## e-Methods supplement

Characteristics of the seven multivariable models presented in Table 2:

Model 1 UPSIT error score ~ 1+ *APOE* ε4 carrier status + sex + education + age

Model 2 UPSIT error score ~ 1+ *APOE* ε4 carrier status + sex + education+ RBANS

Model 3 UPSIT error score ~ 1+ *APOE* ε4 carrier status + sex + education + CSF total-*tau*/$A\beta_{1-42}$

Model 4 UPSIT error score ~ 1+ *APOE* ε4 carrier status + sex + education + age + RBANS

Model 5 UPSIT error score ~ 1+ *APOE* ε4 carrier status + sex + education + age + CSF total-*tau*/$A\beta_{1-42}$

Model 6 UPSIT error score ~ 1+ *APOE* ε4 carrier status + sex + education + RBANS + CSF total-*tau*/$A\beta_{1-42}$

Model 7 UPSIT error score ~ 1+ *APOE* ε4 carrier status + sex + education + age + RBANS + CSF total-*tau*/$A\beta_{1-42}$

We considered the need for adjusting by education, sex, and *APOE* ε4 carrier status. Inclusion of these variables did not change the iterative modeling output, however, we kept these known determinants in to be comparable to studies of Alzheimer's disease.

## e-Results

To evaluate the odor identification-CSF marker relationship in individuals likely to have more advanced pathology, we conducted sub-analyses among individuals with CSF $A\beta_{1-42}$ concentrations below the $25^{th}$ percentile (864.621 pg/mL) (Figure 1 E & F, red circles). These individuals showed correlations between UPSIT error

score and CSF $A\beta_{1-42}$ levels ($\beta$=-8.27 x $10^{-4}$; p=0.0135; n=25), t-*tau*/$A\beta_{1-42}$ ($\beta$ = 0.399; p=0.00260), and $P_{181}$-*tau*/$A\beta_{1-42}$ ($\beta$ = 0.301; p = 0.0109) (the latter not shown). As these CSF ratios are driven by elevated tau or decreasing amyloid levels, this analysis reproduces the relationships observed across the entire dataset for the ratio and odor identification in individuals with low CSF $A\beta_{1-42}$. We explored the relationship of the UPSIT error score and CSF *tau* above 335.1243 pg/mL, CSF $P_{181}$-*tau* above 55.3472 pg/mL, CSF t-*tau*/$A\beta_{1-42}$ above 0.2867, CSF $P_{181}$-*tau*/$A\beta_{1-42}$ above 0.0498 in individuals in these various CSF upper quartile levels. Similarly, among persons above the 75$^{th}$ percentile for CSF markers of neurodegeneration, UPSIT error score was related to CSF t-*tau* ($\beta$ = 8.16 x $10^{-4}$; p = 0.0151; n=25), t-*tau*/$A\beta_{1-42}$ ($\beta$ = 0.313, p = 0.0358), and $P_{181}$-*tau*/$A\beta_{1-42}$ ($\beta$ = 2.6386, p = 0.0314; n=25), but not $P_{181}$-*tau* ($\beta$= 1.76 x $10^{-3}$; p = 0.587). Whereas individuals with CSF $A\beta_{1-42}$ levels below the 25$^{th}$ percentile included a high proportion of *APOE* $\varepsilon$4 carriers (48%) the proportion of $\varepsilon$ 4 carriers was 28% for individuals in the upper three quartiles of CSF $A\beta_{1-42}$ concentration.

There was no evident relationship of odor identification and CSF $A\beta_{1-42}$ alone. However, after inspection of the curve, the data suggest the possibility of such a relationship among people with low CSF $A\beta_{1-42}$ level. Therefore, we explored interaction models looking at individuals more likely to have advanced pathology. Exploratory analyses suggested a possible interaction among persons with CSF $A\beta_{1-42}$ concentrations below the 25$^{th}$ percentile (864.621 pg/mL) and a trend among persons with CSF t-*tau* levels above the 75$^{th}$ percentile (335.124 pg/mL) (Figure e-4 A & C; B & D).

