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ORIGINAL PAPER

Pure LATE-NC: Frequency, clinical impact, and the importance of considering *APOE* genotype when assessing this and other subtypes of non-Alzheimer's pathologies

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Abstract

Pure limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (pure LATE-NC) is a term used to describe brains with LATE-NC but lacking intermediate or severe levels of Alzheimer's disease neuropathologic changes (ADNC). Focusing on pure LATE-NC, we analyzed data from the National Alzheimer's Coordinating Center (NACC) Neuropathology Data Set, comprising clinical and pathological information aggregated from 32 NIH-funded Alzheimer's Disease Research Centers (ADRCs). After excluding subjects dying with unusual conditions, n = 1,926 autopsied subjects were included in the analyses. For > 90% of these participants, apolipoprotein E (*APOE)* allele status was known; 46.5% had at least one *APOE* 4 allele. In most human populations, only 15–25% of people are *APOE* ε4 carriers. ADRCs with higher documented AD risk allele (*APOE* or *BIN1*) rates had fewer participants lacking ADNC, and correspondingly low rates of pure LATE-NC. Among *APOE* ε4 non-carries, 5.3% had pure LATE-NC, 37.0% had pure ADNC, and 3.6% had pure neocortical Lewy body pathology. In terms of clinical impact, participants with pure LATE-NC tended to die after having received a diagnosis of dementia: 56% died with dementia among *APOE* ε4 non-carrier participants, comparable to 61% with pure ADNC. LATE-NC was associated with increased Clinical Dementia Rating Sum of Boxes (CDR-SOB) scores, i.e. worsened global cognitive impairments, in participants with no/low ADNC and no neocortical Lewy body pathology ($p = 0.0023$). Among pure LATE-NC cases, there was a trend for higher LATE-NC stages to be associated with worse CDR-SOB scores ($p = 0.026$ for linear trend of LATE-NC stages). Pure LATE-NC was not associated with clinical features of disinhibition or primary progressive aphasia. In summary, LATE-NC with no or low levels of ADNC was less frequent than pure ADNC but was not rare, particularly among individuals who lacked the *APOE* 4 allele, and in study cohorts with *APOE* 4 frequencies similar to those in most human populations.

Keywords Epidemiology · Prevalence · Community-based · DLB · FTLD · FTD

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Abbreviations

ADNC	Alzheimer's disease neuropathologic changes
ADGC	Alzheimer's Disease Genetics Consortium
ADRC	Alzheimer's disease research center
CDR-SOB	Clinical dementia rating sum of boxes
FTLD-TDP	Frontotemporal lobar degeneration with TDP-43 inclusions
LATE-NC	Limbic predominant age-related TDP-43 Encephalopathy neuropathologic changes
LB	Lewy bodies
MCI	Mild cognitive impairment
NACC	National Alzheimer's Coordinating Center
NP	Neuropathology
TDP-43	TAR DNA-binding protein 43
UDS	Uniform Data Set

Introduction

Limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC) and Alzheimer's disease neuropathologic changes (ADNC) are two dementia-associated pathologies that are highly prevalent in older brains. LATE-NC is characterized by TDP-43 proteinopathy that is most prominent in the medial temporal lobes, i.e. amygdala and hippocampus [57]. The hallmarks of ADNC are Aβ amyloid plaques and tau neurofibrillary tangles [49], and these microscopic lesions are widely distributed in brains of severe ADNC cases. Both ADNC and LATE-NC are associated independently with substantial cognitive impairment [51, 62]. The overall public health impact of ADNC is larger than LATE-NC, but in advanced old age the dementia-associated attributable risk of LATE-NC approaches or even surpasses the aggregate impact of ADNC according to high-quality data from large autopsy cohorts [10, 39, 47, 73].

It has become increasingly clear that ADNC, LATE-NC, and other dementia-associated pathologies frequently coexist in the same brains. Indeed, it is the rule and not exception for older persons' brains to harbor more than one subtype of dementia-associated pathology [25, 59, 63, 66]. The concept of comorbid ("mixed") pathologies – particularly for ADNC and LATE-NC – has important implications about clinical trials and clinical management. More specifically, the presence of both ADNC and LATE-NC as co-pathologies in the same brain is associated with a relatively swiftly progressing and severe disease course, in comparison to either LATE-NC or ADNC alone [27, 29, 52], and, theoretically, may impact therapeutic responses.

To gain perspective on how often the different pathologies are comorbid in human populations requires an epidemiologic perspective, which is challenging since no human population has 100% autopsy rate, and there may be differences between human subpopulations. Thus, we are forced to make inferences based on data from the known autopsy series, while hoping for more comprehensive data (including better clinical biomarkers) in the future. With those caveats in mind a basic question is, how often do LATE-NC and ADNC coexist in the same brains?

According to the published literature, among people who die in advanced old age, i.e. > 85 years at death, at least incipient levels of ADNC was observed in ~ 80% of brains, and LATE-NC in ~ 30% or more [11, 47, 56]. Therefore, a substantial subset of brains should show both ADNC and LATE-NC even if the processes occurred independently of each other. Yet the rate at which ADNC and LATE-NC have been observed together in the same brains is substantially higher than would be expected by chance. In community- and population-based autopsy cohorts, approximately 50% of brains with severe levels of ADNC have comorbid LATE-NC, whereas in brains that lack any ADNC, approximately 25% of brains have LATE-NC [1, 15, 56]. The relatively high rates of co-pathology could occur via common upstream factors (e.g., shared risk factors), or downstream "pathologic synergy" [58, 82].

