Received: 20 October 2022 | Revised: 6 January 2023 | Accepted: 9 January 2023

DOI: 10.1002/alz.12990

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Neuropathology-based *APOE* genetic risk score better quantifies Alzheimer's risk

Yuetiva Deming[1,2,3] | **Eva Vasiljevic**[2,4] | **Autumn Morrow**[2] | **Jiacheng Miao**[5] | **Carol Van Hulle**[1,3] | **Erin Jonaitis**[3,6] | **Yue Ma**[1,3] | **Vanessa Whitenack**[1] | **Gwendlyn Kollmorgen**[7] | **Norbert Wild**[7] | **Ivonne Suridjan**[8] | **Leslie M. Shaw**[9] | **Sanjay Asthana**[1,3,10] | **Cynthia M. Carlsson**[1,3,10] | **Sterling C. Johnson**[1,3,10] | **Henrik Zetterberg**[11,12,13,14,15] | **Kaj Blennow**[11,12] | **Barbara B. Bendlin**[1,3] | **Qiongshi Lu**[4,5] | **Corinne D. Engelman**[2,3,4] | **the Alzheimer's Disease Neuroimaging Initiative**

[1]Department of Medicine, School of Medicine and Public Health, University of Wisconsin–Madison, Madison, Wisconsin, USA

[2]Department of Population Health Sciences, School of Medicine and Public Health, University of Wisconsin–Madison, Madison, Wisconsin, USA

[3]Wisconsin Alzheimer's Disease Research Center, University of Wisconsin–Madison, Madison, Wisconsin, USA

[4]Center for Demography of Health and Aging, University of Wisconsin–Madison, Madison, Wisconsin, USA

[5]Department of Biostatistics and Medical Informatics, School of Medicine and Public Health, University of Wisconsin–Madison, Madison, Wisconsin, USA

[6]Wisconsin Alzheimer's Institute, University of Wisconsin–Madison, Madison, Wisconsin, USA

[7]Roche Diagnostics GmbH, Penzberg, Germany

[8]Roche Diagnostics International Ltd, Rotkreuz, Switzerland

[9]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[10]William S. Middleton Memorial Veterans Hospital, Geriatric Research Education and Clinical Center, Madison, Wisconsin, USA

[11]Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at University of Gothenburg, Mölndal, Sweden

[12]Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

[13]UK Dementia Research Institute at UCL, London, UK

[14]Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

[15]Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China

Correspondence
Yuetiva Deming, Department of Medicine, University of Wisconsin–Madison, 600 Highland Avenue, J5/1M Clinical Science Center, Madison, WI 53792, USA.
Email: yrobles@wisc.edu

Funding information
National Institutes of health (NIH), Grant/Award Numbers: R01AG27161, R01AG054047, P50AG033514,

Abstract

Introduction: Apolipoprotein E (*APOE*) *ε4*-carrier status or *ε4* allele count are included in analyses to account for the *APOE* genetic effect on Alzheimer's disease (AD); however, this does not account for protective effects of *APOE ε2* or heterogeneous effect of *ε2*, *ε3*, and *ε4* haplotypes.

Methods: We leveraged results from an autopsy-confirmed AD study to generate a weighted risk score for *APOE* (*APOE*-npscore). We regressed cerebrospinal fluid

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

P30AG062715, R01 AG021155, UL1TR000427; NIH National Center for Advancing Translational Sciences, Grant/Award Numbers: S10 OD025245-01, R01AG037639; The Biology of Aging and Age-Related Diseases training, Grant/Award Number: T32 AG000213-28; The National Institute on Aging; The Center for Demography of Health and Aging NIA Training, Grant/Award Number: T32AG000129; The Swedish Research Council, Grant/Award Number: #2018-02532; European Union's Horizon Europe research and innovation programme under grant agreement, Grant/Award Number: 101053962; Swedish State Support for Clinical Research, Grant/Award Number: #ALFGBG-71320; The Alzheimer Drug Discovery Foundation (ADDF), USA, Grant/Award Number: #201809-2016862; The AD Strategic Fund and the Alzheimer's Association, Grant/Award Numbers: #ADSF-21-831376-C, #ADSF-21-831381-C, #ADSF-21-831377-C; The Bluefield Project, the Olav Thon Foundation; The Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Grant/Award Number: #FO2022-0270; The European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie, Grant/Award Number: 860197; European Union Joint Programme – Neurodegenerative Disease Research, Grant/Award Number: JPND2021-00694; The UK Dementia Research Institute at UCL, Grant/Award Number: UKDRI-1003; The Swedish Research Council, Grant/Award Number: #2017-00915; Alzheimer Drug Discovery Foundation (ADDF), Grant/Award Number: #RDAPB-201809-2016615; The Swedish Alzheimer Foundation, Grant/Award Numbers: #AF-930351, #AF-939721, #AF-968270; Hjärnfonden, Sweden, Grant/Award Numbers: #FO2017-0243, #ALZ2022-0006

(CSF) amyloid and tau biomarkers on *APOE* variables from the Wisconsin Registry for Alzheimer's Prevention (WRAP), Wisconsin Alzheimer's Disease Research Center (WADRC), and Alzheimer's Disease Neuroimaging Initiative (ADNI).

Results: The *APOE*-npscore explained more variance and provided a better model fit for all three CSF measures than *APOE ε4*-carrier status and *ε4* allele count. These findings were replicated in ADNI and observed in subsets of cognitively unimpaired (CU) participants.

Discussion: The *APOE*-npscore reflects the genetic effect on neuropathology and provides an improved method to account for *APOE* in AD-related analyses.

KEYWORDS
Alzheimer's disease, amyloid beta, *APOE*, biomarkers, cerebrospinal fluid endophenotypes, phosphorylated tau

1 | INTRODUCTION

The apolipoprotein E gene (*APOE*) is the predominant genetic risk factor for late-onset Alzheimer's disease (AD), with three alleles contributing to disease risk: *ε2* (reduced risk), *ε3* (reference), and *ε4* (increased risk). *APOE* genotype is associated with many AD endophenotypes, biomarkers reflecting the underlying neuropathology of amyloid plaques and neurofibrillary tangles, such as cerebrospinal fluid (CSF)[1] and positron emission tomography (PET) measures of amyloid and tau.[2] The importance of accounting for the strong genetic effect of *APOE* on AD risk has been recognized in many analyses of AD-related outcomes and researchers often use *APOE ε4*-carrier status (APOE4-status: *ε4+*/*ε4−*)[2,3] or, less frequently, the number of *APOE ε4* alleles (*ε4*-count: 0, 1, 2).[4] Using these methods to model *APOE* genetic risk has limitations: (1) APOE4-status and the *ε4*-count do not account for the effects of reduced risk conferred by *APOE ε2*; (2) an assumption of the allele count approach is that genetic risk of *APOE ε4* is strictly additive; and (3) as a dichotomous variable APOE4-status has limitations in statistical modeling such as loss of statistical power or problems with model convergence.[5] To overcome these limitations, we previously used a weighted score for *APOE* genotype based on risk for AD diagnosis.[1,6] Another group used a similar method to model the *APOE* genetic effect in polygenic risk scores, weighting the number of *APOE ε2* alleles and the number of *APOE ε4* alleles by the effect sizes reported in the Kunkle et al. genome-wide association study[7] for single nucleotide polymorphisms (SNPs) rs7412 (encoding *ε2*) and rs429358 (encoding *ε4*).[8] One limitation of these *APOE* risk scores is that they are based on clinical diagnosis of AD dementia which can include preclinical AD appearing as controls and dementia cases due to non-AD causes.[9–11] Here, we propose an improved method to account for *APOE* genetic risk for AD in statistical analyses using a weighted score based on AD neuropathology, providing a pseudo-continuous