Ultimately, we clarified the differences between the ε4 carriers and non-carriers by exploring the interaction between *APOE* ε4 carrier status and amyloid levels to predict odor identification. There was a statistical interaction of *APOE* ε4 carrier state and CSF $A\beta_{1-42}$ levels that predicted the UPSIT error score ($\beta$=-4.28 $x10^{-4}$, p=0.0104, n=100) (Figure e-5 A & C). This suggests that odor identification was substantially worse in those with lower CSF $A\beta_{1-42}$ concentrations and an *APOE* ε4 allele. There was no interaction for any other CSF marker. We attempted but failed to reproduce the ε4 carrier and CSF $A\beta_{1-42}$ interaction effect with RBANS total index score (Figure e-5 B & D). This could be because odor identification deficit precedes cognitive loss.

Finally, we explored the multivariable Model 1, 2, 4 using the full data set. We assessed the relationships between odor identification and age, cognition added in sequence, after adjustment for sex, education, and *APOE*ε4 carrier status. We found that there are strong associations of greater UPSIT error score with older age ($\beta$=0.0119, p=3.55 $x10^{-5}$) and lower RBANS ($\beta$= -0.00515, p=9.41 $x10^{-3}$). Model 4 suggested that age and cognition were independent predictors of OI but the association of odor identification with cognition was weakened after adjustment for age (Age, $\beta$=0.00941, p=0.002; RBANS $\beta$=-0.00328, p=0.0397 see Table e-2).

| | *PREVENT-AD cohort participants* | | | |
|---|---|---|---|---|
| **Demographics** | **Average** | **S.D.** | **range (min median max)** | **n** |
| Age (years) | 63.41 | 5.43 | 55 - 62 - 84 | 274 |
| Sex (% Female) | 73 | 44 | | 274 |
| Education (years) | 15.15 | 3.47 | 7 - 15 - 29 | 274 |
| E4 carrier status (%) | 33 | 47 | | 268 |
| Caucasian (%) | 98 | 13 | | 274 |
| Francophone (%) | 81 | 39 | | 274 |
| MoCA total score | 28.09 | 1.52 | 23 - 28 - 30 | 274 |
| RBANS | 101.92 | 11.16 | 73 - 101 - 140 | 270** |
| UPSIT total score | 35.41 | 3.65 | 13 - 36 - 40 | 265*** |
| $A\beta_{1\text{-}42}$ (pg/mL) | 1062.91 | 280.65 | 402.35 - 1068.4 - 1596.9 | 101 |
| t-*tau* (pg/mL) | 273.09 | 129.97 | 90 - 259.06 - 851 | 101 |
| $P_{181}$-*tau* (pg/mL) | 46.83 | 18 | 12. 1 - 43.9 - 114.4 | 101 |
| t-*tau* / $A\beta_{1\text{-}42}$ | 0.28 | 0.21 | 0.11 - 0.22 - 1.20 | 101 |
| $P_{181}$-*tau*/ $A\beta_{1\text{-}42}$ | 0.05 | 0.03 | 0.01 - 0.04 - 0.18 | 101 |

*Four RBANS reports of individuals who underwent the lumbar puncture were lost.

**One person refused the olfactory testing and was not included in the reported analyses. Additionally, there were 8 incomplete tests or completed when congested not included in any analysis.

**Table e-1. Demographics of PREVENT-AD cohort participants**

MoCA = Montreal Cognitive Assessment; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; UPSIT = University of Pennsylvania Smell Identification Test.

