



OPEN ACCESS

Original research

Neuropsychiatric symptoms in cognitive decline and Alzheimer's disease: biomarker discovery using plasma proteomics

Miriam Rabl ,¹ Christopher Clark ,¹ Loïc Dayon ,^{2,3} Julius Popp ,^{1,4} For the Alzheimer's Disease Neuroimaging Initiative

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/jnnp-2024-333819>).

¹Department of Psychiatry, Psychotherapy and Psychosomatics, University of Zurich, Psychiatric University Hospital, Zurich, Switzerland

²Nestlé Institute of Food Safety & Analytical Sciences, Nestlé Research, Lausanne, Switzerland

³Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland

⁴Old-Age Psychiatry Service, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland

Correspondence to

Dr. Julius Popp; julius.popp@uzh.ch

Received 13 March 2024

Accepted 7 August 2024

Published Online First 17

September 2024

ABSTRACT

Background and objectives Neuropsychiatric symptoms (NPS) are common in older people with cognitive impairment and Alzheimer's disease (AD). No biomarkers to detect the related pathology or predict the clinical evolution of NPS are available yet. This study aimed to identify plasma proteins that may serve as biomarkers for NPS and NPS-related clinical disease progression.

Methods A panel of 190 plasma proteins was quantified using Luminex xMAP in the Alzheimer's Disease Neuroimaging Initiative cohort. NPS and cognitive performance were assessed at baseline and after 1 and 2 years. Logistic regression, receiver operating characteristic analysis and cross-validation were used to address the relations of interest.

Results A total of 507 participants with mild cognitive impairment (n=396) or mild AD dementia (n=111) were considered. Selected plasma proteins improved the prediction of NPS (area under the curve (AUC) from 0.61 to 0.76, $p<0.001$) and future NPS (AUC from 0.63 to 0.80, $p<0.001$) when added to a reference model. Distinct protein panels were identified for single symptoms. Among the selected proteins, ANG1, CCL1 and IL3 were associated with NPS at all three time points while CCL1, serum glutamic oxaloacetic transaminase and complement factor H were also associated with cognitive decline. The associations were independent of the presence of cerebral AD pathology as assessed using cerebrospinal fluid biomarkers.

Conclusions Plasma proteins are associated with NPS and improve prediction of future NPS.

INTRODUCTION

Neuropsychiatric symptoms (NPS) are common in older people with cognitive decline and are associated with worse long-term outcomes, including faster cognitive decline and earlier death.^{1,2} NPS include a wide range of symptoms such as depression, anxiety, apathy and agitation and are particularly common in individuals with cognitive impairment, including Alzheimer's disease (AD) dementia with rates up to 97%.^{3,4} Diagnosis of NPS is mostly based on clinical assessments and proxy questionnaires, and little is known about the related molecular and biological pathway alterations. Making an aetiological assignment based on the clinical evaluation of NPS remains difficult. Easily accessible and reliable biomarkers could be

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ No biomarkers to detect neuropsychiatric symptom (NPS) and predict their evolution in patients with cognitive decline are available, yet.

WHAT THIS STUDY ADDS

⇒ This study identified specific protein biomarker panels for overall NPS and for the most common single NPS as well as for the prediction of future NPS, with good predictive performance. The associations were mostly independent from the core Alzheimer's disease pathology suggesting distinct alterations underlying the manifestation of NPS and related clinical progression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Pending further validation, these easily accessible biomarkers could be used in clinical practice to detect pathologies underlying NPS and inform decision-making on NPS treatment and prevention.

helpful for the clinician to understand the aetiology of NPS, and to treat NPS in patients with cognitive decline. Such biomarkers may also help to identify patients at risk for persistence of NPS over time and associated cognitive and functional decline.

Only a few studies have investigated potential biomarkers of NPS, in most cases focusing on a priori selected molecules like markers of inflammation or cortisol.^{4,5} Some studies investigated associations of NPS with biomarkers of the core AD pathology, but most findings were yet inconsistent.^{6,7} For single symptoms such as depression and apathy, interleukin-6,⁸ chemokines,⁸ homocysteine⁹ or vitamin B¹⁰ have been investigated. However, the findings have not been replicated yet and the usefulness of these molecules as biomarkers of NPS remains uncertain.

Recent advances in proteomic approaches have identified blood-based biomarker candidates for different chronic disorders, including AD.^{11,12} However, previous studies very rarely investigated proteome alterations in relation to NPS. Using untargeted proteomics in a single-centre memory clinic cohort we previously identified a



© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

To cite: Rabl M, Clark C, Dayon L, et al. *J Neurol Neurosurg Psychiatry* 2025;**96**:370–382.

Table 1 Characteristics of the study participants grouped by the presence of NPS

	Total n=507	NPS+ n=234	NPS- n=273	P value
Demographic data				
Sex, female (%)	187 (36.9)	83 (35.5)	104 (38.1)	0.580
Age, years	74.3±7.5	74.1±7.3	74.5±7.7	0.546
Education, years	15.5±3.1	15.3±3.0	15.7±3.1	0.090
White race (%)	480 (94.7)	223 (95.3)	257 (94.1)	0.353
Clinical data				
NPI-Q	2.2±2.9	4.4±2.9	0.3±0.5	<0.001
CDR	0.6±0.2	0.6±0.2	0.5±0.1	<0.001
CDR-SB	2.2±1.5	2.7±1.8	1.7±1.2	<0.001
MMSE	26.3±2.3	26.0±2.5	26.5±2.1	0.007
AD diagnosis	111 (21.9)	73 (31.2)	38 (13.9)	<0.001
Amyloid pathology (%)	240 (79.7)	125 (83.9)	115 (75.6)	0.086
APOEε4 carrier (%)	286 (56.4)	138 (59.0)	148 (54.2)	0.323

Criteria for the NPS positive group (NPS+) were NPI-Q score >1, for the NPS negative group (NPS-) NPI-Q score <2.
AD, Alzheimer's disease; APOEε4, apolipoprotein E epsilon 4; CDR, clinical dementia rating; CDR-SB, CDR sum-of-boxes; MMSE, mini mental status examination; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptom.

panel of 15 plasma proteins associated with current NPS and future NPS.¹³

Herein, using the Alzheimer's Disease Neuroimaging Initiative (ADNI) database,¹⁴ our main objective was to identify further plasma protein biomarker candidates for NPS in subjects with cognitive impairment and to test their performance to predict the persistence of NPS and cognitive decline over time.

METHODS

Study population

We included all participants from the ADNI database (adni.loni.usc.edu) with available plasma proteomic data (V.2013-08-02). Cognitively unimpaired individuals (n=58, 10.3% of the participants, of which n=5 having NPS) were excluded. This resulted in a total number of 508 participants with either amnesic mild cognitive impairment (MCI) or mild AD dementia.^{15,16} Subjects taking concomitant psychotropic medication except for the following were excluded: stable doses of antidepressants lacking significant anticholinergic side effects, oestrogen replacement therapy and Ginkgo biloba. Demographic data, apolipoprotein E epsilon 4 (APOEε4) status and cerebrospinal fluid (CSF) AD biomarkers were available at baseline. Other clinical data (Neuropsychiatric Inventory Questionnaire (NPI-Q),¹⁷ Clinical Dementia Rating (CDR), CDR-sum of boxes (CDR-SB)¹⁸) was used corresponding to the time points proteomic analysis was performed for baseline and 1 and 2 years follow-up within a range of ±3 months.

NPSs at baseline and follow-up were assessed using NPI-Q. This is a self-administered questionnaire completed by informants with regular contact with the individual. It includes 12 different symptoms (delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, night-time behavioural disturbances and appetite/eating changes), each rated from 1 to 3 based on their severity, and subsequently all 12 scores were summarised in 1 total score. The presence of NPS was defined as NPI-Q>1 (further details are

shown in online supplemental section 1). Cognitive decline at follow-up was defined as ΔCDR-SB>0.5.¹⁹

Biological assessments

A multiplexed immunoassay panel measuring 190 protein analytes with the Luminex xMAP platform (Luminex, Austin, Texas, USA) was used at Rules-Based Medicine (RBM, Austin, Texas, USA). It contained selected proteins previously reported to be associated with inflammation, metabolic disorders, cardiovascular diseases, cancer and with proteins involved in cell signalling and believed to play a role in AD.²⁰ More details on the methods and the quality control procedures are available from the ADNI website.

CSF samples were available for 301 participants (50.5% in MCI and 90.1% in AD). Concentrations of beta-amyloid 1-42 (Aβ42), total tau (τTau) and tau phosphorylated at threonine-181 (pTau181) were measured using the multiplex xMAP Luminex platform with immunoassay kit-based reagents of Innogenetics (INNO-BIA AlzBio 3; Ghent, Belgium).²¹ Each participant was classified according to both the presence of amyloid pathology and the ATN classification system.²² Three ATN groups were defined as follows: A-/T-/N- were classified as normal, A-/T±/N± as non-AD pathological changes and A+/T±/N± as belonging to the AD continuum. The cut-offs for A, T and N previously derived from the ADNI cohort were Aβ42<192 pg/mL, pTau181>93 pg/mL and τTau>93 pg/mL, respectively.²³

The APOE genotyping was performed using DNA extracted by Cogenics to determine two single nucleotide polymorphisms (rs429358, rs7412) that define the epsilon (ε) 2, 3 and 4 alleles.²⁴ The APOEε4 status was defined based on the presence of one or more ε4 alleles.

Data preparation

One participant with a CDR score of 2 was excluded to include only mild dementia. Therefore, we analysed the data from 507 participants. After quality control, we excluded 44/190 plasma proteins due to too many missing data points (>10%) and 15 analytes with a coefficient of variation >25% to ensure the reliability of the remaining data. Outliers, defined as values ±5 SD from the mean, were adjusted to the value of the nearest non-outlier. Analytes with levels below the least detectable dose (LDD) were imputed as LDD/2. For missing value imputation, we used the mean of the non-missing values for replacement. All variables with a variance inflation factor >5 (n=16) were excluded from further analysis, resulting in a total of 115 proteins (online supplemental table S1). To approach a Gaussian distribution, all proteins were log10 transformed before analysis.

Statistical analysis

For the descriptive statistics and the logistic regression analysis, SPSS (IBM, V.28.0) was used. All other analyses were performed using RStudio V.2022.12.0+353 including the MASS,²⁵ partial receiver operating characteristic (ROC),²⁶ caret²⁷ and glmnet²⁸ packages. Categorical variables were described showing absolute and relative frequencies, and continuous variables the mean and SD. For cohort characteristics, two-tailed t-test and Mann-Whitney-U-test were performed for continuous and Pearson's χ² test for categorical variables. The Shapiro-Wilk test was used to test normality of each variable. Multicollinearity of all variables included in the regression analysis was tested using the variance inflation factor. To verify a possible overfitting of the models, the Hosmer-Lemeshow test for goodness-of-fit was used with

