Usefulness of plasma amyloid as a prescreener for the earliest Alzheimer pathological changes depends on the study population

Prins, S.; Zhuparris, A.; Groeneveld, G.J.

Usefulness of Plasma Amyloid as a Prescreener for the Earliest Alzheimer Pathological Changes Depends on the Study Population

Samantha Prins, Ahnjili Zhuparris, and Geert Jan Groeneveld

Recently, Verberk et al showed that plasma Aβ42/Aβ40 ratio has potential to identify Alzheimer pathological changes in subjects with subjective memory decline.[1] Furthermore, the inclusion of age and APOEε4 carriership in their multivariate model improved the likelihood of identification. Based on these results, Verberk and colleagues postulated that plasma Aβ42/Aβ40 ratio could be a potential prescreener to identify the earliest Alzheimer disease (AD) pathological changes in individuals with subjective memory decline.

We aimed to extend the findings of Verberk et al, using the same statistical methods, but in a different population, namely healthy elderly subjects *without* memory complaints (N = 189). Subjects in this study were male and female, aged 72 years (mean; range = 65–86), with a mean Mini-Mental State Examination score of 28.8 (range = 25–30), and 15-item Geriatric Depression Scale score of 0.7 (mean; range = 0–5). Subjects were excluded if they had a cognitive or psychiatric disorder, or a history of drug and/or alcohol abuse. If a subject used medication that affected the central nervous system, or medication with a contraindication for a lumbar puncture, they would also be excluded. Self-reported memory performance and daily functioning were assessed with the Clinical Dementia Rating scale–sum of boxes (CDR) and the Instrumental Activities of Daily Living scale (IADL) in participating subjects only. Average CDR and IADL scores were 0 in all subjects.

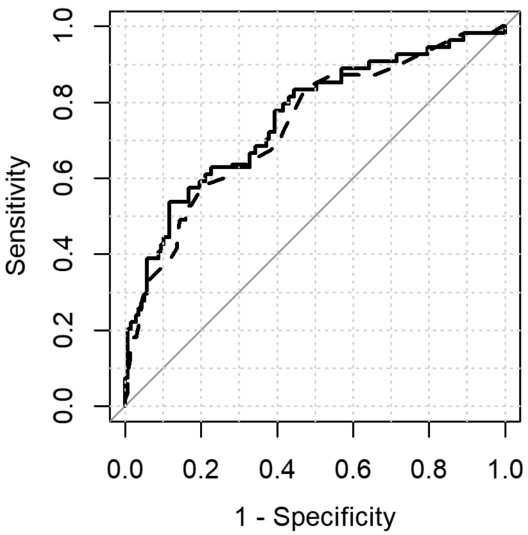

FIGURE 1: Receiver operating characteristic (ROC) curves of logistic regression models that discriminate between cerebrospinal fluid (CSF) amyloid abnormal and amyloid normal (based on CSF amyloid beta 42 scores) among healthy elderly subjects. Solid black line: Variables within the logistic regression model are Aβ ratio, APOEε4 carriership, and age. The area under the curve (AUC) is 75.7%, and the 95% confidence interval (CI) is 67.8–83.6%. Dashed line: Variables within this logistic regression model only include APOEε4 carriership and age. AUC = 73.8%, 95% CI = 65.8–81.8%. Gray line indicates 50% reference line.

The sensitivity and specificity of the plasma Aβ42/Aβ40 ratio in our study were 30.8% and 71%, respectively, compared to 76% and 75% in Verberk et al. The results of our logistic regression and receiver operating characteristic (ROC) analyses showed that the plasma Aβ42/Aβ40 ratio did not significantly affect ROC curves discriminating between cerebrospinal fluid amyloid abnormal and amyloid normal individuals, in a multivariate model including age and APOEε4 carriership (Fig).

Applying Verberk's model to subjects in our sample would theoretically identify "preclinical" elderly, defined as elderly with biomarker evidence consistent with AD but without cognitive complaints.[2] However, due to the low sensitivity (30.8%) of the model in our sample, we would miss a substantial number of healthy elderly with AD pathology, whom we need for participation in clinical trials on the prevention of AD.

To build a model generalizable to an independent dataset, cross-validation of the regression model is crucial.[3] Knowing that Verberk et al did not cross-validate their model, overfitting of the sampled data is a possible explanation for the discrepancy between Verberk's and our findings. Although there is a maximum of 3 features included in Verberk's multivariate model, if the model is trained on a homogenous population, overfitting can be a likely occurrence. We therefore think that the findings from the study of Verberk et al can only be limitedly extrapolated to a different population, and that their conclusion that plasma amyloid is a prescreener for the earliest AD pathological changes, as stated in the title of their article, seems as yet too strong.

Another possible explanation for the divergent outcomes in the study by Verberk et al and ours may simply be the difference in populations. Past research has shown that subjects *with* subjective memory complaints are more likely to progress to dementia than healthy elderly without. Also, these subjects tend to have a higher chance of being Apoe4 carriers.[4] Based on our findings, we can either conclude that Verberk's regression model was overfitted and cannot be extrapolated to new data, or that plasma Aβ42/Aβ40 ratio is not a potential prescreener to identify elderly *without* memory complaints.

Potential Conflicts of Interest

Nothing to report.

