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TDP-43 Neuropathologic Associations in the Nun Study and the Honolulu-Asia Aging Study

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Abstract

Transactive response binding protein-43 (TDP-43) cytoplasmic neuronal and glial aggregates (pathologic TDP-43) have been described in multiple brain diseases. We describe the associations between neuropathologically confirmed TDP-43 and cognition in two population-based cohorts: the Nun Study (NS) and the Honolulu-Asia Aging Study (HAAS). In the HAAS, there was a significant association between hippocampal sclerosis (HS) and TDP-43 (OR = 11.04, $p < 0.0001$, 95% CI 3.57 – 34.13). In the NS, there were significant associations between TDP-43 and HS (OR=16.44, $p < 0.001$ 95%, CI 7.10 – 38.00) and Alzheimer's disease (AD) severity (OR=1.74, $p = 0.009$, 95% CI 1.15 – 2.64). When cognitive scores were added to the model, HS remained significant but the other variables were not. When HS was removed from the model, the overall model remained significant and the associations between cognitive performance and TDP-43 (OR= 2.11, $p = 0.022$, 95% CI 1.11 – 4.02) were significant. In the NS, there was a significant association between cognitive performance and TDP-43 (OR 1.94 $p = 0.005$, 95% CI 1.22 – 3.09) (HS remained significant, but AD did not). When HS was removed from the model, only CERAD was significant (OR = 2.43 $p < 0.001$, 95% CI 1.58 – 3.74). These results support a consistent association between pathologic TDP-43, HS, and the development of cognitive impairment in two large studies of brain aging, while the relationship between AD pathology and TDP-43 may vary according to cohort-specific features.

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Keywords

TDP43; hippocampal sclerosis; Alzheimer's disease; associations

INTRODUCTION:

Transactive response binding protein-43 (TDP-43) is a highly conserved nuclear riboprotein that plays a role in a variety of cellular functions including RNA processing[1,2]. Since the identification of TDP-43 cytoplasmic neuronal and glial protein aggregates (hereafter referred to as pathologic TDP-43) in amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) [3–6], they also have been described in association with numerous other neurodegenerative diseases including Alzheimer's disease (AD) [7–12], argyrophilic grain disease (AGD) [13,14], Lewy body disease (LBD) [15,16], hippocampal sclerosis (HS) [17–20] and chronic traumatic encephalopathy (CTE) [21]. Not only is pathologic TDP-43 identified in these other neurodegenerative disease, but it also appears to modulate clinical presentation, particularly in the context of AD pathologic change, where pathologic TDP-43 has been associated with worse performance and increased rates of decline on cognition [8,22]. A study conducted to determine the contributions of AD pathology, cerebrovascular disease, HS and the altered expression of three synaptic proteins to cognitive status and global cognitive function showed that tangle pathology, HS, TDP-43 and perforant pathway synaptic loss are the major contributors to dementia in the oldest-old [23].

The Nun Study (NS) and the Honolulu-Asia Aging Study (HAAS) are population-based longitudinal studies that have contributed to our knowledge of brain aging [24–26]. The HAAS cohort comprises men of Japanese ancestry born on Oahu between 1900 and 1919. In contrast, the NS comprises U.S. members of the Roman Catholic School Sisters of Notre Dame who are mostly Caucasian and born between 1890 and 1916. Harmonized neuropathologic data from these two studies has allowed comparisons to be made with respect to sex, ethnicity, culture, and lifestyle [25]. The neuropathologic evaluations carried out in these two studies was recently expanded by applying the revised NIA-AA neuropathologic guidelines which include the ABC score for the neuropathologic assessment of AD [27, 28] to directly compare neuropathologic features of the two cohorts and investigate resistance and apparent resilience [29]. Here, we report the frequency of pathologic TDP-43 in each cohort and associations with clinical and concomitant neuropathologic findings.

METHODS:

Standard protocol approvals, registrations, and participant consents.

