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Original Article

Association of vascular and degenerative brain pathologies and past medical history from the National Alzheimer's Coordinating Center Database

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ABSTRACT

The relationship between past medical histories (PMH) and dementia-related neuropathologies is not well understood. Using the National Alzheimer's Coordinating Center (NACC) database, we explored the relationship between patient-reported PMH and various vascular and degenerative neuropathologies. We examined the following PMH: transient ischemic attack (TIA), stroke, traumatic brain injury, seizures, hypertension, cardiovascular events, hypercholesterolemia, B12 deficiency, diabetes mellitus, and thyroid disease. We dichotomized the following neuropathologies: atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy (CAA), Alzheimer disease neuropathology (ADNP), Lewy bodies (LB), hippocampal sclerosis, frontotemporal lobar degeneration (FTLD), and TAR DNA-binding protein-43 (TDP-43). Separate logistic regression models assessed the relationship between the outcome of individual neuropathologies and all PMHs. Additional logistic regressions were stratified by sex to further examine these associations. Hypertension history was associated with an increased likelihood of atherosclerosis (OR = 1.7) and arteriolosclerosis (OR = 1.3), but decreased odds of ADNP (OR = 0.81), CAA (OR = 0.79), and LB (OR = 0.78). History of TIA was associated with an increased likelihood of atherosclerosis (OR = 1.3) and arteriolosclerosis (OR = 1.4) and lower odds of ADNP (OR = 0.72). Seizure history was associated with an increased likelihood of ADNP (OR = 1.9) and lower odds of FTLD (OR = 0.49). Hypertension history was associated with a greater likelihood of vascular pathologies yet a lower likelihood of ADNP and other neurodegenerative pathologies.

KEYWORDS: Alzheimer disease, Arteriolosclerosis, Atherosclerosis, Diabetes mellitus, Hypertension, Lewy bodies, Neuropathology

INTRODUCTION

Degenerative and vascular pathologies are considered the necessary requirement for the development of cognitive impairment and dementia in older individuals. Many of these pathologies accumulate over the years and identification of their risk factors is important in modifying their course (1–3). Past medical history (PMH) data provide a window to previous exposure to diseases that can be risk factors for the future development of neuropathologies. Although multiple studies have investigated the relationship between various past medical histories and clinical dementia outcomes (4–22), the association between PMH and specific degenerative pathologies is less well understood. The select studies that have explored the relation between PMH and degenerative pathologies have mainly focused on the impact of vascular diseases on pathologies (23, 24).

Given the sizeable and increasing burden of dementia worldwide, it is imperative to investigate specific relationships between dementia-causing pathologies and the history of common diseases to recognize modifiable risk factors. The large-scale multicenter National Alzheimer's Coordinating Center (NACC) database provides an unprecedented opportunity for addressing this important issue.

MATERIALS AND METHODS

Database

The NACC maintains a large database that includes standardized, longitudinal measures collected for over 20 years from more than 42 Alzheimer's Disease Research Centers (ADCs) across 26 different states. The NACC Uniform Data Set (5) collects participants' demographics, medical history, and neuropsychological measures (5, 25). Furthermore, study participants are accompanied by a study partner who can provide additional information regarding the participant's medical and cognitive history. Follow-up visits occur annually. One major drawback of the NACC database population is the lack of racial and ethnic diversity that is reflective of recruitment practices at local level. Therefore, NACC participants are more of

a convenience cohort and not a population-based sample. Version 3 of the UDS was implemented in March 2015 and contains an updated set of questions in the medical history form (26). The Neuropathology (NP) Form records neuropathological findings at autopsy with the Version 10 form, implemented in January 2014 (27). In addition to new variables added to the Version 10 form, variables from previous forms were incorporated. The NACC utilizes standard guidelines for the classification of various neurodegenerative pathologies (28). Version 3 of the UDS and Version 10 of the NP Form were used to assess the variables in the current study. Version 3 of the UDS and Version 10 of NP Form also incorporate variables from the previous versions enabling the inclusion of historic cases that preceded these versions. Longitudinal assessments and neuropathological data for 5863 participants between September 2005 and March 2019 were acquired. Two hundred and forty-eight participants were excluded due to having any of the following disorders: multiple system atrophy, prion disease, pigment-spheroid degeneration, trinucleotide disease, cortical development malformation, metabolic or storage disorder, leukodystrophy, demyelinating disease (including multiple sclerosis), neoplasm (primary or metastatic), infectious process, herniation, and Down syndrome. Additionally, to minimize possible undocumented changes in medical history, 506 participants whose last visit was more than 4 years before death were excluded resulting in a total of 5136 participants eligible for analysis. We used data from the last visit to assess the cumulative medical history.

Standard protocol approvals, registrations, and patient consent

Individual ADCs are responsible for obtaining IRB approval and acquiring written informed consent of participants.

NACC variables

Each participant's health history was assessed using the NACC medical history form which is completed by both the participant and their accompanying study partner. Of the 38 variables collected, the following were selected: transient ischemic attack (TIA), traumatic brain injury (TBI), stroke, seizures, hypertension, hypercholesterolemia, diabetes, B12 deficiency, and thyroid disease. Additionally, the presence of 1 or more of the following cardiovascular histories resulted in a positive cardiovascular composite score: heart attack, atrial fibrillation, angioplasty, cardiac bypass surgery, and congestive heart failure. A total of 24/38 PMH variables from the Subject Health History form were not included in the analysis mostly due to over 50% missingness of data points. Several of these variables with higher rates of missingness were implemented in UDS Version 3, a form version that only 1074 (20.9%) participants were given. As participants were not excluded by their completed version form, we considered PMH variables that were consistent across the forms. Each of the included variables was dichotomized as "absent" if there was no reported history or "present". "Present" was further divided as "recent/active" for events that happened within a year of the last visit/were actively being treated, and "remote/inactive" for events that took place more than a year prior, had been resolved, or for which participants were not undergoing treatment. Recent and remote cases were eventually combined for analysis as the number of remote cases for each medical history was too small to enable studying them independently.

We considered the following neuropathologies for analysis: atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy (CAA), Alzheimer disease neuropathology (ADNP), Lewy body (LB), hippocampal sclerosis of aging (HS), frontotemporal lobar degeneration (FTLD), infarcts, microinfarcts, and TAR DNA-binding protein 43 (TDP-43). As some pathologies, such as FTLD and HS, are already dichotomized at the time of data collection, all neuropathologies were dichotomized to maintain consistency. Infarcts and microinfarcts were dichotomized as present versus absent. CAA, atherosclerosis, and arteriolosclerosis were dichotomized as absent (for cases that had been scored as none or mild) or present (for pathological ratings of moderate or severe). ADNP was defined as present in those with Braak tau-tangle Stages IV, V, or VI and moderate or frequent amyloid neuritic plaques. LB was dichotomized as present (for those with the limbic, amygdala, or neocortical Lewy bodies) or absent (none or limited to olfactory bulb or brainstem). All subtypes of FTLD were combined into 1 variable that was dichotomized as present or absent. An exploratory assessment of FTLD subdivided by underlying pathology (tau, TDP-43, and ubiquitin) has been included as well (Supplementary Data Table S1). Version 10 of the NP Form added the variable HS to replace an older variable, medial temporal lobar sclerosis (MTLS). Therefore, we combined the 2 variables into 1 variable dichotomized as present (unilateral or bilateral HS or presence of MTLS) or absent (absence of HS or MTLS).

Similar to HS, TDP-43 is a new variable added to the NP Form Version 10 and had been collected in 1630 of 5136 participants. Furthermore, of the TDP-43 data collected, some samples were only assessed in 1 or 2 regions rather than the 4 indicated on the NP Form. Therefore, to assess TDP-43 in this cohort, we took a subset of participants ($n = 940$) who had available TDP-43 data in all 4 regions including the amygdala, hippocampus, inferior temporal cortex, and neocortex. Participants were not excluded based on the presence or absence of FTLD. TDP-43 was then dichotomized in this sample as present (present in the hippocampus, inferior temporal cortex, and/or neocortex) or absent (none or amygdala only).

Statistical analysis

Logistic regression models were used to assess the relationship between PMH and individual neuropathologies. The covariates of the model included age of death, sex, race, and education. An additional logistic regression model stratified the group by sex to explore the relationship between PMH variables and pathology in males and females separately. Chi squares were performed to assess the differences in the observed versus expected prevalence of pathology or PMH across the sexes. JASP (Version 0.11.1, 2019) was used to perform the statistical analysis and RStudio (Version 1.1.456, 2018) was used for handling and organizing data.

