

Supplementary materials to MS entitled: Characterizing the effects of sex, *APOE* ϵ 4, and literacy on mid-life cognitive trajectories: Application of Information-Theoretic model-averaging and multi-model inference techniques to the Wisconsin Registry for Alzheimer’s Prevention Study

Overview of Supplementary Tables and Figures

Our group presented an analysis using the IT framework at the 2016 Alzheimer’s Association International Conference (AAIC) in Toronto, Canada (Koscik et al., n.d.). The model set used for those analyses and the weights corresponding to each model are provided in Supplementary Table 1. Results clearly indicated at most quadratic age trends. In addition, small cell sizes for some sex**APOE* genotypes and a desire to add age, sex, and *APOE* interactions with literacy to the current analyses contributed to the development of the model set used in the current study.

The remainder of supplemental materials correspond to analyses reported in the manuscript. Supp. Table 2 provides the weights for each model by outcome. Supp. Table 3 shows the Spearman correlations among outcomes (using baseline data). Supp. Figures 1-2 depict 95% CI’s for significant model-averaged parameters (left-hand panel) and predicted values vs age using the model-averaged parameters and stratified by sex, literacy level, and/or *APOE* ϵ 4 count. To facilitate comparison of the results from our IT approach with the “Best Fit” and “Backwards Selection” approaches, Supp. Figure 3 depicts the 95% CI’s for any terms that were significant via one or more of these methods for AVLT Total and AVLT Delay.

Reference

Koscik, R. L., Norton, D. L., Clark, L. R., Mueller, K. D., Hermann, B. P., Engelman, C. D., ... Johnson, S. C. (n.d.). INFORMATION-THEORETIC MODEL AVERAGING TO CHARACTERIZE EFFECTS OF AGE, GENDER, AND APOE ϵ 4 ON MID-LIFE COGNITIVE TRAJECTORIES: RESULTS FROM THE WISCONSIN REGISTRY FOR ALZHEIMER’S PREVENTION. *Alzheimer’s & Dementia: The Journal of the Alzheimer’s Association*, 12(7), P966–P968. <https://doi.org/10.1016/j.jalz.2016.06.1985>

Supplementary Tables

Supp. Table 1: Table of original model set presented at the Alzheimer's Association International Conference (AAIC) 2016.

Model #	Model Terms*	K	AVLT Total	AVLT Delay	Log(Trails A)	Log(Trails B)	C,F,I Fluency	BNT	DigSpBack	IICV**
M1	Random effects, intercept, covariates, gender, APOE, c_age and c_age ²	22	0.0013	0.0262	0.0131	0.0287	0.3126	0.2863	0.1959	0.1574
M2	M1 + age*gender	23	0.5908	0.5587	0.0048	0.0108	0.1844	0.2174	0.2313	0.3070
M3	M1 + age*apoe	27	7.92E-05	0.0012	0.7378	0.0463	0.0050	0.0025	0.0659	0.0019
M4	M1 + gender*apoe	26	8.51E-05	0.0171	0.0003	0.0009	0.0840	0.0259	0.0088	0.2054
M5	M1 + age*gender*apoe	36	5.11E-05	0.0023	0.0220	7.85E-05	6.45E-05	4.23E-05	0.0001	9.98E-05
M6	M2 + age^2*gender	24	0.2805	0.3010	0.0064	0.0045	0.1762	0.2639	0.1128	0.1118
M7	M3 + age^2*apoe	32	3.90E-06	0.0004	0.0577	0.7144	0.0016	0.0003	0.0028	2.20E-05
M8	M4 + age^2*gender*apoe	46	2.01E-07	5.18E-06	0.0002	1.94E-05	1.61E-05	1.79E-07	2.60E-07	3.14E-08
M9	M1 + age^3	23	0.0016	0.0188	0.1086	0.0435	0.1957	0.1440	0.2566	0.1173
M10	M6 + age^3*gender	26	0.1255	0.0743	0.0336	0.0246	0.0403	0.0597	0.1251	0.0991
M11	M7 + age^3*apoe	38	5.39E-08	9.85E-06	0.0154	0.1261	0.0002	2.07E-06	0.0006	5.59E-07
M12	M8 + age^3*gender*apoe	53	9.93E-10	1.01E-07	0.0001	2.54E-05	7.39E-05	2.85E-09	7.80E-08	4.12E-10