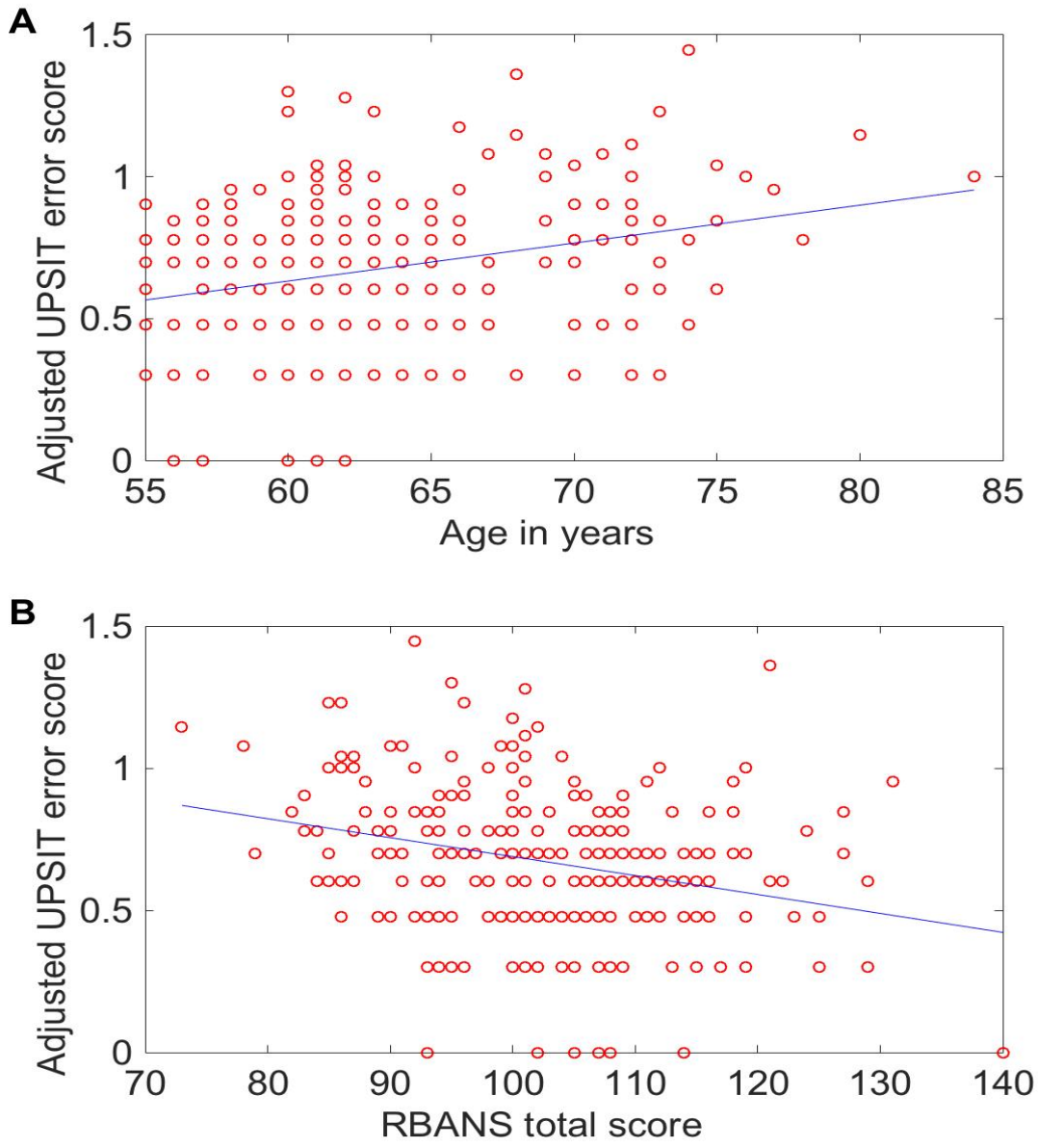


**Figure e-1. Robust-fit linear regression models of UPSIT error score vs. age and cognition.**

A) UPSIT error score vs. age (β = 0.0134,p= 2.24 x10-6, n=265),
B) UPSIT error score vs. RBANS total score (β = -0.00666, p= 1.28 x10-6, n=261)
RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; UPSIT=University of Pennsylvania