Table 1. Demographics, frequency of PMH, and association between PMH and neuropathology for all participants and TDP-43 subsample

	All participants (n = 5136)	Male (n = 2847)	Female (n = 2289)	TDP-43 subsample (n = 940)
Age of death (mean [SD])	80.2 (11.5)	78.8 (11.0)	**82.1 (11.8)****	**78.1 (11.9)****
Months between last visit and death (mean [SD])	13.1 (11.1)	13.0 (11.0)	13.3 (11.3)	**15.6 (12.5)****
Sex (% male)	55.4	100	0	55.3
Race (% White)	94.2	95.7	93.2**	93.1
Education years (mean [SD])	15.3 (3.17)	16.0 (3.21)	**14.6 (2.95)****	**15.7 (3.03)****
College education or higher (%)	60.2	68.6	**49.7****	**63.7****

The cardiovascular composite score includes participants who had a heart attack, atrial fibrillation, angioplasty, cardiac bypass surgery, and/or congestive heart failure. Asterisks represent significant differences between males and females and between all participants and TDP-43 subsample; bolded significant findings.

* $p < 0.05$.

** $p < 0.001$.

Table 2. Prevalence of past medical histories in all participants, stratified by sex and cognitive status

	No dementia (N = 1009)	Dementia (N = 4127)	TDP-43 subsample (N = 940)
Hypertension (%) (N = 4311)	550 (68.1)	**1859 (55.5)****	73 (57.5)
Transient ischemic attack (TIA) (%) (N = 4252)	111 (13.9)	**325 (9.8)***	5 (4.0)
Seizures (%) (N = 4291)	28 (3.5)	**269 (8.1)****	3 (9.5)
Traumatic brain injury (TBI) (%) (N = 4250)	112 (13.8)	438 (13.3)	14 (11.0)
Hypercholesterolemia (%) (N = 4277)	414 (51.9)	1808 (54.3)	75 (58.6)
Diabetes (%) (N = 4323)	121 (14.9)	**403 (12.0)***	13 (10.2)
Thyroid disease (%) (N = 4309)	238 (29.5)	**706 (21.1)****	28 (22.0)
B-12 deficiency (%) (N = 4265)	69 (8.7)	311 (9.4)	12 (9.5)
Stroke (%) (N = 4300)	101 (12.5)	379 (11.4)	6 (4.7)
Cardiovascular score (%) (N = 4313)	368 (45.5)	**971 (29.0)****	37 (29.4)

The cardiovascular composite score includes participants who had a heart attack, atrial fibrillation, angioplasty, cardiac bypass surgery, and/or congestive heart failure. No dementia includes participants with normal cognition, cognitive impairment with no dementia, and mild cognitive impairment. Significant group differences in the prevalence of the past medical history are bolded.

* $p < 0.05$.

** $p < 0.001$.

Data availability

The NACC is a publicly available dataset and can be accessed by all qualified researchers.

RESULTS

Of the 5863 participants in the total sample, only participants with available NACC data, no known neurological disorders, and a time interval of 4 years or less between their last visit and death were included for analysis resulting in a final sample of 5136 participants. The mean age at death was 80.2 ± 11.5 years, the average time interval between the last visit and death was 13.1 ± 11.1 months, 55.4% were men, 94.2% were White, and 60.2% completed college education or higher (Table 1). The average age at death in the male population was 78.8 ± 11.0 years whereas the average age of death for females was 82.1 ± 11.8 years old ($p < 0.001$). The sample included for analyses statistically differed from the sample we excluded due to the time interval (≥4 years) between their last visit and death. Using a Chi-square test, sex distribution, average age of death, and education demonstrated a significant difference between the 2 groups. However, the overall average values were comparable. Additionally, we estimated the prevalence of PMH across cognitive status (Table 2) and sex (Table 3). Further, we examined the prevalence of neuropathologies (Table 4), and the frequency of PMH in each neuropathology (Table 5). Hypertension (57.9%) was the most commonly reported PMH followed by hypercholesteremia (53.9%). A significant group difference in gender was found in hypertension, TIA, seizures, diabetes, thyroid disease, and cardiovascular events. Further, we found a significant group difference among individuals with and without dementia with a greater frequency of hypertension, TIA, diabetes, thyroid disease, and cardiovascular score among individuals with no dementia. However, seizures had a greater frequency among individuals with dementia.

Among the neuropathologies, ADNP was most prevalent in the sample (55.8%) followed by arteriolosclerosis (42.7%) and atherosclerosis (38.7%). Presence of atherosclerosis (OR = 1.8 [1.68–1.96]), arteriolosclerosis (OR = 1.2 [1.16–1.34]), microinfarcts (OR = 1.6 [1.41–1.71]), infarcts (OR = 1.6 [1.46–1.77]), CAA (OR = 1.0 [0.98–1.12]), and HS (OR = 1.4 [1.22–1.52]) were associated with an older age at death, while, as expected, FTLD had an association with a younger age at death (OR = 0.7 [0.67–0.79]) (Table 5). Education was not significantly associated with the presence of any pathology.

We examined the relationship between PMH and neuropathologies using logistic regression models (Table 5). History of hypertension had contrasting associations with vascular versus neurodegenerative pathologies. While hypertension was associated with an increased likelihood of atherosclerosis (OR = 1.7 [1.44–1.97]), arteriolosclerosis (OR = 1.3 [1.11–1.52]), microinfarcts (OR = 1.3 [1.09–1.60]), and infarcts (OR = 1.27 [1.04–1.52]), it was associated with a decreased likelihood of ADNP (OR = 0.81 [0.70–0.94]), CAA (OR = 0.79 [0.68–0.92]), and LB (OR = 0.78 [0.66–0.92]). Also, the history of TIA was associated with an increased likelihood of atherosclerosis (OR = 1.3 [1.02–1.63]), arteriolosclerosis (OR = 1.4 [1.13–1.84]), microinfarcts (OR = 1.5 [1.19–1.96]), and infarcts (OR = 1.6 [1.24–2.05]), but the decreased likelihood of ADNP (OR = 0.7 [0.57–0.90]). Hypercholesterolemia was associated with an increased likelihood of CAA (OR = 1.2 [1.06–1.44]) and ADNP (OR = 1.2 [1.05–1.39]). Seizures were associated with an increased likelihood of ADNP (OR = 1.9 [1.41–2.49]), but a reduced likelihood of FTLD (OR = 0.5 [0.34–0.71]). History of stroke was associated with an increased likelihood of arteriolosclerosis (OR = 1.6 [1.23–1.97]), atherosclerosis (OR = 1.7 [1.38–2.17]), microinfarcts (OR = 1.9 [1.49–2.39]), and infarcts (OR = 3.8 [3.06–4.82]) across all participants, but the decreased likelihood of LB (OR = 0.5 [0.39–0.71]). Decreased likelihood of CAA (OR = 0.83 [0.70–0.98]), ADNP (OR = 0.69, [0.59–0.81]), HS (OR = 0.75 [0.58–0.96]), and FTLD (OR = 0.81 [0.67–0.98]) were associated with cardiovascular events. Diabetes was associated with an increased likelihood of infarcts (OR = 1.4 [1.13–1.85]). Finally, no significant associations were found for thyroid disease or B12 deficiency.

We further stratified the groups by sex to examine differential relationships between PMH and neuropathologies (Table 6). We found in both sexes atherosclerosis (males OR = 1.8 [1.64–2.02]; females OR = 1.8 [1.61–2.04]), arteriolosclerosis (males OR = 1.3 [1.15–1.40]; females OR = 1.2 [1.01–1.34]), infarcts (males OR = 1.7 [1.51–1.97]; females OR = 1.5 [1.28–1.69]), microinfarcts (males OR = 1.5 [1.32, 1.70]; females OR = 1.6 [1.40–1.87]), and HS (males OR = 1.4 [1.22–1.65]; females OR = 1.3 [1.08–1.52]) remained associated with an older age while FTLD remained associated with a younger age of death (males OR = 0.77 [0.69–0.85]; females OR = 0.69 [0.61–0.77]). In both sexes, hypertension continued to be associated with an increased likelihood of atherosclerosis (males OR = 1.7 [1.37–2.09]; females OR = 1.6 [1.29–2.09]). Hypertension was also associated with an increased likelihood of arteriolosclerosis (OR = 1.5 [1.18–1.91]), infarcts OR = 1.4 [1.04–1.84]), and microinfarcts (OR = 1.4 [1.01–1.81]) in females only. Similarly, hypertension continued to be associated with an increased likelihood of microinfarcts among males (OR = 1.3 [1.03–1.71]). Furthermore, hypertension only remained associated with a reduced likelihood of LB (OR = 0.66 [0.50–0.87]) and CAA (OR = 0.76 [0.59–0.97]) in females. Hypertension continued to be associated with a reduced likelihood of ADNP (OR = 0.73 [0.60–0.88]) in males but not females.