variable that does not collapse important genotype categories. By comparing AD cases and controls that were confirmed at autopsy, Reiman et al. showed that the odds ratio (OR) has been overestimated for *APOE ε2/ε2* individuals and underestimated for *APOE ε4/ε4* individuals in clinical risk studies.[12] Similar results have been obtained using CSF endophenotypes as surrogate measures of AD pathology.[13] We propose that using this *APOE* neuropathology-based score (*APOE*-npscore) will help researchers more accurately account for the genetic effect of *APOE* on the underlying neuropathology of AD. This can increase statistical power, avoid modeling issues that result from low-frequency genotypes with low counts, and allows for a more nuanced variable that may help distinguish AD from diseases with similar clinical appearance. Furthermore, most studies can immediately incorporate the *APOE*-npscore in analyses because it is easily derived from existing *APOE* genotype data (*ε2*, *ε3*, *ε4*).

CSF biomarkers for amyloid-beta1-42 (Aβ42) and amyloid-beta1-42/1-40 (Aβ42/40) ratio and phosphorylated tau 181 (ptau181) are among the gold standard biomarkers for AD. CSF Aβ42 and the Aβ42/40 ratio decrease early in AD and are negatively correlated with amyloid PET[14] and amyloid plaques presence, a hallmark neuropathology of AD.[15] CSF Aβ42/40 ratio has been reported to predict PET amyloid-positivity more accurately than CSF Aβ42 alone, regardless of clinical diagnosis.[16,17] Another key pathological hallmark of AD, neurofibrillary tangles composed of hyperphosphorylated tau, is positively correlated with CSF ptau181 concentration.[18] The ratio of CSF ptau181/Aβ42 is predictive of cognitive decline and conversion to AD dementia.[19–21] These CSF biomarkers change before cognitive symptoms appear[19,22] and can help distinguish AD from other diseases that are clinically similar.[23–25] The correlation with AD neuropathology and measurable changes early in disease made these CSF biomarkers ideal for testing our hypothesis that the *APOE*-npscore is an improvement over other methods in accounting for the *APOE* genetic risk for AD in statistical analyses.

RESEARCH IN CONTEXT

1. **Systematic Review**: We reviewed existing literature for current methods used to account for *APOE* genetic risk in Alzheimer's disease (AD) research. Although some studies used variables other than dichotomous *APOE ε4*-carrier status (APOE4-status), none used weighted scores based on autopsy-confirmed AD. There have been no direct comparisons of different variables used to account for *APOE* genetic risk.
2. **Interpretation**: We observed the neuropathology-based weighted *APOE* risk score (*APOE*-npscore) consistently provided better model fit for cerebrospinal fluid (CSF) AD endophenotypes than either APOE4-status or *ε4*-count. Our findings demonstrate the benefit of using a pseudo-continuous variable like the *APOE*-npscore, which increases statistical power and avoids modeling issues from small sample sizes.
3. **Future Directions**: The *APOE*-npscore can easily be implemented by studies with *APOE* genetic data for their participants. Additional studies in diverse cohorts are necessary to create a more refined *APOE*-npscore to account for *APOE* genetic risk in a broader context.

2 | METHODS

2.1 | Participants

The Institutional Review Boards of all participating institutions approved the study, and research was carried out in accordance with approved protocols. Written informed consent was obtained from participants or their family members. Data were obtained from longitudinal studies of preclinical and clinical AD from the Wisconsin Registry for Alzheimer's Prevention (WRAP)[26] and the Wisconsin Alzheimer's Disease Research Center (WADRC). WRAP is a longitudinal observational cohort study, established in 2001, of middle-aged participants that is enriched with people who have a parental history of probable-AD dementia. The WADRC was established in 2009 and is one of the National Institute on Aging (NIA) –designated ADRCs across the United States. Participants enrolled in these studies provided CSF within 1 year of cognitive testing. Diagnoses were determined by consensus conference of dementia specialists based on NIA-Alzheimer's Association (NIA-AA) criteria without reference to biomarker status.[27,28] The combined data in these analyses include participants with mild cognitive impairment (MCI), dementia due to suspected AD (dementia-AD), or cognitively unimpaired (CU) individuals.

Data used for replication analyses were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu).[29] The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

2.2 | Genotyping and scoring

DNA extracted from whole blood samples from WADRC and WRAP participants was genotyped for *APOE ε2* and *APOE ε4* using competitive allele-specific PCR-based KASP genotyping for rs7412 and rs429358, respectively.[6] Data downloaded from the ADNI database were obtained from DNA extracted from blood, as described previously.[30]

To generate the *APOE*-npscore we used a natural log (ln) transformation of the OR values reported in a study of *APOE* genetic risk in autopsy-confirmed AD cases ($n = 4018$) and controls ($n = 989$), none

of whom were participants in our analyses.[12] OR values were obtained from the Reiman et al., supplementary table which had OR calculated for each *APOE* genotype, using *ε3ε3* as the reference, after adjusting for age and sex: *ε2ε2* OR = 0.16, *ε2ε3* OR = 0.40, *ε3ε3* OR = 1, *ε2ε4* OR = 2.47, *ε3ε4* OR = 5.71, and *ε4ε4* OR = 26.93[12]. By using the ln(OR), the *APOE*-npscore is negative for haplotypes associated with reduced risk for AD compared to *ε3ε3*, resulting in the *APOE*-npscore: *ε2ε2* = −1.833, *ε2ε3* = −0.916, *ε3ε3* = 0, *ε2ε4* = 0.904, *ε3ε4* = 1.742, and *ε4ε4* = 3.293.

2.3 | CSF collection and assays

CSF samples from WADRC and WRAP were acquired as described previously.[31] Briefly, samples were collected by lumbar puncture (LP) in the morning after an 8- to 12-h fast, centrifuged to remove red blood cells or other debris, then 0.5 mL CSF was aliquoted into 1.5-mL polypropylene tubes and stored at −80°C within 30 min of collection. WRAP and WADRC CSF samples were assayed at the Clinical Neurochemistry Laboratory, University of Gothenburg under strict quality control procedures. Aβ42, ptau181, and Aβ40 levels in CSF were measured using the Elecsys *β*-Amyloid(1-42) CSF, Elecsys Phospho-Tau (181P) CSF, and Elecsys *β*-Amyloid(1-40) electrochemiluminescence immunoassays, respectively, on the cobas e 601 analyzer (all Roche Diagnostics International Ltd.).

ADNI CSF samples, obtained as described in the ADNI procedures manual (http://www.adni-info.org), were also measured using Elecsys CSF immunoassays on a cobas e 601 analyzer at the University of Pennsylvania.[32] ADNI CSF data (versions 2021-01-04 and 2019-07-29) were downloaded in early 2022 from the ADNI database (https://ida.loni.usc.edu) with corresponding participant demographics such as age, sex, diagnosis, and *APOE* genotypes. Data were verified to be the most currently available as of September 7, 2022.

