicitly defines a cognitive impairment; b) assesses the current presence and/or severity, by self- or proxy-report, of the following symptoms: depression, anxiety, apathy, agitation, irritability, sleep disturbances and/or subsyndromes; c) examines the association between affective symptoms and APOE genotype. Studies were excluded if the study sample included a) non-AD dementia types (e.g. vascular dementia (VaD), Lewy body disease (LBD), frontotemporal dementia (FTD), Parkinson's disease (PD)) or, in case this was defined, vascular cognitive impairment (VCI); b) primary somatic or psychiatric patients in whom cognition is studied (e.g. patients with major depression).

Two reviewers (L.B. and I.R.) independently screened titles and abstracts for potential eligibility. Doubtful records were discussed until consensus was reached. Records of research protocols, and abstracts/posters from scientific meetings were excluded. Reference lists of retrieved publications and secondary literature (review articles, editorials, etc.) were screened to identity possible additional studies. Eligibility for inclusion was assessed based on full-text screening.

2.1. Data collection and extraction

According to a predefined data extraction form, data on the design, sample size and demographics of the included studies, as well as characteristics of the biomarkers and affective symptoms (assessment and diagnostic definition (symptom vs. disorder)) were extracted. Quantifiable data on the relation between biomarker and affective symptoms were extracted. In case studies provided demographic information per group, weighted overall mean was calculated.

2.2. Assessment of Study Quality

Study quality was assessed with the Newcastle-Ottawa Scale (NOS) for cohort studies and with a modified NOS for cross-sectional studies[26], see Appendix 2 Tables 3 and 4. Classification of studies with low or high quality resulted from a median split of the total quality score.

2.3. Statistical Analyses

Statistical analyses were performed in R (version 3.3.2.[27]) using the metafor package (version 2.0[28]). Random-effects models were fitted using restricted maximum likelihood (REML) estimations. Pooled OR with corresponding 95% confidence intervals (CI) were generated to examine the association between APOE genotype and affective symptoms. Both crude and fully adjusted model estimates were used. In case a study did not report effect sizes, contingency tables were extracted whenever possible to obtain the log odds ratios (OR) and corresponding sampling variances. For a few studies this information was estimated based on figures[29-32]. Funnel plot asymmetry, as an indicator for publication bias, was visually inspected by plotting effect sizes against their standard errors. In addition, Egger's regression test was conducted to test for significant asymmetry. The I^2 statistic was computed to quantify the proportion of variation across studies due to heterogeneity. Heterogeneity was considered to be small when I^2 <= 25%, moderate for I^2 = 26–74%, and large for I^2 > = 75% [33]. First, analyses were performed per symptom by use of adjusted or unadjusted estimates. In case significant heterogeneity was present, the variation was examined further by conducting stratified analyses and meta-regression (e.g. setting, design, symptom assessment method, syndromal diagnosis, mean age, mean educational level, mean MMSE score, percentage of APOE ε4 carriers, percentage of patients with symptom present and study quality).

3. RESULTS

Of 2.355 identified abstracts 92 were selected for full-text screening (see Figure 1). Of these, 53 articles (57.6%) met inclusion criteria. Four additional studies were found from cross-references, but were excluded after full-text screening due to different reasons: matched subjects[34], comment[35], animal study[36] and unavailable record[37].

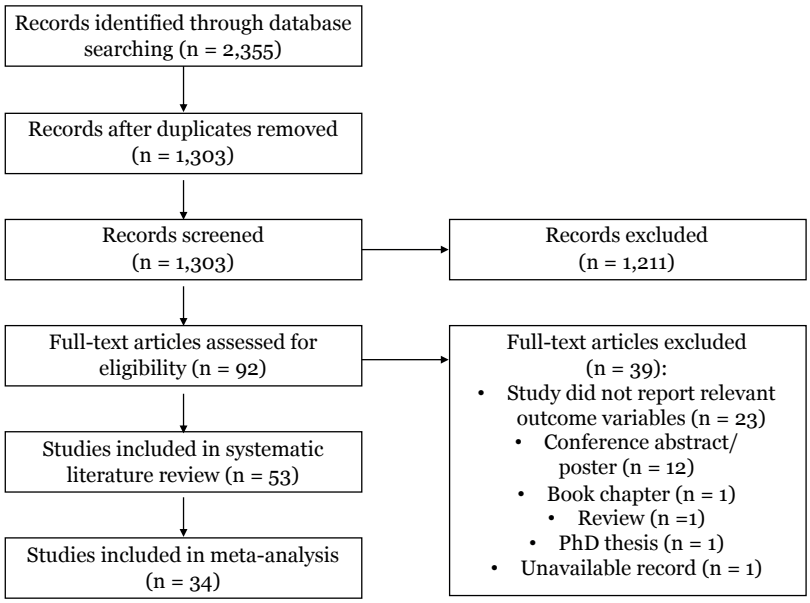

Figure 1. Flow diagram of study selection

3.1. Study characteristics

Characteristics of studies assessing APOE genotype in relation to affective symptoms (n = 53) are presented in Table 1. The majority of subjects were from clinical research settings, such as (hospital based) memory clinics (42 studies with 11,536 subjects), of which 16 were multi-center studies. Subjects with MCI (n = 1,551) and AD dementia (n = 10,833) were the primary interest of the current study, although some studies did not differentiate AD from other types of dementia in their analyses[32, 38-42], adding 417 dementia subjects, resulting in a total of 12,801 (55.4% females) subjects.

Overall, DNA was prepared from blood and APOE genotypes were obtained by polymerase chain reaction (PCR) methods, except for two studies that used buccal cell swaps[32, 42]. Thirty studies reported information on APOE ε4 carriership, 13 studies on zygosity (i.e. no ε4 allele, one or two alleles), 9 studies on allele frequencies (i.e. ε2, ε3, ε4) and 28 on distribution of genotypes (i.e. ε2/ε2, ε2/ε3, ε3/ε3, ε3/ε4, ε4/ε4).

Median splitting of the quality assessment score resulted in 56.5% of the cross-sectional studies (n = 46) scoring below the median (score of 4 out of 7) and in 44.4% of the longitudinal studies (n = 7) scoring below the median (score of 8 out 9).

Table 1. Characteristics of studies assessing APOE genotype in relation to affective symptoms in cognitively impaired subjects

First author (year)	Design	Setting	Syndromal diagnosis	N	Age	Females, %	Education	MMSE	Depression	Anxiety	Apathy	Agitation	Irritability	Sleep disorders	Subsyndromes	Symptom measurement
Borroni (2009)	C	C	AD	264	77.4	70.8	5.4	17.2	+							DSM-IV
Borroni (2006)	C	C	AD	232	75.5±8.9	65.1	6±3.2	17.7±7.1	+	+	+	+	+	+		NPI-12
Bowirrat (2006)	C	P	AD	168	82.6±8.1	65.5	15(8.9)[e]		+							DSM-IV
Cantillon (1997)[a]	C	C	AD	162	75[c]			17.6	+							Cornell
Chang (2004)	L	C	AD	135	73.1±8.8	66.7	7.7±6		+							SCID
Chen (2012)	C	C	AD	96	77.7±7.8	78.1	4.8±5.1	17.1±5.2							+	NPI-12
Christie (2012)	C	C	AD	790	76.7	67.2	12.7	17.6				+				CERAD, BRSD
Class (1997)[a]	C	C	Dem	26	83.2				+							GDS-30
Craig (2004)	C	C	AD	400	78±7.5	65.3		13.1±9.2	+			+				NPI-D
Craig (2005)	C	C	AD	404	78±7.5	68		13±9.2	+							NPI-D
Craig (2006)	C	C	AD	405	78	63.3		13						+		NPI-D
D'Onofrio (2011)	C	C	AD	201	79.3±6.9	64.7	4.0±3.7[g]	13.8±5.2							+	NPI-12
De Oliveira (2014)	C	C	AD	217	78±6.1	67.7	4.2±3.7	15.6±4.9						+		Interview[i]
De Oliveira (2017)	C	C	AD	201	73.5±6.3[c]	70.1	4.2±3.7		+	+	+	+	+			NPI-10
Delano-Wood (2008)[a]	C	C	AD	323	72.6	49.5		20.4	+							DIS
Engelsborghs (2006)	L	C	AD	186	79±7	67.7		12.6±6.7	+							Behave-AD
Farlow (2004)[a]	C	C	MCI	494	70.7	52.2	11.2	26.9	+	+	+	+	+			NPI-10, BDI
Flirski (2012)[a]	L	C	MCI, AD	147	74.8	71.4	10.4	22.3	+	+	+	+	+	+		NPI-12
Forsell (1997)[a]	C	P	Dem	184	86.4	82.6	20(10.9)[f]	15.3	+							DSM-IV
Fritze (2011)[b]	C	C	AD	138	77(70-82)[d]	69.3		24(22-25)[d]	+							NPI-12

First author (year)	Design	Setting	Syndromal diagnosis	N	Age	Females, %	Education	MMSE	Depression	Anxiety	Apathy	Agitation	Irritability	Sleep disorders	Subsyndromes	Symptom measureme[illegible]
Gabryelewicz (2002)	C	C	AD	139	75.9±7.1	62.6	[h]		+	+						Behave-AD
Hall (2014)	C	C	AD	190	77.5±8.3	65.3	14.2±3.16	19.4±6.0							+	NPI-Q
Harwood (1999)	C	C	AD	501	74.8±7.8[c]	64		18±6.2	+							HAM-D
Hirono (1999)	C	C	AD	175	71.98.1	83.4	9.3±2.5	19.3±4.6	+	+	+	+	+			NPI-10
Hollingworth (2006)[b]	C	C	AD	1120	81.2±6.5	70.2	10.4±2.7	12.8±9							+	NPI-12
Holmes (1996)	C	P	AD	164	81.9±6.6			10.7							+	PBE, Cornell
Holmes (1998)	C	C	AD	210	82.5±6.7				+							CAMDEX, 2 MOUSEPAD, Cornell
Jefferson (2001)	C	C	Dem	50					+							Interviewer observed lability of mood, Cornell
Levy (1999)	C	C	AD	605	75	52.6		20	+	+	+	+	+			NPI-10
Liu (2002)	C	C	AD	149	73.1±8.7	64.4	7.8±5.9	13.9±7[j]	+							SCID, HDRS
Lopez (1998)[a]	C	C	AD	194	68.5[c]	72.2			+							DSM-III-R, BRS
Lyketsos (1997)	C	C	AD	120	73.6±8.5	68	12.3±4.1		+[k]							DSM-IV
Mackin (2013)[a]	C	C	MCI	405		35.8	16[b]	27[b]	+							GDS-15
Michels (2012)[a]	C	C	MCI, AD	589	67.8	47.3			+	+						ICD-10, DSM-IV criteria
Monastero (2006)[a]	C	C	AD	197	74.0	67.0	5.8	18.0	+	+	+	+	+	+		NPI-12
Mou (2015)	C	C	AD	237	73.8±9.5	49.4		14.5							+	BPRS, HAMD, HAMA
Muller-Thomsen (2002)[a]	C	C	AD	137	71.3	67.9	9.3	18.1	+							ICD-10[m]
Park (2015)[a]	C	C	AD	870	69.5	38.1	5.7	19.6	+	+	+	+	+	+		
Pink (2015)	C	P	MCI	332	82.1(77.7-85.0)[d]	45.4	12(12-15)[d]		+		+	+		+		NPI-12
Pritchard (2007)	L	C	AD	388	74.4±7.0	56			+	+		+				NPI-Q

Ramachandran (1996)	C	P	AD	46	79.2±7.3	78.3	5.3±4		+						HDRS
Scarmeas (2002)	L	C	AD	87	70.7±7.8	46	13.6±3.7		+						CUSPAD
Schmand (1998)[a]	C	P	Dem	43	80.5	79.1	7.2	17.4	+						GMS, AGECAT
Schutte (2011)	L	C	AD	36	85.8±7.3	75	[i]					+			CMAI
Slifer (2009)	C	C	AD	528	72.2±6.2[c]	64			+						GDS-15, medical record
Spalletta (2006)[a]	C	C	AD	171	76.1	67.3	5.7	18	+	+	+	+	+		NPI-10
Steinberg (2006)[a]	L	P	Dem	328	83.4	37.8			+	+	+	+	+		NPI-10
van der Flier (2006)[a]	C	C	AD	110	70.1	58.2		20.8	+	+	+	+	+		NPI-10
Vercelletto (2002)	C	C	AD	32	76.6±5.8	81	7.7±2.5	20.6±3.9			+				PANSS-N
Woods (2009)	C	C	Dem	36	88.4±6.8	88		10.4±7.5				+			mABRS
Xing (2015)[a]	C	C	AD	315	69.3	55.9	6.9	14.9	+	+	+	+	+	+	NPI-12
Yoo (2014)	C	C	AD	95	78.5±7.2	76.0	4.9±5.8	15.1±5.4	+	+	+	+	+	+	NPI-12
Zdanys (2007)[a]	C	C	AD	266	74.6	64.3	13.3	17.0	+	+	+	+	+	+	NPI-12

a = demographic information given per group, weighted overall mean was calculated; b = demographics given for total sample but APOE genotype only known for subset, assumption is made that there is no difference between demographical characteristics for those with and without APOE genotype available; c = age of onset; d = median (IQR); e = number and percentage of people with an education; f = number and percentage of people with less than 7 years education; g = instruction level; h = < 8 years (n = 48), 8-11 years (n = 60), > 11 years (n = 31); i = 36% of the subjects had not completed high school, 28% had completed high school, and 36% had completed at least some college; j = estimated score from Cognitive Abilities Screening Instrument (CASI); k = with prevalence of depression, sum of minor and major depression; l = "patients were asked if their sleep was satisfactory (yes or no) with confirmation by their caregivers. In case patients were unable to describe their sleep, preference was given to caregiver reports"; m = research criteria for depression. Abbreviations Design, C = cross-sectional and L = longitudinal; Setting, C = clinical and P = population; Syndromal diagnosis, MCI = mild cognitive impairment, AD = Alzheimer's disease-type dementia; Dem = dementia. Abbreviations measurement instruments: CAMDEX = Cambridge Mental Disorders of the Elderly Examination; BDI = Beck Depression Inventory; Behave-AD = Behavioural Pathology in Alzheimer's Disease Rating Scale; BRSD = Behavioural Rating Scale for Dementia; BPRS = Brief Psychiatric Rating Scale; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CMAI = Cohen-Mansfield Agitation Inventory; Cornell = Cornell Scale for Depression in Dementia; CUSPAD = Columbia University Scale for Psychopathology in Alzheimer's Disease; DIS = Diagnostic Interview Schedule ; DSM-III-R = Diagnostic Statistical Manual of Mental Disorders, Third Edition, Revised; DSM-IV = Diagnostic Statistical Manual of Mental Disorders, Fourth Edition; GDS-15 = Geriatric Depression Screening Scale, 15 items; GDS-30 = Geriatric Depression Screening Scale, 30 items; GMS = Geriatric Mental State Scale; HAMD-D = Hamilton Depression Rating Scale/HDRS = Hamilton Rating Scale for Depression; ICD-10 = International Classification of Disease – 10 Classification of Mental and Behavioural Disorders; mABRS = Modified Agitated Behaviour Rating Scale; NPI = Neuropsychiatric Inventory, either 10 or 12 items; NPI-D = Neuropsychiatric Inventory Caregiver Distress Scale; NPI-Q = Neuropsychiatric Inventory Questionnaire; PANSS-N = Positive and Negative Symptoms Scale, negative items; PBE = Present Behavioural Examination; SCID = Structured Clinical Interview for Diagnostic and Statistical manual of Mental Disorders, Third Edition, Revised

3.2. Participant characteristics

As described above, data from in total 12,801 subjects were included for the present study. The pooled mean baseline characteristics were as follows: age 75.7 years (range 67.8 to 88.4), MMSE score 17.3 (range 10.4 to 26.9) and education 8.9 years (range 4.0 to 14.2). APOE ε4 carriership was known for 10,710 subjects (5,346 ε4-carriers, of whom 24.0% had additional information on zygosity). See Table 2 for number of subjects with affective symptoms present according to genotype.

Table 2. APOE genotype by presence of symptoms

		Symptoms present					
Baseline sample		Agitation	Depression	Anxiety	Apathy	Irritability	Sleep distur.
ε4+	5,346	815	1,359	717	562	448	297
ε4-	5,364	878	1,521	769	708	518	447
Total	10,710	1,693	2,880	1,486	1,270	966	774
ε4 homozygotes	800	90	118	59	62	44	31
ε4 heterozygotes	3,373	429	471	239	252	215	137

Note. The definition of APOE ε4 carriership differed per study: 21 studies included - next to the genotypes APOE ε3/ε4 and ε4/ε4 - also the genotype ε2/ε4[29, 32, 39, 48, 50, 52, 55, 59, 61, 62, 65, 67-69, 71, 77, 80, 82, 84-86]; whereas 9 studies did not include ε2/ε4, e.g. because ε2/ε4 frequencies were too low or because of the protective effect of the ε2 allele[38, 40, 44, 49, 51, 54, 58, 66, 79], and without specification in the remaining studies.

ε4+, APOE ε4 allele carriers; ε4-, APOE ε4 allele non-carriers

3.3. Depression

Forty-one studies investigated the association between APOE genotype and depression. Based on the available data to calculate effect sizes, the results of 28 studies could be included in the meta-analysis[29-31, 38, 40-63], representing 9,476 subjects (44.5% females). Overall, there was no association between APOE ε4 carriership and the presence of depression (OR = 1.09, 95% CI 0.98-1.22; Figure 1). Similar results were found for adjusted estimates, hetero- and homozygotes. Based on unadjusted estimates, a positive association between APOE ε4 carriership and the presence of depression was found (OR = 1.23, 95% CI 1.08-1.40), with a small amount of heterogeneity (I^2 = 8.45%, p = 0.298), with an asymmetrical funnel plot (see Appendix 4, Figure 4) and with suggestion of small-study effects (Egger test, p = 0.002). In meta-regression, higher mean MMSE score and less

females included were shown to significantly increase the effect (resp. p = 0.025 and p = 0.046). Further, stratified analyses showed that the association only hold true for studies that were clinical based (but not population based), cross-sectional studies (but not longitudinal) that assessed depressive symptoms with self- and clinician reports (but not caregiver report). The overall effects and heterogeneity across studies, also within stratifications, are shown in Appendix 3 Table 1.

Thirteen studies could not be included due to incomplete data reporting, and in line with the results of the meta-analysis, nearly all studies did not find an association between APOE ε4 and depression: not with severity of depression[64, 65], nor with presence of depression[39, 64, 66-74]. Only one study reported an association between APOE ε4 and presence of depression in subjects with AD[75], which is a multi-center, clinically based, cross-sectional study that assessed depressive symptoms using caregiver-reports.

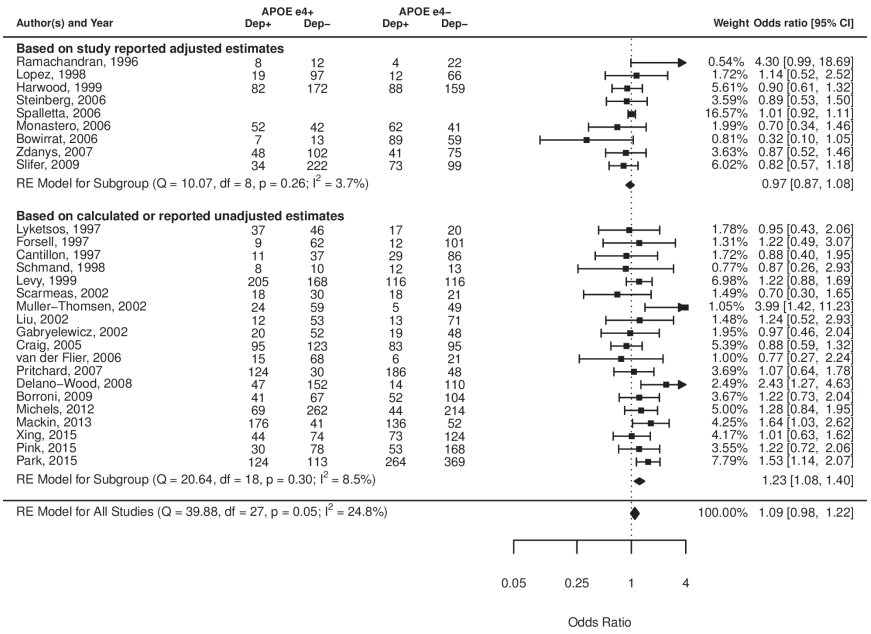

Figure 2. Forest plot of the relationship between APOE ε4 carriership and presence of depression. Subanalyses on adjusted odds ratios and unadjusted odds ratios.

APOE e4+ = APOE ε4 allele carriers; APOE e4- = APOE ε4 allele non-carriers; Dep + = depression present; Dep - = depression absent; CI = confidence interval

3.4. Anxiety

Seventeen studies investigated the association between APOE genotype and anxiety. Results of 11 studies were included in the meta-analysis[29-31, 40, 42, 48, 54, 57, 61-63], representing 4148 subjects (44.8% females). Overall, there was no association between APOE ε4 carriership and the presence of anxiety (OR = 1.25, 95% CI 0.97-1.62; Figure 3). Similar results were found for adjusted estimates, hetero- and homozygotes. Based on unadjusted estimates, a positive association was found (OR = 1.53, 95% CI 1.09-2.15), with moderate heterogeneity (I^2 = 66.89%, p = 0.017), with an asymmetrical funnel plot (see Appendix 4, Figure 6) and with suggestion of small-study effects (Egger test, p = 0.014). In meta-regression, assessment method was identified as having a significant effect on the association (p < 0.001) and was therefore used to further stratify the meta-analysis thereby reducing I^2 substantially (see Figure 4). Additionally, subgroup analysis showed that the overall effect was due to one longitudinal study[57], as pooling of the remaining 6 cross-sectional studies resulted in no association found (OR = 1.47, 95% CI 0.99-2.19). The overall effects and heterogeneity across studies, also within stratifications, are shown in Appendix 3 Table 2.

Six studies could not be included and, in line with the results of the meta-analysis, nearly all studies did not found an association between APOE ε4 and anxiety[65, 66, 68, 70, 71]. Only one study reported APOE ε4 carriers having more severe symptoms of anxiety in subjects with AD[74], which is a single-center, clinically based, cross-sectional study that assessed anxiety symptoms using caregiver-reports.

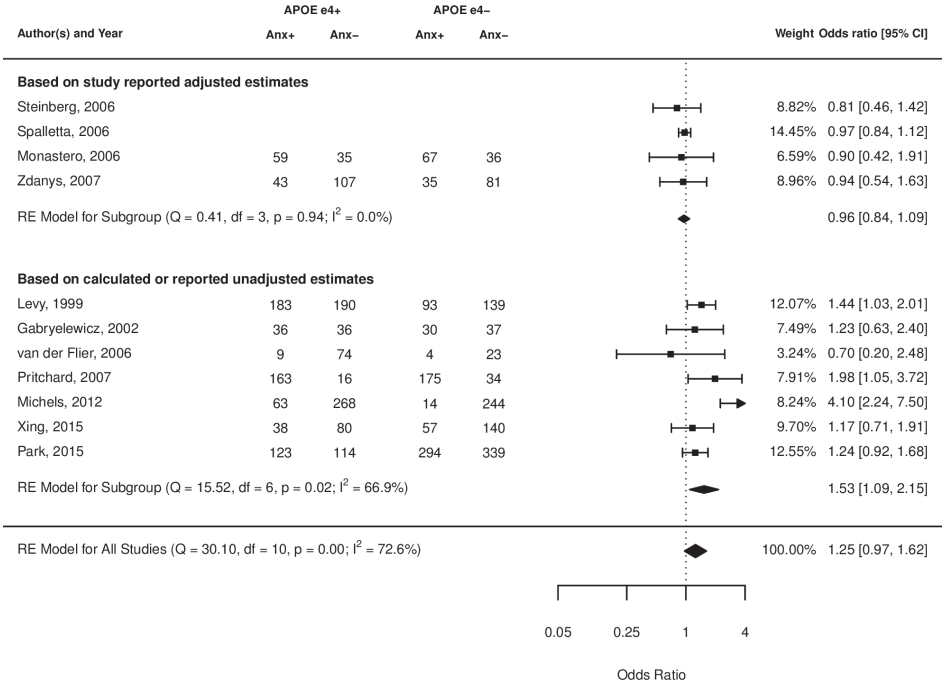

Figure 3. Forest plot of the relationship between APOE ε4 carriership and presence of anxiety. Subanalyses on adjusted odds ratios and unadjusted odds ratios.

APOE e4+ = APOE ε4 allele carriers; APOE e4- = APOE ε4 allele non-carriers; Anx + = anxiety present; Anx - = anxiety absent; CI = confidence interval

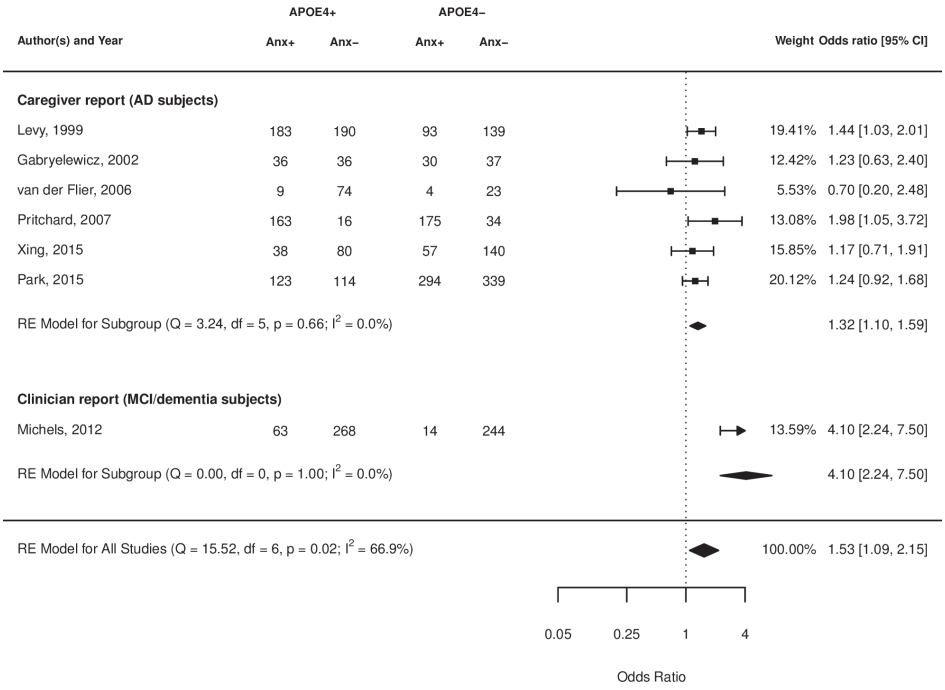

Figure 4. Forest plot of the relationship between APOE ε4 carriership and presence of anxiety, unadjusted estimates. Subanalyses on caregiver (all AD patients) vs. clinician report (MCI and dementia patients).

APOE e4+ = APOE ε4 allele carriers; APOE e4- = APOE ε4 allele non-carriers; Anx + = anxiety present; Anx - = anxiety absent; CI = confidence interval

3.5. Apathy

Sixteen studies investigated the association between APOE genotype and apathy. Results of 9 studies were included in the meta-analysis[29-31, 42, 54, 56, 61-63], representing 3194 subjects (49.5% females). There was no association between APOE ε4 carriership and the presence of apathy (OR = 1.00, 95% CI 0.84-1.19; Figure 5). Similar results were found for adjusted and unadjusted estimates, for hetero- and homozygotes. The overall effects and (possible sources of -) heterogeneity across studies, within stratifications, are shown in Appendix 3 Table 3.

Seven studies could not be included and, in line with the results of the meta-analysis, the majority did not found an association between APOE ε4 and apathy[65, 66, 70, 71]. Two studies report an association, one with APOE ε4 carriers having more severe symptoms of apathy[74] whereas the other reports APOE ε4 carriers having less symptoms of apathy[68], although this effect was only found in moderately severe AD dementia.

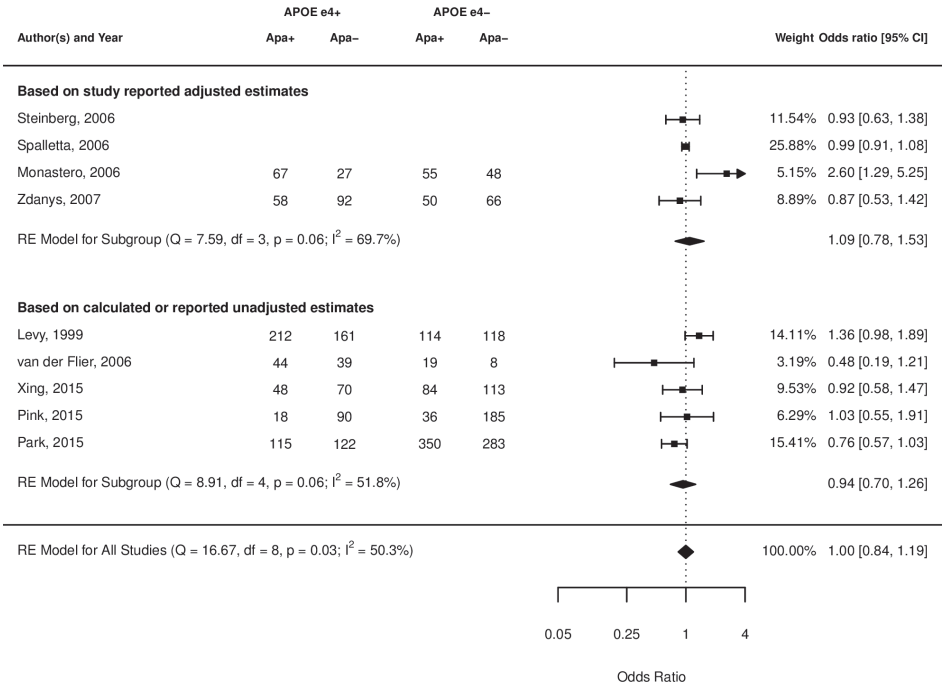

Figure 5. Forest plot of the relationship between APOE ε4 carriership and presence of apathy. Subanalyses on adjusted odds ratios and unadjusted odds ratios.

APOE e4+ = APOE ε4 allele carriers; APOE e4- = APOE ε4 allele non-carriers; Apa + = apathy present; Apa - = apathy absent; CI = confidence interval

3.6. Agitation

Twenty studies investigated the association between APOE genotype and agitation. Results of 12 studies were included in the meta-analysis[29-31, 42, 54, 56, 57, 61-63, 76, 77], representing 4772 subjects (54.3% females). Overall, there was no association between APOE ε4 carriership and the presence of agitation (OR = 1.07, 95% CI 0.94-1.20; Figure 6). Similar results were found for adjusted and unadjusted estimates, for hetero- and homozygotes. The overall effects and (possible sources of -) heterogeneity across studies, within stratifications, are shown in Appendix 3 Table 4.

Eight studies could not be included and, in line with the results of the meta-analysis, the majority did not found an association between APOE ε4 and agitation[65, 66, 68, 70, 71, 74, 78]. One study reports a positive association between APOE ε4 and agitation in subjects with dementia[32], which is a single-center, clinically based, cross-sectional study that assessed symptoms of agitation with clinician ratings.

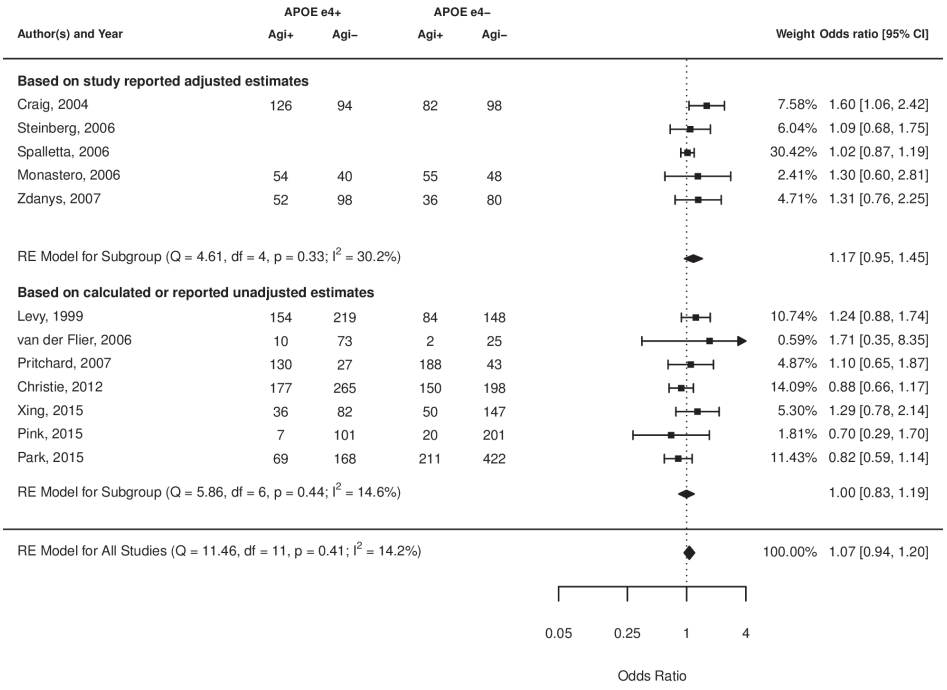

Figure 6. Forest plot of the relationship between APOE ε4 carriership and presence of agitation. Subanalyses on adjusted odds ratios and unadjusted odds ratios.

APOE e4+ = APOE ε4 allele carriers; APOE e4- = APOE ε4 allele non-carriers; Agi + = agitation present; Agi - = agitation absent; CI = confidence interval

3.7. Irritability

Fourteen studies investigated the association between APOE genotype and irritability. Results of 8 studies were included in the meta-analysis[29-31, 42, 54, 61-63], representing 2862 subjects (50.0% females). Overall, there was no association between APOE ε4 carriership and the presence of irritability (OR = 1.17, 95% CI 0.93-1.48; Figure 7). Similar results were found for adjusted and unadjusted estimates, for hetero- and homozygotes. The overall effects and (possible sources of -) heterogeneity across studies, within stratifications, are shown in Appendix 3 Table 5.

Six studies could not be included and, in line with the results of the meta-analysis, none of the studies found an association between APOE ε4 and irritability[65, 66, 68, 70, 71, 74].

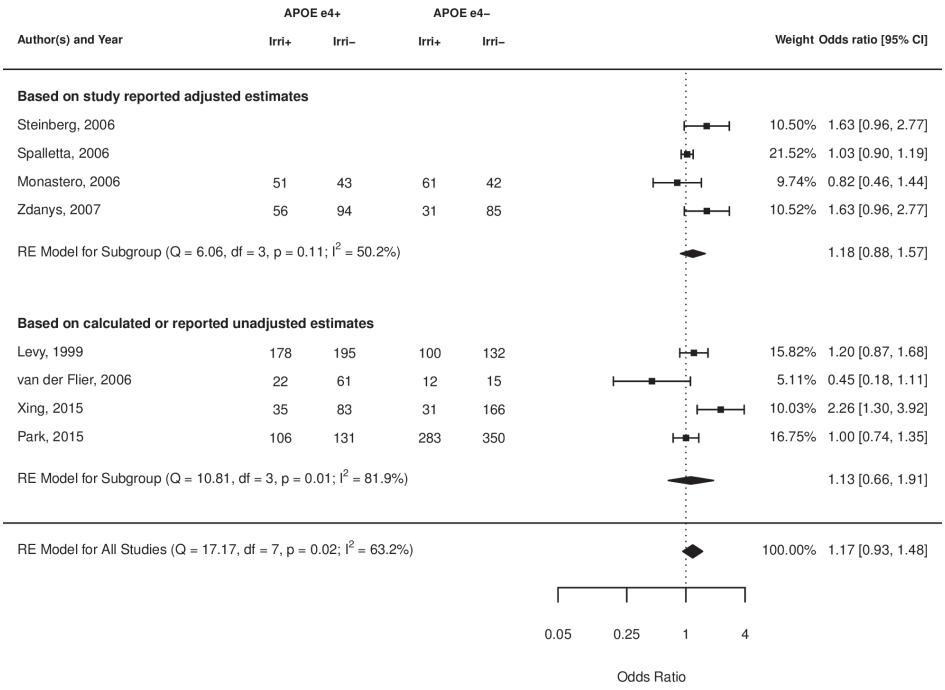

Figure 7. Forest plot of the relationship between APOE ε4 carriership and presence of irritability. Subanalyses on adjusted odds ratios and unadjusted odds ratios.

APOE e4+ = APOE ε4 allele carriers; APOE e4- = APOE ε4 allele non-carriers; Irri + = irritability present; Irri - = irritability absent; CI = confidence interval

3.8. Sleep disturbances (night-time behaviour and sleep disturbances)

Ten studies investigated the association between APOE genotype and sleep disturbances. Results of 8 studies were included in the meta-analysis[30, 54, 56, 62, 63, 70, 79, 80], representing 2749 subjects (53.4% females). Overall, there was no association between APOE-e4 carriership and the presence of sleep disturbances (OR = 0.89, 95% CI 0.68-1.18; Figure 8). Similar results were found for adjusted and unadjusted estimates, for hetero- and homozygotes. The overall effects and (possible sources of -) heterogeneity across studies, within stratifications, are shown in Appendix 3 Table 6.

Two studies could not be included, of which one reported APOE ε4 carriers experiencing less sleep disturbances[66], whereas the other study found no association[74] in subjects with AD.

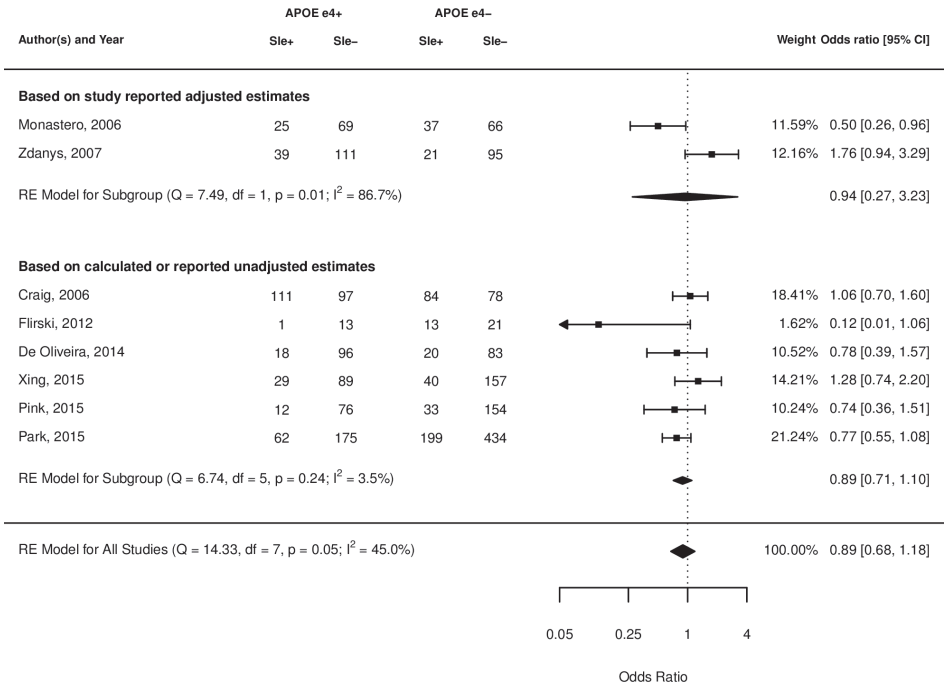

Figure 8. Forest plot of the relationship between APOE ε4 carriership and presence of sleep disturbances. Subanalyses on adjusted odds ratios and unadjusted odds ratios.

APOE e4+ = APOE ε4 allele carriers; APOE e4- = APOE ε4 allele non-carriers; Sle + = sleep disturbances present; Sle - = sleep disturbances absent; CI = confidence interval

3.9. Subsyndromes

Six studies assessed APOE genotype in relation to subsyndromes of neuropsychiatric symptoms (NPS). Of these, two used the European Alzheimer Disease Consortium factor analysis[1, 81] that formed a psychotic, affective, hyperactive and apathetic subsyndrome. APOE-e4 carriers were found to have an increased risk of affective and apathetic syndromes[82] whereas another study did not find associations[83]. One study identified agitation/aggression-delusion, euphoria-disinhibition, depression-apathy, hallucination-nighttime behaviour, and appetite as subsyndromes and found APOE ε4 carriers to have higher scores in the agitation/aggression-delusion subsyndrome[84]. Another study identified behavioural dyscontrol (euphoria, disinhibition, aberrant motor behaviour, and sleep and appetite disturbances), psychosis (delusions and hallucinations), mood (depression, anxiety, and apathy), and agitation (aggression and irritability) subsyndromes, of which none was associated with APOE ε4[85]. Another identified disorders of thought, disorders of perception, disorders of mood, disorders of behaviour (into wandering and stereotypical behaviours) and neurovegetative features; none of these subsyndromes were associated with APOE ε4[72]. One study grouped anxiety, depression and psychotic symptoms together and report APOE ε4 carriers having more often these symptoms[86].

4. DISCUSSION

In this systematic review and meta-analysis an overview is provided of association data between APOE genotype and affective symptoms, pooling data from 12,801 subjects with cognitive decline. Overall, it could be concluded that meta-analyses showed no association between APOE genotype and depression, anxiety, apathy, agitation, irritability and sleep disturbances, neither for APOE ε4 carriership nor zygosity. These results were in line with descriptive results of studies that could not be included in meta-analysis due to incomplete data-reporting.

This meta-analysis and systematic review extends on previous reviews on the topic[22, 23]. While these reviews suggested that assessing APOE status in either ε4-carriership or number of ε4-alleles possibly could account for the discrepancy in findings, analyses of the current study on APOE ε4 carriership and zygosity all pointed in the same direction: namely, there is no association between APOE genotype and affective symptoms. It was also suggested that differences in sample composition could be a possible source of discrepancy[22, 23]. Indeed, moderate heterogeneity that was observed for the positive association for (unadjusted estimates) anxiety was (partly) explained by variation in diagnostic groups included. However, the only study including MCI subjects next to subjects with dementia was also the only one using clinician reported presence of anxiety symptoms instead of

caregiver reported symptoms[40]. Thus, it is difficult to disentangle the contributing effect of underlying heterogeneity. Further, removal of studies that did not differentiate between types of dementia from meta-analyses (i.e. number of subjects with AD dementia was not specified[38, 40-42]) did not change the results. Of the five studies including MCI subjects, only one specified MCI subtypes (i.e., amnestic/non-amnestic, single/multiple-domain)[56]. This subtyping however, was used for another research question addressed by the paper (i.e. to examine whether an interaction between subtype and any NPS influenced the outcome of incident dementia). MCI was diagnosed according to (or in accordance with) Petersen criteria[40, 53, 56, 65, 70]. It is important to note that all diagnostic criteria employed were syndromal (i.e., based on clinical consequences of the disease, such as the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA[87]), DSM, ICD-10 and National Institute on Aging-Alzheimer's Association (NIA-AA[88]) criteria and not, as was recently suggested by the NIA-AA AT(N) research framework[89], biologically based. It is therefore currently not possible to explore the differential effect between MCI subtypes or disease etiologies. Increased incorporation in future research of the NIA-AA criteria[89] will provide an interesting opportunity for this.

The use of a wide-range of instruments to assess affective symptoms can be a possible cause of heterogeneity. Meta-regression findings showed that this was indeed the case for anxiety (as described above) and depression, but not for the other symptoms. Additionally, measuring symptoms vs. a syndromal diagnosis was not identified as having a significant effect on the association. Further, as overall burden of NPS is observed to be more severe in later stages of the disease, the previous mentioned reviews concluded that disease severity or disease duration should be corrected for[22, 23], something that few studies did. Indeed, disease severity based on MMSE score showed to explain some of the variance across depression, agitation and irritability studies (see S4 Appendix Tables 1, 4 and 5).

In addition to the above-described factors (i.e. diagnostic groups included, symptom assessment (self- or proxy) and definitions (symptom or disorder) used), study design and setting were also identified to explain the observed heterogeneity for depression and anxiety studies. That is, the association only held true for depression in cross-sectional and clinical studies (but not longitudinal or population based studies) and for anxiety the positive effect was driven by one longitudinal study[57]. Further, age and MMSE score were identified in meta-regression analysis as explaining some of the variance across studies. Thus, it is very likely that, in case these studies would have corrected for sample characteristics, the association would have disappeared.

The tendency of affective symptoms to wax and wane over time, e.g. depression decreases whereas apathy increases over time[90], and the inherent limitation of cross-

sectional studies to interpret causality in the association implies that the association should be assessed in longitudinal designs. Indeed, only a limited number of studies assessing the prospective associations could be identified in the literature search (n = 7). The majority of these studies did not report the predictive value of APOE genotype on the development of affective symptoms over time, although one study suggested a protective effect of the ε4-allele in MCI subjects for developing sleep disturbances[70]. Three studies stratified their sample according to gender, and showed associations of APOE ε4 and affective symptoms to be higher within female subjects as compared to males (depression and irritability, resp.[47, 62]), although another study reported the opposite, with a (negative) association being stronger in males[44]. Here, the effect between APOE ε4 carriership and depression and between APOE ε4 homozygosity and apathy was found to be smaller when more females were included, i.e. contrasting prior results.

