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Evaluation of TDP-43 proteinopathy and hippocampal sclerosis in relation to *APOE* ε4 allele status: a community-based cohort study

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Contributors

HSY conceptualized and designed the study, analyzed and interpreted the data, and drafted and critically revised the manuscript for the intellectual content. LY conceptualized and designed the study, analyzed and interpreted the data, and critically revised the manuscript for the intellectual content. CCW, LBC, JPC, and RAS interpreted the data and critically revised the manuscript for the intellectual content. DAB, JAS, and PLDJ conceptualized and designed the study, collected and interpreted the data, and critically revised the manuscript for the intellectual content.

Declaration of Interests

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Abstract

BACKGROUND: Transactive response DNA-binding protein of 43 kDa (TDP-43) proteinopathy in older adults frequently coexists with Alzheimer's disease pathology and hippocampal sclerosis. It is unclear whether there is a link between APOE ε4 and TDP-43 proteinopathy, and the role of APOE ε4 in the association of TDP-43 proteinopathy with hippocampal sclerosis remains to be examined. We investigated the relationships of TDP-43 proteinopathy and hippocampal sclerosis with APOE ε4.

METHODS: We used data from two community-based cohort studies of ageing and dementia: the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP). A battery of cognitive tests examining multiple cognitive domains is given to ROS-MAP participants each year, and a measure of annual global cognitive function for each participant is derived by averaging Z scores of these tests. The final clinical diagnosis is assigned after death by a neurologist using all available clinical data without access to post-mortem pathology. Amyloid-β, paired helical filament tau, Lewy bodies, TDP-43, and hippocampal sclerosis were microscopically evaluated in the midbrain, medial temporal, and neocortical regions that capture the progression of each neuropathology. TDP-43 proteinopathy topographic stage was recorded as an ordinal variable, and TDP-43 burden was defined by averaging a semi-quantitative six-point scale across six brain regions. The relationships among APOE ε4, TDP-43 proteinopathy, and hippocampal sclerosis were tested with regression models controlled for sex and age at death, and they were further explored with a mediation analysis using the quasi-Bayesian Monte Carlo method.

FINDINGS: ROS began data collection in 1994, and MAP began data collection in 1997. The data included in this study were analysed from Jan 16, 2017, to July 12, 2017. When analysis began in January, 2017, a total of 1059 ROS-MAP participants who were deceased had APOE genotype and complete pathological measures for amyloid-β, paired helical filament tau, and TDP-43 proteinopathy stage. After excluding 15 participants with other pathological diagnoses, 1044 participants, 1042 of whom also had measures of Lewy body pathology, were included in this study (470 from ROS and 574 from MAP). APOE ε4 count was associated with higher TDP-43 proteinopathy stage (odds ratio [OR] 2·0, 95% CI 1·6·2·6; $p=1{\cdot}9 \times 10^{-9}$) and TDP-43 burden (0·40, 0·28–0·52; $p=1{\cdot}2 \times 10^{-10}$). Amyloid-β, paired helical filament tau, or Lewy body pathology did not fully explain this association. APOE ε4 increased the odds of hippocampal sclerosis (OR 2·1, 95% CI 1·4–3·0; $p=1{\cdot}7 \times 10^{-4}$); this effect was largely mediated by TDP-43 burden (mediated effect $p<1{\cdot}0 \times 10^{-4}$) but not directly by APOE ε4 (direct effect p=0·40). APOE ε4 was associated with worse global cognition proximate to death even after adjusting for amyloid-β and paired helical filament tau (estimated effect –0·18, 95% CI –0·31 to –0·04; p=0·010), but this association was attenuated by additionally adjusting for TDP-43 burden (–0·09, –0·22 to 0·04; p=0·18).

INTERPRETATION: APOE ε4 seems to increase TDP-43 burden, and this effect in turn was associated with higher odds of hippocampal sclerosis, a pathology potentially downstream of TDP-43 proteinopathy. TDP-43 proteinopathy contributes to the detrimental effect of APOE ε4 on

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late-life cognition through mechanisms independent of Alzheimer's disease pathology, and future research should consider that TDP-43 proteinopathy might be an integral component of APOE-related neurodegeneration.

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Introduction

Transactive response DNA-binding protein 43kDa proteinopathy (TDP-43) is a core pathology of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with TDP-43 (FTLD-TDP),[1] but it is also commonly observed in older adults without ALS or FTLD-TDP. TDP-43 in older adults has clinical and pathological characteristics distinct from FTLD-TDP.[2–5] TDP-43 commonly coexists with hippocampal sclerosis (HS)[3,6–8] and Alzheimer's disease (AD) pathology in older adults.[2,4,6,9] An association between HS and AD pathology has also been also reported, and this association was no longer significant when TDP-43 was concurrently considered.[3] As TDP-43 has a large impact on hippocampal atrophy, cognitive decline, and the risk of AD dementia beyond what can be explained by AD pathology alone,[4,9–12] it is critical to understand the relationship of TDP-43 with other neurodegenerative pathologies in older adults.

Genetic association studies can provide a unique opportunity in examining the relationship between post-mortem neuropathologies: genetic risk factors are not subject to reverse causation, as the random assignment of parental genotypes to an individual during conception cannot be affected by post-natal phenotypes, a property referred to as "Mendelian randomization."[13] Notably, two previous studies examining participants with autopsy-confirmed AD pathology have reported that *APOE* ε4 was enriched in participants with comorbid TDP-43.[10,12] However, it is unclear whether the link between *APOE* ε4 and TDP-43 is independent from other *APOE* ε4-related pathologies, and the role of the *APOE* ε4 in the association of TDP-43 with HS remains to be examined.

Therefore, we have analyzed more than 1,000 participants from two large community-based clinical pathologic cohorts of aging and dementia to investigate the relationship among *APOE* ε4, TDP-43, and other *APOE* ε4-related proteinopathies, such as β-amyloid (Aβ), paired helical filament tau (PHFtau) or Lewy body pathology (LB).[14] Then, leveraging Mendelian randomization of *APOE* ε4, we investigated the causal relationship between TDP-43 and HS. Finally, we examined the clinical implication of the *APOE* ε4 – TDP-43 association.