*M1 covariates include: SES, Caucasian (no/yes), CESD score, WRAT reading; APOE class variable with APOE pair=ε3/ε3 (or 33) as the reference group; c_age is age centered around the baseline median. In models where an interaction was added, all lower order terms (including interactions) were included in the model.

Yellow shading indicates model contributing greatest weight; pink shading indicates 2nd greatest weight; BF indicates Weight>3%

**IICV calculated as the SD of z-score versions (i.e., ~N(0,1)) of each neuropsychological test score in the table.

Supp. Table 2: Table with weights for current model set.

Model number	AVLT Total	AVLT Delayed	log ₁₀ Trails A	log ₁₀ Trails B	Sqrt CFL	Boston Naming	Digit Span Forwards	Digit Span Backwards	Sqrt 4 test IICV
1	<0.001	<0.001	0.006	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
2	0.001	0.052	0.006	0.007	0.019	<0.001	0.020	0.002	<0.001
3	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
4	<0.001	<0.001	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
5	0.001	0.017	0.001	0.002	0.003	<0.001	0.003	<0.001	<0.001
6	0.023	0.012	0.004	0.330	0.012	0.63	0.307	0.583	<0.001
7	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
8	0.012	0.004	0.001	0.075	0.002	0.128	0.042	0.104	<0.001
9	<0.001	<0.001	0.003	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
10	<0.001	<0.001	0.014	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
11	<0.001	0.020	0.004	0.003	0.012	<0.001	0.009	0.004	<0.001
12	0.005	0.002	0.001	0.124	0.008	0.239	0.124	0.168	<0.001
13	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
14	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
15	0.011	0.123	0.002	0.001	0.006	<0.001	0.003	0.003	<0.001
16	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
17	<0.001	0.001	<0.001	<0.001	0.001	<0.001	<0.001	0.001	<0.001
18	0.001	0.01	<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001
19	0.012	0.062	0.574	0.109	0.416	<0.001	0.163	0.006	<0.001
20	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
21	0.562	0.531	0.248	0.040	0.251	<0.001	0.065	0.006	<0.001
22	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
23	0.001	0.005	0.011	0.004	0.091	<0.001	0.01	<0.001	<0.001
24	0.049	0.036	0.005	0.001	0.058	<0.001	0.004	<0.001	<0.001
25	0.139	0.119	0.064	0.006	0.062	<0.001	0.015	0.005	0.041
26	0.183	0.006	0.054	0.297	0.060	0.003	0.234	0.117	0.959
27	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
28	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Gray shading for any model contributing <0.05 weight to parameter estimates for that outcome; boxes indicate highest weight (greatest contributing model) for an outcome.

Supplemental figures – titles and figure legends

Supplemental Figure 1 Title: AVLT Delay, Digit Span Backward, Trails A, and Digit Span Forward: Significant Model-Averaged Terms (Left) and Predicted Values (Right)

Supplemental Figure 1 legend: Results in Supplemental Figure 1 are for the outcomes: A) AVLT Delay, B) Digit Span Backward, C) Trails A (\log_{10} transformed), and Digit Span Forward. The left panel depicts parameter estimates and 95% confidence intervals (CI's) for CI's that do not overlap 0. The right panel depicts predicted values and 95% confidence limits using the model averaged parameter estimates for both sexes and high vs low literacy. SES=Socioeconomic status; URG = Underrepresented groups; WRAT = Wide Range Achievement Test (3rd edition).