Perhaps the most impactful upstream factor in dementia risk is genetics. Twin studies indicated that dementia risk is up to 80% heritable [28, 41, 72] but the underlying pathologies and affected pathogenetic pathways are complex. The dementia-associated apolipoprotein E (*APOE*) ε4 allele has been associated with increased risk for ADNC, LATE-NC, and other pathologic changes [19, 68, 88, 90, 94]. Not all studies found evidence of a direct association between *APOE* genotype and risk for LATE-NC [13, 43, 61, 65, 84]. Few individuals with the *APOE* ε4 allele survive into advanced old age without any Aβ plaques [74, 75], and it remains to be seen exactly how the *APOE* ε4 allele promotes TDP-43 proteinopathy (there may be multiple pathways involved). Genetic risk factor genes for ADNC are now known to include many genes other than *APOE*, and of these, genetic variation in and near the *BIN1* gene is a particularly robust non-*APOE* genetic risk factor for clinical AD and ADNC [6, 32, 77].

Although mixed pathology phenotypes are the norm in old people's brains, questions remain about the frequency and correlative impacts of pathologic changes among the individuals that have only one ("pure") subtype of pathology. The focal-point of the present work is pure LATE-NC—cases with LATE-NC that lack comorbid intermediate or severe ADNC. There remain unanswered questions about the frequency of pure LATE-NC and its cognitive impact. Comparing and contrasting the findings across different research centers, mindful of covariates involved, may elucidate reasons why different cohorts may find

apparently different results, i.e., why some autopsy cohorts seem to show more and some less of this brain pathology.

To gain more insights into pure LATE-NC, we examined data from the National Alzheimer's Coordinating Center (NACC) which provides extensive granular data from dozens of U.S. NIH/NIA-funded Alzheimer's Disease Research Centers (ADRCs) [4, 8, 9]. ADRCs that contribute data to NACC follow participants to autopsy whenever possible. By analyzing this data set we found clues about the frequency and impact of pure LATE-NC, and uncovered strong evidence that *APOE* ε4 (and the *BIN1* risk allele) are important covariates to be considered in studying the phenomenon of pure LATE-NC.

Materials and methods

Participants, data source, and inclusion/exclusion criteria

Data were obtained from NACC, which is the data repository for past and present National Institute on Aging (NIA) funded ADRCs located at medical institutions across the United States. Participants are assessed using the standardized Uniform Data Set (UDS) at their local ADRC approximately annually. The UDS collects a robust set of data including participant demographics, health history, family history, medications, physical and neurological exams, clinical diagnoses, AD and related dementias symptomology, neuropsychological test scores (from a battery of 12 neuropsychological tests), the Clinical Dementia Rating (CDR®) Dementia Staging Instrument plus NACC frontotemporal lobar degeneration (FTLD) Behavior & Language Domains. Standardized data collected on neuropathological features present at the time of death are available for participants who were assessed with the UDS and who consented to autopsy [5, 9]. ADRC participants are enrolled from various sources including clinic samples, other existing studies, and referrals from clinicians and other participants. Data are maintained and actively curated by NACC and are freely available to researchers. NACC has been in existence since 1999. Additional details about the UDS are described elsewhere [4, 5, 8, 9, 50]. Participants who met the study's eligibility criteria were selected from the June 2024 data freeze, which included data from the participant's initial and most recent UDS visits, collected from September 2005 to June 2024. Participants who had at least one disease listed out in Supplementary Table 1, died at age of younger than 75 years, or had missing data on NP category were then excluded (Supplementary Fig. 1).

Neuropathology data

The NACC neuropathology (NP) data (https://www.alz.washington.edu/) were derived from the June 2024 data freeze and measured via the NACC NP v10-11 forms; this included data from 39 different NIA-funded ADRCs. Brain autopsies were performed on site at each of the contributory ADRCs. ADNC evaluated with an "ABC" score including Aβ Phase ratings (A score), Braak neurofibrillary tangle (NFT) stage (B score), and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) ratings (C score) according to NIA and Alzheimer's Association (NIA-AA) guidelines. TDP-43 pathologies were measured as the presence of inclusions in three brain regions: amygdala, hippocampus. Lewy body pathology (LBP) data were dichotomized: 0 = none or present in non-neocortical regions and 1 = present in neocortical region. Hippocampal sclerosis was dichotomized as 0 = none and 1 = unilateral, bilateral or present but laterality not assessed. Brain arteriolosclerosis was measured as ordinal data (0 = none, 1 = mild, 2 = moderate, and 3 = severe) and aging-related tau astrogliopathy (ARTAG) pathology as binary data (0 = no and 1 = yes).

Neuropathological Category Definition

Pure LATE-NC was operationalized to indicate LATE-NC with either ADNC = Not or ADNC = Low severity according to the NIA-AA consensus-based criteria [49]. We defined the presence of ADNC as intermediate ADNC or high ADNC of NIA-AA Alzheimer's disease neuropathologic change (i.e., NPADNC = 2 or 3), LATE-NC as distribution of TDP-43 immunoreactive inclusions at least in hippocampus (i.e., NPTDPC = 1), and LB as LB pathology in neocortical region (i.e., NACCLEWY = 3 or NPLBOD = 3). We then categorized participants into seven groups: "pure ADNC" = ADNC positive (+), LATE-NC negative (−), and LB −, "pure LATE-NC" = ADNC −, LATE-NC +, and LB −, "pure LB" = ADNC −, LATE-NC −, and LB +, "ADNC + LATE-NC" = ADNC +, LATE-NC +, and LB −, "ADNC + LB" = ADNC +, LATE-NC −, and LB +, "ADNC + LATE-NC + LB" = ADNC +, LATE-NC +, and LB +, and "others". (**Supplementary Table 2**).