Methods

Participants

Religious Orders Study and the Rush Memory and Aging Project MAP (ROS-MAP) are community-based longitudinal cohort studies of aging and dementia that enroll older adults without known dementia and collect annual clinical and post-mortem pathologic data.[15,16] Each participant has signed a written informed consent and a written Anatomical Gift Act document at the time of enrollment, and the data collection and usage protocols of ROS and MAP have been approved by the Rush University Medical Center Institutional Review

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Board. ROS launched in 1994 and enrolls Catholic priests, brothers, and nuns from more than 40 religious communities across the United States. MAP started in 1997 and targets participants from diverse backgrounds, including continuous care retirement communities throughout northeastern Illinois and individual homes across the Chicago metropolitan area. Further details about the participants are available through previous publications[15,16] and Rush Alzheimer Disease Center Research Resource Sharing Hub (https://www.radc.rush.edu/). At the time of analysis in January 2017, a total of 3,225 ROS-MAP participants have completed baseline evaluation (1,349 from ROS, 1,876 from MAP). Among these participants, 1,396 out of 1,624 deceased participants had an autopsy (autopsy rate 86·0%; 691/760 (90·9%) from ROS, 705/864 (81·6%) from MAP).

Cognitive phenotypes and final clinical diagnosis

A battery of cognitive tests including mini-mental state exam (MMSE) and 19 other tests examining multiple cognitive domains (supplementary methods) was given to ROS-MAP participants each year,[15–17] and annual global cognitive function for each participant was derived by averaging z-score of these tests (excluding the MMSE).[15–17] Then, random slope of global cognition was derived from linear mixed models with annual global cognitive function as the longitudinal outcome, adjusting for age at baseline, sex, and years of education.[18] The final clinical diagnosis was assigned after death by a neurologist using all available clinical data without access to postmortem pathology,[15,16] and cases with probable AD dementia (AD + no other cause of cognitive impairment) or possible AD dementia (AD + other cause contributing to cognitive impairment) were considered to have AD dementia.

Genotypes and pathological phenotypes

Codon 112 and 158 from *APOE* exon 4 were sequenced to derive *APOE* haplotypes (ε2/ε3/ε4).[19] We derived genotype dosage of *TMEM106B* rs1990622^{A}, a known TDP-43 risk allele,[5,20] as previously reported (supplementary methods).[21,22] Neuropathologic evaluation was done as previously reported.[15,16] Pathologic diagnosis of Alzheimer's disease (pathoAD) was assigned for cases with high or intermediate likelihood per the modified National Institute of Aging–Reagan Institute criteria. Aβ was quantified as the mean percent area of cortex occupied by Aβ, assessed with immunohistochemistry in 8 regions (hippocampus, entorhinal cortex, midfrontal cortex, inferior temporal cortex, angular gyrus, calcarine cortex, anterior cingulate cortex, and superior frontal cortex), generating a continuous variable.[15,16] PHFtau was detected with anti-phosphotau (AT8) antibody in the same 8 regions and quantified with mean cortical density (per mm^2), generating a continuous variable.[15,16] LB, another pathology that have been linked with *APOE* ε4,[14] was assessed with α-synuclein immunostain and each subject was assigned a previously described topographic stage, generating an ordinal variable (stage 0: not present; stage 1: nigral-predominant; stage2: limbic; and stage 3: neocortical).[19,23] TDP-43 was assessed with monoclonal antibodies to phosphorylated TDP-43 (pS409/410; 1:100), and its topographic stage was recorded as an ordinal variable (stage 0: none; stage 1: amygdala only; stage 2: amygdala and limbic (entorhinal or hippocampus); stage 3: amygdala, limbic, and neocortical).[3,5] TDP-43 cytoplasmic inclusion burden was defined by averaging a semi-quantitative 6-point scale (0 to 5; treated as a continuous variable in our analyses) across 6 brain regions that captures topographic progression of TDP-43 (amygdala, hippocampus

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CA1/subiculum, dentate gyrus, entorhinal cortex, midfrontal cortex, and middle temporal cortex).[4] TDP-43 dystrophic neurite (thread) burden was quantified separately, using the same scale and regions as the TDP-43 cytoplasmic inclusions. HS was evaluated in a coronal section of mid-hippocampus at the level of lateral geniculate body, and was recorded as present if there is a severe neuronal loss and gliosis in the CA1 sector and/or subiculum, generating a binary variable.[3] HS was diagnosed independent of coexisting AD or TDP-43, but the diagnosis was not considered in the cases with hippocampal changes related to FTLD or gross/microscopic infarcts. Presence of one or more gross chronic cerebral infarcts was recorded as a binary variable (present/absent).[15,16] A total of 1,059 deceased participants had *APOE* genotype and complete pathologic measures for Aβ, PHFtau, and TDP-43 stage. After excluding 15 participants with pathologic diagnoses of FTLD, ALS, progressive supranuclear palsy, or corticobasal degeneration, 1,044 participants were included in our study (470 from ROS, 574 from MAP).

Statistical analyses

All statistical analyses were done with R version 3.3. ROS and MAP were combined in our analyses, as both cohorts capture common clinical and pathologic measures, and are managed by the same team of investigators who designed both cohort studies to enable combined analyses.[15,16] All regression analyses were controlled for age at death and sex. We excluded participants with missing values, and indicated the number of participants included in each analysis.

