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RESEARCH ARTICLE

Concomitant neurodegenerative pathologies contribute to the transition from mild cognitive impairment to dementia

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Abstract

Introduction: The aged brain frequently exhibits multiple pathologies, rather than a single hallmark pathology (pure pathology [PurP]), ranging from low/intermediate levels of additional pathology (LowP) to mixed severe pathology (mixed SevP). We investigated the frequency of PurP, LowP, and mixed SevP, and the impact of additional LowP on cognition.

Methods: Data came from 670 cases from the Brains for Dementia research program. Cases were categorized into PurP, mixed SevP, or a main disease with additional LowP; 508 cases had a clinical dementia rating.

Results: 69.9% of cases had LowP, 22.7% had PurP, and 7.5% had mixed SevP. Additional LowP increased the likelihood of having mild dementia versus mild cognitive impairment (MCI) by almost 20-fold (odds ratio = 19.5).

Discussion: Most aged individuals have multiple brain pathologies. The presence of one additional LowP can significantly worsen cognitive decline, increasing the risk of transitioning from MCI to dementia 20-fold. Multimorbidity should be considered in dementia research and clinical studies.

KEYWORDS
cerebral multimorbidity, clinicopathological study, cognitive impairment, concomitant pathology, dementia, hyperphosphorylated tau, multiple pathologies, neuropathology

1 | INTRODUCTION

Age-associated dementias are characterized by intracellular and extracellular deposition of misfolded and aggregated proteins or by cerebrovascular lesions (CVLs). Currently, *post mortem* neuropathological assessment of brain tissue is the only definitive way to diagnose and classify the underlying disease. Identification of aggregates of hallmark proteins, for example, extracellular amyloid beta (Aβ) plaques and intracellular hyperphosphorylated tau (Hpτ; neurofibrillary tangles and neuropil threads) in Alzheimer's disease (AD) or intracellular α-synuclein (α-syn; Lewy bodies and Lewy neurites) in Lewy body dementia (LBD), which include Parkinson's disease (PD), PD with dementia (PDD), and dementia with Lewy bodies (DLB), lead to the neuropathological diagnosis of a disease if the proteins are present to a severity and extent that fulfill the diagnostic criteria for the respective disease. In addition, cerebrovascular disease (CVD) and CVL may be the neuropathological correlate of neurological disease. However, these hallmark lesions are not mutually exclusive and in brains of elderly individuals the presence of only one characteristic pathology, that is, a pure pathology (PurP), is the exception: the majority of brains show multiple pathologies, a condition referred to as cerebral multimorbidity.[1,2] The degree of cerebral multimorbidity in neurologically impaired individuals ranges from one main disease with low/intermediate level additional pathology (additional LowP) with a low likelihood of causing clinical symptoms on its own, for example, AD with minor CVL, to cases in which the hallmark pathologies of two (or more) diseases are so severe that any one of these could independently cause cognitive impairment,[1] for example, AD and DLB, which can be categorized as mixed severe pathology (mixed SevP) and would be diagnosed as Mixed AD/DLB.[3] Data from large autopsy studies show that additional LowP and mixed SevP together are seen in up to 74% of brains of elderly people [2,4–6] and suggest that the presence of additional pathologies (either additional LowP or mixed SevP) is associated with a greater risk of dementia or accelerated cognitive impairment[7–15] due to possibly lowering the burden of major pathology necessary for clinical symptoms, for example, the presence of CVL in AD lowers the threshold at which AD pathology causes clinical dementia.[16] Another example of the clinical impact of cerebral multimorbidity is the presence of limbic predominant TDP-43 protein aggregates, a condition recently termed limbic-predominant age-associated TDP-43 encephalopathy neuropathological change (LATE-NC). LATE-NC has been suggested to cause a distinct disease (i.e., LATE[17]) but is more commonly additional LowP, present in up to 50% of individuals over 80 years in age[17] and highly prevalent in AD (74%[18]) where its presence is associated with accelerated cognitive decline.[19] The terminology used to describe to cerebral multimorbidity varies with different studies defining it as presence of more than one pathology,[8] or combined diagnoses,[6] or additional pathologies[13,20].Few studies have differentiated between "mixed dementia" (mixed SevP) and additional low-severity concomitant pathology (additional LowP)[5] or classified comorbidity based on the severity of the co-pathologies.[7,12,15]

The Brains for Dementia Research (BDR) program was started in 2008 in the UK to address the shortage of banked *post mortem* brain tissue with prospective, systematic recording of clinical information for dementia research, especially from individuals with no history of neurological disease.[21] The program recruited a cohort from across England and Wales who underwent standardized longitudinal clinical and psychometric assessments. All participants consented to brain donation at one of five UK brain banks (ie, Bristol, London [King's College], Manchester, Newcastle upon Tyne, and Oxford), which implemented a prospectively agreed protocol for brain sampling and standardized neuropathological assessment.