In this meta-analysis, three studies, all related to depression, had a sample size smaller than 100 subjects (resp. n = 46, 87 and 43;[41, 58, 59]) but exclusion of these studies did not change the results (OR = 1.09, 95% CI 0.98-1.22). Although methodological quality of studies was found to be moderate, it did not influence the effects found. The quality ratings might be underestimated, as ratings were based on information provided in the paper and not all included studies had the APOE genotype – affective symptom association as main research question[39, 41, 49, 53, 56, 78, 83].

The findings of this meta-analysis have implications for the view on the relationship between affective symptoms and AD, of which the exact mechanisms are still not fully understood. Possibly, the affective symptomatology is a non-cognitive manifestation of already ongoing AD pathology or act as a risk factor for AD, where affective symptoms induce a biological cascade in the brain. Even though affective symptoms were not found to be associated with APOE genotype, this does not undermine the clinical importance of identifying and monitoring the highly prevalent affective symptoms in (prodromal) AD dementia. The complex nature of affective symptoms indicates that clinicians should approach affective symptoms in a multifactorial manner.

Strengths and limitations

By using all the available evidence, pooling a large amount of information and adjusting for a large number of known confounders, this study concluded that APOE genotype is not associated with affective symptomatology in MCI and AD dementia. The current study showed that factors that fueled discussions as potential sources of discrepancies do not contribute to the contrasting findings. As the percentage of APOE ε4 carriers was found to be higher in clinical settings than in population settings (resp. 50.9 and 40.8%), studies per

study setting (i.e. population vs. clinical studies) were stratified in order to minimize the risk that the results were primarily driven by referral bias of the clinical samples.

Some methodological issues warrant further discussion. Analyses were not limited to studies reporting fully adjusted ORs only, as this would have led to the exclusion of 63% of the estimates. Thus, it is possible that confounders influenced the associations. Further, adjusted estimates were corrected for different sets of possible confounders. However, most studies adjusted minimally for age and sex – where additional adjusting for education or disease severity did not change the results. In addition, although a large number of confounders were included in the meta-regressions, some factors were not commonly reported at study level (e.g. educational level) and thus could not be considered for all symptoms in the analyses.

Surprisingly, only six studies provided information on psychiatric history of their subjects. Except for one study[52], these data were used for descriptive purposes only[38, 45, 46, 73, 77]. Studying underlying biological mechanisms of NPS in dementia and not controlling for psychiatric history could have implications for the interpretation of the findings. That is, first-time onset of depressive symptoms in AD is probably due to a different disease etiology when compared to depressive symptoms in AD that are recurrent (i.e. history of depressive disorder). In addition, presence of somatic comorbidities or prescription of medication potentially confounds the relationship between APOE genotype and affective symptoms. However, only one[68] out of eight[32, 38, 63, 66, 68, 75, 80, 82] studies that have provided information on medication use (e.g. antidepressants or antipsychotics) corrected for this in their analyses; none of the seven studies[32, 38, 42-44, 51, 66] mentioning somatic comorbidities (e.g. hypertension, diabetes and cardiovascular diseases) corrected for this in their analyses.

Finally, the most important limitation is, although inherent to genetic studies, the fact that investigating the association between one gene and complex traits such as affective symptoms is an oversimplification. The effect of individual polymorphisms, here APOE ε4, is usually weak and requires large cohorts to demonstrate associations. It is more probable that gene-environment interactions take place or that multiple genes are involved, which is an important topic for future research. In addition, future work should focus on the interplay between other biological factors, such as alterations in the hypothalamus-pituitary-adrenal axis[91], (nor)adrenergic, serotoninergic and dopaminergic neurotransmitter systems[92], neuroinflammation markers[93] amyloid plaques and neuronal injury markers[18], and cerebrovascular changes[94] that have been linked to affective symptoms in AD. An important starting point can be the interpretation of neuropathological evidence, such as amyloid plaques and neuronal injury markers.

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SUPPLEMENTARY DATA

Appendix 1. Complete search strategy

PubMed

S1	((cognitiv* OR cognition or memory) AND (declin* OR impair* OR deteriora* OR change* OR deficit* OR complaint*)) OR dementia OR Alzheimer* OR "pre-clinical AD" OR "preclinical AD" OR predementia* OR "prodromal AD" [Title/Abstract]
S2	"neuropsychiatric symptoms" OR "neuro-psychiatric symptoms" OR "neuropsychiatric syndromes" OR "neuro-psychiatric syndromes" OR "psycho-behavioral symptoms" OR "psycho-behavioural symptoms" OR "psychiatric symptoms" OR "behavioral symptoms" OR "behavioural symptoms" OR "psychological symptoms" OR "disruptive behavior" OR "disruptive behaviour" OR "non-cognitive symptoms" OR "neuropsychological symptoms" OR "bpsd" OR "nps" OR dysphoria OR depression OR depressive OR depressed OR anxiety OR anxious OR apathy OR "lack of interest" OR sleep OR irritability OR lability OR "mood change" OR "mood changes" OR agitation OR agitated OR aggression OR rage OR "catastrophic reactions" OR anger OR angry OR complaining OR negativism OR screaming [Title/Abstract]
S3	apolipoprotein* OR apoe*
S4	"humans"[MeSH Terms]
S5	Dutch[lang] OR English[lang] OR French[lang] OR German[lang])

CINAHL (EBSCOhost)

S1	TI ((((cognitiv* or cognition or memory) and (declin* or impair* or deteriora* or change* or deficit* or complaint*)) or dementia or Alzheimer* or "pre-clinical AD" or "preclinical AD" or predementia* or "prodromal AD")) OR AB ((((cognitiv* or cognition or memory) and (declin* or impair* or deteriora* or change* or deficit* or complaint*)) or dementia or Alzheimer* or "pre-clinical AD" or "preclinical AD" or predementia* or "prodromal AD"))
S2	TI (("neuropsychiatric symptoms" or "neuro-psychiatric symptoms" or "neuropsychiatric syndromes" or "neuro-psychiatric syndromes" or "psycho-behavioral symptoms" or "psycho-behavioural symptoms" or "psychiatric symptoms" or "behavioral symptoms" or "behavioural symptoms" or "psychological symptoms" or "disruptive behavior" or "disruptive behaviour" or "non-cognitive symptoms" or "neuropsychological symptoms" or "bpsd" or "nps" or dysphoria or depression or depressive or depressed or anxiety or anxious or apathy or "lack of interest" or sleep or irritability or lability or "mood change" or "mood changes" or agitation or agitated or aggression or rage or "catastrophic reactions" or anger or angry or complaining or negativism or screaming)) OR AB (("neuropsychiatric symptoms" or "neuro-psychiatric symptoms" or "neuropsychiatric syndromes" or "neuro-psychiatric syndromes" or "psycho-behavioral symptoms" or "psycho-behavioural symptoms" or "psychiatric symptoms" or "behavioral symptoms" or "behavioural symptoms" or "psychological symptoms" or "disruptive behavior" or "disruptive behaviour" or "non-cognitive symptoms" or "neuropsychological symptoms" or "bpsd" or "nps" or dysphoria or depression or depressive or depressed or anxiety or anxious or apathy or "lack of interest" or sleep or irritability or lability or "mood change" or "mood changes" or agitation or agitated or aggression or rage or "catastrophic reactions" or anger or angry or complaining or negativism or screaming))
S3	apolipoprotein* or apoe*
S4	S1 AND S2 AND S3
Limiters	Language: Dutch, English, French, German; Population Group: Human

PsycINFO (EBSCOhost)

S1	TI ((((cognitiv* or cognition or memory) and (declin* or impair* or deteriora* or change* or deficit* or complaint*)) or dementia or Alzheimer* or "pre-clinical AD" or "preclinical AD" or predementia* or "prodromal AD")) OR AB ((((cognitiv* or cognition or memory) and (declin* or impair* or deteriora* or change* or deficit* or complaint*)) or dementia or Alzheimer* or "pre-clinical AD" or "preclinical AD" or predementia* or "prodromal AD"))
S2	TI (("neuropsychiatric symptoms" or "neuro-psychiatric symptoms" or "neuropsychiatric syndromes" or "neuro-psychiatric syndromes" or "psycho-behavioral symptoms" or "psycho-behavioural symptoms" or "psychiatric symptoms" or "behavioral symptoms" or "behavioural symptoms" or "psychological symptoms" or "disruptive behavior" or "disruptive behaviour" or "non-cognitive symptoms" or "neuropsychological symptoms" or "bpsd" or "nps" or dysphoria or depression or depressive or depressed or anxiety or anxious or apathy or "lack of interest" or sleep or irritability or lability or "mood change" or "mood changes" or agitation or agitated or aggression or rage or "catastrophic reactions" or anger or angry or complaining or negativism or screaming)) OR AB (("neuropsychiatric symptoms" or "neuro-psychiatric symptoms" or "neuropsychiatric syndromes" or "neuro-psychiatric syndromes" or "psycho-behavioral symptoms" or "psycho-behavioural symptoms" or "psychiatric symptoms" or "behavioral symptoms" or "behavioural symptoms" or "psychological symptoms" or "disruptive behavior" or "disruptive behaviour" or "non-cognitive symptoms" or "neuropsychological symptoms" or "bpsd" or "nps" or dysphoria or depression or depressive or depressed or anxiety or anxious or apathy or "lack of interest" or sleep or irritability or lability or "mood change" or "mood changes" or agitation or agitated or aggression or rage or "catastrophic reactions" or anger or angry or complaining or negativism or screaming))
S3	apolipoprotein* or apoe*
S4	S1 AND S2 AND S3
Limiters	Language: Dutch, English, French, German; Population Group: Human

EMBASE (Ovid)

S1	(((cognitiv* or cognition or memory) and (declin* or impair* or deteriora* or change* or deficit* or complaint*)) or dementia or Alzheimer* or "pre-clinical AD" or "preclinical AD" or predementia* or "prodromal AD").ti,ab.
S2	("neuropsychiatric symptoms" or "neuro-psychiatric symptoms" or "neuropsychiatric syndromes" or "neuro-psychiatric syndromes" or "psycho-behavioral symptoms" or "psycho-behavioural symptoms" or "psychiatric symptoms" or "behavioral symptoms" or "behavioural symptoms" or "psychological symptoms" or "disruptive behavior" or "disruptive behaviour" or "non-cognitive symptoms" or "neuropsychological symptoms" or "bpsd" or "nps" or dysphoria or depression or depressive or depressed or anxiety or anxious or apathy or "lack of interest" or sleep or irritability or lability or "mood change" or "mood changes" or agitation or agitated or aggression or rage or "catastrophic reactions" or anger or angry or complaining or negativism or screaming).ti,ab.
S3	(apolipoprotein* or apoe*).mp.
S4	1 and 2 and 3
S5	limit 4 to (humans and (dutch or english or french or german))

Appendix 2. Quality assessment

Table 1. Quality assessment form according to Newcastle-Ottowa Scale (NOS)[151] for cohort studies

Selection (max★★★)	
S1: Representativeness of the exposed cohort (biomarker positives)	a) For population based studies: truly representative of the average person with cognitive impairment in the community.★ b) For clinical population studies: truly representative of the average person with cognitive impairment in the (memory-) clinic.★ c) Selected group of users e.g. volunteers. d) No description of the derivation of the cohort.
S2: Selection of the non-exposed cohort (biomarker negatives)	a) Drawn from the same source as the exposed cohort★ b) Drawn from a different source. c) No description of the derivation of the non-exposed cohort.
S3: Ascertainment of predictor (biomarker)	a) Validated measurement tool.★ b) Non-validated measurement tool, but the tool is available or described.★ c) No description.
Comparability (max★★)	
Comparability of cohorts on the basis of the design or analysis	a) Study controls for the most important factor (age/).★ b) Study controls for any additional factor (e.g. sex/education/MMSE).★ c) No control for important factors.
Outcome (max★★★★)	
O1: Assessment of outcome	a) Validated measurement tool (affective symptoms must be assessed by either self- or proxy report)★ b) Non-validated measurement tool, but the tool is available or described.★ c) No description.
O2: Was follow-up long enough for outcomes to occur	a) Yes (longer than 6 months).★ b) No.
O3: Adequacy of follow up of cohorts	a) Complete follow up - all patients accounted for.★ b) Patients lost to follow up unlikely to introduce bias (small number lost, i.e. follow up rate is more than 70 %, or description provided of those lost).★ c) Follow up rate < 70% and no description of those lost. d) No statement.
O4: Statistical test	a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value).★ b) The statistical test is not appropriate, not described or incomplete.

Table 2. Quality assessment form according to Newcastle-Ottowa Scale (NOS)[151] adapted for cross-sectional studies

Selection (max★★★)	
S1: Representativeness of exposed cohort (biomarker positives)	a) For population based studies: truly representative of the average person with cognitive impairment in the community.★ b) For clinical population studies: truly representative of the average person with cognitive impairment in the (memory-) clinic.★ c) Selected group of users e.g. volunteers.

	d) No description of the derivation of the cohort.
S2: Sample size, response rate, and comparability between predictor positives and negatives	a) Sample size is justified, response rate AND the comparability between positives and negatives (either A or B) characteristics are described.★ b) Sample size is justified and the response rate OR the comparability between predictor positives and negatives characteristics is described.★ c) Sample size is justified, but no description of the response rate and the characteristics of the predictor positives and negatives . d) Sample size is not justified, and there is no description of the response rate or the characteristics of the predictor positives and negatives . *dependent on definition of predictor and outcome used either (A) biomarker positives and negatives or (B) affective symptoms positives and negatives
S3: Ascertainment of predictor (either biomarker or affective symptoms)	a) Validated measurement tool.★ b) Non-validated measurement tool, but the tool is available or described.★ c) No description.
Comparability (max★★)	
C: Comparability of predictor positives and negatives on the basis of the design or analysis	a) Study controls for the most important factor (age).★ b) Study controls for additional factor (e.g. sex/education/MMSE).★ c) No control for important factors.
Outcome (max★★)	
O1: Assessment of outcome	a) Validated measurement tool, either self- or proxy report★ b) Non-validated measurement tool, but the tool is available or described. c) No description.
O2: Statistical test	a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value).★ b) The statistical test is not appropriate, not described or incomplete.

Table 3. Quality assessment scores according to NOS, cohort studies

		Selection			Comparability	Outcome				Overall	
Author	Year	S1	S2	S3	C1	O1	O2	O3	O4	Sum	Bias
Chang	2004	1	1	1	2	1	1	1	1	9	0
Engelsborghs	2006	1	1	1	0	1	1	0	1	6	1
Flirski	2012	1	1	1	0	1	1	0	0	5	1
Pritchard	2007	1	1	1	2	1	0	1	1	8	1
Scarmeas	2002	1	1	1	2	1	1	1	1	9	0
Schutte	2011	0	1	1	2	1	1	1	0	7	1
Steinberg	2006	1	1	1	2	1	1	1	1	9	0

NOS = Newcastle-Ottowa Scale

Table 4. Quality assessment scores according to NOS, cross-sectional studies

		Selection			Comparability	Outcome		Overall	
Author	Year	S1	S2	S3	C1	O1	O2	Sum	Bias
Borroni	2009	1	1	1	0	0	0	3	1
Borroni	2006	1	0	1	2	1	0	5	0
Bowirrat	2006	1	1	1	1	1	1	6	0
Cantillon	1997	1	1	0	0	1	0	3	1
Chen	2012	1	1	1	1	1	1	6	0
Christie	2012	0	1	1	2	1	1	6	0
Class	1997	1	1	1	0	1	0	4	1
Craig	2004	1	1	1	0	1	1	5	0
Craig	2005	1	0	1	0	1	1	4	1
Craig	2006	1	0	1	0	1	1	4	1
D'Onofrio	2010	1	0	1	0	1	1	4	1
De Oliveira	2014	1	0	1	0	0	0	2	1
Delano-Wood	2007	1	1	1	0	1	1	5	0
Engelborghs	2006	1	0	1	0	1	1	4	1
Farlow	2004	1	1	1	2	1	0	6	0
Forsell	1997	1	1	1	0	1	0	4	1
Fritze	2011	1	1	1	1	1	0	5	0
Gabryelewicz	2002	1	0	1	0	1	0	3	1
Hall	2014	1	0	0	1	1	0	3	1
Harwood	1999	1	0	0	1	1	1	4	1
Hirono	1999	1	0	1	2	1	0	5	0
Hollingworth	2006	0	0	1	0	1	0	2	1
Holmes	1996	1	1	1	0	1	0	4	1
Holmes	1998	1	0	1	1	1	0	4	1
Jefferson	2001	1	0	1	0	0	0	2	1
Levy	1999	1	1	1	0	1	0	4	1
Liu	2002	1	1	1	0	1	0	4	1
Lopez	1998	1	1	1	1	1	1	6	0
Lyketsos	1997	1	1	1	0	1	1	5	0
Mackin	2013	1	0	1	0	1	1	4	1
Michels	2012	1	1	1	0	1	1	5	0
Monastero	2006	1	1	1	2	1	1	7	0
Mou	2015	1	0	1	0	0	0	2	1
Muller-Thomsen	2002	1	1	1	1	1	0	5	0
Oliveira	2017	1	0	1	1	1	1	5	0
Park	2015	1	1	0	0	1	0	3	1

Pink	2015	1	0	1	0	1	0	3	1
Ramachandran	1996	1	1	0	2	1	1	6	0
Scarmeas	2002	1	0	1	1	1	1	5	0
Schmand	1998	1	0	1	0	1	0	3	1
Slifer	2009	1	0	1	2	1	1	6	0
Spalletta	2006	1	1	1	2	1	1	7	0
van der Flier	2006	1	1	1	0	1	0	4	1
Vercelletto	2002	1	0	0	0	1	1	3	1
Woods	2009	1	1	1	0	1	1	5	0
Xing	2015	1	0	1	2	1	1	6	0
Yoo	2014	1	1	1	0	1	0	4	1
Zdanys	2007	1	1	1	2	1	1	7	0

NOS = Newcastle-Ottowa Scale

Appendix 3. Overall effect sizes, heterogeneity and publication bias measures per affective symptom

Table 1. Depression: overall effect sizes, heterogeneity and publication bias measures

	Study (k)	Effect size			Heterogeneity		Publication bias	
Stratification per		Odd's ratio	95% CI		I^2 (%)	p-value	Egger's bias coefficient	p-value
All studies	28	1.09	0.98	1.22	24.8	0.05	1.60	0.11
Adjusted estimates								
All	9	0.97	0.87	1.08	3.7	0.26	-0.61	0.54
Population studies	3	1.00	0.27	3.76	79.7	0.03	0.00	1.00
Clinical studies	6	0.98	0.89	1.08	2.4	0.76	-0.44	0.66
Longitudinal studies	1	0.89	0.53	1.50	-	-	-	-
Cross-sectional studies	8	0.97	0.87	1.08	4.2	0.19	-0.55	0.58
Self-report	1	0.82	0.57	1.18	-	-	-	-
Caregiver report	4	1.00	0.91	1.09	0.0	0.70	-0.09	0.93
Clinician report	4	1.00	0.47	2.16	68.5	0.06	0.01	0.99
Unadjusted estimates								
All[1]	19	1.23	1.08	1.40	8.4	0.30	3.09	0.00
Population studies	3	1.17	0.76	1.79	0.0	0.88	0.72	0.47
Clinical studies	16	1.23	1.07	1.43	15.8	0.16	2.83	0.00
Longitudinal studies	2	0.96	0.62	1.48	0.0	0.41	-0.20	0.84
Cross-sectional studies	17	1.26	1.10	1.45	9.4	0.29	3.26	0.00
Self-report	1	1.64	1.03	2.62	-	-	-	-
Caregiver report	11	1.11	0.94	1.32	16.1	0.59	1.20	0.23
Clinician report	7	1.44	1.10	1.87	11.2	0.22	2.70	0.01
Studies on zygosity								
All homozygosity studies	10	0.89	0.64	1.22	21.7	0.34	-0.74	0.46
All heterozygosity studies	10	1.01	0.85	1.20	0.0	0.79	0.16	0.88

CI Confidence interval

[1]Meta-regression showed significant effects of mean MMSE score (p = 0.0247) and percentage of females (p = 0.0455)

Table 2. Anxiety: overall effect sizes, heterogeneity and publication bias measures

	Study (k)	Effect size			Heterogeneity		Publication bias	
Stratification per		Odd's ratio	95% CI		I^2 (%)	p-value	Egger's bias coefficient	p-value
All studies	11	1.25	0.97	1.62	73	0.00	1.72	0.09
Adjusted estimates								
All	4	0.96	0.84	1.09	0	0.94	-0.67	0.51
Population studies	1	0.81	0.46	1.42	-	-	-	-
Clinical studies	3	0.97	0.84	1.10	0	0.98	-0.51	0.61
Longitudinal studies	1	0.81	0.46	1.42	-	-	-	-
Cross-sectional studies	3	0.97	0.84	1.10	0	0.98	-0.51	0.61
Unadjusted estimates								
All[1]	7	1.53	1.09	2.15	67	0.02	2.46	0.01
Longitudinal studies	1	1.98	1.05	3.72	-	-	-	-
Cross-sectional studies	6	1.47	0.99	2.19	73	0.01	1.91	0.06
Caregiver report	6	1.32	1.10	1.59	0	0.66	3.00	0.00
Clinician report	1	4.10	2.24	7.50	-	-	-	-
All homozygosity studies[2]	4	1.46	0.69	3.13	68	0.03	0.99	0.32
All heterozygosity studies	4	1.53	0.73	3.18	83	0.00	1.13	0.26

CI Confidence interval

[1]Meta-regression showed significant effects of way of symptom assessment ($p < .001$) and diagnostic group ($p < .001$), [2]meta-regression showed significant effects of way of symptom assessment ($p < .001$) and mean age ($p < .001$)

Table 3. Apathy: overall effect sizes, heterogeneity and publication bias measures

	Study (k)	Effect size			Heterogeneity		Publication bias	
Stratification per		Odd's ratio	95% CI		I^2 (%)	Odd's ratio	95% CI	p-value
All studies[1]	9	1.00	0.84	1.19	50	0.03	-0.02	0.98
Adjusted estimates								
All	4	1.09	0.78	1.53	70	0.06	0.50	0.61
Population studies	1	0.93	0.63	1.38	-	-	-	-
Adj. clinical studies	3	1.22	0.68	2.20	83	0.02	0.67	0.50
Longitudinal studies	1	0.93	0.63	1.38	-	-	-	-
Cross-sectional studies	3	1.22	0.68	2.20	83	0.02	0.67	0.50
Unadjusted estimates								
All[2]	5	0.94	0.70	1.26	52	0.06	-0.44	0.66
Population studies	1	1.03	0.55	1.91	-	-	-	-
Clinical studies	4	0.91	0.63	1.31	64	0.03	-0.51	0.61
All homozygosity studies[3]	3	0.95	0.47	1.92	53	0.12	-0.14	0.89
All heterozygosity studies	3	0.93	0.54	1.58	64	0.07	-0.28	0.78

CI Confidence interval

[1]Meta-regression showed significant effects of year of publication ($p = 0.025$), [2]meta-regression showed significant effects of year of publication ($p = 0.026$), mean age ($p < 0.01$), [3]meta-regression showed significant effects of year of publication ($p = 0.039$) and percentage of females ($p = 0.047$)

Table 4. Agitation: overall effect sizes, heterogeneity and publication bias measures

	Study (k)	Effect size			Heterogeneity		Publication bias	
Stratification per		Odd's ratio	95% CI		I^2 (%)	p-value	Egger's bias coefficient	p-value
All studies[1]	12	1.07	0.94	1.20	14	0.41	1.02	0.31
Adjusted estimates								
All	5	1.17	0.95	1.45	30	0.33	1.49	0.14
Population studies	1	1.09	0.68	1.75	-	-	-	-
Clinical studies	4	1.21	0.93	1.58	42	0.20	1.45	0.15
Longitudinal studies	1	1.09	0.68	1.75	-	-	-	-
Cross-sectional studies	4	1.21	0.93	1.58	42	0.20	1.45	0.15
Unadjusted estimates								
All	7	1.00	0.83	1.19	15	0.44	-0.03	0.97
Population studies	1	0.70	0.29	1.70	-	-	-	-
Clinical studies	6	1.01	0.84	1.22	20	0.39	0.14	0.89
Longitudinal studies	1	1.10	0.65	1.87	-	-	-	-
Cross-sectional studies	6	0.99	0.81	1.21	22	0.34	-0.11	0.91
All homozygosity studies[2]	5	1.10	0.64	1.90	62	0.03	0.35	0.73
All heterozygosity studies[3]	5	1.21	0.92	1.59	44	0.17	1.38	0.17

CI Confidence interval

[1]Meta-regression showed significant effects of year of publication (p = 0.040), [2]meta-regression showed significant effects of mean MMSE score (p = 0.029), [3]meta-regression showed significant effects of year of publication (p = 0.022)

Table 5. Irritability: overall effect sizes, heterogeneity and publication bias measures

	Study (k)	Effect size			Heterogeneity		Publication bias	
Stratification per		Odd's ratio	95% CI		I^2 (%)	p-value	Egger's bias coefficient	p-value
All studies[1]	8	1.17	0.93	1.48	63	0.02	1.36	0.17
Adjusted estimates								
All[2]	4	1.18	0.88	1.57	50	0.11	1.10	0.27
Population studies	1	1.63	0.96	2.77	-	-	-	-
Clinical studies	3	1.08	0.84	1.39	33	0.17	0.58	0.56
Longitudinal studies	1	1.63	0.96	2.77	-	-	-	-
Cross-sectional studies	3	1.08	0.84	1.39	33	0.17	0.58	0.56
Unadjusted estimates								
All[3]	4	1.13	0.66	1.91	82	0.01	0.44	0.66
All homozygosity studies	3	0.93	0.60	1.44	0	0.90	-0.31	0.75
All heterozygosity studies[4]	3	1.12	0.53	2.37	81	0.03	0.30	0.76

[1]Meta-regression showed significant effects of percentage of APOE ε4 carriers ($p = 0.025$), [2]meta-regression showed significant effects of study quality ($p = 0.011$), [3]meta-regression showed significant effects of mean MMSE score ($p = 0.011$), [4]meta-regression showed significant effects of percentage APOE ε4 heterozygotes ($p < 0.01$)

Table 6. Sleep disturbances: overall effect sizes, heterogeneity and publication bias measures

	Study (k)	Effect size			Heterogeneity		Publication bias	
Stratification per		Odd's ratio	95% CI		I^2 (%)	p-value	Egger's bias coefficient	p-value
All studies	8	0.89	0.68	1.18	45.0	0.05	-0.78	0.44
Adjusted estimates								
All	2	0.94	0.27	3.23	86.7	0.01	-0.10	0.92
Unadjusted estimates								
All	6	0.89	0.71	1.10	3.5	0.24	-1.06	0.29
Population studies	1	0.74	0.36	1.51	-	-	-	-
Clinical studies	5	0.91	0.71	1.16	11.7	0.17	-0.78	0.44
Longitudinal studies	1	0.12	0.01	1.07	-	-	-	-
Cross-sectional studies	5	0.91	0.73	1.13	4.0	0.48	-0.88	0.38
All homozygosity studies	3	0.85	0.49	1.44	13.5	0.35	-0.62	0.54
All heterozygosity studies	3	1.03	0.73	1.46	8.3	0.29	0.19	0.85

CI Confidence interval

Appendix 4. Funnel plots

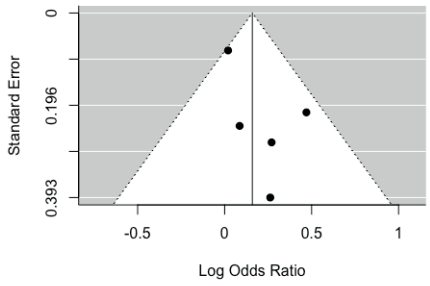

Fig 1. Agitation studies with adjusted estimates

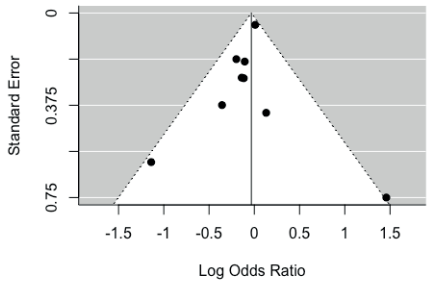

Fig 3. Depression studies with adjusted estimates

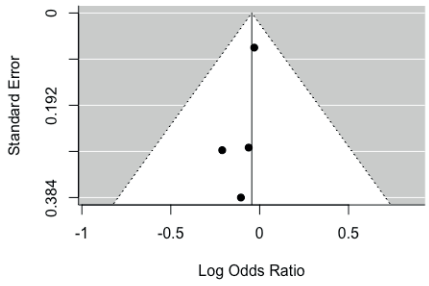

Fig 5. Anxiety studies with adjusted estimates

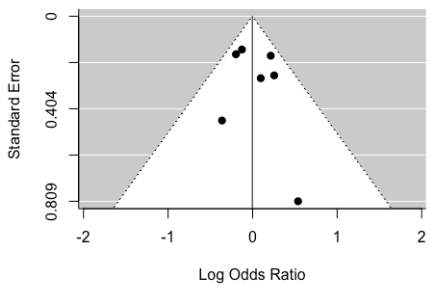

Fig 2. Agitation studies with unadjusted estimates

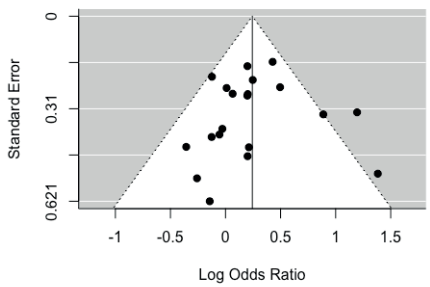

Fig 4. Depression studies with unadjusted estimates

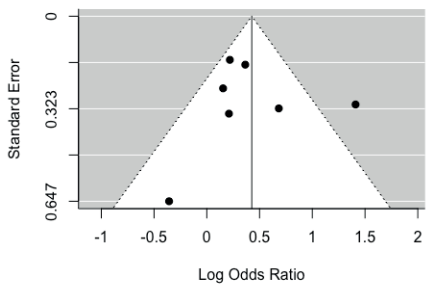

Fig 6. Anxiety studies with unadjusted estimates

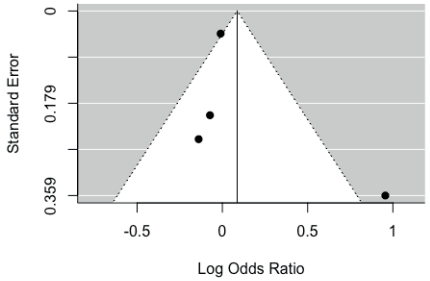

Fig 7. Apathy studies with adjusted estimates

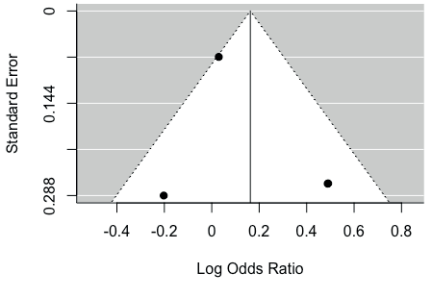

Fig 9. Irritability studies with adjusted estimates

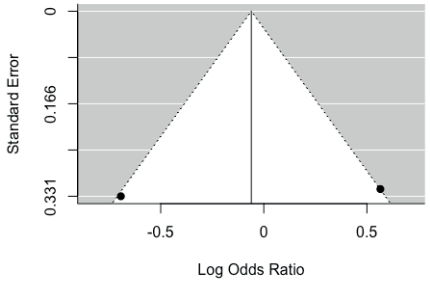

Fig 11. Sleep studies with adjusted estimates

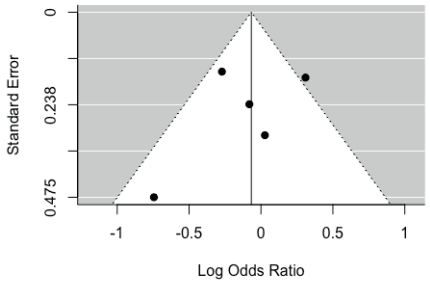

Fig 8. Apathy studies with unadjusted estimates

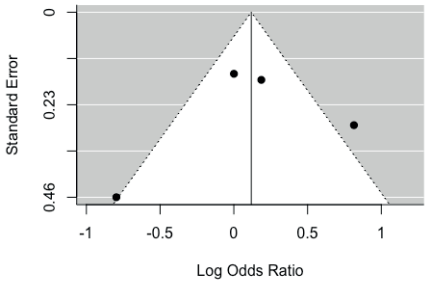

Fig 10. Irritability studies with unadjusted estimates

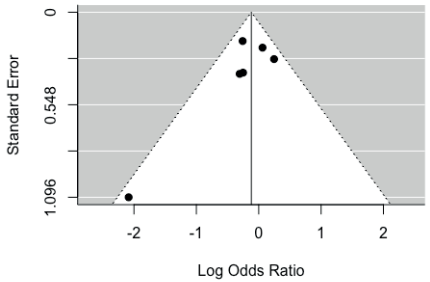

Fig 12. Sleep studies with unadjusted estimates

3

AFFECTIVE SYMPTOMS AND AT(N) BIOMARKERS IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE: A SYSTEMATIC LITERATURE REVIEW

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NEUROSCIENCE & BIOBEHAVIORAL REVIEWS, 2019

ABSTRACT

Background: Alzheimer's disease (AD) biomarkers such as amyloid, p-tau and neuronal injury markers have been associated with affective symptoms in cognitively impaired individuals, but results are conflicting.

Methods: CINAHL, Embase, PsycINFO and PubMed were searched for studies evaluating AD biomarkers with affective symptoms in mild cognitive impairment and AD dementia. Studies were classified according to AT(N) research criteria.

Results: Forty-five abstracts fulfilled eligibility criteria, including in total 8,293 patients (41 cross-sectional studies and 7 longitudinal studies). Depression and night-time behaviour disturbances were not related to AT(N) markers. Apathy was associated with A markers (PET, not CSF). Mixed findings were reported for the association between apathy and T(N) markers; anxiety and AT(N) markers; and between agitation and irritability and A markers. Agitation and irritability were not associated with T(N) markers.

Discussion: Whereas some AD biomarkers showed to be associated with affective symptoms in AD, most evidence was inconsistent. This is likely due to differences in study design or heterogeneity in affective symptoms. Directions for future research are given.

1. INTRODUCTION

Alzheimer's disease (AD) dementia is characterized by impaired cognition but is often accompanied by non-cognitive changes, such as symptoms of depression, anxiety and apathy[1]. These symptoms occur in the vast majority of patients over the disease course, including in its prodromal phase (i.e. mild cognitive impairment, MCI)[2, 3], and although they fluctuate[4], they are highly persistent[5].

Affective symptoms impact caregiver burden substantially[6] and patient outcomes such as quality of life[7, 8] and institutionalization[9], and may accelerate disease progression[10]. Several hypotheses have been posed that explain the presence of affective symptomatology in AD. For example, in the prodromal hypothesis, affective symptoms are thought to result from AD pathology and are therefore considered non-cognitive symptoms of the disease[11]. On the other hand, the risk factor hypothesis states that a non-AD pathology causes affective symptoms, which also fastens the development of AD pathology[11]. In order to improve our understanding of underlying biological mechanisms, validated biomarkers that are widely used as proxies for AD neuropathological changes (i.e. plaques and tangles) have been related to affective symptoms in AD, cerebrospinal fluid (CSF) amyloid-beta $(A\beta)_{42}$ concentrations or $A\beta_{42}/_{40}$ ratio, amyloid load on positron emission tomography (PET) scans (denoted as category "A"), CSF phosphorylated tau, cortical tau PET ligand binding (category "T") and atrophy on magnetic resonance imaging (MRI), hypometabolism on a fluorodeoxyglucose (FDG) PET scan or CSF total tau concentrations (category "N")[12]. However, as might be expected from the heterogeneity of these biomarker modalities, in addition to the variety in clinical assessment methods for affective symptoms, the reported findings differ profoundly.

Despite the importance of increasing our understanding of the aetiology of affective symptoms in AD, the current literature has not been reviewed systematically. Therefore, the aim of this review is to systematically assess studies that have investigated the association between AD biomarkers and affective symptoms in MCI and AD dementia, adhering to the recent AT(N) research framework[12]. It gives an overview of the current knowledge on the relation between AT(N) biomarkers and presence of the most common affective symptoms in MCI and AD dementia[3, 13, 14] that also have been clustered together in factor analyses most often[15], i.e. depression, anxiety, apathy, agitation, irritability, and night-time behaviour disturbances.

2. METHODS

2.1. Search strategy and selection criteria

CINAHL, Embase, PsycINFO and PubMed were searched until June 2018 to identify publications examining the association between AD biomarkers and affective symptoms. In

short, the search query consisted of various combinations of the following keywords: (cognitive impaired, dementia, AD) and (((amyloid beta or total tau or phosphorylated tau) and (CSF or plasma or PET)) or ((medial temporal lobe or hippocampus or MTA) and MRI))) and (affective symptoms). A full description of the search strategy is provided in Appendix 1. Two reviewers (L.B. and I.R.) independently assessed titles and abstracts for broad suitability based on the following eligibility criteria:

1. The study is population or clinically based and explicitly defines a cognitive impairment *in at least one subgroup*. Studies were excluded in case the sample consisted of primarily somatic or psychiatric patients in whom cognition is studied (e.g. patients with major depression), or in case of non-AD dementia types.
2. The study assesses the current presence and/or severity, by self- or proxy-report, of "affective symptoms", which we defined as affective or emotional dysregulation, including the following symptoms: depression, anxiety, apathy, agitation, irritability, and night-time behaviour disturbances. Studies that clustered these symptoms together (e.g. by factor analysis) in subsyndromes were also included.
3. The study examines the association between the above-mentioned affective symptoms and AD biomarkers.
4. The study includes humans and is published in Dutch, English, French or German.

In addition to this electronic search, a lateral search was undertaken, i.e. reference lists of retrieved publications and secondary literature (review articles, editorials, etc.) were screened to identify possible additional studies ("snowballing", as recommended by Greenhalgh and Peacock[16]). Research protocols and conference abstracts or posters were excluded. After this first screen, a full text review was conducted to assess eligibility. The selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[17].

2.2. Data extraction

Descriptive data on the design, sample size and demographics, as well as characteristics of the (assessment of) biomarkers and affective symptoms were extracted from the included studies according to a predefined and standardized data extraction form. Possible sources of heterogeneity were examined, including effects of syndromal diagnosis, whether affective symptoms were proxy- or self-rated and whether these were treated as a continuous measure or dichotomized (i.e. present vs. absent), whether biomarker values were categorized or treated as a continuous scale, and whether the study was considered to be of low or high quality.

2.3. Study quality

Study quality was evaluated with the Newcastle-Ottawa Scale (NOS) for each of the cohort studies and with a modified NOS for cross-sectional studies[18], see Appendix 2. Each study was classified as high quality evidence if the majority (>50%) of the quality items were satisfied.

3. RESULTS

Results of the database search yielded 3,323 abstracts, of which 162 (4.9%) were selected for full-text screening (Figure 1). Of these, 43 studies met eligibility criteria. Two additional studies were found from cross-references[19, 20], resulting in a total of 45 eligible articles published since 2008 that were assessed and incorporated into this review.

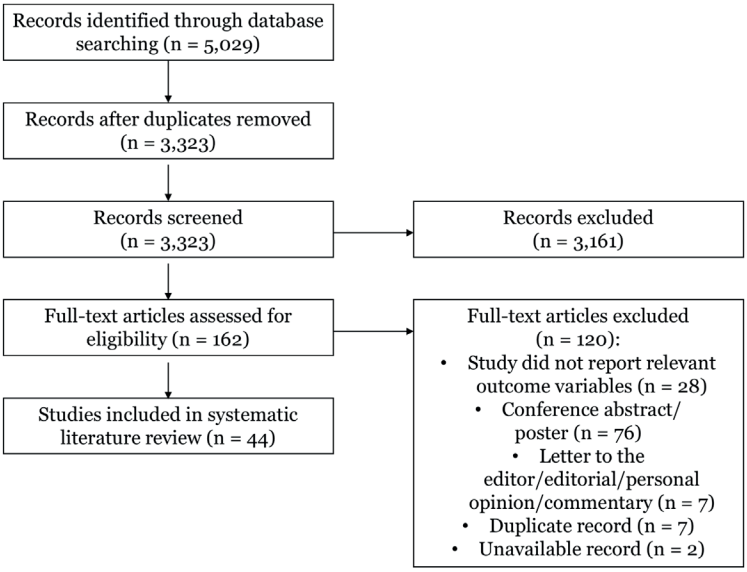

Figure 1. Flow diagram of study selection

3.1. Population characteristics and study design

A summary of the study characteristics is shown in Table 1. All studies were systematically classified for the biomarkers investigated adhering to the recent NIA-AA research framework AT(N) classification system[12], with the exception of FDG PET:

A. amyloid-beta deposition: CSF $A\beta_{42}$ or $A\beta_{42/40}$ ratio, or amyloid PET

T. pathologic tau (aggregated tau, neurofibrillary tangles): CSF p-tau or tau PET

(N). neurodegeneration (neuronal injury): MRI, CSF t-tau

Generally, patients were recruited from outpatient populations (e.g. (hospital based-) memory clinics) while only one study comprised both outpatient and community recruited

patients[21], and one study was entirely community based[22]. Thirteen out of 24 multicentre studies utilized pre-existing data banks, mainly the Alzheimer's disease Neuroimaging Initiatives (ADNI).

The majority of studies implemented a cross-sectional design, whereas seven longitudinal studies were included which had an average follow-up of two years (range follow-up: 12-37 months). There were no prospective follow-up studies conducting repeated measurements across different disease states (i.e. from subjective cognitive decline (SCD) to AD dementia) so as to decipher possible phase dependent biomarker disparities.

In the present review, 8,293 patients (54.1% females) were included. Although subjects with MCI (58.1%, mean age 71.9) and AD dementia (33.2%, mean age 75.1) were of primary interest (see eligibility criterium 1), some studies also included cognitively normal subjects (6.9%, mean age 74.4[21, 23-27]) and subjects with SCD (4.4.%, mean age 63.6[20, 28-30]), within their analyses. For completeness, therefore, the results of these subgroups will be briefly discussed.

3.2. Biomarkers and assays

Thirteen studies assessed biomarker abnormality or levels in CSF, one in blood plasma and eight via PET scans. With regard to CSF, the most frequently utilized kit was the enzyme-linked immunosorbent assay (ELISA) kit[19, 20, 27, 28, 30-33], others included xMAP[23, 25, 32, 34] or did not specify the kit[35]. With regard to blood plasma, INNO_BIO plasma Aβ forms assay was used[36]. With regard to PET, either PiB[37, 38], 18F-AV-45[24, 39-41] or FDDNP[42] as ligands were used.

The majority of studies (n = 24, 80.0%) examining neuronal injury focused on quantitative assessment of volumes or cortical thickness measures, obtained through volumetric MRI[21, 22, 25, 26, 28-30, 38, 43-58]. Segmentation strategies varied between studies. The majority of these studies (n = 23, 95.8%) used (semi-) automatic segmentation approaches, such as segmentation by FreeSurfer (i.e. calculating cortical thickness after inflating the folded cortical surface)[21, 25, 26, 28, 47, 49-51, 57] or voxel-based morphometry (VBM; regional volume and tissue concentration differences are characterized throughout the global brain)[38, 44, 48, 52-54, 56] by SPM[59]. Two studies also measured hippocampal volumes manually[43, 46]. Both a-priori regions of interest and whole-brain analyses were used. Six studies focused on qualitative (i.e. visual) interpretation of structural brain images[35, 46, 60-63], all utilizing the Scheltens scale[64].