The Elecsys CSF immunoassays had measuring ranges of 200–1700 pg/mL for Aβ42, 0.006–40.3 ng/mL for Aβ40 (specific for lot used), and 8–120 pg/mL for ptau181.[31,32] Performance of the assays above these technical limits had not been formally established. Therefore, we only analyzed values within the technical limits. CSF Aβ42/40 and ptau181/Aβ42 ratios were derived from the CSF Aβ42, Aβ40, and ptau181 values.

2.4 | Statistical analyses

There were 1045 individuals available for analyses in WADRC (n = 380), WRAP (n = 238), and ADNI (n = 427). Initial analyses used WADRC and WRAP combined data, then replication analyses were performed using ADNI data. Statistical analyses were performed in R (version 4.2.0).[33] Sample characteristics were compared between studies using analysis of variance for continuous measures and chi-square for categorical measures.

Associations between CSF biomarker (Aβ42/40 ratio, ptau181, or ptau181/Aβ42 ratio) and *APOE* variable (*APOE*-npscore, APOE4-status, or *ε4*-count) were each tested using linear mixed-effects regression in the lmerTest R package (version 3.1-3)[34] with random intercepts for each participant to account for multiple LP visits. Self-reported sex, clinical diagnosis (CU, MCI-AD, dementia-AD), and linear and quadratic terms for mean centered age at LP were entered as fixed covariates. CSF ptau181 values and the ptau181/Aβ42 ratio were ln-transformed and standardized within study. Residual diagnostics, used to verify covariate selection and check model assumptions, were performed using the DHARMa R package (version 0.4.5).[35] To determine goodness-of-fit and quantify differences in model fit between *APOE*-npscore, APOE4-status (0, 1), and *ε4*-count (0, 1, 2), we compared the Akaike information criterion (AIC), Bayesian information criterion (BIC), and the proportion of variance explained by models differing only by the *APOE* variable as predictor. Pseudo-R^2 statistics were calculated using the MuMIn R package (version 1.47.1)[36] and the marginal R^2 were compared to determine the difference in variance attributable to the fixed effects portion of each model. Relative improvement between models was calculated using the ratio of marginal R^2 values.

Other R packages used included kableExtra (version 1.3.4),[37] tableone (version 0.13.2),[38] and sjPlot (version 2.8.11).[39]

3 | RESULTS

3.1 | Participant characteristics by study

The characteristics of participants in WADRC, WRAP, and ADNI are shown by study in Table 1. Comparisons between WADRC and WRAP are provided in Table S1 and characteristics by ADNI protocol (ADNI1, ADNI2, ADNIGO, and ADNI3) are shown in Table S2. Participant characteristics are based on the most recent LP visit; information about multiple LP visits and biomarker values are provided based on longitudinal data (1566 CSF samples). Table S3 shows characteristics by study (WADRC, WRAP, and ADNI) for a subset of CU participant samples used in sensitivity analyses.

All studies included predominantly non-Hispanic white (NHW) and mostly female individuals. There were significant differences in clinical diagnosis across studies. WRAP was comprised of CU individuals with a few MCI-AD, both WADRC and ADNI had similar numbers of dementia-AD, and ADNI had the largest proportion of MCI-AD. Mean *APOE*-npscores were lower in WRAP (0.54 ± 1.02) than WADRC (0.79 ± 1.20) and ADNI (0.75 ± 1.18). Less than 14% of WADRC, almost 27% of WRAP, and less than 17% of ADNI participants had 2 or more LPs with a mean difference ~2.5 years between visits. Mean age at LP across longitudinal samples was similar in WADRC and WRAP (~63 years) but older in ADNI (73 years). ADNI participants had significantly higher levels of both CSF Aβ42 (913 ± 372 pg/mL) and ptau181 (24.6 ± 12.9 pg/mL) than WADRC (Aβ42: 826 ± 364 pg/mL; ptau181: 20.3 ± 11.4 pg/mL) and WRAP (Aβ42: 861 ± 354 pg/mL; ptau181: 18.6 ± 6.62 pg/mL). Scatterplots of age at LP against CSF Aβ42, Aβ42/40 ratio, and ptau181 values by study are shown in Figure 1.

TABLE 1 Cohort demographics at most recent lumbar puncture and longitudinal biomarkers.

	Overall	WADRC	WRAP	ADNI
n (individual participants)	1045	380	238	427
Summary diagnosis, *n* (%)***				
Dementia-AD	95 (9.1)	48 (12.6)	0 (0.0)	47 (11.0)
MCI-AD	168 (16.1)	42 (11.1)	3 (1.3)	123 (28.8)
CU	782 (74.8)	290 (76.3)	235 (98.7)	257 (60.2)
Female, *n* (%)*	622 (59.5)	231 (60.8)	156 (65.5)	235 (55.0)
Self-reported race, *n* (%)				
NHB	34 (3.3)	14 (3.7)	4 (1.7)	16 (3.7)
Other	20 (1.9)	3 (0.8)	5 (2.1)	12 (2.8)
NHW	991 (94.8)	363 (95.5)	229 (96.2)	399 (93.4)
APOE genotype, *n* (%)*				
ε2ε2	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)
ε2ε3	91 (8.7)	35 (9.2)	24 (10.1)	32 (7.5)
ε3ε3	535 (51.2)	177 (46.6)	131 (55.0)	227 (53.2)
ε2ε4	27 (2.6)	15 (3.9)	5 (2.1)	7 (1.6)
ε3ε4	308 (29.5)	116 (30.5)	71 (29.8)	121 (28.3)
ε4ε4	83 (7.9)	36 (9.5)	7 (2.9)	40 (9.4)
APOE-npscore, mean (SD)*	0.72 (1.16)	0.79 (1.20)	0.54 (1.02)	0.75 (1.18)
Longitudinal biomarkers				
n samples	1566	498	515	553
LP visit, *n* (%)***				
1	1045 (67.0)	380 (76.3)	238 (46.2)	427 (77.2)
2	295 (18.8)	65 (13.1)	137 (26.6)	93 (16.8)
3	145 (9.3)	26 (5.2)	93 (18.1)	26 (4.7)
4	66 (4.2)	18 (3.6)	41 (8.0)	7 (1.3)
5	12 (0.8)	6 (1.2)	6 (1.2)	0 (0.0)
6	2 (0.1)	2 (0.4)	0 (0.0)	0 (0.0)
7	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)
Age at LP (years), mean (SD)***	66.94 (9.15)	63.26 (9.31)	63.97 (6.93)	73.01 (7.55)
Years between visits, mean (SD)***	2.55 (1.51)	2.57 (2.22)	2.42 (1.12)	2.84 (1.41)
Aβ42 (pg/mL), mean (SD)**	865 (364)	826 (364)	861 (354)	913 (372)
Aβ42/40 ratio, mean (SD)***	0.06 (0.02)	0.06 (0.02)	0.06 (0.02)	0.06 (0.02)
ptau181 (pg/mL), mean (SD)***	21.3 (11.1)	20.3 (11.4)	18.6 (6.62)	24.6 (12.9)
ptau181/Aβ42 ratio, mean (SD)***	0.03 (0.03)	0.03 (0.03)	0.03 (0.02)	0.04 (0.03)

Note: *p*-values from Pearson's Chi-squared test; Wilcoxon rank sum test.