Supplemental Figure 2 Title: BNT Significant Model-Averaged Terms (Left) and Predicted Values (Right)

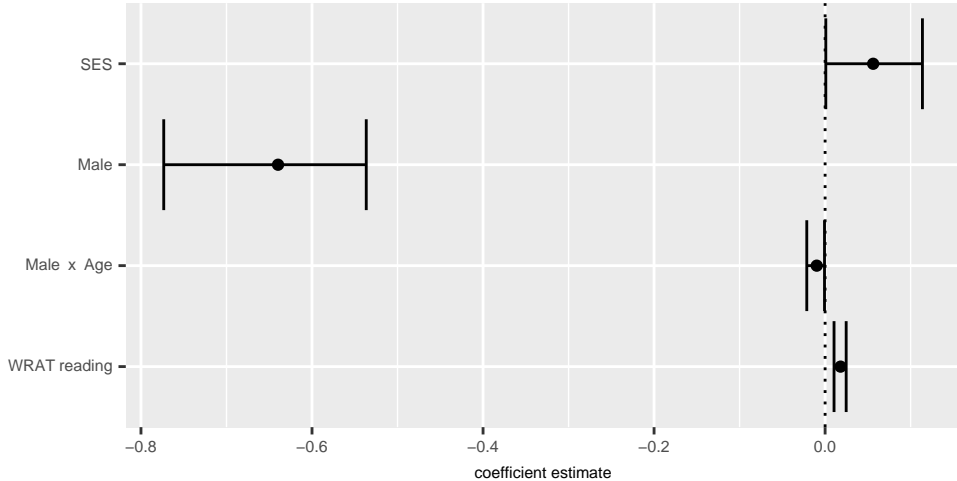
Supplemental Figure 2 legend: Results in Figure 2 are for the Boston Naming Task (BNT). The left panel depicts parameter estimates and 95% confidence intervals (CI's) for CI's that do not overlap 0. The right panel depicts predicted values and 95% confidence limits using the model averaged parameter estimates for both sexes, high vs low literacy, and *APOE* $\epsilon 4$ allele count. SES=Socioeconomic status; URG = Underrepresented groups; WRAT = Wide Range Achievement Test (3rd edition).

Supplemental Figure 3 Title: AVLT Total and Delay Significant Results by IT, Best Fit, and Backward Selection Methods

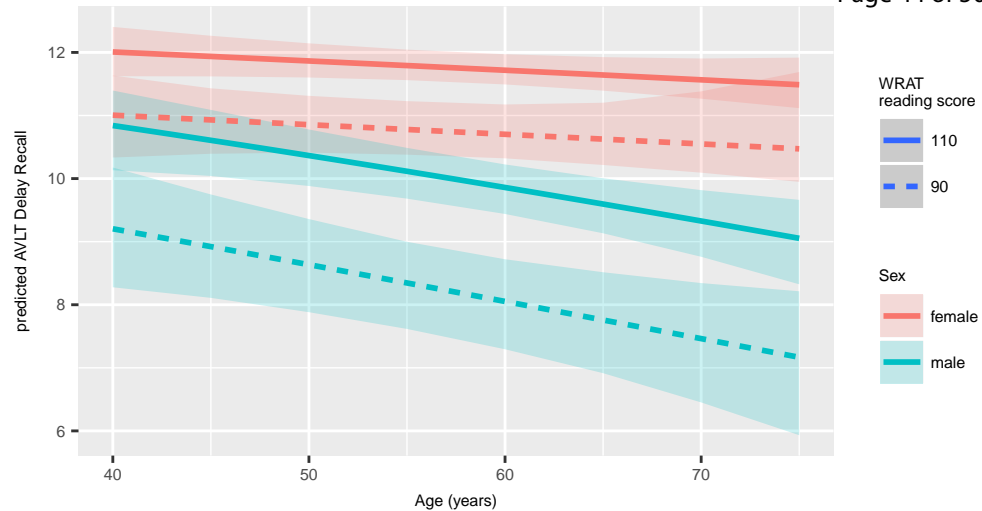
Supplemental Figure 3 legend: Parameter estimates and 95% CI's are depicted for each of three modeling methods (IT, AICc Best Fit, and Backward Elimination) for parameters that were significant by at least one of the three methods for AVLT Total (Figure 4A) and AVLT Delay (Figure 4B). CI's that overlap 0 (i.e., not significant) are shown in blue. For AVLT Total, significance of model terms varied for quadratic age and quadratic age * one *APOE* $\epsilon 4$. For AVLT Delay, results differed only on a three way interaction (male x quadratic age x two one *APOE* $\epsilon 4$). IT=Information Theoretic model averaging method; AICc best = AICc best fit model selection method; back. Elim.= backward elimination model selection method; SES=Socioeconomic status; URG = Underrepresented groups; WRAT = Wide Range Achievement Test (3rd edition).