Clinical data

Clinical diagnosis of dementia was defined using cognitive status at UDS visit (NACCUDSD = 4). Disinhibition in the last month was measured at the UDS visit with 0 = No and 1 = Yes under Neuropsychiatric Inventory Questionnaire (NPI-Q). Diagnosis of primary progressive aphasia was determined using the NACCPPA variable.

Genetic data

The number of *APOE* ε4 allele data (0 = no ε4 allele, 1 = one copy of ε4 allele, and two copies of ε4 allele) were obtained from the NACC Genetic Data (NACCNE4S). The *BIN1* rs6733839 (which was reported by Bellenguez et al. 2022 [6]) single nucleotide polymorphism (SNP) data came from the Alzheimer's Disease Genetics Consortium (ADGC) genotype data (PLINK format file sets) which were provided by ADGC collaborators. The allele frequencies of the *APOE* and *BIN1* risk alleles are shown in **Supplemental Table 3** and their associations with ADNC, LATE-NC, and LBD are shown in **Supplemental Table 4**.

Statistical analysis

We used analysis of covariance (ANCOVA) including age at death, sex, *APOE* ε4, and ordinal arteriolosclerosis variables as a covariate to estimate adjusted means of standard clinical dementia rating (CDR®) sum of boxes (CDR-SOB) by LATE-NC status and its association with LATE-NC stages [60]. To estimate probability of pure LATE-NC over age at death in a general population, we employed the survey weighting method implemented with the "pewmethods" R package (https://github.com/pewresearch/pewmethods). We first estimated marginal population distributions of *APOE* ε4 and the T allele of *BIN1* rs6733839 by the "create_raking_targets" function using the 1000 Genomes Project Phase 3 [21] (1000 g) in European (EUR) population. The *APOE* ε4 status was determined by rs429358 and rs7412. We then calculated the sample weights using the "rake_survey" function so that the weighted distributions of *APOE* ε4 and the T allele of rs6733839 in our study samples became identical with those in the 1000 g EUR population. Since the range of the weights was 0.27 to 1.42, we did not apply weight truncation. The estimated probabilities of pure LATE-NC were finally computed for the unweighted and weighted samples using the "glm" and "svyglm" (the "survey" R package version 3.5) functions, respectively.

Results

Exclusion and inclusion criteria, and the numbers of participants excluded using them, along with other definitional criteria, are depicted in Supplemental Table 1 and Supplemental Fig 1. Following the application of exclusion criteria, a total of 1,926 participants were included from 32 different ADRCs in the NACC NP Data Set (Table 1). Of these participants, 52.9% were female, and 92.4% were White. In terms of cognitive status, 69.1% were documented to have dementia, 12.1% were MCI, leaving 18.7% Normal or impaired-not-MCI prior to death.

Table 1 Characteristics of included research participants

Characteristic	n (%)		
	Overall (n = 1,926)	*APOE* ε4*	
		No (n = 932)	At least one ε4 allele (n = 810)
Female	1,019 (52.9)	492 (52.8)	433 (53.5)
White	1,780 (92.4)	867 (93.0)	746 (92.1)
Cognitive status			
Normal/Impaired-not-MCI	361 (18.7)	262 (28.1)	76 (9.4)
MCI	234 (12.1)	144 (15.5)	61 (7.5)
Dementia	1,331 (69.1)	526 (56.4)	673 (83.1)
BIN1 (rs6733839)**			
C/C	506 (35.8)	282 (37.0)	224 (34.4)
T/C	673 (47.6)	352 (46.2)	321 (49.4)
T/T	234 (16.6)	128 (16.8)	105 (16.2)

*$n = 184$ had no *APOE* genetic data (NACCNE4S) in the NACC UDS dataset

**$n = 513$ did not have *BIN1* genetic data in the Alzheimer's Disease Genetics Consortium (ADGC)

MCI Mild cognitive impairment

Our primary interest was in pure LATE-NC, for which there is no consensus-based operational definition, but the implication of the term is that LATE-NC is present in a brain that lacks intermediate- or high-level ADNC (as ADNC is formally defined [49]). We note that low severity of ADNC is not associated with substantial cognitive impairment [24, 55]. A preliminary assessment of pure LATE-NC versus ADNC + LATE-NC and ADNC + LATE-NC + LB pathology indicated that there was a trend for pure LATE-NC cases to be older at death, with a possible trend to have a higher frequency of comorbid hippocampal sclerosis (Table 2).

We wanted to evaluate the correlation between ADNC risk alleles (as a reflection of presumed recruitment bias favoring persons with risk of AD per se) and the detected frequencies of pure versions of non-ADNC pathologies. We hypothesized that ADRCs with higher levels of genetic risk for ADNC would have lower percentage of participants that lack ADNC, and thus could have pure LATE-NC. We found that among included participants in the NACC NP Data Set with known genotypes, the frequencies of AD risk alleles related to *APOE* and *BIN1* were highly enriched in comparison to human populations: 46.5% of participants had at least one *APOE* ε4 allele, and 64.2% had at least one *BIN1* AD risk allele (T allele of rs6733839). The reason that we evaluated *BIN1* in addition to *APOE* is that we wanted to test whether the ADNC-related genetic risk factors that may influence recruitment bias (the enrichment for research participants with ADNC genetic risk factors in ADRC cohorts,

Table 2 Characteristics in people with LATE-NC by pathology-based disease categories

Characteristic	Pure LATE-NC	ADNC + LATE-NC	ADNC + LATE-NC + LB
Female, n (%)	35 (53.0)	232 (56.4)	37 (53.6)
Age at death, mean (SD)	90.7 (7.5)	87.3 (6.9)	84.8 (6.3)
Arteriolosclerosis, n (%)			
None	16 (24.2)	39 (9.7)	5 (7.4)
Mild	19 (28.8)	113 (28.1)	18 (26.5)
Moderate	20 (30.3)	169 (42.0)	28 (41.2)
Severe	11 (16.7)	81 (20.1)	17 (25.0)
Hippocampal sclerosis, n (%)	35 (53.0)	173 (43.0)	24 (35.3)
Aging-related tau astrogliopathy (ARTAG), n (%)*	15 (57.7)	67 (57.3)	10 (43.5)