The NS and HAAS are population-based studies of health and functioning in late life. Some data used for this report were included in previous publications. Standard protocol approvals, registrations, and participant consents were previously described [25]. The NS was reviewed and approved by Universities of Kentucky and Minnesota institutional review boards (IRBs). Participating School Sisters of Notre Dame agreed to autopsy prior to death,

with authorizations provided by the Provincial Leader; a brain autopsy was completed for >90% of NS participants. The HAAS was reviewed and approved by the Kuakini Hospital IRB. A consent form was signed by participants at every cycle (12 from 1965 to 2012), including consent for use of information and materials for research purposes by researchers and their colleagues, including NIH, in perpetuity. HAAS autopsy required notification of a participant's death by family member, hospital, medical examiner's office, or other source, with permission for autopsy and research use of information provided by next of kin. Brain autopsies were completed for 25% of HAAS participants [25]. It has been previously shown that autopsied and non-autopsied decedents in the HAAS cohort who had been cognitively normal or low-normal were similar with respect to demographic, social and medical characteristics [39, 40]. Additionally, although the families of demented HAAS participants were substantially more likely to contact the study when death occurred, and to give consent for autopsy examination than those without dementia, the demented HAAS decedents who were autopsied were also similar to demented decedents who were not autopsied [39, 40]. It has been previously concluded that the autopsied subset of HAAS participants is similar to the stratified sample of all cohort decedents, with stratification based on dementia recognized during life [39, 40]. Nearly all participants in the NS underwent brain autopsy at time of death. Information on participants with brain autopsies for HAAS and NS is shown in Table 1.

Neuropathologic evaluations.

The total sample for NS and HAAS comprised all participants with complete neuropathologic data, which was extensively harmonized as previously described [25,29]. For both cohorts, 5–6 µm thick paraffin-embedded tissue sections of mid-hippocampus previously fixed in 10% neutral buffered formalin, were cut with Sakura Accu-edge low profile microtome blades on Leica RM2245 microtomes, floated on a warm water bath, placed on Plus-slides, and then baked for two hours at 65°C. Slides were stained with anti-phospho TDP-43 (Ser409/Ser410) antibody, clone 1D3, EMD (Millipore, Darmstadt, Germany) at a dilution of 1:250. Antigen detection was automated with a Bond Polymer Refine Detection System (Leica Biosystems) followed by hematoxylin counterstaining. Hippocampal pathologic TDP-43 was assessed as none or any phospho-TDP-43 neuronal or glial cytoplasmic aggregates [30]. Severity of hippocampal TDP-43 pathology was graded on a semi-quantitative scale that has been previously described using conventional TDP-43 immunohistochemistry [13]. We used this same previously described scale [13] for assessment, but applied it to the phospho-TDP43 immunohistochemically stained slides, where the presence of any staining is defined as aberrant due to these specific antibodies only binding pathological TDP-43 via recognition of phosphorylation independent, but disease specific pathologic conformation in abnormal TDP43 [29]. Briefly, stage 0 was defined as absent staining; stage 1 was defined as mostly cells that lack staining but with very focal areas or cells that appear abnormal (less than 5 40x fields with up to 2 TDP-43 positive structures); stage 2 was defined as extensive staining (more than 5 40x fields with more than 2 TDP-43 positive structures or any degree of TDP-43 immunoreactive neuropil threads) [13].

Cognitive function.

NS primary cognitive testing was done annually with the Consortium to Establish a Registry for AD neuropsychological battery (CERAD-NB) [31]. HAAS participants were screened at each examination with the Cognitive Abilities Screening Instrument (CASI) [32]. NS cognitive performance is reported as a summary CERAD total score at the final examination prior to death [33]. The cognitive sample was defined as the subset of autopsies from each cohort where the last cognitive evaluation was performed within two years or less of time of death. Although neuropathologic harmonization has been performed previously which included application of the revised NIA-AA neuropathologic guidelines [26,27] to directly compare neuropathologic features of the two cohorts the CASI and CERAD summary scores are not directly comparable, as they emphasize different cognitive domains. Because the cognitive testing approaches used by the cohorts may play a role in the identifiable differences between cohorts, we specifically chose to use quartiles of performance for our analyses.

Indices of Disease Burden.

Frequencies and correlates of individual neuropathologic abnormalities were examined at 3 levels of severity for each. We have shown previously that relative risk for dementia from standardized AD neuropathologic change, cerebral microinfarcts, and cortical LBs are similar, supporting analogous contributions of these disease processes to dementia in community settings [19]; similar analyses support analogous contributions from HS and low brain weight [13, 28]. Thus, index values of 1, 0.4, or 0 were assigned for severe, moderate, or negligible, respectively, based on prior analyses relating lesion measures to cognitive decline and dementia. Choosing 0.4 as the intermediate level allowed us to distinguish the influence of cases with a single severe lesion type (comorbid index 1.0) from those with 2 or 3 moderate lesions (comorbid indices 0.8 and 1.2, respectively).

Statistical analyses.