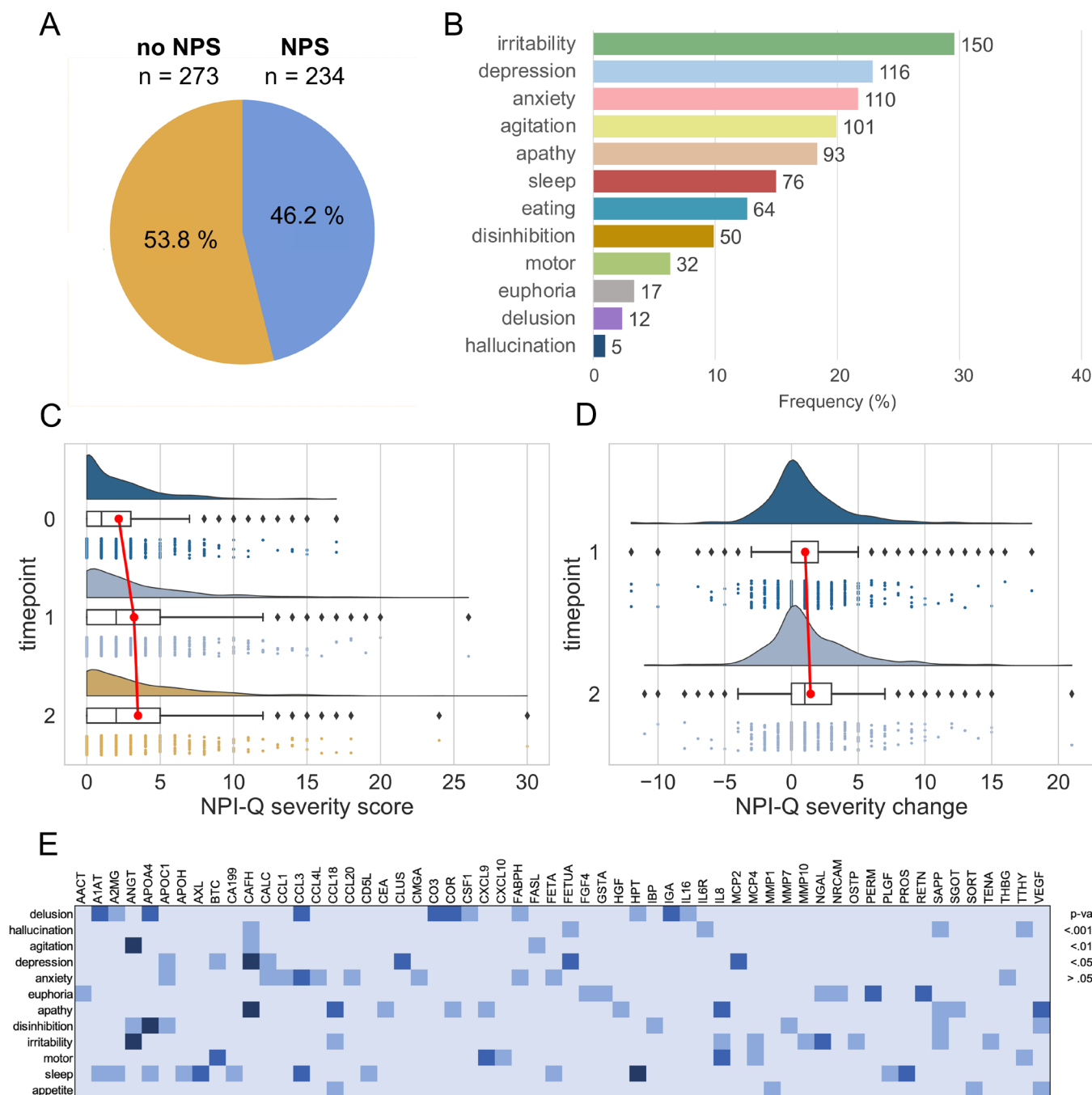


Figure 1 (A) Grouping of the study cohort (n=507) into participants with NPS (NPI-Q>1) and without NPS (NPI-Q<2). (B) Frequency of the single items (symptoms) of the NPI-Q in the whole cohort. (C) Raincloud plot showing the distribution of NPI-Q total severity scores in the whole cohort at baseline (0), at 1-year follow-up (1) and 2-year follow-up (2). (D) Raincloud plot showing the distribution of NPS severity change (Δ NPI-Q from baseline to 1 or 2-year follow-up). Higher values show an increasing (ie, worsening) NPI-Q score. (E) Spearman's rank correlation of plasma proteins with all symptoms measured by the NPI-Q. P values of significant correlations are highlighted with colours according to the legend on the right. n, number; NPI-Q, Neuropsychiatric Inventory Questionnaire; NPS, neuropsychiatric symptoms.

the cut-off of a $p > 0.05$. For all statistical tests, two-tailed tests were used and the alpha value was set at 0.05.

Associations of protein levels with the presence of NPS at baseline

To determine the proteins that may independently be associated with the presence of NPS at baseline and determine the best predictive model, we applied binary logistic regression analysis using baseline NPS (NPI-Q>1) as the dependent variable and the 115 proteins as independent variables along with age, sex, education years, APOE ϵ 4 status and diagnosis, with a backward

stepwise selection method. Variables were chosen based on p values, and a p value threshold of 0.1 was used to set a limit on the total number of variables included in the final model. Before regression analysis, all continuous variables were transformed into standardised z-scores to ensure equal variance.

To further confirm the protein selection, we applied a cross-validation approach considering the proteins selected by the last step of backwards regression. The study population was randomly partitioned into a training (n=409, 80% of participants) and testing (n=98, 20% of participants) dataset. The

Table 2 Best models for different NPS-related prediction outcomes

Prediction outcome	Included variables	χ^2 (df)	P value	R ²
Baseline NPS	AD dementia 25 proteins	117.81 (26)	<0.001	0.28
Irritability	Male sex 19 proteins	113.92 (26)	<0.001	0.19
Depression	AD dementia 10 proteins	59.10 (11)	<0.001	0.17
Anxiety	Young age AD dementia 35 proteins	141.15 (38)	<0.001	0.38
Agitation	13 proteins	57.44 (13)	<0.001	0.17
Apathy	AD dementia 15 proteins	92.27 (17)	<0.001	0.27
NPS after 1 year	Young age male sex APOEε4 carrier AD dementia 12 proteins	90.88 (16)	<0.001	0.23
NPS after 2 years	AD dementia 29 proteins	122.19 (31)	<0.001	0.34

Table shows the best predictive models for different outcomes including all variables resulting from logistic regression analysis. For all models age, sex, education years, APOEε4 carrier status and diagnosis (MCI or AD dementia) were considered. χ^2 (df), R² and p values are shown for all models. AD, Alzheimer's disease; APOEε4, apolipoprotein E allele ε4; df, degrees of freedom; MCI, mild cognitive impairment; NPS, neuropsychiatric symptom.

training dataset was used to perform fivefold cross-validation before evaluating the model using the testing dataset.

To investigate the correlations of the selected protein levels with NPS severity (NPI-Q severity score), we used Spearman's rank correlation.

To test whether the selected protein panels can improve the prediction of NPS we added the proteins selected before ('full model') and after cross-validation ('parsimonious model') to a reference model including age, sex, education years, APOEε4 status and diagnosis. To compare the predictive performance of the different models, we calculated the area under the curve (AUC) of ROC. We applied the DeLong method²⁹ to compare all models.

To further determine the best models predictive for single symptoms of NPS, we applied the same approach except for the cross-validation.

Prediction of future NPS and of cognitive decline

To determine the best model for the prediction of future NPS (NPI-Q>1) at 1 and 2 years follow-up, we used the same approach as described above. In a further exploratory step, we determined the best predictive models for the worsening of the NPI-Q (Δ NPI-Q>1) and for NPS severity change (Δ NPI-Q score) between baseline and follow-up visits, with the same independent variables as above.

To investigate whether the proteins selected after cross-validation were predictive of cognitive decline at 1 or 2 years follow-up, we used the Mann-Whitney U test.

Associations with AD pathology

To explore the associations between NPS and the presence of AD pathology as measured by CSF biomarkers, we performed binary logistic regression analysis using baseline NPS (NPI-Q>1) as dependent variable and possible confounders (age, sex, education years, APOEε4 status and diagnosis) together with either amyloid pathology or ATN groups as independent variables.

Pathways related to overall NPS and to individual symptoms of NPS

Details on the pathway enrichment analysis can be found in online supplemental section 2.

RESULTS

Study participants

Table 1 displays the subject characteristics of the 507 participants grouped according to the presence of NPS at baseline (NPI-Q>1).

Details on the group differences regarding the core AD biomarkers can be found in online supplemental table S2. Figure 1 displays the frequency of all 12 symptoms, the distribution of NPI-Q severity scores at baseline and both follow-up visits, the NPI-Q severity change over time, as well as an overview on correlations between all measured proteins with total NPS and the single symptoms at baseline.

Proteins associated with NPS at baseline

Results of the best model to predict NPS at baseline are shown in table 2 and online supplemental table S3. After cross-validation, 15 proteins were selected (figure 2A, right) with an accuracy of 69% (specificity of 76% and sensitivity of 61%). ROC curves of the models are shown in figure 2A, left. When compared with the reference model, both models improved the prediction of NPS. Five of the 15 proteins additionally correlated with higher NPS severity at baseline, as shown in online supplemental figure S1.

Associations with single symptoms of NPS at baseline

We investigated the five most common single symptoms of NPS in this cohort. The co-occurrence of two or more symptoms per participant is shown in the Venn diagram in figure 3A. The determined models each included a different number of associated proteins and covariables, as shown in table 2. Angiotensinogen (ANGT) was the most commonly shared protein, which was found to predict all symptoms except for depression. Figure 3B shows a Venn diagram with the number of shared proteins. For all symptoms, adding the selected proteins to the reference model improved the prediction when compared with the reference model ($p<0.01$). The selected proteins from all models as well as the ROC curves for all five symptoms are shown in figure 4 and are listed in detail in online supplemental tables S4–S8.

Prediction of future NPS

Follow-up data for future NPS based on the NPI-Q score were available in 488/507 after 1 year and 426/507 after 2 years.

Results of the best model to predict future NPS at 1-year follow-up (full model) are shown in table 2 and online supplemental table S9. After cross-validation, eight proteins were selected for the 'parsimonious model' (figure 2B, right) with an accuracy of 65% (specificity of 52% and sensitivity of 75%). ROC curves of both models are shown in figure 2B, left. When compared with the 'reference model', both models improved the prediction of NPS at 1-year follow-up.

Results of the best model to predict future NPS at 2-year follow-up (full model) are shown in table 2 and online supplemental table S10. After cross-validation, 20 proteins were selected for the 'parsimonious model' (figure 2C, right) with an accuracy of 68% (specificity of 49% and sensitivity of 81%). ROC curves of the models are shown in figure 2C, left. When compared with the 'reference model', both models improved the prediction of NPS at 2-year follow-up.

ANGT, interleukin-3 (IL3) and T lymphocyte-secreted protein I-309 (CCL1) were the only proteins from the 'parsimonious models' that were associated with NPS at baseline and both follow-up visits (figure 5). Results on the prediction models of

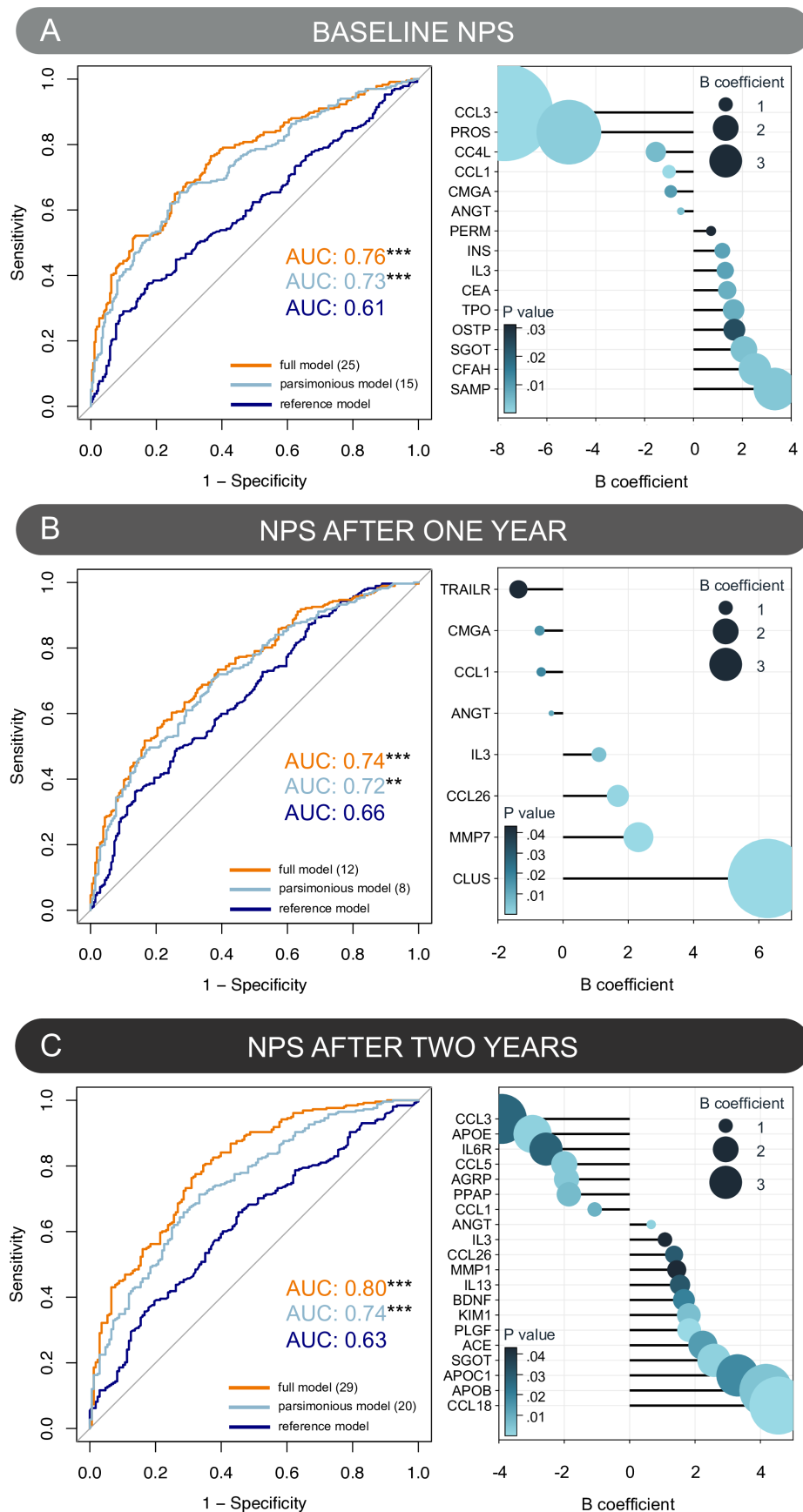


Figure 2 Prediction of overall NPS at baseline (A) and follow-up visits after 1 year (B) and after 2 years (C). On the left side ROC curves indicating the AUC of the three different predictive models are shown. In brackets, the number of included proteins is shown. On the right side, the correlation dot plot is shown including all cross-validated proteins from the parsimonious model with their beta coefficients. The size of each dot corresponds to the B coefficient of the single protein. ** $p < 0.01$, *** $p < 0.001$. AUC, area under the curve; NPS, neuropsychiatric symptoms; ROC, receiver operating characteristics.