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; *APOE*, apolipoprotein E; *APOE*-npscore, neuropathology-based *APOE* genetic risk score; Aβ42, CSF amyloid-beta1-42; Aβ42/40, CSF amyloid-beta1-42 /CSF amyloid-beta1-40 ratio; CU, cognitively unimpaired; Dementia-AD, dementia suspected due to AD; LP, lumbar puncture; MCI-AD, mild cognitive impairment suspected due to AD; NHB, self-reported non-Hispanic Black; NHW, self-reported non-Hispanic white; ptau/Aβ42 ratio, CSF phosphorylated tau 181/CSF amyloid-beta1-42 ratio; ptau181, CSF phosphorylated tau 181; SD, standard deviation; WADRC, Wisconsin Alzheimer's Disease Research Center; WRAP, Wisconsin Registry for Alzheimer's Prevention.

$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

3.2 | Using *ε4*-count provided a better model fit than APOE4-status and explained more variance in CSF AD endophenotypes

Some researchers use *ε4*-count instead of the binary APOE4-status, so we tested if *ε4*-count provides a better model fit than APOE4-status. In our preliminary analyses of WADRC and WRAP, APOE4-status and *ε4*-count were associated with CSF Aβ42/40 ratio ($\beta = -0.012$, $p = 3.98 \times 10^{-21}$ and $\beta = -0.010$, $p = 1.04 \times 10^{-23}$, respectively), ptau181 ($\beta = 0.258$, $p = 6.49 \times 10^{-4}$ and $\beta = 0.238$, $p = 9.20 \times 10^{-5}$, respectively), and ptau181/Aβ42 ratio ($\beta = 0.524$, $p = 2.52 \times 10^{-14}$ and $\beta = 0.460$, $p = 7.42 \times 10^{-17}$, respectively); however, models using

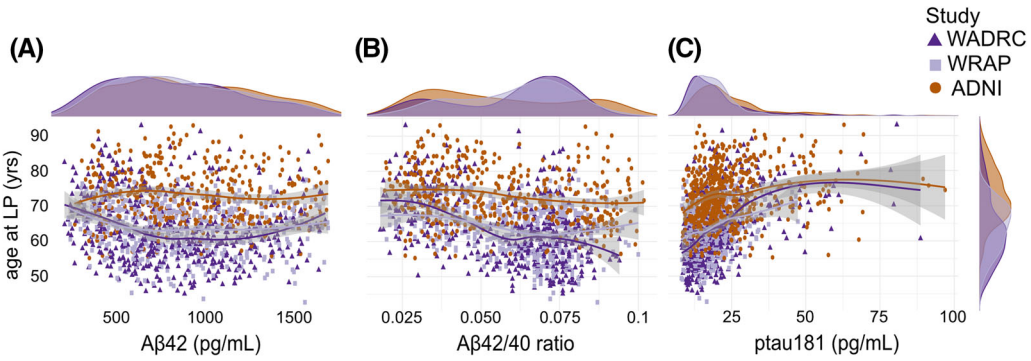

FIGURE 1 Cerebrospinal fluid (CSF) biomarker levels by age at time of lumbar puncture (LP). Scatterplots of the age at time of LP against CSF Aβ42 (A), Aβ42/40 ratio (B), and ptau181 (C) with density plots for each biomarker on top and a density plot for age at LP for all three panels on the right-hand side of (C). Each point represents an individual CSF sample. Densities, loess curves, and points are all color-coded by study as shown in the legend; triangle-shaped points indicate CSF sample data from Wisconsin Alzheimer's Disease Research Center (WADRC), square-shaped points indicate CSF sample data from Wisconsin Registry for Alzheimer's Prevention (WRAP), and circle-shaped points indicate CSF sample data from Alzheimer's Disease Neuroimaging Initiative (ADNI).

TABLE 2 Linear-mixed effects model comparisons between APOE genetic variables

	CSF Aβ42/40 ratio				CSF ptau181				CSF ptau181/Aβ42 ratio			
	n	R^2	AIC	BIC	n	R^2	AIC	BIC	n	R^2	AIC	BIC
WADRC/WRAP												
APOE4-status	948	0.344	−5728	−5684	971	0.203	1641	1685	924	0.358	1781	1825
ε4-count	948	0.355	−5740	−5696	971	0.208	1637	1681	924	0.370	1770	1813
APOE-npscore	948	0.360	−5746	−5702	971	0.210	1635	1679	924	0.378	1761	1805
ADNI												
APOE4-status	423	0.315	−2285	−2248	548	0.200	1156	1195	418	0.344	909	945
ε4-count	423	0.359	−2309	−2272	548	0.208	1152	1190	418	0.394	880	917
APOE-npscore	423	0.375	−2318	−2282	548	0.218	1147	1186	418	0.409	872	908

Abbreviations: ADNI, Alzheimer's Disease Neuroimaging Initiative; AIC, Akaike Information Criterion; APOE4-status, *APOE4*-carrier status (0, 1); *APOE*-npscore, *APOE* neuropathology-based score; Aβ42/40, CSF amyloid-beta1-42/amyloid-beta1-40 ratio; BIC, Bayesian Information Criterion; CSF, cerebrospinal fluid; *n*, number of observations; ptau/Aβ42 ratio, CSF phosphorylated tau 181/CSF amyloid-beta1-42 ratio; ptau181, CSF phosphorylated tau 181; R^2, marginal R^2 (variation explained by fixed effects); WADRC, Wisconsin Alzheimer's Disease Research Center; WRAP, Wisconsin Registry for Alzheimer's Prevention; *ε4*-count, number of *APOE ε4* alleles (0, 1, 2).

ε4-count explained more variance than APOE4-status with 3.2% relative increase in CSF Aβ42/40 ratio (marginal $R^2 = 0.355$ vs. 0.344), 2.5% relative increase in ptau181 (marginal $R^2 = 0.208$ vs. 0.203), and 3.4% increase in ptau181/Aβ42 ratio (marginal $R^2 = 0.370$ vs. 0.358). Model fit comparisons are shown in Table 2 and detailed regression results in Tables S4–S6.

As shown in Table 2, our findings were replicated in ADNI. Models with *ε4*-count explained more variance than APOE4-status with 14% relative increase explained in CSF Aβ42/40 ratio (marginal $R^2 = 0.359$ vs. 0.315), 4% increase in ptau181 (marginal $R^2 = 0.208$ vs. 0.200), and 14.5% increase in ptau181/Aβ42 ratio (marginal $R^2 = 0.394$ vs. 0.344). Detailed results are shown in Tables S7–S9.