Unadjusted univariate comparisons between HAAS and NS participants and between those with and without pathologic TDP-43 were assessed using t-tests for continuous variables (age at death, years of education, time from last cognitive evaluation to death), chi-square tests for categorical variables (APOE), and Wilcoxon rank-sum tests for ordinal variables (cognitive, neuropath variables). Ordinal logistic regression was used to model the relationship between pathologic TDP-43 (0, 1, 2) and other brain lesion index scores (AD index, cerebral microinfarcts index, LBD index, HS index, low brain weight index), controlling for age at death and APOE $\epsilon 4$ status, separately for the NS and HAAS. To determine whether cognitive test performance was associated with pathologic TDP-43 over and above other brain pathology among those who had cognitive testing within two years of death, cognitive summary scores (divided into quartiles) were added to the ordinal regression model; years of education and time from last cognitive evaluation to death were included in the model as additional covariates. Alpha level was set a priori at 0.05. All analyses were performed using Stata 14.2.

RESULTS:

Study participants.

Characteristics of NS and HAAS participants for both the brain autopsy and cognitive samples are shown in Table 2. In addition to known sex and ethnicity differences, education was higher in the NS for both cognitive and autopsy samples ($p<0.0001$) and time from last cognitive examination to death was longer in the HAAS ($p<0.0001$). Mean age and proportion of the sample with an *APOE* $\epsilon 4$ allele did not differ. There was a greater proportion of participants with neuropathologic TDP-43 in HAAS than NS in the autopsy sample ($p<0.001$). This was true even after controlling for age at death, *APOE* status, and AD severity ($p=0.001$). The difference did not reach statistical significance in the cognitive sample, however.

Table 3 demonstrates differences between those with and without pathologic TDP-43 in the autopsy and cognitive samples. There were no differences between those with and without pathologic TDP-43 in age at death or in years of education for either the HAAS or NS samples. However, there was a higher proportion of participants with at least one *APOE* $\epsilon 4$ allele observed in both NS and HAAS cohorts for those with pathologic TDP-43 when compared to those without.

Pathologic TDP-43 and other neuropathological lesions

The relationship between TDP-43 and other brain lesions was assessed using an ordinal logistic regression model controlling for age at death and *APOE* status (Table 4). In the HAAS, there was a significant association between HS and TDP-43 (OR = 11.04, $p<0.0001$, 95% CI 3.57 – 34.13). In the NS, there were significant associations between TDP-43 and HS (OR=16.44, $p<0.001$ 95% CI 7.10 – 38.00) and AD severity (OR=1.74, $p=0.009$ 95% CI 1.15 – 2.64).

Pathologic TDP-43 and Cognitive Test Results

As seen in Table 3, lower cognitive test scores were observed among those with pathologic TDP-43 in both cohorts. Figure 1 demonstrates the proportion of subjects with pathologic TDP-43 by cognitive performance quartiles for the two cohorts. In the HAAS, when the cognitive scores were added to the model, HS remained the only variable significantly associated with TDP-43. However, when HS was removed from the model, the overall model remained significant and the associations between the CASI and TDP-43 (OR= 2.08, $p=0.021$ 95% CI 1.12 – 3.88) were also significant. In the NS, there was a significant association between the CERAD total score and TDP-43 (OR 1.94 $p= 0.005$ 95% CI 1.22 – 3.09) (HS remained significant, but AD did not). When HS was removed from the model, only the CERAD total score was significant (OR = 2.43 $p<0.001$ 95% CI 1.58 – 3.74).

The Supplementary Material contains detailed cognitive performance information for each cohort as well as proportions of TDP43 positivity by each cognitive performance group.

DISCUSSION:

This study extends our current knowledge of the associations between pathologic TDP-43 and other lesions and its relationship to cognitive performance. TDP-43 proteinopathy has been found to frequently co-exist with AD neuropathologic change and to be associated with a higher likelihood of dementia when beyond the amygdala stage and involving limbic or neocortical regions [12]. Here, taking advantage of two community based studies of brain aging, we report lower cognitive test scores among those with pathologic TDP-43 and a strong association between pathologic TDP-43 and coexisting HS in both the NS and HAAS. An association between pathologic TDP-43 and AD neuropathologic change was seen only in the NS however. No association was identified between pathologic TDP-43 and microvascular lesions, brain weight, or age at death in either cohort. Interestingly, the frequency of LBD was found to be higher in those with pathologic TDP-43 in the NS but not in the HAAS which differs from what has been previously reported [19]. Boyle et al. previously examined the effects of age-related neuropathologic lesions on cognition change over time. AD pathology, macroscopic infarcts, LBD, TDP-43 pathology, and HS were shown to be associated with progressive cognitive decline, with their deleterious effects increasing over time [34]. In another study, TDP-43 immunoreactive dystrophic neurites reportedly developed as a consequence of aging processes in the human brain. Cykowski et al., studied HS of aging and demonstrated that cellular inclusions of TDP-43 are frequent in this setting [36]. Additionally, the same group did not identify an association between basal forebrain TDP-43 pathology and AD or LBD neuropathologic changes. Here we report similar findings in the HAAS cohort and an association between pathologic TDP-43 and AD neuropathologic in the NS. Therefore, the pathogenic relationship between basal forebrain TDP-43 and non-HS-Aging comorbid diseases remains unclear [37].

Despite evidence that pathologic TDP-43 is associated with brain aging and cognitive decline, discerning the exact contribution of pathologic TDP-43 in the context of multiple pathologic changes has been challenging [25,44–46]. It has been suggested that hippocampal and entorhinal TDP-43 inclusions are important substrates of late onset dementia which appear to co-localize with severe neuronal loss, but not with AD markers of amyloid and tau [43]. TDP-43-ir pathological changes have also found to be significantly more common in late onset AD, than early onset with no demographic differences, other than age of onset, between AD patients with or without TDP-43-ir pathological changes [47]. Evaluation of pathologic TDP-43 in a population of aged subjects lacking AD pathologic change observed cognitive dysfunction in specific domains [19]. Of note, HS also was identified in this group, potentially obscuring clear clinicopathologic correlation. Pathologic TDP-43 has also been reportedly infrequently identified in the brains of cognitively intact elderly individuals [22] but a different study described the presence of phosphorylated TDP-43 deposits in the hippocampus and/or amygdala in 36.4% of 110 non-demented aged individuals [14]. Pathologic TDP-43 in cognitively intact aged individuals (i.e. healthy aging) is an area that requiring further study. We plan to investigate pathologic TDP-43 and aging further with future work focusing on the subset of centenarians within each cohort.

In both the NS and HAAS, pathologic TDP-43 was more frequently observed in the lowest cognitive test performers, consistent with suggestions that pathologic TDP-43 may signal

pathophysiologic processes contributing to the development of cognitive impairment. We specifically performed our analyses with and without HS included in the model. This was done to enable us to specifically examine potential mediation by HS for the identified relationship between decreased cognition and pathologic TDP-43 in each cohort. In the NS, the association between pathologic TDP-43 and decreased cognitive performance was indeed observed whether or not HS was included in the model. In contrast, in the HAAS, inclusion of HS removed the association between cognition and TDP-43. Thus, in certain groups, the relationship between cognition and pathologic TDP-43 may be mediated by HS, supporting the possibility that HS may act sequentially with other diseases to impair cognitive function [29]. The proportion of APOE ϵ 4 was also significantly higher in TDP-43 groups in both NS and HAAS, at roughly the same rate in each cohort, a bit higher for NS. Interestingly, AD pathology was much higher in the NS overall, particularly within the pathologic TDP-43 group. No association between APOE ϵ 4 and pathologic TDP-43 was identified in either cohort despite the observation of higher proportion of APOE ϵ 4 seen in individuals with pathologic TDP-43 overall.

Observed variations between the NS and HAAS could be due to differences in genetic, sex, ethnic or other risk factor differences. There are also other potential explanations to consider, including differences in total number of individuals with dementia in each cohort, length of time between last exam and autopsy, sample size and regions available. Differing cognitive testing approaches may also play a role in the identifiable differences between the cohorts, as the CASI and CERAD emphasize different underlying cognitive constructs. Lower power resulting from the smaller sample size in the HAAS could also be an important factor contributing to some of our findings, thus, further investigation in other cohorts is necessary. There was unfortunately also limited availability of HAAS brain regions for analyses due to lost samples which prevented examination of additional brain regions, such as amygdala, across the two cohorts for this work. We do plan to complete comprehensive bilateral phospho-TDP43 assessments in the NS in the future however.