An association between TIA and an increased likelihood of microinfarcts persisted across both sexes (males OR = 1.6 [1.13–2.17]; females OR = 1.5 [1.01–2.18]). TIA was also associated with an increased likelihood of atherosclerosis (OR = 1.5 [1.05–2.22]), arteriolosclerosis (OR = 1.7 [1.21–2.30]), and infarcts (OR = 1.7 [1.21–2.36]) among males whereas a decreased likelihood of ADNP (OR = 0.52 [0.36–0.75]) in relation with TIA remained in females only. A new

Table 3. Prevalence of neuropathologies in all participants and stratified by sex

	All participants	Male	Female
Atherosclerosis (%) (N = 5079)	1966 (38.7)	**1026 (36.4)****	940 (41.5)
Arteriolosclerosis (%) (N = 4551)	1944 (42.7)	**1023 (40.8)***	921 (45.1)
Infarcts (%) (N = 5113)	981 (19.2)	**514 (18.1)***	467 (20.5)
Microinfarcts (%) (N = 5120)	1022 (20.0)	544 (19.2)	478 (20.1)
CAA (%) (N = 5010)	1549 (30.9)	884 (31.8)	665 (29.9)
ADNP (%) (N = 5053)	2885 (55.8)	1544 (55.2)	1276 (56.5)
HS (%) (N = 4946)	558 (11.3)	296 (10.8)	262 (11.8)
LB (%) (N = 5105)	1311 (25.7)	**805 (28.4)****	506 (22.3)
FTLD (%) (N = 5136)	1165 (22.7)	**679 (23.8)***	486 (21.2)

"N" for each of the neuropathological variables represents the number of individuals with data for that variable. Asterisks represent significant differences in male: female comparison; bolded significant findings.
* $p < 0.05$.
** $p < 0.001$.
ADNP, Alzheimer disease neuropathology; CAA, cerebral amyloid angiopathy; FTLD, frontotemporal lobar degeneration; HS, hippocampal sclerosis; LB, Lewy body.

Table 4. Frequency of past medical history variables for each neuropathologic feature

	Arteriolosclerosis (N = 1944)	Atherosclerosis (N = 1966)	Infarcts (N = 981)	Microinfarcts (N = 1022)	CAA (N = 1549)	ADNP (N = 2885)	HS (N = 558)	LB (N = 1311)	FTLD (N = 1165)
Hypertension (%)	970 (63.7)	1108 (69.1)	600 (69.7)	550 (68.3)	675 (54.6)	1259 (55.7)	261 (60.1)	533 (52.8)	533 (52.8)
Transient ischemic attack (TIA) (%)	206 (13.7)	229 (14.6)	166 (19.8)	136 (17.2)	125 (10.3)	206 (9.3)	54 (12.6)	96 (9.6)	96 (9.6)
Seizures (%)	115 (7.6)	104 (6.5)	62 (7.2)	54 (6.8)	109 (8.9)	201 (9.0)	30 (6.9)	86 (8.6)	86 (8.6)
Traumatic brain injury (TBI) (%)	204 (13.6)	188 (11.9)	110 (13.0)	113 (14.2)	159 (13.0)	281 (12.7)	54 (12.7)	138 (13.9)	138 (13.4)
Hypercholesterolemia (%)	843 (56.0)	867 (54.7)	479 (56.2)	455 (57.1)	682 (55.7)	1219 (54.5)	229 (53.8)	544 (54.3)	544 (54.3)
Diabetes (%)	210 (13.8)	213 (13.3)	156 (18.1)	119 (14.8)	140 (11.3)	267 (11.8)	46 (10.6)	106 (10.5)	106 (10.5)
Thyroid disease (%)	369 (24.3)	409 (25.5)	211 (24.5)	186 (23.3)	276 (22.4)	493 (21.9)	102 (23.6)	197 (19.6)	197 (19.6)
B-12 deficiency (%)	151 (10.0)	157 (9.9)	91 (10.7)	78 (10.0)	111 (9.1)	197 (8.8)	37 (8.6)	93 (9.3)	93 (9.3)
Stroke (%)	236 (15.6)	268 (16.8)	248 (29.0)	166 (20.8)	147 (12.0)	236 (10.5)	54 (12.6)	77 (7.6)	77 (7.6)
Cardiovascular score (%)	542 (35.6)	617 (38.5)	375 (43.6)	316 (39.4)	369 (29.9)	645 (28.6)	133 (30.9)	298 (29.5)	298 (29.5)

ADNP, Alzheimer disease neuropathology; CAA, cerebral amyloid angiopathy; FTLD, frontotemporal lobar degeneration; HS, hippocampal sclerosis; LB, Lewy body; N, the number of individuals who have the specified neuropathology.

Table 5. Relationship between neuropathologies and past medical histories in all participants

