



Development and validation of dementia risk prediction models in *APOE4* carriers: findings from DRPP consortium data

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We developed and validated a prediction model for dementia risk among *APOE4* carriers in the DRPP consortium. Elastic-Net Cox regression was used for feature selection and Cox prediction model was built in randomly selected discovery samples. The final selected predictors highlighted modifiable risk factors including physical activity, diabetes, hypertension, and diet.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES																																																																																				
❖ <i>APOE</i> ε4 allele (<i>APOE4</i>) is the strongest generic risk factor for late-onset dementia. Its prevalence and effect on AD risk vary by race/ethnicity.¹⁻⁴ ❖ Among <i>APOE4</i> carriers, risk factors' impact on dementia risk may differ by race as well.^{5,6} ❖ No prediction models has yet been developed specific to <i>APOE4</i> carriers. ❖ This study aims to build a prediction model among <i>APOE4</i> carriers, based on individual risk factors that can be monitored in clinics and targeted for prevention.	❖ We randomly split data into discovery (80%) and validation (20%) samples, balance on age, race and dementia incidence. ❖ Elastic-Net Cox regression was used to select predictors among age, sex, race, education, <i>APOE</i> genotype, smoking, alcohol consumption, physical activity, diet, diabetes, hypertension, hypercholesterolemia, depression, BMI, and interactions with race, <i>APOE</i> genotype or both. ❖ Missing data were imputed using MICE and analyses were conducted in 25 imputed datasets. ❖ The final Cox prediction model was developed in the discovery samples, and coefficients of selected predictors were estimated using Rubin's rule. ❖ Model performance was assessed using the integrated AUC and the integrated Brier Score (IBS) over corresponding follow-up time window. ❖ Calibration plots were used to assess whether predicted risks agree with observed risks at 15 years of follow-up in both samples.	❖ The Elastic-Net Cox model selected 14 features (Table1). ❖ Modifiable risk factors included physical activity, diabetes, hypertension, and diet. ❖ Prediction model had excellent discrimination (integrated AUC>0.91) and prediction accuracy (IBS<0.05, Table 2) in both discovery and validation samples. ❖ Model had great calibration for predicted risk at 15 years of follow-up. <table><caption>Table 1. Coefficient estimates of the prediction model</caption><thead><tr><th>Features selected ^a</th><th>Hazard Ratio</th><th colspan="2">95% Confidence Interval</th></tr></thead><tbody><tr><td>Age (years) ^b</td><td>1.152</td><td>1.129</td><td>1.176</td></tr><tr><td>White (yes)</td><td>0.884</td><td>0.787</td><td>0.992</td></tr><tr><td>Male (yes)</td><td>0.896</td><td>0.813</td><td>0.987</td></tr><tr><td><i>APOE34</i> (yes)</td><td>1.227</td><td>1.010</td><td>1.490</td></tr><tr><td><i>APOE44</i> (yes)</td><td>2.353</td><td>1.485</td><td>3.727</td></tr><tr><td>No physical activity (yes)</td><td>1.192</td><td>1.072</td><td>1.327</td></tr><tr><td>Diabetes (yes)</td><td>1.138</td><td>0.786</td><td>1.647</td></tr><tr><td>Hypertension stage II (yes)</td><td>1.149</td><td>1.029</td><td>1.283</td></tr><tr><td>Diet^c</td><td>0.990</td><td>0.903</td><td>1.086</td></tr><tr><td><i>APOE34</i>*Age</td><td>1.002</td><td>0.980</td><td>1.024</td></tr><tr><td><i>APOE44</i>*Diet</td><td>1.019</td><td>0.776</td><td>1.337</td></tr><tr><td><i>APOE34</i>*Diabetes</td><td>1.482</td><td>0.983</td><td>2.234</td></tr><tr><td>White*Age</td><td>1.021</td><td>0.998</td><td>1.045</td></tr><tr><td>White*<i>APOE34</i>*Age</td><td>1.008</td><td>0.983</td><td>1.034</td></tr></tbody></table> <table><caption>Table 2. Prediction model evaluations in the discovery and validation samples.