Weaknesses of our study include the described differences between the cohorts, with neither cohort being representative of the general population. Another weakness is the lack of arteriosclerosis data which we do hope to complete moving forward to include in future analyses which is of particular interest due to the previously described association between arteriolosclerosis and HS of aging [20]. The range of intervals between final cognitive assessment and death was relatively short among NS participants, but longer in HAAS excluding a large proportion of the HAAS cohort from the cognitive sample. As in our previous study, analyses were performed using quartiles to more readily describe cognitive performance within each group and to make broad comparisons of general cognitive functioning, with the understanding that the cognitive instruments did not necessarily measure the same underlying cognitive constructs, nor were they measured to the same extent [29]. In the future, we plan to clarify any differences between the cohorts by comparing those items and domains that align between the CASI and CERAD neuropsychological battery. Unfortunately these summary scores, while providing greater range for the evaluation of variability, emphasize different cognitive domains and are not directly comparable. Harmonization of the cognitive evaluations is beyond the scope of this paper. We hope that alignment will help to address the difficulties in comparing across

groups with such disparate educational differences, demographics and lifestyles in the future.

In summary, our findings of lower cognitive test scores among those with pathologic TDP-43 and a strong association between pathologic TDP-43 and coexisting HS in both the NS and HAAS support what has been previously described in other cohorts [17–19]. Our findings support that pathologic TDP-43 may signal pathophysiologic processes contributing to the development of cognitive impairment. Our findings also support that in certain groups, the relationship between cognition and pathologic TDP-43 may be mediated by HS, supporting the possibility that HS may act sequentially with other diseases to impair cognitive function [29]. The overlap of findings in these two very different populations provides further support of the generalizability of these associations. Pathologic TDP-43's associations with AD neuropathologic change was observed only in NS and the frequency of LBD was found to be higher in those with pathologic TDP-43 in the NS but not the HAAS which differs from what has been previously reported 1 differing from previous reports [19]. Differences between the two distinct cohorts also raise the possibility of disease susceptibility 2 differences due to genetic, sex, ethnic, or risk factor exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Proportion of subjects with pathologic TDP-43 staining by cognitive performance (quartiles), HAAS and NS. CERAD/CASI quartiles: 1=highest performance quartile, 4=lowest performance as previously performed [29].

Table 1.

Total sample sizes in the NS and HAAS cohorts

	NS	HAAS	Total
Total with complete pathologic TDP43 scores (TDP-43 sample)	382	321	703
...with complete evaluation for other neuropathologic changes & <i>APOE</i> genotype (autopsy sample)	308	238	546
... with cognitive evaluation 2 years from brain autopsy (cognitive sample)	304	89	393

Abbreviations: APOE, apolipoprotein E; HAAS, Honolulu Asia Aging Study; NS, Nun Study; TDP-43, Transactive responsive sequence (TAR) DNA-binding protein 43-kDa

Table 2.

Characteristics of autopsied NS and HAAS participants in the autopsy and cognitive samples

	NS		HAAS	
	Autopsy sample (n = 308)	Cognitive sample (n = 304)	Autopsy sample (n = 238)	Cognitive sample (n = 89)
Age at death mean (sd)	91.0 (4.8)	91.0 (4.8)	90.2 (4.2)	90.3 (3.8)
Education mean (sd)	15.9 (3.0)	15.9 (3.0)	11.4 (3.4)	11.4 (3.1)
<i>APOE</i> e4 allele n, % of sample	68, 22.1	67, 22.0	54, 22.7	21, 23.6
Last cognitive score* median (25 th – 75 th %ile)	-	50.0 (22.0 – 68.0)	-	69.7 (42.3 – 83.0)
Last examination to death, yrs mean (sd)	-	0.73 (0.48)	-	0.96 (0.60)
Neuropathologic Index Scores n, % [‡]				
TDP-43				
Index 0	258, 83.8	254, 83.6	177, 74.4	67, 75.2
Index 1	30, 9.7	30, 9.9	59, 21.8	15, 16.9
Index 2	20, 6.5	20, 6.6	9, 3.8	7, 7.9

Characteristics of participants with and without pathologic TDP-43 in the autopsy and cognitive samples of the HAAS and NS cohorts