AVLT Delay: MA regression coefficient estimates and 95% CI's

significant coefficients only

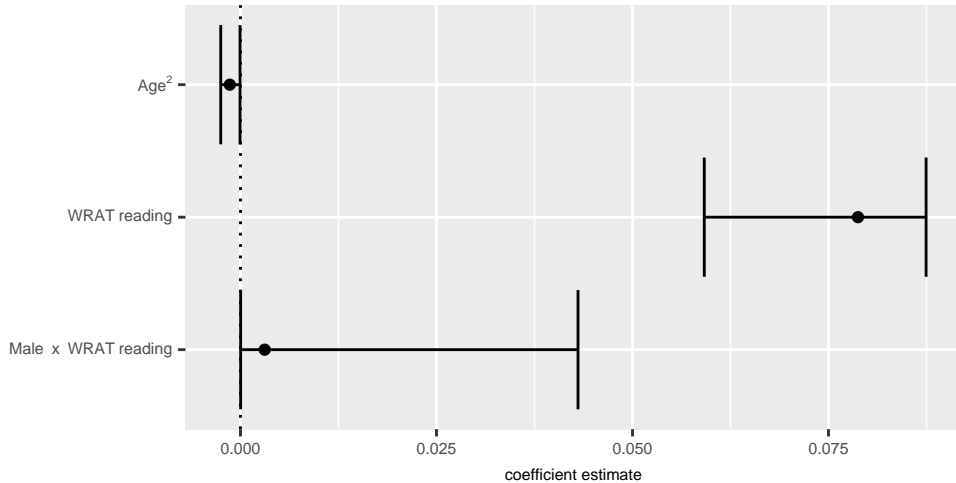


AVLT Delay: sex*age interaction

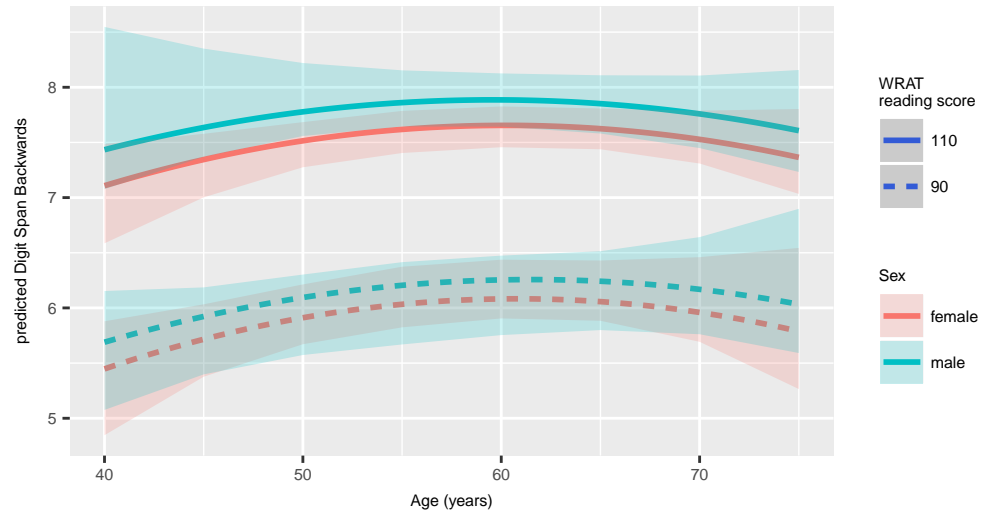