3.3 | APOE-npscore provided a better model fit than *ε4*-count and explained more variance in CSF AD endophenotypes

After determining that *ε4*-count provided a better model fit than APOE4-status, we tested if the *APOE*-npscore improved the model fit even more than *ε4*-count. In the WADRC and WRAP, *APOE*-npscore was associated with CSF Aβ42/40 ratio ($\beta = -0.006$, $p = 6.63 \times 10^{-25}$), ptau181 ($\beta = 0.140$, $p = 2.35 \times 10^{-5}$), and ptau181/Aβ42 ratio ($\beta = 0.264$, $p = 1.09 \times 10^{-18}$). Models using *APOE*-npscore explained more variance than *ε4*-count with a relative increase of 1.4% variance explained in CSF Aβ42/40 ratio (marginal $R^2 = 0.360$ vs. 0.355), 1% increase in ptau181 (marginal $R^2 = 0.210$ vs. 0.208), and 2.2% increase

explained in ptau181/Aβ42 ratio (marginal R^2 = 0.378 vs. 0.370). As shown in Table 2, both AIC and BIC model selection criteria consistently supported models using the *APOE*-npscore over models using the *ε4*-count and models using the APOE4-status. Detailed results are shown in Tables S4–S6.

Our findings were replicated in the ADNI. *APOE*-npscore explained more variance than *ε4*-count with a relative increase of 4.5% explained in CSF Aβ42/40 ratio (marginal R^2 = 0.375 vs. 0.359), 4.8% increase in ptau181 (marginal R^2 = 0.218 vs. 0.208), and 3.8% increase in ptau181/Aβ42 ratio (marginal R^2 = 0.409 vs. 0.394). Detailed results are shown in Tables S7–S9.

3.4 | APOE-npscore provided a better model fit in a subset of cognitively unimpaired participants

Previous studies have reported preclinical effects of APOE4-status and *ε4*-count on CSF AD biomarkers.[40,41] To test if the *APOE*-npscore could provide a better model fit than APOE4-status and *ε4*-count when analyzing CSF AD endophenotypes before cognitive symptoms appear, we reran the analyses in a subset of longitudinal samples from participants who were CU at LP (described in Table S3). There were significant associations between CSF Aβ42/40 ratio and the *APOE*-npscore ($\beta = -0.005$, $p = 1.06 \times 10^{-18}$), APOE4-status ($\beta = -0.011$, $p = 1.47 \times 10^{-16}$), and *ε4*-count ($\beta = -0.010$, $p = 4.63 \times 10^{-18}$); between ptau181 and *APOE*-npscore ($\beta = 0.110$, $p = 1.52 \times 10^{-3}$), APOE4-status ($\beta = 0.217$, $p = 4.68 \times 10^{-3}$), and *ε4*-count ($\beta = 0.191$, $p = 3.32 \times 10^{-3}$); and between ptau181/Aβ42 ratio and *APOE*-npscore ($\beta = 0.241$, $p = 1.17 \times 10^{-13}$), APOE4-status ($\beta = 0.491$, $p = 1.04 \times 10^{-11}$), and *ε4*-count ($\beta = 0.437$, $p = 7.85 \times 10^{-13}$). There was also more variance explained by the *APOE*-npscore than the APOE4-status with a relative increase of 3.7% in CSF Aβ42/40 ratio (marginal R^2 = 0.222 vs. 0.214), 1.4% in CSF ptau181 (marginal R^2 = 0.150 vs. 0.148), and 4.9% in CSF ptau181/Aβ42 ratio (marginal R^2 = 0.216 vs. 0.206). *APOE*-npscore also explained more variance than *ε4*-count with a relative increase of 1% in CSF Aβ42/40 ratio (marginal R^2 = 0.222 vs. 0.220) and 1.4% in ptau181/Aβ42 ratio (marginal R^2 = 0.216 vs. 0.213), but no difference in ptau181 (marginal R^2 = 0.150 vs. 0.150). Both AIC and BIC model selection criteria consistently supported models using the *APOE*-npscore (Aβ42/40 ratio: AIC = −5175, BIC = −5137; ptau181: AIC = 1304, BIC = 1342; ptau181/Aβ42 ratio: AIC = 1512, BIC = 1550) over models using the *ε4*-count (Aβ42/40 ratio: AIC = −5172, BIC = −5134; ptau181: AIC = 1305, BIC = 1343; ptau181/Aβ42 ratio: AIC = 1516, BIC = 1553) and models using the APOE4-status (Aβ42/40 ratio: AIC = −5165, BIC = −5127; ptau181: AIC = 1306, BIC = 1344; ptau181/Aβ42 ratio: AIC = 1521, BIC = 1558). Detailed results are shown in Tables S10–S12.

These findings were replicated in a subset of samples from participants who were CU in ADNI (described in Table S3). CSF Aβ42/40 ratio was associated with the *APOE*-npscore ($\beta = -0.009$, $p = 8.13 \times 10^{-12}$), APOE4-status ($\beta = -0.018$, $p = 5.94 \times 10^{-9}$), and *ε4*-count ($\beta = -0.016$, $p = 6.78 \times 10^{-11}$). CSF ptau181 was associated with *APOE*-npscore ($\beta = 0.181$, $p = 3.74 \times 10^{-4}$), APOE4-status ($\beta = 0.324$, $p = 4.04 \times 10^{-3}$), and *ε4*-count ($\beta = 0.298$, $p = 1.54 \times 10^{-3}$). The CSF ptau181/Aβ42 ratio was associated with *APOE*-npscore ($\beta = 0.335$, $p = 8.55 \times 10^{-11}$), APOE4-status ($\beta = 0.602$, $p = 3.26 \times 10^{-7}$), and *ε4*-count ($\beta = 0.583$, $p = 8.93 \times 10^{-10}$). There was more variance explained by the *APOE*-npscore than the APOE4-status with a relative increase of 20.5% in CSF Aβ42/40 ratio (marginal R^2 = 0.264 vs. 0.219), 9% in CSF ptau181 (marginal R^2 = 0.182 vs. 0.167), and 22.5% in CSF ptau181/Aβ42 ratio (marginal R^2 = 0.299 vs. 0.244). *APOE*-npscore also explained more variance than *ε4*-count with a relative increase of 6.5% in CSF Aβ42/40 ratio (marginal R^2 = 0.264 vs. 0.248), 5.8% in ptau181 (marginal R^2 = 0.182 vs. 0.172), and 6% in ptau181/Aβ42 ratio (marginal R^2 = 0.299 vs. 0.282). Both AIC and BIC model selection criteria consistently supported models using the *APOE*-npscore (Aβ42/40 ratio: AIC = −1422, BIC = −1387; ptau181: AIC = 657, BIC = 696; ptau181/Aβ42 ratio: AIC = 508, BIC = 543) over models using the *ε4*-count (Aβ42/40 ratio: AIC = −1418, BIC = −1382; ptau181: AIC = 660, BIC = 699; ptau181/Aβ42 ratio: AIC = 513, BIC = 548) and models using the APOE4-status (Aβ42/40 ratio: AIC = −1409, BIC = −1373; ptau181: AIC = 662, BIC = 701; ptau181/Aβ42 ratio: AIC = 525, BIC = 560). Detailed results are shown in Tables S13–S15.