Table 1. Characteristics of included studies

Study	Design	Participants, N	Mean age (SD)	Females, N (%)	Mean education in years (SD)	Mean MMSE (SD)	Biomarker analyses	Medium and assays	NPS instrument	NPS
Arnold (2012)	C	CN: 58, MCI: 396, AD: 112	CN: 75.1 (5.8), MCI: 74.6 (7.4), AD: 74.8 (8.1)	CN: 30 (51.7), MCI: 256 (64.6), AD: 65 (58.0)	CN: 15.6 (2.7), MCI: 15.7 (3.0), AD: 15.1 (3.2)	CN: 28.9 (1.2), MCI: 27.0 (1.8), AD: 23.59 (1.9)	Aβ, t-tau, p-tau	CSF, xMAP	GDS-15	Dep
Auning (2015)	C	SCD: 22, MCI: 38; Dep+: 24, Dep-: 36	SCD: 58.5 (6.5), MCI: 60.8 (6.6); Dep+: 60.0 (6.5), Dep-: 59.9 (7.1)	SCD: 13 (59.1), MCI: 16 (42.1); Dep+ 13 (50.0), Dep-: 16 (47.1)	NS	SCD: 29.2 (0.9), MCI 27.7 (1.5); Dep+: 9.2 (2.7), Dep-: 2.9 (1.6)	$A\beta_{42}$, p-tau; Hippocampal volume, cortical thickness	CSF, ELISA; MRI, 1.5T (FA, segm. by FreeSurfer. A priori ROIs)	GDS-15	Dep
Barca (2017)	L	aMCI: 105, AD: 177	aMCI: 70.7 (10.1), AD: 74.7 (7.6)	aMCI: 50 (47.6), AD: 102 (57.6)	aMCI: 12.7 (3.5), AD: 11.1 (3.5)	aMCI: 26.7 (2.5), AD: 22.0 (4.3)	Aβ, t-tau, p-tau; MTA	CSF, NS; MRI, NS (VS, Scheltens).	CSDD	Dep
Bensamoun (2016)	C	CN: 230, MCI: 308, AD: 119	CN: 73.1 (6.0), MCI: 71.5 (7.4), AD: 74.8 (8.1)	CN: 126 (54.8), MCI: 139 (45.1), AD: 47 (39.5)	CN: 16.6 (2.5), MCI: 16.4 (2.6), AD: 15.9 (2.6)	CN: 29.0 (1.2), MCI: 28.0 (1.8), AD: 23.1 (2.1)	Aβ	PET, 18F-florbetapir (18F-AV-45)	NPI-12; GDS-15	Agi, dep, anx, apa, irri, sle
Berlow (2010)	C	AD: 37	AD: 77.6 (8.5)	AD: 19 (51)	NS	AD: 19.5 (7.5)	Hippocampal volume	MRI, 1.5T (SA, segm. by SIENAX + manual. A priori ROI)	NPI-12	Agi, dep, anx, apa, irri, sle
Bilgic (2013)	C	AD: 45	AD: 70.0 (8.08)	AD: 25 (55.6)	NS	NS	MTA	MRI, 1.5T (Scheltens	GDS-30	Dep

Study	Design	Participants, N	Mean age (SD)	Females, N (%)	Mean education in years (SD)	Mean MMSE (SD)	Biomarker analyses	Medium and assays	NPS instrument	NPS
								Scale)		
Bloniecki (2014)	C	AD: 33	AD: 78.7 (7.6)	AD: 19 (57.6)	NS	AD: 19.1 (4.2)	$A\beta_{42}$, t-tau, p-tau	CSF, ELISA	CMAI	Agi
Brendel (2015)	C	All MCI= AB+Dep-: 141, AB+Dep+: 65, AB-Dep-: 124, AB-Dep+: 41	AB+Dep-: 73.4 (6.8), AB+Dep+: 73.7 (7.3), AB-Dep-: 70.3 (7.7), AB-Dep+: 70.1 (9.4)	AB+Dep-: 63 (45), AB+Dep+: 30 (46), AB-Dep-: 44 (55), AB-Dep+: 19 (46)	AB+Dep-: 16.1 (2.8), AB+Dep+: 16.2 (2.6), AB-Dep-: 16.5 (2.5), AB-Dep+: 16.0 (2.6)	AB+Dep-: 27.8 (1.9), AB+Dep+: 27.6 (1.7), AB-Dep-: 28.5 (1.4), AB-Dep+: 28.3 (1.8)	Aβ	PET, 18F-florbetapir (18F-AV-45)	NPI-Q	Dep
Bruen (2008)	C	AD: 31	AD: 77.1 (8.6)	AD: 12 (38.7)	AD: 11.3 (3.1)	AD: 23.3 (2.8)	Volume, VBM (GM)	MRI, 1.5T (FA, VMB by SPM5. Whole brain)	NPI-12	Agi, dep, anx, apa, irri, sle
Chung (2016)	L	all aMCI, DEP+: 38, DEP-: 38	DEP+: 73.0 (8.2), DEP-: 74.5 (7.3)	DEP+: 22 (57.9), DEP-: 21 (55.3)	DEP+: 16.0 (2.7), DEP-: 16.3 (2.7)	DEP+: 27.6 (1.9), DEP-: 27.4 (1.9)	Hippocampal volume	MRI, 1.5/3T (FA, segm. by MAGeT. A priori ROI)	GDS-15	Dep
Chung (2016)	C	MCI: 455, AD: 153	MCI: 72.7 (7.7), AD: 75.3 (7.8)	NS	MCI: 19.1 (2.7), AD: 16.1 (2.6)	MCI: 28.0 (1.8), AD: 22.5 (3.3)	Aβ	PET, 18F-florbetapir (18F-AV-45)	NPI-12; GDS-15	Dep
Dhikav (2014)	C	MCI: 11, AD: 26	All: 72.3 (6.5)	All: 7 (18)	NS	All: 19 .0 (6.7)	MTA	MRI, NS (Scheltens Scale)	CSDD	Dep
Donovan 2014*	C + L	CN: 229, MCI: 395, AD: 188	CN: 76.0 (5.0), MCI: 74.8 (7.5), AD: 75.3 (7.5)	CN: 110 (48.0), MCI: 110 (35.7), AD: 49 (48.4)	NS	CN: 29.1 (1.0), MCI: 27.0 (1.8), AD: 23.3 (7.6)	$A\beta_{42}$, t-tau, p-tau; cortical thickness	CSF, xMAP; MRI, NS (FA, segm. by Freesurfer. A	NPI-Q	Apa

							priori ROIs)			
Elcombe (2015)	C	Total: 218, of which MCI: 148, subjective cognitive or mood concerns: NS, lifetime history of MD: 85#	All: 67.3 (8.1)	All: 125 (57)	All: 13.9 (3.1)	All: 28.7 (1.3)	Hippocampal volume	MRI, 3T (FA, segm. by FIRST. A priori ROI)	GDS-15	Dep
Enache (2015)	C	SCDDEP-: 60, SCDDEP+: 79, MCIDEP-: 69, MCIDEP+:61, ADDEP-: 57, ADDEP+: 42	SCDDEP-: 62.3 (5.6), SCDDEP+: 60.7 (4.2), MCIDEP-: 65.3 (7.9), MCIDEP+: 66.3 (8.5), ADDEP-: 67.2 (8.7), ADDEP+: 68.1 (8.4)	SCDDEP-: 38 (63.3), SCDDEP+: 61 (77.2), MCIDEP-: 29 (42.0), MCIDEP+:41 (67.2), ADDEP-: 38 (67.2), ADDEP+: 31 (73.8)	SCDDEP-: 12.3 (3.3), SCDDEP+: 13.2 (3.79), MCIDEP-: 12.0 (3.1), MCIDEP+: 11.3 (3.8), ADDEP-: 11.1 (3.7), ADDEP+: 10.1 (3.8)	SCDDEP-: 29 (24-30), SCDDEP+: 29 (22-30), MCIDEP-: 28 (20-30), MCIDEP+:27 (22-30), ADDEP-: 25 (14-29), ADDEP+: 23 (15-29)@	$A\beta_{42}$, t-tau, p-tau; MTA, hippocampal volume	CSF, NS; MRI, 1.5T (VS, Scheltens; M segm. A priori ROI).	CSDD	Dep
Engelborghs (2005)	C	AD: 201	AD: 79.2 (7.4)	AD: 128 (63.7)	NS	AD: 13.5 (6.8)	$A\beta_{42}$, t-tau, p-tau	CSF, ELISA	Behave-AD, CMAI, CSDD	Agi, dep, anx, sle
Fuijshima (2014)	C	CN: 136, MCI: 186	CN: 78 (76-81), MCI: 80 (76-83)	CN: 81 (59.6), MCI: 102 (54.8)	CN: 9 (8-11), MCI: 8 (8-9)	CN: 26 (24-27), MCI: 23 (21-25)	Cortical thickness	MRI, 1.5T (SA, segm. by Atropos and DiReCT. Whole brain)	GDS-15	Dep
Guercio (2015)	C	CN: 19, MCI: 47	CN: 75.1 (5.9), MCI: 74.5 (8.4)	CN: 15 (78.9), MCI: 12 (25.5)	CN: 17.1 (2.9), MCI: 17.0 (2.4)	CN: 29.6 (0.7), MCI: 27.6 (1.8)	Cortical thickness	MRI, 3T (FA, segm. by Freesurfer. A priori ROIs)	AES-C	Apa
Hayata (2015)	C	CN: 29, AD: 33	CN: 71.1 (7.2), AD: 74.1 (6.8)	NS	CN: 11.1 (5.2), CN: 5.6 (4.8)	CN: 28.6 (1.7), MCI: 16.6 (5.7)	Cortical thickness	MRI, 3T, (FA, segm. by FreeSurfer.	NPI-12	Subsyndromes

Study	Design	Participants, N	Mean age (SD)	Females, N (%)	Mean education in years (SD)	Mean MMSE (SD)	Biomarker analyses	Medium and assays	NPS instrument	NPS
								Whole brain).		
Hsu (2015)	C	MCI: 31, AD: 129	CN: 75.4 (8.6), AD: 79.6 (7.8)	MCI: 12 (38.7), AD: 65 (50.4)	MCI: 11.1(4.7), AD: 9.9 (4.4)	MCI: 25.5 (3.3), AD: 18.9 (5.5)	MTA	MRI, 3T (VS: Scheltens)	NPI-12	Subsyndromes
Hsu (2017)	L	AD: 322	AD: 80.4 (6.2)	AD: 149 (46.3)	AD: 10.1 (4.4)	AD: 18.1 (5.9)	$A\beta_{42/40}$ ratio	Blood plasma, INNO-BIA plasma Aβ forms assay	NPI-Q	Subsyndromes
Huey (2017)	C	AD: 57	AD: 76.5 (9.1)	NS	NS	AD: 22.8 (2.2)	Volume	MRI, 1.5T (FA, segm. by FreeSurfer. Whole brain)	NPI-12	Agi, dep, anx, apa, irri, sle
Kim (2016)	C	CN: 36, AD+RBD: 9, AD-RBD: 14	CN: 72.9 (5.7), AD+RBD: 70.1 (6.9), AD-RBD: 67.7 (8.4)	CN: 17 (47.2), AD+RBD: 6 (66.7), AD-RBD: 8 (57.1)	CN: 4.8 (3.7), AD+RBD: 2.0 (2.5), AD-RBD: 8.6 (5.1)	CN: 29.3 (1.2), AD+RBD: 17.3 (6.0), AD-RBD: 22.9 (4.5)	Volume, VBM	MRI, 3T (FA, VBM by SPM5. Whole brain)	RBDSQ-K	Sle
Kramberger (2012)	C	SCDDEP-: 51, SCDDEP+: 41, ADDEP-: 60, ADDEP+: 31	SCDDEP-: 65.0 (5.6), SCDDEP+: 62.7 (3.0), ADDEP-: 72.0 (8.2), ADDEP+: 70.1 (6.6)	SCDDEP-: 32 (62.7), SCDDEP+: 32 (78.0), ADDEP-: 38 (63.3), ADDEP+: 20 (64.5)	SCDDEP-: 13.4, SCDDEP+: 12.4, ADDEP-: 11.0, ADDEP+: 11.2	SCDDEP-: 28.9 (1.4), SCDDEP+: 28.7 (1.5), ADDEP-: 23.1 (3.6), ADDEP+: 23.2 (3.9)	$A\beta_{42}$, t-tau, p-tau	CSF, ELISA	CSDD	Dep
Kuo (2015)	C	CN: 9, aMCI: 9, AD: 9	CN: 69 (65.5-74.5), aMCI: 73 (70.5-79), AD: 77	CN: 3 (33.3), aMCI: 3 (66.7), AD: 4 (44.4)	CN: 6 (6-7), MCI: 9 (6-10.5), AD: 6 (6-9)	CN: 29 (28.3-30), aMCI: 20 (18.5-23), AD: 18 (14.5-	$A\beta_{42}$	CSF, ELISA	BEHAVE-AD	Agi, dep, anx, sle

			(64-79)			19)			
Lavretsky (2009)	C	CN: 20, MCI: 23	CN: 63.7 (12.5), MCI: 68.2 (12.2)	CN: 8 (40.0), MCI: 14 (60.9)	CN: 17.7 (2.7), MCI: 16.6 (3.4)	CN: 29.4 (0.9), MCI: 27.6 (1.4)	Aβ/tau	PET, FDDNP	GDS-30; STAI	Dep
Lebedev (2014)^	C	ADDep-: 30, ADDep+: 23	ADDep-: 76.5 (6.3), ADDep+: 73.0 (7.7)	ADDep-: 9 (30), ADDep+: 3 (13)	ADDep-: 8.5 (1.96), ADDep+: 9.6 (2.8)	ADDep-: 23.7 (2.3), ADDep+: 23.7 (1.6)	Cortical thickness	MRI, 1.5T (FA, segm. by FreeSurfer. Whole brain)	MADRS	Dep
Lebedeva (2014)	C	KIDEP+: 16, KIDEP-: 25, ADNIDEP+: 84, ADNIDEP-: 64	KIDEP+: 66.0 (62.5–75), KIDEP-: 67.5 (61.5–73), ADNIDEP+: 76.0 (70.6–80.3), ADNIDEP-: 75.0 (69.5–80.7)	KIDEP+: 7 (44), KIDEP-: 18 (72), ADNIDEP+: 39 (47), ADNIDEP-: 31 (48)	KIDEP+: 12.0 (9–14.5), KIDEP-: 12.0 (9–16.5), ADNIDEP+: 16.0 (12–18), ADNIDEP-: 15.0 (12–16)	KIDEP+: 22.0 (20–26), KIDEP-: 25.0 (22–27), ADNIDEP+: 24.0 (23–25), ADNIDEP-: 23.0 (22–25)	Cortical thickness	MRI, 1.5/3T (FA, segm. by FreeSurfer. Whole brain)	CSDD; GDS-15	Dep
Lee (2012)	C + L	MCI+DEP: 23, MCI+OTHER:47, MCI+NOSYMP: 59	MCI+DEP: 75.0 (6.8), MCI+OTHER: 74.8 (7.0), MCI+NOSYMP: 75.3 (6.9)	MCI+DEP: 16 (68.2), MCI+OTHER: 15 (32.2), MCI+NOSYMP: 20 (34.0)	MCI+DEP: 16.4 (2.9), MCI+OTHER: 15.8 (2.9), MCI+NOSYMP: 15.7 (3.1)	MCI+DEP: 27.1 (1.9), MCI+OTHER: 27.1 (1.7), MCI+NOSYMP: 27.2 (1.8)	$A\beta_{42}$, t-tau, p-tau, t-tau/$A\beta_{42}$, p-tau/$A\beta_{42}$	CSF, Luminex xMAP;	NPI-Q	Dep
Mah (2015)	L	MCI+ANX: 140, MCI-ANX: 192	MCI+ANX: 74.7 (6.5), MCI-ANX: 75.2 (7.6)	MCI+ANX: 62 (44), MCI-ANX: 58 (30)	MCI+ANX: 15.6 (3.0), MCI-ANX: 15.6 (3.1)	MCI+ANX: 26.9 (1.8), MCI-ANX: 27.0 (1.7)	Subcortical volume, cortical thickness	MRI, 1.5T (FA, segm. by FreeSurfer. A priori ROIs)	NPI-Q	Anx
Marshall (2013)	C	MCI: 24	MCI: 73.6 (9.2)	MCI: 7 (28.0)	MCI: 17.3 (2.4)	27.4 (1.9)	Aβ	PET, PiB	AES	Apa
Moon (2017)	C + L	All MCI AB+Dep-: 137, AB+Dep+: 49, AB-Dep-: 124, AB-Dep+: 26	AB+Dep-: 73.5 (6.8), AB+Dep+: 72.6 (6.4), AB-Dep-: 70.9 (7.6), AB-Dep+: 66.6	AB+Dep-: 62 (45.3), AB+Dep+: 24 (49.0), AB-Dep-: 58 (46.8), AB-Dep+: 11	AB+Dep-: 16.1 (3.0), AB+Dep+: 16.4 (2.5), AB-Dep-: 16.3 (2.5), AB-Dep+: 16.4	AB+Dep-: 27.8 (1.8), AB+Dep+: 27.3 (1.9), AB-Dep-: 28.6 (1.3), AB-Dep+: 28.4 (1.9)	Volume, VBM (GM)	MRI, 3T (FA, VBM by SPM8. Whole brain)	NPI-Q	Dep

Study	Design	Participants, N	Mean age (SD)	Females, N (%)	Mean education in years (SD)	Mean MMSE (SD)	Biomarker analyses	Medium and assays	NPS instrument	NPS
			(6.6)	(42.3)	(2.4)					
Mori (2014)	C	AD: 28	AD: 73.9 (7.9)	AD: 15 (53.6)	AD: 11.1 (3.5)	AD: 19.9 (5.1)	Aβ; Volume, VBM (GM)	PET, PiB; MRI, 1.5T (FA, VBM by SPM5. Whole brain).	NPI-10	Agi, dep, anx, apa, irri
Nathan (2017)	C	MCIAB+: 55, MCIAB-: 90	AB+: 69.8 (6.7), AB-: 68.8 (7.7)	AB+: 32 (57.8), AB-: 52 (57.8)	*AB+: 25 (45.5), AB-: 51 (56.8)	AB+: 26.0 (1.8), AB-: (27.0 (1.8)	$A\beta_{42}$	CSF, ELISA	GDS-15	Dep
Ramakers (2013)	C	MCI: 267	MCI: 73.1 (7.9)	MCI: 101 (38)	14.3 (4.01)	26.7 (2.1)	$A\beta_{42}$, t-tau	CSF, ELISA and xMAP	NPI-12; NPI-Q	Agi, dep, anx, apa, irri
Reijs (2017)	C	SCD: 111, MCI: 353	SCD: 67.0 (7.6), MCI: 70.6 (6.9)	SCD: 57 (51), MCI: 208 (59)	SCD: 11.4 (4.1), MCI: 87 (3.8)	SCD: 28.5 (1.5), MCI: 26.2 (2.9)	$A\beta_{42}$, t-tau; hippocampal volume	CSF, ELISA; MRI, 1/1.5T (FA, pipeline by Lötjönen et al., 2010. A priori ROIs).	Reported in clinical interview or NPI-12	Sle
Serra (2010)	C	CN: 23, aMCI; 19, ADe: 15, ADm: 12	CN: 63.9 (6.9), aMCI: 73.3 (6.9), ADe: 75.5 (7.0) ADm: 70.0 (8.2)	CN: 6 (26.0), aMCI: 8 (42.1), ADe: 8 (53.3), ADm: 9 (75.0)	CN: 13.1 (3.8), aMCI: 11.9 (4.1), ADe: 9.2 (4.4), ADm: 10.3 (4.3)	CN: 28.4 (1.8), aMCI: 25.4 (1.4), ADe: 21.4 (2.7), ADm: 15.4 (1.8)	Volume, VBM (GM)	MRI, 3T (FA, VBM by SPM8. Whole brain)	NPI-12	Agi, dep, anx, apa, irri, sle, subsyndr
Skogseth (2008)	C	AD: 32	AD: 73.9 (9.0)	AD: 23 (71)	NS	AD: 24.2 (2.3)	$A\beta_{42}$, t-tau, p-tau	CSF, ELISA	MADRS; Apathy Scale; NPI	Dep, apa
Son (2013)	C	CN: 50, MCI+DEP: 31, MCI-DEP: 26, AD+DEP: 17, AD-DEP: 32	CN: 77.2 (7.9), MCI+DEP: 74.0 (5.6), MCI-DEP: 75.0 (6.3),	CN: 28 (56.0), MCI+DEP: 14 (53.8), MCI-DEP: 16 (51.6),	CN: 51. (4.2), MCI+DEP: 6.2 (3.8), MCI-DEP: 5.9 (3.2),	CN: 25.2 (1.7), MCI+DEP: 22.9 (3.3), MCI-DEP: 21.9 (17.7),	Volume, VBM (GM)	MRI, 3T (FA, VBM by SPM5. Whole	GDS-30	Dep

			AD+DEP: 77.0 (8.3), AD-DEP: 76.1 (4.9)	AD+DEP: 10 (58.9), AD-DEP: 20 (62.5)	AD+DEP: 5.4 (3.4), AD-DEP: 5.0 (3.8)	AD+DEP: 17.7 (3.5), AD-DEP: 18.0 (3.4)		brain).		
Staekenborg (2008)	C	AD: 111	AD: 70 (9)	AD: 62 (57)	NS	AD: 20 (5)	MTA	MRI, 1.0T (VS, Scheltens)	NPI-10	Agi, dep, anx, apa, irri
Starkstein (2009)	C	APA-DEP-: 40, APA+DEP-: 14, APA-DEP+: 15, APA+DEP+: 10	APA-DEP-: 70.5 (7.1), APA+DEP-: 72.6 (7.1), APA-DEP+: 72.2 (9.0), APA+DEP+: 75.5 (7.5)	APA-DEP-: 23 (58), APA+DEP-: 9 (64), APA-DEP+: 9 (60), APA+DEP+: 7 (70)	NS	APA-DEP-: 22.0 (5.8), APA+DEP-: 19.3 (6.0), APA-DEP+: 20.9 (3.2), APA+DEP+: 18.7 (4.6)	Volume	MRI, 1.5T (FA, segm. by BRAINS. A priori ROIs)	AS; HAM-D	Dep, apa
Sturm (2013)	C	CN: 111, MCI: 62, AD: 64	CN: 69.1 (8.1), MCI: 69.4 (10.6), AD: 64.4 (11.3)	CN: 70 (63.1), MCI: 33 (53.2), AD: 30 (46.9)	CN: 16.9 (2.4), MCI: 17.0 (2.5), AD: 15.9 (3.0)	CN: 29.4 (0.7), MCI: 28.6 (1.5), AD: 20.7 (5.2)	Volume, VBM (GM)	MRI, 1.5/3/4 T (FA, VBM by SPM5. Whole brain)	GDS-15	Dep
Tateno (2015)	C	CN: 22, MCIAB+: 13, MCIAB-: 20 (MCI with history of depression)	CN: 72.0 (4.5), MCIAB+: 76.6 (3.9), MCIAB-: 76.8 (4.5)	CN: 10 (45.5), MCIAB+: 12 (92.3), MCIAB-: 17 (85.0)	NS	CN: 28.3 (1.9), MCIAB+: 23.5 (3.8), MCIAB-: 23.8 (3.4)	Aβ	PET, 18F-florbetapir (18F-AV-45)	GDS-15	Dep
Tunnard (2011)	C	AD+APA: 63, AD-APA: 48	AD+APA: 75.7 (6.8), AD-APA: 74.6 (5.2)	AD+APA: 44 (70), AD-APA: 32 (66)	AD+APA: 8.7 (3.9), AD-APA: 7.2 (4.1)	AD+APA: 20.5 (4.8), AD-APA: 21.2 (4.9)	Cortical thickness	MRI, 1.5T (FA, segm. by Fischl and Dale pipeline. A priori ROIs)	NPI-12	Apa
Trzepacz (2013)	L	MCI conv: 122, MCI stable: 177, AD: 163	MCI stable: 74.4 (7.8), MCI con 74.4 (7.8), AD: 75.3 (7.5)	MCI stable: 58 (33), MCI con 42 (34.5), AD: 77 (47.4)	MCI stable: 15.7 (4–20), MCI con: 15.7 (6–20), AD: 14.7 (4–20)	MCI stable: 27.2 (1.8), MCI con: 26.6 (1.7), AD: 23.3 (2.1)	Cortical thickness and volume	MRI, 1.5T (FA, segm. by FreeSurfer. A priori ROIs)	NPI-Q	Subsynd

N = number of individuals; SD = standard deviation; MMSE = mini-mental state examination; NPS = neuropsychiatric symptoms; C = cross-sectional; L = longitudinal; CN = cognitively normal; SCD = subjective cognitive decline; MCI = mild cognitive impairment; aMCI = amnestic mild cognitive impairment; AD = Alzheimer's disease (dementia); AB+Dep- = amyloid levels abnormal, depression absent; AB+Dep+ = amyloid levels abnormal, depression present; AB-Dep- = amyloid levels normal, depression absent; AB-Dep+ = amyloid levels normal, depression present; NS = not specified; MD = major depression; SCDDEP- = in SCD, depression absent; SCDDEP+ = in SCD, depression present; MCIDEP- = in MCI, depression absent; MCIDEP+ = in MCI, depression present; ADDEP- = in AD, depression absent; ADDEP+ = in AD, depression present; AD+RBD = in AD, rapid eye movement sleep behaviour disorder present; AD-RBD = in AD, rapid eye movement sleep behaviour disorder absent; KIDEP+ = in Karolinska Institute cohort, depression present; KIDEP- = in Karolinska Institute cohort, depression absent; ADNIDEP+ = in ADNI cohort, depression present; ADNIDEP- = in ADNI cohort, depression absent; MCI+DEP = in MCI, depression present; MCI+OTHER, in MCI, non-depressed with other neuropsychiatric symptom; MCI+NOSYMP = in MCI, no neuropsychiatric symptoms; MCI+ANX = in MCI, anxiety present; MCI-ANX = in MCI, anxiety absent; MCIAB+ = in MCI, amyloid levels abnormal; MCIAB- = in MCI, amyloid levels normal; ADe = early AD; ADm = moderate AD; APA-DEP- = apathy and depression absent; APA+DEP- = apathy present, depression absent; APA-DEP+ = apathy absent, depression present; APA+DEP+ = apathy and depression present; AD+APA = in AD, apathy present; AD-APA = in AD, apathy absent; MCI conv = MCI subjects that converted to AD; MCI stable = MCI subjects that remained MCI; MTA = medial temporal lobe atrophy; CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay; xMAP = multiplex xMAP Luminex platform; MRI = magnetic resonance imaging; PET = positron emission tomography; PiB = Pittsburgh compound-B; 18F-AV-45 =florbetapir; VS = visual scale, SA = semi-automated, FA = fully-automated, M = manual; segm. = segmentation; T = tesla; ROI = region of interest; AES = Apathy Evaluation Scale; AS = Apathy Scale; BEHAVE-AD = Behavioural Pathology in Alzheimer's Disease Scale; CMAI = Cohen-Mansfield Agitation Inventory; CSDD = Cornell Scale for Depression in Dementia; GDS-15 = Geriatric Depression Scale-15 items; GDS-30 = Geriatric Depression Scale-30 items; MADRS = Montgomery and Asberg Depression Rating Scale; MFS = Middelheim Frontality Score; NPI-10 = Neuropsychiatric Inventory-10 items; NPI-12 = Neuropsychiatric Inventory-12 items; NPI-Q = Neuropsychiatric Inventory-Questionnaire; RBDSQ-K = Korean version of REM sleep behaviour disorder screening questionnaire; STAI = State-Trait Anxiety Inventory; Agi = agitation; Dep = depression; Anx = anxiety; Apa = apathy; Irri = irritability; Sle = night-time behaviour and sleep disturbances; # possible overlap; @ median (range); ^in total group, assumption Lewy Body dementia and AD comparable demographic and clinical characteristics; * CN: 230, MCI: 308, AD: 101 subset in CSF study, with comparable demographic and clinical characteristics to the full cohort

Table 2. Summary of results

		Amyloid-beta disposition			Pathologic tau (NFT)			Neurodegeneration		
Presence or more severe symptoms of	N studies	↓ CSF or ↑ PET Aβ levels	↑ CSF or ↓ PET Aβ levels	= CSF or PET Aβ levels	↑ CSF p-tau or PET tau	↓ CSF p-tau or PET tau	= CSF p-tau or PET tau	↑ MRI atrophy*, FDG PET, CSF t-tau	↓ MRI atrophy, FDG PET, CSF t-tau	= MRI atrophy, FDG PET, CSF t-tau
Depression	33	35, 39, 42§		12, 17, 23, 24, 27, 28, 31, 32, 33, 34, 38, 40	42§		12, 19, 23, 28, 33, 34, 35	22, 49, 50, 54 (AD), 61	12 (t-tau), [28, hip vol, trend]; 32 (hip vol), 46 (MTA: in AD)	19, 23, 28 (cortical thickness), 29, 32 (t-tau), 33, 34 (t-tau), 35 (t-tau and MTA), 38, 43, 44, 45 (L: hip vol), 46 (MTA: in MCI; hip vol.: in AD), 47, 52$, 53, 54 (MCI), 55, 56, 60, 63
Anxiety	12	24 (MCI), 32, 42§ (trait but not state),		19, 24 (AD), 27, 38	42§ (trait but not state)		19	32 (t-tau), 51 (C)		19, 32 (hip vol), 38, 43 (hip vol), 44 (GM density), 47, 51 (L), 53, 63
Apathy	14	37, 38		24, 25 (C + L), 32, 33	33		25 (C + L), 44 (GM density)	21, 25 (cortical thickness, L), 33, 47		25 (t-tau, C+ L; cortical thickness, C), 32 (t-tau and hip vol), 38,43 (hip vol), 53, 55, 58, 63
Agitation	12	19, 27, 32		24, 33, 38, 65	65		19, 32, 33	65		19, 32 (t-tau and hip vol), 33, 38, 43 (hip vol), 44 (GM density), 47, 53, 63
Irritability	8	24 (AD, parietal), 32		24 (MCI), 38						32 (t-tau and hip vol), 38, 43 (hip vol), 44 (GM density), 47, 53, 63
Night-time behaviour disturbances	9			19, 24, 27, 30			19	48		19, 30 (t-tau and hip vol), 43, 44 (GM density), 47, 53
Subsyndromes	4	24 (PC3)#, 36 (agi)		24 (PC1, PC2, PC4)#, 36 (mood, frontal)				26 (affect), 57 (agi)		26 (apa, psy, hyper), 53 (apa, psy, hyper, affect), 62 (agi, mood)

↓, ↑ and = CSF, = resp. lower, high and equal cerebrospinal fluid concentrations in those with symptom present; ↓, ↑ and = PET, = resp. lower, higher and equal uptake on PET scan; NFT = neurofibrillary tangles; * of temporal lobe/hippocampus; AD = Alzheimer's disease; MCI = mild cognitive impairment; hip vol = hippocampal volume; MTA = medial temporal lobe atrophy; C = cross-sectional analyses, L = longitudinal analyses; $ in amyloid-positive subjects; § non-specific binding for amyloid and tau protein aggregates, results displayed for both amyloid and p-tau; agi = agitation, neuropsychiatric inventory subscale, including agitation/aggression, disinhibition, irritability, aberrant motor behaviour items; mood = mood, neuropsychiatric inventory subscale including depression, anxiety, and irritability items; frontal = neuropsychiatric inventory subscale including apathy, disinhibition, irritability, and euphoria items; affect = neuropsychiatric inventory subscale, including depression and anxiety items; apa = apathy, neuropsychiatric inventory subscale including apathy and eating disorders items; psy = psychosis, neuropsychiatric inventory subscale, including delusions, hallucinations, and night-time behaviour disturbance items; affect = neuropsychiatric inventory subscale including depression and anxiety items; hyper = hyperactivity, neuropsychiatric inventory subscale including agitation, disinhibition, irritability, euphoria, and aberrant motor behaviour scores; # PC 1 (agitation, euphoria, apathy, disinhibition, irritability), PC2 (sleep and eating disturbances), PC3 (depression, anxiety, aberrant motor behaviour, delusion), PC4 (hallucinations)

3.2 Summary of outcomes

A summary of study results is given in Table 2. In the following section, the study outcomes will be discussed per symptom (depression, anxiety, apathy, agitation, irritability, sleep/night-time disturbances, subsyndromes), in the order of the above-outline AT(N) framework (first category A, then T, and finally, N).

3.2.1. Depression

3.2.1.1. Depression and amyloid-B pathophysiology (category "A")

Sixteen studies examined the association between Aβ and the presence or severity of depressive symptoms. Of these, thirteen studies covering the disease spectrum reported no significant association between Aβ and depression. That is, no association was found in MCI[24, 28, 31, 32, 34, 40, 41], AD dementia[19, 20, 24, 33, 38, 40], MCI and AD dementia[27], and CN/MCI/AD dementia[23]. Four of these studies utilized the ADNI cohort for their analyses[23, 32, 34, 40].

Three studies reported a significant association between Aβ and depressive symptoms. Of these, one study was based on global Aβ levels and two were region specific (i.e. temporal lobe). Further, lower baseline CSF Aβ was associated with increasing depressive symptoms over time (at ~2 year follow-up) in patients with MCI and AD ([35], n = 282). Region specific differences were found in MCI, where amyloid positives with depressive symptoms had higher Aβ deposition in frontotemporal areas as compared to amyloid positive non-depressed patients ([39], n = 371). In a relatively small sample of 23 patients with MCI, depression scores correlated with lateral temporal FDDNP binding[42]. However, it is important to note that FDDNP is a non-specific marker of both amyloid and tau protein aggregates.

The results were independent of possible sources of heterogeneity, as described in section 2.2, although studies that reported an association included younger individuals compared to studies that did not find an association (69.4 vs. 77.6 years old). Collectively, the majority (80%) of the cross-sectional studies did not report an association between depressive symptoms and Aβ.

3.2.1.2. Depression and tau pathophysiology (category "T")

No association between phosphorylated tau and presence or severity of depressive symptoms was found in six out of seven studies, including MCI[28, 34], AD dementia[19, 20, 33], MCI and AD dementia[35], and CN/MCI/AD dementia[23]. The results were independent of the examined possible sources of heterogeneity. One study found severity of depression to be positively related to tau, using a non-specific measure for CSF p-tau (see 3.2.1.1[42]). Collectively, these findings imply that p-tau is neither cross-sectionally nor longitudinally associated with depression across the AD spectrum.

3.2.1.3. Depression and neuronal injury (category "N")

3.2.1.3.1. Neurodegeneration "N" fluid biomarkers

Seven out of eight studies examining the association between neuropathologic markers and depression reported no association with CSF t-tau. That is, no association was found in MCI[28, 32, 34], AD dementia[19, 33], MCI/AD dementia[35], and CN/MCI/AD dementia[23]. One study reported a negative association between CSF t-tau and depression in AD dementia[20]. Overall, t-tau is not associated with depression across the AD spectrum. Potential sources of heterogeneity did not contribute to the contrasting findings.

3.2.1.3.2. Neuroimaging "N" biomarkers

Neuronal injury (i.e. atrophy) can be measured using qualitative (i.e. visual interpretation of structural brain images) or quantitative (i.e. volumes or cortical thickness measures, obtained through volumetric MRI) measures. Four studies used a validated visual rating scale[64] to score medial temporal lobe (MTL) atrophy (MTA). Of the following studies, only three were rated as low quality[20, 41, 53], due to incomplete reporting of methods used and results obtained (Appendix 2. Table 5). MTA scores were not associated with depressive symptoms in MCI[46] and AD dementia[60, 63], and trajectories of depressive symptoms in MCI/AD dementia[35]. However, a relatively small study reported more MTA in MCI/AD dementia ([61], n = 37), although an association in opposite direction was also found [46]. That is, the right MTL was less atrophic in AD patients, but not in MCI, with depressive symptoms compared to those without[46].

One longitudinal and ten cross-sectional studies used whole-brain volumetric approaches. In MCI, depressive symptoms were associated with more cortical thinning in temporal regions[22] and with changes in cingulate gyrus over time in Aβ positives[52]. In contrast, no association between depressive symptoms and grey matter (GM) volume in MCI was found[54], although in AD dementia an association with decreased GM volume in the left inferior temporal gyrus was observed. In line with this latter finding, more cortical thinning in prefrontal and temporal regions[49] and (left) temporal regions[50] was observed in patients with AD dementia and depressive symptoms. Other studies found no association between GM (temporal) volume and depressive symptoms[38] or severity of depressive symptoms[44, 47, 55] in AD dementia. Additionally, two studies, who did not differentiate between diagnostic groups in their analyses, reported no association between GM volume and severity of depressive symptoms in CN/MCI/AD dementia[56], and presence of depressive symptoms in MCI/AD dementia[53].

Five studies used a region of interest (ROI) approach to examine specific GM thickness or volumes. Depressive symptoms were not associated with (change in)

hippocampal volume in MCI[29, 45] and AD dementia[43, 46]. A somewhat unexpected finding was that of (a trend towards) larger hippocampal volumes with depressive symptoms in SCD/MCI[28] and MCI[32].

Together, these findings suggest that hippocampal volume and MTA scores are not associated with depression in AD dementia. For MCI, the relationship is less clear. The discordant findings of the studies utilizing whole-brain approaches make it difficult to draw any conclusions in that regard.

3.2.2. Anxiety

3.2.2.1. Anxiety and amyloid-B pathophysiology (category "A")

Five studies examined the association between Aβ and the presence or severity of anxiety. Levels of CSF $A\beta_{42}$ were not associated with severity of anxiety and phobias in MCI/AD dementia[27] and AD dementia[19] nor were levels of PiB PET retention[38] and Aβ deposition (18F-AV-45 PET[24]) related to anxiety in AD dementia. In contrast, anxiety severity was correlated with frontal and global Aβ deposition (18F-AV-45 PET) in MCI[24]. In line with this, severity of trait anxiety (but not state anxiety, as measured with the State-Trait Anxiety Inventory), correlated with posterior cingulate FDDNP binding in MCI[42]. Further, abnormal Aβ was associated with increased risk of presence of anxiety in MCI[32]. Due to the mixed nature of these findings – irrespective of study quality – the relationship between Aβ with anxiety in cognitively impaired individuals remains to be elucidated.

3.2.2.2. Anxiety and tau pathophysiology (category "T")

None of the identified papers in this review examined the association between CSF p-tau and anxiety.

3.2.2.3. Anxiety and neuronal injury (category "N")

In the majority of studies, no relationship between anxiety and MTA scores[63] or (hippocampal) brain volumes[32, 38, 43, 44, 47, 53] was found in MCI and AD dementia. However, abnormal levels of CSF t-tau were associated with anxiety symptoms in MCI[32] and smaller hippocampal volumes were found in MCI with anxiety as compared to those without[51]. Further, baseline symptoms of anxiety predicted greater rates of decrease in entorhinal cortical volumes, but not changes in hippocampal volume, over 36 months[51]. These findings might suggest that fluid markers of neuronal injury are possibly more sensitive in terms of diagnostic utility than GM changes.

3.2.3. Apathy

3.2.3.1. Apathy and amyloid-B pathophysiology (category "A")

No cross-sectional or longitudinal association between CSF $A\beta_{42}$ levels and presence of apathy in MCI[32] or severity of apathy in AD[33] or CN/MCI/AD dementia[25] was found. Aβ deposition (18F-AV-45 PET) was not associated with apathy in MCI nor in AD dementia[24]. However, two smaller studies utilizing PiB PET scans, found a positive association between Aβ deposition and apathy in MCI ([37], n = 24) and AD dementia ([38], n = 28). These findings suggest that CSF $A\beta_{42}$ is not related to apathy. In contrast, the association with PiB PET scans needs further research given the small sample sizes of the two studies.

3.2.3.2. Apathy and tau pathophysiology (category "T")

CSF p-tau was associated with severity of apathy in AD dementia[33] but not in a combined sample of CN/MCI/AD dementia, neither cross-sectional nor longitudinal[25]. Thus, further research is needed with regard to this association.

3.2.3.3. Apathy and neuronal injury (category "N")

CSF t-tau correlated with severity of apathy in AD dementia ([33], n = 32, low quality study, Appendix 2. Table 5). However, in MCI[32] and in CN/MCI/AD dementia[25] no association between CSF t-tau and apathy was found, both studies were considered of high quality. Further, MTA scores were not associated with apathy in AD dementia[63] and no association was found using whole-brain approaches and presence of apathy in MCI/AD dementia[53] and AD dementia[38, 43]. In addition to whole-brain analyses, the hippocampus, as an a priori ROI, was not associated with apathy in AD dementia[43] and MCI[32].

In contrast, severity of apathy was found to associate negatively with ventromedial prefrontal cortex (PFC), ventrolateral PFC, posterior cingulate cortex and adjacent lateral cortex, and bank of the superior temporal sulcus volumes[47]; and anterior cingulate cortex, orbitofrontal cortex, regions of the dorsolateral prefrontal cortex and putamen (bilateral), and caudate nucleus (left), but no temporal lobe, volumes[44] in AD dementia. In addition, utilizing an ROI approach, severity of apathy in CN/MCI was associated with lower inferior temporal cortical thickness and greater anterior cingulate cortical thickness[21] and presence of apathy with greater cortical thinning in the caudal ACC, lateral OFC and pars triangularis (all left) in AD dementia[58]. When comparing patients with AD dementia with and without apathy no GM volume differences were found[55] and severity of apathy was not related to any a priori cortical thickness measure, although lower baseline inferior temporal thickness was associated with greater increase in apathy over 2.3 year follow-up in a group of CN, MCI and

AD dementia[25]. Taken together, the nature of these mixed findings suggest a need for further investigation.

3.2.4. Agitation

Two studies showed a positive association between severity of agitation and CSF $A\beta_{42}$ levels, one in AD dementia[19] and one in MCI/AD dementia [27] across the AD spectrum. In line with this, presence of agitation was associated with abnormal levels of $A\beta_{42}$ in MCI[32]. However, others reported no association between agitation and CSF $A\beta_{42}$ levels in AD dementia[33, 65] or Aβ deposition (PiB PET in AD dementia[38] and 18F-AV-45 PET in MCI and AD dementia[24]). CSF t-tau and p-tau was associated with agitation in AD[65]. However, others found no association between agitation and CSF p-tau in AD dementia[19, 33], CSF t-tau in MCI and AD dementia[19, 32, 33], MTA scores in AD dementia[63], hippocampal volume in MCI and AD dementia[32, 43], or GM volumes in MCI and AD dementia[38, 44, 47, 53]. Thus, the association between amyloid and agitation needs further evaluation, especially given the fact that three out of four CSF studies were considered to be of low quality[19, 27, 33]. No evidence for category T and N markers was found.

3.2.5. Irritability

Irritability was associated with CSF $A\beta_{42}$ but not t-tau in MCI[32] and with parietal Aβ deposition (18F-AV-45 PET) in AD dementia but not in MCI[24]. However, no association was found between PiB PET amyloid load and irritability in AD dementia[38]. Further, no association was found between irritability and MTA scores in AD dementia[63], hippocampal volume in MCI and AD dementia[32, 43], or GM volumes in MCI and AD dementia[38, 44, 47, 53]. Although all papers were considered high-quality, the association between amyloid and irritability needs further evaluation. No evidence for category T and N markers was found.

3.2.6. Night-time behaviour disturbances

Night-time behaviour disturbances were not associated with Aβ deposition (18F-AV-45 PET in MCI and AD dementia[24]), CSF $A\beta_{42}$ (in AD dementia, CN/MCI/AD dementia, and SCD/MCI, respectively[19, 27, 30]), CSF p-tau in AD dementia[19] or CSF t-tau (in AD dementia, and SCD/MCI respectively[19, 30]) across the diagnostic spectrum. Utilizing whole-brain volume approaches, one study reported more atrophy in posterior and inferior (bilateral temporal and occipital cortices) parts of the brain in patients with AD dementia and rapid eye movement sleep behaviour disorder[48], contrasting others who reported no association with night-time behaviour disturbances measured with the Neuropsychiatric Inventory (NPI)[43, 44, 47, 53]. Hippocampal volumes were not associated with night-time behaviour

disturbances in SCD/MCI[30] and AD[43]. Taken together, these findings of mainly high-quality studies show that night-time behaviour disturbances are not associated with AT(N) markers.

3.2.7. Subsyndromes

Four studies examined the relationship between AD biomarkers and neuropsychiatric subsyndromes, according to the four factors as identified by Aalten et al[66] (i.e. hyperactivity, psychosis, affective and apathy). Overall, no cross-sectional association between these factors and cortical thickness in CN/AD dementia[26], MTA in AD dementia[62] and regional GM volumes in MCI/AD dementia[53] was found, except for a correlation between cortical thickness and the affective syndrome[26]. One study reported an association between higher Aβ global uptake and a principal component factor comprising of depression, anxiety, aberrant motor behaviour and delusions in CN/MCI/AD dementia[24]. In MCI and AD dementia, hippocampal volume was correlated with agitation/aggression at any visit over two years, and increased atrophy of the left hippocampus was associated with increased agitation/aggression over time[57]. Another longitudinal study showed that baseline plasma $A\beta_{42/40}$ ratio significantly predicted agitation/aggression scores but not mood or frontal syndrome scores, after 2-year follow-up[36].

4. DISCUSSION

The aim of the present systematic review was to synthesize all available evidence on the relationship between AD biomarkers and affective symptoms in cognitively impaired individuals, using the recent AT(N) research framework[12]. Depression and night-time behaviour disturbances were not related to amyloid, pathologic tau or neuronal injury markers. Mixed findings were reported for the association between anxiety and amyloid and neuronal injury markers. Anxiety was associated with CSF neuronal injury markers but not with imaging atrophy markers. Apathy was associated with amyloid on PET scans, but not with CSF amyloid markers. No support was found for the association between apathy and pathologic tau or neuronal injury markers. Both for agitation and irritability, mixed findings for the association with amyloid were found and there was no association with pathologic tau or neuronal injury markers.

Although the presence of affective symptoms (and depression in particular) in cognitively impaired individuals is often explained to be caused by a common neuropathological mechanism between affective symptoms and cognitive impairment[67], we found no evidence that depression is associated with AT(N) markers and that evidence for other symptoms is still inconclusive. Possibly, these symptoms might be (better) explained by psychosocial or environmental factors (e.g. relationship with caregivers) or other

biological factors which were not examined here, such as the influence of the hypothalamic–pituitary–adrenal axis, (chronic) inflammation, or vascular disease[68]. On the other hand, it can be hypothesized that affective symptoms in cognitively impaired individuals include heterogeneous phenotypes, and that these associations are now masked by grouping these subtypes together. For example, heterogeneity exists within the depressive illness itself, e.g. time of (first) onset and duration of symptoms. In this line, previous studies showed that a lifetime history of depression (LMD) predicted Aβ levels more strongly than current depressive symptoms[40] and smaller hippocampal volumes were found to be associated with increasing years of untreated illness in those with LMD[29]. Further, it has been reported that amyloid positive individuals have a later age of onset of first major depression episode (MDE) and less total number of MDEs than amyloid negative individuals[41]. Thus, a person with current affective symptoms and a history of depression might be fundamentally different from a person with current affective symptoms without history of depression. Yet, in the present review only one study controlled for the confounding effect of lifetime history of/(number of) earlier episodes of affective symptoms[40].

