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Title:

Frequency of LATE neuropathologic change across the spectrum of Alzheimer's disease neuropathology: an analysis of data from 13 community-based or population-based autopsy studies

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Abstract

Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) and Alzheimer's disease neuropathologic change (ADNC) are each associated with substantial cognitive impairment in aging populations. However, the prevalence of LATE-NC across the full range of ADNC remains uncertain. To address this knowledge gap, a set of neuropathologic, genetic, and clinical data were compiled from 13 high quality community- and population-based longitudinal studies. Participants were recruited from the United States (8 cohorts, including one focusing on Japanese-American men); United Kingdom (2 cohorts); and, Brazil, Austria, and Finland (one cohort each). The total number of participants included was 6,196, and the average age of death was 88.1 years. Not all data were available on each research volunteer and there were differences between the cohorts in study designs and data missingness. Among those with known cognitive status before death (n=5,665), 43.0% were cognitively normal, 14.9% had MCI, and 42.4% had dementia – broadly consistent with epidemiologic data in this age group. Approximately 99% of participants (n=6,125) had available CERAD neuritic amyloid plaque score data. In this subsample, 39.4% had autopsy-confirmed LATE-NC of any stage. Among brains with "frequent" neuritic amyloid plaques, 54.9% had comorbid LATE-NC, whereas in brains with no detected neuritic amyloid plaques, 27.0% had LATE-NC. Data on LATE-NC stages were available for 3,803 participants, of which 25% had LATE-NC stage>1 (associated with cognitive impairment). In the subset of individuals with known Thal Aβ phase = 0 (n=787 lacking detectable Aβ plaques), the brains with LATE-NC had relatively severe primary age-related tauopathy (PART). A total of 3,267 participants had available clinical data relevant to frontotemporal dementia (FTD), and none were given the clinical diagnosis of definite FTD nor the pathological diagnosis of frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP). In the 10 cohorts with detailed neurocognitive assessments proximal to death, cognition tended to be worse with LATE-NC across the full spectrum of ADNC severity. LATE-NC often, but not always, coexisted with Alzheimer's disease, and was seen in almost 40% of participants. This study provides a credible estimate of the current prevalence of LATE-NC in advanced age.

Key-words:

ADRD; tau; NFT; nondemented; oldest-old; epidemiology; APOE

If possible, please consider these additional key-words:

ROS-MAP, Vantaa 85+, HAAS, CFAS, CC75C, The 90+ Study, ACT, VITA, Nun Study, Biobank for Aging Studies, Mayo Clinic Study of Aging

Introduction

Brain autopsies of persons with documented amnestic dementia often reveal evidence of Alzheimer's disease neuropathologic change (ADNC) [74], limbic predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) [85], or both. However, the independent and joint prevalence of each of these disorders are unclear. There remain uncertainties about optimal classification of LATE-NC and some individual brains are challenging to categorize, as is the case for other subtypes of neurodegenerative disease [8, 30, 45, 56, 71, 86, 102]. Thus, high-quality data, derived from different geographical locations and including autopsy results, are required to shed light on the prevalence and co-existence of these high-morbidity brain pathologies.

The cardinal diagnostic feature of LATE-NC is TDP-43 pathology – aberrant TDP-43 protein deposits visualized with immunohistochemistry [85]. TDP-43 pathology was discovered in 2006 as the primary pathological hallmark of frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP) and amyotrophic lateral sclerosis [88]. However, TDP-43 pathology is now appreciated to occur in many other conditions [19]. Although diagnostic ambiguities still exist in TDP-43 neuropathologic assessments, LATE-NC has distinguishing characteristics including the neuroanatomical distribution of TDP-43 pathology, clinical features, genetic risk factors, and epidemiology [22, 42, 55, 85, 99]. For example, the demographic group most likely to show LATE-NC is persons beyond 85 years of age [85], and, LATE-NC is strongly associated with amnestic dementia, independent of other known brain pathologies [12, 33, 39, 42, 43, 46, 49, 53, 62, 75, 76, 83, 97].

Like LATE-NC, ADNC is prevalent in the older population and is also associated with amnestic dementia. ADNC and LATE-NC are genetically pleiotropic: the *APOE* ε4 ADNC risk allele is also associated with increased risk for LATE-NC [3, 29, 46, 127]. LATE-NC and ADNC are often present in the same brains [47, 48, 65, 69], and TDP-43 pathology may colocalize with tau-immunoreactive neurofibrillary tangles (NFTs), a hallmark ADNC lesion [46, 108, 119]. The presence of "mixed" pathologies is important – the clinical manifestations vary with different combinations of pathologies [67]. For example, "pure LATE-NC" is, on average, associated with a less severe clinical phenotype than "pure ADNC", whereas the common combination (ADNC+LATE-NC) is associated with a more aggressive clinical course than either alone [50, 51, 78, 118, 128].

Despite recent progress, questions persist. Investigators have considered whether TDP-43 pathology in aging is best defined as a subtype of ADNC [45]. While there is heterogeneity in the

genetic, pathologic, and clinical features of AD, as yet there are no consensus-based criteria for delineating subtypes of ADNC. Other questions include: What is the overall end-of-life frequency of LATE-NC in the brains of older persons? How does prevalence vary across populations? How frequently is LATE-NC seen in brains with no, low, intermediate, or high severity ADNC, and in those with varying severities of primary age-related tauopathy (PART)?

Addressing questions about the prevalence of different pathologies requires relatively population-representative autopsy cohorts. Dementia clinic- and hospital-based cohorts are invaluable resources for research, but they tend to be substantially enriched for unusual subtypes of dementia [104], early-onset diseases, and genetic risk factors, which limit the generalizability of the findings. While there have been prior reports about LATE-NC from individual research centers, and from various consortia [5, 60, 73], there has not been a prior study bringing together findings from a large number of community-based autopsy cohorts.

In the current study, summary information was gathered related to LATE-NC and ADNC from 13 separate well-established study cohorts with available autopsy information. These cohorts included participants who were mostly recruited without dementia and followed longitudinally to autopsy at research centers in the United States (8 cohorts), United Kingdom (2 cohorts), and, Brazil, Austria, and Finland (one cohort each). Several of the included cohorts can be described as "population-based", in that the individual donors were recruited from a general population within a geographical boundary in a study design that aimed to recruit from all subgroups within the population. While the cohorts that are not population-based did not use probability-sampling and are not completely generalizable to their target populations, they are likely to be far more representative of the populations from which they were derived than clinic- or hospital-based cohorts. The combined data from multiple research cohorts provided the bases for gaining insights into how common LATE-NC is at autopsy, with or without comorbid ADNC.

