Supplementary materials for: *Neuropathologic changes of Alzheimer Disease and Related Dementias – Relevance to Future Prevention*

Contents

Correlation Matrix

Spearman Correlation Matrix showing relationships among the six types of neuropathologic change (NC), and of each NC with education, age at death, and cognitive impairment.

The SAS System

The CORR Procedure

9 Variables:	ADINDEX_II uVBIindex_ii LBINDEX_II hs_pureii tdp_pureii tdpHS_mixii agedth10 edgp3 ci3

Simple Statistics

Variable	N	Mean	Std Dev	Median	Minimum	Maximum	Label
ADINDEX_II	1040	0.36250	0.48095	0	0	1.00000	alzeimer neuropath change 0 or 1
uVBIindex_ii	1040	0.19423	0.39580	0	0	1.00000	microvascular brain injury path change 0 or 1
LBINDEX_II	1040	0.13558	0.34250	0	0	1.00000	cortical Lewy body path change 0 or 1
hs_pureii	1040	0.05385	0.22582	0	0	1.00000	hippocampal sclerosis, uni or bilat, pure (unassociated with tdp-43) 0 or 1
tdp_pureii	1040	0.15962	0.36643	0	0	1.00000	LATE tdp-43 encephalopathy, pure (unassociated with hip scler) 0 or 1
tdpHS_mixii	1040	0.07885	0.26963	0	0	1.00000	mixed HS and TDP-43 encephalopathy 0 or 1
agedth10	1040	9.32537	0.54669	9.30616	7.81311	10.86000	
edgp3	1040	2.34423	0.76921	3.00000	1.00000	3.00000	education categories -- 1 < HS, 2 >= High school, 3 >=college completed
ci3	1040	1.03846	0.83962	1.00000	0	2.00000	cognitive impairment categories: 0=unimpaired 1=CIND 2=dementia

Spearman Correlation Coefficients, N = 1040
Prob > |r| under H0: Rho=0

	ADINDEX_II	uVBIindex_ii	LBINDEX_II	hs_pureii	tdp_pureii	tdpHS_mixii	agedth10	edgp3	ci3
ADINDEX_II **alzeimer neuropath change 0 or 1**	1.00000	-0.08709 0.0049	0.10451 0.0007	-0.02924 0.3461	0.10827 0.0005	0.12079 <.0001	0.20740 <.0001	0.12192 <.0001	0.36213 <.0001
uVBIindex_ii **microvascular brain injury path change 0 or 1**	-0.08709 0.0049	1.00000	-0.00274 0.9296	0.02286 0.4614	-0.00161 0.9587	0.00968 0.7552	-0.19494 <.0001	-0.19887 <.0001	0.05937 0.0556
LBINDEX_II **cortical Lewy body path change 0 or 1**	0.10451 0.0007	-0.00274 0.9296	1.00000	0.05485 0.0771	0.00379 0.9028	0.04047 0.1923	-0.01873 0.5462	-0.00514 0.8686	0.12663 <.0001
hs_pureii **hippocampal sclerosis, uni or bilat, pure (unassociated with tdp-43) 0 or 1**	-0.02924 0.3461	0.02286 0.4614	0.05485 0.0771	1.00000	-0.10397 0.0008	-0.06979 0.0244	0.00292 0.9250	-0.03397 0.2737	0.05032 0.1048
tdp_pureii **LATE tdp-43 encephalopathy, pure (unassociated with hip scler) 0 or 1**	0.10827 0.0005	-0.00161 0.9587	0.00379 0.9028	-0.10397 0.0008	1.00000	-0.12750 <.0001	0.14139 <.0001	0.03550 0.2527	0.12431 <.0001
tdpHS_mixii **mixed HS and TDP-43 encephalopathy 0 or 1**	0.12079 <.0001	0.00968 0.7552	0.04047 0.1923	-0.06979 0.0244	-0.12750 <.0001	1.00000	0.02650 0.3933	-0.08267 0.0076	0.19182 <.0001
agedth10	0.20740 <.0001	-0.19494 <.0001	-0.01873 0.5462	0.00292 0.9250	0.14139 <.0001	0.02650 0.3933	1.00000	0.02709 0.3828	0.15423 <.0001
edgp3 **education categories -- 1 < HS, 2 >= High school, 3 >=college completed**	0.12192 <.0001	-0.19887 <.0001	-0.00514 0.8686	-0.03397 0.2737	0.03550 0.2527	-0.08267 0.0076	0.02709 0.3828	1.00000	-0.07273 0.0190
ci3 **cognitive impairment categories: 0=unimpaired 1=CIND 2=dementia**	0.36213 <.0001	0.05937 0.0556	0.12663 <.0001	0.05032 0.1048	0.12431 <.0001	0.19182 <.0001	0.15423 <.0001	-0.07273 0.0190	1.00000