Following this line of reasoning, one might consider AD pathology vs. non-AD pathology subtypes, where affective symptoms can be considered as a prodrome of AD in biomarker positive individuals or driving the cognitive impairment in biomarker negative individuals. Individuals with (higher) amyloid load and comorbid affective symptoms might, for example, be at risk of faster progression to AD dementia[39]. One of the hypotheses is that the link between affective symptoms and AD dementia relates to region specific deposition of Aβ, mood related neurocircuits in particular[39]. In this line, region specific amyloid/tau deposition, i.e. lateral temporal FDDNP binding, were found to correlate with depression scores[42].

Only a small part of the studies (16%) examined longitudinal associations, asking two types of questions: (1) whether baseline affective symptoms were predictive of change in biomarkers[45, 51, 52], and (2) whether baseline biomarkers were predictive of (change in) affective symptoms over time[25, 35, 36, 57]. Baseline anxiety[51] and depression[45, 52] status did not predict rates of hippocampal atrophy. Baseline CSF amyloid was associated with increasing symptoms of depression[35] and agitation[36] symptoms over time, but not with apathy over time[25]. CSF tau was not associated with depression[35] or apathy[25] over time. Baseline hippocampal atrophy was associated with increasing agitation over time[57] and baseline inferior temporal cortical thickness with increasing apathy over time[25]. This small number of longitudinal studies limits our ability to draw conclusions with regard to the prognostic and monitoring use of AT(N) biomarkers, but also interpretations of causality. That is, affective symptoms in (prodromal) AD might induce a biological cascade causally leading to AD pathology or AD pathology might lead to affective symptoms. It is intriguing that, although

overall no association between AT(N) markers and depression was found, some studies reported depression to be associated with larger hippocampal volumes[28, 32, 46]. In other words, subjects with less atrophy (i.e. less AD pathology) had more often or more severe symptoms of depression. This implies that depressive symptoms in (prodromal) AD are not a manifestation of an already ongoing pathology but might represent different subtypes of AD or are psychological reactions to cognitive decline. Due to mixed findings with regard to the association between (a) anxiety, agitation and irritability and amyloid, and (b) between apathy and pathologic tau and neuronal injury markers, no clear conclusions could be drawn.

The ambiguity of the overall evidence might be due to the complex relationship between the neurodegenerative process and affective symptoms, but might also be related to methodological aspects. For example, the studies included in this review utilized a wide range of instruments to assess presence or severity of affective symptoms, likewise for methods to assess biomarker values or abnormalities (Table 1). It is questionable whether the implicit assumption that all these instruments are measuring the same underling construct holds true. In addition, the option to dichotomize continuous data allows for selective reporting of analyses, also because one can select from multiple cut-off points. AD biomarkers are generally dichotomized in order to classify a given patient as having AD or not. Although markers such as CSF and PET have been shown to correlate strongly with senile pathology[69, 70], cut-offs might not accurately reflect pathology. It is thus important to keep in mind that choices of cut-offs can be considered arbitrary. In the current review, for example, nearly all studies that conducted analyses with categorical fluid biomarkers used pre-defined cut-off points and appropriate cross-referencing. However, although the cut-off points were predefined, they were still dissimilar. For example, the four out of ten depression studies that dichotomized the CSF markers from the ELISA assay[28, 30-32], used reference values from Fagan et al[71] and Sjögren et al[72]. Further, the heterogeneity that exists between laboratories and between batches of reagents must be acknowledged as a methodological limitation.

Another methodological consideration is the re-use of existing data. Although this has greatly enhanced AD research in terms of time, resources, and costs, we must be aware of its consequences. In the current systematic review, a large number of reports (n = 13) was based on (subgroups of) the ADNI cohort. These studies utilizing the same cohort were included because they provided results for different biomarker modalities in different disease stages with different affective symptoms (Appendix 3 Table 1). The fact that findings from different methodologies all point towards the same direction might be considered as a strength. However, we must also consider the potential bias that was introduced. Would we have used the results for meta-analysis, including data from the same patient more than

once would have resulted in biased estimates and exaggerated accuracy[73]. In a systematic review, some conclusions might be given more emphasis than deserved.

The following consideration pertains to the inclusion of mixed samples. The results imply that different mechanisms might underlie affective symptoms differently throughout the course of AD. For example, an association between anxiety and amyloid was found in studies including subjects with MCI only, but not in studies including AD dementia. In this line, anxiety was associated with total-tau but not GM changes (i.e., both markers belonging to the (N) category), suggesting more sensitivity for the fluid markers in terms of diagnostic utility or reflecting the fact that accumulation of tangles is an earlier event than cortical thinning. However, it is important to keep in mind that these studies are cross-sectional and that the association might not be causal. Thus, it might be that the association is mediated by cognitive status, i.e. impaired cognition (as predictor) is associated with anxiety (as outcome) and Aβ (as predictor) is associated with impaired cognition (as outcome). In other words, cognitive status, for example measured by the MMSE, might act as a mediator on the relationship between Aβ and anxiety. The existence of such mediation would have implications for the current review, because seven out of 21 (33.3%) studies did not differentiate between diagnostic groups in their analyses. This might have diluted existing relationships. Indeed, the studies grouping diagnoses together found no association on the majority (80%) of examined associations. However, five out of seven *did* correct for global cognition (MMSE[35, 53]), global functioning (CDR[23]) or diagnosis[21, 25]. Thus, these studies will not have influenced the results of this systematic review.

In addition, the generalizability to population-based studies or primary care settings (e.g. nursing homes) is limited given that nearly all studies included subjects from memory clinics or research settings. The use of clinical samples might have resulted in referral bias, possibly leading to overestimation of affective symptom prevalences.

Assessing study quality with a predefined format allowed us to systematically identify methodological shortcomings. Most studies were subject to several (Appendix 2). Cross-sectional studies were overall of low methodological quality: for amyloid, 13 out of 20 (65%), for pathologic tau, 4 out of 8 (50%) and for neuronal injury, 23 out of 31 (74%) studies were rated as low quality. Of note, only considering high quality papers did not change the results of the review. We observed that the majority of studies was limited by small sample sizes (18 studies included < 100 patients, of which three were CSF, four were PET and eleven MRI studies), studies were subjected to selection bias due to non-random sampling strategies, the majority of studies relied entirely on significance values while omitting to report confidence intervals (or reporting only significant results, see Appendix 2. NOS criteria, for cross-sectional studies “O2” and for longitudinal studies “O4”) and only few studies adjusted for important factors like pharmacological treatment. Further, affective symptoms examined

were generally of low severity. This is not surprising giving the mild stages of (prodromal) dementia of the included subjects, which led some researches to argue that more (significant) relations would have emerged if a wider range of symptom severity was included. The prevalence rates of the affective symptoms that were reported in the included studies are in line with those reported in a systematic review and meta-analysis from 2016[14], although for apathy, we found somewhat lower prevalence rates (28.2%, ranging from 15%[25] to 78%[43]) than those earlier reported (49%, 95% CI: 41-57%)[14].

5. PERSPECTIVES and CONCLUSION

This review shows that some AD biomarkers are associated with affective symptoms, whereas evidence for others is largely inconsistent. The ambiguous findings might be caused by the large heterogeneity observed with regard to study designs, settings, samples, measurement instruments, and concept definitions. Data harmonization and more uniformity in statistical approaches is needed to compare and replicate future findings. In this line, more discussion is needed on the definition of affective symptoms in neurodegenerative diseases. For example, it might be questioned whether the studies that were included were able to capture the heterogeneity in the (clinical manifestation of) affective symptoms. Therefore, we would like to direct future research towards identifying or predicting specific phenotypes (e.g. those with history of vs. new onset of symptoms) associated with well-defined biomarker profiles. Further, research should not be limited to AT(N) markers covered in this review, as less specific AD markers as vascular, inflammation, lipidomic/metabolomic factors also have shown to be associated with affective symptoms and the AT(N) framework was designed in such a way that it can be expanded to include new biomarkers. It would also be informative to include multiple of the afore-mentioned biomarkers at once, showing possibly interactions between mechanisms.

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SUPPLEMENTARY DATA

Appendix 1. Complete search strategy

CINAHL (EBSCOhost)

S1	TI ((((cognitiv* or cognition or memory) and (declin* or impair* or deteriora* or change* or deficit* or complaint*)) or dementia or Alzheimer* or "pre-clinical AD" or "preclinical AD" or predementia* or "prodromal AD")) OR AB ((((cognitiv* or cognition or memory) and (declin* or impair* or deteriora* or change* or deficit* or complaint*)) or dementia or Alzheimer* or "pre-clinical AD" or "preclinical AD" or predementia* or "prodromal AD"))
S2	TI (("neuropsychiatric symptoms" or "neuro-psychiatric symptoms" or "neuropsychiatric syndromes" or "neuro-psychiatric syndromes" or "psycho-behavioral symptoms" or "psycho-behavioural symptoms" or "psychiatric symptoms" or "behavioral symptoms" or "behavioural symptoms" or "psychological symptoms" or "disruptive behavior" or "disruptive behaviour" or "non-cognitive symptoms" or "neuropsychological symptoms" or "bpsd" or "nps" or dysphoria or depression or depressive or depressed or anxiety or anxious or apathy or "lack of interest" or sleep or irritability or lability or "mood change" or "mood changes" or agitation or agitated or aggression or rage or "catastrophic reactions" or anger or angry or complaining or negativism or screaming)) OR AB (("neuropsychiatric symptoms" or "neuro-psychiatric symptoms" or "neuropsychiatric syndromes" or "neuro-psychiatric syndromes" or "psycho-behavioral symptoms" or "psycho-behavioural symptoms" or "psychiatric symptoms" or "behavioral symptoms" or "behavioural symptoms" or "psychological symptoms" or "disruptive behavior" or "disruptive behaviour" or "non-cognitive symptoms" or "neuropsychological symptoms" or "bpsd" or "nps" or dysphoria or depression or depressive or depressed or anxiety or anxious or apathy or "lack of interest" or sleep or irritability or lability or "mood change" or "mood changes" or agitation or agitated or aggression or rage or "catastrophic reactions" or anger or angry or complaining or negativism or screaming))
S3	((tau or T-tau or Ttau or P-tau or Ptau or amyloid* or abeta* or a-beta* or beta-amyloid* or AB42) and (cerebrospinal fluid or CSF or plasma or positron emission tomography or PET))
S4	((magnetic resonance imaging or MRI) and (temporal* or hippocampal* or medial temporal lobe or MTA))
S1 AND S2 AND S3	Limiters - Language: Dutch, English, French, German; Population Group: Human
S1 AND S2 AND S4	Limiters - Language: Dutch, English, French, German; Population Group: Human

EMBASE (ovid)

1	(((cognitiv* or cognition or memory) and (declin* or impair* or deteriora* or change* or deficit* or complaint*)) or dementia or Alzheimer* or "pre-clinical AD" or "preclinical AD" or predementia* or "prodromal AD").ti,ab.
2	("neuropsychiatric symptoms" or "neuro-psychiatric symptoms" or "neuropsychiatric syndromes" or "neuro-psychiatric syndromes" or "psycho-behavioral symptoms" or

	"psycho-behavioural symptoms" or "psychiatric symptoms" or "behavioral symptoms" or "behavioural symptoms" or "psychological symptoms" or "disruptive behavior" or "disruptive behaviour" or "non-cognitive symptoms" or "neuropsychological symptoms" or "bpsd" or "nps" or dysphoria or depression or depressive or depressed or anxiety or anxious or apathy or "lack of interest" or sleep or irritability or lability or "mood change" or "mood changes" or agitation or agitated or aggression or rage or "catastrophic reactions" or anger or angry or complaining or negativism or screaming).ti,ab.
3	((tau or T-tau or Ttau or P-tau or Ptau or amyloid* or abeta* or a-beta* or beta-amyloid* or AB42) and (cerebrospinal fluid or CSF or plasma or positron emission tomography or PET)).mp.
4	1 and 2 and 3
5	limit 4 to (humans and (dutch or english or french or german))
6	((magnetic resonance imaging or MRI) and (temporal* or hippocampal* or medial temporal lobe or MTA)).mp.
7	1 and 2 and 6
8	limit 7 to (humans and (dutch or english or french or german))

PsycINFO (EBSCOhost)

S1	TI ((((cognitiv* or cognition or memory) and (declin* or impair* or deteriora* or change* or deficit* or complaint*)) or dementia or Alzheimer* or "pre-clinical AD" or "preclinical AD" or predementia* or "prodromal AD")) OR AB ((((cognitiv* or cognition or memory) and (declin* or impair* or deteriora* or change* or deficit* or complaint*)) or dementia or Alzheimer* or "pre-clinical AD" or "preclinical AD" or predementia* or "prodromal AD"))
S2	TI (("neuropsychiatric symptoms" or "neuro-psychiatric symptoms" or "neuropsychiatric syndromes" or "neuro-psychiatric syndromes" or "psycho-behavioral symptoms" or "psycho-behavioural symptoms" or "psychiatric symptoms" or "behavioral symptoms" or "behavioural symptoms" or "psychological symptoms" or "disruptive behavior" or "disruptive behaviour" or "non-cognitive symptoms" or "neuropsychological symptoms" or "bpsd" or "nps" or dysphoria or depression or depressive or depressed or anxiety or anxious or apathy or "lack of interest" or sleep or irritability or lability or "mood change" or "mood changes" or agitation or agitated or aggression or rage or "catastrophic reactions" or anger or angry or complaining or negativism or screaming)) OR AB (("neuropsychiatric symptoms" or "neuro-psychiatric symptoms" or "neuropsychiatric syndromes" or "neuro-psychiatric syndromes" or "psycho-behavioral symptoms" or "psycho-behavioural symptoms" or "psychiatric symptoms" or "behavioral symptoms" or "behavioural symptoms" or "psychological symptoms" or "disruptive behavior" or "disruptive behaviour" or "non-cognitive symptoms" or "neuropsychological symptoms" or "bpsd" or "nps" or dysphoria or depression or depressive or depressed or anxiety or anxious or apathy or "lack of interest" or sleep or irritability or lability or "mood change" or "mood changes" or agitation or agitated or aggression or rage or "catastrophic reactions" or anger or angry or complaining or negativism or screaming))
S3	((tau or T-tau or Ttau or P-tau or Ptau or amyloid* or abeta* or a-beta* or beta-

	amyloid* or AB42) and (cerebrospinal fluid or CSF or plasma or positron emission tomography or PET))
S4	((magnetic resonance imaging or MRI) and (temporal* or hippocampal* or medial temporal lobe or MTA))
S1 AND S2 AND S3	Limiters - Language: Dutch, English, French, German; Population Group: Human
S1 AND S2 AND S4	Limiters - Language: Dutch, English, French, German; Population Group: Human

PubMed	
S1	((cognitiv* OR cognition or memory) AND (declin* OR impair* OR deteriora* OR change* OR deficit* OR complaint*)) OR dementia OR Alzheimer* OR "pre-clinical AD" OR "preclinical AD" OR predementia* OR "prodromal AD" [Title/Abstract]
S2	"neuropsychiatric symptoms" OR "neuro-psychiatric symptoms" OR "neuropsychiatric syndromes" OR "neuro-psychiatric syndromes" OR "psycho-behavioral symptoms" OR "psycho-behavioural symptoms" OR "psychiatric symptoms" OR "behavioral symptoms" OR "behavioural symptoms" OR "psychological symptoms" OR "disruptive behaviOR" OR "disruptive behaviour" OR "non-cognitive symptoms" OR "neuropsychological symptoms" OR "bpsd" OR "nps" OR dysphoria OR depression OR depressive OR depressed OR anxiety OR anxious OR apathy OR "lack of interest" OR sleep OR irritability OR lability OR "mood change" OR "mood changes" OR agitation OR agitated OR aggression OR rage OR "catastrophic reactions" OR anger OR angry OR complaining OR negativism OR screaming [Title/Abstract]
S3	(tau OR T-tau OR Ttau OR P-tau OR Ptau OR amyloid* OR abeta* OR a-beta* OR beta-amyloid* OR AB42) AND (cerebrospinal fluid OR CSF OR plasma OR positron emission tomography OR PET)
S4	(magnetic resonance imaging OR MRI) AND (temporal* OR hippocampal* OR medial temporal lobe OR MTA)
S5	"humans"[MeSH Terms]
S6	Dutch[lang] OR English[lang] OR French[lang] OR German[lang])
S7	S1 AND S2 AND S3 AND S5 AND S6
S8	S1 AND S2 AND S4 AND S5 AND S6

Appendix 2. Quality assessment

Table 1. Quality assessment form according to Newcastle-Ottowa Scale (NOS)[151] for cohort studies

Selection (max★★★)	
S1: Representativeness of the exposed cohort (biomarker positives)	a) For population based studies: truly representative of the average person with cognitive impairment in the community.★ b) For clinical population studies: truly representative of the average person with cognitive impairment in the (memory-) clinic.★ c) Selected group of users e.g. volunteers. d) No description of the derivation of the cohort.
S2: Selection of the non-exposed cohort (biomarker negatives)	a) Drawn from the same source as the exposed cohort★ b) Drawn from a different source. c) No description of the derivation of the non-exposed cohort.
S3: Ascertainment of predictor (biomarker)	a) Validated measurement tool.★ b) Non-validated measurement tool, but the tool is available or described.★ c) No description.
Comparability (max★★)	
Comparability of cohorts on the basis of the design or analysis	a) Study controls for the most important factor (age/).★ b) Study controls for any additional factor (e.g. sex/education/MMSE).★ c) No control for important factors.
Outcome (max★★★★)	
O1: Assessment of outcome	a) Validated measurement tool (affective symptoms must be assessed by either self- or proxy report)★ b) Non-validated measurement tool, but the tool is available or described.★ c) No description.
O2: Was follow-up long enough for outcomes to occur	a) Yes (longer than 6 months).★ b) No.
O3: Adequacy of follow up of cohorts	a) Complete follow up - all patients accounted for.★ b) Patients lost to follow up unlikely to introduce bias (small number lost, i.e. follow up rate is more than 70 %, or description provided of those lost).★ c) Follow up rate < 70% and no description of those lost. d) No statement.
O4: Statistical test	a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value).★ b) The statistical test is not appropriate, not described or incomplete.

Table 2. Quality assessment form according to Newcastle-Ottowa Scale (NOS)[151] adapted for cross-sectional studies

Selection (max★★★)	
S1: Representativeness of exposed cohort (biomarker positives)	a) For population based studies: truly representative of the average person with cognitive impairment in the community.★ b) For clinical population studies: truly representative of the average person with cognitive impairment in the (memory-) clinic.★ c) Selected group of users e.g. volunteers.

	d) No description of the derivation of the cohort.
S2: Sample size, response rate, and comparability between predictor positives and negatives	a) Sample size is justified, response rate AND the comparability between positives and negatives (either A or B) characteristics are described.★ b) Sample size is justified and the response rate OR the comparability between predictor positives and negatives characteristics is described.★ c) Sample size is justified, but no description of the response rate and the characteristics of the predictor positives and negatives . d) Sample size is not justified, and there is no description of the response rate or the characteristics of the predictor positives and negatives . *dependent on definition of predictor and outcome used either (A) biomarker positives and negatives or (B) affective symptoms positives and negatives
S3: Ascertainment of predictor (either biomarker or affective symptoms)	a) Validated measurement tool.★ b) Non-validated measurement tool, but the tool is available or described.★ c) No description.
Comparability (max★★)	
C: Comparability of predictor positives and negatives on the basis of the design or analysis	a) Study controls for the most important factor (age).★ b) Study controls for additional factor (e.g. sex/education/MMSE).★ c) No control for important factors.
Outcome (max★★)	
O1: Assessment of outcome	a) Validated measurement tool, either self- or proxy report★ b) Non-validated measurement tool, but the tool is available or described. c) No description.
O2: Statistical test	a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value).★ b) The statistical test is not appropriate, not described or incomplete.

Table 3. Quality assessment scores according to NOS, cross-sectional studies, category "A" (amyloid)

	Selection			Comparability	Outcome		Overall	
Author (year)	S1	S2	S3	C1	O1	O2	Sum	Bias
Arnold (2012)	1	1	1	2	1	1	7	0
Auning (2015)	1	0	1	0	1	0	3	1
Bensamoun (2016)	1	1	1	2	1	1	7	0
Blioniecki (2014)	0	0	1	2	1	1	5	0
Brendel (2015)	1	1	1	2	1	0	6	0
Chung (2016)	1	1	1	2	1	0	6	0
Donovan (2014)	1	1	1	2	1	1	7	0
Engelborghs (2005)	1	0	1	0	1	0	3	1
Kramberger (2012)	1	1	1	2	1	0	6	1
Kuo (2015)	0	0	1	0	1	0	2	0
Lavretsky (2009)	0	0	1	1	1	0	3	1
Lee (2012)	1	0	1	0	1	0	3	1
Marshall (2013)	0	0	1	2	1	0	4	0
Moon (2017)	1	1	1	0	1	0	4	0
Mori (2014)	0	0	1	2	1	0	4	0
Nathan (2017)	1	1	1	2	1	0	6	0
Ramakers (2013)	1	1	1	2	1	1	7	0
Reijs (2017)	1	0	1	2	1	1	6	0
Skogseth (2008)	1	0	1	0	1	0	3	1
Tateno (2015)	0	1	1	0	1	0	3	1

Table 4. Quality assessment scores according to NOS, cross-sectional studies, category "T" (pathologic tau)

	Selection			Comparability	Outcome		Overall	
Author	S1	S2	S3	C1	O1	O2	Sum	Bias
Arnold (2012)	1	1	1	2	1	1	7	0
Auning (2015)	1	0	1	0	1	0	3	1
Blioniecki (2014)	0	0	1	2	1	1	5	0
Donovan (2014)	1	1	1	2	1	1	7	0
Engelborghs (2005)	1	0	1	0	1	0	3	1
Kramberger (2012)	1	1	1	2	1	0	6	0
Lee (2012)	1	0	1	0	1	0	3	1
Skogseth (2008)	1	0	1	0	1	0	3	1

Table 5. Quality assessment scores according to NOS, cross-sectional studies, category "N" (neurodegeneration)

	Selection			Comparability	Outcome		Overall	
Author	S1	S2	S3	C1	O1	O2	Sum	Bias
Arnold (2012)	1	1	1	2	1	1	7	0
Auning (2015)	1	0	1	0	1	0	3	1
Berlow (2010)	1	1	1	1	1	0	5	0
Bilgic (2013)	0	0	1	2	1	0	4	0
Blioniecki (2014)	0	0	1	2	1	1	5	0
Bruen (2008)	0	0	1	2	1	0	4	0
Donovan (2014)	1	1	1	2	1	1	7	0
Dhikav (2014)	1	0	1	0	1	0	3	1
Elcombe (2015)	0	0	1	0	1	0	2	1
Enache (2015)	1	1	1	2	1	1	7	0
Engelborghs (2005)	1	0	1	0	1	0	3	1
Fuijshima (2014)	0	1	1	2	1	0	5	0
Guercio (2015)	1	0	1	2	1	1	6	0
Hayata (2015)	0	0	1	0	1	0	2	1
Hsu (2015)	1	0	1	2	1	0	5	0
Huey (2017)	0	0	1	2	1	0	4	0
Kim (2016)	1	0	1	2	1	0	5	0
Kramberger (2012)	1	1	1	2	1	0	6	0

Lebedev (2014)	1	1	1	2	1	1	7	0
Lebedeva (2014)	1	1	1	2	1	0	6	0
Lee (2012)	1	0	1	0	1	0	3	1
Mori (2014)	0	0	1	2	1	0	4	0
Ramakers (2013)	1	1	1	2	1	1	7	0
Reijs (2017)	1	0	1	2	1	1	6	0
Serra (2010)	1	0	1	2	1	0	5	0
Skogseth (2008)	1	0	1	0	1	0	3	1
Son (2013)	1	1	1	0	1	0	4	0
Staekenborg (2008)	1	1	1	2	1	0	6	0
Starkstein (2009)	1	1	1	2	1	0	6	0
Sturm (2013)	0	0	1	0	1	0	2	1
Tunnard (2011)	1	1	1	1	1	0	5	0

Table 6. Quality assessment scores according to NOS, cohort studies, category "A" (amyloid)

	Selection			Comparability	Outcome				Overall	
Author	S1	S2	S3	C1	O1	O2	O3	O4	Sum	Bias
Barca (2017)	1	1	0	1	1	1	1	1	7	0
Donovan (2014)	1	1	1	2	1	1	1	0	8	0
Hsu (2017)	1	1	1	2	1	1	1	0	8	0

Table 7. Quality assessment scores according to NOS, cohort studies, category "T" (pathologic tau)

	Selection			Comparability	Outcome				Overall	
Author	S1	S2	S3	C1	O1	O2	O3	O4	Sum	Bias
Barca (2017)	1	1	0	1	1	1	1	1	6	0
Donovan (2014)	1	1	1	2	1	1	1	0	7	0

Table 8. Quality assessment scores according to NOS, cohort studies, category "N" (neuronal injury)

	Selection			Comparability	Outcome				Overall	
Author	S1	S2	S3	C1	O1	O2	O3	O4	Sum	Bias
Barca (2017)	1	1	1	1	1	1	1	1	8	0

Chung (2016)	1	1	1	1	1	1	1	0	6	0
Donovan (2014)	1	1	1	2	1	1	1	0	7	0
Lee (2012)	1	1	1	0	1	1	0	0	5	0
Mah (2015)	1	1	1	0	1	1	1	0	5	0
Moon (2017)	1	1	1	0	1	1	1	0	5	0
Trzepacz (2013)	1	1	1	2	1	1	0	0	7	0

Appendix 3. Results stratified to biomarker modality

Table 1. Results stratified to biomarker modality, only unique study cohorts

		Amyloid-beta disposition			Pathologic tau (NFT)			Neurodegeneration		
Presence or more severe symptoms of	N studies	↓ CSF or ↑ PET AB levels	↑ CSF or ↓ PET AB levels	= CSF or PET AB levels	↑ CSF p-tau or PET tau	↓ CSF p-tau or PET tau	= CSF p-tau or PET tau	↑ MRI atrophy*, FDG PET, CSF t-tau	↓ MRI atrophy, FDG PET, CSF t-tau	= MRI atrophy, FDG PET, CSF t-tau
Depression	33	CSF 35	CSF	CSF 19, 20, 23, 27*, 28, 31, 33 Excl.^: 32, 34	CSF	CSF 20	CSF 19, 23, 28, 33, 35 Excl.^: 34	CSF	CSF 20, [28, hip vol trend]; 32	CSF 19, 23, 28 (t-tau), 33, 35
		PET (18-F-45) 24 PET (FDDNP) 42# Excl.^: 39	PET	PET (18-F-45) 41 PET (PiB) 38 Excl.^: 40	PET (FDDNP) 42	PET	PET	MTA 61	MTA 46 (AD)	MTA 35, 46 (SCD/MCI), 60, 63
								Volume 22, 46 (SCD), 49, 50, 52#, 54(AD)	Volume [28 trend]; 32	Volume 29, 38, 43, 44, 46 (AD), 55, 53, 54 (MCI pts), 56 Excl.^: 45, 47

Anxiety	12	CSF 32 PET (18-F-45) 24 PET (FDDNP) 42#	CSF PET	CSF 19, 27 PET (PiB) 38	CSF	CSF	CSF 19	CSF 32 MTA Volume 51(C)	CSF MTA Volume	CSF 19 MTA 63 Volume 38, 43, 44, 53 51 (L) Excl.^: 47, 32
Apathy	14	CSF PET (PiB) 37, 38	CSF PET	CSF 25, 33 Excl.^: 32 PET (18F-AV- 45) 24	CSF 33	CSF	CSF 25	CSF 33 MTA Volume 21, 25 (L), 47	CSF MTA Volume	CSF 25 (C + L), 32 MTA 63 Volume 25 (C), 38, 43, 44, 53, 55, 58
Agitation	12	CSF 19, 27, 32	CSF	CSF 33				CSF 19, 32, 33	CSF	CSF 19

		PET	PET	PET (PiB) 38 PET (18F-AV- 45) 24				MTA Volume	MTA Volume	MTA 63 Volume 32, 38, 43, 44, 53 Excl.^: 47
Irritability	8	CSF 32 PET (18F-AV-45) 24	CSF	CSF PET (PiB) 38				CSF MTA Volume	CSF MTA Volume	CSF 32 MTA 63 Volume 32, 38, 43, 44, 53 Excl.^: 47
Night-time behaviour disturbances	9	CSF	CSF	CSF 19, 27, 30 PET (18F-AV- 45) 24	CSF	CSF	CSF 19	CSF MTA	CSF MTA	CSF 19, 30 MTA

					Volume 48	Volume	Volume 30, 43, 44, 47, 53
Subsyndromes	4	CSF 36*** (agi)	CSF	CSF 36*** (mood, frontal)			
		PET (18F-AV-45) 24 (PC3)#,	PET	PET (18F-AV- 45) 24 (PC1, PC2, PC4)#			
					MTA	MTA	MTA 62 (agi, mood)
					Volume 26 (dep, anx), 57	Volume	Volume 26 (apa, psy, hyper), 53

↓, ↑ and = CSF, = resp. lower, high and equal cerebrospinal fluid concentrations in those with symptom present; ↓, ↑ and = PET, = resp. lower, higher and equal uptake on PET scan; NFT = neurofibrillary tangles; hip vol = hippocampal volume; C = cross-sectional analyses, L = longitudinal analyses; mood = neuropsychiatric inventory subscale including depression, anxiety, and irritability items; frontal = neuropsychiatric inventory subscale including apathy, disinhibition, irritability, and euphoria items; agi = agitation; dep = depression; anx = anxiety; apa = apathy, psy = psychosis, syndrome including delusions, hallucinations, and night-time behaviour disturbance; hyper = hyperactivity, syndrome including agitation, disinhibition, irritability, euphoria, and aberrant motor behaviour scores; ^ exclusion of paper due to smallest sample size in duplicated cohort, e.g. ADNI, * of temporal lobe/hippocampus; # PC 1 (agitation, euphoria, apathy, disinhibition, irritability), PC2 (sleep and eating disturbances), PC3 (depression, anxiety, aberrant motor behaviour, delusion), PC4 (hallucination); ***Hsu 2017, in APOE e4 carriers

4

THE ASSOCIATION BETWEEN BIOMARKERS AND NEUROPSYCHIATRIC SYMPTOMS ACROSS THE ALZHEIMER'S DISEASE SPECTRUM

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ABSTRACT

Objective: Here we investigate the relationship between Alzheimer's disease (AD) biomarkers and neuropsychiatric symptoms (NPS).

Methods: Data from two large cohort studies, the Dutch Parelsnoer Institute – Neurodegenerative Diseases and the Alzheimer's Disease Neuroimaging Initiative was used, including subjects with Subjective Cognitive Decline (SCD, N = 650), Mild Cognitive Impairment (MCI, N = 887) and AD dementia (N = 626). Cerebrospinal fluid (CSF) levels of Aβ42, t-tau, p-tau, and hippocampal volume (HCV) were associated with NPS (measured with the Neuropsychiatric Inventory) using multiple logistic regression analyses. The effect of the Mini-Mental State Examination (as proxy for disease severity) on these relationships was assessed with mediation analyses.

Results: AD biomarkers were not associated with depression, agitation, irritability, and sleep disturbances. Lower levels of CSF Aβ42, higher levels of t- and p-tau were associated with presence of anxiety. Lower levels of Aβ42 and smaller HCV were associated with presence of apathy. All associations were mediated by MMSE score, which suggests that the association between AD pathology and anxiety and apathy is due to severity of the disease.

1. INTRODUCTION

Neuropsychiatric symptoms (NPS) occur in nearly all patients with Alzheimer's disease (AD) dementia over the disease course and have prognostic consequences[1-4]. Although AD pathology differs between patients with and without certain NPS, the etiology of NPS remains unclear[5]. An increased understanding of the underlying biological mechanisms of NPS in AD would result in better understanding and improve earlier treatment of these multifactorial symptoms[6].

AD pathology is reflected by biomarkers, such as cerebrospinal fluid (CSF) levels of amyloid-β ($A\beta_{42}$) protein, total tau (t-tau) and phosphorylated-tau (p-tau)[7], and reduced hippocampal volume (HCV)[8, 9]. Previous research showed that symptoms of depression and anxiety are related to lower CSF $A\beta_{42}$ [5, 10] and higher t-tau[11] levels, although others have not supported this finding[12-17]. These inconsistent findings apply to other NPS as well, such as apathy, agitation, and irritability, and might be explained by differences in study design such as sample size, sample characteristics, or differences in the measurement of both biomarkers and NPS.

The association of AD pathology with NPS as reported in several studies suggests that these symptoms are a non-cognitive manifestation of underlying AD pathology. In the cases that AD pathology was not associated with NPS, hypotheses were posed that the presence of NPS itself might result in cognitive impairment (e.g. where NPS deplete cognitive resources) or that awareness of cognitive decline results in NPS. The association between NPS and AD pathology might be dependent on the severity of the disease.

The primary aim of the current study was to study (inter)relations of AD biomarkers (CSF $A\beta_{42}$, t-tau and p-tau; hippocampal volume) and the most common NPS in MCI and AD dementia (depression, anxiety, agitation, apathy, irritability, and sleep/night-time behavior disturbances[2, 4, 18]). This study also examines how global cognitive functioning, as a proxy for disease severity, might impact this relationship, in a large clinically representative sample of subjects with subjective cognitive decline (SCD), MCI (mild cognitive impairment) and AD dementia.

2. MATERIALS and METHODS

2.1. Sample

Individuals were included from two large, multicenter and longitudinal studies, the Dutch Parelsnoer Institute – Neurodegenerative Diseases (PSI-NDZ[19], parelsnoer.org) and the Alzheimer's Disease Neuroimaging Initiative (ADNI; adni.loni.usc.edu). The PSI-NDZ study is a collaborative cohort study of the Memory Clinics of eight Dutch University Medical Centers (UMCs), focusing on the role of

biomarkers in early and differential diagnosis and course monitoring of neurodegenerative diseases[19]. The ADNI study has 59 acquisition sites in the USA and primarily evaluates whether MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure progression of MCI and AD. ADNI phases 1, GO and 2 were used for the current study. These three ADNI phases are consecutive cohorts with slightly different data collection protocols (see adni-info.org).

For the present study, baseline data was used from subjects with subjective or objective cognitive complaints (i.e. SCD, MCI, AD dementia) who had information on NPS and at least one of the following biomarkers available: $A\beta_{42}$, t-tau and p-tau in CSF, and HCV on MRI. Exclusion criteria were 1) the presence of any psychiatric or neurological disorders other than dementia that could cause cognitive impairment and 2) a diagnosis of dementia due to non-AD etiology (n = 143, 28 subjects for whom this information was missing).

2.2. Clinical assessment

The comprehensive assessment procedures included a clinical interview, standardized physical and neurological examinations, and neuropsychological assessments. Assessment of global cognitive functioning, as a proxy of disease severity, was assessed using the MMSE[20]. In both studies, the clinical diagnosis of dementia was based on DSM-IV criteria and etiological diagnosis of AD according to standardized clinical criteria (NINCDS-ADRDA criteria for probable AD[21]). Diagnosis of MCI was made in accordance to the Petersen criteria[22], i.e. (1) memory complaints, (2) abnormal memory function based on norm-based cut scores, (3) normal activities of daily living. Participants were diagnosed with SCD when significant memory concerns could not be objectified.

2.2.1. Neuropsychiatric symptoms

In the PSI-NDZ cohort and ADNI 2, the presence of NPS was assessed with the full Neuropsychiatric Inventory (NPI), a commonly used informant-based scale that examines 12 neuropsychiatric domains through a structured interview with the caregiver[23]. In the ADNI 1 and ADNI GO studies, the informant-based NPI-Questionnaire (NPI-Q) was used[24]. Both formats assess the presence and severity (1-3, mild-severe) of each domain, but only the full NPI assesses the frequency (1-4, rarely-very often) of the symptoms, where multiplying the severity by frequency results in a continuous domain score (1-12) per NPS. In order to harmonize the different datasets, NPS were dichotomized simply as present (severity score ≥ 1) or

absent (severity score = 0). For the current study, the most prevalent symptoms in MCI and AD dementia were selected: depression, anxiety, apathy, agitation, irritability and night-time behavior disturbances[2, 4, 18, 25, 26].

Information on NPS was available for 1,313 (99.6%) ADNI subjects and for 756 (89.5%) PSI-NDZ subjects (95.7% for whole sample). Subjects for whom NPS data were available differed from subjects for whom these were not available with regard to age (72.1 vs 66.8 years, $p < .001$), and education (14.0 vs 12.2 years, $p < .001$). Distribution of diagnosis, gender, and MMSE scores were similar in both groups.

2.3. Biomarker assessment

2.3.1. CSF

CSF was collected by lumbar puncture. The CSF procedures have been described in detail elsewhere for PSI-NDZ[19] and ADNI[7]. To measure $A\beta_{42}$, t-tau and p-tau levels, PSI-NDZ used commercially available single-parameter enzyme-linked immunosorbent assay (ELISA) methods whereas ADNI used Roche Elecsys and cobas e immunoassay analyzer system. To combine both measures of CSF, scores were converted into z-scores based on the means and standard deviations of the SCD subjects, as these were considered as control group.

CSF data were available for 941 (71.4%) ADNI subjects and for 205 (24.3%) PSI-NDZ subjects (53.0% for whole sample). Subjects for whom CSF data were available differed from subjects for whom these were not available with regard to gender (58.7 vs 53.9% females), education (15.2 vs 12.6 years, $p < .001$), and MMSE score (26.7 vs 26.0 years, $p < .001$). Age was similar in both groups.

2.3.2. MRI

Both PSI-NDZ and ADNI used standardized acquisition protocols performed at 1.5 and 3.0 Tesla, which are described in detail elsewhere[19, 27]. Total intracranial volume (ICV) and HCV were measured centrally at the Biomedical Imaging Group Rotterdam (BIGR, Erasmus MC, Rotterdam, Netherlands) using a multi-atlas segmentation procedure, according to methods described previously[28], and obtaining gray matter (GM) volumes from the T1-weighted image using the unified tissue segmentation method[29] of SPM8 (Statistical Parametric Mapping, London, UK). To correct for head size, HCV was divided by ICV, then further normalized to have zero mean and unit variance.

MRI data were available for 1,304 (98.9%) ADNI subjects and for 556 (65.8%) PSI-NDZ subjects (86.0% for whole sample). Subjects for whom MRI data were available differed from subjects for whom these were not available with regard to age

(72.3 vs 69.2 years, $p < .001$), education (14.4 vs 11.5 years, $p < .001$), and MMSE score (26.5 vs 25.9, $p < .001$). Gender distribution was similar in both groups.

2.4. Statistical analyses

Statistical analyses were performed with R version 3.3.2.[30], with significance set at $p < 0.01$ in two-sided tests. Group differences (i.e., between ADNI and PSI, between subjects with vs. without available biomarker data and NPS, between diagnostic groups) were analyzed using t tests, one-way ANOVA (in case more than two groups) or Kruskal-Wallis test by rank (non-parametric) for continuous variables and chi-square tests for categorical variables. Logistic regression models were used to estimate odds ratios (ORs) of biomarker levels for predicting the presence of individual NPS, corrected for age, gender, and study cohort. To further understand these relationships, the effect of amyloid independent of neuronal injury (i.e. tau and HCV) and vice versa (i.e. neuronal injury independent of amyloid) was tested. In addition, mediation models were ran to test the hypothesis that disease severity (i.e. MMSE score) mediates the relationship between biomarkers and NPS, following the Baron & Kenny approach[31]. In the first step of this approach, the total association between biomarker and NPS was assessed (Figure 1A, path c). In the second step, the direct associations between biomarker and MMSE (Figure 1B, path a), MMSE and NPS (Figure 1B, path b) and biomarker and NPS (Figure 1B, path c') was assessed. The indirect mediating effect of MMSE (a*b) was tested in case both path a and path b from the first steps showed significant associations. All analyses were corrected for age, gender, and study cohort. The scaling issue that occurred in these mediation models, due to a linear mediator and binary outcome, was addressed by standardizing the coefficients. The standard error parameters were bootstrapped (5000 resamples). The 95% confidence intervals were determined using the adjusted bootstrap percentile method to correct for bias in the distribution of bootstrap estimates.

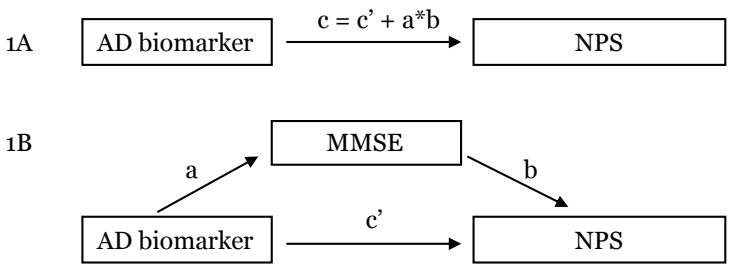

Figure 1. Schematic model of analyses

Note. Panels 1A and 1B show the schematic model of mediation analyses. Panel 1A shows the total effect of biomarker on NPS, denoted by path c. Panel 1B shows the direct effect of biomarker on affective symptom, which is denoted by path c', and the indirect effect of biomarker on affective symptom through disease severity (path a*b). Analyses were adjusted for age, gender, and cohort.

3. RESULTS

In total, 2,163 subjects were included (mean age = 71.9, SD = 9.1; 56.5% females). Baseline characteristics are presented in Table 1 (maximum available data). There were significant differences between the cohorts, with ADNI being older, higher educated, having lower CSF values of t-tau and p-tau, lower hippocampal volumes, and having less often NPS. CSF $A\beta_{42}$ levels, MMSE scores, percentage females and APOE-ε4 carriers were similar across the cohorts.

Table 1. Baseline characteristics per syndrome diagnosis

	SCD (N = 650)	MCI (N = 887)	AD dementia (N = 626)	Total (N=2,163)	p value
Cohort (ADNI/PSI), %	64.3/35.7	63.7/36.3	53.5/46.5	60.9/39.1	< 0.001
Female	363 (55.8)	530 (60.0)	327 (52.2)	1220 (56.5)	0.011
Age, years, m (sd)	68.7 (9.6)	72.8 (8.2)	73.9 (8.8)	71.9 (9.1)	< 0.001
Education, years, m (sd)	14.5 (3.7)	14.2 (3.9)	13.1 (3.9)	14.0 (3.9)	<0.001
MMSE, m (sd)	28.4 (1.7)	27.0 (2.0)	23.4 (2.2)	26.4 (2.8)	<0.001
Biomarkers					
CSF present	422 (64.9)	421 (47.5)	288 (46.0)	1,131 (52.3)	< 0.001
$A\beta_{42}$, m (sd)[a]	0.0 (1.0)	-0.6 (1.0)	-1.0 (0.7)	-0.5 (1.0)	< 0.001
t-tau, m (sd)[a]	0.0 (1.0)	0.6 (1.3)	1.2 (1.6)	0.5 (1.4)	< 0.001
p-tau, m (sd)[a]	0.0 (1.0)	0.6 (1.3)	1.2 (1.6)	0.5 (1.4)	< 0.001
$A\beta_{42}$, abnormal[b]	169 (38.7)	280 (67.0)	238 (81.8)	687 (59.9)	< 0.001
t-tau, abnormal[b]	169 (38.7)	259 (62.0)	229 (78.7)	657 (57.3)	< 0.001
p-tau, abnormal[b]	177 (40.6)	267 (63.9)	238 (81.8)	682 (59.6)	< 0.001
MRI scan present	547 (84.2)	785 (88.5)	528 (84.3)	1,860 (86.0)	0.020
Hippocampal volume, % ICV[c]	3.7 (0.6)	3.4 (0.6)	3.1 (0.6)	3.4 (0.6)	< 0.001
APOE-ε4 carrier	251 (40.5)	438 (53.0)	372 (64.8)	1061 (52.6)	< 0.001
Neuropsychiatric symptoms					
NPI present	618 (95.1)	849 (95.7)	602 (96.2)	2,069 (95.7)	0.630
Depression	182 (29.6)	241 (28.7)	223 (37.4)	646 (31.5)	< 0.001
Anxiety	101 (16.4)	166 (19.8)	205 (34.3)	472 (23.0)	< 0.001
Apathy	115 (18.8)	192 (23.0)	266 (44.9)	573 (28.1)	< 0.001
Agitation	96 (15.7)	182 (21.8)	183 (30.8)	461 (22.6)	< 0.001
Irritability	203 (33.1)	260 (31.2)	236 (39.7)	699 (34.2)	0.003
Sleep/night-time behavior disturbances	161 (26.3)	157 (18.7)	137 (23.1)	455 (22.3)	0.002
(history of-) any psychiatric diagnosis	246 (65.6)	258 (55.7)	169 (45.6)	673 (55.7)	< 0.001
(history of-) depression^	159 (71.3)	185 (65.1)	131 (55.7)	475 (64.0)	0.002
(history of-) anxiety^	41 (59.4)	27 (60.0)	24 (72.7)	92 (62.6)	0.392
(history of-) diagnosis, other	64 (9.8)	67 (7.6)	38 (6.1)	169 (7.8)	0.040

Note. Data are n (%), unless specified otherwise. SCD = subjective cognitive decline; MCI = mild cognitive impairment; AD = Alzheimer's disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; PSI = Parelsnoer Institute – Neurodegenerative Diseases; MMSE = mini-mental state examination; $A\beta_{42}$ = amyloid-β protein; t-tau = total tau; p-tau = phosphorylated-tau; MRI = magnetic resonance imaging; NPI = neuropsychiatric inventory; ICV = intracranial volume; APOE-ε4 = Apolipoprotein E; [a] z-scores; [b] For ADNI, concentrations below 980 pg/ml for $A\beta_{42}$, above 245 pg/ml for t-tau and above 21.8 pg/ml for p-tau were classified as abnormal (correspondence with L. M. Shaw, 2018). For PSI-NDZ, concentrations below 551 pg/ml for $A\beta_{42}$, above 375 pg/ml for t-tau and above 52 pg/ml for p-tau were classified as abnormal [32]. Information on psychiatric history was available for 742 (depression) and 147 (anxiety) patients; [c] Total hippocampal volume (left + right) divided by total intracranial volume

Table 2. Multivariable effects of baseline AD biomarkers and presence of NPS in the pooled cohort

	AD biomarker			
NPS	CSF $A\beta_{42}$[a]	CSF t-tau	CSF p-tau	AHV[a]
Depression	1.12 (0.98-1.28), p = 0.101	1.06 (0.97-1.17), p = 0.209	1.08 (0.98-1.19), p = 0.113	0.95 (0.84-1.07), p = 0.406
Anxiety	1.34 (1.14-1.57), p < 0.001	1.21 (1.09-1.35), p < 0.001	1.22 (1.10-1.36), p < 0.001	1.14 (1.01-1.30), p = 0.039
Apathy	1.25 (1.08-1.46), p = 0.003	1.12 (1.01-1.24), p = 0.039	1.11 (1.00-1.23), p = 0.056	1.28 (1.13-1.45), p < 0.001
Agitation	1.13 (0.98-1.32), p = 0.101	1.08 (0.97-1.20), p = 0.156	1.12 (1.01-1.24), p = 0.036	1.12 (0.98-1.27), p = 0.084
Irritability	1.08 (0.94-1.23), p = 0.272	1.10 (0.99-1.21), p = 0.071	1.11 (1.00-1.22), p = 0.052	1.10 (0.97-1.23), p = 0.125
Sleep/night-time	0.93 (0.80-1.07), p = 0.281	0.98 (0.88-1.09), p = 0.700	1.01 (0.91-1.12), p = 0.856	0.93 (0.81-1.06), p = 0.258

Results are displayed as: odds ratios (95% confidence interval), p-value. Analyses are corrected for age, gender, and study cohort. Significance was set at p < 0.01.