Methods

The main goals of this study were to examine the frequency of LATE-NC at the end of life in community-based research participants and to stratify results by the level of reported ADNC severity. Based on those goals, summary data were requested related to ADNC and LATE-NC from 13 high-quality community-based and population-based cohorts of brain aging and dementia. (The term

"community-based" is mostly used from here forward to refer to the present collection of cohorts.) Data were collected from each of the following autopsy cohorts (in alphabetical order): Adult Changes in Thought (ACT) [61]; Brazilian Biobank for Aging Studies (BAS) of the University of Sao Paulo [113]; Cambridge City over-75s Cohort (CC75C) [16]; Medical Research Council Cognitive Function and Ageing Study (CFAS) [123]; Duke/University of North Carolina University AD Research Center (Duke/UNC-ADRC) [39]; Honolulu Asia-Aging Study (HAAS) [125]; Mayo Clinic Study of Aging (MCSA) [96]; Nun Study[120]; Rush University Religious Orders Study/Memory and Aging Project (ROS-MAP) [10]; University of California Irvine The 90+ Study (The 90+Study) [52]; University of Kentucky AD Research Center (UKy-ADRC) [103]; Vantaa 85+ Study [54]; and, Vienna Trans-Danube Aging (VITA) study [57]. See **Supplemental Table 1**, online resource, for more information on each cohort. All study procedures were approved by the respective Institutional Review Boards or Research Ethics Boards. Each participant (or their next of kin if they lacked capacity) provided informed consent for cohort participation. No additional approvals were needed for analysis of the de-identified summary data from each cohort. Many of the research participants were recruited from the community using methods such as local media advertising, health fairs, and presentations to community groups.

The structured data requests sent to a representative of each cohort are shown in **Supplemental Table 2**, online resource. For the collection of data on ADNC, different pathology-based measures were requested: Braak NFT distribution staging (0-VI scale) [14] performed using anti-phospho-Tau antibodies; CERAD neuritic amyloid plaque density stages (graded as "None", "Sparse plaques", "Moderate plaques", or "Frequent plaques"), which indicate density of neuritic plaques in cerebral cortex [72]; and, Thal Aβ Phases (a 0-5 scale based on anatomic distribution of Aβ plaques detected with Aβ immunostaining) [6, 116]. The rationale for incorporating these parameters was that they are all used for determining the presence and severity of ADNC according to current consensus-based criteria [74].

During data harmonization, cohort-specific data format variations were identified. For example, not all of the cohorts used the same cognitive testing instruments. To operationalize global cognitive status, the cohorts used Mini-Mental State Examination (MMSE) scores [35], except HAAS used the Cognitive Abilities Screening Instrument (CASI) [115], and both the Brazil BAS cohort and MCSA used the Clinical Dementia Rating sum of boxes scores [28]. For the UKy-ADRC, only participants who were recruited while cognitively normal were included and 11

subjects were excluded from the cognitive assessments due to no MMSE scores. For the BAS, participants 50 years or older at death were included and participants were excluded from this cohort with inconsistent clinical information, a postmortem interval greater than 24 hours, or if the brain tissue was incompatible for neuropathological analyses (e.g., cerebrospinal fluid pH < 6.5 or major acute brain lesions including hemorrhages). The Nun Study used MMSE cut points as follows: scores of <17: dementia; 17-21: mild cognitive impairment (MCI); and, >21 nondemented. For HAAS, the CASI scores were used at cutoffs >=74 (normal), 60-73.9 (MCI), or <60 (dementia). ROS/MAP data on clinical status were missing for 1 subject (0.05%). For The 90+ Study, 14 participants were excluded from the MMSE analyses due to missing scores. For the Duke/UNC-ADRC cohort, participants 90 years or over at death were included in the study. Approximately 70% from this cohort were cognitively normal at recruitment, and 29 participants were excluded from the cognitive assessment due to no MMSE score. For the Vantaa 85+ Study, DSM-IIIR criteria were used to diagnose dementia and MMSE scores were assessed for most participants in the baseline study and follow-ups. For the MCSA, 37 participants did not have the Clinical Dementia Rating sum of boxes scores [28] within 3 years of death.

There also were differences among the cohorts in the methods of tissue-processing at autopsy, neuropathologic evaluations, and data missingness. For the MCSA, there were n=209 with available LATE-NC data from autopsied study participants whose consensus diagnosis was cognitively normal at baseline. Of these, 13 were missing Thal phase, 4 were missing CERAD neuritic plaque score. For the CC75C cohort, data on neocortical Lewy bodies were missing for 12 (5.3%); Thal phase missing for 5 (2.2%); Braak stage missing for 1.

Cohorts were also queried as to whether they had clinical evaluations during life and corroborating neuropathologic studies, that likely would have captured cases of FTD/FTLD-TDP if they were in the cohort. The specific question posed to each autopsy cohort was: how many clear-cut FTD/FTLD-TDP cases were in their cohort? The symptoms of FTD include behavioral disturbances and language problems [55, 94, 111], but variants of these cognitive signs and symptoms (*e.g.,* disinhibition and aphasia) may also occur in Alzheimer's disease and other dementia disorders, so there was some subjectivity in the clinical diagnosis.

To address whether multiple blinded neuropathologic raters from different institutions would agree with the results of Braak NFT staging, particularly in the context of cases with LATE-NC but lacking ADNC, a multi-center digital pathology study was performed. Brain sections from

10 individuals were included in this focused study, of which 7 had LATE-NC, 1 had FTLD-TDP, and 1 had severe ADNC. The following slides had been stained for phospho-Tau IHC (PHF-1 antibody[37]): hippocampus at the level of the lateral geniculate nucleus; anterior hippocampus and entorhinal cortex; occipital neocortex (Brodmann Area [BA] 17/18/19); superior and mid-temporal neocortex (BA 21/22); and, middle frontal gyrus (BA 9). Slides were anonymized and then converted to digital format using a Leica/Aperio ScanScope AT2 slide scanner at 40x resolution. Four separate raters with experience in digital neuropathologic evaluation (coauthors M.D.C., J.D., B.N.D., and J.H.N.) scored the pathologies via internet connection, using either the Aperio ImageScope™ or QuPath open-source software, to derive Braak NFT scores for each case while blinded to other information.

For data analyses, the joint distribution of neuropathologic ratings parameters were obtained from each cohort via structured questionnaires. The overall joint distributions were simply summations of each cell in the joint distribution from each cohort. For demographic characteristics age at death and sex, a single summary measure was provided by each cohort. To compute the overall summary of age at death and sex distribution, as well as *APOE* ε4 positivity, cohort-specific results were combined by weighting each cohort by its sample size. The association between *APOE* ε4 positivity and LATE-NC rate was evaluated using simple meta-regression that ignored sample weights, did not include the VITA cohort (where *APOE* genotype data were unavailable), and did not factor in *APOE* genotype data missingness. For the comparisons of Braak NFT stages (PART severity [23]) in Thal Aβ phase = 0 cases (comparing the results with versus without LATE-NC), a Fisher's exact test was applied to determine statistical significance.