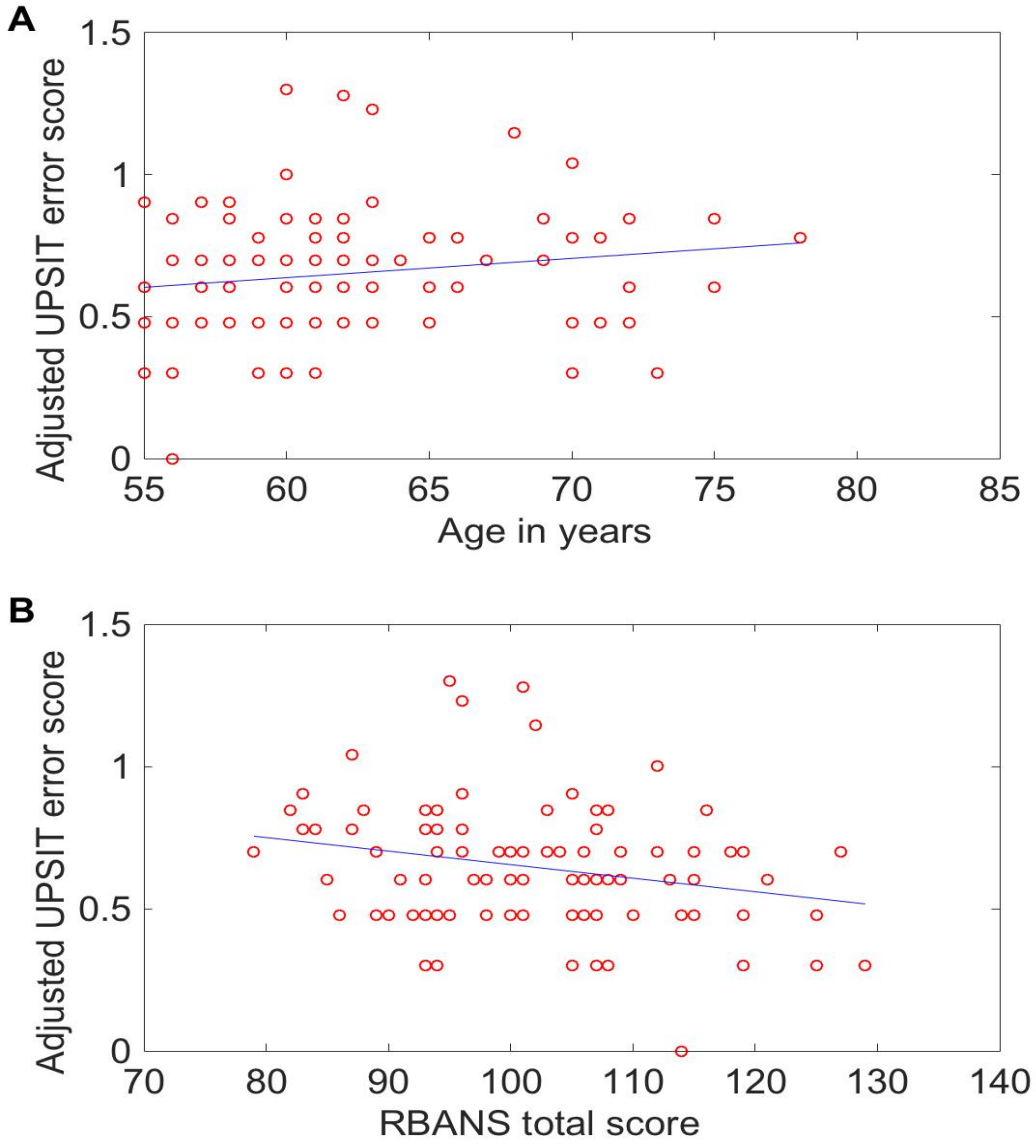


**Figure e-2. Robust-fit linear regression models of UPSIT error score vs. age and cognition in those with both CSF and odor identification data.**

A) UPSIT error score vs. age ($\beta=6.79 \times 10^{-3}$, p=0.095, n=100),
B) UPSIT error score vs. RBANS total score ($\beta=-4.76 \times 10^{-3}$, p=0.011, n=100)
RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; UPSIT=University of Pennsylvania