After observing a very tight correlation between two semi-quantitative measures of TDP-43 burden (cytoplasmic inclusion, dystrophic neurite; Spearman's rho=0.96, $p<2.2\times10^{-16}$), we chose to use the TDP-43 cytoplasmic inclusion burden for the TDP-43 burden analyses. We estimated general population prevalence of *APOE* ε4 allele in individuals of European descent from the allele frequency of rs429358^{T} in 1000 Genome Project EUR population.[24] The association of *APOE* ε4 count (continuous ordinal variable: 0, 1, or 2; independent variable) with TDP-43 stage (outcome variable) was examined with multivariable ordinal logistic regression (R "MASS" package), and the association of *APOE* ε4 count (independent variable) with TDP-43 burden (outcome variable) was assessed with multivariable linear regression. Effect of each *APOE* genotype (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε4, ε4/ε4) on TDP-43 burden was compared to the reference *APOE* ε3/ε3 homozygotes, as detailed in the legend of supplementary table 5. Additional analyses controlling for Aβ, PHFtau, and LB were performed, and we also assessed whether age at death or other proteinopathies modified the *APOE* ε4 – TDP-43 association by including interaction terms. We used square-root transformed values of the quantitative Aβ and PHFtau variables to account for their positively skewed distributions. *APOE* ε4 count and rs1990622^{A} dosage was analyzed for their statistical interaction in increasing TDP-43. The association between *APOE* ε4 and HS was assessed with logistic regression without and with adjustment of TDP-43, to examine whether TDP-43 explains this association. Next, we performed a mediation analysis with *APOE* ε4 carrier status as an independent (causal) variable, TDP-43 burden as a mediator and HS as a binary outcome, and the mediated effect and direct effect were estimated with the default quasi-Bayesian Monte Carlo method and bootstrap simulation from the R "mediation" package.[25] Finally, the residual association of *APOE* ε4

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count with global cognitive function proximate to death (continuous variable; linear regression) or AD dementia (binary variable; logistic regression) was evaluated after controlling for Aβ, PHFtau, age at death, sex, and years of education, and the we added TDP-43 to these models as a covariate in order to assess whether TDP-43 explains this residual effect of *APOE* ε4 on cognition and dementia. To assess clinical characteristics of each subgroup defined by TDP-43 stage, HS, and *APOE* ε4 carrier status, we defined advanced TDP-43 as TDP-43 stage 2 and 3, the stages that are associated with increased odds of dementia.[9] Residual global cognitive decline (or residual global cognitive function) was defined as the residual from a linear model having the random slope of global cognition (or global cognitive function proximate to death adjusted for demographics) as the outcome and Aβ and PHFtau as predictors. Further details on the covariate selection procedure, power calculation for subgroup analyses, and mediation analyses are described in the supplementary methods.

Data sharing

Researchers may apply for data access at Rush Alzheimer's Disease Center Research Resource Sharing Hub (http://www.radc.rush.edu) to access all ROS-MAP data.

Role of the funding source

The sponsors of this study (National Institutes of Health and Alzheimer's Association) had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the paper for publication. The first and corresponding authors had full access to all the data in the study, and the corresponding author has final responsibility for the decision to submit this manuscript for publication.

Results

ROS and MAP began data collection in 1994 and 1997, respectively, and the data included in this study was analyzed from January 16, 2017 through July 12, 2017. The characteristics of the 1,044 ROS-MAP participants included in our study were similar to all deceased ROS-MAP participants (table 1). A majority of the participants self-reported their race to be white (n=1,010; 97%), and 26% of the participants (n=270) were *APOE* ε4 carriers (heterozygote n=251, homozygote n=19), similar to the estimated general population prevalence in individuals of European descent (26%). The ROS and MAP participants are compared in supplementary table 1.

APOE ε4 count showed a dose-response relationship with TDP-43 stage and burden (figure 1). Higher *APOE* ε4 count was associated with higher TDP-43 stage and burden in regression models (table 2 model 1), and this association was statistically significant in both ROS and MAP (supplementary table 3). Age at death did not moderate the *APOE* ε4 – TDP-43 association (supplementary table 4), and the presence of *APOE* ε2 did not significantly affect TDP-43 burden (supplementary table 5). The effect of *APOE* ε4 was much stronger than that of *TMEM106B* rs1990622^{A} (supplementary table 6). There was no statistically significant interaction between *APOE* ε4 and rs1990622^{A} in predicting TDP-43 (supplementary table 6).

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The *APOE* ε4 – TDP-43 association was only partially attenuated after controlling for Aβ, PHFtau, and LB (table 2 models 2 and 3). Conversely, the associations of *APOE* ε4 with other proteinopathies were not fully explained by TDP-43 (supplementary table 7). To more explicitly confirm the independent associations of *APOE* ε4 with TDP-43 and other proteinopathies, we also did a logistic regression with *APOE* ε4 carrier status as the outcome, TDP-43 as an independent variable, and Aβ, PHFtau, and LB as covariates. This analysis confirmed the independent association between TDP-43 and *APOE* ε4 (supplementary table 8). Furthermore, pathoAD diagnosis or AD/LB pathology burden did not show statistically significant interaction with the *APOE* ε4 count (table 2, models 4 and 5), suggesting no strong evidence that the effect of *APOE* ε4 count on TDP-43 varies with AD or LB pathologic burden. We failed to observe a statistically significant *APOE* ε4 – TDP-43 association when we limited our analysis to the subgroup without pathoAD (pathoAD(−); n=372 with 45 *APOE* ε4 carriers; supplementary figure1). However, our pathoAD(−) subgroup is underpowered due to lower *APOE* ε4 allele frequency in this subgroup: we would need approximately 1,100 participants without pathoAD (supplementary methods) to show the same *APOE* ε4 – TDP-43 association that was observed in the pathoAD(+) subgroup. Clinical and pathological characteristics of pathoAD(−) and pathoAD(+) subgroups were shown in supplementary table 9.

Then, we examined the relationship between *APOE* ε4 and HS. In logistic regression models, *APOE* ε4 count was associated with HS (OR 2·1 per each additional *APOE* ε4 allele, 95% CI 1·4 to 3·0, $p=1{\cdot}7\times10^{-4}$), even when Aβ, PHFtau, and LB were adjusted for (supplementary table 10), but this association was no longer significant when TDP-43 was considered (p>0·05; supplementary table 10). As there are strong associations between *APOE* ε4 and TDP-43, and TDP-43 and HS, TDP-43 could be a mediator of the association between *APOE* ε4 and HS (supplementary methods). By contrast, HS is unlikely to be a strong mediator of the *APOE* ε4 – TDP-43 association, because the association between *APOE* ε4 count and TDP-43 was still strong after controlling for HS (supplementary table 11). Therefore, we performed a causal mediation analysis with the quasi-Bayesian Monte Carlo method, with HS (binary) as the outcome, *APOE* ε4 carrier status (binary) as the independent (causal) variable, and TDP-43 burden (continuous) as a mediator. The effect of *APOE* ε4 carrier status on HS was largely mediated by TDP-43 burden, while the direct effect of *APOE* ε4 on HS (independent from TDP-43) was not statistically significant (figure 2). A non-parametric bootstrap method yielded a similar result (supplementary figure 2), and a sensitivity analysis further supported validity of our result (supplementary methods, supplementary figure 3).

