Pragmatic, Data-Driven Method to Determine Cutoffs for CSF Biomarkers of Alzheimer Disease Based on Validation Against PET Imaging

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
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acquisition of data
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Figure Count:
2

Table Count:
3

Search Terms:

Acknowledgment:
H.Z. is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018-02532), the European Research Council (#681712), Swedish State Support for Clinical Research (#ALFGBG-720931), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), and the UK Dementia Research Institute at UCL. K.B. is supported by the Swedish Research Council (#2017-00915), the Alzheimer Drug Discovery Foundation (ADDF), USA (#RDAPB-201809-2016615), the Swedish Alzheimer Foundation (#AF-742881), Hjärnfonden, Sweden (#FO2017-0243), the Swedish state under the agreement between the government and the County Councils, the ALF-agreement (#ALFGBG-715986), and European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236). ASM is supported by grants from the National Institute on Aging, NIH (R01AG056477, RF1AG06255).

Study Funding:
The authors report no targeted funding

Disclosures:
H. Zetterberg has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinten Therapeutics, and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. C. E. Teunissen has a collaboration contract with ADx Neurosciences and Quanterix, performed contract research or received grants from AxonNeurosciences, Biogen, Boehringer, Brainstorm Therapeutics, Celgene, EIP Pharma, Esai, Janssen prevention center, Roche, Toyama, Vivoryon. T. Lebouvier has served at scientific advisory boards for Biogen and Roche and has given lectures in symposia sponsored by Biogen. K. Blennow has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. The remaining authors report no disclosures relevant to the manuscript.

Preprint DOI:

Received Date:
2021-09-08

Accepted Date:

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Abstract

Objective:
To elaborate a new algorithm to establish a standardized method to define cutoffs for CSF biomarkers of Alzheimer’s disease (AD) by validating the algorithm against CSF classification derived from PET imaging.

Methods:
Low and high levels of CSF phosphorylated tau were first identified to establish optimal cutoffs for CSF amyloid-β peptide (Aβ) biomarkers. These Aβ cutoffs were then used to determine cutoffs for CSF tau and phosphorylated tau markers. We compared this algorithm to a reference method, based on tau and amyloid PET imaging status (ADNI study), and then applied the algorithm to 10 large clinical cohorts of patients.

Results:
A total of 6,922 subjects with CSF biomarkers data were included (mean (SD) age: 70.6 (8.5) years, 51.0% women). In the ADNI study population (n=497), the agreement between classification based on our algorithm and one based on amyloid/tau PET imaging was high with Cohen’s kappa coefficient between 0.87 and 0.99. Applying the algorithm to 10 large cohorts of patients (n=6,425), the proportion of persons with AD ranged from 25.9% to 43.5%.

Discussion:
The proposed novel, pragmatic method to determine CSF biomarkers cutoffs for AD does not require assessment of other biomarkers or assumptions concerning the clinical diagnosis of patients. Use of this standardized algorithm is likely to reduce heterogeneity in AD classification.
Alzheimer’s disease (AD) is the most common cause of dementia, and it currently affects more than 40 million people worldwide. The disease is neuropathologically characterized by extraneuronal accumulation of amyloid β peptide (Aβ) in the brain (amyloid plaques), tau pathology in the form of intraneuronal deposits (neurofibrillary tangles) and dystrophic neurites surrounding plaques, massive synaptic loss, and neuronal death. The clinical consequence of the disease entails progressive deterioration of cognitive function leading to dementia.

The diagnosis of AD in health care settings and population studies is primarily based on clinical criteria, undertaken at the stage of dementia or of mild cognitive impairment (MCI). The clinical criteria have poor specificity due to similarity in symptoms between many degenerative and non-degenerative disorders. The discovery of specific biomarkers of AD neuropathological lesions over the two past decades, consisting mainly of cerebrospinal fluid (CSF) biomarkers and PET imaging radio-ligands, has improved specificity of AD diagnosis and is likely to play a crucial role in the elaboration of therapeutic solutions in the future. Tau and Aβ peptide biomarkers have been included in the new research diagnostic criteria of AD with the aim of increasing biological homogeneity of diagnosed cases. The research criteria are based on the A/T/(N) classification with markers of Aβ deposition (A), pathologic tau (T), and neurodegeneration (N); each biomarker is categorized as positive or negative to yield AD diagnosis without use of clinical diagnostic criteria. 