	HAAS				NS			
	Autopsy sample		Cognitive sample		Autopsy sample		Cognitive sample	
	TDP43+ (n=61)	TDP43- (n=177)	a p	TDP43+ (n=22) TDP43- (n=67)	a p	TDP43+ (n=50) TDP43- (n=258)	a p	TDP43+ (n=50) TDP43- (n=254)
Age at death mean (sd)	90.9 (4.8)	89.9 (4.0)	ns	91.0 (4.5) 90.1 (3.6)	ns	91.4 (4.3) 90.9 (4.9)	ns	91.4 (4.3) 90.9 (4.9)
Education mean (sd)	11.6 (3.3)	11.3 (3.4)	ns	11.8 (3.1) 11.3 (3.1)	ns	15.9 (3.0) 15.9 (2.9)	ns	15.9 (3.0) 15.9 (3.0)
APOE ε4 allele n, % of sample	19, 31.2	35, 19.8	0.067	9, 40.9 12, 17.9	0.027	18, 36.0 50, 19.4	0.010	18, 36.0 49, 19.3
Cognitive score ^b median (25 th – 75 th %ile)	-	-	-	60.9 (49.9 – 71.7) 71.8 (49.9 – 84.0)	ns	-	-	53 (30 – 73)
Neuropathologic Index Scores n, % ^c								
Alzheimer severity								
None	17, 27.9	58, 32.8		7, 31.8 28, 41.8		1, 2.0 24, 9.3		1, 2.0 24, 9.5
Low	19, 31.2	58, 32.8	0.085	6, 27.3 15, 22.4	ns	13, 26.0 112, 43.4	<0.0001	13, 26.0 111, 43.7
Intermediate	8, 13.1	48, 27.1		4, 18.2 19, 28.4		8, 16.0 63, 24.4		8, 16.0 61, 24.0
High	17, 27.9	13, 7.3		5, 22.7 5, 7.5		28, 56.0 59, 22.9		28, 56.0 58, 22.8
Hippocampal sclerosis severity								
Index 0	41, 67.2	166, 93.8		14, 63.6 66, 98.5		24, 48.0 246, 95.3		24, 48.0 242, 95.3
Index 4	11, 18.0	8, 4.5	<0.0001	6, 27.3 0, 0	<0.0001	7, 14.0 6, 2.3	<0.0001	7, 14.0 6, 2.4
Index 1	9, 14.8	3, 1.7		2, 9.1 1, 1.5		19, 38.0 6, 2.3		19, 38.0 6, 2.4
Neocortical Lewy body severity								
Index 0	53, 86.9	156, 88.1		19, 86.4 64, 95.5		37, 74.0 229, 88.8		37, 74.0 226, 89.0
Index 4	2, 3.3	12, 6.8	ns	1, 4.6 1, 1.5	ns	8, 16.0 14, 5.4	0.007 ^d	8, 16.0 13, 5.1
Index 1	6, 9.8	9, 5.1		2, 9.1 2, 3.0		5, 10.0 15, 5.8		5, 10.0 15, 5.9
Microinfarct severity								
Index 0	35, 57.4	94, 53.1		13, 59.1 32, 47.8		44, 88.0 223, 86.4		44, 88.0 220, 86.6
Index 4	13, 21.3	47, 26.6	ns	6, 27.3 22, 32.8	ns	4, 8.0 22, 8.5	ns	4, 8.0 21, 8.3
Index 1	13, 21.3	36, 20.3		3, 13.6 13, 19.4		2, 4.0 13, 5.0		2, 4.0 13, 5.1
Low brain weight								
Index 0	23, 37.7	88, 49.7		15, 68.2 29, 43.3		25, 50.0 146, 56.6		25, 50.0 143, 56.3

Table 4.

Relationship between TDP-43 and neuropathologic indices in the HAAS and NS cohorts: ordinal logistic regression results

	HAAS				NS			
	<u>OR</u>	<u>SE</u>	<u>95% CI</u>	<u>p</u> *	<u>OR</u>	<u>SE</u>	<u>95% CI</u>	<u>p</u> *
Alzheimer's Disease severity	1.16	0.19	0.84 – 1.61	0.367	1.74	0.37	1.15 – 2.64	0.009
Hippocampal Sclerosis severity	11.04	6.36	3.57 – 34.13	<0.001	16.44	7.03	7.11 – 38.0	<0.001
Neocortical Lewy body severity	0.78	0.48	0.23 – 2.60	0.682	1.67	0.87	0.53 – 5.26	0.383
Microinfarct severity	0.83	0.34	0.37 – 1.85	0.646	0.49	0.39	0.10 – 2.45	0.387
Low brain weight	0.95	0.36	0.46 – 1.98	0.896	1.45	0.36	0.65 – 3.22	0.363

* p values based on ordinal logistic regression controlling for age at death and *APOE*ε4 status

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; HAAS, Honolulu Asia Aging Study; NS, Nun Study; OR, odds ratio; SE, standard error; Transactive responsive sequence (TAR) DNA-binding protein 43-kDa