Results

Selected demographic, clinical, genetic, and summary neuropathologic data on included participants from each of the 13 community-based cohorts are shown in **Table 1**. The total number of included participants was 6,196. Subset analyses were performed and the included numbers of subjects from each center for each analysis are provided in **Supplemental Table 3**, online resource. The median number of research participants included per cohort was 321, with a range of 109-1,620 participants per cohort. Mean weighted age of death for all included cohorts was 88.1 years; age ranges for the cohorts was 72.2-97.2 years. Overall, 62.3% of participants were women.

A chart depicting the clinical features of participants at their last cognitive evaluation is shown in **Fig. 1** (n=5,665 participants had those data available). Slightly over 40% were judged to be cognitively normal at their last clinical examination, and approximately the same proportion had documented dementia. In the 12 cohorts reporting the parameter, ~15% had MCI (See **Supplemental Table 3**, online resource).

In terms of FTD/FTLD cases, data were only considered from a cohort if FTD cases and/or FTLD-TDP cases would likely have been documented in that cohort. Having applied those criteria, data were provided from 9 different cohorts, comprising n=3,267 participants. In this subsample, no clinical FTD/FTLD-TDP cases were identified (**Table 2**). Although all these participants were evaluated by a clinician, it is conceivable that early FTLD-TDP cases were present but not detected.

APOE ε4 allele genotype data were available from a total of n=5,157 included participants (83.2% of the combined cohort). *APOE* allele data missingness by cohort is indicated on **Table 1**. Of the participants with known *APOE* genotype, 25.5% carried at least one copy of the *APOE* ε4 allele (range: 13.0-33.6%). In the 12 cohorts with available *APOE* genotyping, there was a marginal positive association between *APOE* ε4 allele carrier prevalence and LATE-NC frequency (r^2=0.36; p=0.039), indicating that cohorts with higher *APOE* ε4 prevalence also had higher LATE-NC frequency (**Fig. 2a**). By contrast, there was no such statistically significant association between LATE-NC frequency with cohorts average age, sex, or percent of included subjects with neocortical Lewy body pathology (**Fig. 2 b-d**)

LATE-NC is classified according to a 0-3 stage classification system, related to the anatomic distribution of TDP-43 pathology [85] and derived from studies that evaluated brains across a broad spectrum of pathologic severity [47, 77]. Cohort neuropathologists applied different antibodies to detect TDP-43 pathology, although most used antibodies against phosphorylated TDP-43 protein (data not shown). Findings in the various subset analyses, stratified by the subsamples evaluated and the LATE-NC results, are depicted in **Table 3**.

The full spectrum of ADNC severity was represented in the sample. Among those with known CERAD neuritic plaque scores (n=6,125), 31.6% were CERAD “None”, 17.6% “Sparse plaques”, 28.3% “Moderate plaques”, and 22.5% “Frequent plaques” (**Table 4, Fig. 3**). In participants with known Braak NFT stage (n=5,977), 33.8% were Braak NFT stages 0-II, 41.4% III/IV, and 24.7% V-VI (**Table 4, Fig. 4**).

In a subset of cases comprising n=3,803 participants, data were available including LATE-NC stages (0-3), Braak NFT stages (0-VI), and Thal Aβ phases (0-5) on each individual subject. The distribution of results stratifying by these parameters is shown in **Table 5**. Selected findings from those data are presented in chart format in **Fig. 5**.

Collectively, these data indicated that brains with more severe ADNC were relatively likely to have comorbid LATE-NC. For example, participants with Braak NFT Stage 0-II had a 22.4% probability of LATE-NC being diagnosed, whereas those with Braak NFT Stage VI had a 54.7% probability of a LATE-NC diagnosis (**Table 4, Fig. 4**). However, most of the participants with LATE-NC (61.2%) coincided with Braak NFT Stages between 0 and IV. Similar trends were observed for neuritic amyloid plaque densities (**Table 4, Fig. 3**), and Aβ amyloid deposition (**Table 5**). Although there were cohort-to-cohort variation, there was broad agreement in findings, as can be appreciated by the 25th-75th percentile error bars in **Figs. 3 and 4**.

Trends could be identified along the full range of ADNC and LATE-NC. Note that in the **Table 5** data, LATE-NC stage 3 brains comprised only 11% of LATE-NC+ cases (168 out of 1,469), and LATE-NC stage 3 was associated with a high rate of severe ADNC – approximately the same frequency of severe ADNC as seen in LATE-NC stage 2. Furthermore, in brains lacking Aβ amyloid deposition (Thal Aβ phase = 0; n=787), PART pathology was relatively more severe, i.e. higher Braak NFT stages, in persons with comorbid LATE-NC (**Fig. 5**).

While LATE-NC was more frequent with more severe ADNC, LATE-NC was nonetheless present across all levels of ADNC and even in those without ADNC. As shown in **Table 2**, 1,935 included participants had "None" neuritic amyloid plaques, and of these, 522 (27.0%) had LATE-NC. In the subset of individuals with known Thal Aβ phase = 0 (i.e. lacking Aβ plaques), 19.4% had LATE-NC, and 11.6% had LATE-NC Stages >1, a severity of LATE-NC which has been consistently associated with cognitive impairment [18, 75, 77, 78, 82].

To assess how different neuropathologic raters would diagnose Braak NFT staging of LATE-NC cases that lacked severe ADNC, a convenience sample of phospho-Tau immunostained slides was evaluated by four separate blinded neuropathology diagnosticians, using digital pathology over the internet. As expected [4], there was some variance in Braak NFT staging by the raters, but the median rendered Braak NFT stages were within 1 Braak stage of the initial diagnosis in 8/10 and within 2 Braak stages in all 10 cases (see **Supplemental Table 4**, online resource).

Summary information on final cognitive status of included participants was requested from each cohort, with the data stratified by Braak NFT stages (bottom of **Supplemental Table 2**, online resource). These data were a focal-point because Braak NFT staging is the widely gathered ADNC parameter that correlates most robustly with cognitive impairment [84]. Detailed stratified cognitive testing results were not available from VITA, CC75C, and CFAS cohorts and thus were not included in the clinical-pathological analyses. Among the cohorts with accessible information, the cognitive status data were variable from cohort to cohort. There were different cognitive assessment instruments, different intervals of testing, and different workflows used in administering the tests. The nature of these combined summary data precluded statistical modeling or other types of statistical testing. However, a recurrent pattern did emerge across the different study groups, despite the many sources of variance and the smaller sample sizes when using data from single cohorts**:** there was a tendency for cognitive scores to be lower in individuals with LATE-NC, across the full spectrum of ADNC severity in terms of Braak NFT stages (**Fig. 6**). Some of the implications and context of the present study are presented in **Fig. 7.**

Discussion

Data related to LATE-NC and ADNC were gathered, combined, and analyzed from 13 community-based and population-based longitudinal cohort studies. Overall, almost 40% of autopsied participants were positive for LATE-NC. LATE-NC was relatively common in donors with severe ADNC – approximately half of severe ADNC cases had comorbid LATE-NC. Also, approximately one in four brains with lacking ADNC had LATE-NC. In persons known to be lacking Aβ amyloid plaques (Thal Aβ Phase = 0), the PART pathology was more severe in persons with comorbid LATE-NC. There was a tendency for cognition to be worse in persons with LATE-NC, across the full spectrum of ADNC severity. These findings address basic questions about LATE-NC in people with and without comorbid ADNC.