Digit Span Backwards: MA regression coefficient estimates and 95% CI's

significant coefficients only

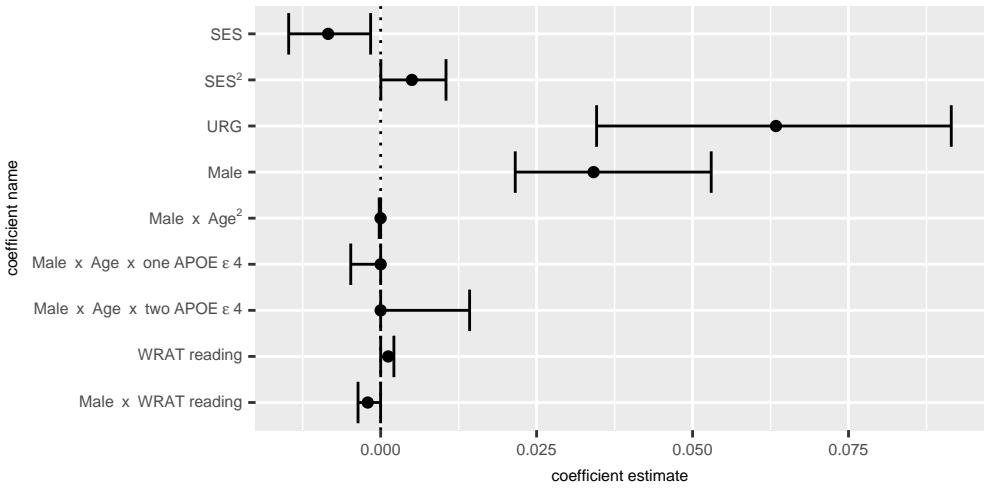


Digit Span Backwards: sex*literacy interactions

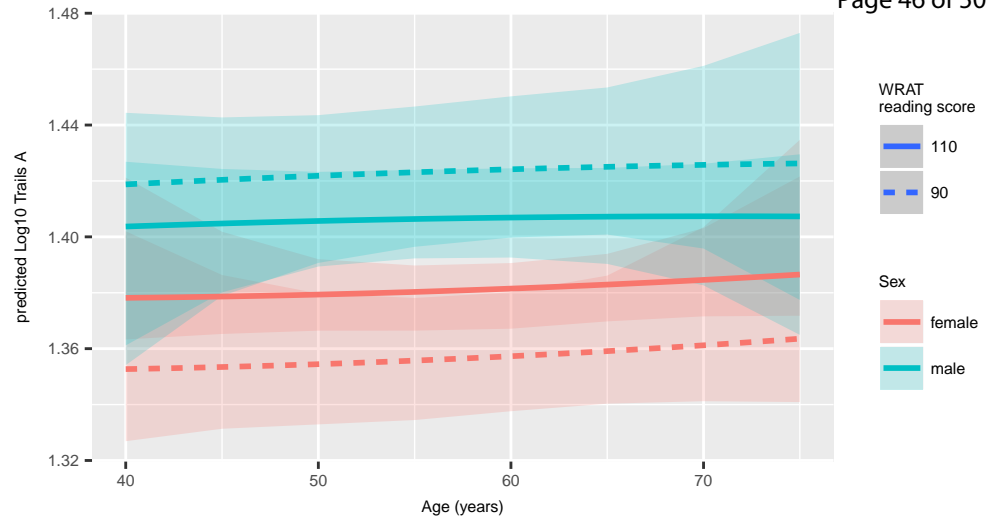