We used the BDR cohort to investigate the neuropathological frequency of common age-associated neurodegenerative pathologies and CVD in a large cohort, and distinguished between PurP, a single main disease with additional LowP, and mixed SevP. We also analyzed the impact of additional LowP on the rate of cognitive decline and the severity of dementia.

Research in context

1. **Systematic review**: We searched PubMed for relevant research and review articles. Although there are multiple studies that have investigated cerebral multimorbidity and its impact on cognition, no study has characterized cerebral multimorbidity based upon its severity and investigated the frequency and clinical impact of minor concomitant pathologies (ConP).
2. **Interpretation**: 63.1% of cases exhibited ConP of which the presence of a single ConP increased the odds of transitioning from mild cognitive impairment to mild dementia by 20-fold, highlighting the clinical significance of presumed incidental pathologies on cognitive decline.
3. **Future directions**: Our findings highlight the clinical impact of ConP and biomarkers of pathologies other than those of a patient's main diagnosis may have important prognostic implications. The high prevalence and spectrum of cerebral multimorbidity should be at the forefront of consideration in dementia research, biomarker development, and clinical trial design and interpretation.

2 | METHODS

2.1 | Study cohort

This study included *post mortem* human brains donated to the BDR Project between 2008 and 2018. We included cases over the age of 60 years with neuropathological diagnoses based on international standardized criteria. Non–age-associated neurological diseases (e.g., Creutzfeldt-Jakob disease [CJD], motor neuron disease) were excluded. A total of 670 cases were selected. All clinical and neuropathological data are available via Dementia Platform UK (DPUK)

and the MRC UK Brain Banks Network (UKBBN) database (see: https://brainbanknetwork.cse.bris.ac.uk); BBNid case numbers for this study are provided in Table S1 in supporting information.

2.2 | Clinical assessment and diagnosis and apolipoprotein E (APOE) genotype

During life, clinical assessments were conducted by a trained psychologist or research nurse. Baseline assessments were conducted face to face, with annual follow-up assessments over the next 1 to 5 years. This study was inclusive of two clinical assessments performed by BDR; Clinical Dementia Rating (CDR; range: 0–3)[22] and the Mini-Mental State Examination (MMSE; range: 0–30). The operational criteria for control, mild cognitive impairment (MCI), and dementia was based on the following assessment measures: control, CDR 0, MMSE 27–30; MCI, CDR 0.5, MMSE 24–26; dementia, CDR ≥1, MMSE ≤23).[21] CDR > 1 was further categorized into mild dementia (CDR 1; MMSE 20–23); moderate dementia (CDR 2; MMSE 12–19); severe dementia (CDR 3; MMSE < 12). Of note, not all cases had clinical scores available as some donors were not able to participate in initial or follow-up assessments due to illness, severity of dementia, or death. APOE genotype information was available for 606 cases.

2.3 | Neuropathological assessment and diagnosis

Standardized neuropathological assessment was performed for all cases and included the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria[23] (inclusive of Thal phases of Aβ deposition, Braak staging of neurofibrillary tangle [NFT] pathology and Consortium to Establish a Registry for Alzheimer's Disease [CERAD] scoring of the density of neuritic plaques), McKeith Lewy body stage,[24] and categorization of the contribution of cerebrovascular pathology to cognitive impairment (vascular cognitive impairment neuropathological guidelines [VCING]).[25] The presence or absence of TDP-43 inclusions indicative of LATE-NC (with or without hippocampal sclerosis [HpSc]) and of hippocampal sclerosis independent of TDP-43 pathology was recorded[17] and, where applicable, assessment for frontotemporal lobar degeneration (FTLD) and argyrophilic grain disease (AGD) was performed.