**Glossary**

Aβ = amyloid β peptide; AD = Alzheimer’s disease; AUC = Area under ROC Curve; CSF = cerebrospinal fluid; p-Tau 181 = Tau phosphorylated at threonine 181.
There exist CSF based measures of Aβ peptide (CSF Aβ42, CSF Aβ42/40 ratio) and protein Tau (total tau: CSF Tau, phosphorylated tau: CSF p-Tau 181), that are amenable to the A/T/(N) classification.\textsuperscript{12} Biomarkers are increasingly being used to diagnose AD, and a previous study showed that faced with discrepancies between the clinical presentation and biomarker profile the final diagnosis was based on the biomarker profile in up to 75\% of cases.\textsuperscript{13} The reliability and accuracy of biomarker-based diagnosis has implications for clinicians involved in AD diagnosis and their patients. A major concern is the considerable inter-site variability in biomarker levels using standard ELISA methods,\textsuperscript{14} leading to the recommendation that each biochemistry laboratory establishes its own cut-offs to determine positive status on these biomarkers.\textsuperscript{2,15,16} Despite recent efforts from manufacturers to develop automated assays\textsuperscript{17,18} and initiatives from research groups to standardize procedures,\textsuperscript{16,19} a universal cut-offs for CSF AD biomarkers remains to be established. In an international systematic review of 40 centers involved in AD diagnosis worldwide, only 16\% reported using cut-offs provided by the manufacturer, and 4\% used cut-offs based on the literature, and the remaining used in-house cut-offs.\textsuperscript{20} The methodology used to determine these cut-offs remains unclear as consensus on the gold-standard method to determine cut-offs to designate positive biomarker status does not yet exist.\textsuperscript{21} Several parameters play a role in the observed variability of CSF biomarkers, including polypropylene tube used during the lumbar puncture.\textsuperscript{22}

The most commonly method used to determine the threshold for CSF Aβ42 positivity is comparison with amyloid PET imaging.\textsuperscript{23} Another method involves use of rank-based thresholds (90th or 95th percentile) as is the case for CSF Aβ42 and tau.\textsuperscript{24} Other methods include comparison between AD and non-AD patients based on clinical criteria,\textsuperscript{14} post-mortem neuropathological criteria,\textsuperscript{25} or cut-offs based on the distribution of CSF Aβ42 across
the total population. All these methods have limitations, with some of them not being readily reproducible.

We propose a new method to standardize the procedure used to determine cut-offs for CSF biomarkers. The objective is to develop a simple algorithm that does not require biomarkers other than CSF biomarkers, and can be used by others to homogenize the manner in which cut-offs are determined. Our strategy consists of using CSF p-tau 181, a specific biomarker of AD, to determine the cut-offs values for beta-amyloid biomarkers to allow cross-validation between biomarkers. We first compared results of our algorithm with cut-offs based on amyloid and tau PET imaging using data from the ADNI study, and then we applied our method to ten patient-cohorts drawn from memory centers.

Methods

Study population
The ADNI study, launched in 2003, is a global research study involving 63 sites in the US and Canada that aims to characterize progression of AD in the human brain with clinical, imaging, genetic and biospecimen biomarkers through the process of normal aging, mild cognitive impairment to dementia or AD.

Memory center patients were drawn from several research centers in Europe (France (Paris, Lille, Montpellier), Sweden (Gothenburg), Spain (Barcelona), Belgium (Brussels), and Netherlands (Amsterdam)). The technique used for CSF biomarkers dosage was the same within each center. All patients had CSF biomarkers assessment as part of their investigation for a cognitive disorder.
Standard Protocol Approvals, Registrations, and Participant Consents

Ethical clearance was obtained by the institutional review boards of all participating sites. All participants provided written, informed consent.

Assessment of CSF biomarkers

CSF concentrations of Aβ42, Aβ40, total Tau, and p-Tau 181 were measured with commercially available immunoassays, using the manufacturer’s procedures. Four different methods were used: 1. The Elecsys immunoassays using the cobas e601 analyzer (Roche Diagnostics GmbH). 2. The INNOTEST immunoassays (Fujirebio Europe, Gent, Belgium). 3. The Lumipulse G 1200 (Fujirebio Europe, Gent, Belgium). 4. The Euroimmun analyzer I-2P (Euroimmun AG, Luebeck, Germany).