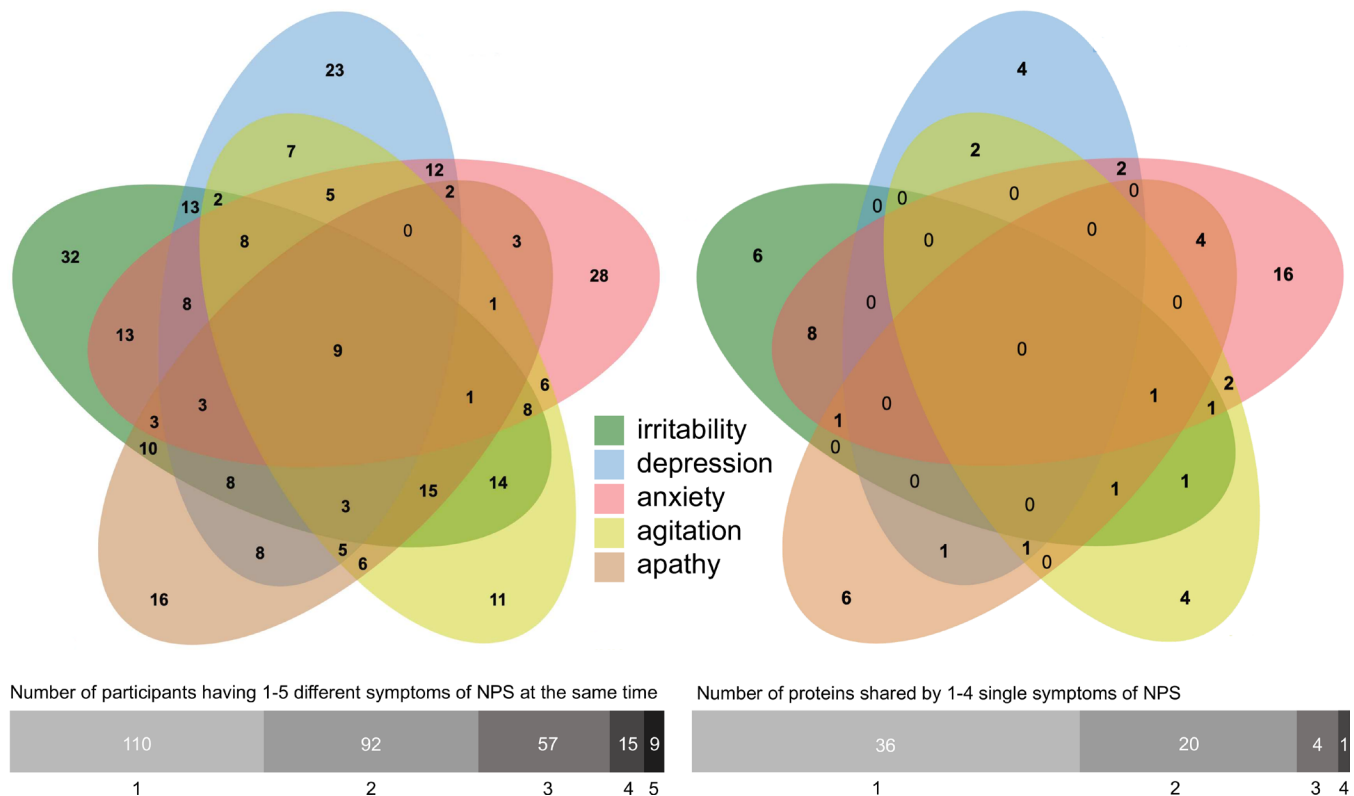
A Co-occurrence of single symptoms of NPS**B Shared proteins in different symptoms**

Figure 3 (A) Venn diagram with the number of patients having 1–5 of the most common symptoms (irritability, depression, anxiety, agitation, apathy) at baseline. (B) Venn diagram with the number of associated and shared proteins between single symptoms. NPS, neuropsychiatric symptoms.

NPS severity change and worsening of NPS are shown in online supplemental tables S11–S14.

Prediction of cognitive decline

We found a significant association between the presence of NPS at baseline and cognitive decline after 1 year (68% of the individuals experiencing NPS vs 57% of those without NPS; χ^2 (1, $n=487$)=5.79, $p=0.019$) and after 2 years (70% vs 54%, χ^2 (1, $n=423$)=10.60, $p=0.001$). From the 15 proteins associated with baseline, 3 were also associated with cognitive decline after 1 year (lower complement factor H (CFAH) ($U=27\,259.5$, $Z=-2.84$, $p=0.005$, $r=-0.13$), lower CCL1 ($U=24\,899.5$, $Z=-2.01$, $p=0.044$, $r=0.09$), and lower serum glutamic oxaloacetic transaminase (SGOT) ($U=24\,918.0$, $Z=-2.00$, $p=0.045$, $r=0.09$)). Only CFAH was associated with cognitive decline after 2 years ($U=18\,734.0$, $Z=-2.12$, $p=0.034$, $r=0.10$).

Associations with AD pathology

CSF biomarkers were available for 64% of the participants with NPS and for 56% without NPS. CSF levels of A β 42, pTau181 and tTau were not different between the NPS positive and NPS negative groups (online supplemental table S2). Neither the presence of amyloid pathology (OR 1.32, 95% CI 0.65 to 2.70, $p=0.442$) nor the classification according to ATN groups (OR 1.02, 95% CI 0.55 to 1.90; $p=0.947$) were associated with the presence of NPS at baseline. Out of the 15 proteins associated with NPS at baseline, only chromogranin A showed an association with all three CSF AD biomarkers, thrombopoietin and macrophage inflammatory protein-1 alpha only with A β 42 and insulin only with pTau181 (online supplemental table S15).

Pathways related to single symptoms

Distinct enriched pathways were found for single symptoms as shown in online supplemental figure S2. The most common over-represented pathways were signal transduction, immune system and protein metabolism.

DISCUSSION

Using targeted plasma proteomics in the ADNI cohort, we identified and cross-validated a panel of proteins associated with NPS at baseline. In addition, selected proteins improved the prediction of future NPS when compared with a reference model relying on clinical parameters only. Some of these proteins additionally predicted cognitive decline. The observed associations between proteins and NPS were independent of the presence of AD pathology as indicated by CSF biomarkers. Furthermore, for overall NPS and for the most common single symptoms, the identified protein signatures indicated biological pathway alterations involving signal transduction, immune system and transport of small molecules.

While plasma proteomics has been successfully applied in AD,^{12,30} very few studies have investigated proteome changes in relation to NPS.³¹ Using untargeted proteomics in plasma in a different cohort, we recently reported a panel of proteins that was associated with NPS at baseline and additionally predicted future NPS.¹³ To our knowledge, no study has used targeted proteomics, giving also access to lower abundant proteins such as signal proteins, to identify and evaluate biomarker candidates of NPS so far.

After cross-validation, 15 proteins remained associated with NPS. Adding these proteins to a reference model significantly

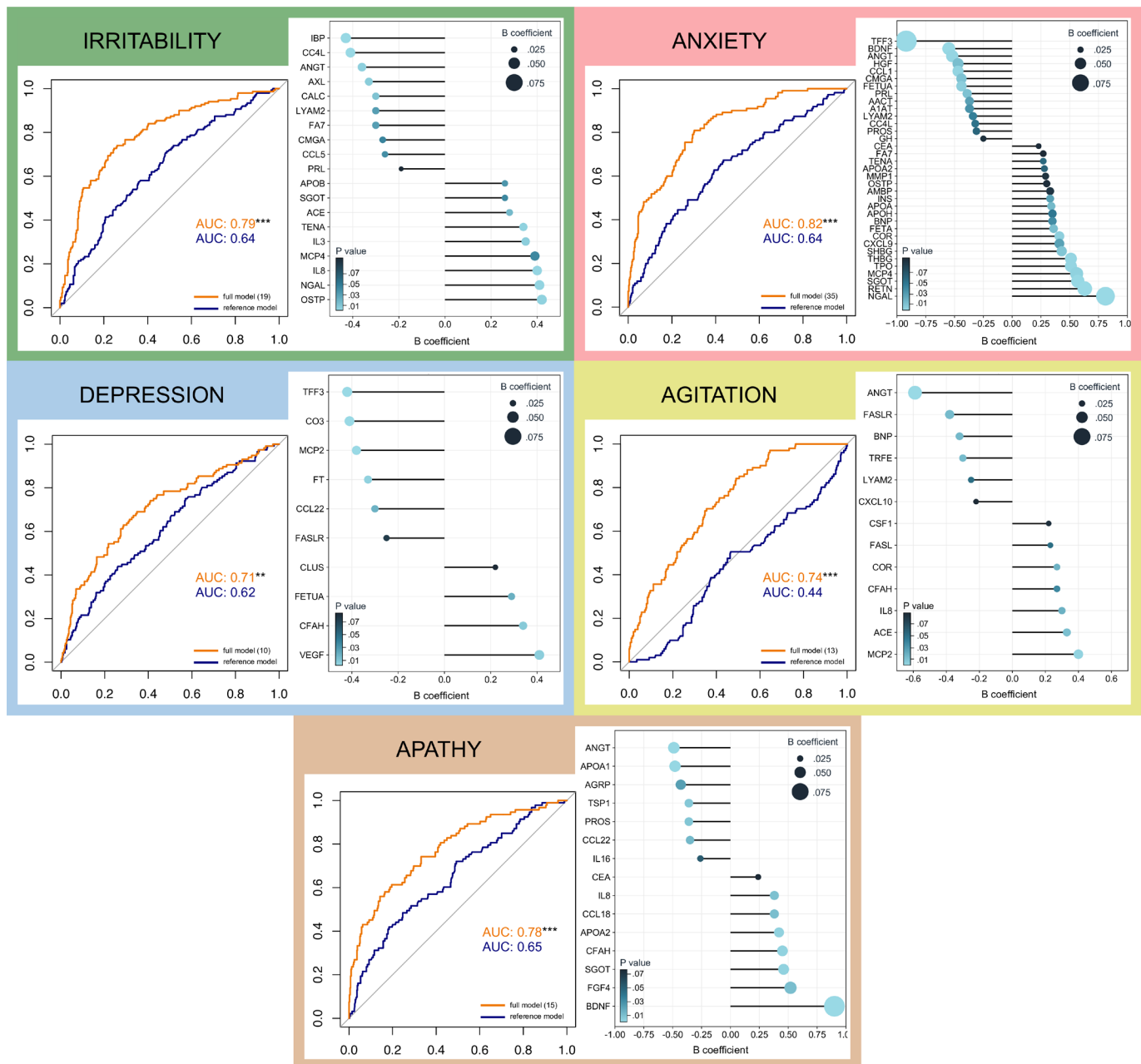


Figure 4 Data for the five most common single symptoms of NPS are displayed. On the left side, ROC curves indicating the AUC of the two different predictive models are shown. The x-axis corresponds to 1–specificity and the y-axis to sensitivity. In brackets, the number of included proteins is shown. On the right side, the correlation dot plot is shown including all proteins from the full model with their beta coefficients. The size of each dot corresponds to the B coefficient of the single protein. ** $p < 0.01$, *** $p < 0.001$. AUC, area under the curve; NPS, neuropsychiatric symptoms; ROC, receiver operating characteristics.

improved the prediction of NPS. From the proteins, we previously identified to be associated with NPS applying untargeted proteomics in a small-sized cohort,¹³ four were quantified in the present study. All four proteins, that is, CFAH, alpha-1 microglobulin, apolipoprotein H and C reactive protein, were associated with NPS in the current study (online supplemental section 3).

