Healthy elderly in clinical trials: how to define preclinical Alzheimer's Disease for clinical trial participation

Prins, S.

CHAPTER V

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

S. Prins,[1,2] A. Zhuparris,[1] G.J. Groeneveld[1,2]

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1. Centre for Human drug Research, Leiden, NL | 2. Leiden University Medical Center, Leiden, NL

Recently, Verberk et al. showed that plasma Aβ42/Aβ40 ratio has potential to identify Alzheimer pathological changes in subjects with subjective memory decline. Further, 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's 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 MMSE score of 28.8 (range 25-30), and Geriatric Depression Scale score-15 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 which affected the central nervous system, or medication with a contraindication for a lumbar puncture, they would also be excluded. Self-reported memory performance/daily functioning were assessed with use of 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.

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 (CSF) amyloid abnormal and amyloid normal individuals, in a multivariate model including age and ApoEε4 carriership (Fig 1).

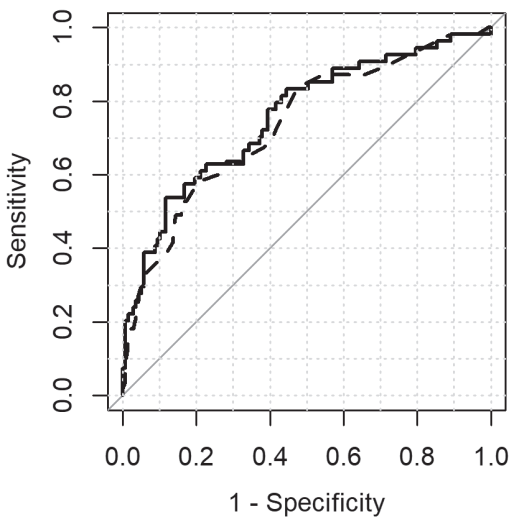
Applying Verberk's model to subjects in our sample would theoretically identify 'preclinical' elderly, defined as elderly with biomarker evidence consistent with AD but without cognitive complaints. However, due to the low sensitivity (30.8%) of the model in our sample, we would miss a substantial number of healthy elderly with AD pathology, who 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. Knowing that Verberk et al. did not cross-validate their model, over-fitting of the sampled data is a possible explanation for the discrepancy between Verberk's and our findings. While there are a maximum of 3 features included in Verberk's multivariate model, if the model was 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 carriers4. 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.

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 line: Variables within the logistic regression model are ABeta ratio, ApoE ε4 carriership and age. The Area under the curve [AUC] is 75.7% and 95% confidence interval [CI] is 67.8-83.6%. Dotted line: Variables within this logistic regression model only include ApoE ε4 carriership and age.* AUC: 73.8% CI: 65.8%-81.8%. *Grey line: 50% reference line.*



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