*$n = 166$ had the aging-related tau astrogliopathy (NPARTAG) data available

ADNC = Alzheimer's disease neuropathologic change, *LATE-NC* Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change, *LB* Lewy bodies

and the corresponding lack of non-ADNC cases in those cohorts) pertained to genotypes other than *APOE*; *BIN1* was chosen for this analysis because variation at the *BIN1* locus appears to be the second-strongest driver of ADNC [6]. Looking across ADRCs with sufficient numbers of participants to be included in the analyses (n = 29 different ADRCs with 5 or more participants), there was a robust negative correlation between the allele frequencies for both *APOE* and *BIN1* and the proportion of participants from those individual ADRCs that lacked ADNC (Fig. 1). The data strongly indicate the existence of recruitment bias into ADRCs (some more than others), which generally favors recruitment of people at high genetic risk. This bias is associated with an artifactually high frequency of ADNC, and a correspondingly low frequency of pure LATE-NC.

Given the above considerations, we sought to visualize the data in a manner that enables better discrimination of results among *APOE* ε4 non-carriers. Table 3 shows the numbers of participants stratified by *APOE* ε4 status, LATE-NC status, and ADNC severity. Note that overall 4.3% (75/1,742) participants had pure LATE-NC (LATE-NC but No/Low ADNC), but among the *APOE* ε4 non-carriers, 6.4% (60/932) participants had pure LATE-NC.

To query the actual (in the NACC data set) and predicted (more generalizable to human populations) probabilities of pure LATE-NC across the lifespan, we performed an analysis of NACC data without and with a correction for *APOE* ε4 and *BIN1* (rs6733839) T risk allele frequencies. The graph in Fig. 2 depicts estimated probabilities of pure LATE-NC by age at death in unweighted samples (blue) (i.e., directly estimated from the NACC NP Data Set) and weighted samples with *APOE* ε4 allele frequency of 15.5% and *BIN1* T allele of 38.0% (red). Consistent with the data shown in Table 3, Fig. 2 indicates that, age-for-age, there is approximately 50% increase of predicted pure LATE-NC, based only on the assumption of more population-generalizable *APOE* and *BIN1* allele frequencies. The model indicates a possible narrowing of the gap between actual and estimated pure LATE-NC rates, with advancing age.

We developed neuropathologic cutoff criteria for defining pure and mixed subtypes of LATE-NC, ADNC, and LB; see Supplemental Table 2. We compared the frequency of pure LATE-NC with pure neocortical LB and pure ADNC. In this subsample lacking *APOE* ε4, pure LATE-NC (lacking neocortical LB, as well as substantial ADNC) was found in 5.3% of participants, whereas pure neocortical LB was 3.6%, and pure ADNC was 37.0% (Table 4).

Applying these same pathology-based diagnostic criteria, we queried what percent of included participants died with dementia, stratifying by the various subtypes of pathology – pure and "mixed types". These data are presented in Table 5. Across all the subtypes of pathology, pure subtypes tended to have died with dementia diagnosis – among *APOE* ε4 non-carrier participants, with pure LATE-NC 56% died with dementia, versus ADNC 61%, and pure LB 70% died with dementia. Notably, people who died with mixed pathologies were even more likely to die with dementia (> 86% of ADNC + LATE-NC and 100% of ADNC + LATE-NC + LB died with dementia).

In terms of other phenomena associated with pure LATE-NC, 47% with pure LATE-NC had moderate or severe brain arteriolosclerosis, 53% had hippocampal sclerosis, and 38% had been given during life the presumptive diagnosis of "Probable AD". Using ANCOVA that took into account covariates including age at death, sex, brain arteriolosclerosis, and *APOE* ε4, the presence of LATE-NC among people with no/low ADNC and no LB in neocortical region was associated with significantly increased CDR-SOB scores ($p < 0.0023$), that is, worsened global cognitive impairments (Fig. 3).

Among the participants with pure LATE-NC and having available neuropathologic data on amygdala, hippocampal,