Some centers (Paris, Montpellier, Lille) contributed 2 patient-cohorts as they used 2 different methods over time for the dosage of biomarkers. CSF samples in the ADNI study were analyzed using Elecsys immunoassays. We decided not to include older CSF ADNI data from the Luminex platform due to the long delay, approximately 5 years, between the CSF and tau PET measures. More complete information regarding CSF data in ADNI is available online.29

Amyloid and tau PET imaging (ADNI)

We used data from the ADNI study on participants with data on CSF biomarkers and at least one PET imaging of beta-amyloid or tau radiotracer; further information on acquisition of PET data in ADNI is provided on the ADNI website.29 Amyloid PET imaging was performed using florbetapir (AV-45) radioligand,30 we used the following data: UCBERKELEYAV45_05_12_20-2.csv. Positivity for florbetapir PET imaging was defined by a global standard uptake value ratio (SUVR) higher than 1.11 using the whole cerebellum
as reference region, this cut-off was defined as the upper 95% confidence interval above the mean in a group of young, cognitively-normal controls in cross-sectional analyses.\textsuperscript{31}

Positivity for tau PET was determined using flortaucipir (AV-1451) imaging,\textsuperscript{32} and we used the following data: UCBERKELEYAV1451_05_12_20.csv. Flortaucipir SUVR maps were generated using the inferior cerebellar gray matter as a reference region.\textsuperscript{32} Positivity of flortaucipir was defined as an SUVR of the Braak 1 and 2 composite region higher than 1.32, which has been found to be the optimal cut points to separate Aβ+ AD patients from Aβ– elderly controls in cross-sectional analyses.\textsuperscript{33}

**Algorithm for CSF cut-offs determination**

The algorithm was defined prior to data analyses, based on consensus between the authors of the manuscript; this group includes clinicians and biologists with extensive experience in the field of AD biomarkers. The steps of the algorithm are shown in Table 1.

The first step consisted of identifying participants with “low CSF p-Tau 181” (between the 10\textsuperscript{th} and 30\textsuperscript{th} percentile of the CSF p-Tau 181 distribution) and “high CSF p-Tau 181” (between 80\textsuperscript{th} and 100\textsuperscript{th} percentile), separately in each cohort. Participants with values between 0 to 10\textsuperscript{th} percentile were removed from the analyses to avoid abnormally low values that reflect either measurement error or normal pressure hydrocephalus.\textsuperscript{34} We then determined the ability of CSF Aβ42/40 ratio and/or CSF Aβ42 to discriminate between participants with “high CSF p-Tau 181” from “low CSF p-Tau 181” using Area under the ROC Curve (AUC). Optimal cut-offs for CSF Aβ42/40 ratio and CSF Aβ42 were defined as the lowest distance to the top left corner of the ROC curve. The known analytical variability in the CSF Aβ42 assays imply that values near the cut-off are difficult to classify as normal or abnormal leading several teams to use the term “gray zone” to describe values 10% around the threshold.\textsuperscript{12,35} We used values ≤ 90\% to identify participants with “low CSF Aβ42/40 ratio” and ≥ 110\% for “high CSF Aβ42/40 ratio” and then performed ROC curve analysis to
determine the AUC and optimum cut-offs for CSF Tau and CSF p-Tau 181 to discriminate between these 2 groups (high vs low CSF Aβ42/40 ratio). In the absence of data on CSF Aβ42/40 ratio, we used CSF Aβ42.

Stata code used to derive the algorithm has been uploaded to a GitHub repository:36 the “Sensspec” Stata module was used to compute sensitivity and specificity.37

Statistical analysis
The characteristics of participants were examined in each cohort; proportions were calculated for categorical variables, and mean and standard deviation for continuous variables.