	Arteriolosclerosis (N = 4551)	Atherosclerosis (N = 5079)	Infarcts (N = 5113)	Microinfarcts (N = 5120)	CAA (N = 5010)	ADNP (N = 5053)	HS (N = 4946)	LB (N = 5105)	FTLD (N = 5136)
Age of death	**OR = 1.247****	**OR = 1.816****	**OR = 1.606****	**OR = 1.552****	OR = 1.047	OR = 1.039	**OR = 1.360****	OR = 0.964	**OR = 0.727****
	p < 0.001	**p < 0.001**	**p < 0.001**	**p < 0.001**	p = 0.202	p = 0.256	**p < 0.001**	p = 0.336	**p < 0.001**
	[**1.16–1.34**]	[**1.68–1.96**]	[**1.46–1.77**]	[**1.41–1.71**]	[0.98–1.12]	[0.97–1.11]	[**1.22–1.52**]	[0.90–1.04]	[**0.67–0.79**]
Male	OR = 0.878	OR = 0.976	OR = 0.942	OR = 1.054	**OR = 1.201***	OR = 1.049	OR = 1.156	**OR = 1.571****	OR = 0.933
	p = 0.101	p = 0.757	p = 0.530	p = 0.576	**p = 0.021**	p = 0.513	p = 0.226	**p < 0.001**	p = 0.424
	[0.75–1.03]	[0.84–1.14]	[0.78–1.14]	[0.88–1.27]	[**1.03–1.40**]	[0.91–1.21]	[0.91–1.46]	[**1.33–1.86**]	[0.79–1.11]
Race (not White)	OR = 1.029	OR = 1.338	**OR = 1.720***	OR = 1.422	OR = 1.130	OR = 1.256	OR = 1.378	OR = 1.071	**OR = 0.516***
	p = 0.860	p = 0.083	**p = 0.003**	p = 0.060	p = 0.491	p = 0.161	p = 0.182	p = 0.711	**p = 0.004**
	[0.75–1.42]	[0.96–1.86]	[**1.20–2.27**]	[0.99–2.05]	[0.80–1.60]	[0.91–1.73]	[0.86–2.21]	[0.75–1.54]	[**0.33–0.81**]
Education	OR = 0.933	OR = 0.954	OR = 0.988	OR = 0.857	OR = 0.951	OR = 0.960	OR = 1.192	OR = 0.970	OR = 1.113
	p = 0.366	p = 0.538	p = 0.894	p = 0.086	p = 0.513	p = 0.565	p = 0.131	p = 0.709	p = 0.205
	[0.80–1.08]	[0.82–1.11]	[0.83–1.18]	[0.72–1.02]	[0.82–1.11]	[0.84–1.10]	[0.95–1.50]	[0.83–1.14]	[0.94–1.31]
Hypertension (N = 4158)	**OR = 1.295****	**OR = 1.679****	**OR = 1.256***	**OR = 1.325***	**OR = 0.789***	**OR = 0.813***	OR = 0.939	**OR = 0.775***	OR = 1.046
	p = 0.001	**p < 0.001**	**p = 0.020**	**p = 0.004**	**p = 0.003**	**p = 0.006**	p = 0.599	**p = 0.003**	p = 0.615
	[**1.11–1.52**]	[**1.44–1.97**]	[**1.04–1.52**]	[**1.09–1.60**]	[**0.68–0.92**]	[**0.70–0.94**]	[0.74–1.19]	[**0.66–0.92**]	[0.88–1.24]
Transient ischemic attack (TIA) (N = 4100)	**OR = 1.441***	**OR = 1.274***	**OR = 1.596****	**OR = 1.527****	OR = 0.931	**OR = 0.715***	OR = 1.050	OR = 0.970	OR = 0.903
	p = 0.004	**p = 0.036**	**p < 0.001**	**p < 0.001**	p = 0.572	**p = 0.004**	p = 0.782	p = 0.828	p = 0.496
	[**1.13–1.84**]	[**1.02–1.60**]	[**1.24–2.05**]	[**1.19–1.96**]	[0.73–1.19]	[**0.57–0.90**]	[0.74–1.49]	[0.74–1.27]	[0.67–1.21]
Seizures (N = 4142)	OR = 1.227	OR = 1.082	OR = 1.062	OR = 1.113	OR = 1.306	**OR = 1.870****	OR = 1.161	OR = 1.144	**OR = 0.486****
	p = 0.168	p = 0.607	p = 0.745	p = 0.549	p = 0.063	**p < 0.001**	p = 0.496	p = 0.378	**p < 0.001**
	[0.92–1.64]	[0.80–1.46]	[0.74–1.52]	[0.78–1.58]	[0.99–1.73]	[**1.41–2.49**]	[0.76–1.79]	[0.85–1.54]	[**0.34–0.71**]
Traumatic brain injury (TBI) (N = 4101)	OR = 1.122	OR = 0.825	OR = 0.922	OR = 1.055	OR = 0.970	OR = 0.871	OR = 0.972	OR = 1.025	OR = 1.098
	p = 0.290	p = 0.081	p = 0.538	p = 0.673	p = 0.781	p = 0.168	p = 0.864	p = 0.829	p = 0.427
	[0.91–1.39]	[0.67 1.02]	[0.72–1.19]	[0.82–1.35]	[0.79–1.20]	[0.72–1.06]	[0.70–1.34]	[0.82–1.28]	[0.87–1.38]
Hypercholesterolemia (N = 4124)	OR = 1.016	OR = 0.911	OR = 0.876	OR = 1.072	**OR = 1.237***	**OR = 1.206***	OR = 1.219	OR = 1.142	OR = 0.985
	p = 0.837	p = 0.228	p = 0.155	p = 0.453	**p = 0.006**	**p = 0.009**	p = 0.089	p = 0.108	p = 0.858
	[0.87–1.18]	[0.78–1.06]	[0.73–1.05]	[0.89–1.29]	[**1.06–1.44**]	[**1.05–1.39**]	[0.97–1.53]	[0.97–1.34]	[0.83–1.16]
Diabetes (N = 4170)	OR = 0.995	OR = 0.916	**OR = 1.442***	OR = 0.930	OR = 0.818	OR = 0.932	OR = 0.793	OR = 0.821	OR = 0.993
	p = 0.965	p = 0.436	**p = 0.004**	p = 0.586	p = 0.092	p = 0.510	p = 0.209	p = 0.122	p = 0.957
	[0.80–1.24]	[0.74–1.14]	[**1.13–1.85**]	[0.72–1.21]	[0.65–1.03]	[0.76–1.15]	[0.55–1.14]	[0.64–1.05]	[0.77–1.28]
Thyroid disease (N = 4156)	OR = 1.016	OR = 0.966	OR = 0.896	OR = 0.863	OR = 1.007	OR = 0.933	OR = 0.990	OR = 0.869	OR = 0.963
	p = 0.857	p = 0.696	p = 0.303	p = 0.168	p = 0.942	p = 0.410	p = 0.943	p = 0.165	p = 0.717
	[0.86–1.21]	[0.81–1.15]	[0.73–1.10]	[0.70–1.06]	[0.84–1.21]	[0.79–1.10]	[0.76–1.29]	[0.71–1.06]	[0.79–1.18]
B-12 deficiency (N = 4114)	OR = 1.018	OR = 0.964	OR = 1.109	OR = 0.988	OR = 0.959	OR = 0.946	OR = 0.943	OR = 1.103	OR = 1.048
	p = 0.887	p = 0.770	p = 0.481	p = 0.933	p = 0.749	p = 0.643	p = 0.766	p = 0.473	p = 0.742
	[0.80–1.30]	[0.75–1.24]	[0.83–1.48]	[0.74–1.32]	[0.74–1.24]	[0.75–1.20]	[0.64–1.38]	[0.84–1.44]	[0.79–1.38]
Stroke (N = 4147)	**OR = 1.562****	**OR = 1.727****	**OR = 3.844****	**OR = 1.884****	OR = 1.048	OR = 0.853	OR = 0.982	**OR = 0.526****	OR = 0.800
	p < 0.001	**p < 0.001**	**p < 0.001**	**p < 0.001**	p = 0.698	p = 0.154	p = 0.919	**p < 0.001**	p = 0.131
	[**1.24–1.97**]	[**1.38–2.17**]	[**3.06–4.83**]	[**1.49–2.39**]	[0.83–1.33]	[0.69–1.06]	[0.69–1.39]	[**0.39–0.71**]	[0.60–1.07]
Cardiovascular score (N = 4160)	OR = 0.953	OR = 0.989	**OR = 1.156**	OR = 0.994	**OR = 0.830***	**OR = 0.691****	**OR = 0.748***	OR = 0.942	**OR = 0.809***
	p = 0.570	p = 0.892	**p = 0.132**	p = 0.952	**p = 0.031**	**p < 0.001**	**p = 0.024**	p = 0.517	**p = 0.032**
	[0.81–1.13]	[0.84–1.16]	[**0.96–1.40**]	[0.82–1.20]	[**0.70–0.98**]	[**0.59–0.81**]	[**0.58–0.96**]	[0.79–1.13]	[**0.67–0.98**]

"N" indicates number of data points for each medical history and neuropathology

* $p < 0.05$.

** $p < 0.001$.

ADNP, Alzheimer disease neuropathology; CAA, cerebral amyloid angiopathy; FTLD, frontotemporal lobar degeneration; HS, hippocampal sclerosis; LB, Lewy body.

association between TIA and a decreased likelihood of FTLD was also found in females only (OR = 0.57 [0.33–0.98]). Males continued to demonstrate an association between hypercholesterolemia and an increased likelihood of CAA (OR = 1.3 [1.05–1.56]) with a new association with HS (OR = 1.4 [1.05–1.97]). Among females, hypercholesterolemia was associated with an increased likelihood of LB (OR = 1.3 [1.01–1.69]). An additional association was found between TBI and a decreased likelihood of ADNP (OR = 0.8 [0.62–0.99]).