Both the quality and quantity of data in this study constituted key strengths. The community- and population-based study designs of the contributory cohorts included many persons recruited while cognitively normal and followed longitudinally to autopsy. At the last exam before death, clinical features of the combined cohort showed slightly over 40% cognitive normal, and no FTD examples were documented. This may underestimate the extent of cognitive impairment at death, although most

of the donors were assessed in the last year of life. We emphasize that this distribution of clinical findings is in accord with epidemiologic data from human populations of this age group [22, 64, 91, 95]. No study with autopsies is perfectly representative of the variability in human populations across demographic and ethnoracial boundaries. However, to optimally address issues of dementia subtype prevalence in human populations, community-based autopsy cohorts are essential. Each of the included cohorts has provided the basis for published work related to LATE-NC [3, 33, 39-42, 53, 59, 81, 87, 93, 112]. Aggregating these data into a combined cohort comprising >6,000 people provided new insight into the prevalence of LATE-NC in aging, while also highlighting between-cohort variability.

One way to evaluate recruitment bias in a dementia research study is to compare the frequency of *APOE* ε4 allele among the enrolled participants with population-based figures. This is especially topical since *APOE* ε4 has previously been shown to be associated with increased risk for LATE-NC [29, 98, 122]. In most human populations, approximately 25% of individuals carry at least one copy of the *APOE* ε4 allele [20, 106] (the ε4 prevalence tends to be somewhat higher in Scandinavia [31, 106]). It is notable that 25.5% of the genotyped participants in the current study had at least one *APOE* ε4 allele. By contrast, in many dementia research cohorts the *APOE* ε4 prevalence is higher [32]. For example, a recent study of LATE-NC derived from multiple clinic-based cohorts included 495 participants of which 47.4% were *APOE* ε4+ (and 11.7% had FTD clinical syndrome) [51]. Many dementia studies have even higher *APOE* ε4 positivity [24]; these studies may provide important insights (some impossible to achieve in community-based cohorts), but the distribution of pathologic findings in such clinic-based cohorts are unlikely to be representative of a broader population.

The current work had important limitations. Although the community-based cohorts encompassed thousands of research participants from five countries on three continents, human populations other than White Caucasians were under-represented. Prior studies compared LATE-NC between ethnoracially defined groups [76, 81], but more work is required in this area [32, 89].

For the present study, there were additional challenges in reconciling the LATE-NC data between cohorts. Neuropathologists used study-specific protocols, including non-identical tissue sampling and different antibodies. Some biologic variance is to be expected given the between-cohort differences in age, cognitive status, geography, and birth cohorts. These factors contribute to the wide variability of frequency of detected LATE-NC across the different included cohorts which ranged

between 11-63%. However, this inclusive approach, encompassing a range of diagnostic methods rather than one specific proscribed protocol, reflects the broad range of neuropathologic methods that are applied in everyday practice around the world, as well as true differences in frequency of neuropathologic lesions.

Another consideration is that TDP-43 pathology restricted to the amygdala was included to operationalize the presence of LATE-NC. There were undoubtedly LATE-NC false-negatives because the amygdala was not examined in some cases. LATE-NC Stage 1 is hypothesized to be an incipient disease stage, analogous to early stages of ADNC and Lewy body diseases [63, 80, 84]—for example, Braak NFT stages I-III and Thal Aβ phases 1-2 are common in neurologically normal people [44, 117]. Among the 3,803 brains in the current study where all the LATE-NC stages were known, LATE-NC Stage 1 comprised 36% of the LATE-NC cases and may correlate with limited, if any, cognitive manifestations [25, 77-79, 85]. However, the counterpoint is that 25% of the entire cohort had LATE-NC Stage>1, which is associated robustly with cognitive impairment [12, 33, 39, 42, 43, 46, 49, 53, 62, 75, 76, 83, 97].

Beyond the evaluation of LATE-NC, there are other challenges in reconciling neuropathologic data on technical grounds. For example, one may expect imperfect agreement regarding low Braak stages as these stages requires standard sectioning and excellent familiarity with neuroanatomy (see [4]). This impression was affirmed in our digital pathological study with 5 separate raters evaluating the same cases using digital pathology assessed over the internet. Different studies have run for varying lengths of time, with brain donations occurring over decades. Changes in tissue handling methods over these time frames is a further potential source of variation.

An interpretation of the public health implications of the present report should consider that the average age at death for included participants was 88.1 years. The percentage of participants with autopsy-confirmed LATE-NC in this study (slightly under 40%), and other findings, do not represent projected population-prevalence, but instead are a readout related to persons dying in that age range and agreeing to research brain donation. The study sample coincides with an age group at relatively high risk for LATE-NC [85]. It may be argued that these are unusually long-lived persons, considering normative data. For example, the average age of death in the United States during 2020 was 80.5 years for women, and 75.1 for men [2] – slightly older in European cohorts. Yet these averaged longevity calculations included many individuals who died at considerably younger ages. U.S. Social Security Administration actuarial data predict that a woman who lives to age 70 years in

the United States has a 32% chance to live until age 90 years, and a 70-year old man a 21% chance to live until age 90 years [1]. Thus, a substantial proportion of adults will probably survive to the ages of research participants included in the current study, with high risk for ADNC and LATE-NC.

This study reported summary information from each cohort rather than individual participant-level data, so most regression models and other descriptive statistics were not appropriate for most of the tabular data. In terms of clinical-pathological correlation, only broad trends were described, because detailed and robust statistical testing require a more standardized cognitive assessment format. There are many possible sources of variability in this regard – *e.g.*, additional pathologies, recruitment and testing variation between cohorts. Importantly, prior studies have established that LATE-NC is independently associated with cognitive impairment in aging when other factors (*e.g.,* pathologic comorbidities) were considered [12, 39, 42, 75, 83, 97]. Thus, the main contribution of current study is not clinical-pathological correlation, but instead it is a relatively sound estimate of LATE-NC prevalence in community- and population-based autopsy cohorts across the ADNC severity spectrum.