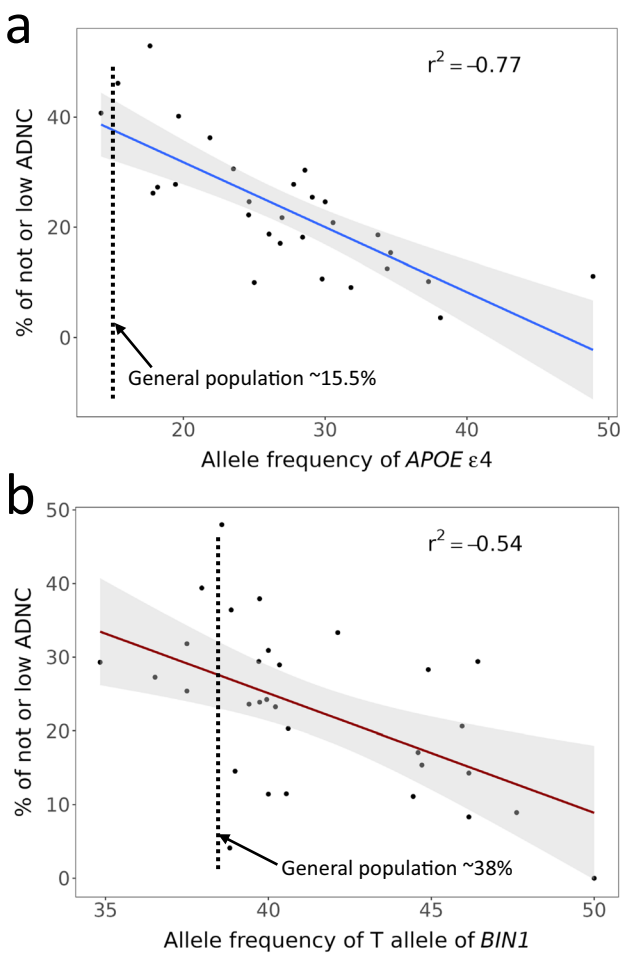

Fig. 1 Associations between *APOE* ε4 allele status **A** and *BIN1* rs6733839 T allele status **B** and lack of ADNC frequency in NIA-funded AD Research Centers (ADRCs). Each data point represents aggregated data from a single ADRC; $n = 29$ ADRCs were included which each had ≥ 5 participants with *APOE* genotype data. Normative allele frequency levels risk alleles in most human populations (~ 15.5%) are shown with a dotted vertical line **A**. Normative allele frequency levels for *BIN1* rs6733839 T (risk) allele in most human populations (~ 38%) are shown with a dotted vertical line **B**. Note that there is a strong negative correlation between the allele frequency of both *APOE* ε4 and the *BIN1* risk allele, and the frequency of participants that lack ADNC. Only participants that lack ADNC can have pure LATE-NC, so the high ADNC-specific risk allele frequency in some ADRCs is linked to lower apparent LATE-NC frequency

and middle frontal gyrus TDP-43 pathology (to enable staging of LATE-NC distribution), there was a trend for higher LATE-NC stages to be associated with higher (i.e., worse) CDR-SOB scores ($p = 0.026$ for linear trend of LATE-NC stages) as shown in Table 6. There was no evidence that pure LATE-NC was associated with clinical features of FTLD-TDP, namely disinhibition or primary progressive aphasia (Table 7); these clinical findings were more likely to have been reported with severe ADNC (bottom row of Table 7), with or without comorbid LATE-NC.

Discussion

Data were analyzed from the multicenter-derived NACC Neuropathology Data Set, focusing on the frequency and clinical impact of pure LATE-NC, i.e. brains with LATE-NC but lacking intermediate or severe ADNC. Prior scholarship has been published analyzing NACC Neuropathology Data Set data related to TDP-43 pathology and LATE-NC phenotypes [9, 14, 18, 20, 23, 29–31, 33, 45, 48, 70, 89, 93], but as far as we know this is the first study with an emphasis specifically on pure LATE-NC in this data set. As expected, most participants evaluated had "mixed" pathology, so that, whereas "pure ADNC" was the most common single "pure" pathologic group in this cohort, the pure subtypes were < 50% overall.

Using *APOE* and *BIN1* alleles as proxies for ADNC genetic risk, we predict that the frequency of pure LATE-NC in a representative human population would comprise > 3% of participants over 80 years of age. This frequency (~ 1:30 presumed lifetime risk) for pure LATE-NC can be compared to other pathologies. For example, there is ~ 1:3 lifetime risk for pure ADNC [56] (the most common subtype of pure dementia-related pathology), and ~ 1:1000 lifetime risk for FTLD-TDP [16, 37] (rare). Given these data, pure LATE-NC is neither particularly common, nor is it rare in comparison to other neurodegenerative diseases, but is of intermediate prevalence in aging brains. The coexistence of LATE-NC and ADNC was highly frequent and many combinatorial mixtures (high ADNC/low LATE-NC, vice versa, &c.) exist along the pathological severity spectrum [56].

Beyond a description of the frequency of pure LATE-NC in the NACC Neuropathology Data Set, we sought to address several other pertinent questions: 1 > What is a credible hypothesis to explain why different research centers have large apparent differences in terms of the percentage of participants with pure LATE-NC? 2 > Is pure LATE-NC likely to have an impact on cognition?; and, 3 > What are some of the other clinical and pathological correlates of pure LATE-NC?

Prior work on TDP-43 pathology and LATE-NC phenotypes in the NACC Neuropathology Data Set [14, 20, 23, 29–31, 33, 48, 70, 93] laid the foundation for the present study. Previous studies from around the world (including ADRCs and many other sources) have touched on the presence, frequency, and correlative impacts of LATE-NC found at autopsy, while prior reviews have been written on the subject of LATE-NC and ADNC co-pathologies [46, 58, 81]. The present study helps to demonstrate why there may be different perspectives on pure LATE-NC according to the study design of the research cohort. The frequency of various pathologic combinations differed across

Table 3 Numbers of participants stratifying by *APOE* ε4 carrier status, ADNC severity, and LATE-NC (presence of absence of LATE-NC Stage > 1)

ADNC	n (%)				
	APOE ε4				
	No (n = 932)			At least one ε4 allele (n = 810)	
	LATE-NC−	LATE-NC+	% of group	LATE-NC−	LATE-NC+
No	115 (16.1)	19 (8.7)	← 14.2	8 (1.5)	2 (0.7)
Low	195 (27.3)	41 (18.7)	← 17.4	39 (7.5)	13 (4.5)
Intermediate	208 (29.2)	43 (19.6)		135 (26.0)	46 (15.9)
High	195 (37.3)	116 (53.0)		338 (65.0)	229 (79.0)

ADNC Alzheimer's disease neuropathologic change, *LATE-NC* Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change