The categorization of cases as PurP, mixed SevP, and additional LowP was conducted as follows: if only the hallmark pathological changes of a single disease were present to a degree that fulfilled the neuropathological criteria to diagnose that disease the case was classified as PurP. If this was seen for two (or more) diseases, the case was classified as mixed SevP and the individual diseases were noted (e.g., Mixed AD/DLB). Cases that fulfilled the neuropathological criteria for a disease and had additional pathological changes that were not extensive enough to meet the criteria for diagnosing an additional disease were recorded as having the main diagnosis together with additional LowP (e.g., AD with moderate CVD). If only LowP without a main disease was present, the case was classified as LowP only.

The neuropathological classification criteria are provided in Table 1. Briefly, for AD pathology, full-blown disease was defined by "high AD neuropathological change,"[23] which included cases with Thal Aβ phase 4/5,[26] Braak stage V/VI,[27] and CERAD stage for neuritic plaques B/C.[28] DLB cases fell into the McKeith stage of either limbic or neocortical LBD, and PD cases had brainstem LBD.[24]

Because the LATE-NC staging criteria[29] and similar criteria for the staging of TDP-43 pathology in AD[30] were only published in 2019 and 2014, respectively, we did not have such stages recorded for our cohort. We had, however, noted the presence or absence of TDP-43 pathology as seen in LATE-NC; because these data did not allow us to estimate the severity of LATE-NC and as many cases are likely to have had TDP-43 pathology limited to the amygdala and hippocampus, we decided to consider LATE-NC as an additional pathology (additional LATE-NC) for statistical analysis of clinicopathological correlations. We listed LATE-NC as a distinct category if associated with only additional LowP; the prevalence of LATE-NC is shown in Table S2 in supporting information. TDP-43 pathology in LATE-NC differs from that in FTLD-TDP with respect to the topographical distribution and morphological features.[17]

We categorized CVD pathology according to the VCING criteria, which categorize cases without any or with only mild cerebrovascular pathology both as having "low likelihood that CVD contributed to cognitive impairment," and therefore, this category was not considered at all in our study, as it includes cases without any CVD. Cases in the VCING category of "moderate" were classified as having additional LowP CVD and those in the category of "high" were classified as having a PurP or mixed SevP diagnosis with CVD.

2.4 | Statistics

We used SPSS version 25 (SPSS Inc.) for statistical evaluation. Variables were tested for normality and variance homogeneity using Shapiro–Wilk and Levene's tests, respectively. Group effects were examined using either parametric (analysis of variance [ANOVA] F, Welch's ANOVA W) or nonparametric (Kruskal–Wallis H) tests, followed by appropriate post hoc procedures (independent *t*, Mann–Whitney *U*). Relationships between categorical variables were explored using a χ^2 or Fisher's exact test. Where applicable, partial Pearson's (r) or Spearman's (ρ) correlation coefficients, controlling for the effect of age, were used to assess associations between variables. Stepwise binary logistic regression was employed to estimate the odds of a categorical increase in CDR score as a function of individual pathological burden (indicated by specific pathological assessment stage), while linear regression was used to investigate pathological predictors of CDR and rate of cognitive decline. Case numbers for each CDR score varied; therefore, all models were matched for number of cases and controlled for the effects of age.

3 | RESULTS

Mean age at death was 83.88 (± 8.33 standard deviation [SD]; range 61.0–104.0) years, 52.9% of donors were male, mean *post mortem* delay