Log10 Trails A: MA regression coefficient estimates and 95% CI's

significant coefficients only

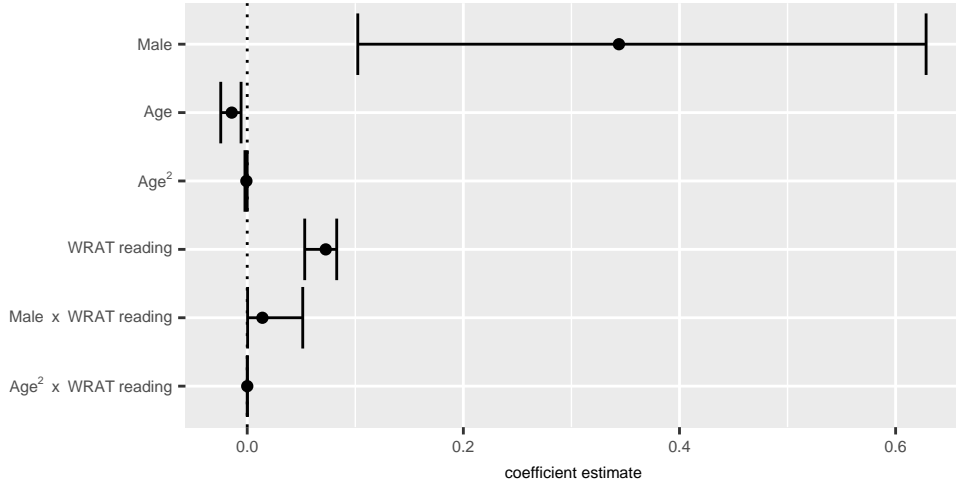


Log10 Trails A: sex*literacy interaction

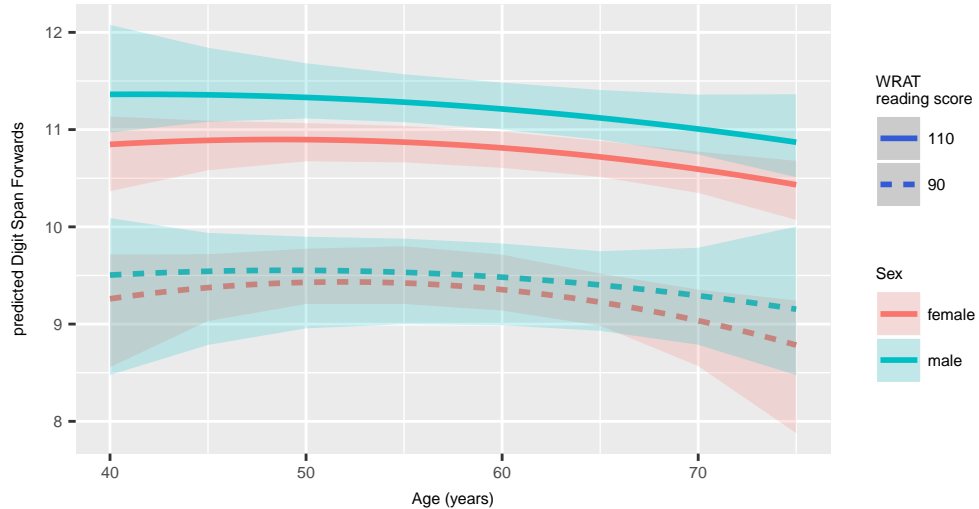