[a]inversely coded as more pathology means lower scores. AD = Alzheimer's disease; NPS = neuropsychiatric symptoms; CSF = cerebrospinal fluid; $A\beta_{42}$ = amyloid-β protein; t-tau = total tau; p-tau = phosphorylated-tau, AHV = adjusted hippocampal volume (total hippocampal volume (left + right) divided by total intracranial volume

3.1. Depression

Levels of $A\beta_{42}$, t-tau and p-tau and HCV were not associated with the presence of depressive symptoms.

3.2. Anxiety

Lower CSF levels of $A\beta_{42}$ (here inversely coded, as lower levels mean more pathology) were significantly associated with the presence of anxiety (OR = 1.34, 95% CI = 1.14-1.57, $p < 0.001$). This direct association was independent of t-tau and p-tau but was attenuated after adding MMSE to the model (OR = 1.18, 95% CI = 0.99-1.41, p = 0.065). Subsequent mediation analyses showed that the association between $A\beta_{42}$ and anxiety indirectly operated through MMSE ($\beta_{indirect}$=-0.054, 95%CI = 0.029-0.079, $p < 0.001$), thereby being consistent with the concept of mediation. Higher levels of CSF t-tau were associated with the presence of anxiety (OR = 1.21, 95% CI = 1.09-1.35, $p < 0.001$). This direct association was independent of $A\beta_{42}$ (OR = 1.16, 95% CI = 1.04-1.30, $p < 0.001$) but was attenuated after adding MMSE to the model (OR = 1.11, 95% CI = 0.98-1.25, p = 0.098). Subsequent mediation analyses showed that the association between t-tau and anxiety indirectly operated through MMSE ($\beta_{indirect}$=0.051, 95%CI = 0.026-0.075, $p < 0.001$). Higher levels of CSF p-tau were associated with the presence of anxiety (OR = 1.22, 95% CI = 1.10-1.36, $p < 0.001$). This direct association was independent of Aβ42 (OR = 1.17, 95% CI = 1.05-1.31, $p < 0.01$) but was attenuated after adding MMSE to the model (OR = 1.12, 95% CI = 0.99-1.26, p = 0.061). Subsequent mediation analyses showed that the association between p-tau and anxiety indirectly operated through MMSE ($\beta_{indirect}$=0.048, 95%CI = 0.024-0.073, $p < 0.001$). HCV was not associated with the presence of anxiety.

3.3. Apathy

Lower levels of $A\beta_{42}$ (inversely coded) were associated with the presence of apathy (OR = 1.25, 95% CI = 1.08-1.46, $p < 0.005$). This direct association was independent of t-tau and p-tau but was attenuated after adding MMSE to the model (OR = 1.14, 95% CI = 0.97-1.34, p = 0.128). Subsequent mediation analyses showed that the association between $A\beta_{42}$ and apathy in the total group indirectly operated through MMSE ($\beta_{indirect}$ = 0.044, 95%CI =0.020-0.067, $p < 0.001$), thereby being consistent with the concept of mediation. Levels of CSF t-tau or p-tau were not associated with the presence of apathy. Smaller HCV (here, inversely coded) was associated with the presence of apathy (OR = 1.28, 95% CI = 1.13-1.45, $p < 0.001$). The association was attenuated after adding MMSE to the model (OR = 1.13, 95% CI = 0.97-1.30, p = 0.110). Subsequent mediation analyses showed that the association between HCV and apathy indirectly operated through MMSE ($\beta_{indirect}$ = -0.053, 95%CI = -0.072;-0.033, $p < 0.001$), again consistent with the concept of mediation.

3.4. Agitation

No association between the presence of agitation and $A\beta_{42}$ values, t-tau, p-tau, and HCV was found.

3.5. Irritability

No association between the presence of irritability and $A\beta_{42}$ values, t-tau, p-tau, and HCV was found.

3.6. Sleep/night-time behavior disturbances

No association between the presence of sleep/night-time behavior disturbances and $A\beta_{42}$ values, t-tau, p-tau, and HCV was found.

4. DISCUSSION

The relationship between AD biomarkers and NPS was examined in 2,163 subjects covering the AD disease spectrum (SCD, MCI, AD dementia), which were included from two large cohort studies (ADNI and PSI-NDZ). Lower CSF levels of $A\beta_{42}$, higher CSF levels of t- and p-tau were associated with presence of anxiety. Lower CSF levels of $A\beta_{42}$ and smaller HCV, but not CSF t- or p-tau, were associated with presence of apathy. All associations were shown to operate indirectly through MMSE. That is, the presence of AD pathology seems to have an effect on the presence of anxiety and apathy via a lower MMSE score. This implies that symptoms of anxiety and apathy across the AD spectrum are associated with AD pathology, due to severity of the disease.

AD biomarkers were not associated with depression, agitation, irritability, and sleep/night-time behavior disturbances. Syndrome diagnosis did not act as a moderator in any of these associations (results not shown), indicating that the effect of AD pathology on presence of NPS did not differ across syndrome diagnoses. Although the null-findings with regard to AD pathology and depression in AD were somewhat unexpected given the vast amount of literature on this relationship, these current results are in line with a recent systematic review[33]. Possibly, symptoms of depression, agitation, irritability and sleep/night-time behavior disturbances are better explained by psychosocial (e.g. awareness and psychological reaction to the disease) or environmental factors (e.g. relationship with caregivers) or other biological factors that were not examined here, such as the influence of the HPA axis, (chronic) inflammation, vascular disease[34] or disturbances in neurotransmitter systems. On the other hand, it can be hypothesized that possible existing associations are masked by grouping together cognitively impaired individuals with affective symptoms that actually represent heterogeneous phenotypes, for example, having a lifetime history of

psychiatry vs. those with new onset. In this line of reasoning, early-onset psychiatry (e.g. depression or anxiety) may act as risk factor for dementia, via mechanisms such as chronically elevated cortisol or neuroinflammation levels, which in turn have neurotoxic effects on the brain, leading to AD pathology. NPS might then be attributable to past depressive/anxious episodes rather than current AD pathology. In contrast, late life depression or anxiety might be an early manifestation of AD pathology. Therefore, as a post hoc analysis, we examined the association between AD pathology and NPS while controlling for the confounding effect of life-time history of depression (LHD) or life-time history of anxiety (LHA). Information on psychiatric history was obtained by patient or caregiver report during intake. Neither LHD (present yes/no) nor LHA (present yes/no) acted as a moderator in the association between AD biomarker and presence of depression and anxiety, respectively (results not shown). However, it must be noted that this information was available for only a small subset of the sample (missing for LHD 65.7%; for LHA 93.2%, see Table 1).

Strengths of this study are its large and well-characterized sample, which allowed us to correct for a large number of covariates and the power to detect subtle effects, even with a conservative p-value. Substantial variation in AD biomarker levels and NPS was ensured by the inclusion of individuals from the various disease stages (i.e., SCD, MCI and AD dementia). However, variability was also induced by merging data of two different cohorts, e.g. individuals in PSI-NDZ showing more often NPS but also the use of different biomarker assays, although both cohorts used highly standardized workup procedures. In order to equalize the different CSF assays – each with a different scaling – and to ease interpretation of results, z-scores were utilized which were based on the SCD subgroup. It is important to note that - although not all reached significance in the smaller PSI-NDZ cohort, probably due to power issues - the associations found in the merged cohort were also found in the cohorts separately (results not shown). That is, the findings were verified in two independent samples. A great amount of NPS comorbidity was observed within subjects (e.g. of individuals with symptoms of depression almost 35% also show symptoms of agitation, 41% symptoms of anxiety, 44% symptoms of apathy, 51% symptoms of irritability and 34% sleep/night-time behavior disturbances). It might be that endorsement of more symptoms (i.e. a higher load) may synergistically contribute to more abnormal biomarker levels (or vice versa). This is something worth further investigating. Further, the possibility of misdiagnosis remains as clinical diagnoses of SCD, MCI and AD dementia were employed. In addition, (selection-) bias might have been introduced as it was observed that individuals with biomarker data available at baseline were cognitively healthier, had higher levels of education, were more often females and were older in comparison to those without biomarker data available. A broad age range (29 – 92) was observed for the PSI-NDZ cohort.

However, excluding the 35 subjects younger than 50 years old did not change the results. NPS were assessed with the NPI. Although this instrument is considered the golden standard in NPS research, its limitations must be acknowledged, for example its dependence on caregiver report which is subject to information bias[35]. Another limitation of the current study is the use of a cross-sectional design as NPS are known to fluctuate over time. This also prevents any conclusions regarding causality as temporality of effects cannot be established. The clinical research setting of the study limits generalizability to population-based or primary care settings.

5. CONCLUSIONS

Our findings have implications for the view on NPS in the context of neurodegenerative diseases. The results suggest that anxiety and apathy are indirectly associated with underlying AD pathology and that the presence of these symptoms might be explained by disease severity. Symptoms such as depression might be better explained by psychosocial, environmental or other biological factors than that were examined in this study. The high prevalence of NPS (22.3-34.2% in the present study) emphasizes the importance for clinicians to examine and monitor NPS in people across the AD spectrum.

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5

ALZHEIMER'S DISEASE BIOMARKERS AS PREDICTORS OF TRAJECTORIES OF DEPRESSION AND APATHY ACROSS THE DISEASE SPECTRUM

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ABSTRACT

Objective: To examine trajectories of depression and apathy over a 5-year follow-up period in (prodromal) AD, and to relate these trajectories to AD biomarkers.

Methods: The trajectories of depression and apathy (measured with the Neuropsychiatric Inventory or its questionnaire) were separately modelled using growth mixture models for two cohorts (NACC, n = 28,717 and ADNI, n = 1,733). The trajectories in ADNI were associated with baseline CSF AD biomarkers ($A\beta_{42,}$ t-tau, and p-tau) using bias-corrected multinomial logistic regression.

Results: Multiple classes were identified, with the largest classes having no symptoms over time and other classes having (steep) increases or decreases. More AD pathology was associated with increased probability of depression and apathy over time, compared to classes without symptoms. Tau but not $A\beta_{42}$ was associated with decreased apathy over time.

Discussion: The trajectories of depression and apathy in individuals on the AD spectrum are associated with AD biomarkers.

1. INTRODUCTION

Neuropsychiatric symptoms (NPS) in Alzheimer's disease (AD) occur in nearly all patients over the disease course, including its prodromal phases[1, 2]. Unlike the deterioration seen for cognition and daily function, "affective" NPS such as depression and apathy do not necessarily progress in one direction over time but rather may persist, remit, or recur episodically[3]. Although depression and apathy frequently co-occur, they are known to be distinct NPS[4]. It has been argued that both must be considered as distinct conditions[5], each with its own biological correlates.

Cerebrospinal fluid (CSF) analytes such as amyloid-$\beta_{1\text{-}42}$ ($A\beta_{42}$), phosphorylated-tau (p-tau), and total tau (t-tau) reflect AD brain pathology by their association with the presence of beta-amyloid deposition, neurofibrillary tangles and neuronal loss[6]. Despite increasing attention to the relationship between these validated AD biomarkers and affective symptoms in cognitively impaired individuals, this association has been mostly examined in cross-sectional studies[7]. To the best of our knowledge, only one study (each) has examined the association between baseline biomarkers and depression[8] or apathy over time[9]. Barca et al., identified three distinct trajectories of depressive symptoms in a sample of persons with mild cognitive impairment (MCI) and AD dementia[8]. Interestingly, the class with moderate and increasing depression scores had lower baseline CSF $A\beta_{42}$ levels compared to the class with stable low depression[8]. Donovan et al. reported no association between CSF biomarkers and apathy over time, but they assumed in their analyses that one single growth trajectory describes the entire population, whilst it is reasonable to hypothesize that subsets of individuals with different trajectories exist[9].

The primary aim of the present study was to examine whether distinct trajectories of depression and apathy exist in individuals comprising the AD spectrum (i.e. cognitively normal (CN), MCI, dementia). We used a large clinical dataset from the National Alzheimer's Coordinating Center (NACC) to identify latent classes of trajectories. Next, we sought to validate the measurement model in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Including the ADNI cohort allowed us to examine the validity of the measurement model, and to investigate whether these trajectories are predicted differentially by baseline AD biomarkers (secondary aim).

2. METHODS

2.1. Sample

Both NACC and ADNI consist of referral/volunteer-based case series of individuals diagnosed as CN, MCI or dementia at Alzheimer's Disease Centers across the US. For NACC, data was used from Uniform Dataset (UDS) visits conducted between September 2005 and December 2018. For ADNI, data was used from visits conducted between September 2005

and January 2018. In NACC, individuals are followed up approximately yearly, whereas in ADNI half-yearly. For the present study, data up to five years were used. Details on the diagnostic, inclusion and exclusion criteria, as well as a description of the study designs can be found elsewhere (NACC[10, 11]; ADNI (http://www.adni-info.org/). Baseline characteristics of the cohorts are in Table 1.

2.2. Clinical assessment

In both cohorts, a comparable standardized assessment took place at study entry. All participants underwent neurological, neuropsychological, and neuropsychiatric examination. This included recording of sociodemographic characteristics (gender, age, educational years and race). Participants and a knowledgeable informant were asked about their medical and psychiatric history (recent/active or remote/inactive episodes of anxiety or depression), and whether they used prescription medications of interest here: (1) antidepressants, (2) other behavioral medications, such as antipsychotics/anxiolytics, sedative or hypnotic agents, or (3) FDA-approved "Alzheimer" medications. Global cognitive functioning was assessed in both cohorts on the Mini-Mental State Examination (MMSE[12]). These data were reviewed by a multidisciplinary team which made diagnoses of MCI based on the Petersen criteria[13]. For ADNI, diagnoses of dementia were based on DSM-IV-TR criteria. For NACC UDS versions 1 and 2, the diagnostic criteria for all-cause dementia were not specified. For UDS version 3, the NIA-AA criteria were used[14]. Etiological diagnoses of AD were established by NINCDS-ADRDA criteria[15] for NACC UDS versions 1 and 2 and ADNI, whereas NACC UDS version 3 utilized NIA-AA criteria[14].

2.3. Neuropsychiatric assessment

The Neuropsychiatric Inventory (NPI) is a widely used measure of neuropsychiatric symptoms (NPS) that follows positive screening responses to characterize frequency, severity and caregiver burden in twelve domains of symptoms, including apathy and dysphoria (depression)[16]. Typically, these frequency and severity ratings are multiplied to yield a total domain score. This "full-NPI" was utilized in ADNI phase II only, whereas in NACC, ADNI phase I and ADNI GO, the NPI-questionnaire (NPI-Q) was used. This is a simplified version of the full questionnaire and unlike NPI, does not assess frequency of symptoms. In the present study, depression and apathy as outcome variables were therefore dichotomized at each visit as present (severity > 0) or absent.

2.4. Biomarker assessment (ADNI)

Baseline biomarker data from ADNI were considered in the present study. The CSF biomarker determination procedures have been described in detail elsewhere (online at

adni-info.org). To measure $A\beta_{42}$, t-tau and p-tau levels, the CSF biomarker aliquots of all available samples were recently re-analyzed using the Roche Elecsys® electrochemiluminescence immunoassay, using the same reagent lot for each biomarker. Raw biomarker levels were converted into z-scores based on the means and standard deviations of the CN subjects. To facilitate further interpretation and comparison of the current results with other cohorts, we also report results for raw CSF scores in Supplementary File 1.

2.5. Statistical analysis

All analyses were done in Mplus, version 8[17]. Further analyses, such as descriptive analyses and plots, were done using R v. 3.5.1[18].

2.5.1. Part I: symptom trajectories in NACC and ADNI

Growth mixture modeling (GMM) was used to model subtypes of trajectories of the occurrence of depression or apathy over time, regardless of syndromal diagnosis or other clinical characteristics, for each cohort separately[19]. These models combine latent classes analysis with growth curves, that is, they allow for the estimation of latent (unobserved) classes of individuals based on similarities on their affective symptom course. Model parameters of each growth trajectory (i.e. intercept, linear slope, quadratic term) are allowed to vary across the latent classes.

Models with both linear and quadratic terms were fit with an increasing number of classes (up to 5). The optimal number of classes was chosen using the Lo-Mendell-Rubin likelihood ratio tests (LMR-LRT). Model fit was assessed via comparison of observed and predicted trajectories. To fit a smooth curve to longitudinal dichotomous data (as depression and apathy were rated as absent/present), a LOESS-curve fitting method was used. This is a non-parametric method where least-squares regression is performed in localized subsets, resulting in a "running average" of zero's and ones[20]. The selection of the "correct" number of classes is central to our interpretation, which is known to be influenced by the method used to impose the random effects structure of the model. Our decisions in model selection were based on parsimony, replicability, and clinical interpretability.

2.5.2. Part II: biomarker association with symptom trajectories in ADNI

Because NACC lacks standardized AD biomarker data, baseline AD biomarkers were associated with symptom trajectories in ADNI only. After deciding upon number of classes for depression or apathy, probabilities of membership in each class were calculated for each participant, based on how well their trajectory matched the mean trajectories of each of the classes. These probabilities can then be used to assign individuals to a class, which in turn

can be used as an outcome in logistic regression analyses. However, this method is known to introduce bias. Therefore, to take uncertainty of assigned class membership into account, the three-step method was used[21, 22]. ADNI baseline biomarker levels were used as predictors.

3. RESULTS

3.1. Sample characteristics

Baseline characteristics of the two cohorts are in Table 1. NACC provided 28,717 participants with a mean follow-up pf 27.5 months. At baseline, the prevalence of symptoms of depression and apathy were 23.4 and 14.1% respectively. ADNI had 1,733 eligible participants available with mean follow-up of 37.1 months. At baseline, the prevalence of depression and apathy were 21.2 and 15.7%.

Those with only one measurement available (i.e. dropouts) were on average younger and more likely to have depression and apathy than those with follow-up measurements available. The subset of ADNI participants with biomarker data available (n = 1,214) was younger, more educated, more often Caucasian, had higher MMSE scores, provided more follow-up data, and were less likely to take FDA-approved AD medications compared to those without biomarker data. As expected, biomarker levels differed significantly by diagnostic group, with CN having the highest $A\beta_{42}$ and lowest tau levels compared to MCI and AD participants.

Table 1. Baseline characteristics

	NACC = 28,717	ADNI, n = 1,733
Diagnosis (% CN/MCI/Dementia)	57.0/28.0/15.0	30.1/50.5/19.5
Dementia due to AD, N (%)	1042 (24.2)	334 (99.1)
Age at baseline, M (SD)	71.8 (10.3)	73.8 (7.2)
Gender, female, N (%)	16,738 (58.3)	778 (44.9)
Education in years, M (SD)	15.4 (3.3)	15.9 (2.9)
Ethnicity, Caucasian, N (%)	23,058 (80.3)	1,601 (92.4)
MMSE, M (SD)	27.548 (2.875)	27.2 (2.7)
Follow-up timepoints, M (SD)	5.6 (3.9)	7.2 (3.1)
Medical history		
History of major depression, N (%)	5,931:28,588 (21.0)	90:254 (35.4)
History of anxiety disorder, N (%)	NA	3:534 (0.6)
Medication use		
Antidepressants, N (%)	6,995: 2,8588 (24.5)	233:913 (25.5)
Other behavioral medication, N (%)	3,777: 2,4811 (13.2)	48:910 (5.3)
Alzheimer medication, N (%)	4,502: 24,811 (15.7)	251:913 (27.5)
Affective symptoms		
Depression present, N (%)	6506 (23.4)	367 (21.2)
Apathy present, N (%)	3918 (14.1)	272 (15.7)

Abbreviations: NACC = National Alzheimer's Coordinating Centre; ADNI = Alzheimer's Disease Neuroimaging Initiative; CN = cognitively normal; MCI = mild cognitive impairment; AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; NA = not available.

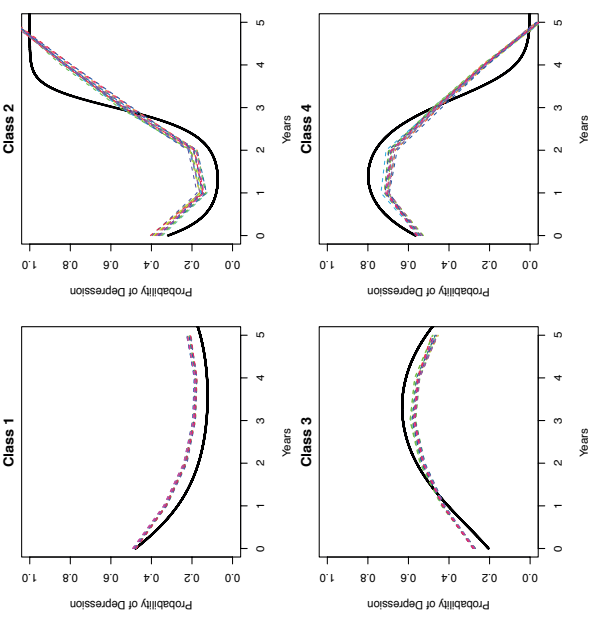

Figure 1a. Depression, 5-class model with random intercept only, NACC data

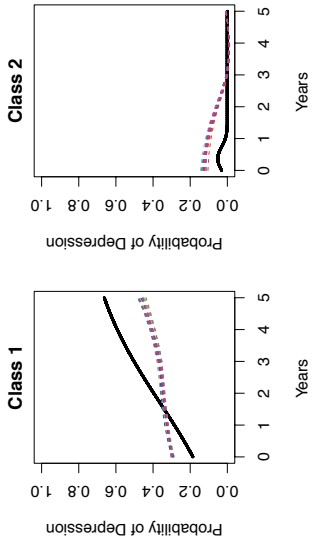

Figure 1b. Depression, 2-class model with random intercept/random slope, ADNI data

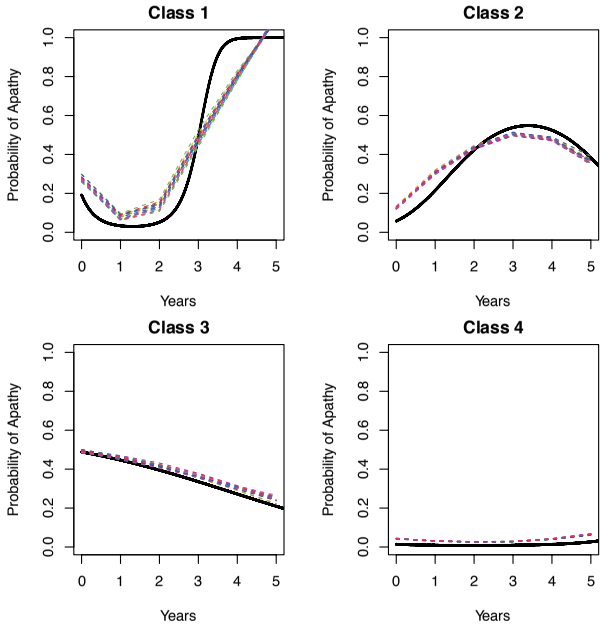

Figure 1c. Apathy, 4-class model with random intercept only, NACC data

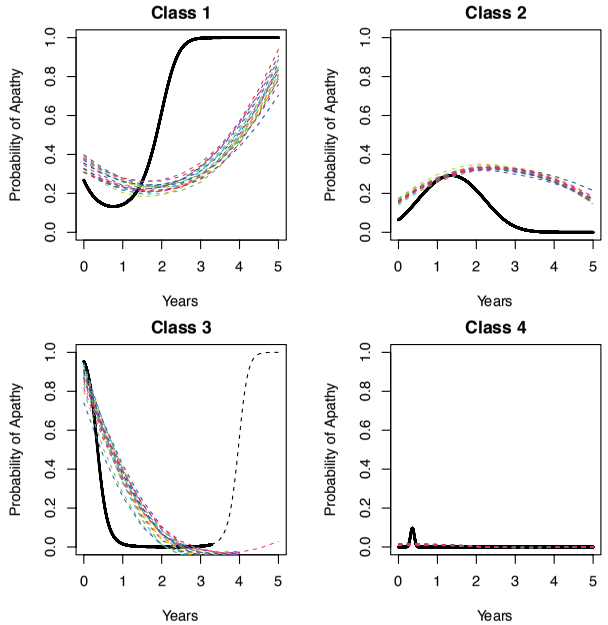

Figure 1d. Apathy, 4-class model with random intercept only, ADNI data

Note. Fitted (black) and observed (dotted) depression and apathy trajectories. The uncertainty of class membership – class membership is a latent unobserved variable, i.e. not deterministic – was taken into account for the observed trajectories by multiple imputation of class membership (i.e. considering class membership as pieces of missing information).

Table 2. Multivariable effects of baseline biomarkers in the growth models for depression and apathy in ADNI

	Depression			Apathy		
	Class	N	OR (95% CI), p value	Class	N	OR (95% CI), p value
$A\beta_{42}$	1. Increasing depression	534	0.43 (0.31-0.60), p < 0.001	1. Steep increasing apathy	50	0.38 (0.16-0.91), p = 0.029
	2. Stable low depression	680	Ref. class	2. Increasing apathy	411	0.30 (0.17-0.52), p < 0.001
				3. Steep decreasing apathy	37	0.88 (0.16-3.24), p = 0.846
				4. Stable low apathy	716	Ref. class
t-tau	1. Increasing depression	534	2.08 (1.43-3.02), p < 0.001	1. Steep increasing apathy	50	1.45 (0.81-2.60), p = 0.214
	2. Stable low depression	680	Ref. class	2. Increasing apathy	411	1.98 (1.43-2.74), p < 0.001
				3. Steep decreasing apathy	37	2.31 (1.59-3.37), p < 0.001
				4. Stable low apathy	716	Ref. class
p-tau	1. Increasing depression	534	2.27 (1.54-3.33), p < 0.001	1. Steep increasing apathy	50	1.53 (0.90-2.60), p = 0.118
	2. Stable low depression	680	Ref. class	2. Increasing apathy	411	2.10 (1.46-3.03), p < 0.001
				3. Steep decreasing apathy	37	2.35 (1.57-3.52), p < 0.001
				4. Stable low apathy	716	Ref. class

Note. The classes do not necessarily retain the original distribution from the measurement model because missingness of the biomarkers is not necessarily evenly distributed across classes. All models are corrected for age and sex.

Abbreviations: N = counts, based on modal (most likely) class assignment; OR = odds ratio; 95% CI = 95% confidence interval.

3.2. Part I: symptom trajectories in NACC and ADNI

We independently repeated the modeling process to arrive at the best-fit model in NACC and thereafter in ADNI. Supplementary File 2 provides a detailed overview of the processes of class enumeration and summarizes the series of model fit indices.

3.2.1. Depression

For NACC, when fitting models with increasing number of classes, the 5-class model provided the best fit according to the LMR-LRT (4- vs 5-class model: -2LL = -41575.957, $p < 0.0001$). The best-fitting model included a quadratic term and random intercept only. Figure 1a shows the fitted depression trajectories for each class, along with the (LOESS-curve smoothed) observed trajectories, where each individual is assigned to the class they most likely belong to. The majority of the sample (47%) would be expected to belong to class 5 with constant *low or no* probability of depression over time. The next most likely classes showed a decrease in the probability of depression over time (class 1, 29%), a shallow increase (class 3, 19%), a steep decrease (class 4, 4%) or finally, a steep increase (class 2, 2%).

For ADNI, when fitting models with increasing number of classes, the 2-class model provided the best fit according to the LMR-LRT (1- vs 2-class model: -2LL = -4131.6-6, $p < 0.0001$; 2- vs 3-class model: -2LL = -4102.809, $p = 0.136$). The best-fitting model included a quadratic term, random intercept and random slope. Figure 1b shows the fitted and observed trajectories for each class. A small majority of the sample (58%) would be expected to belong to a class with increasing probability of depression over time (class 1). The other class showed constant low or no probability of depression (class 2, 42%).

3.2.2. Apathy

For NACC, when fitting models with increasing number of classes, the 4-class model provided the best fit according to the LMR-LRT (2- vs 3-class model: -2LL = -37935.333, $p < 0.0001$; 3- vs 4-class model: -2LL = -37917.142, $p = 0.0702$). The best-fitting model included a quadratic term, random intercept and random slope. Figure 1f shows the fitted and observed trajectories for each class. The majority of the sample (65%) would be expected to belong to class 4 with the absence of apathy over time. The next most likely classes showed decreasing apathy over time (class 3, 17%), an increase and then decrease (class 2, 15%), or an initial decrease and thereafter a steep increase (class 1, 2%).

For ADNI, when fitting models with increasing number of classes, the 4-class model provided the best fit according to the LMR-LRT (3- vs 4-class model: -2LL = -3474.942, $p = 0.0369$; 5-class model did not converge). The best-fitting model included a quadratic term and random intercept only. Figure 1e shows the fitted and observed trajectories for each

class. The majority of the sample (47%) would be expected to belong to class 2 with an initial increase and then decrease in apathy. The next most likely classes showed no apathy over time (class 4, 35%), an increase (class 1, 14%), or decrease over time (class 3, 3%).

3.3. Part II: biomarker association with symptom trajectories in ADNI

The association between baseline biomarkers and predicted class membership in ADNI was examined whilst adjusting for age and gender.

3.3.1. Depression

In ADNI, more pathology (reflected in lower CSF $A\beta_{42}$ and higher t-tau and p-tau levels) was significantly associated with membership in the class with increasing probability of depression over time (class 1) compared to the class with stable low or no depression over time (class 2) (Table 2). For descriptive purposes, class 1 comprised relatively more dementia subjects, whereas class 2 relatively more CN subjects. The classes were similar with regard to age, but class 1 had lower MMSE scores, greater use of psychotropic medications (antidepressants, other behavioral and AD medication), and had more pathology (i.e. lower $A\beta_{42}$ and higher tau values) as compared to class 2 (see Supplementary File 3, Table 1a).

3.3.2. Apathy

In ADNI, more pathology (reflected in lower CSF $A\beta_{42}$ and higher t-tau and p-tau levels) was associated with membership in the class with increasing probability of apathy over time (class 2); lower CSF $A\beta_{42}$ but not t-tau or p-tau levels were associated with membership in the class with a steep increase of apathy over time (class 1); and higher CSF tau and p-tau levels but not $A\beta_{42}$ were associated with membership in the class with a steep decrease of apathy over time (class 3), all compared to the class with low or no probability of apathy over time (class 4) (Table 2). For descriptive purposes, it is noteworthy that the class with low or no probability of apathy over time (class 4) contained less dementia subjects and had most normal $A\beta_{42}$, t-tau and p-tau scores (Supplementary File 2, Table 2a).

4. DISCUSSION

The present study identified 5-year trajectories of depression and apathy in two separate, well-characterized cohorts, including CN individuals, as well as others with MCI or dementia. More AD pathology was associated with membership in classes with increased probability of depression or apathy over time, compared to asymptomatic classes.

Previous studies examined trajectories of NPS utilizing NPI total score[23] or symptom clusters[24]. Here we report distinct trajectories specifically for depression and apathy, treating them as different syndromes. In both cohorts, for both symptoms, a large class was identified

with stable low or no symptoms over time. For depression, we identified an additional four trajectories in NACC (steep in- and decrease; shallow in- and decrease of depression over time) and one in ADNI (increase over time). It is likely that these "extra" trajectories in NACC were captured in this single class with increasing probability of depression over time in ADNI, due to a smaller sample size. The trajectories identified in ADNI are comparable to Holmes et al.[25], who identified one stable trajectory with low depressive symptoms and another with consistent increasing depressive symptoms in CN. For apathy, the two cohorts showed similar trajectories. In addition to the class with stable low or no symptoms over time, decreasing, increasing and steep increasing classes were identified. To the best of our knowledge, this is the first study in AD literature examining trajectories of apathy.

Next, we related these trajectories to baseline biomarkers in ADNI. We found the presence of AD pathology to be related with de novo or (initially) rising symptoms of depression and apathy. This increase in symptomatology was associated with more $A\beta_{42}$ *and* tau pathology in the largest classes ($N_{\text{depression class 1}} = 534$ and $N = {}_{\text{apathy class 2}} = 411$). For depression, these findings are in line with Barca et al. who reported baseline CSF $A\beta_{42}$ levels to be associated with increasing depression over time[8]. For apathy, these findings contrast Donovan et al., who reported no association with AD pathology, possibly because they assumed one growth trajectory for the entire population[9]. The two smaller classes for apathy, with steep increases and decreases, were respectively associated with $A\beta_{42}$ but not tau ($N_{\text{apathy class 1}} = 50$) and tau but not $A\beta_{42}$ ($N_{\text{apathy class 3}} = 37$) pathology. Possibly, different mechanisms underlie these more extreme symptom presentations, also reflected by the different types of subjects included in these classes: the class showing a steep increase of apathy over time (class 1) contains in general older MCI males, in comparison to the class with a steep decrease over time (class 3) which contains in general younger MCI and AD females, with lower MMSE scores and fewer follow-up measurements available. Class 3 might therefore reflect individuals who were given a clinical diagnosis of AD but who actually might have a tauopathy, where NPS might take a different trajectory. Having a high probability of apathy at first visit (class 3), might lead to symptom specific interventions of clinicians and caregivers, resulting in improvement of the symptoms. The latter hypotheses was endorsed by the higher use of behavioral mediations in class 3 compared to the other classes (14.3% vs. 2.9, 2.3 and 5.8%).

Thus, these findings imply AD biomarkers, either $A\beta_{42}$ alone or $A\beta_{42}$ and tau pathology, are associated with an increase of symptoms of depression or apathy over time. The predictive value of AD pathology for symptoms of depression and apathy suggests that these symptoms are associated with the underlying pathology, confirming the view that they are a non-cognitive symptom of the disease. However, we should be cautious with making cause-and-effect inferences as the possibility that the presence of these symptoms induces a

biological cascade in the brain leading to AD pathology cannot be excluded. It is also possible that the observed relationships are indirect and are being mediated by, for example, cognitive decline and one's awareness thereof.

The major strength of our study is the use of well-characterized longitudinal data in large samples, which allows modelling of the heterogeneity between subjects in growth trajectories. NACC (with information on affective symptoms available for 28,717 participants) proved to be most suitable to model the symptom trajectories, whereas ADNI had standardized baseline biomarker information available for 70% of the total sample. It is important to consider some methodological limitations. First, it was not possible to constrain the measurement model (i.e. trajectory model) to be exactly the same in both cohorts. Modelling these complex random structures proved to be challenging because of the non-monotonic trajectories the affective symptoms take (i.e. symptoms may increase and decrease at different points in time) and because of the dichotomous outcome (i.e. we are modeling probabilities). Secondly, the NPI relies on caregiver report which may introduce bias in data collection, and has been validated in MCI and AD but not CN. Third, because of power, the corrected 3-step procedure did not allow consideration of use of psychotropic medications or history of depression as covariates in addition to age and sex. However, we have tried to include this information in a descriptive way (see Supplementary File 2). This shows for example that use of antidepressants is very common in all groups, and that in ADNI, history of depression was less common in class 1 (31.5%) compared to class 2 (41.8%). However, spouses or children might not be aware of such history, making this type of information less reliable. Fourth, the nature of the study sample (highly selective samples that consists memory clinic visitors, with add-on of highly educated, Caucasian volunteers that have low vascular burden) might have affected the external validity. Finally, another source of bias might be introduced by the fact that ADNI has inclusion criteria restricting the severity of NPS at screening (i.e., exclusion of subjects with Geriatric Depression Scale score of 6 or more).

The current study is a first step in studying heterogeneity within and between persons with regard to progression of affective symptoms *and* their underlying etiology. The latter was defined as the association with AD pathology (CSF $A\beta_{42}$, t-tau and p-tau) but future research should consider the implementation of other pathologies (e.g. vascular components, neurotransmitter systems or inflammation markers) or even integrate psychosocial factors. More advanced imaging data could provide more information on the relationship between affective symptoms and localization of amyloid and tau burden. Parallel-process GMMs could be utilized to investigate the interplay between trajectories of depression and apathy, or between cognition or biomarkers and individual symptoms. The fact that AD pathology was shown to be related with development of depression and apathy

over time indicates that information on AD biomarkers could serve as a predictor for clinicians to be aware of the increased probability of affective symptomatology in the future. Further, biomarker information could be used to enrich cohorts for treatment and prevention trials of NPS. In addition, the findings show that there is considerable fluctuation of affective symptoms over time, suggesting that clinicians should monitor affect continuously over an extended period, even when affective symptoms are absent at any point in time.

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SUPPLEMENTARY DATA

Appendix 1. Multivariable effects of raw baseline biomarkers in the growth models for depression and apathy in ADNI

Table 1. Baseline biomarkers as raw-scores

	Depression			Apathy		
	Class	N	OR (95% CI), p value	Class	N	OR (95% CI), p value
$A\beta_{42}$ [range: 200-1700 pg/ml]	1	534	0.998 (0.997-0.999), p < 0.001	1	50	0.998 (0.996-1), p = 0.029
	2	680	Ref. class	2	411	0.997 (0.996-0.999), p < 0.001
	Total	1214		3	37	1 (0.997-1.003), p = 0.8447
				4	716	Ref. class
				Total	1214	
t-tau [range: 80-1300 pg/ml]	1	534	1.008 (1.004-1.012), p < 0.001	1	50	1.004 (0.998-1.011), p = 0.214
	2	680	Ref. class	2	411	1.008 (1.004-1.011), p < 0.001
	Total	1214		3	37	1.009 (1.005-1.014), p < 0.001
				4	716	Ref. class
				Total	1214	
p-tau [range: 8-120 pg/ml]	1	534	1.094 (1.048-1.141), p < 0.001	1	50	1.047 (0.998-1.11), p = 0.118
	2	680	Ref. class	2	411	1.084 (1.042-1.129), p < 0.001
	Total	1214		3	37	1.098 (1.051-1.147), p < 0.001
				4	716	Ref. class
				Total	1214	

Note. The classes do not necessarily retain the original distribution from the measurement model because missingness of the biomarkers is not necessarily evenly distributed across classes. All models are corrected for age and sex.

Abbreviations: N = counts, based on modal (most likely) class assignment; OR = odds ratio; 95% CI = 95% confidence interval;

Appendix 2. Overview of class enumeration

For the first study aim, identifying classes of trajectories of depression and apathy in both cohorts, measurement invariance between the two cohorts was hypothesized (i.e. the measurement model estimated in NACC would be a good fit in ADNI as well). However, we were unable to constrain the model in ADNI to the estimates of the model found in NACC, by simplifying the model in constraining only to the estimates for the largest NACC group, or by using predetermined starting values for the classes at the NACC estimates. This might be due to the much smaller sample size in ADNI, a hypothesis which was supported when we modeled a representative subsample from NACC (n = 2,000 with the same diagnostic composition as ADNI). Therefore, the process to arrive at the best-fit model was independently repeated in both cohorts.

Text 1. Overview of class enumeration for depression

For NACC, depression, all model comparisons (1, 2, 3, 4 and 5 classes) of unconditional latent class growth models without random effects showed that inclusion of a quadratic term significantly improved model fit as compared to a model with a linear term only. Moving forward to fitting models with a quadratic term and increasing number of classes, the 5-class model without random effects provided the best fit according to the LMR-LRT (4- vs. 5-class model: -2LL = -41568.548, p = 0.0000). Moving forward to the inclusion of a random intercept, when fitting models with increasing number of classes, the 5-class model with random intercept provided the best fit according to the LMR-LRT (4- vs. 5-class model: -2LL = -41543.225, p = 0.005). Moving forward to the inclusion of random intercept/random slope (and covariance between intercept/slope), the 5-class model with random intercept/slope was not favored over the 5-class random intercept model (-2LL = 0.974, non-significant).

For ADNI, depression, all model comparisons (1, 2, 3, 4 and 5 classes) of unconditional latent class growth models without random effects showed that inclusion of a quadratic term significantly improved model fit as compared to a model with a linear term only. Moving forward to fitting models with a quadratic term and increasing number of classes, the 5-class model without random effects provided the best fit according to the LMR-LRT (4- vs. 5-class model: -2LL = -4113.753, p = 0.0007) although the entropy statistic favored the 2-class model (2-class model = 0.726, 5-class model = 0.579). Moving forward to the inclusion of a random intercept, when fitting models with increasing number of classes, the 2-class model with random intercept provided the best fit according to the LMR-LRT (1- vs. 2-class model: -2LL = -4131.506, p < 0.0001). In addition, a comparison of the 2-class model with random intercept vs. the 2-class model without random effects favored the 2-class

model with random intercept (-2LL = 145.184, p < 0.01); whereas the 5-class model with random intercept was not favored over the 5-class model without random effects (-2LL = 5.414, non-significant). Moving forward to the inclusion of random intercept/random slope (and covariance between intercept/slope), the 2-class model with random intercept/random slope was favored over the 2-class model with random intercept only (-2LL 7.018, p < 0.05). Moving forward to the inclusion of class specific random intercept, the 2-class model with random intercept was favored (-2LL = 3.724, non-significant). Therefore, the 2-class model with random intercept/random slope was chosen.

Table 1. Summary of Latent Class Analysis Model Fit Statistics, class-invariant random intercept.

	No. classes	1	2	3	4	5
NACC depression[a]	No. parameters	4	8	12	16	20
	-2LL	-41770.053	-41605.969	-41567.079	-41543.226	-41529.008
	BIC	83581.168	83294.059	83257.342	83250.695	83199.762
	Entropy	NA	0.111	0.212	0.417	0.398
	VLMR p-value	NA	0.000	0.050	0.000	0.005
	Smallest class, %	NA	4	15	3	2

Abbreviations: BIC, Bayesian information criterion (lower values imply better model fit); Entropy, higher values imply better classification quality; LMR, Lo-Mendell-Rubin likelihood ratio test.

Text 2. Overview of class enumeration for apathy

For NACC, apathy, all model comparisons (1, 2, 3, 4 and 5 classes) of unconditional latent class growth models without random effects showed that inclusion of a quadratic term significantly improved model fit as compared to a model with a linear term only. Moving forward to fitting models with a quadratic term and increasing number of classes, the 5-class model without random effects provided the best fit according to the LMR-LRT (4- vs. 5-class model, -2LL = -32529.146, p = 0.0002). Moving forward to the inclusion of a random intercept, when fitting models with increasing number of classes, the 4-class model with random intercept provided the best fit according to the LMR-LRT (3- vs. 4-class model, -2LL = -32488.617, p = 0.0000; 4- vs 5-class model = -32467.982, p = 0.1064). Both the 4- and 5- class models with random intercept are a significantly better fit than the 4- or 5-class model without random effects (resp. -2LL = 43.888, p < 0.01; -2LL = 11.61, p < 0.01). Moving forward to fitting models with random intercept/random slope (and covariance between intercept/slope) and increasing number of classes, the 4-class model provided the best fit according to the LMR-LRT (3- vs. 4-class model, -2LL = -32478.124, p = 0.000; 4- vs 5-class model, -2LL =

-32467.507, p = 0.6138). The 4-class model with random intercept/slope was not favored over the 4-class model with random intercept (-2LL = 1.204, non-significant).