When addressing associations with single symptoms, we found distinct protein panels associated with irritability, depression, anxiety, agitation and apathy. The selected proteins improved the prediction of the respective symptoms when added to the reference model. These findings indicate potential utility of plasma protein biomarkers in identifying and monitoring

syndrome-specific pathologies. As co-occurrence of the single symptoms was frequent, in line with previous literature,³² future studies may investigate biomarker candidates in relation to symptom clusters.

After cross-validation, 8 and 20 proteins measured at baseline were associated with future NPS after 1 year and after 2 years, respectively. Using plasma protein biomarkers could help to identify patients at high risk for persisting or developing NPS over time, which could support personalised decision-making on monitoring and treatment of NPS.

Among the selected proteins, ANG1, CCL1 and IL3 were associated with NPS at all three time points, suggesting an important role of these proteins in persisting NPS. Proinflammatory

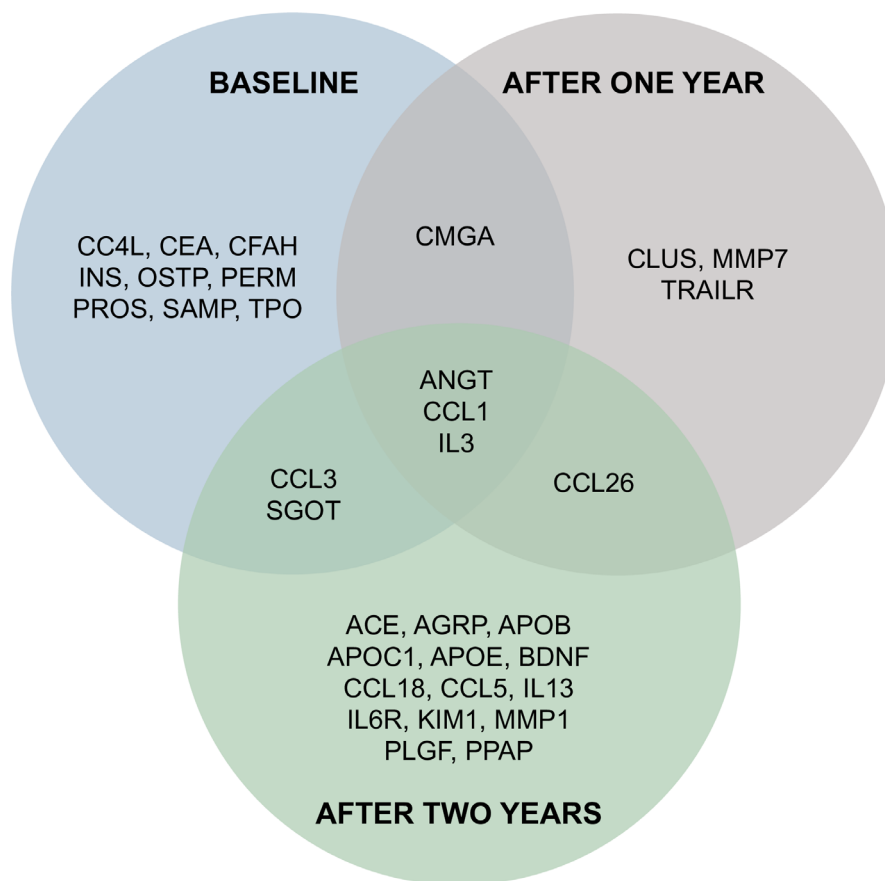


Figure 5 Proteins commonly associated with neuropsychiatric symptoms at baseline, 1 and 2 years follow-up visits.

cytokines, including CCL1 and IL3, have been linked to AD^{20 33} but also to NPS before.^{34 35} Also, ANGT as part of the renin-angiotensin system has been linked to symptoms like anxiety or emotional stress.^{36 37} The association between elevated RAS activity and NPS was also reported to be mediated at least partly through the induction of neuroinflammation, and oxidative stress and may be further pronounced in APOE carriers.^{38 39} Additional studies are needed to evaluate the potential of these novel biomarker candidates for the prediction and monitoring of persisting NPS in older people with cognitive decline.

We found CCL1, SGOT and CFAH to be associated with cognitive decline, in line with previous reports,^{33 40} together suggesting that these markers may be useful to evaluate the risk of (more rapid) cognitive decline, in particular in patients with NPS.

NPSs were neither associated with amyloid pathology nor with AD pathology in the AD continuum as defined according to the ATN classification. Furthermore, the observed associations of 15 proteins with NPSs were independent of the presence of AD pathology. Among these proteins, only chromogranin A was associated with the single AD CSF biomarkers, in line with a previous report.⁴¹ Of note, the proteomics panel used in this study included proteins previously reported to be associated with (clinically diagnosed) AD. Accordingly, and also considering the high frequency of NPS in AD, it may be expected that the observed associations with NPS are mostly associated with AD pathology. However, previous studies have not addressed the possible role of NPS in the associations of proteins with AD. Previous reports on the associations of NPS with biomarkers of AD were inconsistent.⁶⁷ Some studies suggested that NPS or mild behavioural impairment may represent an early manifestation of

cerebral AD pathology⁴² while others, in line with our findings, indicated that NPS may also relate to alterations at least in part independent from the core AD pathology.¹³

In an exploratory approach addressing pathophysiological alterations associated with NPS, we found distinct enriched pathways for the most common symptoms, involving primarily signal transduction, immune system and protein metabolism. Especially, the involvement of the immune system in NPS has been described before and consistently seems to play an important role in NPS.^{4 35}

This is, to our knowledge, the first study applying targeted proteomics to identify and test biomarkers of NPS. The sample size for this study was large and allowed for a cross-validation approach. Other strengths of the study are its longitudinal and multicentric design as well as the availability of the CSF AD biomarkers in a subset of the participants. We were also able to evaluate potential biomarker candidates for the most common single NPS separately. However, evaluating associations between proteins and less frequent single symptoms was not possible. Also, we were not able to investigate the effects of concomitant use of psychotropic substances in dept as those medications were an exclusion criterion. However, psychotropic medication may have relevant effects on different clinical outcomes (ie, impact on cognition or NPS) and may lead to molecular changes.^{43–45} Importantly, the targeted approach allowed for the quantification of target proteins and is a more suitable approach for the validation of biomarker candidates.⁴⁶

We identified and cross-validated plasma protein panels as biomarker candidates for NPS and related disease progression. ANGT, CCL1 and IL3 were consistently associated with NPS at different time points while CCL1, SGOT and CFAH were also

associated with future cognitive decline. Overall, ANGT showed the most robust associations and was also related to irritability, anxiety, agitation and apathy. Together, our findings suggest that pathological alterations relevant to NPS can be detected with blood-based protein biomarkers. Using easily accessible plasma biomarkers for NPS and related clinical disease progression could open the door to new personalised treatment options in the context of cognitive decline and AD. Pending further validation, these biomarkers could be used in clinical practice not only to detect pathologies related to NPS and differentiate between the aetiology but also to monitor changes in these pathologies over time.

Collaborators Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: Michael Weiner (University of California, San Francisco Northern California Institute for Research and Education), Paul Aisen (University of Southern California), Ronald Petersen (Mayo Clinic, Rochester (co-PI of of Clinical Core)), Clifford R Jack (Mayo Clinic, Rochester), William Jagust (University of California, Berkeley), Susan Landau (University of California, Berkeley), Monica Rivera-Mindt (Fordham University; Mt. Sinai Medical Center), Ozioma Okonkwo (University of Wisconsin), Leslie M Shaw (University of Pennsylvania), Edward B Lee (University of Pennsylvania), Arthur W Toga (University of California, Los Angeles), Laurel Beckett (University of California, Davis), Danielle Harvey (University of California, Davis), Robert C Green (Boston University), Andrew J Saykin (Indiana University), Kwangsik Nho (Indiana University), Richard J Perrin (Washington University St. Louis), Duygu Tosun (University of California, San Francisco), Pallavi Sachdev (Eisai (Chair, 2023-2024)), Erin Drake (Harvard University), Tom Montine (University of Washington (Chair)), Cat Conti (Northern California Institute for Research and Education), Rachel Nosheny (University of California, San Francisco), Diana Truran Sacrey (Northern California Institute for Research and Education), Juliet Fockler (University of California, San Francisco), Melanie J Miller (Northern California Institute for Research and Education), Winnie Kwang (University of California, San Francisco), Chengshi Jin (University of California, San Francisco), Adam Diaz (Northern California Institute for Research and Education), Miriam Ashford (Northern California Institute for Research and Education), Derek Flenniken (Northern California Institute for Research and Education), Adrienne Kormos (Northern California Institute for Research and Education), Michael Rafii (University of Southern California), Rema Raman (University of Southern California), Gustavo Jimenez (University of Southern California), Michael Donohue (University of Southern California), Jennifer Salazar (University of Southern California), Andrea Fidell (University of Southern California), Virginia Boatwright (University of Southern California), Justin Robison (University of Southern California), Caileigh Zimmerman (University of Southern California), Yuliana Cabrera (University of Southern California), Sarah Walter (University of Southern California), Taylor Clanton (University of Southern California), Elizabeth Shaffer (University of Southern California), Caitlin Webb (University of Southern California), Lindsey Hergesheimer (University of Southern California), Stephanie Smith (University of Southern California), Sheila Ogowang (University of Southern California), Sheila Ogowang (University of Southern California), Payam Mahboubi (University of Southern California), Jeremy Pizzola (University of Southern California), Cecily Jenkins (University of Southern California), Laurel Beckett (University of California, Davis (Core PI)), Danielle Harvey (University of California, Davis (Core PI)), Michael Donohue (University of Southern California), Naomi Saito (University of California, Davis), Adam Diaz (Northern California Institute for Research and Education), Kedir Adem Hussen (University of Southern California), Hannatu Amaza (University of Wisconsin), Mai Seng Thao (University of Wisconsin), Shaniya Parkins (Mt. Sinai), Omobolanle Ayo (Mt. Sinai), Matt Glittenberg (University of Wisconsin), Isabella Hoang (University of Wisconsin), Kaori Kubo Germano (Fordham University), Joe Strong (University of Wisconsin), Trinity Weisenel (University of Wisconsin), Fabiola Magana (University of Wisconsin), Lisa Thomas (University of Wisconsin), Vanessa Guzman (Mt. Sinai), Adeyinka Ajayi (Mt. Sinai), Joseph Di Benedetto (Mt. Sinai), Sandra Talavera (Fordham University), Joel Felmlee (Mayo Clinic, Rochester), Nick C Fox (University College London), Paul Thompson (UCLA School of Medicine), Charles DeCarli (University of California, Davis), Arvin Forghanian-Arani (Mayo Clinic, Rochester), Bret Borowski (Mayo Clinic, Rochester), Calvin Reyes (Mayo Clinic, Rochester), Caitie Hedberg (Mayo Clinic, Rochester), Chad Ward (Mayo Clinic, Rochester), Christopher Schwarz (Mayo Clinic, Rochester), Denise Reyes (Mayo Clinic, Rochester), Jeff Gunter (Mayo Clinic, Rochester), John Moore-Weiss (Mayo Clinic, Rochester), Kejal Kantarci (Mayo Clinic, Rochester), Leonard Matoush (Mayo Clinic, Rochester), Matthew Senjem (Mayo Clinic, Rochester), Prashanthi Vemuri (Mayo Clinic, Rochester), Robert Reid (Mayo Clinic, Rochester), Ian Malone (University College London), Sophia I Thomopoulos (University of Southern California School of

