Associations of potential ADRD plasma biomarkers in cognitively normal volunteers

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Introduction

- One in three deaths in adults 65 years of age and older are associated with dementia[1]. With no known cure[2], research is focused on identification and prevention.
- Blood biomarkers show potential as an alternative to CSF and neuroimaging biomarkers for many reasons[3,4,5].
- This study examined the relationships between 13 blood-plasma biomarkers and dementia-related demographic and health factors in a cohort of 237 cognitively normal research volunteers whose average age was ≈82 years and who were 63% female.

Key Findings

- Among N=237 cognitively normal adults, we studied candidate Alzheimer's disease and related dementia (ADRD) plasma biomarkers.
- Biomarkers were largely not associated with demographic or health factors.
- Apolipoprotein E (APOE) status was associated with amyloid beta (Aβ)42/Aβ40 ratio.
- These results suggest that plasma biomarkers may be examined in ADRD research without excessive loss of interpretability from confounding.

Methods

- Biomarkers were categorized into three subgroups:
  i. Neurodegenerative/AD (Aβ40, Aβ42, Aβ42/40, tau, tau/Aβ42, and NfLight)
  ii. Vascular (PlGF, and MMP9)
  iii. Inflammatory (IL6, IL8, IL10, IL1β, and TNFα).
- Covariate selection was guided via sufficient adjustment sets from DAG's created for each biomarker subtype[6]. These sets of covariates theoretically eliminate confounding and bias along the causal pathway from biomarkers to cognition.
- We regressed each biomarker on selected covariates to explore the associations between the biomarkers and selected factors to assess whether they may contribute to biomarker values.
- Post hoc sensitivity analyses were done with updated data (with all biomarker assays run on the same machine) and consistent variable sets (using all available variables identified in the DAG's) for robustness and batch effects.

Results

- Data produced by Quanterix SiMOA HD-1 and HD-X machines showed statistically significantly different results via batch coefficients and calculated effect sizes.
- Biomarker concentrations were largely not associated with demographics or health conditions.
- Apolipoprotein E [APOE] status was associated with amyloid beta Aβ42/Aβ40.
- Hypertension was significantly positively associated with Aβ40 and tau.
- Cancer history was significantly positively associated with IL6. Gender was not significantly associated with any biomarker.
- Associations with age were not consistent across biomarkers.
- Direction, magnitude, and significance of beta coefficients varied across models and data from the main to the post hoc sensitivity analyses.

Conclusions

- Bias may be prevalent in this sample due to geographic location, self-selection, and autopsy consent.
- Although batch effects remained in the post hoc analysis after standardization of machine used for the biomarker assays, researchers should take caution in utilizing data that comes from multiple machines, even in the same lab.
- The absence of strong associations in this study does not discount the possibility that these plasma biomarkers, or their temporal changes, may predict or detect the presence of ADRD. Instead, it suggests that changes in these biomarkers, when observed, may be attributable to neuropathological changes, as opposed to confounding factors.

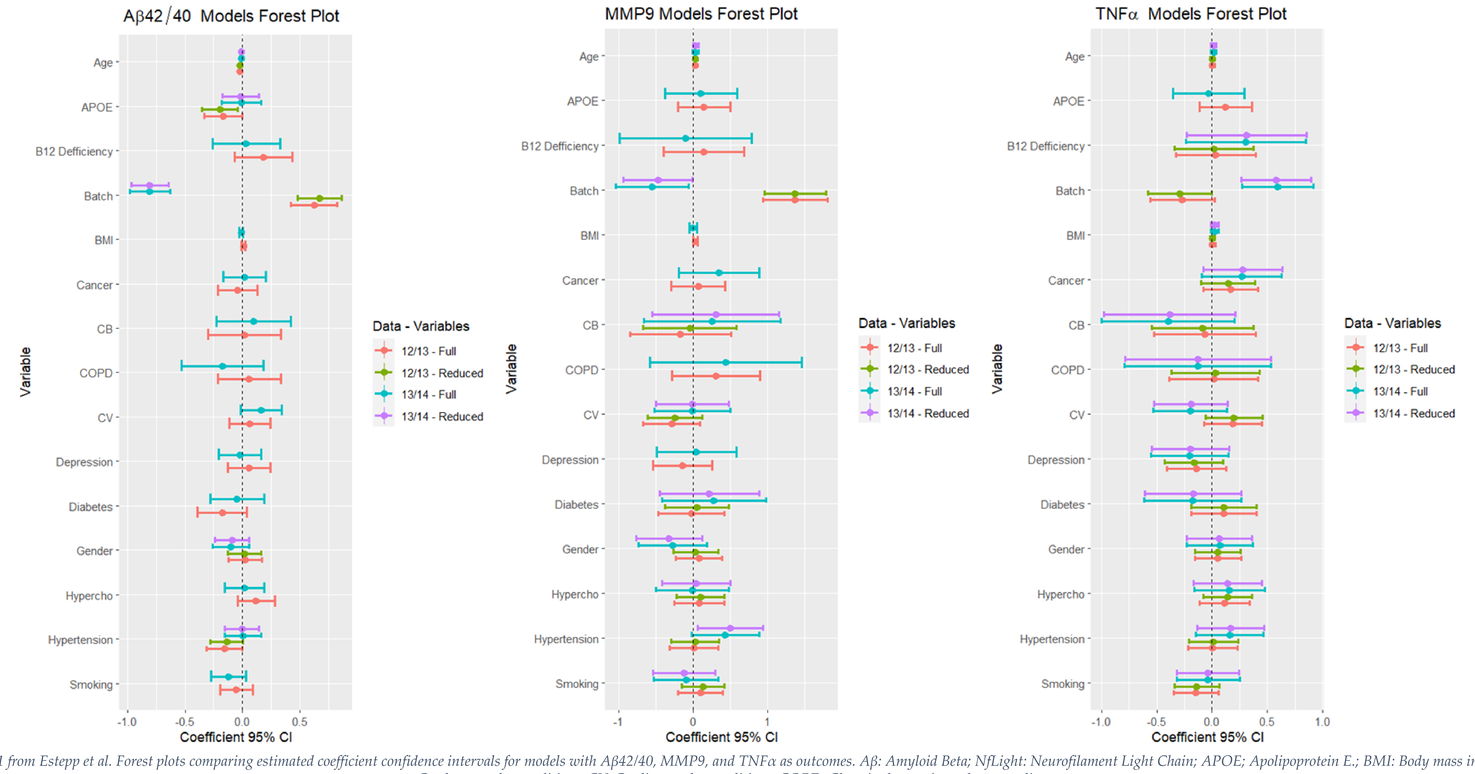

Figure 1 from Estepp et al. Forest plots comparing estimated coefficient confidence intervals for models with Aβ42/40, MMP9, and TNFα as outcomes. Aβ: Amyloid Beta; NfLight: Neurofilament Light Chain; APOE; Apolipoprotein E.; BMI: Body mass index; CB: Cerebrovascular conditions; CV: Cardiovascular conditions; COPD: Chronic obstructive pulmonary disease.

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