</caption><thead><tr><th>Samples</th><th>N</th><th>follow-up years</th><th>Evaluation time window</th><th>integrated AUC</th><th>Integrated Brier Score</th><th>15y Calibration intercept</th><th>15y Calibration slope</th></tr></thead><tbody><tr><td>Discovery</td><td>7901</td><td>2.0-57.4</td><td>3-30 years</td><td>0.918</td><td>0.044</td><td>-0.006</td><td>0.93</td></tr><tr><td>Validation</td><td>1981</td><td>2.0-47.0</td><td>3-30 years</td><td>0.917</td><td>0.046</td><td>-0.002</td><td>0.94</td></tr></tbody></table>	Features selected ^a	Hazard Ratio	95% Confidence Interval		Age (years) ^b	1.152	1.129	1.176	White (yes)	0.884	0.787	0.992	Male (yes)	0.896	0.813	0.987	<i>APOE34</i> (yes)	1.227	1.010	1.490	<i>APOE44</i> (yes)	2.353	1.485	3.727	No physical activity (yes)	1.192	1.072	1.327	Diabetes (yes)	1.138	0.786	1.647	Hypertension stage II (yes)	1.149	1.029	1.283	Diet ^c	0.990	0.903	1.086	<i>APOE34</i> *Age	1.002	0.980	1.024	<i>APOE44</i> *Diet	1.019	0.776	1.337	<i>APOE34</i> *Diabetes	1.482	0.983	2.234	White*Age	1.021	0.998	1.045	White* <i>APOE34</i> *Age	1.008	0.983	1.034	Samples	N	follow-up years	Evaluation time window	integrated AUC	Integrated Brier Score	15y Calibration intercept	15y Calibration slope	Discovery	7901	2.0-57.4	3-30 years	0.918	0.044	-0.006	0.93	Validation	1981	2.0-47.0	3-30 years	0.917	0.046	-0.002	0.94	❖ We developed and validated a prediction model for dementia risk among <i>APOE4</i> carriers in the DRPP consortium. ❖ The selected predictors in model highlighted the potential intervention suggestions: ➢ exercise more ➢ eat a heart-healthy diet ➢ maintain good cardiovascular health ❖ Future work ➢ validate the results using external datasets ➢ evaluate impact of modifiable risk factors ➢ conduct personalized risk analysis ^a For predictors noted with “(yes)”, the reference group is the category with answer equal to “no”. Variables included in interaction terms used the same coding as the individual term. ^b Age was centered at 60 years old. ^c Diet is coded as a reversed diet score by AHA guideline, with 0=ideal, 1=intermediate, 2=poor. Bolded results indicate that the associations between features and dementia risk were statistically significant.	1. Powell DS, et al. (2021) The Relationship of <i>APOE</i> ε4, Race, and Sex on the Age of Onset and Risk of Dementia. <i>Front. Neurol.</i> 12:735036. doi: 10.3389/fneur.2021.735036. 2. Kornblith E, et al. (2022) Association of Race and Ethnicity With Incidence of Dementia Among Older Adults. <i>JAMA.</i> 19:327(15):1488-1495. doi: 10.1001/jama.2022.3550. 3. Belloy ME, et al. (2023) <i>APOE</i> Genotype and Alzheimer Disease Risk Across Age, Sex, and Population Ancestry. <i>JAMA Neurol.</i> 1:80(12):1284-1294. doi: 10.1001/jamaneurol.2023.3599. 4. Durodoye RO, et al (2026) Deviations from additivity in <i>APOE4</i>-mediated late-onset Alzheimer's disease risk across races and ethnicities. <i>Hum Genet.</i> 22:145(1):16. doi: 10.1007/s00439-025-02810-5. 5. Barnes LL and Bennett DA. (2015) Dementia: Cognitive resilience in <i>APOE</i>*ε4 carriers—is race important? <i>Nat Rev Neurol.</i> 11(4):190-1. doi: 10.1038/nrneurol.2015.38. 6. Makkar SR, et al. (2020) <i>APOE</i> ε4 and the Influence of Sex, Age, Vascular Risk Factors, and Ethnicity on Cognitive Decline. <i>J Gerontol A Biol Sci Med Sci.</i> 75(10):1863-1873. doi: 10.1093/gerona/glaa116.
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❖ Data: <i>APOE4</i> carriers from 13 cohorts across 8 studies participating in the DRPP consortium ❖ A total of 9882 dementia-free adults (baseline age≥40) who were followed ≥2 years until ≥65: • 49% Female • 70% White • 83% <i>APOE34</i> • 7.7% <i>APOE44</i>	Xinhui Wang, PhD MS xinhuiwa@usc.edu AAIC 26																																																																																							