Medicine), Talia M Nir (University of Southern California School of Medicine), Neda Jahanshad (University of Southern California School of Medicine), Alexander Knaack (University of California, Davis), Evan Fletcher (University of California, Davis), Danielle Harvey (University of California, Davis), Duygu Tosun-Turgut (University of California, San Francisco), Stephanie Rossi Chen (Northern California Institute for Research and Education), Mark Choe (Northern California Institute for Research and Education), Karen Crawford (University of Southern California School of Medicine), Paul A Yushkevich (University of Pennsylvania), Sandhitsu Das (University of Pennsylvania), Robert A Koeppe (University of Michigan), Gil Rabinovici (University of California San Francisco), Victor Villemagne (University of Pittsburgh), Brian LoPresti (University of Pittsburgh), John Morris (Washington University St. Louis), Erin Franklin (Washington University St. Louis), Haley Bernhardt (Washington University St. Louis), Nigel J Cairns (Washington University St. Louis), Lisa Taylor-Reinwald (Washington University St. Louis), Edward B Lee (University of Pennsylvania (Core PI)), Virginia M Y Lee (UPenn School of Medicine), Magdalena Korecka (UPenn School of Medicine), Magdalena Brylska (UPenn School of Medicine), Yang Wan (UPenn School of Medicine), J Q Trojanowski (UPenn School of Medicine (*former Core PI, deceased)), Karen Crawford (University of Southern California), Scott Neu (University of Southern California), Tatiana M Foroud (Indiana University School of Medicine (Dir. NCRAD)), Taeho Jo (Indiana University School of Medicine), Shannon L Risacher (Indiana University School of Medicine), Hannah Craft (Indiana University School of Medicine), Liana G Apostolova (Indiana University School of Medicine), Kelly Nudelmann (NCRAD/Indiana University School of Medicine), Kelley Faber (NCRAD/Indiana University School of Medicine), Zoë Potter (NCRAD/Indiana University School of Medicine), Kaci Lacy (NCRAD/Indiana University School of Medicine), Rima Kaddurah-Daouk (Duke University/AD Metabolomics Consortium), Li Shen (University of Pennsylvania), Jason Karlawish (University of Pennsylvania), Claire Erickson (University of Pennsylvania), Joshua Grill (University of California, Irvine), Emily Largent (University of Pennsylvania), Kristin Harkins (University of Pennsylvania), Leon Thal, Zaven Kachaturian (Khachaturian, Radebaugh & Associates (KRA), Inc), Richard Frank (General Electric), Peter J Snyder (General Electric, Alzheimer's Association's Ronald and Nancy Reagan's Research Institute), Neil Buckholtz (National Institute on Aging), John K Hsiao (National Institute on Aging), Laurie Ryan (National Institute on Aging), Susan Molchan (National Institute on Aging/National Institutes of Health), Maria Carrillo (Alzheimer's Association), William Potter (National Institute of Mental Health), Lisa Barnes (Rush University), Marie Bernard (NIA), Hector González (University of California, San Diego), Carole Ho (Denali Therapeutics), John K Hsiao (NIH), Jonathan Jackson (Massachusetts General Hospital), Eliezer Masliah (NIA), Donna Masterman (Biogen), Laurie Ryan (NIA), Nina Silverberg (NIA), Lisa Silbert (Oregon Health and Science University), Jeffrey Kaye (Oregon Health and Science University), Sylvia White (Salazar) (Oregon Health and Science University), Aimee Pierce (Oregon Health and Science University), Amy Thomas (Oregon Health and Science University), Tera Clay (Oregon Health and Science University), Daniel Schwartz (Oregon Health and Science University), Gillian Devereux (Oregon Health and Science University), Janet "Janae" Taylor (Oregon Health and Science University), Jennifer Ryan (Oregon Health and Science University), Mike Nguyen (Oregon Health and Science University), Madison DeCapo (Oregon Health and Science University), Yanan Shang (Oregon Health and Science University), Lon Schneider (University of Southern California), Cynthia Munoz (University of Southern California), Diana Ferman (University of Southern California), Carlota Conant (University of Southern California), Katherin Martin (University of Southern California), Kristin O'Leary (University of Southern California), Sonia Pawluczyk (University of Southern California), Elizabeth Trejo (University of Southern California), Karen Dagerman (University of Southern California), Liberty Teodoro (University of Southern California), Mauricio Becerra (University of Southern California), Madiha Fairouz (University of Southern California), Sonia Garrison (University of Southern California), Julia Boudreau (University of Southern California), Yair Avila (University of Southern California), James Brewer (University of California--San Diego), Aaron Jacobson (University of California--San Diego), Antonio Gama (University of California--San Diego), Chi Kim (University of California--San Diego), Emily Little (University of California--San Diego), Jennifer Frascino (University of California--San Diego), Nichol Ferng (University of California--San Diego), Socorro Trujillo (University of California--San Diego), Judith Heidebrink (University of Michigan), Robert Koeppe (University of Michigan), Steven MacDonald (University of Michigan), Dariya Malyarenko (University of Michigan), Jaimie Ziolkowski (University of Michigan), James O'Connor (University of Michigan), Nicole Robert (University of Michigan), Suzan Lowe (University of Michigan), Virginia Rogers (University of Michigan), Barbara Hackenmiller (Mayo Clinic, Rochester), Bradley Boeve (Mayo Clinic, Rochester), Colleen Albers (Mayo Clinic, Rochester), Connie Kreuger (Mayo Clinic, Rochester), David Jones (Mayo Clinic, Rochester), David Knopman (Mayo Clinic, Rochester), Hugo Botha (Mayo Clinic, Rochester), Jessica Magnuson (Mayo Clinic, Rochester), Jonathan Graff-Radford (Mayo Clinic, Rochester), Kerry Crawley (Mayo Clinic, Rochester), Michael Schumacher (Mayo Clinic, Rochester), Sanna McKinzie (Mayo Clinic, Rochester), Steven Smith (Mayo Clinic, Rochester), Tascha Helland (Mayo Clinic, Rochester), Val Lowe (Mayo Clinic, Rochester), Vijay Ramanan (Mayo Clinic, Rochester), Valory Pavlik (Baylor College of Medicine), Jacob Faircloth (Baylor College of Medicine), Jeffrey Bishop (Baylor College of Medicine), Jessica Nath (Baylor College of Medicine), Maria Chaudhary (Baylor College of Medicine), Maria

Kataki (Baylor College of Medicine), Melissa Yu (Baylor College of Medicine), Nathiel Pacini (Baylor College of Medicine), Randall Barker (Baylor College of Medicine), Regan Brooks (Baylor College of Medicine), Ruchi Aggarwal (Baylor College of Medicine), Lawrence Honig (Columbia University Medical Center), Yaakov Stern (Columbia University Medical Center), Akiva Mintz (Columbia University Medical Center), Jonathan Cordona (Columbia University Medical Center), Michelle Hernandez (Columbia University Medical Center), Justin Long (Washington University, St. Louis), Abbey Arnold (Washington University, St. Louis), Alex Groves (Washington University, St. Louis), Anna Middleton (Washington University, St. Louis), Blake Vogler (Washington University, St. Louis), Cierra McCurry (Washington University, St. Louis), Connie Mayo (Washington University, St. Louis), Cyrus Raji (Washington University, St. Louis), Fatima S Amtashar (Washington University, St. Louis), Heather Klemp (Washington University, St. Louis), Heather Nicole Elmore (Washington University, St. Louis), James Ruszkiewicz (Washington University, St. Louis), Jasmina Kusuran (Washington University, St. Louis), Jasmine Stewart (Washington University, St. Louis), Jennifer Horenkamp (Washington University, St. Louis), Julia Greeson (Washington University, St. Louis), Kara Wever (Washington University, St. Louis), Katie Vo (Washington University, St. Louis), Kelly Larkin (Washington University, St. Louis), Lesley Rao (Washington University, St. Louis), Lisa Schoolcraft (Washington University, St. Louis), Lora Gallagher (Washington University, St. Louis), Madeline Paczynski (Washington University, St. Louis), Maureen McMillan (Washington University, St. Louis), Michael Holt (Washington University, St. Louis), Nicole Gagliano (Washington University, St. Louis), Rachel Henson (Washington University, St. Louis), Renee LaBarge (Washington University, St. Louis), Robert Swarm (Washington University, St. Louis), Sarah Munie (Washington University, St. Louis), Serena Cepeda (Washington University, St. Louis), Stacey Winterton (Washington University, St. Louis), Stephen Hegedus (Washington University, St. Louis), TaNisha Wilson (Washington University, St. Louis), Tanya Harte (Washington University, St. Louis), Zach Bonacorsi (Washington University, St. Louis), David Geldmacher (University of Alabama Birmingham), Amber Watkins (University of Alabama Birmingham), Brandi Barger (University of Alabama Birmingham), Bryan Smelser (University of Alabama Birmingham), Charna Bates (University of Alabama Birmingham), Cynthia Stover (University of Alabama Birmingham), Emily McKinley (University of Alabama Birmingham), Gregory Ikner (University of Alabama Birmingham), Haley Hendrix (University of Alabama Birmingham), Harold Matthew Cooper (University of Alabama Birmingham), Jennifer Mahaffey (University of Alabama Birmingham), Lindsey Booth Robbins (University of Alabama Birmingham), Loren Brown Ashley (University of Alabama Birmingham), Marissa Natelson -Love (University of Alabama Birmingham), Princess Carter (University of Alabama Birmingham), Veronika Solomon (University of Alabama Birmingham), Hillel Grossman (Mount Sinai School of Medicine), Alexandra Groome (Mount Sinai School of Medicine), Allison Ardolino (Mount Sinai School of Medicine), Anthony Kaplan (Mount Sinai School of Medicine), Faye Sheppard (Mount Sinai School of Medicine), Genesis Burgos -Rivera (Mount Sinai School of Medicine), Gina Garcia -Camilo (Mount Sinai School of Medicine), Joanne Lim (Mount Sinai School of Medicine), Judith Neugroschl (Mount Sinai School of Medicine), Kimberly Jackson (Mount Sinai School of Medicine), Kirsten Evans (Mount Sinai School of Medicine), Laili Soleimani (Mount Sinai School of Medicine), Mary Sano (Mount Sinai School of Medicine), Nasrin Ghesani (Mount Sinai School of Medicine), Sarah Binder (Mount Sinai School of Medicine), Xiomara Mendoza Apuango (Mount Sinai School of Medicine), Ajay Sood (Rush University Medical Center), Amelia Troutman (Rush University Medical Center), Kimberly Blanchard (Rush University Medical Center), Arlene Richards (Rush University Medical Center), Grace Nelson (Rush University Medical Center), Kirsten Hendrickson (Rush University Medical Center), Erin Yurko (Rush University Medical Center), Jamie Plenge (Rush University Medical Center), Victoria Rufo (Rush University Medical Center), Raj Shah (Rush University Medical Center), Ranjan Duara (Wein Center), Brendan Lynch (Wein Center), Cesar Chirinos (Wein Center), Christine Dittrich (Wein Center), Debbie Campbell (Wein Center), Diego Mejia (Wein Center), Gilberto Perez (Wein Center), Helena Colvée (Wein Center), Joanna Gonzalez (Wein Center), Josalen Gondrez (Wein Center), Joshua Knaack (Wein Center), Mara Acevedo (Wein Center), Maria Cereijo (Wein Center), Maria Greig -Cust (Wein Center), Michelle Villar (Wein Center), Morris Wishnia (Wein Center), Sheryl Detling (Wein Center), Warren Barker (Wein Center), Marilyn Albert (Johns Hopkins University), Abhay Moghekar (Johns Hopkins University), Barbara Rodzon (Johns Hopkins University), Corey Demsky (Johns Hopkins University), Gregory Pontone (Johns Hopkins University), Jim Pekar (Johns Hopkins University), Leonie Farrington (Johns Hopkins University), Martin Pomper (Johns Hopkins University), Nicole Johnson (Johns Hopkins University), Tolulope Alo (Johns Hopkins University), Martin Sadowski (New York University), Anasztasia Ulyse (New York University), Arjun Masurkar (New York University), Brittany Marti (New York University), David Mossa (New York University), Emilie Geesey (New York University), Emily Petrocca (New York University), Evan Schulze (New York University), Jennifer Wong (New York University), Joseph Boonsiri (New York University), Sunnie Kenowsky (New York University), Tatianne Martinez (New York University), Veronica Briglall (New York University), P Murali Doraiswamy (Duke University Medical Center), Adaora Nwosu (Duke University Medical Center), Alisa Adhikari (Duke University Medical Center), Cammie Hellegers (Duke University Medical Center), Jeffrey Petrella (Duke University Medical Center), Olga James (Duke University Medical Center), Terence Wong (Duke