Diabetes was found to be associated with a decreased likelihood of LB in males (OR = 0.71 [0.52–0.96]) but not in females. In males only, there was also a new significant association between diabetes and an increased likelihood of infarcts (OR = 1.7 [1.25–2.35]). In both sexes, seizures remained associated with an increased likelihood of ADNP (males OR = 1.9 [1.30–2.68]; females OR = 2.0 [1.28–3.08]), and a decreased likelihood of FTLD (males OR = 0.6 [0.35–0.90]; females OR = 0.4 [0.21–0.70]). In relation to stroke, both sexes maintained an increased likelihood of arteriolosclerosis (males OR = 1.4 [1.01–1.91]; females OR = 1.8 [1.26–2.52]), atherosclerosis (males OR = 1.6 [1.16–2.13]; females OR = 1.9 [1.37–2.73]), infarcts (males OR = 4.3 [3.18–5.90]; females OR = 3.5 [2.47–4.84]), and microinfarcts (males OR = 1.9 [1.35–2.62]; females OR = 1.9 [1.33–2.68]) and a decreased likelihood of LB (males OR = 0.5 [0.35–0.74]; females OR = 0.55 [0.35–0.89]). Further, cardiovascular events were associated with a decreased likelihood of FTLD (OR = 0.8

Table 6. Relationship between neuropathologies and past medical histories stratified by gender

	Male (N = 2847)								
	Arteriolosclerosis (N = 2510)	**Atherosclerosis (N = 2816)**	**Infarcts (N = 2834)**	**Microinfarcts (N = 2837)**	**CAA (N = 2783)**	**ADNP (N = 2796)**	**HS (N = 2731)**	**LB (N = 2833)**	**FTLD (N = 2847)**
Age of death	**OR = 1.272**** **p < 0.001** [**1.15–1.40**]	**OR = 1.817**** **p < 0.001** [**1.64–2.02**]	**OR = 1.726**** **p < 0.001** [**1.51–1.97**]	**OR = 1.497**** **p < 0.001** [**1.32–1.70**]	OR = 1.047 p = 0.339 [0.95–1.15]	OR = 1.027 p = 0.550 [0.94–1.12]	**OR = 1.418**** **p < 0.001** [**1.22–1.65**]	OR = 0.962 p = 0.432 [0.88–1.06]	**OR = 0.768**** **p < 0.001** [**0.69–0.85**]
Race (not White)	OR = 0.982 p = 0.939 [0.61–1.58]	OR = 1.716 p = 0.027 [1.06–2.77]	**OR = 1.740*** **p = 0.043** [**1.02–2.98**]	OR = 1.64 p = 0.065 [0.97–2.76]	OR = 1.131 p = 0.628 [0.69–1.86]	OR = 1.368 p = 0.187 [0.86–2.18]	OR = 0.732 p = 0.475 [0.31–1.73]	OR = 0.934 p = 0.797 [0.56–1.57]	**OR = 0.488*** **p = 0.031** [**0.25–0.94**]
Education	OR = 0.935 p = 0.531 [0.76–1.15]	OR = 0.869 p = 0.184 [0.71–1.07]	OR = 1.040 p = 0.767 [0.80–1.34]	OR = 0.845 p = 0.176 [0.66–1.08]	OR = 1.051 p = 0.636 [0.86–1.29]	OR = 1.096 p = 0.345 [0.91–1.33]	OR = 1.201 p = 0.261 [0.87–1.65]	OR = 0.843 p = 0.106 [0.69–1.04]	OR = 0.997 p = 0.979 [0.80–1.25]
Hypertension (N = 2396)	OR = 1.165 p = 0.161 [0.94–1.44]	**OR = 1.696**** **p < 0.001** [**1.40–2.09**]	OR = 1.194 p = 0.189 [0.92–1.56]	**OR = 1.325*** **p = 0.032** [**1.03–1.71**]	OR = 0.820 p = 0.058 [0.67–1.01]	**OR = 0.742**** **p = 0.001** [**0.60 0.88**]	OR = 0.885 p = 0.439 [0.65–1.21]	OR = 0.835 p = 0.093 [0.68–1.03]	OR = 1.071 p = 0.553 [0.85–1.34]
Transient ischemic attack (TIA) (N = 2369)	**OR = 1.664*** **p = 0.002** [**1.21–2.30**]	OR = 1.185 p = 0.275 [0.87–1.61]	**OR = 1.695*** **p = 0.002** [**1.22–2.36**]	**OR = 1.562*** **p = 0.008** [**1.13–2.17**]	OR = 1.035 p = 0.829 [0.76–1.42]	OR = 0.885 p = 0.416 [0.66–1.19]	OR = 1.341 p = 0.177 [0.88–2.06]	OR = 0.773 p = 0.150 [0.54–1.10]	OR = 1.170 p = 0.386 [0.82–1.67]
Seizures (N = 2383)	OR = 1.282 p = 0.214 [0.87–1.90]	OR = 1.154 p = 0.475 [0.78–1.71]	OR = 1.222 p = 0.409 [0.76–1.97]	OR = 1.103 p = 0.678 [0.69–1.76]	OR = 1.196 p = 0.348 [0.82–1.74]	**OR = 1.893**** **p < 0.001** [**1.30–2.69**]	OR = 1.625 p = 0.068 [0.97–2.74]	OR = 1.012 p = 0.951 [0.68–1.50]	**OR = 0.556*** **p = 0.016** [**0.35–0.90**]
Traumatic brain injury (TBI) (N = 2359)	OR = 1.045 p = 0.742 [0.80–1.36]	OR = 0.817 p = 0.135 [0.63–1.07]	OR = 0.836 p = 0.291 [0.60–1.17]	OR = 0.946 p = 0.730 [0.69–1.30]	OR = 0.980 p = 0.876 [0.76–1.27]	**OR = 0.780*** **p = 0.041** [**0.62–0.99**]	OR = 0.880 p = 0.533 [0.59–1.32]	OR = 1.085 p = 0.538 [0.84–1.41]	OR = 1.146 p = 0.328 [0.87–1.51]
Hypercholesterolemia (N = 2379)	OR = 1.185 p = 0.113 [0.96–1.46]	OR = 0.816 p = 0.055 [0.66–1.01]	OR = 0.986 p = 0.913 [0.76–1.28]	OR = 1.101 p = 0.454 [0.86–1.42]	**OR = 1.294*** **p = 0.014** [**1.06–1.59**]	OR = 1.197 p = 0.066 [0.99–1.45]	OR = 1.435* p = 0.025 [1.05–1.97]	OR = 1.051 p = 0.639 [0.85–1.30]	OR = 0.893 p = 0.321 [0.71–1.12]
Diabetes (N = 2402)	OR = 1.016 p = 0.911 [0.77–1.35]	OR = 0.781 p = 0.086 [0.59–1.04]	**OR = 1.713**** **p < 0.001** [**1.25–2.35**]	OR = 0.964 p = 0.827 [0.69–1.34]	OR = 0.814 p = 0.158 [0.61–1.08]	OR = 0.865 p = 0.279 [0.67–1.13]	OR = 0.802 p = 0.332 [0.51–1.25]	**OR = 0.706*** **p = 0.026** [**0.52–0.96**]	OR = 1.115 p = 0.487 [0.82–1.52]
Thyroid disease (N = 2399)	OR = 1.090 p = 0.535 [0.83–1.43]	OR = 1.011 p = 0.937 [0.77–1.32]	OR = 1.055 p = 0.741 [0.77–1.45]	OR = 1.203 p = 0.240 [0.88–1.64]	OR = 1.231 p = 0.125 [0.94–1.61]	OR = 1.058 p = 0.666 [0.82–1.36]	OR = 1.066 p = 0.718 [0.72–1.58]	OR = 0.808 p = 0.153 [0.60–1.08]	OR = 0.929 p = 0.644 [0.68–1.27]
B-12 deficiency (N = 2373)	OR = 1.075 p = 0.666 [0.77–1.49]	OR = 0.899 p = 0.529 [0.65–1.25]	OR = 1.068 p = 0.741 [0.72–1.58]	OR = 0.873 p = 0.504 [0.59–1.30]	OR = 1.161 p = 0.358 [0.84–1.60]	OR = 1.010 p = 0.950 [0.74–1.37]	OR = 1.157 p = 0.541 [0.72–1.85]	OR = 0.985 p = 0.931 [0.70–1.39]	OR = 1.009 p = 0.962 [0.70–1.45]
Stroke (N = 4300)	**OR = 1.390*** **p = 0.041** [**1.01–1.91**]	**OR = 1.574*** **p = 0.003** [**1.16–2.13**]	**OR = 4.338**** **p < 0.001** [**3.18–5.93**]	**OR = 1.897**** **p < 0.001** [**1.37–2.62**]	OR = 1.231 p = 0.189 [0.90–1.68]	OR = 0.912 p = 0.542 [0.68–1.23]	OR = 0.805 p = 0.385 [0.49–1.31]	**OR = 0.506**** **p < 0.001** [**0.35–0.74**]	OR = 0.830 p = 0.332 [0.57–1.21]
Cardiovascular score (N = 4313)	OR = 0.883 p = 0.273 [0.71–1.10]	OR = 1.033 p = 0.769 [0.83–1.28]	OR = 0.969 p = 0.812 [0.75–1.26]	OR = 0.940 p = 0.635 [0.73–1.21]	OR = 0.893 p = 0.310 [0.31–1.11]	OR = 0.848 p = 0.110 [0.69–1.04]	OR = 0.761 p = 0.100 [0.55–1.05]	OR = 1.051 p = 0.665 [0.84–1.32]	**OR = 0.776*** **p = 0.044** [**0.61–0.99**]