4 | DISCUSSION

We report here a method for translating *APOE* haplotype (*ε2ε2*, *ε2ε3*, *ε2ε4*, *ε3ε3*, *ε3ε4*, and *ε4ε4*) into a pseudo-continuous measure reflecting *APOE* genetic risk for autopsy-confirmed AD. We demonstrated the *APOE*-npscore provides a better model fit than dichotomous APOE4-status, and even *ε4*-count, in statistical models of CSF endophenotypes for AD neuropathology (Aβ42/40 ratio, ptau181, and ptau181/Aβ42 ratio). Although some of the statistical improvements we reported in this study were small, there are several benefits of using *APOE*-npscore in AD-related research. Not only does it more accurately represent corresponding risk for each haplotype, the *APOE*-npscore more closely reflects the genetic effect of *APOE* on AD neuropathology. It allows researchers to account for effects of *ε2* and *ε4* in one variable. As an improvement to *APOE* clinical risk scores, by using the results of a large autopsy-confirmed AD case-control study,[12] we minimize bias from misclassified dementia cases and preclinical controls.

CSF biomarkers change years before cognitive symptoms appear and are not only correlated with AD neuropathology but also with *APOE*.[1,22,42] As expected, all the methods we tested for encoding *APOE* genotype were significantly associated with CSF Aβ42/40 ratio, ptau181, and ptau181/Aβ42 ratio. In all three AD endophenotypes, *APOE*-npscore appeared to provide a better model fit than APOE4-status and *ε4*-count and there was more variance explained by the *APOE*-npscore models, consistently observed in WADRC, WRAP, and ADNI as well as subsets of CU individuals. These findings suggest that studies of preclinical AD, such as personalized prevention trials, could benefit from using the *APOE*-npscore instead of separating groups by APOE4-status. The *APOE*-npscore provides a better model

fit for CSF AD endophenotypes and likely would do the same for trial endpoints. The *APOE*-npscore could easily be translated to APOE4-status or *ε4*-count if needed, but the opposite isn't necessarily true. Using the *APOE*-npscore in trial design would require genotyping both *APOE* SNPs (rs429358 for *ε4*, rs7412 for *ε2*) and place greater emphasis on recruiting rarer *ε2* carriers than designs that use APOE4-status, but the added benefit is that the precision of the *APOE*-npscore could help personalize treatment.

There are important limitations in this study to consider for future research. The Reiman et al. study that provided OR used to derive the *APOE*-npscore consisted of NHW individuals[12] and the cohorts included in our analyses comprised > 94% NHW participants. With reported disparities in biomarker outcomes and in *APOE* genetic risk, there is evidence our findings may not translate directly to other populations.[43–54] Self-identified non-Hispanic Black (NHB) individuals are at a greater risk of AD dementia than NHW; however, even though *APOE ε4* is more common in African genetic ancestry (rs429358 MAF: 0.26 in AFR vs. 0.14 in EUR), studies suggest *APOE ε4* has a weaker effect, or no effect, on AD dementia in NHB individuals.[45–49] Linkage disequilibrium structure of the *APOE* gene region varies across genetic ancestries,[50] and studies show there are genetic haplotypes predominantly present in African genetic ancestry that may explain some of the differences in *APOE* genetic effect on AD risk.[3,51] Disparities in the *APOE ε4* genetic effect on AD risk have been observed in other populations. Although studies of Chinese patients show that *APOE ε4* increases risk for AD similar to NHW,[52,53] a study of neuroimaging and cognitive testing from 811 American Indians in the Strong Heart Study found no evidence of increased risk from *APOE ε4*.[54] Racial disparities in these examples and other AD biomarker studies demonstrate that although race is not a biological construct, the biological outcomes of interest are confounded by racial disparities in study recruitment and research.[55,56] Further research with diverse cohorts will be necessary to test and adapt the *APOE*-npscore to be useful for a much broader group of people, many of whom are at an even greater risk for AD dementia than NHW individuals.

Another limitation is that we were unable to evaluate *APOE*-npscore performance directly because the training data from Reiman et al. was available as summary statistics, not individual-level data, and our current testing data do not have the same phenotype (autopsy-confirmed AD diagnosis) for validating the *APOE*-npscores. Future research to evaluate the *APOE*-npscore will require an independent dataset with individual-level autopsy data; ideally a diverse cohort that could help fine-tune the *APOE*-npscore to be useful for the broader population. Our findings in WRAP and WADRC were replicated in the independent ADNI cohort, which is promising. Since the *APOE*-npscore is easily derived from the *APOE ε2/ε3/ε4* haplotypes, we anticipate several studies will be able to benefit from the improved method for accounting for *APOE* genetic risk.

ACKNOWLEDGMENTS

The authors thank the WRAP and WADRC research participants and their families for their generosity; none of this research would be possible without them. We also thank the staff of the WRAP and WADRC for all of their hard work. We appreciate the ADNI investigators and the contribution of the late John Q. Trojanowski, as co-leader of the ADNI Biomarker Core at the University of Pennsylvania, for providing data for replication. CSF assay kits were provided by Roche Diagnostics GmbH, Penzberg, Germany. COBAS, COBAS E, and ELECSYS are trademarks of Roche. The Elecsys *β*-Amyloid(1-42) CSF and Phospho-Tau (181P) CSF immunoassays are approved for clinical use in CE-mark accepting countries. The robust prototype *β*-Amyloid(1-40) CSF immunoassay is for investigational use only and not commercially available. This research is supported by National Institutes of health (NIH) grants R01AG27161 (WRAP: Biomarkers of Preclinical AD), R01AG054047 (Genomic and Metabolomic Data Integration in a Longitudinal Cohort at Risk for AD), P50AG033514 and P30AG062715 (Wisconsin ADRC Grant), R01 AG021155 (Longitudinal Course of Imaging Biomarkers in People At Risk for AD); UL1TR000427 (Clinical and Translational Science Award (CTSA) program through the NIH National Center for Advancing Translational Sciences (NCATS), S10 OD025245-01 (Biomedical Research Support Shared Instrumentation grant from NIH), R01AG037639 (LEAD). Author Y.D. was supported by the Biology of Aging and Age-Related Diseases training grant T32 AG000213-28 from the National Institute on Aging. Author E.V. was supported by the Center for Demography of Health and Aging NIA Training Grant (Population, Life Course and Aging) (T32 AG000129). Author H.Z. is a Wallenberg Scholar supported by grants from the Swedish Research Council (#2018-02532), the European Union's Horizon Europe research and innovation programme under grant agreement No 101053962, Swedish State Support for Clinical Research (#ALFGBG-71320), the Alzheimer Drug Discovery Foundation (ADDF), USA (#201809-2016862), the AD Strategic Fund and the Alzheimer's Association (#ADSF-21-831376-C, #ADSF-21-831381-C, and #ADSF-21-831377-C), the Bluefield Project, the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen för Gamla Tjänarinnor, Hjärnfonden, Sweden (#FO2022-0270), the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 860197 (MIRIADE), the European Union Joint Programme – Neurodegenerative Disease Research (JPND2021-00694), and the UK Dementia Research Institute at UCL (UKDRI-1003). Author K.B. is supported by the Swedish Research Council (#2017-00915), the Alzheimer Drug Discovery Foundation (ADDF), USA (#RDAPB-201809-2016615), the Swedish Alzheimer Foundation (#AF-930351, #AF-939721, and #AF-968270), Hjärnfonden, Sweden (#FO2017-0243 and #ALZ2022-0006), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (#ALFGBG-715986 and #ALFGBG-965240), the European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236), the National Institute of Health (NIH), USA, (grant #1R01AG068398-01), and the Alzheimer's Association 2021 Zenith Award (ZEN-21-848495). These funding sources had no role in the design and conduct of the study or collection, management, and analysis of the data. All authors critically reviewed and edited the article. ADNI data collection and sharing for this