University Medical Center), Thomas Hawk (Duke University Medical Center), Sanjeev Vaishnavi (University of Pennsylvania), Hannah McCoubrey (University of Pennsylvania), Ilya Nasrallah (University of Pennsylvania), Rachel Rovere (University of Pennsylvania), Jeffrey Maneval (University of Pennsylvania), Elizabeth Robinson (University of Pennsylvania), Francisco Rivera (University of Pennsylvania), Jade Uffelman (University of Pennsylvania), Martha Combs (University of Pennsylvania), Patricia O'Donnell (University of Pennsylvania), Sara Manning (University of Pennsylvania), Richard King (University of Kentucky), Alayne Nieto (University of Kentucky), Amanda Glueck (University of Kentucky), Anjana Mandal (University of Kentucky), Audrie Swain (University of Kentucky), Bethanie Gamble (University of Kentucky), Beverly Meacham (University of Kentucky), Denece Forenbach (University of Kentucky), Dorothy Ross (University of Kentucky), Elizabeth Cheatham (University of Kentucky), Ellen Hartman (University of Kentucky), Gary Cornell (University of Kentucky), Jordan Harp (University of Kentucky), Laura Ashe (University of Kentucky), Laura Goins (University of Kentucky), Linda Watts (University of Kentucky), Morgan Yazell (University of Kentucky), Prabin Mandal (University of Kentucky), Regan Buckler (University of Kentucky), Sylvia Vincent (University of Kentucky), Triana Rudd (University of Kentucky), Oscar Lopez (University of Pittsburgh), Ann Arlene Malia (University of Pittsburgh), Caitlin Chiado (University of Pittsburgh), Cary Zik (University of Pittsburgh), James Ruszkiewicz (University of Pittsburgh), Kathleen Savage (University of Pittsburgh), Linda Fenice (University of Pittsburgh), MaryAnn Oakley (University of Pittsburgh), Paige C Tacey (University of Pittsburgh), Sarah Berman (University of Pittsburgh), Sarah Bowser (University of Pittsburgh), Stephen Hegedus (University of Pittsburgh), Xanthia Saganis (University of Pittsburgh), Anton Porsteinsson (University of Rochester Medical Center), Abigail Mathewson (University of Rochester Medical Center), Asa Widman (University of Rochester Medical Center), Bridget Holvey (University of Rochester Medical Center), Emily Clark (University of Rochester Medical Center), Esmeralda Morales (University of Rochester Medical Center), Iris Young (University of Rochester Medical Center), James Ruszkiewicz (University of Rochester Medical Center), Kevin Hopkins (University of Rochester Medical Center), Kimberly Martin (University of Rochester Medical Center), Nancy Kowalski (University of Rochester Medical Center), Rebecca Hunt (University of Rochester Medical Center), Roberta Calzavara (University of Rochester Medical Center), Russell Kurvach (University of Rochester Medical Center), Stephen D'Ambrosio (University of Rochester Medical Center), Gabby Thai (University of California, Irvine), Beatriz Vides (University of California, Irvine), Brigit Lieb (University of California, Irvine), Catherine McAdams -Ortiz (University of California, Irvine), Cyndy Toso (University of California, Irvine), Ivan Mares (University of California, Irvine), Kathryn Moorlach (University of California, Irvine), Luter Liu (University of California, Irvine), Maria Corona (University of California, Irvine), Mary Nguyen (University of California, Irvine), Melanie Tallakson (University of California, Irvine), Michelle McDonnell (University of California, Irvine), Milagros Rangel (University of California, Irvine), Neetha Basheer (University of California, Irvine), Patricia Place (University of California, Irvine), Romina Romero (University of California, Irvine), Steven Tam (University of California, Irvine), Trung Nguyen (University of Texas Southwestern Medical School), Abey Thomas (University of Texas Southwestern Medical School), Alexander (Alex) Frolov (University of Texas Southwestern Medical School), Alka Khera (University of Texas Southwestern Medical School), Amy Browning (University of Texas Southwestern Medical School), Brendan Kelley (University of Texas Southwestern Medical School), Courtney Dawson (University of Texas Southwestern Medical School), Dana Mathews (University of Texas Southwestern Medical School), Elaine Most (University of Texas Southwestern Medical School), Elizeva (Ellie) Phillips (University of Texas Southwestern Medical School), Lynn Nguyen (University of Texas Southwestern Medical School), Maribel Nunez (University of Texas Southwestern Medical School), Matalin Miller (University of Texas Southwestern Medical School), Matthew R Jones (University of Texas Southwestern Medical School), Natalie Martinez (University of Texas Southwestern Medical School), Rebecca Logan (University of Texas Southwestern Medical School), Roderick McColl (University of Texas Southwestern Medical School), Sari Pham (University of Texas Southwestern Medical School), Tiffani Fox (University of Texas Southwestern Medical School), Tracey Moore (University of Texas Southwestern Medical School), Allan Levey (Emory University), Abby Brown (Emory University), Andrea Kippels (Emory University), Ashton Ellison (Emory University), Casie Lyons (Emory University), Chadwick Hales (Emory University), Cindy Parry (Emory University), Courtney Williams (Emory University), Elizabeth McCorkle (Emory University), Guy Harris (Emory University), Heather Rose (Emory University), Inara Jooma (Emory University), Jahmila Al -Amin (Emory University), James Lah (Emory University), James Webster (Emory University), Jessica Swiniarski (Emory University), Latasha Chapman (Emory University), Laura Donnelly (Emory University), Lauren Mariotti (Emory University), Mary Locke (Emory University), Phyllis Vaughn (Emory University), Rachael Penn (Emory University), Sallie Carpenter (Emory University), Samira Yeboah (Emory University), Sarah Basadre (Emory University), Sarah Malakauskas (Emory University), Stefka Lyrone (Emory University), Tara Villinger (Emory University), Terra Burney (Emory University), Jeffrey Burns (University of Kansas, Medical Center), Ala Abusalim (University of Kansas, Medical Center), Alexandra Dahlgren (University of Kansas, Medical Center), Alexandria Montero (University of Kansas, Medical Center), Anne Arthur (University of Kansas, Medical Center), Heather Dooly (University of Kansas, Medical Center), Katelynn Kreszyn

(University of Kansas, Medical Center), Katherine Berner (University of Kansas, Medical Center), Lindsey Gillen (University of Kansas, Medical Center), Maria Scanlan (University of Kansas, Medical Center), Mercedes Madison (University of Kansas, Medical Center), Nicole Mathis (University of Kansas, Medical Center), Phyllis Switzer (University of Kansas, Medical Center), Ryan Townley (University of Kansas, Medical Center), Samantha Fikru (University of Kansas, Medical Center), Samantha Sullivan (University of Kansas, Medical Center), Ella Wright (University of Kansas, Medical Center), Maryam Beigi (University of California, Los Angeles), Anthony Daley (University of California, Los Angeles), Ashley Ko (University of California, Los Angeles), Brittney Luong (University of California, Los Angeles), Glen Nyborg (University of California, Los Angeles), Jessica Morales (University of California, Los Angeles), Kelly Durbin (University of California, Los Angeles), Lauren Garcia (University of California, Los Angeles), Leila Parand (University of California, Los Angeles), Lorena Macias (University of California, Los Angeles), Lorena Monserratt (University of California, Los Angeles), Maya Farchi (University of California, Los Angeles), Pauline Wu (University of California, Los Angeles), Robert Hernandez (University of California, Los Angeles), Thao Rodriguez (University of California, Los Angeles), Neill Graff-Radford (Mayo Clinic, Jacksonville), A'Ilana Marolt (Mayo Clinic, Jacksonville), Anton Thomas (Mayo Clinic, Jacksonville), Deborah Aloszka (Mayo Clinic, Jacksonville), Ercilia Moncayo (Mayo Clinic, Jacksonville), Erin Westerhold (Mayo Clinic, Jacksonville), Gregory Day (Mayo Clinic, Jacksonville), Kandise Chrestensen (Mayo Clinic, Jacksonville), Mary Imhansiemhonehi (Mayo Clinic, Jacksonville), Sanna McKinzie (Mayo Clinic, Jacksonville), Sochenda Stephens (Mayo Clinic, Jacksonville), Sylvia Grant (Mayo Clinic, Jacksonville), Jared Brosch (Mayo Clinic, Jacksonville), Amy Perkins (Mayo Clinic, Jacksonville), Aubree Saunders (Mayo Clinic, Jacksonville), Debra Silberberg Kovac (Mayo Clinic, Jacksonville), Heather Polson (Mayo Clinic, Jacksonville), Isabell Mwaura (Mayo Clinic, Jacksonville), Kassandra Mejia (Mayo Clinic, Jacksonville), Katherine Britt (Mayo Clinic, Jacksonville), Kathy King (Mayo Clinic, Jacksonville), Kayla Nichols (Mayo Clinic, Jacksonville), Kayley Lawrence (Mayo Clinic, Jacksonville), Lisa Rankin (Mayo Clinic, Jacksonville), Martin Farlow (Mayo Clinic, Jacksonville), Patricia Wiesenaue (Mayo Clinic, Jacksonville), Robert Bryant (Mayo Clinic, Jacksonville), Scott Herring (Mayo Clinic, Jacksonville), Sheryl Lynch (Mayo Clinic, Jacksonville), Skylar Wilson (Mayo Clinic, Jacksonville), Traci Day (Mayo Clinic, Jacksonville), William Korst (Mayo Clinic, Jacksonville), Christopher van Dyck (Yale University School of Medicine), Adam Mecca (Yale University School of Medicine), Alyssa Miller (Yale University School of Medicine), Amanda Brennan (Yale University School of Medicine), Amber Khan (Yale University School of Medicine), Audrey Ruan (Yale University School of Medicine), Carol Gunnoud (Yale University School of Medicine), Chelsea Mendonca (Yale University School of Medicine), Danielle Raynes -Goldfinger (Yale University School of Medicine), Elaheh Salardini (Yale University School of Medicine), Elisa Hidalgo (Yale University School of Medicine), Emma Cooper (Yale University School of Medicine), Erawadi Singh (Yale University School of Medicine), Erin Murphy (Yale University School of Medicine), Jeanine May (Yale University School of Medicine), Jesse Stanhope (Yale University School of Medicine), Jessica Lam (Yale University School of Medicine), Julia Waszak (Yale University School of Medicine), Kimberly Nelsen (Yale University School of Medicine), Kimberly Sacaza (Yale University School of Medicine), Mayer Joshua Hasbani (Yale University School of Medicine), Meghan Donahue (Yale University School of Medicine), Ming -Kai Chen (Yale University School of Medicine), Nicole Barcelos (Yale University School of Medicine), Paul Eigenberger (Yale University School of Medicine), Robin Bonomi (Yale University School of Medicine), Ryan O'Dell (Yale University School of Medicine), Sarah Jefferson (Yale University School of Medicine), Siddharth Khasnavis (Yale University School of Medicine), Stephen Smilowitz (Yale University School of Medicine), Susan DeStefano (Yale University School of Medicine), Susan Good (Yale University School of Medicine), Terry Camarro (Yale University School of Medicine), Vanessa Clayton (Yale University School of Medicine), Yanis Cavrel (Yale University School of Medicine), YuQuan "Oliver" Lu (Yale University School of Medicine), Howard Chertkow (McGill Unive rsity, Montreal -Jewish General Hospital), Howard Bergman (McGill Unive rsity, Montreal -Jewish General Hospital), Chris Hosein (McGill Unive rsity, Montreal -Jewish General Hospital), Sandra Black (Sunnybrook Health Sciences, Ontario), Anish Kapadia (Sunnybrook Health Sciences, Ontario), Aparna Bhan (Sunnybrook Health Sciences, Ontario), Benjamin Lam (Sunnybrook Health Sciences, Ontario), Christopher Scott (Sunnybrook Health Sciences, Ontario), Gillian Gabriel (Sunnybrook Health Sciences, Ontario), Jennifer Bray (Sunnybrook Health Sciences, Ontario), Ljubica Zotovic (Sunnybrook Health Sciences, Ontario), Maria Samira Gutierrez (Sunnybrook Health Sciences, Ontario), Mario Masellis (Sunnybrook Health Sciences, Ontario), Marjan Farshadi (Sunnybrook Health Sciences, Ontario), Maurylette Gui (Sunnybrook Health Sciences, Ontario), Meghan Mitchell (Sunnybrook Health Sciences, Ontario), Rebecca Taylor (Sunnybrook Health Sciences, Ontario), Ruby Endre (Sunnybrook Health Sciences, Ontario), Zhala Taghi-Zada (Sunnybrook Health Sciences, Ontario), Robin Hsiung (University of British Columbia Clinic for AD & Related Disorders), Carolyn English (University of British Columbia Clinic for AD & Related Disorders), Ellen Kim (University of British Columbia Clinic for AD & Related Disorders), Eugene Yau (University of British Columbia Clinic for AD & Related Disorders), Haley Tong (University of British Columbia Clinic for AD & Related Disorders), Laura Barlow (University of British Columbia Clinic for AD & Related Disorders), Lauren Jennings (University of British Columbia Clinic for AD & Related Disorders), Michele Assaly