We then investigated whether TDP-43 contributes to poor clinical outcomes associated with *APOE* ε4 that is not fully explained by AD pathology. *APOE* ε4 count was associated with worse global cognitive function proximate to death and higher odds of AD dementia (table 3 model 1), and nominal residual associations were observed even after adjusting for AD pathology (Aβ, PHFtau) (table 3 model 2). TDP-43 attenuated this residual association (table 3 model 4 and 5). In table 4, we showed adjusted global cognitive decline and adjusted global cognition proximate to death for each subgroups defined by the presence of advanced TDP-43 (TDP-43 stage 2 or 3), HS, and *APOE* ε4 carrier status. We note that the subgroup with both advanced TDP-43 and HS had the highest *APOE* ε4 carrier rate, highest

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TDP-43 burden, and the worst cognitive trajectory (adjusted for Aβ and PHFtau and demographics; see supplementary table 12 for cognitive measures in each subgroup only adjusted for demographics).

Discussion

In this study of more than 1,000 well-characterized older adults from community-based cohorts, we found that *APOE* ε4 is a strong genetic predictor of the presence and severity of TDP-43 in older adults. This association was not fully explained or significantly moderated by other *APOE* ε4 – related proteinopathies (Aβ, PHFtau, and LB). Further, TDP-43 contributed to the worse cognition and increased odds of dementia associated with *APOE* ε4, above and beyond what could be explained by Aβ and PHFtau. Therefore, in addition to Aβ, PHFtau, and LB,[14] out results indicate that TDP-43 is another major neurodegenerative proteinopathy linked to *APOE* ε4, and has an independent contribution to the pleiotropic role of *APOE* ε4 in late-life dementia.[19,26]

The association between *APOE* ε4 and TDP-43 adds important insights into the relationship between TDP-43 and AD: they not only coexist, but also share a common genetic risk factor. On the other hand, the association between TDP-43 and AD was not fully explained by *APOE* ε4 alone (table 2 model 3). Thus, multiple linking points other than *APOE* might underlie the intricate relationship among the neurodegenerative proteinopathies in older adults. We note that TDP-43 in older adults is unlikely to be a simple downstream or upstream pathology of AD, as *APOE* ε4 had an independent association with TDP-43 or AD even when the other entity was controlled for.

Notably, the effect of *APOE* ε4 on TDP-43 was independent of and stronger than that of *TMEM106B* rs1990622[A], a previously reported genetic risk factor of TDP-43 in older adults and FTLD-TDP.[5,20] Thus, although TDP-43 in older adults shares the *TMEM106B*-related pathogenic pathway with FTLD-TDP, our result shows that the pathway downstream of *APOE* likely plays an independent and more important role in TDP-43 in older adults, supporting that TDP-43 in older adults is a process distinct from FTLD-TDP. Larger-scale studies would be required to confirm these genetic associations, but the association between *APOE* ε4 and TDP-43 was statistically robust, and exceeded the significance threshold of an unbiased genome-wide association study ($p < 5{\cdot}0\times10^{-8}$).

Our results also provide an important insight into the relationship between TDP-43 and HS. It has been suspected that TDP-43 might be pathogenically upstream of, or at least precede, most cases of HS in older adults,[8] but the causal relationship between two cross-sectional neuropathologic measures has remained elusive. We leveraged Mendelian randomization[13] to show that TDP-43 is likely to be pathogenically upstream of HS in the pathway connecting *APOE* and HS. Therefore, we suggest that TDP-43 in older adults is on a pathogenic continuum with HS: most cases of HS might represent downstream consequences of TDP-43 – mediated neurodegeneration.

Of note, the association between *APOE* ε4 and HS was not present in multiple previous studies.[7,14,27] Although ROS and MAP have a healthy volunteer effect and have socio-

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demographic differences from the general population, they are community-based cohort studies that enjoy very high rates of follow-up participation and autopsy, minimizing biases that affect many large longitudinal studies. This might have resulted in a more genetically representative sampling in our study, as shown by the *APOE* ε4 carrier rate that is very close to the estimated general population prevalence, a condition that may have been critical to capture the relatively weak association between *APOE* ε4 and HS.

The mechanism of the *APOE* ε4 – TDP-43 association is currently unclear. Besides its well-characterized impact on Aβ aggregation and clearance, *APOE* might also impact transport and clearance of other misfolded proteins. There is a suggestion that APOE and TDP-43 form complexes *in vivo*, thereby aggravating TDP-43 proteinopathy and related neurodegeneration.[28] On the other hand, we cannot rule out the possibility that toxic Aβ or tau oligomers could explain the link between *APOE* and TDP-43, as neuropathologic evaluation through microscopic examination cannot quantify the oligomers present in the tissue.

Our study has several limitations. First, our study is mainly based on highly educated healthy volunteers, and their average age at death was close to 90. Although the age does not significantly moderate the *APOE* ε4 – TDP-43 association, our findings might not apply to younger individuals or people from other socio-economic background. Second, the majority of participants from both cohorts were of European descent, so our findings cannot be easily extrapolated to other racial groups. Third, we combined ROS and MAP in our analyses, but these two cohorts are comprised of participants from different social background. The study cohort did not significantly confound the association between *APOE* ε4 and TDP-43 in our study (supplementary table 2), but given the larger effect size of *APOE* ε4 on TDP-43 in MAP compared to ROS (supplementary table 3), further studies in independent cohorts are required for a better estimation of the effect size. Finally, we have evaluated only a subset of regions known to harbor TDP-43.[2] Also, HS was only evaluated on a single coronal section of mid-hippocampus from each participant, whereas previous work showed that HS can be segmental in appearance;[29] therefore, we likely misclassified some HS cases. Thus, by underestimating TDP-43 and HS, we could have underestimated the strength of the association of *APOE* ε4 with TDP-43 and HS.