Centre for Human Drug Research, Leiden, the Netherlands

References

1. Verberk IMW, Slot RE, Verfaillie SCJ, et al. Plasma amyloid as prescreener for the earliest Alzheimer pathological changes. Ann Neurol 2018;84:648–658.
2. Jack CR Jr, Bennet DA, Blennow K, et al. NIAA-AA Research Framework: Toward a biological definition of Alzheimer's disease. Alzheimer Dement 2018;14:535–562.
3. Picard RR, Cook D. Cross-validation of regression models. J Am Stat Assoc 1984;79:387,575–583.
4. Zwan MD, Villemagne VL, Doré V, et al. Subjective memory complaints in APOE ε4 carriers are associated with high amyloid-β burden. J Alzheimers Dis 2016;49:1115–1122.

DOI: 10.1002/ana.25634

Reply to "Usefulness of Plasma Amyloid as Prescreener of the Earliest Alzheimer Pathological Changes Depends on the Study Population"

Inge M. W. Verberk, MSc,[1,2] Charlotte E. Teunissen, PhD,[2] and Wiesje. M. Van der Flier, PhD[1]

We thank Prins et al for applying the methods of our article on "Plasma Amyloid as Prescreener for the Earliest Alzheimer Pathological Changes"[1] to their research. Designing prescreening tools for amyloid positivity will ultimately facilitate recruitment of cognitively normal participants for Alzheimer disease clinical trials.

Current studies comparing the performance of blood-based amyloid assays, as well as efforts to compare effects of preanalytical sample handling procedures, show that accurate blood-based amyloid measurement is highly complex. Nevertheless, Prins and colleagues did not provide information on the plasma type, preanalytical sample handling procedures, and method of plasma amyloid measurement. Also, essential details on the lumbar puncture procedure and cerebrospinal fluid (CSF) measurement method were lacking, as were details on the demographics of the included population, such as recruitment method, medical history, prevalence of amyloid positivity, and distribution of APOEε4 carriership. None of these is a trivial issue, and yet they are the main variables on which their statistical analysis focused. The missing details make a head-to-head comparison between the study results and identification of causes of discrepancies very difficult, if not impossible. Therefore, we are not able to place their results in a wider context.

In our study, we observed that plasma amyloid was useful for prescreening amyloid positivity in a 2-step diagnostics approach, with application of a blood test first and subsequently funneling a smaller number of individuals toward amyloid testing with established tests such as positron emission tomography or CSF. Prins et al observed low sensitivity in their cohort, raising the question as to whether our results could be explained by overfitting. We acknowledge that cross-validation in external cohorts is essential. Of note, our results do not stand alone; multiple recent studies using highly sensitive immunoassays for blood-based amyloid beta quantification showed capability to discriminate between amyloid-positive and amyloid-negative cognitively normal individuals, with or without subjective cognitive complaints,[2–4] providing independent support for our findings. Moreover, in our article we not only investigated the association of plasma amyloid and CSF amyloid, but showed that low plasma amyloid levels are related to a higher risk of subsequent clinical disease progression to mild cognitive impairment or dementia. Investigating two types of statistical outcomes (ie, CSF amyloid positivity and change in clinical syndrome during follow-up) provides converging evidence for the diagnostic potential of the plasma amyloid biomarker.

We therefore conclude that plasma amyloid measurement is promising for prescreening Alzheimer pathological changes in cognitively normal individuals with subjective cognitive decline.

Potential Conflicts of Interest

Nothing to report.

[1]Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam University Medical Center, Amsterdam, the Netherlands and
[2]Neurochemistry Laboratory, Department of Clinical Chemistry, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam University Medical Center, Amsterdam, the Netherlands

References

1. Verberk IMW, Slot RE, Verfaillie SCJ, et al. Plasma amyloid as prescreener for the earliest Alzheimer pathological changes. Ann Neurol 2018;84:648–658.
2. Vergallo A, Mégret L, Lista S, et al. Plasma amyloid β 40/42 ratio predicts cerebral amyloidosis in cognitively normal individuals at risk for Alzheimer's disease. Alzheimers Dement 2019;15:764–775.
3. Palmqvist S, Janelidze S, Stomrud E, et al. Performance of fully automated plasma assays as screening tests for Alzheimer disease-related β-amyloid status. JAMA Neurol 2019;76:1060–1069.
4. Chatterjee P, Elmi M, Goozee K, et al. Ultrasensitive detection of plasma amyloid-β as a biomarker for cognitively normal elderly individuals at risk of Alzheimer's disease. J Alzheimers Dis 2019;71:775–783.

DOI: 10.1002/ana.25633

Medicare for All?

Joseph C. Masdeu, MD, PhD

Dr Saper's timely article on Medicare[1] emphasizes how ensuring excellent health care for all is a major accomplishment of developed societies. For this purpose, Europeans devised prepaid medicine, which since the mid-1980s has pervaded the United States; we pay insurance premiums and taxes so that insurance companies and the government pay for our health care expenses. Prepaid medicine leads to poor quality, expensive health care, as I have learned by practicing academic medicine since 1970—11 years in Europe, 8 of them recently, and the rest in Chicago, New York, Bethesda, and Houston. When I moved to Chicago in 1972, Western Europeans considered US health care the best in the world; at that