Compatible with prior published work, the current study found that LATE-NC is more common in brains with comorbid ADNC than in those without ADNC. There was a ~2 to 2.5-fold enrichment for LATE-NC in persons with severe ADNC versus those lacking ADNC. Notably, most individuals in advanced age were found to have some detectable ADNC by age 85 – as shown previously [15, 117]. Thus, the generalization is true that "most people with LATE-NC have ADNC", yet, most old people's brains *without* LATE-NC *also* have ADNC. Moreover, >60% of participants with LATE-NC lacked severe (Braak NFT Stage V or VI) ADNC. Even among those with severe ADNC, approximately one-half lacked TDP-43 pathology, indicating that LATE-NC is not an integral feature of ADNC. This point is further supported by the observation that LATE-NC is unusual (<10% prevalence) in severe ADNC linked to Down syndrome [121].

LATE-NC is not the only pathology that tends to be increased in parallel with ADNC. For example, Lewy body pathology subtypes and cerebrovascular pathologies such as arteriolosclerosis are also relatively prevalent in persons with ADNC [11, 17, 93, 100], as are white matter hyperintensities visualized with neuroimaging [7, 107], and other, rarer, phenomena [26, 70, 105]. The tendency for these brain conditions to coexist with ADNC may be due to 'upstream' factors such as the *APOE* ε4 allele which is known to be pleiotropic for multiple diseases (see above). 'Downstream' of genetic and environmental risk factors, one subtype of pathology may directly promote other deleterious changes in the same cells. In particular, TDP-43 pathology often co-occurs with tau pathology in neurons that

are vulnerable to NFT formation (hippocampal CA1 and entorhinal cortex) in ADNC [46, 119]. Conversely, tau inclusions coexist in cells prone to TDP-43 pathology such as the hippocampal dentate granule neurons in LATE-NC [108]. The finding of increased severity of PART pathology in cases with LATE-NC in the present study also underscores the tendency for there to be pathologic synergies between tau and TDP-43 pathologies.

Although many participants included in the current study had LATE-NC with comorbid ADNC, there also was a substantial subgroup with LATE-NC but with none or very mild ADNC. Specifically, persons with Braak NFT stages 0-II had a 22.4% probability of LATE-NC whereas persons with "No Alzheimer's" according to CERAD neuritic amyloid plaque scores had 26.9% probability of LATE-NC. Thus, in community dwelling older persons with no or minimal evidence of ADNC, LATE-NC was still relatively common and was not associated with a clinical diagnosis of FTD (in the nine cohorts where that clinical evaluation was made). The nature of the multi-center evaluation raises the possibility that a handful of FTLD cases may have been overlooked. However, their extreme paucity in such a large combined cohort implies that FTD/FTLD-TDP is a very uncommon occurrence in community-based cohorts. These results underscored that LATE-NC is a separate entity from FTD/FTLD and also far from inevitable in ADNC. If the ~25% autopsy frequency is considered an estimate, albeit imprecise, of lifetime risk for LATE-NC in persons without ADNC, it can be contrasted with the epidemiologic studies that have found ~0.1% lifetime risk for FTLD-TDP [22, 55].

In conclusion, the current study underscores that LATE-NC is a common pathology in older brains – 25% of participants had LATE-NC Stage >1. Most of the LATE-NC cases in the combined cohort were seen among individuals with Braak NFT Stages 0-IV. In the subset of brains lacking Aβ amyloid (Thal Aβ Phase =0), PART pathology was more severe in brains with comorbid LATE-NC. Encompassing the full spectrum of ADNC severity, the presence of LATE-NC tended to be associated with more cognitive impairment among subjects where the clinical findings were reported proximal to death. These data are interpreted to indicate that LATE-NC, with or without comorbid ADNC, is highly prevalent and impactful in advanced age.

Table 1. Selected demographic, genetic, clinical, and neuropathologic data on the 13 included cohorts*

Characteristics	ACT	Brazil-ian BAS	CC75C	CFAS	Duke/ UNC ADRC	HAAS	Mayo/ MCSA	Nun study	ROS-MAP	The 90+ Study	UKy-ADRC	Vantaa 85+	VITA	Total or Weighted Avg**
Country	USA	Brazil	UK	UK	USA	USA	USA	USA	USA	USA	USA	Finland	Austria	
Sample size	863	625	228	510	109	321	209	382	1,620	402	318	302	307	6,196
Avg age at death, Yrs	89.0	72.2	91.5	87.0	94.1	90.3	86.6	91.1	89.9	97.2	88.4	92.4	83.2	88.1**
% Female	59.4	48.7	70.6	60.4	67.0	0	40.0	100	69.2	69.7	63.2	83.1	58.6	62.3%**
# Known *APOE* status	831	306	216	289	109	303	209	369	1,554	371	318	282	0	5,157
% *APOE* ε4+	27.4	13.0	32.5	29.0	27.6	21.8	24.9	23.0	24.9	20.8	33.6	31.6	N/A	25.5%**
Final cognitive status														
# Clinical dementia	381	101	113	275	49	97	22	136	718	174	110	195	26	2,397
# Clinical MCI/proxy	17	44	39	10	26	68	44	48	372	113	49	N/A	11	841
# Clinical normal	308	461	63	189	29	139	142	167	529	114	142	107***	37	2,427
Neuropathologic features														
% Neocortical LBs	12.9	3.4	4.8	3.7	3.9	6.2	6.2	6.9	14.2	9.2	13.2	14.2	4.1	9.5%**
% Braak Stages 0-II	25.6	67.6	17.6	36.7	12.8	49.8	41.1	44.5	15.7	7.2	43.4	17.6	59.5	31.5%**
% Braak Stages III-IV	36.3	23.9	60.8	41.5	67.0	31.2	41.6	23.6	56.0	54.0	26.7	47.2	20.3	42.0%**
% Braak Stages V-VI	38.1	8.5	21.6	21.9	20.2	19.0	17.2	31.9	28.3	38.8	29.9	35.2	20.3	26.5%**
% LATE-NC****	47.9	11.1	48.7	67.7	30.3	24.7	24.9	16.2	52.2	36.1	36.0	37.1	16.9	39.4%**

*-See text for details on data missingness and cohort-specific operationalizations; **-weighted average; ***- number of subjects with no dementia according to the DSMIIIR criteria; ****-these percentages are for cases with full CERAD neuritic plaque data; see **Supplemental Table 3**, online resource.

Abbreviations: Adult Changes in Thought (ACT) [61]; Brazilian Biobank for Aging Studies (BAS) of the University of Sao Paulo [113]; Cambridge City over-75s Cohort (CC75C) [16]; Medical Research Council Cognitive Function and Ageing Study (CFAS) [123]; Duke/University of North Carolina University AD Research Center (Duke/UNC-ADRC) [39]; Honolulu Asia-Aging Study (HAAS) [125]; Mayo Clinic Study of Aging (MCSA) [96]; Nun Study[120]; Rush University Religious Orders Study/Memory and Aging Project (ROS-MAP) [10]; University of California Irvine The 90+ Study (The 90+Study) [52]; University of Kentucky AD Research Center (UKy-ADRC) [103]; Vantaa 85+ Study [54]; and, Vienna Trans-Danube Aging (VITA) study [57]; Apolipoprotein E (APOE); MCI (mild cognitive impairment); LBs (Lewy bodies); Limbic-predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC).