Despite these limitations, our study leveraged the largest TDP-43 dataset reported to date, to add important insights to the relationship among AD, TDP-43, and HS through a shared genetic risk factor, *APOE* ε4. Beyond classic one-to-one clinical-pathologic correlations, it has been well known that coexisting multiple neuropathologies is the rule rather than an exception in late-onset dementia.[9] Our results suggest that the coexistence of multiple neurodegenerative proteinopathies is not a coincidence: AD and TDP-43 share *APOE* as a common risk gene, which implies further mechanistic link between them. Therefore, future clinical trials and clinical-translational investigations should consider TDP-43 as an integral component of *APOE*-related neurodegeneration, and assess TDP-43 whenever possible.

Supplementary Material

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Research in context

Evidence before this study:

We searched PubMed with search term "(TDP-43 OR hippocampal sclerosis) AND (genetic association OR APOE)" for articles published before May 1, 2018, yielding 189 articles. We reviewed these studies to summarize previously identified genetic risk loci of transactive response DNA-binding protein 43kDa proteinopathy (TDP-43) and/or hippocampal sclerosis (HS), and to outline the relationship between *APOE* and TDP-43. A previous study reported that rs1990622 near *TMEM106B*, which is a risk variant for frontotemporal lobar degeneration with TDP-43 (FTLD-TDP), is also associated with TDP-43 in older adults without FTLD or ALS. Two studies from a group of investigators reported higher *APOE* ε4 carrier rate in participants with Alzheimer's disease (AD) pathology and comorbid TDP-43 proteinopathy. For HS in older adults (that is not from epilepsy or FTLD), genetic association studies have identified several risk variants: rs704178 within *ABCC9*, rs5848 near *GRN*, rs1990622 near *TMEM106B*, and rs9637454 within *KCNMB2*. By contrast, multiple studies have reported that *APOE* haplotypes are not associated with HS in older adults.

Added value of this study:

This is the first study reporting the independent association of *APOE* ε4 with the presence and severity of TDP-43, accounting for other *APOE* ε4-related proteinopathies (AD and Lewy body pathology (LB)), in large community-based cohorts of older adults. We also report that the independent *APOE* ε4 – TDP-43 association is not moderated by other *APOE* ε4-related proteinopathies. Our results show that the association of *APOE* ε4 with HS is largely mediated through TDP-43, reinforcing prior literature that suggests TDP-43 proteinopathy is a central component in the pathologic cascade leading to HS. Finally, we observed that TDP-43 could contribute to *APOE* ε4's detrimental effect on late-life cognition, above and beyond AD pathology.

Implications of all the available evidence:

Multiple neurodegenerative pathologies commonly coexist in the aging brain and synergistically contribute to cognitive decline and dementia. We now know that *APOE* ε4 is associated with an increased risk of multiple major neurodegenerative proteinopathies associated with cognitive decline in older adults (β-amyloid, paired helical filament tau, α-synuclein, and TDP-43). Also, accumulating evidence suggest that HS is a pathologic entity downstream of TDP-43. Thus, beyond their common coexistence, major neurodegenerative proteinopathies in older adults might share common pathogenic pathways, a potentially critical point to consider in future clinical trials and clinical-translational research.

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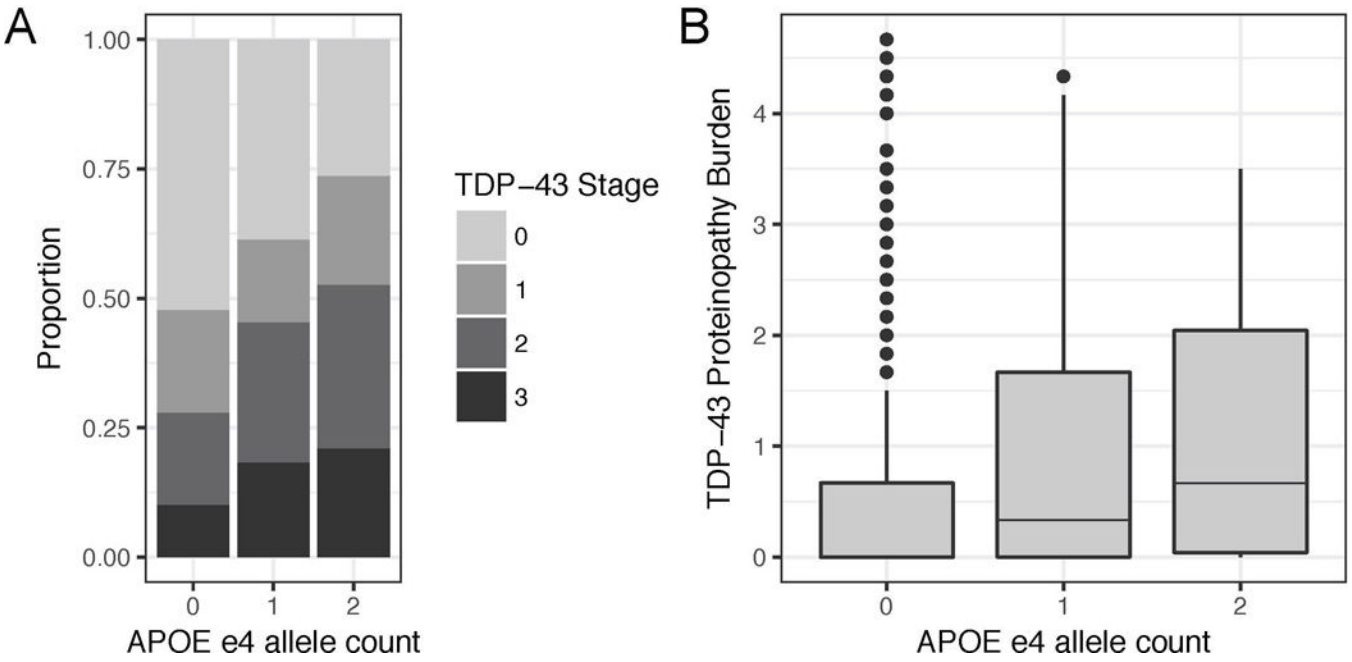

Figure 1. *APOE* ε4 count and TDP-43

(A) *APOE* ε4 count and TDP-43 stage (0=none, 1=limited to amygdala, 2=extension to entorhinal cortex and/or hippocampus CA1, 3=extension to neocortex)

(B) *APOE* ε4 count and semi-quantitative TDP-43 burden (0–5). The upper and lower hinges of the box mark the 75th and 25th percentiles, respectively. The whiskers extend from the hinge to the largest and smallest values, but no further than 1.5 × interquartile range from the hinge. Data points beyond the end of whiskers (outliers) are plotted individually.