For ADNI, apathy, all model comparisons (1, 2, 3, 4 and 5 classes) of unconditional latent class growth models without random effects showed that inclusion of a quadratic term significantly improved model fit as compared to a model with a linear term only. Moving forward to fitting models with a quadratic term and increasing number of classes, the 3-class model without random effects provided the best fit according to the LMR-LRT (3- vs 4-class model: -2LL = -3543.408, p = 0.0068, although 4- vs 5-class model was borderline significant, -2LL = -3500.007, p = 0.0699). Moving forward to the inclusion of a random intercept, when fitting models with increasing number of classes, the 4-class model with random intercept provided the best fit according to the LMR-LRT (3- vs. 4-class model, -2LL = -3474.942, p = 0.0369; 4- vs 5-class model: NA, given that "the standard errors of the model parameters may not be trustworthy for some parameters due to a non-positive definite first-order derivative product matrix"). The 4-class model with random intercept showed a significantly better fit than the 4-class model without random effects (-2LL = 23.278, p < 0.01). Moving forward to the inclusion of random intercept/random slope (and covariance between intercept/slope), the 4-class model with random intercept/random slope was not favored over the 4-class model with random intercept (-2LL = 5.764, non-significant).

Table 2. Overview of class enumeration for apathy

	No. classes	1	2	3	4	5
NACC apathy[1]	No. parameters	4	8	12	16	20
	-2LL	-32618.071	-32515.475	-32490.449	-32468.008	-32465.339
	BIC	65277.202	65113.072	65104.081	65100.26	65135.984
	Entropy	NA	0.189	0.260	0.471	0.545
	VLMR p-value	NA	-32618.071	-32515.478	-32488.617	-32467.982
	Smallest class, %	NA	29	19	2	2
ADNI apathy[1]	No. parameters	4	8	12	16	20
	-2LL	-3504.092	-3485.041	-3474.933	-3470.555	NA
	BIC	7038.014	7029.743	7039.357	7060.432	
	Entropy	NA	0.545	0.284	0.435	
	VLMR p-value	NA	-3504.092	-3485.041	-3474.942	

Smallest class	NA	0.0027	0.0437	0.0369

Abbreviations: BIC, Bayesian information criterion (lower values imply better model fit); Entropy, higher values imply better classification quality; LMR, Lo-Mendell-Rubin likelihood ratio test. The process of class enumeration was based on models with [1]class-invariant random intercept.

Appendix 3. Baseline descriptive data by modal class assignment

Note that all counts are based on modal (most likely) class assignment and not *true* class assignment, as the latter is unknown. In addition, *for ADNI*, these class descriptions are based on subjects *with at least one biomarker available* (i.e. they were included in the 3-step analyses). Because missingness of the biomarkers is not necessarily evenly distributed across classes, the classes have not necessarily retained the original distribution from the measurement model.

Table 1a. Baseline descriptives by modal class assignment, depression trajectories in ADNI

	Class 1	Class 2
N	534 (44.0)	680 (56.0)
Diagnosis		
CN	74 (13.9)	293 (43.1)
MCI	316 (59.2)	303 (44.6)
Dementia	144 (27.0)	84 (12.4)
Age, M (SD)	73.0 (7.5)	73.3 (7.1)
Gender, female, N (%)	244 (45.7)	299 (44.0)
Education in years, M (SD)	15.8 (2.8)	16.2 (2.7)
Ethnicity, Caucasian, N (%)	506 (94.8)	628 (92.4)
MMSE, M (SD)	26.7 (2.7)	27.8 (2.5)

History of depression, N (%)	34 (31.5)	33 (41.8)
Antidepressants, N (%)	126 (35.7)	84 (18.1)
Other behavioral medication, N (%)	25 (7.1)	15 (3.2)
AD medication, N(%)	141 (39.9)	92 (19.8)
Biomarkers, z-scores		
$A\beta_{42}$, M (SD)	-0.658 (0.967)	-0.305 (1.022)
t-tau, M (SD)	0.818 (1.593)	0.346 (1.339)
p-tau, M (SD)	0.944 (1.723)	0.392 (1.434)
Biomarkers, raw-scores		
$A\beta_{42}$, M (SD)	891.259 (436.182)	1050.593 (461.144)
t-tau, M (SD)	310.449 (143.078)	268.081 (120.251)
p-tau, M (SD)	30.440 (15.762)	25.389 (13.117)

CN = cognitively normal; MCI = mild cognitive impairment; AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; NA = not available; $A\beta_{42}$ = amyloid-$\beta_{1\text{-}42}$; t-tau = total tau; p-tau = phosphorylated-tau

Table 1b. Baseline descriptives by modal class assignment, depression trajectories in NACC

	Class 1	Class 2	Class 3	Class 4	Class 5
N	6663 (23.2)	203 (0.7)	2956 (10.3)	193 (6.7)	18729 (65.2)
Diagnosis					
CN	2525 (38.1)	123 (60.6)	1299 (43.9)	73 (37.8)	12341 (65.9)
MCI	2445 (36.8)	59 (29.1)	1049 (35.5)	74 (38.3)	4424 (23.6)
Dementia	1666 (25.1)	23 (10.3)	608 (20.6)	46 (23.8)	1964 (10.5)

Age, M (SD)	70.9 (10.1)	74.3 (9.5)	72.7 (10.1)	70.0 (9.2)	71.9 (10.3)
Gender, female, N (%)	3782 (57.0)	125 (61.6)	1701 (57.5)	105 (54.5)	11025 (58.9)
Education in years, M (SD)	15.0 (3.5)	15.3 (3.2)	15.2 (3.4)	15.3 (3.2)	15.5 (3.1)
Ethnicity, Caucasian, N (%)	5489 (83.3)	188 (93.5)	2515 (85.2)	177 (92.2)	14689 (78.8)
MMSE, M (SD)	27.8 (3.3)	29.1 (2.1)	28.1 (3.1)	28.2 (2.7)	28.9 (2.6)
History of depression, N (%)	4149 (35.7)	48 (23.9)	780 (26.9)	55 (29.7)	2741 (14.8)
Antidepressants, N (%)	2723 (41.3)	64 (31.5)	1026 (34.8)	80 (41.7)	3102 (16.6)
Other behavioral medication, N (%)	1282 (19.4)	22 (10.8)	475 (16.1)	34 (17.7)	1964 (10.5)
AD medication, N(%)	1612 (24.4)	27 (13.3)	713 (24.2)	50 (26.0)	2100 (11.3)

CN = cognitively normal; MCI = mild cognitive impairment; AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; NA = not available

Table 2a. Baseline descriptives by modal class assignment, apathy trajectories in ADNI

	Class 1	Class 2	Class 3	Class 4
N	50	411	37	716
Diagnosis				
CN	5 (10.0)	41 (10.0)	1 (2.7)	320 (44.7)
MCI	37 (74.0)	240 (58.4)	21 (56.8)	321 (44.8)
Dementia	8 (16.0)	130 (31.6)	15 (40.5)	75 (10.5)
Age, M (SD)	74.5 (6.8)	74.1 (7.4)	72.4 (9.5)	72.7 (7.1)
Gender, female, N (%)	13 (26.0)	158 (38.4)	19 (51.4)	353 (49.3)
Education in years, M (SD)	16.0 (2.9)	15.8 (2.8)	15.8 (2.2)	16.2 (2.7)
Ethnicity, Caucasian, N (%)	46 (92.0)	390 (94.9)	35 (94.6)	663 (92.6)
MMSE, M (SD)	27.2 (2.7)	26.2 (2.7)	26.4 (3.0)	28.0 (2.3)
History of depression, N (%)	1 (11.1)	24 (33.8)	1 (50.0)	41 (39.0)
Antidepressants, N (%)	11 (32.4)	75 (29.3)	10 (35.7)	114 (22.8)
Other behavioral medication, N (%)	1 (2.9)	6 (2.3)	4 (14.3)	29 (5.8)
AD medication, N(%)	11 (32.4)	129 (50.4)	11 (39.4)	82 (16.4)
Biomarkers, z-scores				
$A\beta_{42}$, M (SD)	-0.588 (1.051)	-0.795 (0.905)	-0.688 (0.943)	-0.247 (1.019)

t-tau, M (SD)	0.576 (1.280)	0.845 (1.603)	1.206 (1.670)	0.351 (1.360)
p-tau, M (SD)	0.644 (1.421)	0.962 (1.711)	1.326 (1.765)	0.411 (1.477)
Biomarkers, raw-scores				
$A\beta_{42}$, M (SD)	922.960 (473.869)	829.380 (407.936)	877.884 (425.124)	1076.579 (459.708)
t-tau, M (SD)	288.768 (114.948)	312.882 (143.970)	345.278 (149.999)	268.529 (122.136)
p-tau, M (SD)	27.696 (13.002)	30.599 (15.654)	33.935 (16.146)	25.563 (13.514)

CN = cognitively normal; MCI = mild cognitive impairment; AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; NA = not available; $A\beta_{42}$ = amyloid-$\beta_{1\text{-}42}$; t-tau = total tau; p-tau = phosphorylated-tau

Table 2b. Baseline descriptives by modal class assignment, apathy trajectories in NACC

	Class 1	Class 2	Class 3	Class 4
N	200 (0.7)	2177 (7.6)	3803 (13.2)	22529 (78.5)
Diagnosis				
CN	63 (31.5)	587 (27.0)	779 (20.5)	14926 (66.3)
MCI	74 (37.0)	900 (41.3)	1521 (40.0)	5555 (24.7)
Dementia	63 (31.5)	690 (31.7)	1503 (39.5)	2048 (9.1)
Age, M (SD)	73.3 (9.5)	73.5 (10.0)	71.2 (10.3)	71.7 (10.2)
Gender, female, N (%)	80 (40.0)	1098 (50.4)	1626 (42.8)	13930 (61.8)
Education in years, M (SD)	15.5 (3.2)	15.2 (3.4)	15.0 (3.4)	15.5 (3.2)
Ethnicity, Caucasian, N (%)	180 (90.0)	1856 (85.4)	3214 (85.2)	17805 (79.4)
MMSE, M (SD)	28.1 (2.9)	27.3 (3.4)	27.1 (3.5)	28.9 (2.6)
History of depression, N (%)	34 (17.2)	469 (21.9)	1083 (29.2)	4341 (19.5)
Antidepressants, N (%)	58 (29.3)	674 (31.1)	1492 (39.4)	4769 (21.3)
Other behavioral medication, N (%)	22 (11.1)	312 (14.4)	688 (18.2)	2754 (12.3)
AD medication, N(%)	77 (38.9)	736 (34.0)	1326 (35.0)	2361 (10.5)

CN = cognitively normal; MCI = mild cognitive impairment; AD = Alzheimer's disease; MMSE = Mini-Mental State Examination; NA = not available

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DETERMINANTS OF CROSS-SECTIONAL AND LONGITUDINAL HEALTH-RELATED QUALITY OF LIFE IN MEMORY CLINIC PATIENTS WITHOUT DEMENTIA

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ABSTRACT

Objective: To identify determinants within three different domains (i.e. somatic comorbidities, cognitive functioning and neuropsychiatric symptoms (NPS)) of Health-Related Quality of Life (HRQoL) over time in memory clinic patients without dementia.

Methods: This longitudinal multi-center cohort study with a 3-year observation period recruited 315 individuals (age 69.8 ± 8.6, 64.4% males, MMSE score 26.9 ± 2.6). A multivariable explanatory model was built using linear mixed effects models (forward selection per domain) to select determinants for self-perceived HRQoL over time, as measured by the EuroQoL-5D visual analogue scale (EQ VAS).

Results: Mean HRQoL at study entry was 69.4 ± 15.6. Presence of agitation, appetite and eating abnormalities and eyes/ears/nose (i.e. sensory impairment) comorbidities were associated with change in HRQoL over time. Agitation was most strongly associated with HRQoL over time.

Conclusions: The association of somatic comorbidities and NPS in memory clinic patients with course of HRQoL shows that these should receive more awareness, detection and monitoring by clinicians.

1. INTRODUCTION

Cognitive decline is thought to have a profound negative impact on health-related quality of life (HRQoL), both in affected patients and their relatives[1]. As no disease-modifying treatment of (prodromal) dementia exists to date, enhancing and maintaining HRQoL is considered the most pivotal goal of management for all prodromal and clinical stages[2]. In the last decades, the broader concept of health and HRQoL has changed to become more dynamic and now includes the ability to adapt and self-manage in daily life despite certain impairments[3].

It has been argued that HRQoL follows the progress of the dementia process, where more severe diagnostic phases are associated with poorer HRQoL[1, 4-8]. Others, however, have reported limited changes in QoL over time in people with dementia (PwD), even in the presence of significant clinical deterioration,[5] and comparable HRQoL scores between mild cognitive impairment (MCI) and cognitively normal controls (CN)[5, 9]. This suggests that other variables than disease stage determine HRQoL.

Several disease-related determinants have been reported to negatively influence HRQoL in PwD, such as the presence of neuropsychiatric symptoms (NPS), impaired activities of daily living and severity of cognitive impairment (e.g. [10]). Data with regard to HRQoL in the prodromal stages of dementia are limited. In individuals with MCI, reduced HRQoL has been related to the presence of NPS, depressive symptoms in particular[7, 8], and decreased memory performance[7], but not with general cognitive status[6] and executive functioning, language and attention[7].

Most studies have been cross-sectional in nature, but research in this field is now moving forward to the examination of longitudinal changes in HRQoL. Depressive symptoms in cognitively impaired individuals have been associated with lower HRQoL at follow-up in some studies[11, 12], but not in others[13], or only when both HRQoL and NPS were caregiver-rated[14]. Some studies showed that an increase in NPS over time was related to a decrease in HRQoL[15, 16]. One study reported that the number of somatic comorbidites was related with a decrease in HRQoL at follow-up[13], whereas another did not find any relation between general health and HRQoL[17]. Baseline cognition was unrelated to change of HRQoL in previous studies[11-14, 18]. However, none of these studies examined the course of HRQoL using multiple assessments over time, and all were limited to a sample of individuals with dementia.

An integrated view of determinants of the natural history of subjective HRQoL over time in prodromal stages of dementia is currently lacking. The relevance of identifying such determinants in memory clinic patients lies in their potential to target and personalize interventions with preventative and supportive strategies, thereby minimizing their impact

on HRQoL. Hence, the aim of the present study was to identify the optimal combination of determinants of HRQoL over time in memory clinic patients without dementia at study entry.

2. MATERIALS and METHODS

The current study is part of the Dutch Clinical Course of Cognition and Comorbidity in Mild Cognitive Impairment (4C-MCI) study[19]. The 4C-MCI study is a longitudinal, multicenter study and focuses on the course of cognitive decline in non-demented memory clinic patients. The study included 315 participants at baseline, who were recruited at the memory clinics of Maastricht University Medical Centre, Radboud University Medical Center and VU Medical Centre between January 2010 and May 2011, with a roughly equal distribution across centres (118/98/99 participants, respectively). Follow-up data were collected annually up to three years after baseline assessments. The medical ethical committee of each center approved the study. All participants gave written informed consent.

Inclusion criteria were: 1) age ≥ 55 years, 2) having cognitive complaints and/or cognitive impairments, in absence of dementia, and 3) Clinical Dementia Rating (CDR) score ≤ 0.5[20]. Exclusion criteria were: 1) absence of a primary informant, 2) prognosis based on clinical judgment that the subject would not be able to have at least one follow-up contact, and 3) presence of specific neurological disorders possibly causing cognitive impairment, such as Parkinson's or Huntington's disease, Normal Pressure Hydrocephalus, Korsakoff's syndrome, a medical history of brain tumor or encephalitis. Participants having any other comorbidities, including cerebrovascular and psychiatric disorders were not excluded in this study.

2.1. Baseline and follow-up assessment

At baseline all participants underwent a standardized clinical assessment, which included a detailed history of the patient, a psychiatric, neurological and physical examination, assessments of daily functioning, an extensive neuropsychological assessment and a cerebral magnetic resonance imaging (MRI) scan. These assessments were part of the regular patient diagnostic procedures of the memory clinics. Participants were invited to take part in a follow-up assessment at one, two and three years after baseline. For the current study we extracted data on age, gender, education, HRQoL, comorbid disease burden, cognitive and emotional functioning.

2.2. Diagnostic procedures

Syndrome diagnoses were based on clinical assessment by the physician and the multidisciplinary team. The diagnosis of MCI was based on the Petersen criteria[21]. Individuals with an objective cognitive impairment, that is, a z-score of more than 1.5 SD below the normative mean of any of the cognitive tests, were classified as MCI. Individuals with cognitive complaints but without objective impairment on cognitive tests were classified as having SCD. Diagnosis of dementia was made based on the Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.; DSM-IV-TR) criteria[22].

2.3. Health-related Quality of Life

The Visual Analogue Scale (VAS) of the EuroHRQoL-5D (EQ-5D)[23] was used to measure self-rated HRQoL. The EQ VAS is a standard vertical scale for recording individuals' rating for their current HRQoL state, ranging from 0 to 100, with a higher EQ VAS indicating better HRQoL. The rationale for using the VAS-score and not the five dimensions of the EQ-5D is that the latter focusses on functioning and consequent impairments on mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, whilst our aim was to evaluate the subjective rating of current well-being and HRQoL, in line with previous conducted studies[24, 25]. In addition, by using the VAS-score, the overlap with the domains of NPS and somatic comorbidities in the predictive model is minimized.

2.4. Somatic comorbidities

The Cumulative Illness Rating Scale for Geriatrics (CIRS-G)[26] was used to rate all available data on medical comorbidities, medication use, smoking and drinking habits and the physical examination. Scores between zero (no problems) and four (extremely severe problems) were given to 14 categories of organ systems (i.e., cardiac; vascular; hematopoietic; respiratory; eyes/ears/nose/throat/larynx; upper gastrointestinal tract; lower gastrointestinal tract; liver; renal; genitourinary; musculoskeletal; neurological; endocrine/metabolic and breast; psychiatric). For the current analyses, we excluded the psychiatric category of the CIRS-G. By excluding this category, the CIRS-G was used as a measure of medical comorbid disease burden only, thus minimizing overlap with the cognitive and emotional functioning domain. Scores of the subcategories were dichotomized as comorbidity present (score of 2 or higher, i.e. moderate, severe and extremely severe disease severity) or absent (score of 0 or 1).

2.5. Cognitive functioning

The neuropsychological assessment consisted of a standardized battery of cognitive tests. Global cognitive functioning was assessed by means of the Mini Mental State Examination (MMSE)[27]. Episodic memory was assessed by use of the Verbal Learning Task (VLT)[28]. Information processing speed (IPS) and executive functions were measured using the Stroop Color Word Test (SCWT)[29], the Letter Digit Substitution Test (LDST)[30] and the Trail Making Test (TMT)[31]. Verbal fluency was assessed by use of the Category Fluency (1-minute animal naming)[32]. In accordance with available Dutch normative data, raw test scores were converted to z-scores, adjusted for age, education and/or sex[28-30, 32].

2.6. Neuropsychiatric symptoms

The Neuropsychiatric Inventory (NPI)[33] was used to assess the frequency and severity of 12 neuropsychiatric symptoms (i.e. delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite/eating disturbances) through a structured interview with an informant. For each symptom, severity and frequency scores are multiplied to acquire a domain score, with higher scores indicating more severe problems. Symptom scores were dichotomized as present (domain score of 1 or higher) or absent (domain score of 0).

The Short Form of the Geriatric Depression Scale (GDS-15)[34] was used to determine the presence and severity of depression by self-rating. The questionnaire does not include somatic symptoms which might be present due to comorbid somatic disorders. Following prior studies, scores were dichotomized with a score of six or higher being indicative of depression[35].

2.7. Statistical analyses

Analyses were performed using SPSS version 25 (Chicago, IL., USA) for Mac OS X. Baseline differences between groups were analyzed using chi-square tests for categorical variables and t-tests for continuous variables. For cognitive functioning, extreme z-score values were handled by winsorising these, that is, they were fixed at the lower (-5) or upper (+5) boundary. Extreme baseline values were found for the SCWT (i.e., 3% of all scores on Stroop card 1, 1.7% of all scores on Stroop card 2 and 4% of all scores on the SCWT interference index) and TMT (i.e., 1.3% of all scores on TMT-A and 0.3% of all scores on TMT-B).

To test for multicollinearity, Spearman's rank-order correlations were computed between all variables within a predictive domain (i.e. somatic comorbidities, cognitive

functioning and NPS). Using a cut-off of 0.7, the VLT delayed recall score was removed from the analyses, since it correlated highly with the VLT immediate recall score ($r = .80$, $p < 0.01$) and the latter had a larger range of scores.

The optimal combination of deteminants of HRQoL over time was examined by modelling linear mixed effects (growth curve) models. This analysis models individual growth curves that take within-subject correlation between repeated measures into account, thus accounting for the hierarchical structure of the data (i.e. time nested in individuals). Missing data can be considered at random (MAR) when we include the covariates that are associated with missingness in the analyses[36]. The missing data points are estimated by maximum likelihood. Thus, these models allow the use of all available longitudinal data, including data from dropouts. First, the association of each determinant with HRQoL over time was analyzed separately, corrected for age at baseline, sex, education (low, middle, high) and study center. An unconditional means model was fitted with random intercepts (i.e. patient factor as random), to account for the correlation between repeated measures within individuals. Next, cognitive measures, somatic comorbidities, neuropsychiatric symptoms, time and interaction terms between each variable and time were added as fixed effects. Time (i.e., point of follow-up) was measured in years and used as a categorical variable, to allow discontinuous change between the follow-ups. The variance component structure were specified according to best fit based on likelihood ratio testing. Time as random slope was allowed if the model was significantly better compared to a model with only random intercepts.

Afterwards, a multivariable model was built using forward selection. Per domain (i.e. cognitive domain, somatic comorbidities domain and neuropsychiatric symptoms domain), the variable with the lowest p value was consecutively added to the model, until $p < 0.10$. Variables were only allowed to remain in the model when the overall model fit improved, as evaluated by the −2 log-likelihood ratio. Last, the multivariable domain models were added into a final total model.

3. RESULTS

Baseline participant characteristics are presented in Table 1. Participants (64.4% male) were on average 69.8 (SD = 8.6) years old. At study entry, 104 (33.0%) individuals had SCD, 27 of whom (26.0%) converted to MCI and 16 (15.4%) to dementia over the course of the study period (up to three years); 211 (67.0%) individuals had MCI, 45 of whom (21.3%) converted to dementia. Of these 315 patients, 247 (78.4%) completed the 1-year follow-up assessment, 225 (71.4%) patients completed the 2-year follow-up assessment, and 198 (62.9%) patients completed the 3-year follow-up assessment. Dropouts were on average older, lower educated, performed worse on several cognitive tests (VLT, fluency, LDST and MMSE) and

had more often somatic comorbidities (hematopoietic, upper digestive tract, kidney conditions) compared to those with at least one follow-up visit. Prevalence of NPS and HRQoL ratings were similar in both groups. The mean EQ5D-VAS score of the entire group at baseline was 69.4 (SD = 15.6), which on average remained stable over time (F (3, 938) = 2.4, p = 0.069). Change within self-rated HRQoL and the three domains over the follow-up period are displayed in Appendix Table 1.

Table 1. Baseline participant characteristics

	SCD	MCI	Total
Demographics	N = 104	N = 211	N = 315
Age, mean years (SD)	68.2 (8.9)	70.6 (8.3)*	69.8 (8.6)
Males	68 (65.4)	135 (64.0)	203 (64.4)
Education			
Low (lower than middle school)	50 (38.5)	86 (40.8)	126 (40.0)
Middle (high school/vocational education)	31 (29.8)	47 (22.3)	78 (24.8)
High (university)	33 (31.7)	78 (37.0)	111 (35.2)
Converted to MCI	27 (26.0)	-	27 (8.6)
Converted to dementia	16 (15.4)	45 (21.3)	61 (19.4)

Data are presented as N (%) unless otherwise specified.

Abbreviations: SCD = Subjective Cognitive Decline; MCI = Mild Cognitive Impairment

* $p < 0.05$

At baseline, the presence of appetite and eating abnormalities, nighttime behavior disturbances, lower digestive tract comorbidities and self-reported depression was significantly associated with lower HRQoL ratings (Table 2, Figure 1 and Appendix Table 2).

Linear mixed models were used to evaluate the associations between the individual determinants and HRQoL over time. Eyes/ears/nose comorbidities, presence of agitation, lower digestive tract, urogenital comorbidities, presence of appetite and eating abnormalities, nighttime behavior disturbances and self-reported depression were associated with HRQoL over time and included in the multivariable analyses.

Using forward selection, the combined model included the following variables. Presence of nighttime behavior disturbances (F (3, 722.7) = 1.3, p = 0.263), self-reported depression (F (3, 719.3) = 1.2, p = 0.292) and lower digestive tract comorbidities (F (3, 695.8) = 0.8, p = 0.491)) were significantly associated with lower baseline HRQoL but were not significantly related to course of HRQoL over time (i.e. averaged over all time points). Presence of agitation (F (3, 715.075) = 4.5, p = 0.004) and eyes/ears/nose comorbidities (F (3, 676.6) = 2.4, p = 0.065) were related to course of HRQoL over time but were not

significantly related to baseline HRQoL. Appetite and eating abnormalities (F (3, 714.4) = 3.0, p = 0.030) was related both to lower baseline HRQoL and course of HRQoL over time.

Table 2. Mean differences in baseline QoL scores and in rate of change (slopes) from baseline to follow-up between subjects with and without baseline determinants

MULTIVARIABLE MODEL	Baseline difference	Change baseline to FU1	Change FU1 to FU2	Change FU2 to FU3
Cognition				
-				
Somatic comorbidities (ref. baseline × comorbidity absent)				
Eyes/ears/nose × time	-2.8 (-6.6; 0.9)	0.4 (-4.8; 5.7)	2.0 (-3.4; 7.4)	4.6 (-0.9; 10.1)
Lower digestive tract × time	-5.3 (-10.1; -0.4)*	2.9 (-4.1; 9.9)	-1.2 (-8.9; 6.4)	-5.2 (-13.8; 3.4)
*Neuropsychiatric symptoms (ref. baseline *NPS absent)*				
Agitation × time	2.1 (-1.4; 5.6)	-3.3 (-8.7; 2.0)	-5.2 (-11.6; 1.3)	-0.6 (-7.4; 6.2)
Appetite and eating abnormalities × time	-4.5 (-8.1; -0.9)*	7.8 (2.6; 13.0)**	-3.2 (-8.9; 2.6)	-1.9 (-8.1; 4.4)
Nighttime behavior disturbances × time	-4.2 (-7.4; -1.0)**	3.1 (-1.9; 8.1)	1.9 (-4.0; 7.7)	-4.4 (-10.3; 1.6)
Self-reported depression × time	-13.9 (-17.3; -10.4)**	1.7 (-3.8; 7.3)	3.8 (-2.5; 10.0)	-3.9 (-10.4; 2.7)

Results of random intercept model (adjusted for age at baseline, sex, education and study center) are presented as effect estimates (beta's and 95% confidence interval). Key: FU = follow-up; ref. = reference group; NPS = neuropsychiatric symptoms

* $p < 0.05$, ** $p < 0.01$

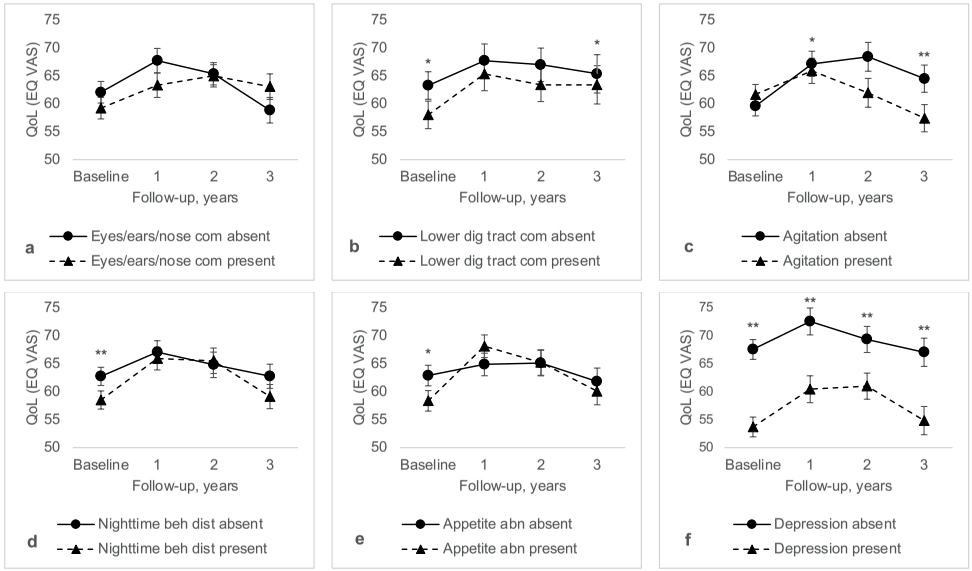

Figure 1. QoL over the course of the study period by status of baseline determinants

a. Course of QoL by eyes/ears/nose comorbidities group. b. Course of QoL by lower digestive tract comorbidities group. c. Course of QoL by agitation group. d. Course of QoL by nighttime behavior disturbances group. e. Course of QoL by appetite and eating abnormalities group. f. Course of QoL by self-reported depression group. Based on random intercept analyses adjusted for age at baseline, sex, highest level of eduction and study center. Shown is the predicted mean score (estimated marginal means of time by group) and standard error. EQ VAS = EQ-5D Visual Analogue Scale; Eyes/ears/nose com = Eyes/ears/nose comorbidities; Lower dig tract com = Lower digestive tract comorbidities; Nighttime beh dist = Nighttime behavior disturbances; Appetite abn = Appetite and eating abnormalities.

* $p < 0.05$, ** $p < 0.01$ between subjects with baseline determinants present vs. absent

4. DISCUSSION

In this longitudinal, multicenter study, the best fitting final model for explaining HRQoL over time consisted of several somatic comorbidities (i.e. eyes/ears/nose and lower digestive tract conditions) and neuropsychiatric symptoms (i.e. agitation, appetite and eating abnormalities, nighttime behavior disturbances and self-reported depression). In contrast, cognitive functioning did not predict HRQoL over time. The most consistent determinant of HRQoL over time was presence of agitation.

Overall, an initial increase of HRQoL was observed at one year follow-up. This might (partially) be the result of a diagnosis disclosure effect as participants were included at first attendance at the memory clinic[37]. However, this effect appeared to diminish over time, as reflected by the decrease of HRQoL at two and three-year follow-up. Hence, even when memory clinic patients show an initial increase in HRQoL after the diagnostic process, it is important to follow these individuals over time and continue to provide support.

From the list of putative NPS determinants, agitation was most consistently associated with HRQoL over time. Previous studies which investigated the relation between NPS and HRQoL in SCD or MCI only focused on depressive symptoms or total NPI scores (resp. [7, 8], [9, 38]), while in dementia, the presence of agitation has been associated with lower HRQoL cross-sectionally[39, 40] and with a decrease of HRQoL over time[41]. Agitation can be interpreted as an expression of emotional distress, manifested in excessive motor activity or verbal or physical aggression[42]. Clinicians should be aware of the influence of caregiver management strategies on patient behavior, as it has been shown that caregiver non-acceptance resulted in more patient hyperactivity behaviors[43].

Next to agitation, self-reported depressive symptoms were associated with lower HRQoL at baseline. The association between depressive symptoms and reduced HRQoL has been reported for both individuals with MCI[6-8] and SCD[2]. More severe depressive symptoms have been associated with better insight into cognitive impairments[44], which suggests that depressive symptoms might be a psychological reaction to the disease in individuals whose illness insight is intact (as can be expected in our sample with on average relatively mild cognitive deficits), although several other hypotheses have been posed to explain the presence of depression in individuals across the disease spectrum. For example, in the prodromal hypothesis, depression is considered a non-cognitive manifestation of underlying neurodegenerative pathology. On the other hand, the risk factor hypothesis states that the presence of depression itself lowers the brains reserve to cope with Alzheimer's disease pathology, e.g. via hypothalamic–pituitary–adrenal -axis dysregulation, and thus fastens progression of disease. Here we found a higher prevalence of informant-rated depressive symptoms compared to self-rated depressive symptoms (40% versus 20%), HRQoL was only related to the latter one. In line with the psychological-reaction hypothesis, this suggests that

subjective ratings of lower HRQoL by patients with cognitive deterioration reflect a psychological reaction to the decline and that this is not recognized by the informants, as corroborated by the finding that only 70% of the self-reported cases with high levels of depressive symptoms was recognized by the informant as such.

In addition, appetite and eating abnormalities were related to change in HRQoL over time. Previous studies have shown that appetite and eating abnormalities were unrelated to HRQoL in patients with mild to moderately severe dementia[39, 40]. This discrepancy might be due to lack of disease insight which occurs more often in the later stages of the disease, that is, the dementia phase versus the SCD and MCI stages, as in the current study. Furthermore, nighttime behavior disturbances were associated to baseline HRQoL. In a recent state-of-the-art review on persons with dementia, sleep disturbances, conceptualized as poor sleep efficiency and increased night awakening, were associated with all four HRQoL domains as defined by Lawton[45]: physical function, social/behavioral function, emotional well-being and cognitive function[46].

Although our findings reveal high informant-reported symptoms of irritability and apathy (resp. 51.7 and 43.7%), these were not related to HRQoL. This is in contrast to prior research where higher levels of irritability and apathy were associated with lower HRQoL in mild dementia[39, 47]. However, Yeager et al[47] assessed apathy by self-report, which is prone to information bias as reduced disease insight can influence the patient-reported HRQoL.

The effect of specific comorbidities on HRQoL in SCD and MCI has not been investigated before, although comorbidity burden has been related to progression of disease[48]. In the current study, eyes/ears/nose and lower digestive tract comorbidities were found to be determinants of lower HRQoL over time. The association between hearing and vision problems and lower HRQoL has also been reported in older adults in general and in the nursing home population[49, 50]. Sensory impairment in older adults resulted in restriction of ADL[51], which might cause a decrease in self-esteem. Also, hearing difficulties may result in social isolation[52], while positive social relationships have been shown to be associated with higher HRQoL[39]. Lower gastro-intestinal tract disorders, such as functional gastro-intestinal disorders (disorders of the gut-brain-interaction), are common in patients with mild psychiatric disorders such as anxiety and depression, which are also often seen in individuals with cognitive dysfunction[53]. An increase in bowel symptoms could therefore link to deterioration of the central nervous system[54]. On the other hand, the gastro-intestinal symptoms can have a significant impact on HRQoL in affected individuals due to the nature of the symptoms themselves, e.g. via impaired physical or social functioning[55].

No association between cognition and HRQoL over time was found in the current study, which is in line with previous cross-sectional studies in SCD or MCI[7, 38] and longitudinal association in SCD[25] and dementia[11-14, 18, 56]. These prior studies only used global

cognitive screening instruments[11-14, 38, 56] or composite cognitive domain scores[7, 18] to assess cognitive functioning, which are less sensitive to detect associations. Therefore, we looked at specific cognitive tests, but also in this manner, no association was found. Together these findings seem to imply that cognitive deterioration in itself is not associated with HRQoL in memory clinic patients, whereas NPS and somatic comorbidities seem to be more directly affecting subjective burden of patients.

This study has several strengths, of which most notably the longitudinal representative sample of memory clinic patients (by keeping the exclusion criteria to a minimum), repeated measures of HRQoL, its sample size and the broad range of possible predictors of HRQoL. Validated measures were used to assess HRQoL, cognitive functioning, NPS and somatic comorbidities. Certain limitations should also be acknowledged. Bias could have been introduced by the fact that the NPI was rated by informants. Salient symptoms might be more often reported, because internal psychological reactions might be difficult to recognize for informants and difficult to communicate for patients with cognitive impairments. Indeed, the NPI items that refer more to concrete behavior (e.g. eating and nighttime behavior disturbances) and are less likely to be influenced by the informants' perception were related to HRQoL. Furthermore, a non-disease specific HRQoL questionnaire was used. However, the EQ VAS has been shown to be a valid and reliable measure in individuals with cognitive impairments[57] and has been used in studies with similar research questions[24]. Moreover, the EQ VAS was specifically chosen for the present study to assess self-perceived HRQoL, in line with the conceptualization of HRQoL as the ability to adapt to the perceive consequences of dementia[45, 58]. Still, a more specific HRQoL instrument for individuals with cognitive impairment could have been implemented. In addition, (selection-) bias could have been introduced, evidenced by the finding that individuals with follow-up data available were healthier at baseline. It might be argued that analyzing the SCD vs. the MCI groups separately would have resulted in different outcomes. However, stratifying the sample according to diagnosis resulted in roughly similar average effect estimates (results not shown). Most importantly, within each subgroup, cognition was not associated with QoL. In this line, inclusion of the VLT delayed recall score rather than the immediate recall score could have changed the results as these represent two different constructs. Sensitivity analysis showed that neither the immediate nor the delayed VLT recall scores were significantly associated with HRQoL, while fitting the univariate linear mixed effects models. The choice of construct thus did not have an influence on the final model. Finally, although an extensive amount of predictors for HRQoL was used, other possible predictors could not be included, such as activities in daily life, socioeconomic status, and factors associated with autonomy and relationships[40, 59].

5. CONCLUSIONS

In people without dementia visiting a memory clinic, specific somatic comorbidities and NPS predicted the level of HRQoL over time. Overall, there was an initial increase of HRQoL during the first year which was followed by a decrease of HRQoL in subsequent years. Therefore, it is important to follow individuals for a longer period of time and to continue providing support. These findings may give direction for tailoring interventions towards personalized needs and may improve HRQoL of memory clinic patients in the future. Future research should focus on the effect of treatment of somatic comorbidities and NPS on HRQoL in individuals with memory complaints.

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APPENDIX

Table 1. Mean values of self-rated QoL and the three domains (i.e. somatic comorbidities, cognitive functioning and neuropsychiatric symptoms (NPS)) over time

	Baseline	1y FU	2y FU	3y FU
EQ-5D, M (SD)	N = 301	N = 235	N = 220	N = 186
VAS total score	69.4 (15.6)	72.6 (14.0)	71.6 (13.9)	71.7 (15.0)
Cognitive tests, M (SD)	N = 265-313	N = 215-245	N = 198-222	N = 169-191
VLT (immediate recall)	-1.1 (1.2)	-0.5 (1.3)	-0.9 (1.4)	-0.6 (1.5)
Fluency	-0.7 (0.8)	-0.7 (0.9)	-0.8 (1)	-0.8 (1)
TMT-A	-0.5 (1.4)	-0.4 (1.5)	-0.4 (1.6)	-0.3 (1.7)
TMT-B	-0.7 (1.5)	-0.6 (1.4)	-0.6 (1.5)	-0.5 (1.6)
SCWT 1-2 †	-1.1 (1.4)	-1.1 (1.5)	-1.1 (1.5)	-1.2 (1.7)
SCWT interference ‡	-0.7 (1.7)	-0.7 (1.8)	-0.7 (1.8)	-0.6 (1.8)
LDST	-0.5 (1.1)	-0.4 (1.2)	-0.4 (1.2)	-0.4 (1.3)
MMSE§	26.9 (2.6)	27.0 (2.7)	26.5 (3.2)	26.4 (3.6)
Neuropsychiatric symptoms, N (%)	N = 307-308	N = 224	N = 209	N = 193-195
NPI				
Delusions	18 (6.0)	6 (2.7)	6 (2.9)	5 (2.9)
Hallucinations	11 (3.6)	4 (1.8)	5 (2.4)	3 (1.7)
Agitation	61 (20.2)	33 (14.9)	26 (12.7)	28 (16.1)
Depression	122 (40.4)	60 (27.1)	56 (27.3)	50 (28.7)
Anxiety	84 (27.8)	41 (18.6)	27 (13.2)	24 (13.8)
Euphoria	29 (9.6)	16 (7.2)	7 (3.4)	5 (2.9)
Apathy	132 (43.7)	76 (34.4)	65 (31.7)	61 (35.1)
Disinhibition	51 (16.9)	34 (15.4)	23 (11.2)	25 (14.4)
Irritability	156 (51.7)	84 (38.0)	79 (38.5)	68 (39.1)
Aberrant motor behavior	35 (11.6)	35 (15.8)	19 (9.3)	12 (6.9)
Nighttime behavior disturbances	82 (27.2)	40 (18.1)	32 (15.6)	36 (20.7)
Appetite and eating abnormalities	62 (20.5)	44 (19.9)	31 (15.1)	27 (15.5)

GDS-15 ¶				
Self-reported depression	63 (20.9)	31 (14.0)	30 (14.6)	26 (14.9)
CIRS categories, N (%)	N = 315	N = 246-249	N = 224	N = 207-208
Cardiac	92 (29.2)	67 (27.2)	61 (27.4)	61 (29.5)
Vascular	144 (45.7)	110 (44.7)	98 (43.9)	92 (44.4)
Hematopoietic	12 (3.8)	6 (2.4)	12 (5.4)	7 (3.4)
Respiratory	74 (23.5)	47 (19.1)	44 (19.7)	39 (18.8)
Eyes, ears, nose	54 (17.1)	38 (15.4)	50 (22.4)	36 (17.4)
Upper digestive tract	48 (15.2)	23 (9.3)	27 (12.1)	27 (13.0)
Lower digestive tract	28 (8.9)	19 (7.7)	20 (9.0)	15 (7.2)
Liver	20 (6.3)	10 (4.1)	10 (4.5)	13 (6.3)
Kidneys	15 (4.8)	9 (3.7)	6 (2.7)	6 (2.9)
Urogenital	57 (18.1)	42 (17.1)	45 (20.2)	37 (17.9)
Neuromuscular	40 (12.7)	41 (16.7)	42 (18.8)	41 (19.8)
Neurological	75 (23.8)	42 (17.1)	48 (21.5)	52 (25.1)
Endocrine	49 (15.6)	36 (14.6)	31 (13.9)	30 (14.5)

N = numbers available. Neuropsychological test scores are presented as z-scores computed using normative means. # computed for those with at least five neuropsychological tests present.
Abbreviations: VAS = Visual Analogue Scale; VLT = Verbal Learning Test; TMT-A = Trail Making Test part A; TMT-B = Trail Making Test part B; SCWT = Stroop Color Word Test; LDST = Letter Digit Substitution Test; MMSE: Mini Mental State Examination; NPI: Neuropsychiatric Inventory; GDS-15: Geriatric Depression Scale-15 items; CIRS: Cumulative Illness Rating Scale.

† SCWT 1–2, average of Stroop Color Word Test card 1 + 2; ‡ SCWT interference index = Stroop Color Word Test card 3 divided by the average of Stroop Color Word Test card 1 + 2; § raw score; ¶ a cut-off score of 6/15 or higher was used;

Table 2. Predicted mean scores of QoL over the course of the study period by status of baseline determinants

	Time							
	Baseline		FU1		FU2		FU3	
	Absent	Present	Absent	Present	Absent	Present	Absent	Present
Cognition								
-								
Somatic comorbidities								
Eyes/ears/nose comorbidities	62.1	59.2	67.7	65.3	65.4	65.0	58.8	63.1
Lower digestive tract comorbidities	63.3	58.0*	67.7	65.3	67.0	63.4	65.4	56.6**
Neuropsychiatric symptoms								
Agitation	59.6	61.7	67.1	65.9*	68.4	62.0	64.5	57.4**
Appetite and eating abnormalities	62.9	58.4*	64.9	68.1	65.1	65.2	61.8	60.0
Nighttime behavior disturbances	62.7	58.5**	67.1	65.9	64.8	65.5	62.8	58.5
Self-reported depression	67.6	53.7**	72.6	60.4**	69.4	61.0**	67.1	54.8**

Based on random intercept analyses adjusted for age at baseline, sex, education and study center. Predicted mean scores are estimated marginal means of time by group. Key: FU = follow-up. * $p < 0.05$, ** $p < 0.01$ between subjects with baseline determinants present vs. absent

EMBARGOED

BIOBANK ALZHEIMER CENTER LIMBURG STUDY: DESIGN AND COHORT CHARACTERISTICS

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8

GENERAL DISCUSSION

To date, the impact of *neuro*psychiatric symptoms (NPS) in Alzheimer's disease (AD) is increasingly recognized. NPS occur specifically in the context of AD and are thought to reflect the *neuro*pathological changes of the disease. With the development and validation of in vivo AD biomarkers, increased research efforts have been made in last decades to study the relationship between underlying AD pathology and NPS as its clinical manifestation[1]. This research is based on the premise that identifying a common neurobiological underpinning implies that NPS act as risk factors for, are consequences of, or function as a biological subtype of AD[2]. Although some studies have confirmed the association between AD pathology and NPS, others have failed to replicate these findings[1]. This would suggest that factors other than neuropathology play a role in the etiology of NPS, such as the myriad of factors depicted in (**chapter 1**, Figure 2, page 13). In 2013, the Expert panel of the Alzheimer's Association called for further systematic testing of the neural underpinnings of NPS in AD and its prodromal stages[3]. The work presented in this thesis focusses on these neuropathological underpinnings of NPS, notably affective symptoms, in AD.

8.1. Main findings

Is underlying AD pathology associated with affective symptoms in individuals across the AD spectrum? Does disease severity have an influence on this relationship? How do symptoms such as depression and apathy develop over time? Is AD pathology associated with such trajectories?

Apolipoprotein E (APOE) is the most important and well-documented genetic risk factor for late onset AD[4]. The ε4 alleles of this gene have also been hypothesized to impact disease phenotypes, such as manifestations of affective symptomatology. In **chapter 2** we conducted a meta-analysis, which showed that APOE ε4 was not associated with the presence of depression, anxiety, apathy, agitation, irritability, or sleep disturbances in cognitively impaired subjects. Thus, NPS cannot be explained by a single gene.