Figure 1 illustrates the overall design of the study. The first step consisted of validation of the proposed algorithm using data from the ADNI study by comparing CSF biomarker positivity determined using our proposed algorithm with that based on tau and amyloid PET imaging. Amyloid positivity in ADNI was defined using florbetapir amyloid PET imaging (cut-off for SUVR=1.11), and then AUC for CSF Aβ42/40 ratio and CSF Aβ42 was used to discriminate between positive and negative cases. The optimal cut-offs for CSF Aβ42/40 and CSF Aβ42 were established as the lowest distance to the top left corner in the ROC curve. We used the same method to determine cut-offs for CSF Tau and CSF p-Tau 181 using flortaucipir tau PET imaging (tau positive if SUVR≥1.32). The agreement between the algorithm and PET method to determine cut-offs was examined using Cohen's kappa coefficient,38 and the overall percent agreement, defined as the number of true positive and true negative divided by the total number of participants.

In a second step, we applied our algorithm (Table 1) to ten patient-cohorts drawn from memory clinics. We compared the AUC of ROC curves between CSF Aβ42/40 ratio and CSF Aβ42 for discriminating between high and low levels of CSF pTau-181 using a non-parametric approach based on an estimated covariance matrix (“roccomp” command in Stata).39 We estimated the reliability of the cut-offs using the following rule: strong reliability
if the three AUC used for the cut-offs determination were higher than 0.85, medium reliability if at least one AUC used was between 0.75 and 0.85, and low reliability if at least one AUC was lower to 0.75.

We then applied the cut-offs established to determine the proportion of CSF biomarkers profiles in each cohort of patients using the AT(N) classification: A+ (CSF $A\beta_{42}/40$ ratio or CSF $A\beta_{42}$ lower than the cut-off), T+ (CSF pTau-181 higher than the cut-off).

As the thresholds used to determine low and high levels of p-tau181 (step 2, Table 1) and $A\beta$ markers (step 5, Table 1) are somewhat arbitrary, in sensitivity analysis we examined other thresholds to test the robustness of the algorithm. These analyses were undertaken on ADNI to compare results with tau and amyloid PET criteria.

All resulting p-values were two-tailed and p<0.05 was considered statistically significant. Statistical analyses were performed using Stata Statistical Software: Release 14 (College Station, TX: StataCorp LP).

**Data Availability**

Data are available for the purposes of replicating procedures and results from the corresponding author upon request.

**Results**

*Characteristics of the participants*

A total of 6,922 subjects from 11 cohorts with data on CSF biomarkers were included in this study; their characteristics are shown in the eTable 1 in the Supplement. The mean (SD) age of patients ranged from 62.8 (7.1) to 72.7 (8.0) years, the mean (SD) MMSE score was between 20.0 (5.7) and 27.2 (2.0) and the proportion of women was from 43.3% to 56.2%. The percentage of patients with dementia in the various cohorts ranged from 13.3% to 54.6%.
Fujirebio Lumipulse was used in 4 cohorts, Fujirebio INNOTEST and Roche Elecsys in 3 cohorts, and Euroimmun in 1 cohort. The distribution of CSF biomarkers in all cohort is shown in eFigure 1.

Validation of the algorithm in the ADNI Study.
In ADNI the CSF biomarkers were assessed using Elecsys immunoassays; the mean (SD) delay between CSF biomarkers assessment and tau PET imaging was 0.77 (1.9) years, and 2.9 (2.8) years for amyloid PET imaging. Table 2 shows the AUC and corresponding optimal cut-offs for CSF biomarkers in the ADNI Study using two methods: one based on amyloid and tau PET imaging and one based on our algorithm. The agreement between these 2 methods was high, with Cohen’s kappa coefficient greater than 0.85 (range 0.87 to 0.99) and overall percent agreement greater than 0.90 (range 0.93 to 0.99) for all biomarkers. The confusion matrix of classification of ADNI participants using the 2 methods is shown in eTable 2.

CSF Aβ markers to discriminate between high and low CSF ptau levels.
The ability of CSF Aβ42 and CSF Aβ42/40 ratio to discriminate "high CSF pTau-181" from "low CSF pTau-181" in the ten patient-cohorts is presented in eTable 3. The AUC associated with CSF Aβ42/40 ratio ranged from 0.86 to 0.99; while the AUC associated with CSF Aβ42 ranged from 0.55 to 0.87. In all centers, CSF Aβ42/40 ratio outperformed CSF Aβ42 in discriminating high from low CSF pTau-181 (p<0.001), Figure 2 illustrates the comparison of ROC curves for these two markers in four cohorts.