Logistic Regression Models (First Set)

Logistic regression models predicting cognitive impairment for each of the three cohorts. The first models include the six types of neuropathologic change.

We have addressed the relationship of the six principal types of neuropathologic change (NC) to end-of-life cognitive impairment and dementia using logistic modeling. For these analyses we have employed a three-level dependent variable: unimpaired, mildly or moderately impaired, or demented/severely impaired. The co-variates include the six NC, a three-level educational attainment variable, and age at death in decades as co-variates. Results are shown below for each of the three cohorts.

Strengths of association with cognitive impairment were strongest for Alzheimer NC and for a mixture of hippocampal sclerosis and TDP-43 NC for all three cohorts. The HAAS and 90+ cohorts also showed strong associations with microvascular NC (uVBI). Associations with the other NC were marginal in each cohort, but statistically significant in a combined cohort analysis.

NUN STUDY N= 363

Logistic Model: Odds Ratio Estimates DEPENDENT VARIABLE: COGNITIVE IMPAIRMENT UNIMPAIRED=0 MOD=1 SEVERE=2			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
edgp3	0.483	0.328	0.713
agedth10	1.364	0.893	2.085
ADINDEX_II	**7.015**	**4.321**	**11.388**
uVBIindex_ii	1.548	0.843	2.844
LBINDEX_II	1.874	0.949	3.703
hs_pureii	3.085	0.955	9.967
tdp_pureii	**2.941**	**1.220**	**7.089**
tdpHS_mixii	**8.147**	**2.826**	**23.487**

HONOLULU-ASIA AGING STUDY N= 304

Logistic Model: Odds Ratio Estimates DEPENDENT VARIABLE: COGNITIVE IMPAIRMENT UNIMPAIRED=0 MOD=1 SEVERE=2			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
edgp3	0.523	0.372	0.736
agedth10	1.929	1.124	3.311
ADINDEX_II	**4.015**	**2.118**	**7.612**
uVBIindex_ii	**2.110**	**1.347**	**3.305**
LBINDEX_II	1.860	0.981	3.527
hs_pureii	**2.880**	**1.239**	**6.694**
tdp_pureii	1.465	0.774	2.773
tdpHS_mixii	**2.484**	**1.151**	**5.361**

90 PLUS STUDY N= 373

Logistic Model: Odds Ratio Estimates DEPENDENT VARIABLE: COGNITIVE IMPAIRMENT UNIMPAIRED=0 MOD=1 SEVERE=2			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
edgp3	0.571	0.404	0.807
agedth10	0.940	0.534	1.655
ADINDEX_II	**2.678**	**1.787**	**4.015**
uVBIindex_ii	**2.808**	**1.035**	**7.622**
LBINDEX_II	1.558	0.860	2.822
hs_pureii	1.470	0.616	3.505
tdp_pureii	**2.498**	**1.553**	**4.016**
tdpHS_mixii	**9.553**	**2.780**	**32.831**

Logistic Regression Models (Second Set)

A second set of logistic regression models replacing the six specific NC with three "dummy variables" for 1, 2, or 3+ levels of the total neuropathologic burden.