Digit Span Forwards: MA regression coefficient estimates and 95% CI's

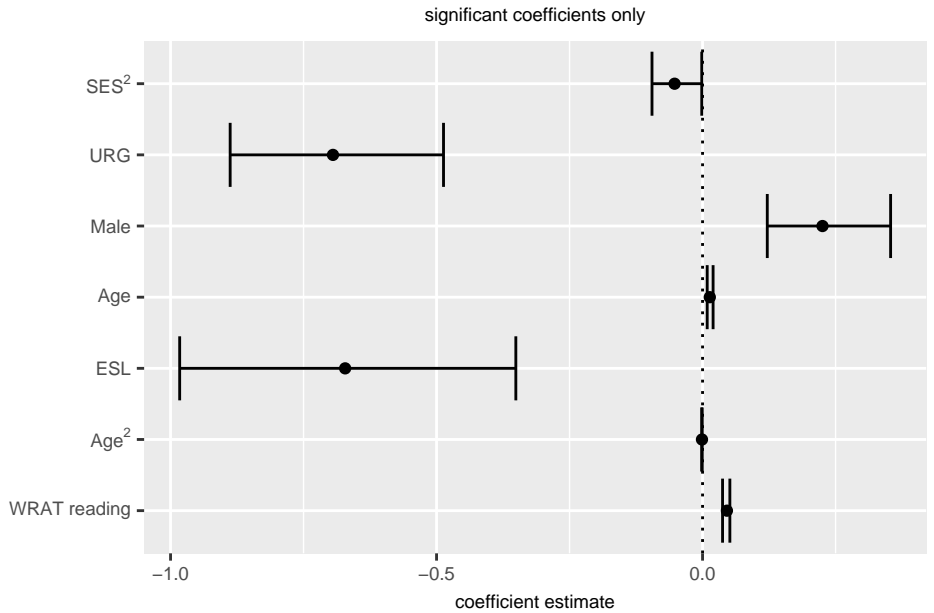
significant coefficients only



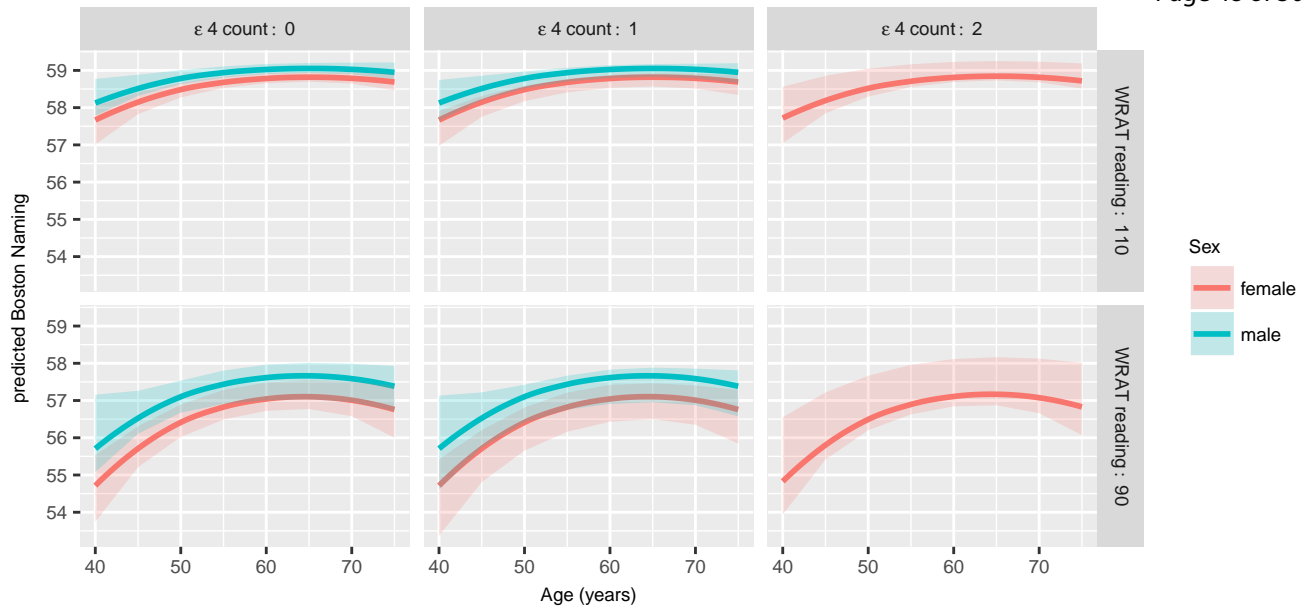
Digit Span Forwards: sex*literacy interactions