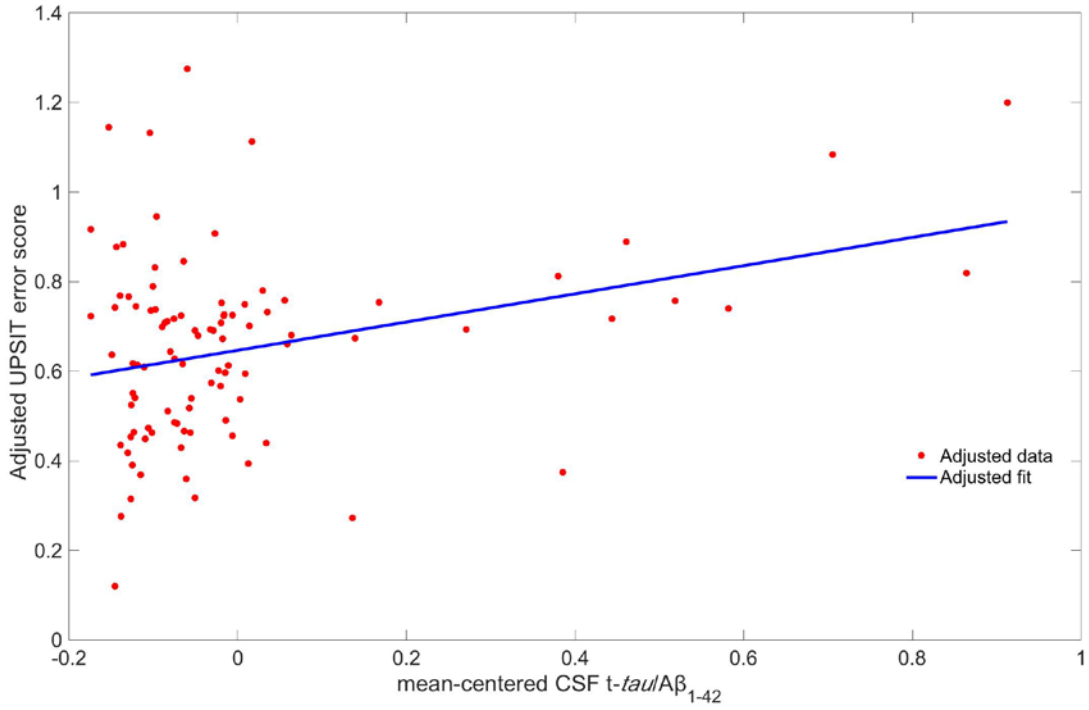


**Figure e-3. Model 7: UPSIT error score vs CSF total-*tau*/Aβ$_{1-42}$ adjusted for age, cognition, *APOE* ε4 status, sex, education**

This is a graph of model 7 from Table 2. It shows an increase in the UPSIT error score with an increase in mean-centered CSF total-*tau*/β$_{1-42}$ after adjusting for age, RBANS total score, *APOE* ε4 status, sex, and education. Worse odor identification ability is correlated with higher levels of AD biomarkers.

RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; UPSIT=University of Pennsylvania