(University of British Columbia Clinic for AD & Related Disorders), Paula Nunes (University of British Columbia Clinic for AD & Related Disorders), Tahlee Marian (University of British Columbia Clinic for AD & Related Disorders), Andrew Kertesz (Cognitive Neurology St. Joseph's Ontario), John Rogers (Cognitive Neurology St. Joseph's Ontario), Dick Trost (Cognitive Neurology St. Joseph's Ontario), Dylan Wint (Cleveland Clinic Lou Ruvo Center for Brain Health), Charles Bernick (Cleveland Clinic Lou Ruvo Center for Brain Health), Donna Munic (Cleveland Clinic Lou Ruvo Center for Brain Health), Ian Grant (Northwestern University), Aaliyah Korkoyah (Northwestern University), Ali Raja (Northwestern University), Allison Lapins (Northwestern University), Caila Ryan (Northwestern University), Jelena Pejic (Northwestern University), Kailey Basham (Northwestern University), Leena Lukose (Northwestern University), Loreece Haddad (Northwestern University), Lucas Quinlan (Northwestern University), Nathaniel Houghtaling (Northwestern University), Carl Sadowsky (Premiere Research Inst (Palm Beach Neurology)), Walter Martinez (Premiere Research Inst (Palm Beach Neurology)), Teresa Villena (Premiere Research Inst (Palm Beach Neurology)), Brigid Reynolds (Georgetown University Medical Center), Angelica Forero (Georgetown University Medical Center), Carolyn Ward (Georgetown University Medical Center), Emma Brennan (Georgetown University Medical Center), Esteban Figueroa (Georgetown University Medical Center), Giuseppe Esposito (Georgetown University Medical Center), Jessica Mallory (Georgetown University Medical Center), Kathleen Johnson (Georgetown University Medical Center), Kathryn Turner (Georgetown University Medical Center), Katie Seidenberg (Georgetown University Medical Center), Kelly McCann (Georgetown University Medical Center), Margaret Bassett (Georgetown University Medical Center), Melanie Chadwick (Georgetown University Medical Center), Raymond Scott Turner (Georgetown University Medical Center), Robin Bean (Georgetown University Medical Center), Saurabh Sharma (Georgetown University Medical Center), Gad Marshall (Brigham and Women's Hospital), Aferdita Haviari (Brigham and Women's Hospital), Alison Pietras (Brigham and Women's Hospital), Bradley Wallace (Brigham and Women's Hospital), Catherine Munro (Brigham and Women's Hospital), Gladiliz Rivera -Delpin (Brigham and Women's Hospital), Hadley Husted (Brigham and Women's Hospital), Isabella Levesque (Brigham and Women's Hospital), Jennifer Ramirez (Brigham and Women's Hospital), Karen Nolan (Brigham and Women's Hospital), Kirsten Glennon (Brigham and Women's Hospital), Mariana Palou (Brigham and Women's Hospital), Michael Erkkinen (Brigham and Women's Hospital), Nicole DaSilva (Brigham and Women's Hospital), Pamela Friedman (Brigham and Women's Hospital), Regina M Silver (Brigham and Women's Hospital), Ricardo Salazar (Brigham and Women's Hospital), Roxanne Polleys (Brigham and Women's Hospital), Scott McGinnis (Brigham and Women's Hospital), Seth Gale (Brigham and Women's Hospital), Tia Hall (Brigham and Women's Hospital), Tuan Luu (Brigham and Women's Hospital), Steven Chao (Stanford University), Emmeline Lin (Stanford University), Jaila Coleman (Stanford University), Kevin Epperson (Stanford University), Minal Vasanawala (Stanford University), Alireza Atri (Banner Sun Health Research Institute), Amy Rangel (Banner Sun Health Research Institute), Brittani Evans (Banner Sun Health Research Institute), Candy Monarrez (Banner Sun Health Research Institute), Carol Cline (Banner Sun Health Research Institute), Carolyn Liebsack (Banner Sun Health Research Institute), Daniel Bandy (Banner Sun Health Research Institute), Danielle Goldfarb (Banner Sun Health Research Institute), Debbie Intorcia (Banner Sun Health Research Institute), Jennifer Olgin (Banner Sun Health Research Institute), Kelly Clark (Banner Sun Health Research Institute), Kelsey King (Banner Sun Health Research Institute), Kylee York (Banner Sun Health Research Institute), Marina Reade (Banner Sun Health Research Institute), Michael Callan (Banner Sun Health Research Institute), Michael Glass (Banner Sun Health Research Institute), Michaela Johnson (Banner Sun Health Research Institute), Michele Gutierrez (Banner Sun Health Research Institute), Molly Goddard (Banner Sun Health Research Institute), Nadira Trncic (Banner Sun Health Research Institute), Parichita Choudhury (Banner Sun Health Research Institute), Priscilla Reyes (Banner Sun Health Research Institute), Serena Lowery (Banner Sun Health Research Institute), Shaundra Hall (Banner Sun Health Research Institute), Sonia Olgin (Banner Sun Health Research Institute), Stephanie de Santiago (Banner Sun Health Research Institute), Michael Alosco (Boston University), Alyssa Ton (Boston University), Amanda Jimenez (Boston University), Andrew Ellison (Boston University), Anh Tran (Boston University), Brandon Anderson (Boston University), Della Carter (Boston University), Donna Veronelli (Boston University), Steven Lenio (Boston University), Eric Steinberg (Boston University), Jesse Mez (Boston University), Jason Weller (Boston University), Jennifer Johns (Boston University), Jessica Harkins (Boston University), Ina Hoti (Boston University), Jane Mwicigi (Boston University), Olivia Schultz (Boston University), Mona Lauture (Boston University), Ridiane Denis (Boston University), Ronald Killiany (Boston University), Sarab Singh (Boston University), Steven Lenio (Boston University), Wendy Qiu (Boston University), Ycar Devis (Boston University), Thomas Obisesan (Howard University), Andrew Stone (Howard University), Debra Ordor (Howard University), Ifreke Udodong (Howard University), Immaculata Okonkwo (Howard University), Javed Khan (Howard University), Jillian Turner (Howard University), Kyliah Hughes (Howard University), Oshoze Kadiri (Howard University), Charles Duffy (Case Western Reserve University), Ariana Moss (Case Western Reserve University), Katherine Stapleton (Case Western Reserve University), Maria Toth (Case Western Reserve University), Marianne Sanders (Case Western Reserve University), Martin Ayres (Case Western Reserve University), Melissa Hamski (Case Western

Reserve University), Parianne Fatica (Case Western Reserve University), Paula Ogrocki (Case Western Reserve University), Sarah Ash (Case Western Reserve University), Stacy Pot (Case Western Reserve University), Doris Chen (University of California, Davis Sacramento), Andres Soto (University of California, Davis Sacramento), Costin Tanase (University of California, Davis Sacramento), David Bissig (University of California, Davis Sacramento), Hafsanoor Vanya (University of California, Davis Sacramento), Heather Russell (University of California, Davis Sacramento), Hitesh Patel (University of California, Davis Sacramento), Hongzheng Zhang (University of California, Davis Sacramento), Kelly Wallace (University of California, Davis Sacramento), Kristi Ayers (University of California, Davis Sacramento), Maria Gallegos (University of California, Davis Sacramento), Martha Forloines (University of California, Davis Sacramento), Meghan Sinn (University of California, Davis Sacramento), Queenie Majorie S Kahulugan (University of California, Davis Sacramento), Richard Isip (University of California, Davis Sacramento), Sandra Calderon (University of California, Davis Sacramento), Talia Hamm (University of California, Davis Sacramento), Michael Borrie (Parkwood Hospital), T-Y Lee (Parkwood Hospital), Rob Bartha (Parkwood Hospital), Sterling Johnson (University of Wisconsin), Sanjay Asthana (University of Wisconsin), Cynthia M Carlsson (University of Wisconsin), Allison Perrin (Banner Alzheimer's Institute), Pierre Tariot (Banner Alzheimer's Institute), Adam Fleisher (Banner Alzheimer's Institute), Stephanie Reeder (Banner Alzheimer's Institute), Horacio Capote (Dent Neurologic Institute), Allison Emborsky (Dent Neurologic Institute), Anna Mattle (Dent Neurologic Institute), Bela Ajtai (Dent Neurologic Institute), Benjamin Wagner (Dent Neurologic Institute), Bennett Myers (Dent Neurologic Institute), Daryn Slazyk (Dent Neurologic Institute), Delaney Fragale (Dent Neurologic Institute), Erin Fransen (Dent Neurologic Institute), Heather Macnamara (Dent Neurologic Institute), Jonathan Falletta (Dent Neurologic Institute), Joseph Hirtreiter (Dent Neurologic Institute), Laszlo Mechtler (Dent Neurologic Institute), Megan King (Dent Neurologic Institute), Michael Asbach (Dent Neurologic Institute), Michelle Rainka (Dent Neurologic Institute), Richard Zawislak (Dent Neurologic Institute), Scott Wisniewski (Dent Neurologic Institute), Stephanie O'Malley (Dent Neurologic Institute), Tatiana Jimenez -Knight (Dent Neurologic Institute), Todd Peehler (Dent Neurologic Institute), Traci Aladeen (Dent Neurologic Institute), Vernice Bates (Dent Neurologic Institute), Violet Wenner (Dent Neurologic Institute), Wisam Elmaliik (Dent Neurologic Institute), Douglas W. Scharre (Ohio State University), Arun Ramamurthy (Ohio State University), Soumya Bouchace (Ohio State University), Maria Katakai (Ohio State University), Rawan Tarawneh (Ohio State University), Brendan Kelley (Ohio State University), Dzintra Celmins (Albany Medical College), Alicia Leader (Albany Medical College), Chris Figueroa (Albany Medical College), Heather Bauerle (Albany Medical College), Katlynn Patterson (Albany Medical College), Michael Reposo (Albany Medical College), Steven Presto (Albany Medical College), Tuba Ahmed (Albany Medical College), Wendy Stewart (Albany Medical College), Godfrey D Pearson (Hartford Hosp, Olin Neuropsychiatry Research Center), Karen Blank (Hartford Hosp, Olin Neuropsychiatry Research Center), Karen Anderson (Hartford Hosp, Olin Neuropsychiatry Research Center), Robert B Santulli (Dartmouth -Hitchcock Medical Center), Eben S Schwartz (Dartmouth -Hitchcock Medical Center), Jeff Williamson (Wake Forest University Health Sciences), Alicia Jessup (Wake Forest University Health Sciences), Andrea Williams (Wake Forest University Health Sciences), Crystal Duncan (Wake Forest University Health Sciences), Abigail O'Connell (Wake Forest University Health Sciences), Karen Gagnon (Wake Forest University Health Sciences), Ezequiel Zamora (Wake Forest University Health Sciences), James Bateman (Wake Forest University Health Sciences), Freda Crawford (Wake Forest University Health Sciences), Deb Thompson (Wake Forest University Health Sciences), Eboni Walker (Wake Forest University Health Sciences), Jennifer Rowell (Wake Forest University Health Sciences), Mikell White (Wake Forest University Health Sciences), Phillip "Hunter" Ledford (Wake Forest University Health Sciences), Sarah Bohlman (Wake Forest University Health Sciences), Susan Henkle (Wake Forest University Health Sciences), Joseph Bottoms (Wake Forest University Health Sciences), Lena Moretz (Wake Forest University Health Sciences), Bevan Hoover (Wake Forest University Health Sciences), Michael Shannon (Wake Forest University Health Sciences), Samantha Rogers (Wake Forest University Health Sciences), Wendy Baker (Wake Forest University Health Sciences), William Harrison (Wake Forest University Health Sciences), Chuang -Kuo Wu (Rhode Island Hospital), Alexis DeMarco (Rhode Island Hospital), Ava Stipanovich (Rhode Island Hospital), Daniel Arcuri (Rhode Island Hospital), Jan Clark (Rhode Island Hospital), Jennifer Davis (Rhode Island Hospital), Kerstin Doyon (Rhode Island Hospital), Marie Amoyaw (Rhode Island Hospital), Mauro Veras Acosta (Rhode Island Hospital), Ronald Bailey (Rhode Island Hospital), Scott Warren (Rhode Island Hospital), Terry Fogerty (Rhode Island Hospital), Victoria Sanborn (Rhode Island Hospital), Meghan Riddle (Butler Hospital), Stephen Salloway (Butler Hospital), Paul Malloy (Butler Hospital), Stephen Correia (Butler Hospital), Charles Windon (University of California San Francisco), Morgan Blackburn (University of California San Francisco), Howard J Rosen (University of California San Francisco), Bruce L Miller (University of California San Francisco), Amanda Smith (University of South Florida, Byrd Institute), Ijeoma Mba (University of South Florida, Byrd Institute), Jenny Echevarria (University of South Florida, Byrd Institute), Juris Janavs (University of South Florida, Byrd Institute), Emily Roglaski (University of Chicago), Meagan Yong (University of Chicago), Rebecca Devine (University of Chicago), Hamid Okhravi (Eastern Virginia Medical School), Edgardo Rivera (Charter Health Research Services), Teresa Kalowsky (Charter Health