(continued)

Table 6. (continued)

		Female (N = 2289)							
	Arteriolosclerosis (N = 2041)	**Atherosclerosis (N = 2263)**	**Infarcts (N = 2279)**	**Microinfarcts (N = 2283)**	**CAA (N = 2227)**	**ADNP (N = 2257)**	**HS (N = 2215)**	**LB (N = 2272)**	**FTLD (N = 2289)**
Age of death	**OR = 1.205** p < 0.001 [1.08–1.34]**	**OR = 1.812** p < 0.001 [1.61–2.04]**	**OR = 1.469** p < 0.001 [1.28–1.69]**	**OR = 1.618** p < 0.001 [1.40–1.87]**	OR = 1.062 p = 0.275 [0.95–1.18]	**OR = 1.046* p = 0.379 [0.95–1.16]**	**OR = 1.280* p = 0.004 [1.08–1.52]**	OR = 0.982 p = 0.763 [0.87–1.11]	**OR = 0.686** p < 0.001 [0.61–0.77]**
Race (not White)	OR = 1.037 p = 0.870 [0.67–1.60]	OR = 1.049 p = 0.836 [0.67–1.65]	**OR = 1.688* p = 0.035 [1.04–2.75]**	OR = 1.228 p = 0.438 [0.73–2.06]	OR = 1.108 p = 0.683 [0.68–1.82]	OR = 1.091 p = 0.698 [0.70–1.70]	**OR = 2.112* p = 0.012 [1.18–3.78]**	OR = 1.208 p = 0.471 [0.72–2.02]	**OR = 0.526* p = 0.040 [0.29–0.97]**
Education	OR = 0.907 p = 0.379 [0.73–1.13]	OR = 1.077 p = 0.500 [0.87–1.34]	OR = 0.928 p = 0.561 [0.72–1.19]	OR = 0.872 p = 0.297 [0.68–1.13]	OR = 0.811 p = 0.065 [0.65–1.01]	**OR = 0.802* p = 0.034 [0.65–0.98]**	OR = 1.151 p = 0.404 [0.83–1.60]	OR = 1.190 p = 0.171 [0.93–1.53]	OR = 1.260 p = 0.063 [0.99–1.61]
Hypertension (N = 1915)	**OR = 1.500** p = 0.001 [1.18–1.91]**	**OR = 1.644** p < 0.001 [1.29–2.09]**	**OR = 1.381* p = 0.027 [1.04–1.84]**	**OR = 1.352* p = 0.043 [1.01–1.81]**	**OR = 0.756* p = 0.026 [0.59–0.97]**	OR = 0.967 p = 0.774 [0.77–1.22]	OR = 0.993 p = 0.971 [0.69–1.44]	**OR = 0.657* p = 0.003 [0.50–0.87]**	OR = 1.026 p = 0.855 [0.78–1.35]
Transient ischemic attack (TIA) (N = 1883)	OR = 1.191 p = 0.370 [0.81–1.75]	**OR = 1.529* p = 0.025 [1.06–2.22]**	OR = 1.454 p = 0.055 [0.99–2.13]	**OR = 1.486* p = 0.042 [1.01–2.18]**	OR = 0.789 p = 0.263 [0.52–1.19]	**OR = 0.521** p < 0.001 [0.36–0.75]**	OR = 0.687 p = 0.235 [0.37–1.28]	OR = 1.424 p = 0.105 [0.93–2.18]	**OR = 0.567* p = 0.043 [0.33–0.98]**
Seizures (N = 1908)	OR = 1.248 p = 0.317 [0.81–1.93]	OR = 1.016 p = 0.946 [0.64–1.63]	OR = 0.901 p = 0.717 [0.52–1.58]	OR = 1.134 p = 0.650 [0.66–1.96]	OR = 1.402 p = 0.124 [0.91–2.16]	**OR = 1.984* p = 0.002 [1.28–3.08]**	OR = 0.634 p = 0.267 [0.28–1.42]	OR = 1.277 p = 0.303 [0.80–2.03]	**OR = 0.387* p = 0.002 [0.21–0.70]**
Traumatic brain injury (TBI) (N = 4250)	OR = 1.278 p = 0.192 [0.88–1.85]	OR = 0.816 p = 0.285 [0.56–1.18]	OR = 1.075 p = 0.733 [0.71–1.63]	OR = 1.243 p = 0.298 [0.83–1.87]	OR = 0.939 p = 0.749 [0.64–1.38]	OR = 1.096 p = 0.607 [0.77–1.56]	OR = 1.132 p = 0.655 [0.66–1.95]	OR = 0.878 p = 0.564 [0.56–1.37]	OR = 1.011 p = 0.961 [0.66–1.55]
Hypercholesterolemia (N = 1898)	OR = 0.856 p = 0.175 [0.68–1.07]	OR = 1.041 p = 0.727 [0.83–1.30]	OR = 0.778 p = 0.059 [0.60–1.01]	OR = 1.039 p = 0.776 [0.80–1.35]	OR = 1.171 p = 0.180 [0.93–1.48]	OR = 1.171 p = 0.145 [0.95–1.45]	OR = 1.004 p = 0.982 [0.71–1.41]	**OR = 1.306* p = 0.044 [1.01–1.69]**	OR = 1.125 p = 0.364 [0.87–1.45]
Diabetes (N = 1921)	OR = 0.928 p = 0.686 [0.65–1.33]	OR = 1.185 p = 0.354 [0.83–1.70]	OR = 1.070 p = 0.742 [0.71–1.61]	OR = 0.856 p = 0.475 [0.56–1.31]	OR = 0.810 p = 0.309 [0.54–1.22]	OR = 1.045 p = 0.806 [0.74–1.48]	OR = 0.713 p = 0.293 [0.38–1.34]	OR = 1.145 p = 0.531 [0.75–1.75]	OR = 0.797 p = 0.320 [0.51–1.25]
Thyroid disease (N = 1910)	OR = 0.977 p = 0.845 [0.77–1.24]	OR = 0.929 p = 0.536 [0.74 1.17]	OR = 0.800 p = 0.108 [0.61–1.05]	**OR = 0.665* p = 0.005 [0.50–0.88]**	OR = 0.894 p = 0.371 [0.70–1.14]	OR = 0.869 p = 0.213 [0.70–1.08]	OR = 0.968 p = 0.860 [0.68–1.39]	OR = 0.920 p = 0.553 [0.70–1.21]	OR = 1.003 p = 0.983 [0.77–1.31]
B-12 deficiency (N = 1892)	OR = 0.974 p = 0.891 [0.67–1.42]	OR = 1.025 p = 0.897 [0.70–1.50]	OR = 1.163 p = 0.487 [0.76–1.78]	OR = 1.186 p = 0.441 [0.77–1.83]	OR = 0.740 p = 0.170 [0.48–1.14]	OR = 0.891 p = 0.536 [0.62–1.28]	OR = 0.677 p = 0.261 [0.34–1.34]	OR = 1.299 p = 0.233 [0.85–2.00]	OR = 1.079 p = 0.733 [0.70–1.67]
Stroke (N = 4300)	**OR = 1.778** p = 0.001 [1.26–2.52]**	**OR = 1.934** p < 0.001 [1.37–2.73]**	**OR = 3.454** p < 0.001 [2.47–4.84]**	**OR = 1.884** p < 0.001 [1.33–2.68]**	OR = 0.819 p = 0.304 [0.56–1.20]	OR = 0.761 p = 0.104 [0.55–1.06]	OR = 1.278 p = 0.338 [0.77–2.11]	**OR = 0.554* p = 0.014 [0.35–0.89]**	OR = 0.775 p = 0.268 [0.49–1.22]
Cardiovascular score (N = 4313)	OR = 1.046 p = 0.728 [0.81–1.35]	OR = 0.962 p = 0.762 [0.75–1.23]	**OR = 1.393* p = 0.019 [1.06–1.84]**	OR = 1.049 p = 0.745 [0.79–1.40]	**OR = 0.698* p = 0.011 [0.53–0.92]**	**OR = 0.504** p < 0.001 [0.40–0.64]**	OR = 0.713 p = 0.101 [0.48–1.07]	OR = 0.784 p = 0.131 [0.57–1.08]	OR = 0.860 p = 0.342 [0.63–1.17]

"N" indicates number of data points for each medical history and neuropathology;.