Table 2. Number of cases with definite FTD/FTLD-TDP in the nine cohorts where this diagnosis was evaluated (among n=3,267 participants)

Cohort	Sample size	Number of definite clinical FTD identified	Notes
ACT	863	0	
CC75C	228	0	Ascertained by post-mortem clinical consensus
CFAS	510	0	Ascertained by post-mortem clinical consensus; 2 with "lobar atrophy"
Duke ADRC	109	0	
HAAS	321	0	
Mayo	209	0	
The 90+ Study	402	0	2 "possible" bvFTD, 1 turned out to have AD, other vasc pathology
Uky ADRC	318	0	
VITA	307	0	
Total number with clinical workup	3,267		
Total number of definite clinical FTD identified		0	

Table 3. Overall percentage of participants with LATE-NC, stratified by the neuropathologic workups and in the subset of cases with low/no ADNC

	Participants with Braak NFT staging*	Participants with CERAD neuritic amyloid plaque scores*	Participants with Braak NFT stages, Thal Aβ phases, and all LATE-NC stages**
Number of cohorts	13	13	8
Total number of individual participants	5,985	6,125	3,803
Overall LATE-NC% in this group	38.4%	39.4%	38.3%
Criterion for low/no ADNC	Braak stages = 0-II	CERAD score = "none"	Thal Aβ Phase = 0
Number of participants with low/no ADNC	1,883	1,935	787
LATE-NC% in low/no ADNC group	22.4%	27.0%	19.4%

-**See **Table 4; *-**See **Table 5**

Table 4. Joint distribution of LATE-NC positivity and CERAD neuritic amyloid plaque Alzheimer's disease ratings in the combined sample [72] and Braak NFT Stage in the combined sample [4, 13]

		Total without LATE-NC	**Total with LATE-NC**	**LATE-NC, %**
CERAD Neuritic Plaque Scores (n=6,125)	None	1,413	522	27.0
	Sparse	702	376	34.9
	Moderate	976	759	43.7
	Frequent	621	756	54.9
Braak NFT Stages (n=5,977)	Braak 0-II	1,461	422	22.4
	Braak III	812	381	31.9
	Braak IV	717	604	45.7
	Braak V	492	643	56.7
	Braak VI	205	248	54.7

Table 5. Numbers of participants with complete data on LATE-NC Stages, Braak NFT Stages, and Thal Aβ Phases, stratified according to all three pathologic readouts (n=3,803)*

LATE-NC Stage 0		Braak NFT Stages							
		0	I	II	III	IV	V	VI	**TOTAL**
Thal Aβ phases	0	110	136	176	128	80	4	0	634
	1	18	76	119	130	101	7	1	452
	2	16	23	72	54	37	5	2	209
	3	7	34	62	130	119	55	8	415
	4	2	10	15	58	106	115	17	323
	5	0	4	10	23	58	138	68	301
									2,334
LATE-NC Stage 1		Braak NFT Stages							
		0	I	II	III	IV	V	VI	**TOTAL**
Thal Aβ phases	0	4	9	15	22	10	2	0	62
	1	1	8	23	34	31	2	0	99
	2	1	2	8	10	7	0	1	29
	3	2	7	8	28	40	28	3	116
	4	0	1	0	9	48	32	7	97
	5	0	0	1	6	19	69	21	116
									519
LATE-NC Stage 2		Braak NFT Stages							
		0	I	II	III	IV	V	VI	**TOTAL**
Thal Aβ phases	0	3	12	9	16	32	3	0	75
	1	1	6	21	22	45	7	1	103
	2	0	0	5	22	21	3	1	52
	3	0	2	11	20	54	40	7	134
	4	0	0	2	10	53	112	11	188
	5	0	0	1	6	31	131	61	230
									782
LATE-NC Stage 3		Braak NFT Stages							
		0	I	II	III	IV	V	VI	**TOTAL**
Thal Aβ phases	0	2	2	3	4	5	0	0	16
	1	2	7	5	5	2	0	0	21
	2	0	1	1	2	1	0	0	5
	3	0	2	1	6	15	14	1	39
	4	0	2	1	2	11	14	3	33
	5	0	0	2	2	6	32	12	54
									168

***-**For the numbers of cases contributory from each cohort, see **Supplemental Table 3**, online resource

Supplemental Table 1. Supplementary information on included cohorts

Cohorts (in alphabetical order)	Notes	Ref(s)
Adult Changes in Thought (ACT)	Population-based prospective cohort study focused on brain aging and risk factors for dementia. The study is based within KPW (formerly GH), an integrated health care delivery system in Washington state, and recruits community-dwelling, nondemented adults aged 65 and older from among KP members living across the Seattle, WA area. Consent for brain donation is not required to join the study but the brain autopsy consent rate is consistently 25-30%. Cognitive screening, physical function, medical history review, and functional status assessments are administered to ACT participants at study entry and subsequently every two years. Participants are administratively censored from the ACT cohort upon a dementia diagnosis. Dementia-free participants continue with biennial follow-up.	[58]
Brazilian Biobank for Aging Studies (BAS)	Community-based autopsy study with subjects who died from non-forensic causes of death in the city of Sao Paulo, Brazil. Participants were 50 years or older, 74% had normal cognition at time of death and 34% were Black. The study has been ongoing since 2003, and all the donations are sourced from the Autopsy Service of the University of Sao Paulo, the only service providing non-forensic autopsies (around 15,000 per year) in this city of over 11 million inhabitants.	[38, 112]
Cambridge City over-75s Cohort Study (CC75C)	Starting in 1985, people in Cambridge aged 75 or older were approached to be part of the study via general practitioner (GP) surgeries and over 2,100 agreed to take part (95% response rate). Participants were followed with repeated interview waves every few years until they died. In total 242 participants agreed to donate their brains with consent also given by next of kin. The sociodemographic characteristics of the brain donors do not differ significantly from the population from which they were drawn. Brain donations were processed according to a modified CERAD protocol. Every stage of the study has ethical approval via local ethics committees. Dementia severity at death consistent with DSM-IV criteria was agreed after death by at least two clinicians blinded to neuropathology findings using post-mortem review of all study data including participant and proxy informant interviews, death certificates, and retrospective informant interviews. In life participant interviews included cognitive assessments using the Mini Mental State Exam and the CAMDEX interview. Dementia severity was rated as none, minimal, mild, moderate, severe, or uncertain. Where possible, dementia subtype diagnoses were identified consistent with the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorder Association (NINDS-ADRDA) and NIA (National Institute on Ageing) Reagan guidelines.	[34]
Cognitive Function and Ageing Studies (CFAS)	Population-based longitudinal study of ageing with brain donor cohort for clinicopathological study. Starting in 1985, people in Cambridge aged 75 or older were approached to be part of the study via general practitioner (GP) surgeries and 2,166 agreed to take part (95% response rate). Participants were followed with repeated interview waves every few years until they died. Approaching participants for brain donation began when ~60% of baseline cohort were still participating. From those participants who agreed to donate their brains in total 242 successful donations were collected with consent also given by next of kin. Sociodemographic characteristics and cognitive distribution of the brain donors do not differ significantly from the population from which they were drawn. Brain donations were processed according to a modified CERAD protocol. All stages of the study have been approved by local ethics committees. In life interviews included cognitive assessments using the Mini Mental State Exam, the CAMDEX interview and the Geriatric Mental State Examination with the associated History and Aetiology	[123]