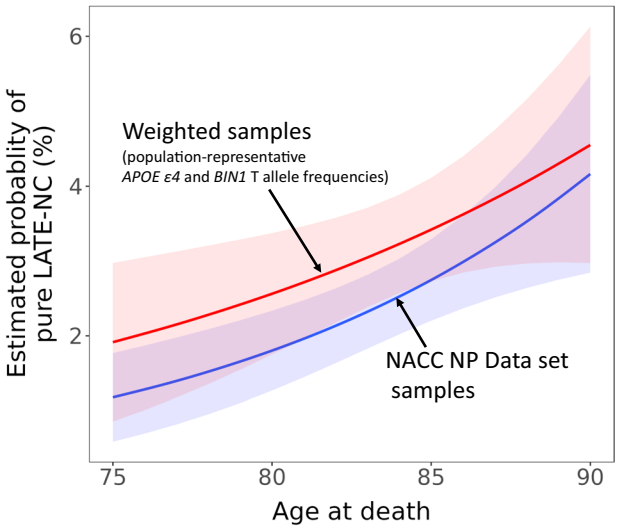

Fig. 2 Estimated probabilities of pure LATE-NC across the aging spectrum in the samples from the NACC Neuropathology dataset (blue) and after being weighted statistically to be population-representative for *APOE* ε4 and *BIN1* risk alleles (red). The weighted samples had the *APOE* ε4 allele frequency of 15.5% and *BIN1* (rs6733839 T allele) frequency of 38.0%. The weighted frequency predicts a ~ 50% increase in pure LATE-NC in a population with more population-representative genetic markers for *APOE* ε4 and *BIN1* risk alleles. Note that this estimation ignores the many additional genetic factors that are associated with variability in AD-type dementia risk (see Bellenguez et al., 2022 [6])

the contributory research centers, as described previously [20]. Of relevance to the topic of pure LATE-NC, ADRCs with research participants who on average had lower genetic vulnerability to ADNC (as demonstrated with *APOE* and *BIN1* genotypes) were more likely to have no/low-ADNC participants and that tendency was correlated with increased frequency of pure LATE-NC. Our inclusion of *BIN1* analyses are to underscore that the ADRCs' (and probably other dementia clinic-based cohorts') recruitment bias in terms of ADNC genetic risk extends beyond the *APOE* risk alleles. In other words, recruitment bias helps to explain some of the findings, which reflects the fact that persons at higher genetic risk for certain pathologies are more likely to be recruited into some studies in comparison to their representation in the general population. More specifically, in European populations, the prevalence of risk alleles in *APOE* is ~ 25%, and risk allele in *BIN1* is ~ 50%. However, in the NACC Neuropathology Data Set, the risk alleles for these genes were both present in > 40% and > 60%, of participants respectively, an indication of recruitment bias in the contributory research centers. Furthermore, given the basic nature of ADRCs, heritable risk may not be the only recruitment bias pertinent to this sample that favor enrichment of participants with ADNC underlying the clinical features. For example, many were recruited while already symptomatic with AD-type dementia [20].

The findings of disparate results when comparing between the ADRC cohorts in the present study provided a basis to interpret the findings in published studies from around the world. Table 8 shows the results for the present study for comparison to prior published work; published papers used for this table necessarily included breakdowns of LATE-NC status by amyloid plaque data. Note that otherwise excellent prior published studies that lacked *APOE* allele frequency [1, 63, 86], or that focused on normal subjects [3, 53] or on chronic traumatic encephalopathy (CTE) [36, 64], were not included in this table. Considered together were community-based cohorts contributory to the combined study that represents the third data row in Table 8 [47, 79, 87]. The community-based studies included Adult Changes in Thought (ACT) [40]; Brazilian Biobank for Aging Studies (BAS) of the University of Sao Paulo [80]; Cambridge City over-75 s Cohort (CC75C) [12]; Medical Research Council Cognitive Function and Ageing Study (CFAS) [91]; Duke/University of North Carolina AD Research Center (Duke/UNC-ADRC) [22]; Honolulu Asia-Aging Study (HAAS) [92]; Mayo Clinic Study of Aging (MCSA) [67]; Nun Study[85]; Rush University Religious Orders Study/Memory and Aging Project (ROS-MAP) [7]; University of California Irvine The

Table 4 Numbers of *APOE* ε4- participants stratifying by neocortical Lewy bodies (present/absent), ADNC severity, and LATE-NC (presence or absence of LATE-NC Stage > 1)

ADNC severity	Among participants who lack *APOE* ε4 allele						
	No LB in neocortical region(s)				LB in neocortical region(s)		
	LATE-NC−		LATE-NC+		LATE-NC−		LATE-NC+
No	102		15	← Pure LATE-NC: 5.3%	13	← Pure LB: 3.5%	4
Low	175		35		20		6
Intermediate	176	← Pure ADNC: 37.0%	39		32		4
High	169		104		26		12

ADNC Alzheimer's disease neuropathologic change, *LB* Lewy bodies, *LATE-NC* Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change

Table 5 Numbers of participants stratifying by documented dementia status and various subtypes and combinations of pathology

Pathology-based disease categories*	*APOE* ε4					
	No (n = 932)			At least one ε4 allele (n = 810)		
	Not demented (n)	Demented (n)	Demented %	Not demented (n)	Demented (n)	Demented %
Pure ADNC	134	211	61.2	72	335	82.3
Pure LATE-NC	22	28	56.0	4	10	71.4
Pure LB	10	23	69.7	0	7	100.0
ADNC + LATE-NC	19	124	86.7	16	212	93.0
ADNC + LB	12	46	79.3	7	59	89.4
ADNC + LATE-NC + LB	0	16	100	4	43	91.5

ADNC Alzheimer's disease neuropathologic change, *LATE-NC* Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change, *LB* Lewy bodies

*See **Supplemental** Tables 2 and 3 for pathology-based category definitions

90 + Study (The 90 + Study) [34]; University of Kentucky AD Research Center (UK-ADRC) [76]; Vantaa 85 + Study [35]; and, Vienna Trans-Danube Aging (VITA) study [38]. As Table 8 indicates, findings in the NACC NP Cohort show lower frequency of pure LATE-NC in comparison to prior results in community-based cohorts. We also note that the observed and predicted frequencies of pure LATE-NC tended to more closely correspond in advanced old age (the trend lines appear to converge in Fig. 2). We speculate that this may reflect that as ADNC risk factors other than *APOE* and *BIN1* recede in advanced old age, the frequency of pure LATE-NC is more predictable. However, more work is required to understand the age- and senescence-related factors that contribute to pure LATE-NC.