project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association, Alzheimer's Drug Discovery Foundation, AracIon Biotech, BioClinica Inc, Biogen, Bristol-Myers Squibb Company, CereSpir Inc, Cogstate, Eisai Inc, Elan Pharmaceuticals Inc, Eli Lilly and Company, EuroImmun, F. Hoffmann-La Roche Ltd and its affiliated company Genentech Inc, Fujirebio, GE Healthcare, IXICO Ltd, Janssen Alzheimer Immunotherapy Research & Development LLC, Johnson & Johnson Pharmaceutical Research & Development LLC, Lumosity, Lundbeck, Merck & Co Inc, Meso Scale Diagnostics LLC, NeuroRx Research, Neurotrack Technologies, Novartis Pharmaceuticals Corporation, Pfizer Inc, Piramal Imaging, Servier, Takeda Pharmaceutical Company, and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

CONFLICT OF INTEREST STATEMENT

I.S. is a full-time employee and shareholder of Roche Diagnostics International Ltd., Rotkreuz, Switzerland. G.K. and N.W. are full-time employees of Roche Diagnostics GmbH, Penzberg, Germany. S.C.J. serves as a consultant to Roche Diagnostics and Prothena and receives research support from Cerveau Technologies for unrelated work. H.Z. has served at scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, ALZPath, Annexon, Apellis, Artery Therapeutics, AZTherapies, CogRx, Denali, Eisai, Nervgen, Novo Nordisk, Passage Bio, Pinteon Therapeutics, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Cellectricon, Fujirebio, Alzecure, Biogen, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). K.B. has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Pharmatrophix, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the work presented in this paper. Other authors have no competing interests to declare. Author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

All ADNI data are available through the LONI Imaging & Data Archive. Interested scientists may apply for access on the ADNI website (http://adni.loni.usc.edu/data-samples/access-data/). Interested scientists may apply to access data from the WADRC and WRAP through the website (https://www.adrc.wisc.edu/apply-resources).

REFERENCES

1. Deming Y, Li Z, Kapoor M, et al. Genome-wide association study identifies four novel loci associated with Alzheimer's endophenotypes and disease modifiers. *Acta Neuropathol*. 2017;133(5):839-856. doi:10.1007/s00401-017-1685-y
2. Baek MS, Cho H, Lee HS, Lee JH, Ryu YH, Lyoo CH. Effect of *APOE ε4* genotype on amyloid-β and tau accumulation in Alzheimer's disease. *Alzheimers Res Ther*. 2020;12(1):1-12.
3. Deters KD, Mormino EC, Yu L, Lutz MW, Bennett DA, Barnes LL. TOMM40-APOE haplotypes are associated with cognitive decline in non-demented Blacks. *Alzheimers Dement*. 2021;17(8):1287-1296.
4. Hansson O, Seibyl J, Stomrud E, et al. CSF biomarkers of Alzheimer's disease concord with amyloid-β PET and predict clinical progression: a study of fully automated immunoassays in BioFINDER and ADNI cohorts. *Alzheimers Dement*. 2018;14(11):1470-1481.
5. Koller M, Stahel WA. Nonsingular subsampling for regression S estimators with categorical predictors. *Comput Stat*. 2017;32(2):631-646.
6. Darst BF, Koscik RL, Racine AM, et al. Pathway-specific polygenic risk scores as predictors of amyloid-β deposition and cognitive function in a sample at increased risk for Alzheimer's disease. *J Alzheimers Dis*. 2017;55(2):473-484. doi:10.3233/JAD-160195
7. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet*. 2019;51(3):414-430. doi:10.1038/s41588-019-0358-2
8. Leonenko G, Baker E, Stevenson-Hoare J, et al. Identifying individuals with high risk of Alzheimer's disease using polygenic risk scores. *Nat Commun*. 2021;12(1):4506. doi:10.1038/s41467-021-24082-z
9. Beach TG, Monsell SE, Phillips LE, Kukull W. Accuracy of the clinical diagnosis of Alzheimer disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. *J Neuropathol Exp Neurol*. 2012;71(4):266-273.
10. Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 2016;12(3):292-323.
11. Jack CR, Therneau TM, Weigand SD, et al. Prevalence of biologically vs clinically defined Alzheimer spectrum entities using the National Institute on Aging – Alzheimer's Association research framework. *JAMA Neurol*. 2019;76(10):1174-1183.
12. Reiman EM, Arboleda-Velasquez JF, Quiroz YT, et al. Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. *Nat Commun*. 2020;11(1):667. doi:10.1038/s41467-019-14279-8
13. Andreasson U, Lautner R, Schott JM, et al. CSF biomarkers for Alzheimer's pathology and the effect size of *APOE ε4*. *Mol Psychiatry*. 2014;19(2):148-149.
14. Hansson O, Lehmann S, Otto M, Zetterberg H, Lewczuk P. Advantages and disadvantages of the use of the CSF Amyloid β (Aβ) 42/40 ratio in the diagnosis of Alzheimer's Disease. *Alzheimers Res Ther*. 2019;11(1):1-15.
15. Strozyk D, Blennow K, White LR, Launer LJ. CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study. *Neurology*. 2003;60(4):652-656.
16. Amft M, Ortner M, Eichenlaub U, et al. The cerebrospinal fluid biomarker ratio Aβ42/40 identifies amyloid positron emission tomography positivity better than Aβ42 alone in a heterogeneous memory clinic cohort. *Alzheimers Res Ther*. 2022;14(1):1-9.