CSF tau and ptau to discriminate between high and low CSF Aβ levels.
eTable 4 shows the AUC corresponding to CSF Tau and CSF p-Tau 181 to discriminate between "low Aβ amyloid" and "high Aβ amyloid ". Overall, CSF p-Tau 181 was associated
with high AUC values to discriminate low from high CSF Aβ42/40 ratio (range from 0.84 to 0.97), while slightly lower AUCs were observed for CSF Tau (range from 0.79 to 0.90).

*Application of the algorithm in the patient-cohorts from memory centers.*

CSF biomarkers cut-offs identified by the proposed algorithm are presented in Table 3. For CSF Aβ42, the cut-offs ranged from 505 pg/mL to 978 pg/mL, depending on the center and the technique used. The reliability of the cut-offs was strong for 7 of the 10 cohorts, medium in 2 cohorts and low for 1 of them.

The proportion of CSF AD profiles (A+/T+) in each center is shown in the eFigure 2, and ranged from 25.9% to 43.5% of persons seen in these centers.

*Sensitivity analyses*

We reran the analyses using other thresholds for defining high/low levels of phosphorylated tau markers (step 2, Table 1) and beta-amyloid peptide markers (step 5, Table 1) in the algorithm; results are shown in eTables 5 and 6. Overall, these analyses did not show improvement in the thresholds chosen in our algorithm.

*Discussion*

Using a large, multi-centre study of around 6,000 participants, we propose a new method to determine cut-offs for CSF biomarkers in clinical settings which was validated against amyloid and tau PET imaging. Our method has the advantage of being applicable in other research settings as it is based on simple statistical analysis and does not require clinical or biomarker data other than CSF biomarkers. Our method, which consists of proposing a method to homogenize the determination of cut-offs, will allow greater transparency in the use of biomarkers for the diagnosis of Alzheimer's disease. Two main lessons can also be learnt from our results. One, despite recent development of automated assays, there remains
significant variation in absolute biomarker thresholds between sites and further efforts to standardize procedures should be pursued, particularly for pre-analytic parameters. Therefore, our algorithm did not aim to provide universal cut-offs for CSF biomarkers. Two, our results plead for the use of CSF Aβ42/40 ratio instead of CSF Aβ42 alone, at least for the identification of patients with fibrillar tau pathology. Amyloid ratio was excellent at discriminating between individuals with high and low phosphorylated tau levels, the AUC was higher than 0.95 in most of the centers, while CSF Aβ42 alone had lower discrimination. The extent to which this translates to diagnostic superiority of CSF Aβ42/40 ratio against CSF Aβ42 alone in clinical settings remains to be demonstrated.

Defining biomarker thresholds is a common challenge in medicine, but it is particularly challenging for AD diagnosis because the difference between normal and pathologic conditions is not always clear and there is great variability in measured biomarkers. The current gold standard uses PET amyloid imaging to determine CSF Aβ cut-offs. However, this method requires identification of “positive” and “negative” cases based on PET results, which raises questions on how to define cut-offs for PET, and the accuracy of such definitions. A further concern is that several studies show discrepancies between PET amyloid imaging and CSF Aβ assessment, as the latter can show abnormalities earlier in the disease process reflected in low value for CSF Aβ42 and normal amyloid PET imaging.

Cut-offs based on clinical diagnosis (AD versus non-AD categorization) has also been proposed but it has limitations due to the lack of specificity of diagnostic criteria, with approximately 30% of false positives compared to neuropathological findings. Phosphorylated tau appears to be the most specific marker of AD; despite elevated levels in rare conditions such as Chronic Traumatic Encephalopathy (CTE). Low levels of CSF Aβ42 has been reported in other frequent causes of dementia, including Lewy Body disease and vascular dementia. Increasingly, attempts are being made to identify blood-based...
biomarkers of AD, particularly phosphorylated tau isoforms in plasma. Whether blood-based biomarkers are useful in clinical settings for the diagnosis of patients remains unclear, particularly for determining cut-offs. Our approach based on cross-validation between biomarkers could be useful in this context.