Our analyses also showed that, in persons lacking ADNC, LATE-NC was associated with cognitive impairment, compatible with results of prior work [26, 44, 54, 73, 78, 93, 95]. Dementia is a clinical syndrome defined by progressive impairment that compromises a person's abilities to perform activities of daily living [71] and most pure LATE-NC participants had premortem dementia documented; however, operationalizing dementia as a dichotomous variable ignores highly prevalent, subtler impairment that still may be disturbing to individuals and caregivers. Our abilities to discriminate subtle changes and cognitive gradations in the current study was not ideal, because we employed the relatively blunt instrument of CDR scores which are indicative of functional impairment and dementia [17]. Further, there was considerable biologic variation on both sides of the clinical-pathological correlation: there were many participants with other subtypes of pathology (e.g., the strong influence of vascular pathologies for which there are not yet optimal rubrics for the purposes of clinical-pathological correlation), and also variation in terms of the severity of TDP-43 proteinopathy that is not fully captured by LATE-NC staging (LATE-NC grades the distribution but not the densities of TDP-43 proteinopathy[60]). There also were not very large sample sizes for some of the subgroupings. With those caveats in mind, there was a statistically significant trend for lower functioning in pure LATE-NC, versus appropriate controls.

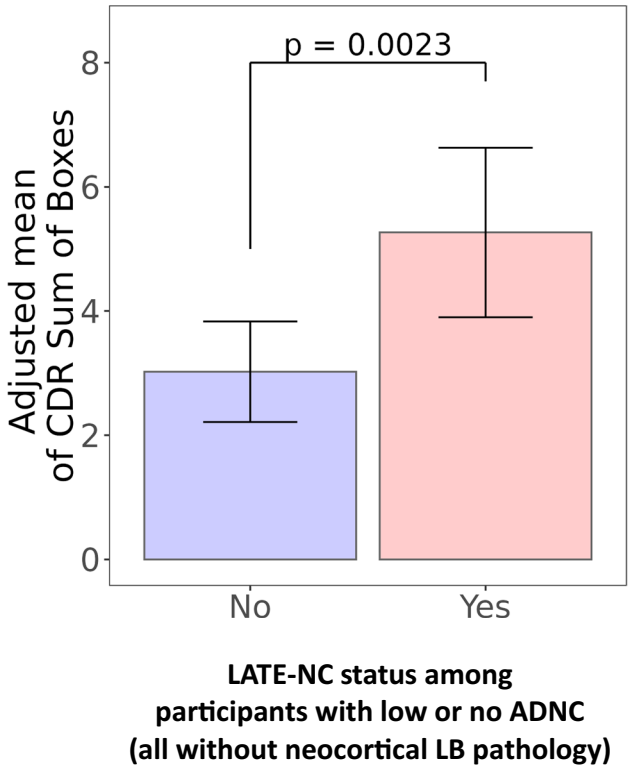

Fig. 3 Adjusted means of Clinical Dementia Rating Sum of Boxes (CDR-SOB) scores, by LATE-NC in people with no or low ADNC (i.e., NPADNC = 0 or 1) and no-neocortical Lewy bodies. Analysis of covariance including age at death, sex, *APOE* ε4, and brain arteriolosclerosis as a covariate was used. Among those with not or low ADNC and no neocortical Lewy bodies, the presence of LATE-NC was associated with deficits in terms of activities of daily living as measured by the CDR-SOB (p = 0.0023). Comparison was according to a two-tailed test and error bars represent 95% confidence interval

Table 6 Adjusted means of CDR sum of boxes scores by LATE-NC pathological staging in pure LATE group with data available on amygdala, hippocampus, and middle frontal gyrus TDP-43 pathology (n = 62)

	LATE-NC stage			
	1	2	3	p = 0.079 (ANCOVA) p = 0.026 (Linear trend)
n (%)	5 (7.6)	45 (68.2)	12 (18.2)	
CDR sum of boxes, mean ± SE	2.4 ± 2.2	6.3 ± 0.9	8.8 ± 1.6	

LATE-NC Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change, *CDR* Clinical dementia rating, *SE* Standard error, *ANCOVA* Analysis of covariance

In terms of other clinical correlates, we did not find evidence that pure LATE-NC is associated with clinical features of FTLD-TDP. More specifically, in this cohort both disinhibition and primary progressive aphasia were associated with severe ADNC, but not with pure LATE-NC. It is important to note that pathologically-confirmed FTLD cases were excluded from the sample. However, concordant with prior studies [29, 69, 93], these results again underscore that LATE-NC is a very different condition than FTLD-TDP. Whereas pure LATE-NC did not tend to resemble FTLD-TDP clinically, the clinical findings in many pure LATE-NC cases did resemble AD-type dementia, given that 38% of pure LATE-NC cases were diagnosed during life as Probable AD. It is important to keep in mind that the diagnoses were all made in state-of-the-art ADRCs, among the most resource- and expertise-rich academic centers in the world. A community hospital would not necessarily have access to the same diagnostic assets. LATE-NC masquerading clinically as AD dementia is a potential confounder to keep in mind for clinicians, but the misdiagnosis of Probable AD in participants of pure LATE-NC will presumably become less common as clinical diagnostics continue to improve.