A central conclusion of this report is that the influence of several different types of brain lesion (i.e., neuropathologic changes – NC) on cognitive impairment appears most strongly related to the ***total neuropathologic burden***. For this report we elect to define each brain's neuropathologic burden based on how many different types of NC were observed in each subject's brain. Our data do not allow actual measurement of volumes or masses of brain tissue injured or disrupted, since the available assessments are almost entirely limited to neuropathologic diagnoses -- based on the presence or absence of specific types of neuropathologic change without descriptions of regional distributions. We infer that different types of NC likely disrupt different regions and different neural systems, so that the injuries inflicted by two, three, or four different types of NC are more widely distributed than if only a single type of NC were involved. We recognize the weakness of this inference since a single type of NC that was more severe might well be widely distributed. Nonetheless, the results of this analysis demonstrate that individuals with fewer different types of NC are less likely to be severely impaired than other individuals with multiple types of NC.

To demonstrate the greater impact on cognitive impairment of multiple different types of NC within each brain we generated three "dummy" variables for the three cohort analyses. They were:

One NC, any type	values:	1= observed	0=all others (reference)
Two NC, any type	values:	1= observed	0=all others (reference)
Three or more NC, any type	values:	1= observed	0=all others (reference)

Results shown below show a dramatic (exponential) increase in the Odds Ratios for impairment with increasing burden.

NUN STUDY N= 363

Logistic Model: Odds Ratio Estimates
DEPENDENT VARIABLE: COGNITIVE IMPAIRMENT
UNIMPAIRED=0 MOD=1 SEVERE=2

Effect	Point Estimate	95% Wald Confidence Limits	
edgp3	0.495	0.339	0.722
agedth10	1.475	0.975	2.231
One NC, any type	**4.257**	**2.685**	**6.749**
Two NC, any type	**11.918**	**6.203**	**22.899**
>=3 NC, any type	**88.224**	**10.889**	**714.790**

HONOLULU-ASIA AGING STUDY N= 304

Logistic Model: Odds Ratio Estimates DEPENDENT VARIABLE: COGNITIVE IMPAIRMENT UNIMPAIRED=0 MOD=1 SEVERE=2			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
edgp3	0.507	0.362	0.710
agedth10	1.821	1.061	3.127
One NC, any type	**1.858**	**1.081**	**3.194**
Two NC, any type	**4.278**	**2.307**	**7.931**
>=3 NC, any type	**25.136**	**7.492**	**84.336**

90 PLUS STUDY N= 373

Logistic Model: Odds Ratio Estimates DEPENDENT VARIABLE: COGNITIVE IMPAIRMENT UNIMPAIRED=0 MOD=1 SEVERE=2			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
edgp3	0.575	0.408	0.810
agedth10	1.048	0.601	1.827
One NC, any type	**2.151**	**1.345**	**3.438**
Two NC, any type	**7.247**	**4.005**	**13.111**
>=3 NC, any type	**9.444**	**3.560**	**25.055**

Logistic Regression Models (Third Set)

A third set of logistic regression model with the six NC variables replaced by a single variable that is simply the count of the number of different types of NC observed in a subject's brain.

We then repeated the logistic analyses for each of the three cohorts, limiting the predictor variables to education, age at death, and *a single variable representing the total number of different NC observed in each brain*. The estimated odds ratios *for each level of total neuropathologic burden* (values of 1, 2, or 3+).

Results of these several logistic models are shown below.

NUN STUDY N= 363

Logistic Model: Odds Ratio Estimates DEPENDENT VARIABLE: COGNITIVE IMPAIRMENT UNIMPAIRED=0 MOD=1 SEVERE=2			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
edgp3	0.495	0.339	0.723
agedth10	1.469	0.971	2.220
No. of different NC types	**3.732**	**2.792**	**4.987**

(Values: 0, 1, 2, or 3+)

HONOLULU-ASIA AGING STUDY N= 304

Logistic Model: Odds Ratio Estimates DEPENDENT VARIABLE: COGNITIVE IMPAIRMENT UNIMPAIRED=0 MOD=1 SEVERE=2			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
edgp3	0.515	0.368	0.719
agedth10	1.848	1.085	3.147
No. of different NC types	**2.361**	**1.807**	**3.086**

(Values: 0, 1, 2, or 3+)

90 PLUS STUDY N= 373

Logistic Model: Odds Ratio Estimates DEPENDENT VARIABLE: COGNITIVE IMPAIRMENT UNIMPAIRED=0 MOD=1 SEVERE=2			
Effect	**Point Estimate**	**95% Wald Confidence Limits**	
edgp3	0.495	0.339	0.723
agedth10	1.469	0.971	2.220
No. of different NC types	**3.732**	**2.792**	**4.987**

(Values: 0, 1, 2, or 3+)

These logistic models demonstrate that the total neuropathologic burden, measured/estimated as the number of different types NC observed in each brain, was nearly as impactful as when each of the six different types of NC were collectively considered as six individual NC.