* $p < 0.05$.

** $p < 0.001$.

ADNP, Alzheimer disease neuropathology; CAA, cerebral amyloid angiopathy; FTLD, frontotemporal lobar degeneration; HS, hippocampal sclerosis; LB, Lewy body.

Table 7. Demographics, frequency of PMH, and association between PMH and neuropathology for the TDP-43 subset

	TDP-43: total sample (N = 940)	TDP-43: odds ratio in total sample	TDP-43: males only (N = 520)	TDP-43: odds ratio in males	TDP-43: females only (N = 420)	TDP-43: odds ratio in females
Age of death (SD)	78.1 (11.9%)	OR = 1.122 p = 0.309 [0.90–1.40]	77.0 (11.5%)	OR = 1.069 p = 0.683 [0.78–1.47]	**79.6 (12.3%)****	OR = 1.235 p = 0.238 [0.87–1.75]
Male (%)	55.3	OR = 0. 909 p = 0.706 [0.56–1.49]	–	–	–	–
Race (% not White)	65 (6.9%)	OR = 1.590 p = 0.325 [0.63–4.00]	25 (4.8%)	OR = 1.024 p = 0.978 [0.18–5.80]	**40 (9.5%)****	OR = 2.174 p = 0.196 [0.67–7.06]
Education (SD)	15.7 (3.0%)	OR = 0.798 p = 0.357 [0.49–1.21]	16.3 (3.0%)	OR = 0.691 p = 0.288 [0.35–1.37]	**14.9 (2.8%)****	OR = 0.811 p = 0.577 [0.39–1.69]
Hypertension	73 (57.5%)	OR = 1.006 p = 0.980 [0.61–1.66]	27 (46.6%)	OR = 1.861 p = 0.077 [0.93–3.71]	124 (27.5%)	OR = 0.464 p = 0.062 [0.21–1.04]
Transient ischemic attack (TIA)	5 (4.0%)	OR = 0.363 p = 0.113 [0.10–1.27]	1 (1.4%)	OR = 0.145 p = 0.070 [0.02–1.07]	4 (7.0%)	OR = 1.451 p = 0.697 [0.22–9.45]
Seizures	3 (9.5%)	**OR = 0.120* p = 0.042 [0.02–0.93]**	3 (4.3%)	OR = 0.361 p = 0.361 [0.41–3.22]	0 (0.0%)	OR = 3.398e−8 p = 0.986 [0.00–inf]
Traumatic brain injury (TBI)	14 (11.0%)	OR = 0.740 p = 0.402 [0.37–1.50]	7 (10.1%)	**OR = 0.326* p = 0.033 [0.12–0.91]**	**7 (12.1%)***	OR = 3.062 p = 0.070 [0.91–10.26]
Hypercholesterolemia	75 (58.6%)	OR = 1.035 p = 0.895 [0.63–1.71]	44 (62.9%)	OR = 0.959 p = 0.908 [0.47–1.95]	31 (53.4%)	OR = 1.112 p = 0.791 [0.51–2.45]
Diabetes	13 (10.2%)	OR = 0.695 p = 0.379 [0.31–1.56]	11 (15.9%)	OR = 0.830 p = 0.700 [0.32–2.14]	**2 (3.4%)***	OR = 0.131 p = 0.074 [0.01–1.22]
Thyroid disease	28 (22.0%)	OR = 0.928 p = 0.790 [0.54–1.61]	10 (14.3%)	OR = 0.856 p = 0.722 [0.36–2.02]	**18 (31.2%)****	OR = 1.014 p = 0.972 [0.47–2.21]
B-12 deficiency	12 (9.5%)	OR = 1.039 p = 0.920 [0.50–2.18]	7 (10.1%)	OR = 1.287 p = 0.621 [0.47–3.50]	5 (8.8%)	OR = 0.801 p = 0.713 [0.25–2.62]
Stroke	6 (4.7%)	OR = 0.530 p = 0.230 [0.19–1.49]	5 (7.1%)	OR = 0.753 p = 0.659 [0.21–2.65]	1 (1. 8%)	OR = 0.204 p = 0.153 [0.02–1.80]
Cardiovascular score	37 (29.4%)	OR = 0.821 p = 0.496 [0.47–1.45]	26 (37.7%)	OR = 0.999 p = 0.998 [0.47–2.12]	11 (19.3%)	OR = 0.437 p = 0.104 [0.16–1.19]

Asterisks represent significant differences in male: female comparison.
* $p < 0.05$.
** $p < 0.001$.
TDP-43, TAR DNA-binding proteinopathy.

[0.61–0.99]) in men and CAA (OR = 0.7 [0.53–0.92]) and ADNP (OR = 0.50 [0.40–0.64]) in women. Cardiovascular events were associated with an increased likelihood in infarcts (OR = 1.4 [1.06–1.84]) and microinfarcts (OR = 1.4 [0.84–1.88]) among females. Finally, thyroid disease was associated with a decreased likelihood of microinfarcts (OR = 0.7 [0.50–0.88]) in females only.

A subset of 940 participants with available TDP-43 data was analyzed to study the relationship between TDP-43 and PMH. Table 7 depicts the demographics of this subset that were similar to that of the main study population. In the whole TDP-43 subset, seizures were associated with a decreased likelihood of TDP-43 (OR = 0.1 [0.02–0.93]). When separating by sex within the TDP-43 subset, among males we found TBI (OR = 0.3 [0.12–0.91]) was associated with a reduced likelihood of TDP-43.

Considering the subtypes of FTLD, we found cardiovascular events are associated with a decreased likelihood of FTLD-Tau (OR = 0.7 [0.57–0.96]). Seizures were associated with a decreased likelihood of FTLD-Ubiquitin (OR = 0.4 [0.22–0.86]). Diabetes was found to be associated with a decreased likelihood of FTLD-TDP (OR = 0.3 [0.11–0.89]) whereas

hypercholesterolemia was associated with an increased likelihood of FTLD-TDP (OR = 1.8 [1.04–3.09]). Younger ages were associated with an increased likelihood of FTLD-TDP (OR = 0.5 [0.42–0.69]) and FTLD-Ubiquitin (OR = 0.8 [0.67–0.86]). Education was associated with an increased likelihood of FTLD-Tau (OR = 1.3 [1.03–1.63]) but a decreased likelihood of FTLD-Ubiquitin (OR = 0.76 [0.67–0.86]).

DISCUSSION

In this study, we leveraged the NACC database to evaluate the relationship between PMH and common vascular and degenerative neuropathologies. Our findings demonstrate an intriguing association between hypertension and a decreased likelihood of common degenerative pathologies namely, ADNP, LB, and CAA, and an increased likelihood of vascular pathologies atherosclerosis and arteriolosclerosis. Furthermore, we found the history of TIA was associated with an increased likelihood of atherosclerosis, arteriolosclerosis, infarcts, and microinfarcts, but a reduced likelihood of ADNP; hypercholesterolemia was associated with an increased likelihood of ADNP and CAA, and seizures were associated with an increased likelihood of ADNP but reduced likelihood of FTLD. Looking at the associations in males and females separately, there were notable differences between the sexes but no conclusive direction for these differential associations emerged. We also investigated the association between PMH and TDP-43 in a subset of participants with available TDP-43 data.

While hypertension is widely considered a risk factor for the development of dementia (16, 29–31), there is a paucity of research on the relationship between hypertension and specific degenerative neuropathologies, and the available literature on the subject does not paint a consistent picture (23, 32, 33). Age of onset of hypertension might be an important factor affecting the relationship between hypertension and dementia as studies focusing on midlife hypertension have shown an increased likelihood of dementia in those with hypertension (16, 31, 34) and a potential protection against cognitive impairment (30, 35–38) and neuropathology (39–41) in those who have been effectively treated. On the other hand, emerging evidence from the oldest-old cohorts indicates the late onset of hypertension may be a cognitive protective factor (42, 43).