Research Services), Caroline Smith (Charter Health Research Services), Christina Rosario (Charter Health Research Services), Joseph Masdeu (Houston Methodist Neurological Institute), Richard Le (Houston Methodist Neurological Institute), Maushami Gurung (Houston Methodist Neurological Institute), Marwan Sabbagh (Barrow Neurological Institute), Angelica Garcia (Barrow Neurological Institute), Micah Ellis Slaughter (Barrow Neurological Institute), Nadeen Elayan (Barrow Neurological Institute), Skieff Acotley (Barrow Neurological Institute), Nunzio Pomara (Nathan Kline Institute), Raymundo Hernando (Nathan Kline Institute), Vita Pomara (Nathan Kline Institute), Chelsea Reichert (Nathan Kline Institute), Olga Brawman-Mintzer (Ralph Johnson Veterans Administration Health Care Services), Allison Acree (Ralph Johnson Veterans Administration Health Care Services), Arthur Williams (Ralph Johnson Veterans Administration Health Care Services), Campbell Long (Ralph Johnson Veterans Administration Health Care Services), Rebecca Long (Ralph Johnson Veterans Administration Health Care Services), Paul Newhouse (Vanderbilt University Medical Center), Sydni Jene Hill (Vanderbilt University Medical Center), Amy Boegel (Vanderbilt University Medical Center), Sudha Seshadri (University of Texas Health, San Antonio), Amy Saklad (University of Texas Health, San Antonio), Floyd Jones (University of Texas Health, San Antonio), William Hu (Rutgers University), V Sotelo (Rutgers University), Yaneicy Gonzalez Rojas (Gonzalez & Aswad Health Services), Jacobo Mintzer (Medical University South Carolina), Crystal Flynn Longmire (Medical University South Carolina), Kenneth Spicer (Medical University South Carolina).

Contributors MR wrote the initial draft of the manuscript, conducted data modelling, statistical analyses, interpreted the data and prepared the figures. CC contributed to data modelling, statistical analyses and data visualisation. LD contributed to data preparation and quality control. JP supervised the work, provided critical feedback on the manuscript, contributed to its writing and data interpretation and is responsible for the overall content as the guarantor. All authors read, reviewed and approved the final manuscript.

Funding Data collection and sharing for this project were funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica; Biogen; Bristol-Myers Squibb Company; CereSpir; Cogstate; Eisai; Elan Pharmaceuticals; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche and its affiliated company Genentech; Fujirebio; GE Healthcare; IXICO; Janssen Alzheimer Immunotherapy Research & Development; Johnson & Johnson Pharmaceutical Research & Development; Lumosity; Lundbeck; Merck & Co.; Meso Scale Diagnostics; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer; Piramal Imaging; Servier; Takeda Pharmaceutical Company and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organisation is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. MR was supported by the 'Filling the Gap' Grant of the University of Zurich. This work has also been supported by grants from the Swiss National Science Foundation (grant number 320030_141179; 320030_204886) and from the Synapsis Foundation—Dementia Research Switzerland (grant number 2017-PI01).

Competing interests MR received speaker honoraria from OM Pharma; CC received consultation and speaker honoraria from OM Pharma; LD is an employee of the Société des Produits Nestlé SA; JP received consultation or speaker honoraria from the Nestlé Institute of Health Sciences, Ono Pharma, OM Pharma, Roche Therapeutics, Eisai, Eli Lilly, Schwabe Pharma and from Fujirebio Europe. All disclosures are unrelated to the present work.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. The data that support the findings of this study are accessible through the ADNI database (<http://adni.loni.usc.edu>). Interested researchers can request access through the ADNI website. The data used in the present study were downloaded in December 2022.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines,

terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Miriam Rabl <http://orcid.org/0000-0002-3189-6554>

Christopher Clark <http://orcid.org/0000-0001-7210-7702>

Loïc Dayon <http://orcid.org/0000-0002-8499-270X>

Julius Popp <http://orcid.org/0000-0002-0068-0312>

REFERENCES

- Eikelboom WS, van den Berg E, Singleton EH, et al. Neuropsychiatric and Cognitive Symptoms Across the Alzheimer Disease Clinical Spectrum: Cross-sectional and Longitudinal Associations. *Neurology (Ecricon)* 2021;97:e1276–87.
- Peters ME, Schwartz S, Han D, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: the Cache County Dementia Progression Study. *Am J Psychiatry* 2015;172:460–5.
- Peters ME, Rosenberg PB, Steinberg M, et al. Neuropsychiatric symptoms as risk factors for progression from CIND to dementia: the Cache County Study. *Am J Geriatr Psychiatry* 2013;21:1116–24.
- Clark C, Richiardi J, Maréchal B, et al. Systemic and central nervous system neuroinflammatory signatures of neuropsychiatric symptoms and related cognitive decline in older people. *J Neuroinflammation* 2022;19:127.
- Ouanes S, Rabl M, Clark C, et al. Persisting neuropsychiatric symptoms, Alzheimer's disease, and cerebrospinal fluid cortisol and dehydroepiandrosterone sulfate. *Alzheimers Res Ther* 2022;14:190.
- Showrak A, Murari G, Ismail Z, et al. Cerebrospinal Fluid Correlates of Neuropsychiatric Symptoms in Patients with Alzheimer's Disease/Mild Cognitive Impairment: A Systematic Review. *J Alzheimers Dis* 2019;71:477–501.
- Ng KP, Chiew H, Rosa-Neto P, et al. Associations of AT(N) biomarkers with neuropsychiatric symptoms in preclinical Alzheimer's disease and cognitively unimpaired individuals. *Transl Neurodegener* 2021;10:11.
- Nie J, Fang Y, Chen Y, et al. Characteristics of Dysregulated Proinflammatory Cytokines and Cognitive Dysfunction in Late-Life Depression and Amnesic Mild Cognitive Impairment. *Front Immunol* 2021;12:803633.
- Castro F, Melgarejo J, Chavez CA, et al. Total Plasma Homocysteine and Depressive Symptoms in Older Hispanics. *J Alzheimers Dis* 2021;82:S263–9.
- Moore K, Hughes CF, Hoey L, et al. B-vitamins in Relation to Depression in Older Adults Over 60 Years of Age: The Trinity Ulster Department of Agriculture (TUDA) Cohort Study. *J Am Med Dir Assoc* 2019;20:551–7.
- Sancesario GM, Bernardini S. Alzheimer's disease in the omics era. *Clin Biochem* 2018;59:9–16.
- Clark C, Rabl M, Dayon L, et al. The promise of multi-omics approaches to discover biological alterations with clinical relevance in Alzheimer's disease. *Front Aging Neurosci* 2022;14:1065904.
- Rabl M, Clark C, Dayon L, et al. Blood plasma protein profiles of neuropsychiatric symptoms and related cognitive decline in older people. *J Neurochem* 2023;164:242–54.
- Petersen RC, Aisen PS, Beckett LA, et al. Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. *Neurol (Ecricon)* 2010;74:201–9.
- Bondi MW, Edmonds EC, Jak AJ, et al. Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. *J Alzheimers Dis* 2014;42:275–89.
- McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263–9.
- Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci* 2000;12:233–9.
- Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. *Br J Psychiatry* 1982;140:566–72.
- Borland E, Edgar C, Stomrud E, et al. Clinically Relevant Changes for Cognitive Outcomes in Preclinical and Prodromal Cognitive Stages: Implications for Clinical Alzheimer Trials. *Neurology (Ecricon)* 2022;99:e1142–53.
- Ray S, Britschgi M, Herbert C, et al. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nat Med* 2007;13:1359–62.
- Kim S, Swaminathan S, Shen L, et al. Genome-wide association study of CSF biomarkers Abeta1-42, t-tau, and p-tau181p in the ADNI cohort. *Neurology (Ecricon)* 2011;76:69–79.
- Jack CR, Bennett DA, Blennow K, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alz Dement* 2018;14:535–62.
- Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol* 2009;65:403–13.
- Saykin AJ, Shen L, Foroud TM, et al. Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans. *Alzheimers Dement* 2010;6:265–73.
- Venables WN, Ripley BD. Modern Applied Statistics with S. Fourth Ed. New York: Springer, 2002.
- Robin X, Turck N, Hainard A, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011;12:77.
- Kuhn M. Building Predictive Models in R Using the caret Package. *J Stat Softw* 2008;28:1–26.
- Friedman J, Hastie T, Tibshirani R. Regularization Paths for Generalized Linear Models via Coordinate Descent. *J Stat Softw* 2010;33:1–22.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.
- Dayon L, Wojcik J, Núñez Galindo A, et al. Plasma Proteomic Profiles of Cerebrospinal Fluid-Defined Alzheimer's Disease Pathology in Older Adults. *J Alzheimers Dis* 2017;60:1641–52.
- Mroczek M, Clark C, Dayon L, et al. Cerebrospinal Fluid Proteome Alterations Associated with Neuropsychiatric Symptoms in Cognitive Decline and Alzheimer's Disease. *Cells* 2022;11:1030.
- Goodwin GJ, Moeller S, Nguyen A, et al. Network analysis of neuropsychiatric symptoms in Alzheimer's disease. *Alzheimers Res Ther* 2023;15:135.
- Zhou F, Sun Y, Xie X, et al. Blood and CSF chemokines in Alzheimer's disease and mild cognitive impairment: a systematic review and meta-analysis. *Alzheimers Res Ther* 2023;15:107.
- Stuart MJ, Singhal G, Baune BT. Systematic Review of the Neurobiological Relevance of Chemokines to Psychiatric Disorders. *Front Cell Neurosci* 2015;9:357.
- Holmgren S, Hjorth E, Schultzberg M, et al. Neuropsychiatric symptoms in dementia—a role for neuroinflammation? *Brain Res Bull* 2014;108:88–93.
- Correa BHM, Becari L, Fontes MAP, et al. Involvement of the Renin-Angiotensin System in Stress: State of the Art and Research Perspectives. *Curr Neuropharmacol* 2022;20:1212–28.
- de Miranda AS, Macedo DS, Rocha NP, et al. Targeting the Renin-Angiotensin System (RAS) for Neuropsychiatric Disorders. *Curr Neuropharmacol* 2022.
- Welcome MQ, Mastorakis NE. Stress-induced blood brain barrier disruption: Molecular mechanisms and signaling pathways. *Pharmacol Res* 2020;157:104769.
- Oliveira FF de, de Almeida SS, Smith MC, et al. Behavioural effects of the ACE insertion/deletion polymorphism in Alzheimer's disease depend upon stratification according to APOE-ε4 carrier status. *Cogn Neuropsychiatry* 2021;26:293–305.
- Nho K, Kueider-Paisley A, Ahmad S, et al. Association of Altered Liver Enzymes With Alzheimer Disease Diagnosis, Cognition, Neuroimaging Measures, and Cerebrospinal Fluid Biomarkers. *JAMA Netw Open* 2019;2:e197978.
- Lechner T, Adlassnig C, Humpel C, et al. Chromogranin peptides in Alzheimer's disease. *Exp Gerontol* 2004;39:101–13.
- Jin P, Xu J, Liao Z, et al. A review of current evidence for mild behavioral impairment as an early potential novel marker of Alzheimer's disease. *Front Psychiatry* 2023;14:1099333.
- de Oliveira FF, de Almeida SS, Chen ES, et al. APOE ε4 Carrier Status as Mediator of Effects of Psychotropic Drugs on Clinical Changes in Patients With Alzheimer's Disease. *J Neuropsychiatry Clin Neurosci* 2022;34:351–60.
- Lenski M, Sidibé J, Gholam M, et al. Metabolomic alteration induced by psychotropic drugs: Short-term metabolite profile as a predictor of weight gain evolution. *Clin Transl Sci* 2021;14:2544–55.
- Patel S, Keating BA, Dale RC. Anti-inflammatory properties of commonly used psychiatric drugs. *Front Neurosci* 2022;16:1039379.
- Masuda T, Mori A, Ito S, et al. Quantitative and targeted proteomics-based identification and validation of drug efficacy biomarkers. *Drug Metab Pharmacokinet* 2021;36:100361.
- Laboratory of Neuro Imaging, USC University of Southern California. Data from: image & data archive, July 23, 2024. n.d. Available: <https://ida.loni.usc.edu/>