Our approach was based on cross-validation of biomarkers by first determining the ability of Aβ markers to discriminate between high versus low levels of phosphorylated tau. The cross-validation of biomarkers has been used previously for defining imaging biomarker cut-offs, using the results of amyloid-PET to define tau PET, FDG PET and structural MRI biomarkers cut-offs. A disadvantage of this approach is that individuals with AD can have variable degrees of tau and Aβ pathology and the approach we used may misclassify some individuals. The existence of multiple pathologies, involving proteins such as TDP-43 or alpha-synuclein, may contribute to the clinical expression of disease but is unlikely to affect AD classification. Our aim was not to compare CSF biomarkers to PET imaging for AD diagnosis. Both techniques have their advantages and disadvantages, and both can be used to define the A/T/N status. While PET imaging is informative on localization of neuropathological lesions as well as change therein over time, CSF biomarkers are more readily available in many diagnostic centers due to cost and feasibility issues.

The main strength of this study is elaboration of a pragmatic method to determine cut-offs for CSF biomarkers for AD so that it can be readily replicated in other centers. The validity of the algorithm was established by comparing findings with amyloid and tau PET imaging. There are also a number of limitations. One, by design the CSF biomarker assessment and PET imaging was not undertaken at the same time in ADNI and whether this affects determination of cut-offs is unclear. It is worth noting that few studies have longitudinal data and they show slow change in CSF AD biomarkers. Two, we used PET biomarkers to validate the algorithm but tau and amyloid imaging positivity remains
somewhat arbitrary, and a true gold standard for identifying AD and non-AD is lacking. Premortem CSF assessment and neuropathological confirmation would be useful in future studies. Three, the data in our analyses did not come from a centralized assessment of CSF biomarkers. However, our objective was not to propose a universal cut-off but a standardized method that can be used to determine cut-offs in each study. Four, we assumed that the distribution of CSF p-Tau among patients offers sufficient variability to establish reliable cut-offs for CSF Aβ markers. Five, the algorithm is best suited for use in memory clinics with sufficient proportion of AD and non-AD patients but whether this method is suited for other settings, for example a population of at-risk older adults, remains to be determined. Finally, many parameters such as age, APOE e4 status, or the stage of disease are likely to affect biomarker levels and how these parameters affect diagnosis of AD needs to be investigated in future studies.

To conclude, we propose a novel, pragmatic method to determine CSF AD biomarkers cut-offs in clinical settings which does not require assessment of other biomarkers or assumptions concerning the clinical profile of patients. The underlying reasoning behind our approach is that a common method for determining cut-offs will be useful in reducing heterogeneity in research and clinical settings that undertake research on AD. Our results suggest that use of CSF Aβ42/40 ratio instead of or in addition to CSF Aβ42 alone, should be promoted to determine the Aβ status based on CSF biomarkers.
References


Figure legend.

Figure 1. Procedures used in the application of the algorithm.
Figure 2. Ability of CSF Aβ42/40 ratio (red) and CSF Aβ42 (blue) to discriminate between high and low levels of CSF p-Tau 181. ROC curve analysis.
## Table 1. Algorithm used to determine cut-offs for CSF biomarkers

1. The method is best applied to a population of at least 100 patients from clinical settings with data on CSF biomarkers.

2. Select patients with "low CSF pTau-181" ($\leq 10^{\text{th}}$ to $30^{\text{th}}$ percentile) and "high CSF pTau-181" ($80^{\text{th}}$ to $100^{\text{th}}$ percentile).

3. Estimate AUC for CSF Aβ42/40 ratio (replaced by CSF Aβ42 if Aβ42/40 ratio not available) to separate "high CSF pTau-181" from "low CSF pTau-181".

4. Determine cut-off for CSF Aβ42/40 ratio and CSF Aβ42 based on ROC curve analysis as the lowest distance to the top left corner.

5. Identify 2 categories of patients based on cut-offs defined in step 4: "high CSF Aβ42/40 ratio" ($\geq 110\%$ using previously determined cut-off) and "low CSF Aβ42/40 ratio" ($\leq 90\%$ using previously determined cut-off). In the absence of CSF Aβ42/40 ratio, CSF Aβ42 should be used.

6. Calculate AUC for CSF Tau and CSF pTau-181 to discriminate "high CSF pTau-181" from "low CSF pTau-181".

7. Determine cut-off for CSF Tau and CSF pTau-181 based on ROC curve analysis as the lowest distance to the top left corner.
Table 2. CSF biomarkers cut-offs in the ADNI Study based on amyloid and tau PET imaging and our algorithm.