General Linear Regression Models

General linear regression models comparing total variance explained for models with all six NC as independent variables, with models using a single variable representing the total neuropathologic burden.

To confirm these observations, we then carried out parallel general linear model regression analyses in the three cohorts using each individual's final cognitive test score as the dependent variable. A first model included education, age at death, and the six NC as independent predictor variables. A second model was then done with the six NC variables replaced by a single summary NC variable defined only as the total number of different NC observed in each brain. The first and second models were then compared based on total variance explained. As shown below, the variances explained using only a single variable for all possible combinations of NC were only slightly less than when each NC was considered individually.

NUN STUDY N= 363

Nun Study -- FIRST General linear model:

Dependent variable: final CERAD neuropsychologic test score
Predictor variables: age at death (in decades), education (3 strata), AD NC, microvascular brain injury NC, cortical Lewy body NC, pure hippocampal sclerosis NC, pure TDP-43 NC, mixed hippocampal sclerosis/TDP-43 NC

TOTAL VARIANCE EXPLAINED: 37.4%

Nun Study -- SECOND General linear model:

Dependent variable: final CERAD neuropsychologic test score
Predictor variables: age at death (in decades), education (3 strata), total neuropathologic burden as number of different types of NC observed with values of 0, 1, 2, or >=3

TOTAL VARIANCE EXPLAINED: 33.5%

HONOLULU-ASIA AGING STUDY N= 304

Honolulu-Asia Aging Study -- FIRST General linear model:

Dependent variable: final CASI neuropsychologic test score
Predictor variables: age at death (in decades), education (3 strata), AD NC, microvascular brain injury NC, cortical Lewy body NC, pure hippocampal sclerosis NC, pure TDP-43 NC, mixed hippocampal sclerosis/TDP-43 NC

TOTAL VARIANCE EXPLAINED: 26.8%

Honolulu-Asia Aging Study -- SECOND General linear model:

Dependent variable: final CASI neuropsychologic test score
Predictor variables: age at death (in decades), education (3 strata), total neuropathologic burden as number of different types of NC observed with values of 0, 1, 2, or >=3

TOTAL VARIANCE EXPLAINED: 23.2%

90 PLUS STUDY N= 373

90 PLUS Study -- FIRST General linear model:

Dependent variable: final MMSE neuropsychologic test score
PREDICTOR VARIABLES: age at death (in decades), education (3 strata), AD NC, microvascular brain injury NC, cortical Lewy body NC, pure hippocampal sclerosis NC, pure TDP-43 NC, mixed hippocampal sclerosis/TDP-43 NC

TOTAL VARIANCE EXPLAINED: 21.5%

90 PLUS study – second General linear model:

Dependent variable: final CERAD neuropsychologic test score
Predictor variables: age at death (in decades), education (3 strata), total neuropathologic burden as number of different types of NC observed with values of 0, 1, 2, or >=3

TOTAL VARIANCE EXPLAINED: 18.9%

Concluding Comment

This report is intended to focus our attention on the challenges of future prevention strategies. If these observations are generalizable to the general population, they imply that future preventive intervention strategies that are limited to any single type of NC, or even to any set of two NC types (as Alzheimer's and microvascular) are likely to be modest and probably not demonstrable with the types of intervention study design now commonly used. If we hope to ever achieve effective prevention of late life dementia, the targets will likely have to include all or most of these six NC types.

This very disturbing conclusion implies a great need for research addressing all of the relevant NC and their individual pathogenic mechanisms to develop methods for their detection and measurement during life.