Boston Naming: MA regression coefficient estimates and 95% CI's

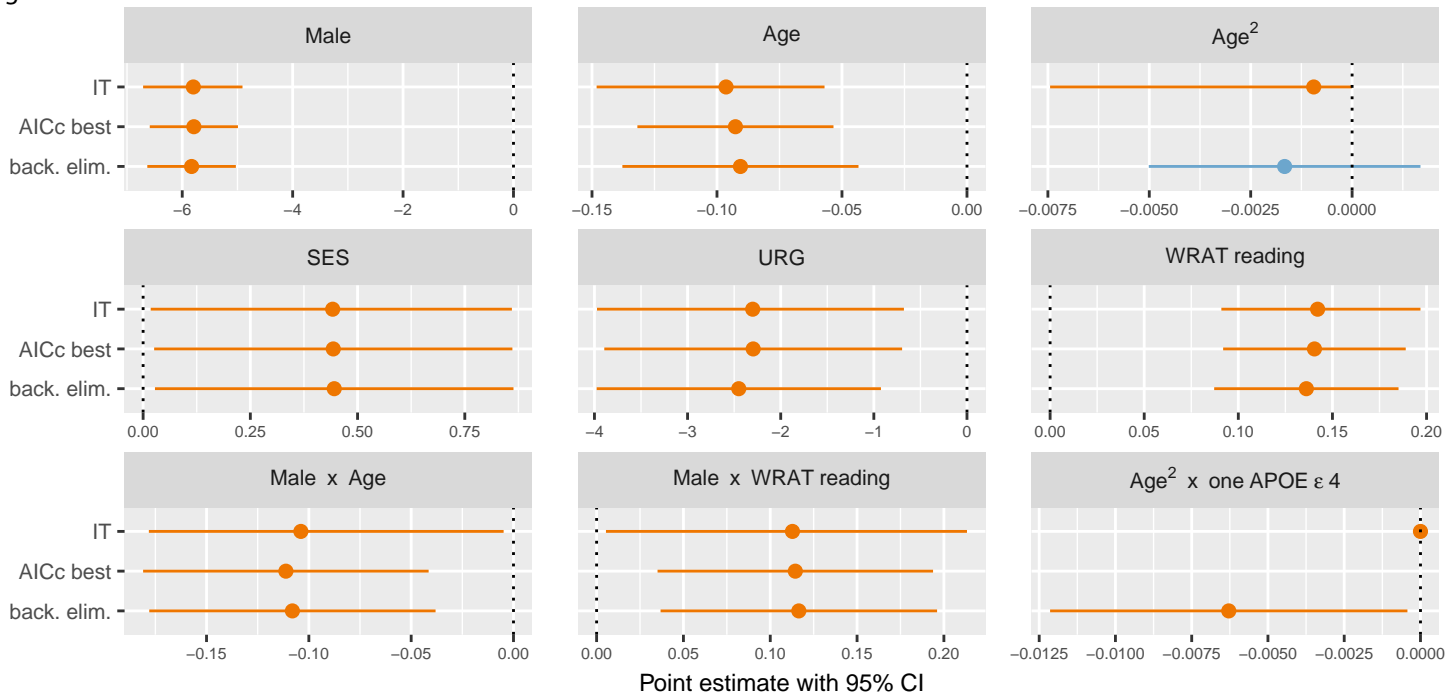


Boston Naming: MA predicted cognitive performance with 95% CI's



AVLT Total: model methods comparison, by any significant coefficient

Modeling method



Confidence Interval... —●— doesn't contain 0 —●— contains 0

Modeling method