17. Janelidze S, Zetterberg H, Mattsson N, et al. CSF Aβ42/Aβ40 and Aβ42/Aβ38 ratios: better diagnostic markers of Alzheimer disease. *Ann Clin Transl Neurol*. 2016;3(3):154-165.
18. Buerger K, Ewers M, Pirttila T, et al. CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease. *Brain*. 2006;129(pt 11):3035-3041. doi:10.1093/brain/awl269
19. Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. *Arch Neurol*. 2007;64(3):343-349. doi:10.1001/archneur.64.3.noc60123
20. Harari O, Cruchaga C, Kauwe JS, et al. Phosphorylated tau-Abeta42 ratio as a continuous trait for biomarker discovery for early-stage Alzheimer's disease in multiplex immunoassay panels of cerebrospinal fluid. *Biol Psychiatry*. 2014;75(9):723-731. doi:10.1016/j.biopsych.2013.11.032
21. Blennow K, Shaw LM, Stomrud E, et al. Predicting clinical decline and conversion to Alzheimer's disease or dementia using novel Elecsys Aβ (1-42), pTau and tTau CSF immunoassays. *Sci Rep*. 2019;9(1):1-11.
22. Fagan AM, Head D, Shah AR, et al. Decreased cerebrospinal fluid A beta(42) correlates with brain atrophy in cognitively normal elderly. *Ann Neurol*. 2009;65(2):176-183. doi:10.1002/ana.21559
23. Mattsson-Carlgren N, Grinberg LT, Boxer A, et al. Cerebrospinal fluid biomarkers in autopsy-confirmed Alzheimer disease and frontotemporal lobar degeneration. *Neurology*. 2022;98(11):e1137-e1150.
24. Schoonenboom NSM, Pijnenburg YAL, Mulder C, et al. Amyloid β (1-42) and phosphorylated tau in CSF as markers for early-onset Alzheimer disease. *Neurology*. 2004;62(9):1580-1584.
25. Turk KW, Geada A, Alvarez VE, et al. A comparison between tau and amyloid-β cerebrospinal fluid biomarkers in chronic traumatic encephalopathy and Alzheimer disease. *Alzheimers Res Ther*. 2022;14(1):1-12.
26. Johnson SC, Koscik RL, Jonaitis EM, et al. The Wisconsin Registry for Alzheimer's Prevention: a review of findings and current directions. *Alzheimers Dement (Amst)*. 2018;10, 130-142. doi:10.1016/j.dadm.2017.11.007
27. Albert MS, DeKosky ST, Dickson D, Dubois B, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):270-279. doi:10.1016/j.jalz.2011.03.008
28. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005
29. Veitch DP, Weiner MW, Aisen PS, et al. Understanding disease progression and improving Alzheimer's disease clinical trials: recent highlights from the Alzheimer's Disease Neuroimaging Initiative. *Alzheimers Dement*. 2019;15(1):106-152.
30. Saykin AJ, Shen L, Yao X, et al. Genetic studies of quantitative MCI and AD phenotypes in ADNI: progress, opportunities, and plans. *Alzheimers Dement*. 2015;11(7):792-814.
31. Van Hulle C, Jonaitis EM, Betthauser TJ, et al. An examination of a novel multipanel of CSF biomarkers in the Alzheimer's disease clinical and pathological continuum. *Alzheimers Dement*. 2021;17(3):431-445. doi:10.1002/alz.12204
32. Bittner T, Zetterberg H, Teunissen CE, et al. Technical performance of a novel, fully automated electrochemiluminescence immunoassay for the quantitation of β-amyloid (1-42) in human cerebrospinal fluid. *Alzheimers Dementia*. 2016;12(5):517-526.
33. R Core Team. R: A language and environment for statistical computing. 2020.
34. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest package: tests in linear mixed effects models. *J Stat Softw*. 2017;82:1-26.
35. Hartig F. DHARMa: Residual diagnostics for hierarchical (multi-level/mixed) regression models. R package version 0.3. 2020;3.
36. Kamil B. 2022 MuMIn: Multi-Model Inference.
37. Zhu H. kableExtra: Construct Complex Table with 'kable' and Pipe Syntax. R package version 1.3.4. 2021.
38. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *J Open Source Softw*. 2019;4(43):1686. doi:10.21105/joss.01686
39. Lüdecke D. sjPlot: Data Visualization for Statistics in Social Science. R package version 2.8.10. 2021.
40. Lautner R, Insel PS, Skillbäck T, et al. Preclinical effects of *APOE ε4* on cerebrospinal fluid Aβ42 concentrations. *Alzheimers Res Ther*. 2017;9(1):1-7.
41. Benson GS, Bauer C, Hausner L, et al. Don't forget about tau: the effects of ApoE4 genotype on Alzheimer's disease cerebrospinal fluid biomarkers in subjects with mild cognitive impairment – data from the Dementia Competence Network. *J Neural Transm*. 2022;129(5-6):477-486.
42. Morris JC, Price JL. Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *J Mol Neurosci*. 2001;17(2):101-118.
43. Garrett SL, McDaniel D, Obideen M, et al. Racial disparity in cerebrospinal fluid amyloid and tau biomarkers and associated cutoffs for mild cognitive impairment. *JAMA Netw Open*. 2019;2(12):e1917363-e1917363. doi:10.1001/jamanetworkopen.2019.17363
44. Deters KD, Napolioni V, Sperling RA, et al. Amyloid PET imaging in self-identified non-Hispanic Black participants of the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study. *Neurology*. 2021;96(11):e1491-e1500. doi:10.1212/WNL.0000000000011599
45. Barnes LL, Arvanitakis Z, Yu L, Kelly J, De Jager PL, Bennett DA. Apolipoprotein E and change in episodic memory in blacks and whites. *Neuroepidemiology*. 2013;40(3):211-219. doi:10.1159/000342778
46. Rajan KB, Barnes LL, Wilson RS, Weuve J, McAninch EA, Evans DA. Apolipoprotein E genotypes, age, race, and cognitive decline in a population sample. *J Am Geriatr Soc*. 2019;67(4):734-740.
47. Rajan KB, McAninch EA, Wilson RS, Weuve J, Barnes LL, Evans DA. Race, APOE ε4, and long-term cognitive trajectories in a biracial population sample. *J Alzheimers Dis*. 2019;72(1):45-53.
48. Sawyer K, Sachs-Ericsson N, Preacher KJ, Blazer DG. Racial differences in the influence of the APOE epsilon 4 allele on cognitive decline in a sample of community-dwelling older adults. *Gerontology*. 2009;55(1):32-40.
49. Weuve J, Barnes LL, de Leon CFM, et al. Cognitive aging in black and white Americans: cognition, cognitive decline, and incidence of Alzheimer disease dementia. *Epidemiology*. 2018;29(1):151.
50. Kulminski AM, Shu L, Loika Y, et al. APOE region molecular signatures of Alzheimer's disease across races/ethnicities. *Neurobiol Aging*. 2020;87(141):e1-141.e8.
51. Babenko VN, Afonnikov DA, Ignatieva EV, Klimov AV, Gusev FE, Rogaev EI. Haplotype analysis of APOE intragenic SNPs. *BMC Neurosci*. 2018;19(suppl 1):16. doi:10.1186/s12868-018-0413-4
52. Ji Y, Liu M, Huo YR, et al. Apolipoprotein E ε4 frequency is increased among Chinese patients with frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2013;36(3-4):163-170.
53. Liu M, Bian C, Zhang J, Wen F. Apolipoprotein E gene polymorphism and Alzheimer's disease in Chinese population: a meta-analysis. *Sci Rep*. 2014;4(1):1-7.
54. Suchy-Dicey A, Howard B, Longstreth WT Jr, Reiman EM, Buchwald D. APOE genotype, hippocampus, and cognitive markers of Alzheimer's disease in American Indians: data from the Strong Heart Study. *Alzheimers Dement*. 2022;18(12):2518-2526.
55. Gleason CE, Zuelsdorff M, Gooding DC, et al. Alzheimer's disease biomarkers in Black and non-Hispanic White cohorts: a contextualized

review of the evidence. *Alzheimer's & Dementia*. 2022;18(8):1545-1564.

56. Morris JC, Schindler SE, McCue LM, et al. Assessment of racial disparities in biomarkers for Alzheimer disease. *JAMA*. 2019;76(3):264-273.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Deming Y, Vasiljevic E, Morrow A, et al. Neuropathology-based *APOE* genetic risk score better quantifies Alzheimer's risk. *Alzheimer's Dement*. 2023;1-11. https://doi.org/10.1002/alz.12990