The overall differential relationship of hypertension and cognition in mid versus late life might provide indirect evidence corroborating our results. Perhaps the development of hypertension in midlife is a risk factor for the development of vascular pathologies, namely atherosclerosis and arteriolosclerosis that in turn lead to cognitive impairment and dementia. Late-life hypertension may also be a compensatory mechanism to maintain cerebral perfusion and therefore, protecting the brain against degenerative pathologies such as Alzheimer and Lewy body (31–45).

Among the additional PMH entities assessed, our results revealed seizures were associated with an increased likelihood of ADNP. Our findings align with previous studies which have indicated a greater prevalence of seizures (eg, grand mal, focal, and epilepsy) among individuals with dementia in comparison to a population without dementia (20, 46, 47). Few studies have explored the relationship between neuropathology and seizures. One study found 17% of their autopsy-confirmed ADNP cases had seizures possibly later in the disease course (48). Opposite to ADNP, FTLD was associated with a decreased likelihood of seizures. In agreement with our results, 1 recent study has suggested a similar finding where seizures had a lower prevalence in comparison to other neurodegenerative pathologies including ADNP (49). Thus, our study provides further evidence for the relationship between ADNP and seizures while also suggesting other neuropathologies may not have as strong of a relationship with seizures, but this requires further research.

TIA and strokes were associated with an increased likelihood of atherosclerosis, arteriolosclerosis, infarcts, and microinfarcts; a finding that is expected given the vascular etiology of both. Our results did not reproduce the previously reported association between diabetes and the increased likelihood of vascular pathology (50). This may be indicative of a survival bias since individuals with diabetes are less likely to live long enough to acquire vascular pathologies. Future studies should address the potential underlying mechanisms of this relationship. Finally, in line with our results surrounding hypertension, we found the presence of cardiovascular events was associated with a decreased likelihood of CAA, ADNP, HS, and FTLD. Similar to diabetes, the relationship between cardiovascular events and decreased neurodegenerative pathology may be explained by competing mortality such that participants with these events may not live long enough to accumulate these pathologies.

Due to the increasing recognition of the importance of the role of biological sex, we examined the relationship between neurodegenerative pathologies and PMH in men and women separately. Interestingly, a significant relationship between history of hypertension and decreased likelihood of ADNP was seen only in males whereas in females, a history of hypertension was associated with a decreased likelihood of LB and TDP-43. Among females, a history of hypertension remained associated with a decreased likelihood of CAA. The putative mechanisms underlying these differential associations require further investigation including the role of antihypertensive medications. Among the vascular pathologies, the increased likelihood of atherosclerosis remained associated with the history of hypertension in both males and females, but the increased likelihood of arteriolosclerosis was only associated with the history of hypertension among females. Arteriolosclerosis has been found to be less common among men (51). This might offer insight into the reasons behind the absence of this association.

Furthermore, we found that the presence of diabetes was associated with a decreased likelihood of LB in men only, in line with previous work (52, 53). We also found an association between a history of hypercholesterolemia and an increased likelihood of CAA in males. Given the ongoing controversy on the relationship of cholesterol and cholesterol-lowering medications (i.e. statins) with vascular and degenerative pathologies, this is an intriguing association warranting further investigation (50, 54). TBI, on the other hand, was associated with a decreased likelihood of ADNP in males only. Previous

work has demonstrated mixed results with some studies indicating no association between TBI and ADNP (21), especially among males (55, 56). Yet, more men report TBI within our sample which may be attributed to higher engagement in activities that may cause a TBI, though reports of TBI were low in comparison to the prevalence of other medical histories. Thus, our findings may be indicative of the lack of participants who do not have a history of TBI. Thyroid disease and B12 deficiency were not associated with any neuropathologies in this sample. This is an important finding since the association between cognitive impairment and thyroid and B12 abnormalities is a classic teaching point in cognitive science. While our results do not challenge this notion, it suggests that the etiology of this relationship is unlikely to be through increasing the burden of degenerative pathologies (18, 19).

While previous literature has indicated a relationship between diabetes and atherosclerosis, we were unable to replicate such a finding. This may in part be due to the low frequency of diabetes present in this sample (12%), which in turn might be related to recruitment strategies at Alzheimer's Disease Research Centers feeding data to the NACC database. Also, given the average age at death of 80 years old, survival bias is another potential explanation. Additionally, we did not see a relationship between vascular pathology and seizures. Though previous studies have suggested a relationship between infarcts and seizures, the different nature of vascular pathology outcomes in this study (i.e. atherosclerosis and arteriolosclerosis) might be the reason for the lack of a relationship between seizures and our vascular pathology outcomes (38, 57, 58).

Finally, we examined cognitive group differences among the frequency of PMH. We found a greater frequency of seizures among individuals with dementia. Given the higher likelihood of ADNP, we may anticipate the underlying pathology may be contributed to cognitive decline. Other PMH, such as hypertension and diabetes, were found to be associated with decreased neuropathologies, thus indicating less cognitive decline due to lack of pathology. In the case of the cardiovascular scores being more frequent among individuals with no dementia, we suspect the relationship with cognition can be more variable, especially when other PMH related to cardiovascular disease, such as hypertension, is more frequent among individuals with no dementia.

There are some limitations to this study. Select medical histories such as arthritis could not be added into this analysis due to the amount of missingness within the sample as they are from the newest UDS version. Furthermore, the newest UDS version collects data at the initial visit whereas the previous UDS versions collected past medical history at each visit. Thus, we acknowledge those who have completed UDS Version 3 may not have the most up-to-date information due to the method of data collection. Due to the exploratory nature of this study, we did not correct our results for multiple comparisons but appreciate the likelihood of having reported spurious associations. Further, we are unable to comment on the impact multiple neuropathologies may have in their relationship with medical history. Overlapping neuropathologies, a common finding in older individuals, is an important consideration that should be addressed in future research.

For the purpose of retaining as many participants as possible, we included individuals who were assessed across different versions of the NP form. The version of the NP form used to collect data can offer different information on neuropathologies. For this reason, we chose to categorize ADNP using the Braak and amyloid staging which were consistently collected across the sample instead of the NIAA-AA staging of Alzheimer disease neuropathological change (ADNC) that was missing on more than half (56%) of the sample. Further, we assessed FTLD regardless of the underlying proteinopathy due to the lack of consistency in labeling the proteinopathy across various NACC versions.

An additional limitation is that NACC does not include the time of onset for the medical histories. Particularly, in the case of hypertension, it is important to understand how the time of onset may have impacted the relationships with pathologies due to differing associations with dementia for midlife versus late-life onset. Our findings related to hypertension may be reflective of the effect of medical treatment rather than hypertension itself. In a follow-up study, we aim to further investigate hypertension including the role of hypertensive medications and blood pressure measurements in neurodegenerative pathology.

While the NACC dataset provides valuable longitudinal data, it is important to note that the data are not racially diverse. With 94% of participants being white, the findings are not generalizable to other races. We also recognize a statistically significant group difference in sex, age of death, and education between our included and excluded samples as a limitation of our analyses. While the overall average values were comparable for each demographic variable, we note this significant difference as a limitation. Finally, information about TDP-43 pathology was missing for a significant portion (63%) of the study population as TDP-43 is a later addition to NACC pathology datasheets. We, however, chose to include TDP-43 data due to increasing recognition of the importance of this pathology in late-life cognition.

In spite of these limitations, our study's major strength is the large number of participants included. We sought to take advantage of the available neuropathological data to address key gaps within our current knowledge. Relatively few studies have examined the relationship between neuropathology and PMH. Investigating the relationships between PMH and neuropathology could reveal potential protective factors as well as offering insight into some of the mechanisms that contribute to neuropathological change.

In conclusion, our study suggests while a history of hypertension appears to be harmful to blood vessels leading to an increase likelihood of vascular pathologies, it may be associated with a reduced likelihood of neurodegenerative pathologies. However, further work is needed to assess the nuances of this relationship and to better understand the role of overlapping pathologies and histories. Concurrently, we found history of TIA was associated with an increased likelihood of vascular pathologies, but a reduced likelihood of ADNP and hypercholesterolemia was associated with an increased likelihood of CAA and ADNP. Furthermore, we found seizure history to be associated with increased odds of ADNP. Our results suggest

further research is needed to untangle the complex role biological sex plays in the relationship between pathologies and PMH.

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CONFLICT OF INTEREST

The authors have no duality or conflicts of interest to declare.

SUPPLEMENTARY DATA

Supplementary Data can be found at academic.oup.com/jnen.

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