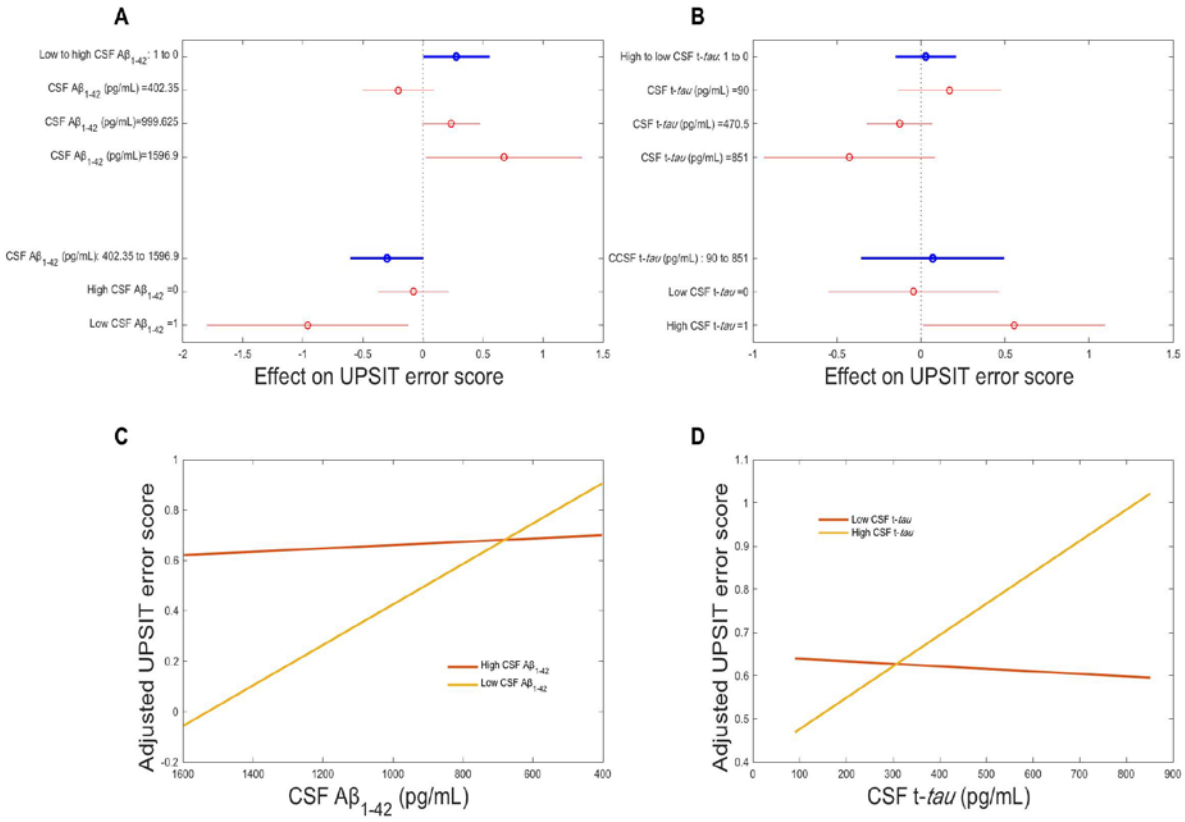


**Figure e-4. Advanced stage progression and CSF biomarker level interaction model for UPSIT error score**

A & B) plot of interaction effect on UPSIT error score, with a horizontal bar showing the confidence interval for the estimated effect

A & B) blue circles indicate main effects and red circles indicate effect for set variables

C ) response curve as a function of CSF $A\beta_{1\text{-}42}$ level, with *ad progression* fixed at 1 for closer to ad or 0 for individuals further away

D ) response curve as a function of CSF t-*tau* level, with *ad progression* fixed at 1 for closer to ad or 0 for individuals further away

A & C) Interaction of CSF $A\beta_{1\text{-}42}$ level predicts UPSIT error score (model, F=1.89, n=100, df=96, $R^2$=0.0558, p=0.136; high low CSF $A\beta_{1\text{-}42}$, β =0.503, p=0.0859; CSF $A\beta_{1\text{-}42}$ level, β=-6.565e-05, p=0.599; high-low CSF $A\beta_{1\text{-}42}$ interaction with CSF $A\beta_{1\text{-}42}$ level, β=-0.000739, p=0.0516).

B & D) Interaction of CSF t-*tau* level predicts UPSIT error score (model, F=2.93, n=100, df=96, $R^2$=0.0839, p=0.0374; high low CSF t-*tau*, β=-0.241, p=0.214, CSF t-*tau* level, β =-5.80e-05, p=0.864; high-low CSF t-*tau* interaction with CSF t-*tau* level, β=0.000784, p=0.114).