	Schedule adapted for CFAS that supported an algorithmic diagnosis of the main psychiatric disorders including dementia (AGECAT). Dementia status at death (consistent with DSM-III-R criteria) for donors was established by combining information from multiple sources including AGECAT, death certificates, retrospective informant interviews with relatives/carers after death, and probability of dementia before death from a Bayesian analysis modelling the prevalence and incidence of dementia in CFAS.	
Duke-UNC Alzheimer's Disease Research Center (ADRC)	Participants over 90 years of age at death were included in this study. Approximately 70% of the cohort had normal cognition at the time of recruitment. More than 95% of participants are White. Consensus meetings were held yearly to review and update the clinical diagnosis, based upon contemporaneous NIA-AA criteria.	[39]
Honolulu Asia Aging Study (HAAS)	The Honolulu Asia Aging Study (HAAS) is a population-based study of health and functioning in late life that was established in 1991 with the goal of determining the prevalence, incidence, and risk factors for dementia. A primary aim of the HAAS was to clarify the relative frequencies of dementing diseases in Japanese-ancestry persons living in the US. The HAAS cohort is comprised of surviving participants in the Honolulu Heart Program (HHP), a prospective, community-based cohort study of heart disease and stroke established in 1965. The details of the HHP have been previously described elsewhere. Of the original 8,006 HHP participants, 3,734 participated in the first HAAS examination which represented approximately 80% of the surviving members of the original HHP cohort. The HAAS was reviewed and approved by the Kuakini Hospital IRB, A consent for was signed by participants at every cycle (12 cycles from 1965 to 2012), including consent for use of information and materials for research purposes by researchers and their colleagues, including NIH-associated, with no ending of this permission. HAAS autopsy acquisition procedure required notification of a participant's death by family member, hospital, medical examiner's office, or other source, with permission for autopsy and research use of information provided by next of kin. Autopsies were completed for 25% of HAAS participants as previously reported. HAAS participants were screened at each examination with the Cognitive Abilities and Screening Instrument (CASI). For HAAS participants, we considered no or mild cognitive impairment as final CASI score of 74 or greater, moderate cognitive impairment as a final CASI score of 60-73.9, and severe cognitive impairment as less than 60^4. HAAS examination cycles began in 1991 and occurred every 2-3 years.	[36, 114, 124, 126]
Mayo Clinic Study of Aging (MCSA)	The Mayo Clinic Study of Aging (MCSA) is a longitudinal, population-based study of cognitive aging in Olmsted County, Minnesota, US. Participants of the MCSA, aged 70–89 years were randomly selected using the Rochester Epidemiology Project. The study was expanded to include those aged 50-69 in 2012. A comprehensive in-person neurological evaluation and neuropsychological testing was performed, including the Clinical Dementia Rating Scale. A consensus agreement for diagnosis was made by an expert panel consisting of the neurologist, neuropsychologist, and nurse from time of evaluation using published criteria [66, 90]. Education, prior occupation, and other information were taken into account before consensus diagnosis of normal cognition, MCI, or dementia was made. Study participants are seen in person every 15 months.	[96]
Nun study	Participants in the Nun Study were all members of the School Sisters of Notre Dame religious congregation. Beginning in 1991, American Sisters born before 1917 were asked to join this longitudinal study of aging and Alzheimer's disease. While it may be difficult to generalize from this unique cohort of Catholic Sisters, many factors that confound most epidemiologic studies were minimized or even eliminated in this cohort. Participants had same reproductive and marital histories; similar social activities and support; did not smoke or drink excessive amounts of alcoholic beverages; had similar occupations, income, and socioeconomic status; lived in	[33, 109, 110, 126]

	similar housing; ate food prepared in similar kitchens; and had comparable access to similar preventative, nursing, and other medical care services. NS primary cognitive testing was done annually with the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery, which includes the Mini-Mental State Examination (MMSE). For NS participants, we considered no or mild cognitive impairment if final MMSE score was 22 or greater, moderate cognitive impairment if final MMSE score was 17-21, and severe cognitive impairment if final MMSE score was less than 17. The NS was reviewed and approved by University of Kentucky, University of Minnesota, and Northwestern University institutional review boards (IRBs). Participating School Sisters of Notre Dame had agreed to brain autopsy prior to death, with final authorizations provided by the Provincial Leader. Brain Autopsies were completed for >90% of Nun Study participants.	
Rush Religious Orders Study – Memory and Aging Project (ROS-MAP)	Both are Rush University ongoing epidemiologic longitudinal clinical-pathologic studies of older persons. The Religious Order Study (ROS) began in 1994 and recruits older priests, nuns, and brothers from 45 sites across the United States. The Rush Memory and Aging Project (MAP) began in 1997 and recruits participants from across the Chicagoland metropolitan area. In both studies, participants were enrolled at age 65 and above without know dementia and agreed to undergo annual clinical evaluation and interview, including detailed neuropsychological testing, and brain donation	[9, 10]
The 90+ Study	Community-based autopsy cohort in Southern California, US. Initially, participants in *The 90+ Study we*re survivors from the Leisure World Cohort Study (LWCS), an epidemiologic investigation of a retirement community in Orange County, CA in the early 1980s. *The 90+ Study* was initiated in 2003 when the surviving participants from the original LWCS who were aged 90 years and older on January 1, 2003 were invited to join**.** We also extended a similar an invitation on January 1, 2008 and every year thereafter to those turning 90 years old. More recently, open recruitment of volunteers aged 90 and older beyond the LWCS was initiated using a variety of recruitment methods including mailing lists of residences believed to have people aged 90 and older, talks at local communities, talks to primary doctors, ads in local newspapers, and relatives or friends of participants. Participants from the LWCS were recruited regardless of cognitive diagnosis, whereas non-cohort volunteers had no or mild dementia. Currently, two thirds of participants are from the original LWCS and one third are non-cohort volunteers. 98% of participants are White.	[21, 68]
U. Kentucky Alzheimer's Disease Research Center (ADRC)	Community-based autopsy cohort in Lexington KY based on an NIH funded AD Research Center. Recruitment began in the mid-1980's. More than 95% of included autopsied subjects were White/Caucasian. Subjects were recruited starting at age 70 while cognitively normal and followed with yearly clinical visits to autopsy. Final diagnosis prior to death refers to the diagnosis of a consensus group including clinicians and pathologists, whereas the FTD clinical syndrome was evaluated by a behavioral neurologist during life.	[103]
Vantaa 85+	A population-based study, which includes all the subjects who lived in the city of Vantaa, Finland, in 1991 and were 85 years or over. > 50% of the population were neuropathologically examined.	[54]
Vienna Transdanube Aging (VITA)	Community-based autopsy cohort in Vienna, Austria. Since 2000, the VITA study follows longitudinally a community-based cohort of every resident of the Vienna area on the left shore of the River Danube (districts 21 and 22) born between May 1925 and June 1926. Subjects were recruited at the age of 75. Clinical follow-up data was included only from 74 individuals.	[57]