For **chapter 3** and **4** we utilized the AT(N) classification scheme from Jack et al. (2018), which divides major AD biomarkers in three binary categories[5]. In this framework, "A" stands for amyloid-β (amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) $A\beta_{42}$), "T" stands for tau (tau PET or CSF phosphorylated tau) and "N" stands for neuronal injury (including structural MRI and CSF total tau). Note that lower CSF amyloid and higher CSF tau levels indicate the presence of more AD pathology.

Although prior studies have reported conflicting results with regard to the association between anxiety and AT(N) markers, we found consistent associations between lower amyloid and higher tau fluid markers, and presence of anxiety. Mixed findings have been reported for apathy as well, whereas we found associations between lower CSF $A\beta_{42}$ and smaller hippocampal volumes and the presence of apathy. Of note, we identified these

associations using more restrictive multivariate models and conservative p-values compared to the studies identified in the systematic review. All identified associations were mediated by MMSE score, indicating that AD pathology may lead to anxiety and apathy, via more severe disease. Indeed, when examining prevalence rates in a cross-sectional manner, both anxiety and apathy were shown to increase with stages of the disease (i.e. symptoms of anxiety and apathy were present in 16.4 and 18.8% of the people in the subjective cognitive decline (SCD) group, in 19.8 and 23.0% of the mild cognitive impairment (MCI) group, and 34.4 and 44.9% of the dementia group, respectively). The presence of anxiety and apathy might therefore parallel underlying disease pathology, with accumulating pathology leading to a higher prevalence of NPS over time. When examining the relationship between AD baseline biomarkers and trajectories of apathy over time (**chapter 5**), either low levels of CSF $A\beta_{42}$ or the combination of low $A\beta_{42}$ and high tau concentrations, but not a high tau concentration alone, was associated with increased probability of apathy over time.

In agreement with prior studies, we found no cross-sectional association between AD pathology and depression at study entry. In longitudinal data, baseline $A\beta_{42}$ and tau pathology was predictive of an increased probability of depression over time. The development of incident depressive symptoms might (partially) be explained by AD pathology whereas already prevalent symptoms are perhaps better explained by mechanisms other than AD pathology. It is important to keep in mind that these seemingly contradicting results might be explained by differences in cohort composition as well as the different statistical approaches. Whereas the cross-sectional approach of chapter 5 classified patients as either depressed (1) or not depressed (0), the longitudinal analyses of chapter 6 classified patients in a less deterministic manner, through a combination of latent class analysis with growth curves. That is, in the case of depression, patients had a certain probability of being in one of the two identified classes: patients assigned to the first class have an increasing probability of depression over time (1), those assigned to the second class have a low probability of depression over time (0). Further, cross-sectional analyses capture only a single moment of NPS while these are in fact dynamic by nature.

Our longitudinal analyses showed that baseline AD pathology predicted the development of apathy and depression over a 5-year period. Prior research showed that awareness of illness decreases as dementia progresses and that lack of this awareness was associated with symptoms of apathy, contrasting the finding that higher awareness was associated with symptoms of depression[6]. Further, whereas apathy is more prominent in later stages, depression occurs more often in earlier stages[7, 8]. It might therefore be hypothesized that depression, as a manifest of underlying disease (either direct/indirect), changes over time into apathic symptomatology, paralleling the downward trajectory of cognitive functioning and increasing anosognosia. Following the findings of chapter 4, where

disease severity was shown to act as a mediator in the relationship between pathology and NPS, the interplay between global cognition (as a proxy of disease severity) and NPS deserves further examination, for example using parallel-growth mixture models. In sum, the association between baseline biomarkers and (a) baseline symptoms of apathy and anxiety and (b) trajectories of depression and apathy over time suggest that these symptoms are manifests of underlying disease, in line with the "symptom" or "prodromal" hypothesis[2]. However, it should also be mentioned that cause-and-effect inferences cannot be inferred from these results (see 8.2 Methodological considerations).

With regard to the association between agitation, irritability, and AT(N) markers, prior findings were conflicting with regard to amyloid-β and none-existing with regard to tauopathies. In this line, in our cross-sectional analyses no association between any of the AD markers and agitation/irritability was found. Similarly to the explanation of depressive symptoms at baseline, these symptoms might thus be better explained by mechanisms other than pathology.

In total, these findings imply that prevalent individual symptoms have different underlying mechanisms, that need to be further elucidated in the future. The high prevalence of NPS in chapter 4 and the findings from chapter 5 further emphasize the need for clinicians to be aware of these symptoms and their considerable fluctuation over time.

What is the impact of NPS, somatic comorbidities, and cognitive functioning on patient quality of life?

The next step was to examine the impact of NPS and other potential determinants on Health-Related Quality of Life (HRQoL) in memory clinic visitors without dementia. In addition to NPS we considered domains such as cognitive functioning and somatic comorbidities as predictors for HRQoL over time. In **chapter 6** we presented the best fitting model of determinants for HRQoL, consisting of presence of agitation, appetite and eating abnormalities, and sensory impairments. Agitation was associated most strongly associated with HRQoL over time. Thought to be an expression of emotional distress, agitation has been associated with a so-called non-adapting care strategy[9]. More specifically, caregivers approaching the patient with impatience, anger, or irritation, reported a significant increase in patient hyperactivity over time[9]. It can be hypothesized that poor interpersonal relationships between patient and caregiver negatively impact patient HRQoL. Interestingly, cognition was not associated with HRQoL over time. Furthermore, there was an initial increase of HRQoL during the first year, followed by a decrease in subsequent years. Again, this emphasizes the importance of continuous monitoring of memory clinic patients by clinicians over time.

How to investigate the natural course of cognitive functioning and its associated factors in a memory clinic population?

The multifactorial underlying mechanisms of AD underline the importance of well-phenotyped, prospective cohort studies, preferably with a broad range of clinical and biobank data, embedded in regular patient care. In **chapter 7** the design of such study is presented, showing the characteristics of the first 855 patients included in the Biobank Alzheimer Center Limburg (BB ACL) study. BB ACL allows for the examination of the natural course of cognitive functioning over up to ten years and its associated factors. Currently, the sample is composed of 38.4% patients with SCD, 37.1% with MCI, and 24.6% with dementia. This shows how in the last decades an increasing number of people present at the memory clinic with cognitive complaints but without dementia, perhaps reflecting the increased societal awareness and recognition of the disease. This is important for both clinical and research purposes, because it allows for timely interventions and care planning, but also opportunities to study factors that are associated with prognostic outcomes.

8.2. Methodological considerations

The systematic rating of study quality in chapter 2 and 3 allowed us to identify several methodological shortcomings in prior literature. These limitations provided important starting points for chapters 4, 5 and 6**.** However, some are inherent to the data being used and could not be overcome. Methodological considerations of the research presented in this thesis will be discussed in the following section.

Biases induced by design

As outlined on page 10 (chapter 1), the five cohorts used in this thesis are situated in memory clinics, where patients are being referred to by the general practitioner. Whereas this allows the findings to be of relevance for clinical practice, generalizability to other populations might be limited. Additionally, the use of clinical samples potentially results in referral/selection bias, which might have led to an overestimation of NPS frequencies. However, the frequency estimates of NPS in mild cognitive impairment (MCI) and AD in these thesis were similar to those reported in recent meta-analyses[10, 11].

In longitudinal aging studies (such as chapter 5 and 6), loss to follow-up is not completely at random since mortality and cognitive or physical deficits result in attrition bias. When comparing subjects with and without missing data at follow-up, it was seen that subjects without follow-up data were on average older, lower educated and performed worse on cognitive tests compared to subjects with follow-up data. However, the inclusion of covariates that were associated with missingness allows that missing data can be considered

"at random", which is assumed by the random effects models utilized, thereby partly overcoming this type of bias[12].

Biases induced by measurement instruments

Next to issues inherent to the sample, bias might also result from errors in measurement instruments of predictors and outcomes. For example, we used "global load" measures of pathology, whereas neuropathology in specific brain areas might be associated with certain symptoms[13]. In addition, we did not categorize individuals as either "abnormal" or "normal" using pre-defined cut-offs. This would be the preferred approach in light of the much cited AT(N) framework, as it allows for uniform definitions regardless of biomarker modality and it provides a convenient shorthand in communicating results[5]. However, in the current phase of exploring the underlying mechanisms of NPS, it is crucial to understand how individual markers, instead of a relatively complex combination of various markers, interact with the presence of NPS. Classifying patients according to biomarker categories also means that one relies on arbitrary cut-off levels. Indeed, various exploratory analyses showed that the choice of cut-off was of great influence on study results (data not shown). In this thesis, we chose to put more weight on understanding underlying mechanisms via continuous biomarker levels, thereby increasing the possibility of reproducing results. We were able to combine the different biomarker assays utilized by each study by converting the biomarker levels into z-scores per cohort.

The measurement of NPS relies on self- or proxy reports of (observable) behaviors and/or mental states since no (validated) direct measures of NPS exist. These types of measurements are influenced by various factors. For example, self-report might not be appropriate given the impaired capacity of those with neurodegeneration to report their mental state in a reliable manner. Input from caregivers, acting as "filters" themselves, might be heavily influenced by the emotional state of the caregiver and cultural background[14]. The Neuropsychiatric Inventory (NPI), a caregiver-based scale, is considered the gold standard for NPS research. The NPI is relatively easy to administer because it is structured and short, "striking the best balance between comprehensiveness and brevity" (p. 67)[13]. In addition, it can distinguish between different syndromes and it has been well-validated for the cognitively impaired population. Thus, while acknowledging its limitations, the NPI is currently the best choice for NPS-research.

Approaches to data-analysis

Although each statistical approach was carefully chosen in line with the research question posed, we are unfortunately unable to draw definite conclusions with regards to temporal

causality, due to the cross-sectional nature of most studies. Even with the use of longitudinal observations studies, the research question whether affective symptoms result in AD pathology or whether AD pathology leads to affective symptoms cannot be answered.

By conducting several multiple regression models the probability of type II error was increased. Further, although the original models were based on theoretical assumptions, the models were revised based on statistical decisions. To overcome the potential problems with multiple testing we report conservative p-values.

Finally, as was mentioned earlier, one can think of several factors that were not taken into account and that might have confounded the relationship between biomarkers and NPS. Confounding factors might be for example psychological factors of patient (stress, social deprivation, hearing or visual problems, awareness, premorbid personality, coping, vulnerability, differential susceptibility, etc.), the presence of medical comorbidities or other NPS, use of medication, and caregiver characteristics.

8.3. Conceptual considerations

The concept of NPS merits a closer look. The current syndrome-based classification system as proposed by the DSM-5 is based on dichotomized diagnosed syndromes based on a set of symptoms to determine whether a disorder is present or absent[15]. This entails that two individuals with the same disorder do not necessarily need to have the same set of symptoms. The fact that phenotypes *within* a disorder are heterogeneous may dilute existing relationships between biomarkers and mental disorders[16]. This translates to the research questions examined in this thesis as well, because of the difficulties differentiating between for example idiopathic depression (early onset) vs. depression that occurs in association with neurodegeneration (late life depression). Although idiopathic mental disorders differ from NPS in terms of symptom profile, course, and response to treatment, it is difficult to differentiate between the two. Thus, having individuals with different types of depression classified as the same may bias estimates of the association with biomarkers downward[16].

Another difficulty stems from the fact that, although each syndrome has its own core symptom, the syndromes overlap in symptoms. For example, both depression and apathy show flattened affect, loss of initiative and motivation, loss of interest, and inertia[17]. Because of this, it has been claimed that for example agitation is not a separate syndrome, but a complication of other syndromes[18]. Some have expressed the view that NPS should be approached as subsyndromes (i.e. factors of individual NPS), because they are so closely related in terms of comorbidity and phenomenology[19]. However, I would argue against this, because (1) although the symptoms occur frequently together, they also exists separately[20], (2) each symptom has its own biological correlates, e.g. in terms of structural brain regions or neurotransmitters[3], (3) each symptom has its own specific course, (4) each symptom

shows a different response to drug treatment, and (5) a systematic review of the literature showed low concordance of studies that examined possible groupings of symptoms in neuropsychiatric clusters. That is, 15 papers on the topic were included, which reported a total of 34 different clusters and *no study* was able to replicate the groupings of other studies[19].

8.4. Strengths

In this thesis we used a wide variety of relatively large cohort-studies such as the Dutch BB ACL, the Clinical Course of Cognition and Comorbidity in Mild Cognitive Impairment (4C-MCI study), and the Parelsnoer Institute – Neurodegenerative Diseases (PSI-NDZ). We also used two large US databases, the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Uniform Data Set of the National Alzheimer's Coordinating Centre. Five out of six studies are multi-center studies and all have follow-up data available. The international nature of the data not only increases generalizability of the results but also the power to detect underlying associations. For example, we pooled data from PSI-NDZ and ADNI, taking the clustered nature of the data into account and using biomarker z-scores defined separately for each cohort. We were also able to answer research questions by complementing data that was lacking in one cohort with data from the other, e.g. in chapter 5.

The use of a wide variety of statistical techniques was needed to summarize data, explore possible associations, and confirm a-priori hypotheses. This provided an interesting variety in perspectives through which we approached the data. We included patients from across the AD spectrum, which is important because biomarkers can be abnormal decades before someone shows clinical symptoms[21] and NPS occur in all disease phases[7, 10].

Throughout this thesis we examined group-level associations whilst it can be hypothesized that one mean trajectory does not provide a good fit for the total population. The relatively new growth mixture modeling approach allowed us to answer interesting and appropriate questions but increased the complexity of estimating model parameters substantially.

8.5. Implications

8.5.1 Clinical implications

In the Netherlands, approximately 254.000 people have dementia, of whom the majority (55%) are living at home[22, 23]. Although living at home as long as possible has many positive sides, we should not neglect the high caregiver burden this might cost. The findings in this thesis support the notion that NPS are common and have an effect on patient HRQoL. It is therefore important that quality of life of both patient and caregiver are adequately

thesis support the notion that NPS are common and have an effect on patient HRQoL. It is therefore important that quality of life of both patient and caregiver are adequately monitored and maintained over the disease period, thereby opening windows of opportunity for intervention.

The presence of AD pathology at study entry was associated with increased probability of the development of symptoms such as depression and apathy. These findings underline the importance that clinicians need to be aware of and provide adequate attention to the possible development of these symptoms *over time*. This provides opportunities for psycho-education of the patient and caregivers in early phases of the disease. Caregiver insight into the multifactorial mechanisms of NPS plays an important role in understanding and accepting challenging behavior[24], whereas a lack of understanding and misinterpretation of NPS is associated higher levels of caregiver distress[25].

The different underlying mechanisms of individual NPS support the notion that NPS are separate constructs. However, although individual NPS were examined, we also observed high rates of comorbidity among the NPS. We should be aware of the fact that NPS do not present in isolation and that individual cases differ in the constellation of NPS. In light of clinical consequences it is important that the clinician focuses on the differentiation of the different NPS, for example, because SSRI's work for depression but are harmful in apathy. In addition, the findings of this thesis emphasize that mechanisms other than neuropathology contribute to the etiology of NPS. Therefore, clinicians should tailor treatments to individual situations and try to assess the myriad of other (interacting) factors that might play a role in the development of NPS.

8.5.2 Research implications and future directions

The systematic summary of the existing literature showed large heterogeneity in the design and setting of studies that have examined the relationship between affective symptoms and AD biomarkers. Since the instruments and definitions used also differed greatly among studies, the disparity between the results is perhaps unsurprising. Therefore, we argue for a smarter use of existing data where appropriate pooling of data from multiple cohorts results in more power to detect associations. In this line, efforts must be made for the harmonization and uniformity of study designs and analytical approaches. This would contribute to better comparability of studies. One alternative approach to data pooling would be that of "coordinated data analyses"[26]. Rather than pooling data to obtain a single result, research networks such as Integrative Analysis of Longitudinal Studies of Aging and Dementia (IALSA) emphasize replication and comparability of results across samples, via the use of comparable statistical models and measurements (*manuscript in preparation).*

One of the challenges that biomarker-NPS research faces is the generation of results that can be replicated, as illustrated by the results of chapter 2 and 3. Especially the measurement of NPS proved to be difficult. In future research emphasis should be placed on continuous development, validation, and standardization of NPS instruments. In addition to self- or proxy rated scales, symptoms could be assessed via multidimensional, objective indicators of behavior, e.g. using audio features and automated video analysis. However, first and foremost, agreement should be reached on the definitions of these symptoms[27]. It is important to also consider the existence of phenotypes underlying NPS, which now possibly dilute existing association as stated in section 8.3.

The research presented in this thesis provides important starting points for future studies. It shows that the etiology of NPS in AD cannot be solely explained by neuropathology. In order to establish and further develop multi-causal models, large longitudinal studies are needed that include factors such as those displayed in Figure 2. However, by including such variety of biopsychosocial factors, in combination with utilization of methods that acknowledge the existence of subsets in the population, we are in need of larger well-defined cohorts. Even relatively large cohorts such as ADNI and NACC were too small to allow the inclusion of several interaction factors. Following the investigation of parallel processes of pathology and NPS over time, it would be interesting to examine the effect that treating NPS has on pathology. In addition, the presence of NPS has been associated with faster disease progression[28]. It can therefore be hypothesized that effective treatments of NPS have the potential to modify disease course. Biomarkers can be used to measure efficacy of such NPS treatment[18].

8.6. Concluding remarks

NPS are common non-cognitive hallmarks of AD. Differences were observed in the association between individual symptoms and underling pathology, emphasizing that NPS are different constructs that should be approached as such. Although the (development of) depression, anxiety and apathy was associated with underlying AD pathology, many other possible attributing factors have not yet been taken into account. The encountered difficulties in terms of study design, statistical analyses, and aligning results, underline the complexity of NPS research. To give justice to this complexity, future research and clinical work must include the broad variety of biopsychosocial factors.

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9

ADDENDUM

SUMMARY

Nearly all patients with Alzheimer's diseases (AD) develop neuropsychiatric symptoms (NPS) over the disease course, which also includes prodromal phases. NPS are associated with negative disease outcomes, such as faster disease progression, earlier institutionalization, increased caregiver distress and burden, and lower quality of life. Although it is now well-acknowledged that NPS are integral parts of the phenotype of AD, their etiology remains unclear. In the last decades, two types of developments provided the opportunity to examine the relationship between AD pathology and NPS: first, the development of in vivo biomarkers, as proxies for disease pathology, and secondly, large cohort studies that that allowed maximization of scope and quality of AD-NPS research. Such well-defined and representative cohort studies were utilized in this thesis, such as the Dutch BioBank Alzheimer Center Limburg (BB ACL) study, the Clinical Course of Cognition and Comorbidity in Mild Cognitive Impairment (4C-MCI study), the Parelsnoer Institute – Neurodegenerative Diseases (PSI-NDZ), and two large US databases, the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Uniform Data Set of the National Alzheimer's Coordinating Centre (UDS-NACC).

This thesis is an answer to the call of the expert panel of the Alzheimer's Association to systematically test the underlying neurobiological mechanisms of NPS in AD. In the first part, we provided an up-to-date overview of the literature regarding the AD-NPS association. In the second part, we examined the AD-NPS association across the AD spectrum, first in a cross-sectional manner and thereafter with longitudinal data. In the final part of this thesis, we related NPS to Health-Related Quality of Life (HRQoL) and we described the design and cohort characteristics of the BB ACL study, Maastricht, the Netherlands.

In **chapter 2** we analyzed data from 53 studies and calculated pooled estimates on the association of apolipoprotein (APOE) ε4 genotype and NPS. No association between APOE ε4 and depression, anxiety, apathy, agitation, irritability, or sleep disturbances in cognitively impaired subjects was found. Thus, NPS cannot be explained by a single gene.

In **chapter 3** the recent NIA-AA AT(N) classification scheme was used as a framework to systematically examine the literature on the AD-NPS topic, including 45 studies. AD biomarkers were classified as A markers (amyloid-β levels in cerebrospinal fluid (CSF) or on PET scans), T markers (CSF phosphorylated tau (p-tau) or tau PET), or N markers (hippocampal atrophy on MRI scans or CSF total tau (t-tau)). Depression and sleep disturbances were not related to AT(N) markers. Apathy was associated with A markers

(PET, not CSF). Conflicting findings were reported for apathy and T(N) markers; anxiety and A(N) markers; and between agitation and irritability and A markers. Agitation and irritability were not associated with T(N) markers.

The included studies in the meta-analysis and systematic review differed from each other in terms of study design, such as sample composition and the way that biomarkers and NPS were assessed, and the statistical approaches that were utilized. An association between pathology and NPS would imply that NPS are non-cognitive manifestations of underlying AD pathology, where NPS could either be a cause or effect of the pathology. In contrast, no association between AD pathology and NPS suggests that factors other than AD-specific pathology would lead to these symptoms. In **chapter 4** we studied the relation between AD pathology and NPS across the AD spectrum in two large independent studies, utilizing the neuropsychiatric inventory to assess NPS. We also examined whether and how disease severity influences this relationship. Again, depression and sleep disturbances were not associated with AD pathology, and neither were agitation and irritability. Anxiety and apathy were associated with AD biomarkers, although these associations were mediated by Mini-Mental State Examination (MMSE) scores. This suggests that the association between AD pathology and anxiety and apathy might be explained by disease severity.

A caveat with these cross-sectional analyses is that they do not capture the fluctuating nature of NPS. That is, the presentation of NPS does not only differ *between* persons, but also *within* a person over time: symptoms may persist, remit, or recur episodically. In **chapter 5**, growth mixture modeling was used to identify trajectories of depression and apathy over time in two large independent cohorts. In both studies, multiple classes (i.e. trajectories) were identified, with the largest classes being stable low or no probability of apathy and depression over time. The other classes included (steep) in- or decreasing symptoms over time. The reliable biomarker measurements that were available in one of the two cohorts were then related to these trajectories. Baseline AD pathology was related with de novo or increasing symptoms of depression and apathy over a 5-year time period. This suggests that depression and apathy are consequences of underlying AD pathology, although we should remain cautious with making such causal inferences.

The impact of NPS, cognitive functioning, and somatic comorbidities on Health-Related Quality of Life (HRQoL) was examined in **chapter 6**. Agitation was most strongly associated with HRQoL over a 3-year time period, followed by appetite and eating abnormalities, and sensory impairments. Cognitive functioning was not associated with HRQoL over time. Importantly, HRQoL was also shown to fluctuate over time: an initial increase of HRQoL

was observed during the first year, followed by a decrease in later years. Thus, it should be emphasized that patients need to be adequately monitored over time.

The design of the prospective cohort BB ACL study and patient characteristics of the first 855 patients that were included is presented in **chapter 7**. BB ACL includes a broad range of clinical and biobank data, and is embedded in regular patient care. The sample includes patients ranging from subjective cognitive decline (SCD) to mild dementia. The study provides valuable opportunities for future research.

Overall, the studies in this thesis contribute to the ongoing debate in the literature with regard to the etiology of NPS, and provide important starting points for future research.

NEDERLANDSE SAMENVATTING (DUTCH SUMMARY)

De meeste mensen met de ziekte van Alzheimer (AD) ontwikkelen neuropsychiatrische symptomen (NPS) gedurende het ziekteproces – waaronder ook in de pre-dementie fase. De aanwezigheid van NPS hangt negatief samen met ziekte-uitkomsten, zoals een snellere progressie van het ziektebeloop, eerdere opname in een verpleeghuis, en een lagere kwaliteit van leven. Hoewel NPS nu als een belangrijk aspect van AD worden erkend, is hun etiologie nog altijd onduidelijk. In de laatste jaren zijn er twee ontwikkelingen geweest die de mogelijkheid om de relatie tussen AD pathologie en NPS te onderzoeken hebben bevorderd: allereerst, de ontwikkeling van *in vivo* biomarkers, welke AD pathologie gedurende het leven kunnen meten, en ten tweede, grote cohort studies welke de omvang en kwaliteit van AD-NPS onderzoek hebben vergroot. In dit proefschrift is gebruik gemaakt van goed gekarakteriseerde en representatieve cohorten, te weten de Nederlandse "BioBank Alzheimer Center Limburg" (BB ACL) studie, de "Clinical Course of Cognition and Comorbidity in Mild Cognitive Impairment" (4C-MCI) studie, de "Parelsnoer Institute – Neurodegenerative Diseases" (PSI-NDZ) studie, en twee grote Amerikaanse databases, de "Alzheimer's Disease Neuroimaging Initiative" (ADNI) en de "Uniform Data Set of the National Alzheimer's Coordinating Centre" (UDS-NACC).

Dit proefschrift is een reactie op de oproep van een expert commissie van de Alzheimer's Association om de onderliggende neurobiologische mechanismen van NPS in AD op systematische wijze te onderzoeken. In het eerste deel van dit proefschrift geven we een overzicht van de huidige stand van zaken in de AD-NPS literatuur. In het tweede deel onderzochten we de AD-NPS associatie bij mensen die zich op het spectrum van AD bevinden, eerst op een cross-sectionele manier en daarna met longitudinale data. In het laatste deel van dit proefschrift relateerden we NPS aan kwaliteit van leven en hebben we het design en cohort karakteristieken van de BB ACL studie beschreven.

In **hoofdstuk 2** analyseerden we data van 53 studies en berekenden we gepoolde schattingen van de associatie tussen apolipoprotein (APOE) ε4 genotype en NPS. Er werd geen associatie tussen APOE ε4 en symptomen als depressie, angst, apathie, agitatie, prikkelbaarheid, of slaapstoornissen gevonden in personen met een cognitieve stoornis. NPS kunnen dus niet door één enkel gen verklaard worden.

In **hoofdstuk 3** werd het recentelijk gepubliceerde NIA-AA AT(N) classificatie framework gebruikt om de NPS-AD literatuur op een systematische wijze te bekijken, daarbij 45 studies includerend. AD biomarkers werden geclassificeerd als A markers (amyloïde-β levels in

hersenvocht (CSF) of op PET scans), T markers (gefosforyleerd tau eiwit in CSF (p-tau) of tau PET), of N markers (atrofie van de hippocampus op MRI scans, of CSF tau (t-tau)). Depressie en slaap stoornissen waren niet geassocieerd met AT(N) markers. Apathie was geassocieerd met A markers (enkel op PET scans, niet in CSF). Tegenstrijdige resultaten werden gevonden voor apathie en T(N) markers; angst en A(N) markers; en tussen agitatie en prikkelbaarheid en A markers. Agitatie en prikkelbaarheid waren niet geassocieerd met T(N) markers.

De studies welke geïncludeerd werden in de meta-analyse en systematische review toonden onderlinge verschillen wat betreft hun studie design, zoals de manier waarop de steekproef was samengesteld alsook in de manier waarop de biomarkers en NPS werden gemeten, en in de gekozen statistische analyses. Een associatie tussen AD pathologie en NPS zou impliceren dat NPS niet-cognitieve uitingen zijn van onderliggende AD pathologie, waarbij NPS zowel een oorzaak als gevolg van AD pathologie kan zijn. Geen associatie zou daarentegen suggereren dat NPS door andere factoren dan AD pathologie worden veroorzaakt. In **hoofdstuk 4** bestudeerden we de associatie tussen AD pathologie en NPS over het AD spectrum in twee grote onafhankelijke studies, welke de "neuropsychiatric inventory" (NPI) gebruikten om NPS vast te stellen. We onderzochten tevens *of* en *hoe* ziekte-ernst deze relatie beïnvloedt. Opnieuw vonden we geen associatie tussen depressie en slaap stoornissen en AD pathologie, en ook niet voor agitatie en prikkelbaarheid. Angst en apathie waren wel geassocieerd met AD biomarkers, hoewel deze associaties gemedieerd waren door de Mini-Mental State Examinatie (MMSE). Dit suggereert dat de associatie tussen AD pathologie en angst en apathie verklaard zou kunnen worden door ziekte-ernst.

Een limitatie van deze cross-sectionele analyses is dat ze de fluctuerende aard van NPS niet weten te vangen. De presentatie van NPS verschilt namelijk niet alleen *tussen* personen, maar ook *binnen* één persoon over de tijd: symptomen kunnen aanhouden, afnemen, of af en toe voorkomen. In **hoofdstuk 5** gebruikten we "growth mixture modeling" in twee grote cohortstudies, om trajecten van depressie en apathie te identificeren. In beide studies werden meerdere groepen (trajecten) geïdentificeerd, waarbij de grootste groep een stabiel lage of zelfs geen kans op apathie of depressie over tijd had. De overige groepen lieten een (sterke) toe- of afname van symptomen over tijd zien. De betrouwbare biomarker metingen welke beschikbaar waren in één van de twee cohorten werden daarna gerelateerd aan deze NPS trajecten. Baseline AD pathologie was geassocieerd met nieuwe of toenemende symptomen van depressie en apathie over een 5-jaar follow-up periode. Dit suggereert dat onderliggende AD pathologie symptomen als depressie en apathie veroorzaakt, hoewel we waakzaam en voorzichtig moeten blijven wanneer we zulke causale interferenties maken.

De impact van NPS, cognitief functioneren, en somatische comorbiditeiten op (gezondheidsgerelateerde) kwaliteit van leven (HRQoL) werd onderzocht in **hoofdstuk 6**. Agitatie was het sterkst geassocieerd met HRQoL over een 3-jarige periode, gevolgd door abnormaliteiten in het eetgedrag en sensorische stoornissen. Cognitief functioneren was niet geassocieerd met HRQoL over tijd. Belangrijk is dat HRQoL over de tijd fluctueerde: waar het eerste jaar een toename van HRQoL werd geobserveerd, werd dit gevolgd door een afname in latere jaren. Patiënten moeten dus over de tijd adequaat gemonitord en gevolgd worden.

Het design van de prospectieve cohort studie BB ACL en karakteristieken van de eerste 855 geïncludeerd patiënten zijn in **hoofdstuk 7** beschreven. BB ACL omvat een breed scala aan klinische en biobank data, en is ingebed in reguliere patiëntenzorg. De studie includeert patiënten met subjectieve cognitieve achteruitgang tot aan de milde dementie fase. Deze studie biedt veel mogelijkheden voor toekomstig onderzoek.

De studies in dit proefschrift dragen bij aan de discussie in de literatuur betreffende de etiologie van NPS, en geven daarnaast ook belangrijke startpunten voor toekomstig onderzoek.

KNOWLEDGE VALORIZATION

In this chapter, the possibilities of valorization of the results presented in this thesis will be described. Valorization of research is the process of creating value from knowledge[1]. In other words, how can the obtained knowledge from this research be of relevance for the society in general, and how it can be (clinically) implemented?

Societal and/or economic relevance

The prevalence of age-related diseases, such as dementia, increases as a function of the growing aging population and an increased recognition and attention of its signs and symptoms from the public, sciences, practitioners and care providers[2]. An estimated 254.000 individuals in the Netherlands met diagnostic criteria for dementia in 2015, and this number is expected to triple by 2050[3]. This makes dementia for many high-income countries, among which the Netherlands, a health- and social-care priority[3].

In addition to the well-known cognitive impairments part of Alzheimer's disease (AD), it is now acknowledged that nearly all patients with AD develop one or more neuropsychiatric symptoms (NPS) over the course of the disease[4, 5]. The implications of AD, and NPS in particular, are multifold. For one, there are direct consequences for the person with AD and his or her caregiver(s), in terms of high distress, increased burden, and lower quality of life (QoL)[6, 7]. An indication of the impact of NPS can be drawn from the finding that presence of NPS are a major determinant of (earlier) nursing home placement, leading to high long term institutionalization costs[8]. In fact, the societal costs of NPS in dementia are staggering: a third of dementia care costs has been attributed to the direct management of NPS, because of the greater use of health services, acute and respite hospitalization, and medication costs[8-10]. Additional costs are for example due to time spend by caregivers supervising the patient, which is time spent away from work or leisure activities[11]. These increased costs of dementia care are even significant in mild cognitive impaired community dwelling people[11]. Thus, NPS have a significant impact on patient and society, in terms of burden and costs.

As there is no cure or disease-modifying treatment available for AD, one major goal is to increase and maintain QoL, for example by prevention and management of NPS. However, the multifactorial and heterogeneous nature of NPS makes this challenging. It is therefore necessary to increase our understanding of the underlying mechanisms of the development of NPS. More knowledge on the ideopathogenesis of NPS has implications for treatment development, as different patients with different NPS might benefit from different treatment strategies. Indeed, it was shown that AD pathology was cross-sectionally associated with anxiety and apathy (albeit indirectly, via disease severity) and with the development of depression and apathy over time, but not with symptoms such as agitation

and irritability. Although the research designs do not allow for differentiation between cause-and-effect, all studies showed that NPS are very common across the disease spectrum. Knowledge and acknowledgement of the high prevalence of NPS may result in better recognition, distinction and earlier detection of NPS. It also further underlines the importance of NPS, next to cognitive decline, as hallmarks of AD, even in prodromal phases of the disease.

Target groups

Mrs. J. is a 76-year old woman with mild AD dementia. A year after her first visit to the memory clinic, she is brought again by her daughter, because of concerns about behavioral changes. Her daughter mentions her decline in interest and sad mood: "Whereas she used to enjoy helping my father with household chores, she now sits in the living room and watches tv. She doesn't even seem to enjoy visits from the grandchildren." Mrs. J. smiles appropriately in social situations but does not further engage in conversations or other activities. Although the daughter is worried about her mother and demands further medical assessment, her father feels that as long Mrs. J. seems content, he should respect her decisions to no longer participate in daily activities.

Various hypotheses have been posed to explain NPS in AD. It has been suggested that NPS are risk factors for AD or that NPS non-cognitive symptoms of the disease, which implies that NPS should be associated with underlying AD pathology[2]. The results of this thesis suggest that Mrs. J's. development of symptoms of apathy experienced by Mrs. J. are (partly) explained by AD pathology.

Knowledge on the relationship between AD pathology and NPS is in the first place of relevance for patients, caregivers, and clinicians. Even when not (yet) apparent, it would be beneficial to educate patient and caregivers that NPS are also considered symptoms of the disease. Oftentimes, NPS are not mentioned spontaneously by patient and caregiver, such that raising awareness of such symptoms will lead to earlier detection and recognition, in turn leading to earlier possibilities of interventions. One can think of modifiable factors other than neurobiology such as unmet needs (where a patient has lack of meaningful activities), factors related to caregiver (negative communication styles), or the environment (lowered stress threshold, difficulties with processing and responding to environmental stimuli). In the case study, the family of Mrs. J. might benefit from professional help to discuss strategies to encourage increased activity. Further, the frustration of Mrs. J.s daughter might be lessened if she is educated about the nature of apathy as part of the disease.

The findings of this thesis are of relevance to health-care professionals as the burden of interpreting clinical and biomarker data rests with them. Perhaps it is not only the patient

and caregiver that should be educated about NPS, but also clinicians. In the presence of AD pathology, increased attention must be given to individualized care options as these patients are at risk for developing NPS. Prior studies showed that the presence of NPS is related to faster progression of the disease, which raises the interesting hypothesis that treatment or management of these symptoms can act as a protective factor for disease progression. The studies in this thesis further showed that the trajectories which individual NPS take are heterogeneous, underlining that cross-sectional assessment of affective symptoms is insufficient. In a like manner, it was shown that QoL does not follow a monotonic trajectory over time. That is, QoL increased after first visit to the memory clinic, after which it showed a decline. It is thus important that clinicians give continuous attention to QoL, even in light of first improvements.

The findings are also of relevance for policy makers and care managers. In the Netherlands, the majority of people with dementia live at home, i.e. are "community-dwelling"[3, 12], which is also promoted by the government via the "Long-term Care Act" (Wet Langdurige Zorg, 2015). This has resulted in various legal frameworks involved with the organization and financing of dementia care, and thus many health care professionals are involved. Although the Dutch Elderly Care Physician guidelines for NPS in dementia[13] recommend the multidisciplinary analysis of NPS, the fragmentation of primary dementia care (and thus involving many health care professionals) does not facilitate coordinated care planning. Thus, it must be emphasized that once NPS have been identified, health care professionals must act together and communicate in order to manage them.

The findings of this thesis provide a framework for researchers in the AD-NPS field. The large heterogeneity observed in prior studies with regard to measurement instruments and definitions suggests that AD-NPS research would likely benefit from uniform definitions. One such framework is the recently proposed AT(N) classification system, where patients are scored according to three biomarker categories[14]. It is not meant as a (clinical) diagnostic system but as a descriptive and standardized system, agnostic to temporal ordering of underlying mechanisms[14]. However, in the current phase of exploring NPS as an expression or cause of the disease, it is crucial to understand how individual biomarkers evolve over time and interact with each other or NPS. One must be aware of the consequences of utilizing arbitrary cut-offs in such research phase. Another implication of this thesis is the identification of the heterogeneity of study designs, instruments and definitions used. More effort must be made to reach consensus on definitions of the concepts under examination.

For pharmaceutical companies who aim to find treatment strategies, this research is of relevance as it suggests that patients with more AD pathology are most likely to develop NPS over time. This means that inclusion criteria can be employed for such clinical trials, selecting those with lower amyloid and higher tau levels. However, this thesis also shows

that, in order to answer any question on causality, we need to extend the amount of measurements on NPS and biomarkers. That is, more frequent follow-up measurements on both parameters would allow modeling of the two in a parallel manner. We also need better characterizations of the psychiatry history of patients, such that in parallel to retrospective self-reports, we use data that is stored with the general practitioner.

Innovation and products

Throughout this thesis, we tried to step away from the thought that estimating one population-average approximates the truth. In the first part of this thesis a comprehensive state-of-the-art view on the association between AD biomarkers and NPS was offered. By combining information from all relevant studies, the systematic review and meta-analysis can provide more precise estimates of the effects than those derived from individual studies[15]. This also allowed the generation of hypotheses that were tested in following chapters, for example, regarding differential effects along the AD disease spectrum. In addition, the nature and relative strength of the associations between AD biomarkers and NPS were explored more in-depth by including cross-sectional mediation analyses. Further, we utilized an innovative statistical technique by which subjects could be grouped into latent classes on the basis of similarities in their trajectories over time. Following the line of reasoning from personalized medicine - where diagnosis and treatment is based on individual characteristics - , we should aim to conduct research in such way that we are able to incorporate multiple indicators and zoom in on an individual level. The main product of this thesis is the implication of the results for clinical practice and future research, as described above. Finally, the collection, cleaning and harmonization of multi-center data done for this thesis (and documentation thereof) will allow future researchers to utilize these beautiful datasets.

Schedule and implementation

A large part of the results of this research has been disseminated via publications in international, peer-reviewed, scientific journals and presentations at international conferences. The results have implications for our ongoing research, where we continue the examination of the association of AD pathology with behavioral changes, for example in the concept of mild behavioral impairment (MBI[16]), in collaboration with the Johns Hopkins University School of Medicine research group at the department of Psychiatry and Behavioral Sciences, Division of Geriatric Psychiatry and Neuropsychiatry. Further, we aim to expand the examination of trajectories of individual NPS, for example by including interactions with other NPS.

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Leonie Banning, Maastricht, 10-10-2019

THESIS DEFENSES FROM ALZHEIMER CENTER LIMBURG AND MHeNS

2013

Rob Havermans: *Bipolar disorder in daily life; Mood and cortisol responses to naturally occurring events*. Supervisor: Prof.dr. M. de Vries; Co-Supervisor: Dr. N. Nicolson.

Véronique Moers-Hornikx: *Deep brain stimulation and the cerebellum*. Supervisors: Prof.dr. J. Vles / Prof.dr. Y. Temel; Co-Supervisor: Dr. G. Hoogland.

Nicole Veldhorst-Janssen: *Intranasal delivery of rapid acting drugs. Supervisors*: Prof.dr. M. Marcus / Prof.dr. C. Neef; Co-Supervisor: Dr. P.H. van der Kuy.

Stéphanie Knippenberg: *Vitamin D and Multiple Sclerosis: immunological and clinical outcome*. Supervisor: Prof.dr. J. Cohen-Tervaert; Co-Supervisors: Dr. J. Damoiseaux / Dr. Y. Bols.

Erik D. Gommer: *Dynamic Cerebral Autoregulation: from methodology towards clinical application*. Supervisors: Prof.dr. W.H. Mess / Prof.dr. R.B. Panerai, UK; Co-Supervisor: Dr.ir. J.P.H. Reulen.

Olga A.H. Reneerkens: *Can PDE inhibition improve cognition ?* Translational insights. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. J. Prickaerts.

Lyzel S. Elias-Sonnenschein: *Clinical and biomarker correlates of genetic risk factors for Alzheimer's disease*. Supervisor: Prof.dr. F.R.J. Verhey; Co-Supervisor: Dr. P.J. Visser.

Diego F. Mastroeni: *Epigenetic Dysregulation and the Pathophysiology of of Alzheimer's Disease*. Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. P.D. Coleman, Sun City, Arizona; Co-Supervisors: Dr. B.P.F. Rutten / Dr. D.L.A. van den Hove.

Leonidas Chouliaras: *Epigenetic Regulation in Aging and Alzheimer's disease: A translational perspective*. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. B.P.F. Rutten / Dr. D.L.A. van den Hove.

Liesbeth Knaepen: *Perinatal events and altered pain sensitivity in later life*. Supervisors: Prof.dr. E.A.J. Joosten / Prof.dr. D. Tibboel, EUR; Co-Supervisor: Dr. J. Patijn.

Marisela Martinez-Claros: *Hippocampal plasticity and corticosterone: From dendrites to behaviour*. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. J.L. Pawluski /Dr. J. Prickaerts.

Marcus D. Lancé: *A circle of improvement in bleeding management: from laboratory to clinic and back*. Supervisors: Prof.dr. M.A.E. Marcu / Prof.dr. J.W.M. Heemskerk; Co-Supervisor: Dr. Y.M.C. Henskens.

Hilde Braakman: *Imaging the brain; neuronal correlates of cognitive impairment in children with frontal lobe epilepsy*. Supervisors: Prof.dr. A.P. Aldenkamp / Prof.dr. J.S.H. Vles; Co-Supervisors: Dr.ir. W.H. Backes / Dr. P.A.M. Hofman.

Willem H. van Zwam: *Aneurysmal subarachnoid hemorrhage: imaging strategies and cost-effectiveness aspects in diagnostic work-up and post-therapeutic follow-up*. Supervisors: Prof.dr. J.T. Wilmink / Prof.dr. J.E. Wildberger; Co-Supervisor: Dr. P.A.M. Hofman.

Klara De Cort: *The Pathogenesis of Panic Disorder. Supervisors:* Prof.dr. I. Myin-Germeys / Prof.dr. E.J.L. Griez; Co-Supervisors: Dr. K.R.J. Schruers / Dr. I. Van Diest, Leuven.

Kim van Wijck: *Mind the Gap; experimental studies on splanchnic hyperfusion and gastrointestinal integrity loss in man*. Supervisors: Prof.dr. W.A. Buurman / Prof.dr. C.H.C. Dejong; Co-Supervisor: Dr. K. Lenaerts.

Yvette Roke: *Antipsychotic-induced hyperprolactinemia in children and adolescents with mainly autism spectrum disorders. Prevalence, symptoms, clinical consequences and genetic risk factors*. Supervisors: Prof.dr. P.N. van Harten / Prof.dr. J.K. Buitelaar (RUN); Co-Supervisor: Dr. A. Boot (UMCG).

Fleur Goezinne: *Retinal detachment surgery: pre and postoperative prognostic factors*. Supervisors: Prof.dr. F. Hendrikse / Prof.dr. C.A.B. Webers; Co-Supervisor: Dr. E.C. La Heij (Amsterdam).

Ralph L.J.G. Maassen: *The Merits of Videolaryngoscopy during Glottic Visualisation for Endotracheal Intubation*. Supervisors: Prof.dr. M. Marcus / Prof.dr. A. van Zundert (University of Queensland).

Maria J. de Sousa Guerreiro: *The role of sensory modality in age-related distraction*. Supervisor: Prof.dr. C.M. van Heugten; Co-Supervisor: Dr. P.W.M. van Gerven.

Ine Rayen: *Effects of developmental fluoxetine exposure on neurobehavioral outcomes*. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-Supervisors: Dr. J.L. Pawluski / Dr. T.D. Charlier (Ohio University, USA).

Nynke M.G. Bodde: *Psychogenic non-epileptic seizures; a separate disorder or part of a continuum?* Supervisors: Prof.dr. R. van Oostenbrugge / Prof.dr. K. Vonck (UZ Gent); Co-Supervisors: Dr. R. Lazeron / Dr. A. de Louw (Epilepsiecentrum Kempenhaeghe, Heeze).

Alejandro M. Gomez: *Novel strategies for making myasthenia less gravis: targeting plasma cells and the neuromuscular junction*. Supervisor: Prof.dr. M.H. De Baets; Co-Supervisors: Dr. M. Losen / Dr. P. Martinez-Martinez.

Mohammad S. Rahnama'i: *Prostaglandins and Phosphodiesterases in the Urinary Bladder Wall*. Supervisors: Prof.dr. Ph. Van Kerrebroeck / Prof.dr. S. de Wachter (Universiteit Antwerpen); Co-Supervisor: Dr. G. van Koeveringe.

Mariken B. de Koning: *Studying biomarkers in populations at genetic and clinical high risk for psychosis*. Supervisors: Prof.dr. T. Amelsvoort / Prof.dr. J. Booij (AMC).
Fabien Boulle: *Epigenetic regulation of BDNF/TrkB signaling in the pathophysiology and treatment of mood disorders*. Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. L. Lanfumey (Universiteit Parijs); Co-Supervisors: Dr. D. van den Hove / Dr. G. Kenis.

2014
Iris Nowak-Maes: *Tinnitus; assessment of quality of life & cost-effectiveness*. Supervisors: Prof.dr. M. Peters / Prof.dr. B. Kremer; Co-Supervisors: Dr. M. Joore / Dr. L. Anteunis.