<table>
<thead>
<tr>
<th>ADNI CSF biomarkers</th>
<th>N</th>
<th>Delay CSF/PET&lt;sup&gt;a&lt;/sup&gt; years, mean (SD)</th>
<th>PET imaging&lt;sup&gt;b&lt;/sup&gt; AUC (SE) Cut-off</th>
<th>Algorithm&lt;sup&gt;c&lt;/sup&gt; AUC (SE) Cut-off</th>
<th>Kappa (SE)</th>
<th>percent agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elecsys</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF A(\beta)42</td>
<td>240</td>
<td>2.9 (2.8)</td>
<td>0.88 (0.02) 981</td>
<td>0.74 (0.04) 963</td>
<td>0.88 (0.05)</td>
<td>0.96</td>
</tr>
<tr>
<td>CSF A(\beta)42/40 ratio</td>
<td>240</td>
<td>2.9 (2.8)</td>
<td>0.90 (0.02) 0.0528</td>
<td>0.91 (0.04) 0.0525</td>
<td>0.99 (0.05)</td>
<td>0.99</td>
</tr>
<tr>
<td>CSF p-Tau 181</td>
<td>373</td>
<td>0.77 (1.9)</td>
<td>0.79 (0.03) 24.3</td>
<td>0.86 (0.02) 22</td>
<td>0.87 (0.05)</td>
<td>0.93</td>
</tr>
<tr>
<td>CSF tau</td>
<td>373</td>
<td>0.77 (1.9)</td>
<td>0.76 (0.03) 254</td>
<td>0.83 (0.02) 241</td>
<td>0.89 (0.05)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

<sup>a</sup>Delay between PET amyloid (AV-45) and CSF A\(\beta\)42 and A\(\beta\)42/40 ratio, and PET Tau (AV-1451) and CSF Tau and p-Tau 181.

<sup>b</sup>Amyloid PET (AV-45) and tau PET (AV-1451) were used for the determination of the cut-offs of CSF amyloid and tau biomarkers respectively.

<sup>c</sup>Algorithm is shown in Table 1.
Table 3. Optimal CSF biomarkers cut-offs in each center, sorted according to technique used in the analyses

<table>
<thead>
<tr>
<th>Centers</th>
<th>Technique</th>
<th>CSF Optimal cut-offs, pg/mL</th>
<th></th>
<th></th>
<th></th>
<th>Reliability</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Aβ42</td>
<td>Aβ42/40 ratio</td>
<td>Tau</td>
<td>pTau-181</td>
<td></td>
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<tr>
<td>Paris-2</td>
<td>Elecsys</td>
<td>865</td>
<td>0.080</td>
<td>228</td>
<td>20.4</td>
<td>Strong</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>Elecsys</td>
<td>978</td>
<td>0.064</td>
<td>282</td>
<td>38</td>
<td>Strong</td>
</tr>
<tr>
<td>Montpellier-2</td>
<td>LumiPulse</td>
<td>614</td>
<td>0.062</td>
<td>358</td>
<td>43</td>
<td>Strong</td>
</tr>
<tr>
<td>Lille-2</td>
<td>LumiPulse</td>
<td>642</td>
<td>0.052</td>
<td>559</td>
<td>75</td>
<td>Strong</td>
</tr>
<tr>
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<td>LumiPulse</td>
<td>764</td>
<td>0.059</td>
<td>370</td>
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<td>Strong</td>
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<tr>
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<td>LumiPulse</td>
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<td></td>
<td>412</td>
<td>56</td>
<td>Low</td>
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<tr>
<td>Paris-1</td>
<td>Innotest</td>
<td>652</td>
<td>0.068</td>
<td>355</td>
<td>56</td>
<td>Strong</td>
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<tr>
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<td>821</td>
<td>0.076</td>
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<td>59</td>
<td>Medium</td>
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<tr>
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<td>0.090</td>
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<td>Strong</td>
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<tr>
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<td>734</td>
<td>0.098</td>
<td>529</td>
<td>55</td>
<td>Medium</td>
</tr>
</tbody>
</table>
Pragmatic, Data-Driven Method to Determine Cutoffs for CSF Biomarkers of Alzheimer Disease Based on Validation Against PET Imaging
Julien Dumurgier, Séverine Sabia, Henrik Zetterberg, et al.

Neurology published online May 26, 2022
DOI 10.1212/WNL.0000000000200735

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