Suppl. Table 2: Blank data templates (data requested of each cohort) in Excel file format (attached Excel file)

Suppl. Table 3: Numbers of participants included on each figure and table from each cohort (attached Excel file)

Suppl. Table 4: Digital neuropathology to assess inter-rater reliability of Braak NFT stage diagnoses in a sample of LATE-NC+/ADNC- cases with cognitive impairment (attached Excel file)

Figure legends

Fig. 1. Frequencies of clinical/cognitive features among the included participants. All cohorts had data on whether participants had normal cognition or dementia prior to death, and most (12 cohorts) had some measure for an intermediate clinical status, usually mild cognitive impairment (MCI). The finding of slightly over 40% cognitive normal prior to death is consistent with epidemiologic data of human populations in this age range [22, 64, 91, 95]. The results of each cohort was weighted equally in order to convey the cohort-to-cohort variance. For numbers of participants included from each cohort, see **Table 1**. Error bars denote 25th and 75th percentiles. *-MCI data were present for all cohorts except Vantaa 85+.

Fig. 2. The association between the percentage of included LATE-NC+ participants in each cohort (x-axis) with percentages carrying the *APOE* ε4 allele (a); age at death (b); sex (percent female; c); and, proportion with neocortical Lewy bodies (LBs; d) on the y-axes. Each of the autopsy cohorts is indicated by a separate circular marker. The only association that was statistically significant in a simple regression analysis was *APOE* ε4 carrier frequency rate (**a**). *APOE* data were missing from a single cohort; see **Table 1** for the numbers of research participants from each contributory cohort.

Fig. 3. LATE-NC absence or presence, stratified by CERAD neuritic amyloid plaques scores. All LATE-NC Stages were combined and the results from each of the cohorts averaged. The frequency of LATE-NC increased with greater neuritic amyloid plaque densities. The distribution of CERAD plaques by frequencies is shown in (**a**). Note that subgroups with none or minimal ADNC were the most well-represented in this combined meta-cohort (see **Table 2**). Correlation with LATE-NC status is shown in (**b**). Given the study design differences between cohorts, the results were generally consistent. For these charts, the results of each cohort were weighted equally in order to convey the cohort-to-cohort variance. For exact numbers of participants included from each cohort, see **Supplemental Table 3**, online resource**.** Error bars denote 25th and 75th percentiles.

Fig. 4. LATE-NC absence or presence, stratified by Braak NFT Stages. Here, all LATE-NC Stages were combined and the results from each of the cohorts averaged. The distribution of NFT groups by frequencies is shown in (**a**). Correlation with LATE-NC status is shown in (**b**).The frequency of LATE-NC increased with higher Braak NFT Stages. Given the study design differences between cohorts, the results were generally consistent. For these charts the results of each cohort were weighted equally in order to convey the cohort-to-cohort variance. For exact numbers of participants included from each cohort, see **Supplemental Table 3**, online resource**.** Error bars denote 25th and 75th percentiles.

Fig. 5. Findings in the 3,803 participants with available LATE-NC stage data (a), Thal Aβ phases (b), and Braak NFT staging (see Table 4), which indicate an association between LATE-NC and PART pathology. A pie chart (**a**) shows the relative frequencies of the different LATE-NC Stages. Note that ~25% of participants have LATE-NC stage 2 (21% of participants) or stage 3 (4% of participants). A separate pie chart (**b**) depicts the relative frequencies of different Thal Aβ phases. The bar chart in panel (**c**) shows the number of cases with Thal Aβ phase = 0, stratified by Braak NFT stages. In these brains lacking Aβ amyloid pathology, the presence of LATE-NC was associated with higher Braak NFT stages (more severe PART pathology). For exact numbers, see **Table 5,** and for a breakdown of the numbers of participants included from each cohort, see **Supplemental Table 3**, online resource**.**

Fig. 6. Association between LATE-NC and cognitive status, across a broad range of Braak NFT stages, in ten community-based cohorts. Data were gathered on cognitive status, stratifying by LATE-NC status and Braak NFT stages. Trends were evaluated from each cohort as to whether the cognitive status tended to be lower in persons with LATE-NC (down-going black arrow) or higher (up-going white arrow) in given Braak NFT stages. To operationalize global cognitive status, final Mini-Mental State Examination scores were used [35], except HAAS used the Cognitive Abilities Screening Instrument [115] and the Brazil BAS and MCSA cohorts used the Clinical Dementia Rating sum of boxes scores [28]. There was a tendency for participants with LATE-NC to have lower cognition across the full range of Braak NFT stages.

Fig. 7. Selected findings and context of the current study. Data were analyzed from participants in 13 high quality community- and population-based cohorts comprising over 6,000 individuals followed longitudinally to autopsy. As such, the findings (with appropriate caveats) have broad implications. In participants that had none or minimal ADNC, a substantial proportion (~25%) had LATE-NC. This indicates that there are ADNC-independent TDP-43 pathology-driving mechanisms, which probably include gene variants in *TMEM106B* and *GRN* [27, 92, 101]. LATE-NC also was associated with more severe PART pathology (and vice versa), indicating pathologic synergy between LATE-NC and PART. Approximately 2/3rd of subjects in advanced age showed moderate or severe ADNC at brain autopsy, in concordance with the published literature [15]. In these individuals, there was a relatively high frequency of LATE-NC: approximately 50% of participants with moderate to severe ADNC had LATE-NC. The "mixed" ADNC-LATE-NC may be driven by pleiotropic genetic factors (e.g., *APOE* ε4 allele [122]) and there may also be pathologic synergies downstream from genetics. For example, intracellular tauopathy may promote TDP-43 pathology in the same cell [46, 108, 119]. The neuron shown here is stained with immunofluorescence in the hippocampal dentate gyrus, and is immunolabeled green (tau), and red (phospho-TDP-43) with overlap depicted in white [108]. More work is required to better understand both the disease-driving mechanisms and the spectrum of "mixed" disease phenotypes in human populations.

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