Marjolein Huijts: *Cognitive function in patients with cerebral small vessel disease*. Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-Supervisors: Dr. A.A. Duits / Dr. J. Staals.

Markus Gantert: *Fetal inflammatory injury as origin of long term disease: Lessons from animal models*. Supervisors: Prof.dr. B. Kramer / Prof.dr. L. Zimmermann; Co-Supervisor: Dr. A. Gavilanes.

Elke Kuypers: *Fetal development after antenatal exposures: Chorioamnionitis and maternal glucocorticoids*. Supervisors: Prof.dr. B.W. Kramer / Prof.dr. H.W. Steinbusch / Prof.dr. Suhas G. Kallapur (University of Cincinnati, Ohio, USA).

Pieter Kubben: *Ultra low-field strength intraoperative MRI for Glioblastoma Surgery*. Supervisor: Prof.dr. J.J. van Overbeeke; Co-Supervisor: Dr. H. van Santbrink.

Laura Baijens: *Surface electrical stimulation of the neck for oropharyngeal dysphagia in Parkinson's disease: therapeutic aspects and reliability of measurement*. Supervisor: Prof.dr. B. Kremer; Co Supervisor: Dr. R. Speyer, Townsville.

Janneke Hoeijmakers: *Small fiber neuropathy and sodium channels; a paradigm shift*. Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-Supervisors: Dr. C.G. Faber / Dr. I.S.J. Merkies.

Stephanie Vos: *The Role of biomarkers in preclinical and prodromal Alzheimer's disease*. Supervisor: Prof.dr. F.R. Verhey; Co-Supervisor: Dr. P.J. Visser.

Muriël Doors: *The Value of Optical Coherence Tomography in Anterior Segment Surgery*. Supervisors: Prof.dr. R.M. Nuijts / Prof.dr. C.A. Webers; Co-Supervisor: Dr. T.T.J.M. Berendschot.

Anneke Maas: *Sleep problems in individuals with genetic disorders associated with intellectual disability*. Supervisors: Prof.dr. I. Curfs / Prof.dr. R. Didden.

Sebastiaan van Gorp: *Translational research on spinal cord injury and cell-based therapies; a focus on pain and sensorimotor disturbances*. Supervisors: Prof.dr. B. Joosten / Prof.dr. M. van Kleef; Co-Supervisors: Dr. J. Patijn /Dr. R. Deumens, KU Leuven.

Andrea Sannia: *High risk newborns and brain biochemical monitoring*. Supervisor: Prof.dr. J.S.H. Vles; Co-Supervisors: Dr. D. Gazzolo, Alessandria, Italy / Dr. A.W.D. Gavilanes.

Julie A.D.A. Dela Cruz: *Dopamine mechanisms in learning and memory: Evidence from rodent studies*. Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. R.J. Bodnar, New York; Co-Supervisor: Dr. B.P.F. Rutten.

René Besseling: *Brain wiring and neuronal dynamics; advances in MR imaging of focal epilepsy*. Supervisors: Prof.dr. A.P. Aldenkamp / Prof.dr.ir. W.H. Backes; Co-Supervisor: dr. J.F.A. Jansen.

Maria Quint-Fens: *Long-term care after stroke; development and evaluation of a long-term intervention in primary care*. Supervisors: Prof.dr. J.F.M. Metsemakers / Prof.dr. C.M. van Heugten / Prof.dr. M. Limburg, Almere; Co-Supervisor: dr. G.H.M.I. Beusmans.

Veronique Moulaert: *Life after survival of a cardiac arrest; the heart of the matter*. Supervisors: Prof.dr. J.A. Verbunt / Prof.dr. C.M. van Heugten / Prof.dr. D.T. Wade, Oxford, UK.

Feikje Smeets: *The hallucinatory-delusional state: a crucial connection in the psychosis symptom network*. Supervisor: Prof.dr. J. van Os; Co-Supervisor: Dr. T. Lataster.

Lies Clerx: *Alzheimer's disease through the MR-eye; novel diagnostic markers and the road to clinical implementation*". Supervisor: Prof.dr. F. Verhey; Co-Supervisors: Dr. P.J. Visser / P. Aalten.

Sonny Tan: *The subthalamic nucleus in Parkinson's disease. Supervisors:* Prof.dr. Y. Temel / Prof.dr. H.W.M. Steinbusch / Prof.dr. T. Sharp, Oxford, UK / Prof.dr. V. Visser-Vandewalle, Koln.

Koen van Boxem: *The use of pulsed radiofrequency in the management of chronic lumbosacral radicular pain*. Supervisors: Prof.dr. M. van Kleef / Prof.dr. E.A.J. Joosten; Co-Supervisor: Assoc. Prof.dr. J. van Zundert.

Jérôme Waterval: *Hyperostosis cranialis interna*. Supervisors: Prof.dr. J.J. Manni / Prof.dr. R.J. Stokroos.

Sylvie Kolfschoten-van der Kruijs*: Psychogenic non-epileptic seizures; the identification of neurophysiological correlates*. Supervisors: Prof.dr. A.P. Aldenkamp / Prof.dr. K.E.J. Vonck,

Universiteit Gent; Co-Supervisors: Dr. J.F.A. Jansen / Dr. R.H.C. Lazeron, Kempenhaeghe.

Wouter Pluijms: *Spinal cord stimulation and pain relief in painful diabetic: polyneuropathy, a translational approach*. Supervisors: Prof.dr. M. van Kleef / Prof.dr. E.A. Joosten; Co-supervisor: Dr. C.G. Faber.

Ron Handels: *Health technology assessment of diagnostic strategies for Alzheimer's disease*. Supervisors: Prof.dr. F.R.J. Verhey / Prof.dr. J.L. Severens (EUR); Co-Supervisor: Dr. M.A. Joore / Dr. C.A.G. Wolfs.

Evelyn Peelen: *Regulatory T cells in the pathogenesis of Multiple Sclerosis: potential targets for vitamin D therapy*. Supervisors: Prof.dr. R.M.M. Hupperts / Prof.dr. J.W. Cohen Tervaert; Co-Supervisor: Dr. J.G.M.C. Damoiseaux / Dr. M.M.G.L.Thewissen, Diepenbeek.

Reint Jellema: *Cell-based therapy for hypoxic-ischemic injury in the preterm brain*. Supervisors: Prof.dr. B.W.W. Kramer / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. W.T.V. Germeraad / Dr. P. Andriessen, Veldhoven.

Maria Wertli: *Prognosis of Chronic Clinical Pain Conditions: The Example of Complex Regional Pain Syndrome 1 and Low Back Pain*. Supervisors: Prof.dr. M. van Kleef; Co-Supervisor: Dr. F. Brunner, Zürich / Dr. R. Perez, VUmc.

Dagmar Zeef: *An experimental model of Huntington's disease: Validation & Stimulation*. Supervisors: Prof.dr. Y. Temel / Prof.dr. H.W.M. Steinbusch; Co-supervisor: Dr. A. Jahanshahi.

Jeroen Decoster: *Breaking Down Schizophrenia into phenes, genes and environment*. Supervisors: Prof.dr. I. Myin-Germeys / Prof.dr. M. De Hert, KU Leuven; Co-Supervisor: Dr. R. van Winkel.
Eaja Anindya Sekhar Mukherjee: *Fetal Alcohol Spectrum Disorders: exploring prevention and management*. Supervisor: Prof.dr. L.M.G. Curfs; Co-Supervisor: Prof. S. Hollins, St. George's University of London, UK.

Catherine van Zelst: *Inside out; On stereotype awareness, childhood trauma and stigma in psychosis*. Supervisors: Prof.dr. Ph. Delespaul / Prof.dr. J. van Os.

Ibrahim Tolga Binbay: *Extended Psychosis Phenotype in the Wider Social Environment*. Supervisor: Prof.dr. J. van Os; Co-Supervisor: Dr. M. Drukker.

Frank Van Dael: *OCD matters in psychosis. Supervisors*: Prof.dr. J. van Os / Prof.dr. I. Myin-Germeys.

Pamela Kleikers: *NOXious oxidative stress: from head toe too and back*. Supervisors: Prof.dr. H.H.H.W. Schmidt / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. B. Janssen.

José Luis Gerardo Nava: *In vitro assay systems in the development of therapeutic interventions strategies for neuroprotection and repair*. Supervisors: Prof.dr.med. J. Weis / Prof.dr. H.W.M. Steinbusch; Co-Supervisor: Dr. G.A. Brook, RWTH Aachen.

Eva Bollen: *Cyclic nucleotide signaling and plasticity*. Supervisors: Prof.dr. H.W.M. Steinbusch / Prof.dr. R. D'Hooge, KU Leuven; Co-Supervisor: Dr. J. Prickaerts.

2015

Jessica A. Hartmann: *A good laugh and a long sleep; Insights from prospective and ambulatory assessments about the importance of positive affect and sleep in mental health*. Supervisor: Prof.dr. J. van Os; Co-Supervisors: C.J.P. Simons / Dr. M. Wichers.

Bart Ament: *Frailty in old age; conceptualization and care innovations*. Supervisors: Prof.dr. G.I.J.M. Kempen / Prof.dr. F.R.J. Verhey; Co-Supervisor: Dr. M.E. de Vugt.

Mayke Janssens: *Exploring course and outcome across the psychosis-continuum*. Supervisor: Prof.dr. I. Myin-Germeys; Co-Supervisor: Dr. T. Lataster.

Dennis M.J. Hernau: *Dopayours is not dopamine: genetic, environmental and pathological variations in dopaminergic stress processing*. Supervisor: Prof.dr. I. Myin-Germeys; Co-Supervisors: Prof.dr. F.M. Mottaghy / Dr. D. Collip.

Ingrid M.H. Brands: *The adaptation process after acquired brain injury Pieces of the puzzle*. Supervisors: Prof.dr. C.M. van Heugten / Prof.dr. D.T. Wade, Oxford UK; Co-Supervisors: Dr. S.Z. Stapert / Dr. S. Köhler.

Francesco Risso: *Urinary and salivary S100B monitoring in high risk infants*. Supervisor: Prof.dr. J.S.H. Vles; Co-Supervisors: Dr. D. Gazzolo, Genoa,Italy / Dr. A.W.D. Gavilanes.

Alessandro Borghesi: *Stem and Progenitor Cells in Preterm Infants: Role in the Pathogenesis and Potential for Therapy*. Supervisor: Prof.dr. L. Zimmermann; Prof.dr. B. Kramer; Co-Supervisors: Dr. D. Gazzolo, Genoa,Italy / Dr. A.W.D. Gavilanes.

Claudia Menne-Lothmann: *Affect dynamics; A focus on genes, stress, and an opportunity for change*. Supervisor: Prof.dr. J. van Os; Co-Supervisors: Dr. M. Wichers / Dr. N. Jacobs.

Martine van Nierop: *Surviving childhood new perspectives on the link between childhood trauma and psychosis*. Supervisors: Prof.dr. I. Myin-Germeys / Prof.dr. J. van Os; Co-Supervisor: Dr. R. van Winkel.

Sylvia Klinkenberg: *VNS in children; more than just seizure reduction*. Supervisors: Prof.dr. J. Vles /

Prof.dr. A. Aldenkamp; Co-Supervisor: Dr. H. Majoie.

Anouk Linssen: *Considerations in designing an adult hearing screening programme*. Supervisor: Prof.dr. B. Kremer; Co-Supervisors: Dr. L. Anteunis / Dr. M. Joore.

Janny Hof: *Hearing loss in young children; challenges in assessment and intervention*. Supervisors: Prof.dr. B. Kremer / Prof.dr. R. Stokroos / Prof.dr. P. van Dijk, RUG; Co-Supervisor: Dr. L. Antheunis.

Kimberly Cox-Limpens: *Mechanisms of endogenous brain protection; Clues from the transcriptome*. Supervisors: Prof.dr. J. Vles / Prof.dr. L. Zimmermann; Co-Supervisor: Dr. A. Gavilanes.

Els Vanhoutte: *Peripheral Neuropathy outcome measures; Standardisation (PeriNomS) study part 2: Getting consensus*. Supervisors: Prof.dr. C. Faber / Prof.dr. P. van Doorn; Co-Supervisor: Dr. I. Merkies, Spaarne ziekenhuis Hoofddorp.

Mayienne Bakkers: *Small fibers, big troubles; diagnosis and implications of small fiber neuropathy*. Supervisors: Prof.dr. C. Faber / Prof.dr. M. de Baets; Co-Supervisor: Dr. I. Merkies, Spaarne ziekenhuis Hoofddorp.

Ingrid Kramer: *Zooming into the micro-level of experience: An approach for understanding and treating psychopathology*. Supervisor: Prof.dr. J. van Os; Co-Supervisors: Dr. M. Wichers, UMC Groningen / Dr. C. Simons.

Esther Bouman: *Risks and Benefits of Regional Anesthesia in the Perioperative Setting*. Supervisors: Prof.dr. M. van Kleef / Prof.dr. M. Marcus, HMC, Qatar / Prof.dr. E. Joosten; Co-Supervisor: Dr. H. Gramke.

Mark Janssen: *Selective stimulation of the subthalamic nucleus in Parkinson's disease; dream or near future*. Supervisors: Prof.dr. Y. Temel / Prof.dr. V. Visser-Vandewalle, Keulen / Prof.dr. A. Benazzouz, Bordeax, France.

Reina de Kinderen: *Health Technology Assessment in Epilepsy; economic evaluations and preference studies*. Supervisors: Prof.dr. S. Evers / Prof.dr. A. Aldenkamp; Co-Supervisor: Dr. H. Majoie / Dr. D. Postulart, GGZ O-Brabant.

Saskia Ebus: *Interictal epileptiform activity as a marker for clinical outcome*. Supervisors: Prof.dr. A. Aldenkamp / Prof.dr. J. Arends, TUE / Prof.dr. P. Boon, Universiteit Gent, België.

Inge Knuts: *Experimental and clinical studies into determinants of panic severity*. Supervisor: Prof.dr. I. Myin-Germeys; Co-Supervisor: Dr. K. Schruers; Influencing panic.

Nienke Tielemans: *Proactive coping post stroke: The Restored4Stroke Self-Management study*. Supervisors: Prof.dr. C. van Heugten / Prof.dr. J. Visser-Meily, UMC Utrecht; Co-Supervisor: Dr. V. Schepers, UMC Utrecht.

Tom van Zundert: *Improvements Towards Safer Extraglottic Airway Devices*. Supervisors: Prof.dr. A.E.M. Marcus / Prof.dr. W. Buhre / Prof.dr. J.R. Brimacombe, Queensland, Australia / Prof.dr. C.A. Hagberg.

Tijmen van Assen: *Anterior Cutaneous Nerve Entrapment Syndrome Epidemiology and surgical management*. Supervisors: Prof.dr. G.L. Beets / Prof.dr. M. van Kleef / Dr. R.M.H. Roumen / Dr. M.R.M. Scheltinga, MMC Veldhoven.

Rohit Shetty: *Understanding the Clinical, Immunological and Genetic Molecular Mechanisms of Keratoconus*. Supervisors: Prof.dr. R.M.M.A. Nuijts / Prof.dr. C.A.B. Webers.

Christine van der Leeuw: *Blood, bones and brains; peripheral biological endophenotypes and their structural cerebral correlates in psychotic disorder*. Supervisor: Prof.dr. J. van Os; Co-supervisor: Dr. M. Marcelis.

Sanne Peeters: *The Idle Mind Never Rests; functional brain connectivity across the psychosis continuum*. Supervisor: Prof.dr. J. van Os; Co-supervisor: dr. M. Marcelis.

Nick van Goethem: *α7 nicotinic acetylcholine receptors and memory processes: mechanistic and behavioral studies*. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisor: Dr. J. Prickaerts.

Nicole Leibold: *A Breath of fear; a translational approach into the mechanisms of panic*. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. K.R.J. Schruers / Dr. D.L.A. van den Hove.

Renske Hamel: *The course of mild cognitive impairment and the role of comorbidity*. Supervisor: Prof.dr. F.R.J. Verhey; Co-supervisors: Dr. I.H.G.B. Ramakers / Dr. P.J. Visser.

Lucia Speth: *Effects of botulinum toxin A injections and bimanual task-oriented therapy on hand functions and bimanual activities in unilateral Cerebral Palsy*. Supervisors: Prof.dr. J. Vles; Prof.dr. R. Smeets; Co-supervisor: Dr. Y. Janssen-Potten, Adelante Hoensbroek.

Yuan Tian: *The effects of Lutein on the inflammatory pathways in age-related macular degeneration (AMD)*. Supervisors: Prof.dr. C. Webers; Prof.dr. A. Kijlstra, WUR; Co-supervisor: Dr. M. Spreeuwenberg; Dr. H. Tange.

Peggy Spauwen: *Cognition and Type 2 diabetes; the interplay of risk factors*. Supervisors: Prof.dr. F. Verhey; Prof.dr. C. Stehouwer; Co-supervisor: Dr. M. van Boxtel

Marc Hilhorst: *Crescentic glomerulonephritis in ANCA associated vasculitis*. Supervisors: Prof.dr. J. Cohen-Tervaert; Co-supervisor: Dr. P. van Paassen

Martin Gevonden: *The odd one out: exploring the nature of the association between minority status and psychosis*. Supervisors: Prof.dr. J-P. Selten; Prof.dr. J. Booij, Uva; Prof.dr. I. Myin-Germeys

Bart Biallosterski: *Structural and functional aspects of sensory-motor Interaction in the urinary bladder*. Supervisors: Prof.dr. Ph. Van Kerrebroeck; Prof.dr. S. De Wachter, UvAntwerpen; Co-supervisors: Dr. G. van Koeveringe; Dr. M. Rahnama'i.

Alexandra König: *The use of information and communication technologies (ICT) for the assessment of patients with Alzheimer's Disease and related disorders*. Supervisors: prof.dr. F. Verhey; prof.dr. Ph. Robert, Nice, Fr; Co-supervisors: dr. P. Aalten; dr. R. David, Nice. Fr.

Michelene Chenault*: Assessing Readiness for Hearing Rehabilitation*. Supervisors: prof.dr. M.P.F. Berger; prof.dr. B. Kremer; Co-supervisor: dr. L.J.C. Anteunis.

Anand Vinekar: *Retinopathy of Prematurity. Recent advances in tele-medicine screening, risk factors and spectral domain optical coherence tomography imaging*. Supervisor: prof.dr. C.A.B. Webers; Co-supervisor: dr. N.J. Bauer

Fleur van Dooren: *Diabetes and Depression: exploring the Interface between Pathophysiological and Psychological factors*. Supervisors: prof.dr. F.R.J. Verhey; prof.dr. J.K.L. Denollet, UvT; prof.dr. F. Pouwer, UvT; Co-supervisor: dr. M.T. Schram.

Gabriëlla Pons van Dijk: *Taekwondo and physical fitness components in middle-aged healthy volunteers; the Sekwondo study*. Supervisors: prof.dr. J. Lodder; prof.dr. H. Kingma; Co-supervisor: dr. A.F. Lenssen.

Yara Pujol López: *Development and psychoneuroimmunological mechanisms in depression*. Supervisor: prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. G. Kenis; Dr. D. van den Hove; Dr. Aye Mu Myint, München.

Romina Gentier: *UBB^{+1}; an important switch in the onset of Alzheimer's disease*. Supervisors: Prof. H. Steinbusch; Prof. D. Hopkins; Co-supervisor: Dr. F. van Leeuwen.

Sanne Smeets: *Insights into insight: studies on awareness of deficits after acquired brain injury*. Supervisor: Prof. C. van Heugten; Prof. R. Ponds; Co-supervisor: Dr. I. Winkens

Kim Beerhorst: *Bone disease in chronic epilepsy: fit for a fracture*. Supervisor: Prof. A. Aldenkamp; Prof. R. van Oostenbrugge; Co-supervisor: Dr. P. Verschuure.

Alex Zwanenburg: *Cerebral and cardiac signal monitoring in fetal sheep with hypoxic-ischemic encephalopathy*. Supervisor: Prof. T. Delhaas; Prof. B. Kramer; Co-supervisors: Dr. T. Wolfs; Dr. P. Andriessen, MMC.

Ismail Sinan Guloksuz: *Biological mechanisms of environmental stressors in psychiatry*. Supervisor: Prof. J. van Os; Co-supervisors: Dr. B. Rutten; Dr. M. Drukker.

Seyed Ehsan Pishva MD: *Environmental Epigenetics in mental health and illness*. Supervisor: Prof.dr. J. van Os; Co-supervisors: Dr. B.P.F. Rutten; Dr. G. Kenis.

Ankie Hamaekers: *Rescue ventilation using expiratory ventilation assistance; innovating while clutching at straws*. Supervisors: Prof.dr. W.F. Buhre; Prof.dr. M. van Kleef.

Rens Evers. *22q11.2 deletion syndrome: intelligence, psychopathology and neurochemistry at adult age*. Supervisors: Prof.dr. L.M.G. Curfs; Prof.dr. T. v. Amelsvoort.

Sarah-Anna Hescham. *Novel insights towards memory restoration*. Supervisor: Prof.dr. Y. Temel; Co-supervisor: Dr. A. Blokland; Dr. A. Jahanshahi.

João P. da Costa Alvares Viegas Nunes. *Insulin receptor sensitization improves affective pathology in various mouse models*. Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. K-P. Lesch; Dr. T. Strekalova; Dr.B.H. Cline, Oxford.

Yanny Ying-Yee Cheng. *Clinical Outcomes After Innovative Lamellar Corneal Transplantation Surgery*. Supervisor: Prof.dr. R.M.M.A. Nuijts; Co-supervisor: Dr. J.S.A.G. Schouten.

2016

Oliver Gerlach. *Parkinson's disease, deterioration during hospitalization*. Supervisor: Prof.dr. R. van Oostenbrugge; Co-supervisor: Dr. W. Weber.

Remo Arts. *Intracochlear electrical stimulation to suppress tinnitus*. Supervisor: Prof.dr. R.J. Stokroos; Co-supervisor: Dr. E.L.J. Georg.

Mitchel van Eeden. *The €- Restore4stroke study: Economic evaluation of stroke care in the Netherlands*. Supervisors: Prof.dr.mr. S.M.A.A. Evers; Prof.dr. C.M. v. Heugten; Co-supervisor: dr. G.A.P. van Mastrigt.

Pim Klarenbeek. *Blood pressure and cerebral small vessel disease*. Supervisor: Prof.dr. R.J. van Oostenbrugge; Co-supervisor: Dr. J. Staals.

Ramona Hohnen. *Peripheral pharmacological targets to modify bladder contractility*. Supervisor: Prof.dr. Ph.E.V. van Kerrebroeck; Co-supervisors: Dr. G.A. van Koeveringe; Dr. M.A. Sahnama'i; Dr. C. Meriaux.

Ersoy Kocabicak. *Deep brain stimulation of the subthalamic nucleus: Clinical and scientific aspects*. Supervisors: Prof.dr. Y. Temel; Prof.dr. K. van Overbeeke; Co-supervisor: Dr. A. Jahanshahi.

Sven Akkerman. *Temporal aspects of cyclic messenger signaling in object recognition memory; a pharmalogical approach*. Supervisor: Prof.dr.

H.W.M. Steinbusch; Co-supervisors: dr. J. Prickaerts; dr. A. Blokland.

Anja Moonen. *Emotion and Cognition in Parkinson's disease; etiology and neurobiological mechanisms*. Supervisor: Prof.dr. F.R.J. Verhey; Co-supervisor: dr. A.F.G. Leentjens.

Anna Schüth. *Three-dimensional bladder tissue morphology*. Supervisors: Prof.dr. G.A. van Koeveringe; Prof.dr. M. v. Zandvoort, Aachen; Prof.dr. Ph. V. Kerrebroeck.

Elisabeth van der Ven. *Ethnic minority position as risk indicator for autism-Spectrum and psychotic disorders*. Supervisors: Prof.dr. J.P. Selten; Prof.dr. J. van Os.

Zuzana Kasanova. *Environmental reactivity for better or worse; The impact of stress and reward on neurochemistry, affect and behavior across the psychosis continuum*. Supervisor: Prof.dr. I. Myin-Germeys, KU Leuven/UM; Co-supervisor: dr. D. Collip.

Danielle Lambrechts. *Ketogenic diet therapies; treatment for children and adults with refractory epilepsy*. Supervisors: Prof.dr. H.J.M. Majoie; Prof.dr. J.S.H. Vles; Prof.dr. A.P. Aldenkamp; Co-supervisor: dr. A.J.A. de Louw, Kempenhaghe, Heeze.

Frank van Bussel. *Advanced MRI in diabetes; cerebral biomarkers of cognitive decrements*. Supervisors: Prof.dr.ir. W.H. Backes; Prof.dr. P.A.M. Hofman; Co-supervisor: dr. J.F.A. Jansen.
Lisa Schönfeldt. *Neurostimulation to treat brain injury?* Supervisors: Prof.dr. Y. Temel; Prof.dr. S. Hendrikx, Hasselt; Co-supervisor: dr. A. Jahanshahi.

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Nele Claes. *B cells as multifactorial players in multiple sclerosis pathogenesis: insights from therapeutics*. Supervisors: Prof.dr. V. Somers, Hasselt; Prof.dr. R. Hupperts; Co-supervisors: Prof.dr. P. Stinissen, dr. J. Fraussen, Hasselt.

Olaf Schijns. *Epilepsy surgery and biomarkers from history to molecular imaging*. Supervisors: Prof.dr. J.J. van Overbeeke; Prof.dr. H. Clustermann, Aachen; Co-supervisors: dr. G. Hoogland; dr. M.J.P. v. Kroonenburgh.

Lizzy Boots. *Balanced and Prepared; development and evaluation of a supportive e-health intervention for caregivers of people with early-stage dementia*. Supervisors: Prof.dr. F.R.J. Verhey; Prof.dr. G.I.J.M. Kempen; Co-supervisor: dr. M.E. de Vugt.

Wouter Donders. *Towards patient-specific (cerebro-) vascular model applications*. Supervisors: Prof.dr. T. Delhaas; Prof.dr.ir. F.N. van de Vosse, TUE; Co-supervisor: dr.ir. W. Huberts.

Sizzle Vanterpool. *The implications of intrauterine invasion by microbes for placental Pathology and the occurrence of adverse pregnancy outcomes*. Supervisor: Prof.dr. B.W. Kramer. Co-supervisors: dr. J.V. Been, Erasmus MC Rotterdam, dr. U von Rango.

Manuela Heins. *The Relationship between Social Adversity, Psychosis, and Depression across an Individual's Life Span*. Supervisor: Prof.dr. I. Myin-Germeys.

Christianus van Ganzewinkel. *NEONATAL PAIN; Out of Sight, Out of Mind?* Supervisor: Prof.dr. B.W.W. Kramer; Co-supervisor: dr. P. Andriessen, MMC Veldhoven.

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Jo Stevens. *Advanced diagnostics and therapeutics for Alzheimer's disease*. Supervisor: Prof.dr. M. de Baets; Co-supervisors: dr. M. Losen, dr. P. Martinez-Martinez.

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M.C. Haanschoten. *Towards efficient cardiac surgery – the integrating role of anesthesiology and intensive care*. Supervisors: Prof. dr. W. Buhre; Prof. dr. A. van Zundert (Queensland); Co-supervisors: Dr. M.A. Soliman Hamad; Dr. A. van Straten (Catharina zkhs.)

Harmen Jan van de Haar. *Microvascular and blood-brain barrier dysfunction in Alzheimer's disease*. Supervisor: Prof.dr.ir. W. Backes; Prof.dr. F. Verhey; Co-supervisor: Dr. J. Jansen; Dr.ir. M. v. Osch, LUMC.

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Supervisor: Prof.dr. H.W.M. Steinbusch; Co-supervisors: Dr. R.M. Weffort de Oliveira, Brazil; Dr. J. Prickaerts

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Claudia Vingerhoets. *Investigating neurobiological mechanisms underlying comorbid cognitive symptoms in psychosis and substance use*. Supervisors: Prof.dr. T. van Amelsvoort; Prof.dr. J. Booij, UvA; Co-supervisor: Dr. O. Bloemen

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Marion Levy. *Evaluation of BDNF/TrkB signaling as a common target in the treatment of major depression and Alzheimer's disease*. Supervisors: Prof.dr. H.Steinbusch; Prof. L. Lanfumey, Université Paris Descartes, France. Co-supervisors: Dr. G. Kenis; Dr. D. van den Hove.

Patrick Domen. *Stay connected: a family-based diffusion imaging study in psychotic disorder*. Supervisor: Prof.dr. J. van Os. Co-supervisor: Dr. M. Marcelis

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Laura Serpero. *Next Generaton Biomarkers in Perinatal Medicine: S100B Protein*. Supervisors: Prof.dr. D. Gazzalo, Alessandria, Italy; Prof.dr. B..W.W. Kramer. Co-supervisor: Dr. A.W.D. Gavilanes.

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Désirée M.J. Vrijens. *Dysfunctions of the Lower Urinary Tract and Affective Symptoms*. Supervisors: Prof.dr. Ph.E.V. van Kerrebroeck; Prof.dr. G.A. van Koeveringe. Co-supervisors: Dr. C. Leue.

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Maarten van Beek. *Spinal Cord Stimulation in Clinical and Experimental Painful Diabetic*

Polyneuropathy. Supervisors: Prof.dr. E.A. Joosten; Prof.dr. M. van Kleef. Co-supervisor: Dr. S.M.J. van Kuijk.

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Steven T.H. Honings. *Exploring psychosis and multidirectional violence: a prospective study in the general population*. Supervisor: Prof.dr. J. van Os. Co-supervisor: Dr. M. Drukker

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Mark B.N. van Winkel. *Lonely at heart and stressed in company of Others; the influence of daily life social experiences and emotions on depression*. Supervisors: prof.dr. F. Peeters; prof.dr. I. Myin-Germeys, KU Leuven/UM; prof.dr. M. Wichers, UMC Groningen

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Ganne Chaitanya. *Epilepsy: A network disorder*. Supervisors: prof.dr. A.P. Aldenkamp; prof. P. Satishchandra, NIMHANS, Bangalore, India. Co-supervisors: Dr. J.F.A. Jansen; Dr. S. Zinger, TUE

Sumitha Rajendrarao. *New Insight into the Multifaceted Pathogenic Mechanisms of Sporadic Amyotrophic Lateral Sclerosis*. Supervisors: prof.dr. B.W. Kamer; prof.dr. H.W. Steinbusch. Co-supervisor: prof. T.R. Raju, NIMHANS, Bangalore, India

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Petronella de Meij. *Quality indicators for the assessment of pain clinic care: A step forward? Quality from professionals and pain patients' perspective (QiPPP)*. Supervisors: Prof.dr. G.D.E.M. van der Weijden, Prof.dr. M. v. Kleef. Co-supervisor: Dr. A.J.A. Köke.

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Loes Leenen. *Self-management in Epilepsy; The Goal is: "Live with a Z(s)mile*. Supervisors: Prof.dr. H.J.M. Majoie; Prof.dr.mr. S.M.A.A. Evers; Prof.dr. C.M. van Heugten.

Chiara Peila. '*Effects of Pasteurization and Refrigerated Storage on Human Milk Neurobiomarkers Concentrations*. Supervisors: Prof.dr. D. Gazzallo, Alessandria, It./MUMC+; Prof.dr. G. Visser, UU; Prof.dr. E. Bertino, Alessandria, It.

Raymond van de Berg. *The Vestibular Implant: Feasibility in humans*. Supervisor: Prof.dr. H. Kingma; Co-supervisor: dr. J.-P. Guyot, Université de Genève, CH.

Nils Guinand. *The Vestibular Implant: a more stable horizon for patients with a bilateral vestibular deficit?* Supervisors: prof.dr. H. Kingma; Prof.dr. J.-P. Guyot, Université de Genève, CH.

Jasper Smit. *Exploring deep brain stimulation as a treatment for tinnitus*. Supervisors: Prof.dr. R.J. Stokroos; Prof.dr. Y. Temel; Co-supervisor: dr. Jahanshahianvar.

Bindu Paravil Sankaran. *Brain MRI in Mitochondrial Disorders: Correlating the Phenotype with Genotype*. Supervisor: Prof.dr. H. Smeets; Prof.dr. A. Taly, NIMHANS, Bangalore, India.

Syenna Schievink. *Vascular cognitive impairment; at the heart of the matter*. Supervisor: Prof.dr. F.R.J. Verhey; Prof.dr. R.J. van Oostenbrugge; Co-supervisor: dr. S. Köhler.

Isabelle Bos. *Biomarkers of Alzheimer's disease; relations with vascular factors and cognition in the pre-dementia stages*. Supervisor: Dr. P.J. Visser; Prof.dr. F.R.J. Verhey; Co-supervisor: dr. S.J.B. Vos.

Stijn Michielse. *Road work ahead; cerebral pathways mediating Psychological mechanisms underlying the psychosis spectrum*. Supervisor: Prof.dr. J.J. van Os; Co-supervisor: dr. M.C. Marcelis.

Georgios Schoretsanitis. *Risperidone-based therapeutic regimens; Drug interactions and adverse drug reactions*. Supervisor: prof.dr. K.R.J. Schruers; Co-supervisor: dr. M. Bak .

Alieske Dam. *INLIFE; An innovative online social support intervention for caregivers of persons with dementia*. Supervisor: Prof.dr. M.E. de Vugt; Prof.dr. F.R.J. Verhey; Co-supervisor: Dr. M.P.J. van Boxtel.

Roel Haeren. *Vascular ventures; Analysis of vascular structures and function in epilepsy*. Supervisor: Prof.dr. Y Temel; Co-supervisor: dr. K. Rijkers; Dr. G. Hoogland.

Chiara Fabbri. *Pharmacogenomics of antidepressant drugs: perspectives for the personalization of treatment in depression*. Supervisors: Prof.dr. K. Schruers; Prof.dr. A. Serretti, Bologna.

Esther van Duin. *Dancing in the (B)rain'; neurobiology of reward, stress & Information processing in 22q11.2 deletion syndrome*. Supervisors: Prof.dr. T. van Amelsvoort; Prof.dr. J. Booij, UvA. Co-supervisor: dr. D. Hernaus.

Rob Verdonschot. *Oropharyngeal dysphagia and its psychiatric Comorbidities; The prevalence of affective symptoms and the unmet clinical need for integrated care in medically unexplained symptoms*. Supervisor: Prof.dr. B. Kremer; Co-supervisors; Dr. L. Baijens; dr. S. Vanbelle.

Lisanne Breuer. *Accelerated Cognitive Ageing in Epilepsy' Does it Exists?* Supervisors: Prof.dr. A. Aldenkamp; Prof.dr. P. Boon, UZ Gent; Co-supervisors: dr. A. de Louw, Kempenhaeghe, Heeze; dr.ir. S. Zinger, TUE.

Liselot Kerpershoek. *Access to formal dementia care; A European perspective*. Supervisors: Prof.dr. F. Verhey; Prof.dr. M. de Vugt; Prof. B. Woods, Bangor University, UK; Co-supervisor: Dr. C. Wolfs.

Henrietta Steinhart. *Same Same but Different; Psychological Interventions and how to Mind the Knowledge Practice Gap*. Supervisor: Prof.dr. I. Myin-Germeys. Co-supervisor: Dr. U. Reininghaus.
Ulrich Mehnert. *The management of urine storage dysfunction in the neurological patient*. Supervisors: Prof.dr. G. van Koeveringe; Prof.dr. Ph.van Kerrebroeck; Prof.dr. S. Wachter, Antwerpen; Prof.dr E. Chartier-Kastler, Sorbonne, Paris.

Giovanne B. Diniz. *Weaning-induced alterations on neuropeptidergic populations of the rat hypothalamus*. Supervisors: Prof.dr. H. Steinbusch; Prof.dr. J. Bittencourt, ICB/USP, Brasil.

Rajani Ravindra Battu. *Inherited Retinal Diseases: New Imaging and Molecular Genetics*. Supervisor: Prof.dr. C.A.B. Webers. Co-supervisors:Dr. J.S.A.G. Schouten, CWZ; dr. T.T.J.M. Berendschot

Jans van Ool. *Diagnostic and neuropsychiatric considerations in epilepsy and intellectual disability; Psychological perspectives*. Supervisor: Prof.dr. A. Aldenkamp. Co-supervisors: Dr. J. Hendriksen; Dr. H. Schelhaas, Kempenhaeghe.

Eveline Janssen. *Depression in the elderly: focus on high risk groups*. Supervisors: Prof.dr. F. Verhey; Prof.dr. M. de Vugt. Co-supervisor: Dr. M. Schram.

Cécile Kicken. *Extreme blood coagulation; investigating the influence of physiological extremes on thrombin generation and platelet activation*. Supervisor: Prof.dr. W. Buhre; Co-supervisors; Dr. B. de Laat; Dr. M. Lancé, Qatar.
Martinus van Eerd. *Diagnosis and Interventional Pain Treatment of Cervical Facet Joint Pain*. Supervisor: Prof.dr. M. van Kleef. Co-supervisor; Dr. J. Patijn, Eindhoven; Dr. M. Sommer.

Chenxing E. Zhang. *Novel insights in the pathophysiology of cerebralsmall vessel disease – a study using advanced imaging techniques*. Supervisors: Prof.dr. R.J. van Oostenbrugge; Prof.dr.ir. W.H. Backes; Co-supervisor: dr. J. Staals.

Ivo Eijkenboom. *A zebrafish model of small-fiber neuropathy*. Supervisors: Prof.dr. H.J.M. Smeets; Prof.dr. C.G. Faber; Co-supervisor: dr. J. Vanoevelen.

Bianca de Greef. *Small fiber neuropathy: from underlying conditions to treatment*. Supervisor: Prof.dr. C.A. Faber; Co-supervisor: Dr. I.S.J. Merkies; Dr. J.G.J. Hoeijmakers.

Lotte Berk. *MINDFULNESS AND AGING: Exploring Mechanisms and Interventions*. Supervisors: Prof.dr. J. van Os; Prof.dr. M.W. de Vugt; Co-supervisor: dr. M.P.J. van Boxtel.

Mor Dickman. *Practice patterns and outcomes of corneal transplantation*. Supervisor: Prof.dr. R.M.M.A. Nuijts; Co-supervisors: Dr. T.J.M. Berendschot; dr. F.J.H.M. van den Biggelaar.

Thyagi Ponnamperuma. *Mental Health Problems in Sri Lankan Adolescents Exposed to the Tsunami and Other Traumatic Events*. Supervisor: Prof.dr. M.W. De Vries; Co-supervisor: Dr. N.A. Nicolson.

Robbert C. Maatman. *Anterior cutaneous nerve entrapment syndrome (acnes): an analysis of various subtypes and alternative treatment modalities*. Supervisor: Prof.dr. M. van Kleef; Co-supervisors: Dr. R.M.H. Roumen, dr. M.R.M. Scheltinga.

Mari Elshout. *Neovascular Age-Related Macular Degeneration in the Era of Value-Based Health Care*. Supervisor: Prof.dr. C.A.B. Webers; Co-supervisor: Dr. J.S.A.G. Schouten.

Jeroen Deenik. *Thinking inside the box; Changing lifestyle to improve the health status of inpatients with severe mental illness*. Supervisor: Prof.dr. P.N. Harten; Co-supervisors: Dr. D.E. Tenback; dr. I.J.M. Hendriksen.

Thomas Draak. *Peripheral Neuropathy outcome measures Standardisation (PeriNomS) study part 3: Capturing the Patient's Voice*. Supervisor: Prof.dr. C.G. Faber; Co-supervisor: Dr. I.S.J. Merkies.

Ana Luisa Gil Martínez. *Neuroprotection in neurodegenerative processes associated with Parkinsonism and aging. Correlation between dopaminergic neuronal death and glial activation*. Supervisor: Prof.dr. H.W.M. Steinbusch, Prof.dr. Maria-Trinidad Herrero Ezquerro, University of Murcia.

Bernice J.A. Gulpers. *Anxiety in older adults; Correlates, comorbidities and prognosis with lifespan perspectives*. Supervisor: Prof.dr. F.R.J. Verhey, Prof.dr. R.C. Oude Voshaar; Co-supervisor: Dr. S. Köhler.

Elke Devocht. *Combining a cochlear implant and a hearing aid in opposite ears: The best of both worlds*. Supervisor: prof.dr. H. Kingma; co-supervisor: dr. E.I.J. George.

Gillian Townend. *Rett Syndrome: Recognising the Communication Challenges, Needs and Potential of Individuals Living with a Rare Disease*. Supervisor: Prof.dr. L.M.G. Curfs; co- supervisor: Dr. P.B. Marschik, Med. University of Graz, Austria.

Takashi Koizumi. *Genetic and neuroinflammatory components of familial and sporadic cerebral Small Vessel Disease*. Supervisor: Prof.dr. H. Steinbusch,Prof.dr. T. Mizuno,Japan; co-supervisor: Dr. S. Foulquier

Muhammad Ali. *Integrative network-based approaches for modelling Human disease*. Supervisor: Prof.dr. J. Kleinjans; co-supervisor: Dr. D. van den Hove; Dr. E. Pishva.

Guillaume Durand. *The adaptive side of psychopathy. Investigating adaptive characteristics associated with the psychopathic personality*. Supervisor: Prof.dr. B. Rutten; co-supervisor: Dr J. Lobbestael.

Darius C. Henatsch. Honey: *A Novel Treatment in Chronic Ear Infections*. Supervisor: Prof.dr. R.J. Stokroos; UMC Utrecht/UM; co-supervisor: Dr. J.J. Briedé.

Reinhilde J. Melles. *Vaginal penetration: pain or pleasure? The role of fear and sexual arousal*. Supervisor: Prof.dr. M.L. Peters; co-supervisor: Dr. M. ter Kuile, LUMC, Dr. M. Dewitte.

Raul Felipe Abella Antón. *Cardiac Surgery Biochemical Monitoring in Congenital Heart Diseases Infants*. Supervisors: Prof. dr. D. Gazzolo, Prof. dr. L.J.I. Zimmermann, Prof. dr. J.S.H. Vles, co-supervisor; Dr. A.W.D. Ga

LIST OF PUBLICATIONS

Banning, L. C. P., Janssen, E.P.C.J., Hamel, R.E.G., de Vugt, M., Köhler, S., Wolfs, C.A.G., Oosterveld, S.M., Melis, R.J.F., Olde Rikkert, M.G.M., Kessels, R.P.C., Pijnenburg, Y.A.L., Koene, K., van der Flier, W.M., Scheltens, P., Visser, P.J., Verhey, F.R.J., Aalten, P. & Ramakers, I.H.G.B. (2019). Determinants of cross-sectional and longitudinal quality of life in memory clinic visitors without dementia. Journal of Geriatric Psychiatry and Neurology. 23:1-9. 10.1177/0891988719882104

Banning, L. C. P., Ramakers, I. H. G. B., Deckers, K., Verhey, F. R. J. & Aalten, P. (2019). Affective symptoms and AT(N) biomarkers in mild cognitive impairment and Alzheimer's disease: A systematic literature review. Neuroscience & Biobehavioral Reviews. 107:346:359. 10.1016/j.neubiorev.2019.09.014

In de Braek, D., Deckers, K., Kleinhesselink, T., **Banning, L**., & Ponds, R. (2019). Working Memory Training in Professional Football Players: A Small-Scale Descriptive Feasibility Study—The Importance of Personality, Psychological Well-Being, and Motivational Factors. Sports, 7(4), 89. 10.3390/sports7040089

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CURRICULUM VITAE

Leonie Christina Petra Banning werd geboren op 8 november 1992, te Overasselt. In 2011 behaalde zij haar vwo-diploma aan het Maaswaal College te Wijchen, waarna zij naar Maastricht verhuisde om aldaar aan de studie Psychologie te beginnen. Het opzetten en uitvoeren van een studie in het kader van haar bachelor-thesis, onder begeleiding van prof. dr. H. Merckelbach, wakkerde haar interesse en enthousiasme voor het onderzoek aan. In 2014 startte Leonie de tweejarige onderzoeksmaster Psychopathologie. Geïnteresseerd in psychogeriatrie, voerde zij een keuzevak uit met als onderwerp de *relatie tussen angst in mild cognitieve klachten en conversie naar dementie* en werkte zij als student-assistent mee aan het *Partner in Zicht* project, beide aan de afdeling Psychiatrie en Neuropsychologie, Universiteit Maastricht. Op dezelfde afdeling liep zij stage onder begeleiding van dr. Inez Ramakers, in het tweede jaar van de master. Deze wetenschapsstage werd gecombineerd met een klinische stage aan de geheugenpoli van het Maastricht Universitair Medisch Centrum+ (MUMC+), onder begeleiding van dr. Chantal Geusgens, waarbij ze haar Basis Aantekening Psychodiagnostiek (BAPD) behaalde. In 2016 studeerde Leonie *cum laude* af, en startte zij als promovendus bij het Alzheimer Centrum Limburg. Onder supervisie van prof. dr. Frans Verhey, dr. Pauline Aalten, en dr. Inez Ramakers onderzocht zij de relatie tussen biomarkers van de ziekte van Alzheimer en neuropsychiatrische symptomen. Als onderdeel van haar PhD was Leonie betrokken als psycholoog bij patiënt onderzoek op de geheugenpoli en vervulde zij diverse onderwijstaken. Tevens heeft zij 2.5 maand gewerkt aan de Johns Hopkins Medical University in Baltimore, waar zij onder supervisie van dr. Jeannie-Marie Leoutsakos ervaring opdeed met *growth mixture modeling*. Leonie werkt momenteel als postdoctoral onderzoeker aan de afdeling Psychiatrie en Neuropsychologie aan de Universiteit Maastricht.