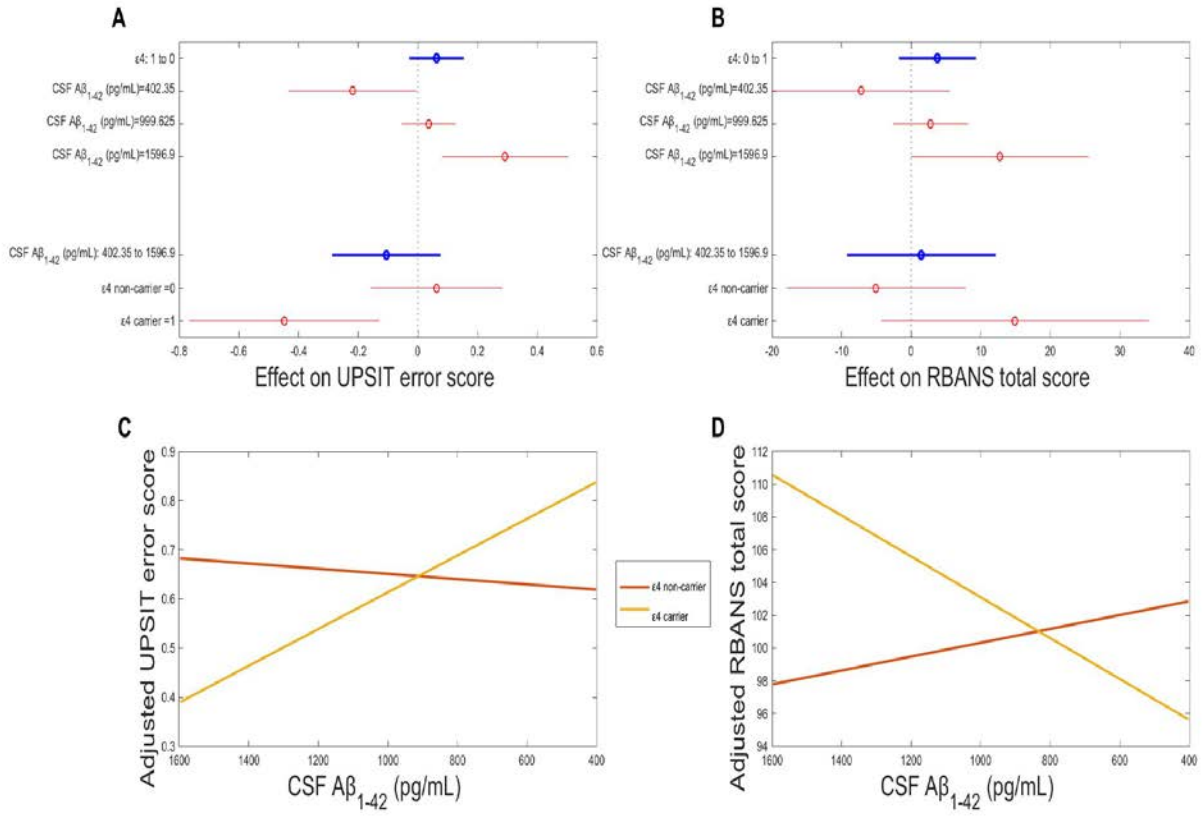


**Figure e-5. *APOE* ε4 carrier status and CSF $A\beta_{1-42}$ level interaction model for UPSIT error score and RBANS prediction**

A) plot of interaction effect on UPSIT error score, with a horizontal bar showing the confidence interval for the estimated effect

B) plot of interaction effect on RBANS total index score, with a horizontal bar showing the confidence interval for the estimated effect

A & B) blue circles indicate main effects and red circles indicate effect for set variables

C) response curve as a function of CSF $A\beta_{1-42}$ level, with *APOE* ε4 carrier fixed at 1 for carriers or 0 for non-carriers

D) response curve as a function of CSF $A\beta_{1-42}$ level, with *APOE* ε4 carrier fixed at 1 for carriers or 0 for non-carriers

A & C) Interaction of CSF $A\beta_{1-42}$ level and *APOE* ε4 carrier status predicts UPSIT error score

(model, F=2.88, n=100, df=96, $R^2$=0.205, p=0.04; ε4 carrier status, β =-0.0641, p=0.167; CSF $A\beta_{1-42}$ level, β =-5.314e-05, p=0.570; ε4 carrier status interaction with CSF $A\beta_{1-42}$ level, β =-0.000428, p=0.0104).

B & D) Interaction of CSF $A\beta_{1-42}$ level and *APOE* ε4 carrier status predicts RBANS total index score (model, F=1.34, n=98, df=94, $R^2$=0.0411, p=0.266; ε4 carrier status, β =3.8284, p=0.17276; CSF $A\beta_{1-42}$ level, β =-0.00423, p=0.438; ε4 carrier status interaction with CSF $A\beta_{1-42}$ level, β =0.0167,p=0.0900).

| | Estimated coefficients [s.e.] | | |
|---|---|---|---|
| **Predictors of OI** | **Model 1** | **Model 2** | **Model 4** |
| **n** | 262 | 258 | 258 |
| **Age in years** | 0.0119 [0.003] *** | | 0.0094 [0.003] ** |
| **RBANS** | | -0.0052 [0.002] *** | -0.0033 [0.002] * |
| **t-*tau*/Aβ1-42** | | | |
| **Sex (Female=1)** | -0.1162 [0.034] *** | -0.1037 [0.035] ** | -0.1024 [0.035] ** |
| **Education in years** | -0.0062 [0.004] | -0.0033 [0.005] | -0.0038 [0.005] |
| **APOE ε4 (Carrier=1)** | -0.0424 [0.032] | -0.0379 [0.032] | -0.0380 [0.032] |

**Table e-2**. **Estimated coefficients from step-wise multiple linear regression modeling to predict UPSIT error score**.

This table looks at combinations of age, RBANS, and CSF total-*tau*/$A\beta_{1\text{-}42}$ as predictors of odor identification. All Models are adjusted for *APOE* ε4 carrier status, sex, and education. Because of different metrics used to measure the several variables, the various coefficients are not commensurable, but the indicated P-values show the importance of individual variables in the overall model. The coefficients are labeled with asterisks according to the size of their p-value (*p<0.05, **p<0.01, ***p<0.001).

RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; UPSIT=University of Pennsylvania Smell Identification Test