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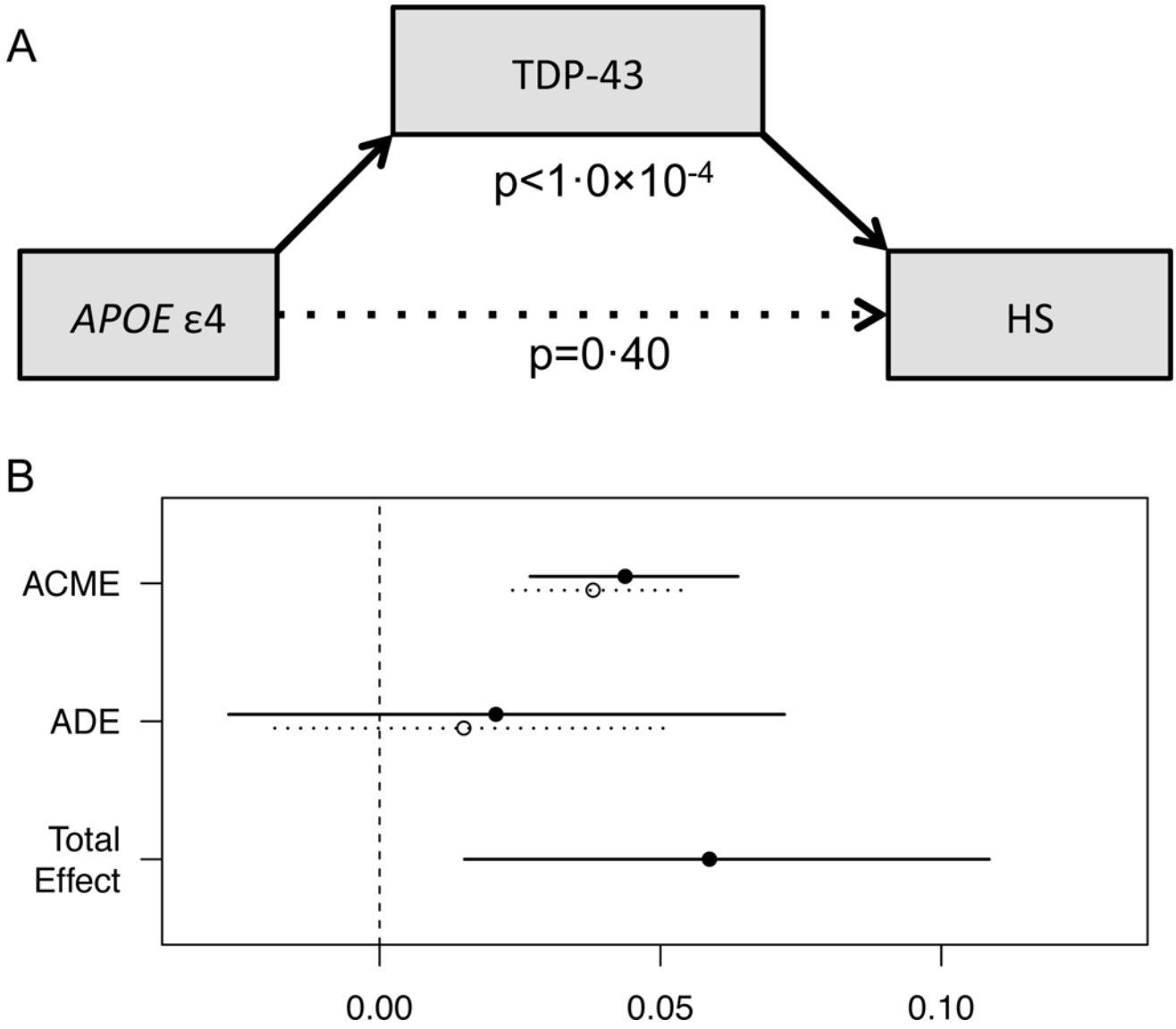

Figure 2. Mediation models of the relationship among *APOE* ε4 carrier status, TDP-43 burden, and HS (using quasi-Bayesian Monte Carlo method)

(A) A Causal mediation analysis using quasi-Baysian Monte Carolo (with 10,000 simulations), having *APOE* ε4 as an independent (causal) variable, HS as the binary outcome, and TDP-43 burden as a continuous mediator shows a statistically significant estimated ACME. By contrast, estimated ADE was not statistically significant, suggesting that most effect of the independent variable on the outcome is mediated through the mediator. P-values for ACME and ADE are noted. Solid arrows indicate significant ACME, and a broken arrow indicates non-significant ADE. n=1,025 participants with non-missing values were used for this analysis.

(B) In this plot, x-axis denotes the size of effect measured by increased probability of the outcome (HS), expressed in a relative scale. A higher value corresponds to a higher likelihood of HS. In the rows for ACME and ADE, a filled circle and solid line indicate the effect and 95% CI in treatment group (*APOE* ε4 carriers), and an empty circle and dotted

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line indicate the effect and 95% CI in control group (*APOE* ε4 non-carriers). Of note, estimated ACME and ADE were reported separately from treatment group and control group in this simulation, as the outcome model was nonlinear. The plot shows that there is no significant difference between *APOE* ε4 carriers and non-carriers in their estimated ACME or ADE. Here, ACME (average) is 0·041 (95% CI 0·026 to 0·058), ADE (average) is 0·018 (95% CI −0·023 to 0·062), and total effect is 0·059 (95% CI 0·015 to 0·109). About 70% of the total effect is through ACME. All models were adjusted for age at death and sex. ACME=average causal mediation effect (the effect of the independent variable to the outcome that is mediated through the mediator), ADE=average direct effect (the effect of the independent variable to the outcome that is independent from the mediator), CI=confidence interval, HS=hippocampal sclerosis, TDP-43=TAR-DNA binding protein-43kDa proteinopathy.

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Table 1.