Table 7 Numbers of participants stratifying by documented clinical disinhibition and primary progressive aphasia diagnoses and subtypes of pathology – ADNC and LATE-NC

ADNC severity	n (%)			
	Disinhibition		Primary progressive aphasia	
	LATE-NC −	LATE-NC +	LATE-NC −	LATE-NC +
No	17 (7.1)	2 (1.7)	1 (3.6)	0 (0)
Low	24 (10.1)	10 (8.3)	0 (0)	0 (0)
Intermediate	48 (20.2)	18 (15.0)	1 (3.6)	0 (0)
High	149 (62.6)	90 (75.0)	26 (92.9)	14 (100)

ADNC Alzheimer's disease neuropathologic change, *LATE-NC* Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change

There were some limitations to the current study. In terms of disease-related pathological cutoffs for group-level criteria designation, different categorizations could be used, e.g. using CERAD neuritic amyloid plaque scores rather than Aβ phase scores for operationalizing ADNC, and therefore for delineating pure LATE-NC. Our rationale for using Aβ phases rather than neuritic plaque scores (or Braak NFT stages) is that the Aβ phases were used in the NIA-AA criteria as the most specific feature of ADNC [49]—by definition, a brain with Aβ plaques but no tau pathology is still ADNC, whereas, by contrast, a brain with tau pathology but no Aβ plaques is not ADNC [49]. (The consensus-based ADNC criteria [49] specify that Aβ plaques without neuritic plaques is still "Low" ADNC, but leave unspecified what the implications are of neuritic plaques without Aβ).

There are limitations of using the NACC data sets in terms of recruitment bias and generalizability—ADRCs tend to be enriched for high socioeconomic Caucasians who are at risk for AD-type dementia [2, 9, 20, 48]. One strategy to

Table 8 Summary data indicating the frequency of pure LATE-NC and other parameters in the current and select prior studies*

Cohort	Ref	Autopsy cohort study design	N **	*APOE* ε4 + % ***	% Pure LATE-NC overall in the cohort	
					No ADNC definition: Aβ Phase 0	No ADNC definition: Aβ Phase 0 or 1
(Current study) NACC Neuropathology data set; all	[9], current study	Multi-center; 30 mostly clinic-based with several community-based cohorts	1926	46.5	1.2	4.3
(Current study) NACC Neuropathology data set; *APOE* ε4-			932	0	2.0	6.4
Combined community-based cohorts****	[56]	Multi-center; 13 community- and population-based cohorts	3803	25.5	4.0	9.9
U. California Irvine, The 90 + Study	[42]	Community-based cohort	364	18.0	2.0	7.7
UZ/KU Leuven biobank – Brain Collection	[82, 83]	Hospital-based cohort	342	34.9	2.0	3.5
Johns Hopkins/Baltimore Longitudinal Study of Aging	[15]	Mixed community- and hospital-based cohort	113	26.1	3.9	7.8

*Additional demographic and neuropathologic data referent to these cohorts are provided as Supplemental Table 5

**These numbers reflect non-FTLD participants

***All cohorts had > 60% APOE genotyping, these percentages refer to the subset of those genotyped

****In this study a subset (n = 3803) had access to Aβ phase and LATE-NC status; these were the data tabulated in Ref. [56] Table 5

overcome some of these biases is to limit the analyses to community- and population-based cohorts; this strategy has been successful in prior work [56, 63]. However, to understand how the different autopsy cohorts may come to differing conclusions, and the covariates that may help explain those differences, it is useful to leverage the multicenter nature of NACC and its contributory ADRCs. ADRCs vary in their recruitment practices and protocols while providing standardized assessment instruments across the different institutions. The hypothesis of there being recruitment bias at clinic-based cohorts such as ADRCs, increasing AD risk in comparison to most human populations, was supported by our results displaying the high frequency of AD risk alleles in *APOE* and *BIN1* in the NACC Neuropathology Data Set. The ADRC system thus provided a useful context to assess the relationships between study designs, recruitment practices, and reported outcomes related to dementia research. As such, some of the current study's results could not have been arrived at by analyzing data derived from any single- or even several-center study cohort.

Conclusions

Mixed pathologies are the norm in old people's brains, but pure LATE-NC is still fairly common (approximately as frequent as "pure" neocortical LB), particularly among individuals who lack the *APOE* ε4 allele, and when analyzing data from autopsy cohorts with lower *APOE* ε4 allele rates. In terms of clinical impact, pure LATE-NC was associated with increased likelihood of global cognitive impairments, and tended to be associated with dementia, but not with clinical features of FTLD-TDP. Taking all of these results together, among people that live to beyond age 85, the frequency of LATE-NC with no or scant ADNC, is predicted to be approximately 5%, most of whom would be expected to be demented before death.

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Data availability The datasets generated and/or analyzed during the current study are available in the NACC data set repository, https://naccdata.org/requesting-data/web-

Declarations

Conflict of interest DRT & SOT received consultant honorary from Muna Therapeutics (Belgium). DRT collaborated with Novartis Pharma AG (Switzerland), and GE-Healthcare (UK). DRT and PTN are members of *Acta Neuropathologica* editorial board. They were not involved in the assessment or decision-making process for this manuscript. The other authors declare that they have no competing interests.

Ethical approval and consent to participate For all NACC data, only anonymized summary information was used. Institutional review board approval and informed consent were obtained from all participants at each of individual AD Research Center (ADRC). Under those auspices, informed consent was obtained from all individual participants included in the study. See https://naccdata.org/requesting-data/nacc-data

Consent for publication Not applicable.

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