Demographic characteristics of the study participants

	***APOE* ε4 Non-carrier (n=774)**	***APOE* ε4 Heterozygote (n=251)**	***APOE* ε4 Homozygote (n=19)**	**All Study Participants (n=1,044)**	**All deceased ROS-MAP (n=1,624)**
Age at enrollment, years (sd)	80·6 (7·1)	79·8 (6·4)	74·5 (7·3)	80·3 (7·0)	80·8 (6·9)
Age at death, years (sd)	89·5 (6·6)	88·9 (6·1)	83·8 (5·9)	89·2 (6·5)	88·7 (6·6)
Female, n (%)	532 (69)	172 (69)	13 (68)	717 (69)	1077 (66)
Education, years (sd)	16·0 (3·6)	16·6 (3·7)	17·3 (4·6)	16·1 (3·6)	16·1 (3·7)
MMSE score proximate to death, (sd)[a]	21·7 (8·6)	17·6 (10·4)	14·9 (10·4)	20·6 (9·3)	21·1 (9·0)
Global cognitive function proximate to death, (sd)[b]	−0·82 (1·11)	−1·34 (1·29)	−1·78 (1·19)	−0·96 (1·19)	−0·94 (1·16)
Random slope of global cognition, (sd)[c]	−0·006 (0·088)	−0·053 (0·109)	−0·098 (0·096)	−0·019 (0·096)	−0·023 (0·099)
Diagnosis of AD dementia, n (%)[d]	284 (37)	139 (56)	14 (74)	437 (42)	634 (41)
Pathologic diagnosis of AD, n (%)	447 (58)	209 (83)	16 (84)	672 (64)	N/A
Aβ burden, mean (sd)	3·8 (4·2)	6·4 (4·2)	8·0 (4·9)	4·5 (4·3)	N/A
PHFtau burden, mean (sd)	5·6 (6·6)	10·0 (9·9)	15·4 (12·6)	6·9 (8·0)	N/A
Presence of TDP-43, n (%)	370 (48)	154 (61)	14 (74)	538 (52)	N/A
Diagnosis of HS, n (%)[e]	59 (8)	37 (15)	3 (16)	99 (9)	N/A

Here, we showed demographic characteristics according to *APOE* ε4 allele count. Aβ and PHFtau burden are quantitative immunohistochemistry measures derived from 8 brain regions.

[a]Data missing for 2 participants.

[b]Data missing for 6 participants.

[c]Data missing for 52 participants.

[d]Data missing for 11 participants.

[e]Data missing for 2 participants.

Aβ=β-amyloid, AD=Alzheimer's disease, HS=hippocampal sclerosis, MMSE=Mini-Mental State Examination, PHFtau=paired helical filament tau, sd=standard deviation, TDP-43=TAR-DNA binding protein-43kDa proteinopathy.

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Table 2.

Association of TDP-43 with *APOE* ε4 count and other neurodegenerative proteinopathies

Models	Independent variable	Outcome	
		TDP-43 Stage Odds ratio (95% CI), p-value	TDP-43 Burden Estimated effect (95% CI), p-value
Model 1[a]	*APOE* ε4	2·0 (1·6 to 2·6), p=$1·9\times10^{-9}$	0·40 (0·28 to 0·52), p=$1·2\times10^{-10}$
Model 2[a]	*APOE* ε4 (adj Aβ +PHFtau)	1·5 (1·2 to 2·0), p=$7·4\times10^{-4}$	0·23 (0·10 to 0·35), p=$4·2\times10^{-4}$
	Aβ	1·1 (1·0 to 1·2), p=0·13	0·08 (0·02 to 0·13), p=$9·5\times10^{-3}$
	PHFtau	1·3 (1·2 to 1·5), p=$7·6\times10^{-9}$	0·14 (0·09 to 0·19), p=$2·5\times10^{-8}$
Model 3[b]	*APOE* ε4 (adj Aβ+PHFtau+LB)	1·5 (1·2 to 2·0), p=$9·9\times10^{-4}$	0·22 (0·09 to 0·35), p=$6·1\times10^{-4}$
	Aβ	1·1 (1·0 to 1·2), p=0·13	0·08 (0·02 to 0·13), p=$9·7\times10^{-3}$
	PHFtau	1·3 (1·2 to 1·5), p=$3·2\times10^{-8}$	0·14 (0·09 to 0·19), p=$1·4\times10^{-7}$
	LB	1·1 (1·0 to 1·2), p=0·10	0·06 (0·01 to 0·12), p=0.015
Model 4[a]	*APOE* ε4×pathoAD	1·5 (0·8 to 2·8), p=0·20	0·21 (−0·09 to 0·51), p=0·18
	APOE ε4	1·3 (0·7 to 2·3), p=0·33	0·16 (−0·10 to 0·43), p=0·23
	pathoAD	1·6 (1·2 to 2·1), p=$1·3\times10^{-3}$	0·27 (0·13 to 0·41), p=$1·2\times10^{-4}$
Model 5[b]	*APOE* ε4×Aβ	0·9 (0·7 to 1·2), p=0·56	0·03 (−0·10 to 0·17), p=0·61
	APOE ε4×PHFtau	1·1 (0·9 to 1·3), p=0·47	0·03 (−0·06 to 0·12), p=0·50
	APOE ε4×LB	1·0 (0·9 to 1·3), p=0·66	0·04 (−0·07 to 0·15), p=0·45
	APOE ε4	1·5 (0·8 to 2·8), p=0·26	0·03 (−0·28 to 0·35), p=0·83
	Aβ	1·1 (1·0 to 1·3), p=0·10	0·07 (0·01 to 0·14), p=0·027
	PHFtau	1·3 (1·1 to 1·5), p=$4·2\times10^{-5}$	0·12 (0·06 to 0·18), p=$1·2\times10^{-4}$
	LB	1·1 (0·9 to 1·2), p=0·27	0·05 (−0·01 to 0·11), p=0·096

Odds ratios of higher TDP-43 stage for each additional *APOE* ε4 allele were reported from ordinal logistic regressions with TDP-43 stage (0 to 3) as an outcome, and estimated effects (adjusted increase in TDP-43 burden per each additional *APOE* ε4 allele) were reported from linear regressions with a semi-quantitative TDP-43 burden (range 0 to 5) as an outcome. Model 1 is our primary analysis, and has *APOE* ε4 count as the independent variable and TDP-43 stage or a burden as the outcome. Model 2 and 3 also have *APOE* ε4 count as the independent variable, and additionally adjusts for other *APOE* ε4-related proteinopathies. Model 4 tests whether the interaction term between *APOE* ε4 count and pathoAD is associated with TDP-43. Model 5 tests whether any of the interaction terms between *APOE* ε4 count and Aβ, PHFtau, or LB stage is associated with TDP-43. All analyses were adjusted for age at death and sex.

[a]n=1,044 for the model with TDP-43 stage as the outcome, and n=1,027 for the model with TDP-43 burden as the outcome.

[b]n=1,042 for the model with TDP-43 stage as the outcome, and n=1,025 for the model with TDP-43 burden as the outcome (n=2 with missing values for LB). Aβ=β-amyloid, adj=adjusted for, CI=confidence interval, LB= Lewy body pathology (stage), pathoAD=pathologic diagnosis of Alzheimer's disease, PHFtau=paired helical filament tau, TDP-43=TAR-DNA binding protein-43kDa proteinopathy.

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Table 3.

Association of *APOE* ε4 count with cognition

Models	Independent variable	Outcome	
		Global Cognitive function	AD dementia
		Estimated effect (95% CI), p-value	OR (95% CI), p-value
Model 1[a]	*APOE* ε4	−0·57 (−0·71 to −0·42), p=$1·3\times10^{-14}$	2·4 (1·8 to 3·1), p=$9·6\times10^{-12}$
Model 2[a]	*APOE* ε4 (adj Aβ +PHFtau)	−0·18 (−0·31 to −0·04), p=0·010	1·4 (1·01 to 1·9), p=0·042
Model 3[b]	*APOE* ε4 (adj Aβ +PHFtau + LB)	−0·17 (−0·31 to −0·04), p=0·010	1·4 (1·004 to 1·9), p=0·047
Model 4[a]	*APOE* ε4 (adj Aβ +PHFtau + TDP-43 stage)	−0·13 (−0·27 to −0·001), p=0·048	1·2 (0·9 to 1·7), p=0·19
Model 5[c]	*APOE* ε4 (adj Aβ +PHFtau + TDP-43 burden)	−0·09 (−0·22 to 0·04), p=0·18	1·2 (0·9 to 1·7), p=0·29

Estimated effects (adjusted difference in global cognitive function per each additional *APOE* ε4 allele) were reported from linear regressions with global cognitive function proximate to death as the outcome, and ORs of AD dementia for each additional *APOE* ε4 allele were reported from logistic regressions with AD dementia as the outcome. In model 1, *APOE* ε4 count was the independent variable and age at death, sex, and years of education were controlled. Aβ and PHFtau were additionally controlled in model 2, and LB stage was also controlled in model 3. TDP-43 stage or TDP-43 burden was adjusted in addition to Aβ, PHFtau, age at death, sex, and years of education in model 4 and 5, respectively.

[a]n=1,038 for global cognitive function, n=1,033 for AD dementia.

[b]n=1,036 for global cognitive function, n=1,031 for AD dementia.

[c]n=1,021 for global cognitive function, n=1,016 for AD dementia. Aβ=β-amyloid, AD=Alzheimer's disease, adj=adjusted for, CI=confidence interval, LB= Lewy body pathology (stage), OR=odds ratio, PHFtau=paired helical filament tau, TDP-43=TAR-DNA binding protein-43kDa proteinopathy.

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Table 4.

Adjusted cognitive decline in subgroups according to TDP-43, HS, and *APOE* ε4

Advanced TDP-43	HS	*APOE* ε4 carrier	n	TDP-43 burden (sd)	MMSE proximate to death (sd)	Adjusted global cognitive decline per year (sd)	Adjusted global cognition proximate to death (sd)
NO	NO	NO	516	0·11 (0·21)	23·0 (7·8)	0·006 (0·079)	0·10 (0·92)
		YES	137	0·12 (0·22)	20·8 (9·0)	−0·005 (0·097)	0·10 (1·05)
YES	NO	NO	154	1·43 (0·81)	19·5 (9·0)	0·016 (0·075)	0·07 (0·90)
		YES	77	1·65 (1·00)	15·8 (10·6)	−0·013 (0·089)	−0·20 (1·12)
YES	YES	NO	42	2·56 (0·82)	14·0 (9·8)	−0·047 (0·090)	−0·86 (1·04)
		YES	35	2·64 (0·84)	11·9 (9·7)	−0·052 (0·094)	−0·60 (1·06)

Advanced TDP-43 was defined as TDP-43 stage 2 or 3. TDP-43 burden, unadjusted MMSE proximate to death, adjusted global cognitive decline per year (random slope of global cognition additionally adjusted for Aβ, PHFtau, age at death, sex, and years of education), and adjusted global cognition proximate to death (global cognition proximate to death adjusted for Aβ, PHFtau, and demographics) are shown for each subgroup. We aimed to capture the cognitive trajectory not explained by AD pathology or demographics with adjusted global cognitive decline per year and adjusted global cognition proximate to death. To calculate adjusted global cognitive decline, we first derived random slope of global cognition from linear mixed models with annual global cognitive function as the longitudinal outcome, adjusting for age at baseline, sex, and years of education. This random slope was additionally adjusted for Aβ and PHFtau to derive adjusted global cognitive decline per year. Data shown here are from a subset of participants with non-missing data for all variables displayed. We note that there were only 15 participants (four *APOE* ε4 carriers) who had HS but did not have advanced TDP-43, and this small subgroup (not displayed in this table) had the following characteristics: TDP-43 burden 0·11 (sd 0·17), unadjusted MMSE proximate to death 17·7 (sd 12·4), adjusted global cognitive decline −0·013 (sd 0·061), and adjusted global cognition proximate to death −0·10 (sd 0·80). Aβ=β-amyloid, HS=hippocampal sclerosis, MMSE=mini-mental state exam, PHFtau=paired helical filament tau, sd=standard deviation, TDP-43=TAR-DNA binding protein-43kDa proteinopathy.