TABLE 1 Neuropathological classification criteria

Neuropathological diagnosis	Description	Pathological criteria and stages
Low AD neuropathological change (Low AD-NC)	Presence of low level Aβ plaques, NFT/NT with low levels/without NP in topographically distinct regions that is not associated with cognitive impairment	Braak NFT stage 0—IIThal Aβ Phase 1—5CERAD: Negative – AVCING: Low
Intermediate AD neuropathological change (IM AD-NC)	Presence of intermediate/severe Aβ plaques, NFT/NT and NP in topographically distinct regions that may or not indicate cognitive impairment	Braak NFT stage III–VIThal Aβ Phase 1–5CERAD: Negative-CVCING: Low
High AD neuropathological change: neuropathological Alzheimer's disease (AD)	Presence of severe Aβ plaques, NFT/ NT and NP in topographically distinct regions	Braak NFT stage V—VI,Thal Aβ Phase 4–5,CERAD: B-C,VCING: Low
Lewy body disease/dementia (LBD)	Presence of α-synuclein aggregations in the form of LB and LN in topographically distinct regions. Presence of limbic and neocortical LB/LN is associated with cognitive impairment	McKeith stage: Brainstem – NeocorticalVCING: Low
Cerebrovascular disease	Presence of a subcortical cerebral infarction (> 10 mm) and/or at least moderate white matter arteriolosclerosis or leptomeningeal cerebral amyloid angiopathy in the occipital lobe	VCING: HighBraak NFT stage: 0–IVThal Aβ Phase 0–5CERAD: Negative - BMcKeith stage: 0 - Brainstem
Mixed Alzheimer's disease and dementia with Lewy bodies disease (Mixed AD/DLB)	Presence of severe Aβ plaques, NFT/NT, NP, and LB/LN in topographically distinct regions	Braak NFT stage V–VIThal Aβ Phase 4–5CERAD: B-CMcKeith stage: Limbic-NeocorticalVCING: Low
Mixed Alzheimer's disease and dementia with cerebrovascular disease (Mixed AD/CVD)	Presence of severe Aβ plaques, NFT/NT, NP in topographically distinct regions and severe cerebrovascular disease/lesions that can initiate cognitive impairment independently	Braak NFT stage V–VIThal Aβ Phase 4–5CERAD: B-CVCING: High
Limbic-predominant age-associated TDP-43 encephalopathy neuropathological change (LATE-NC)	Presence of TDP-43 inclusion in topographically distinct regions with/without hippocampal sclerosis (HpSc)	LATE-NC: PresentHpSc: Absent/presentBraak NFT stage 0-IIThal Aβ Phase 1-5CERAD: Negative -A VCING: Low
Frontotemporal lobar degeneration (FTLD) with tau	Presence of specific 3/4R hyperphosphorylated tau inclusions in neurones and/or glia cells	FTLD subtype and inclusionFTLD-Pick's: neuronal inclusions (3R)FTLD-PSP: globose NFT; tufted astrocytes (4R)FTLD-CBD: astrocytic plaques (4R)Argyrophilic grain disease grain disease (AGD):neuronal processes (4R)
Frontotemporal lobar degeneration (FTLD) with TDP-43 inclusions	Presence of TDP-43 inclusions in neurons	FTLD-TDP: TDP-43 (not LATE-NC)
Hippocampal Sclerosis (HpSc)	Presence of severe pyramidal cell loss in CA1 and subiculum of the hippocampal formation, that is out of proportion to AD neuropathological change	HpSc: PresentBraak NFT stage 0-IIThal Aβ Phase 1-5CERAD: Negative - AVCING: Low
Neuropathological diagnosis plus low/intermediate level additional low pathology	Staging criteria for the most prevalent neuropathological lesion(s) is met but there is additional distinct pathological lesion(s) present that do not fulfil their associated criterion	Staging of additional pathology onlyBraak NFT stage 0–IVThal Aβ Phase 0–5CERAD: Negative - BMcKeith stage: Amygdala and/or BrainstemVCING: ModerateLATE-NC: PresentHpSc: Present

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NFT, neurofibrillary tangle; NT, neuropil thread; VCING, vascular cognitive impairment neuropathological guidelines.

was 54.08 (± 33.17 SD) hours and mean pH of brain tissue at dissection was 6.21 (± 0.37 SD). Average disease duration, calculated in months from first CDR until death, was available in 508 cases. For first CDR 0, average disease duration was 41.49 (± 30.41) and for CDR > 0.5 average disease duration was 31.68 months (± 27.98). CDR > 0.5 had a significantly shorter disease duration compared to CDR 0 (*t* test, $P = 0.001$). There was no association between *post mortem* delay (PMD) and pH ($r = -0.078$; $P = 0.118$) indicating that PMD did not significantly influence tissue quality.[31] Final neuropathological diagnoses, frequencies, and significant differences in age at death are presented in

TABLE 2 Final neuropathological diagnosis, frequencies, and mean ages at death

Neuropathological diagnosis	Frequency (%)	Sex (% male)	Mean age at death (y)	Sig. diff in age (post hoc Mann–Whitney *U* test)
LowP only	137 (20.4)	44.4	85.12 (± 8.57)	*P* = 0.06 - AD*P* = 0.001 – Mixed AD/DLB*P* = 0.017 – FTLD-tau*P* = 0.017 – FTLD-TDP-43
IM AD-NC	68 (10.1)	48.5	87.46 (± 6.26)	*P* = 0.0001 - AD*P* = 0.02 - DLB*P* = 0.0001 – Mixed AD/DLB*P* = 0.001 – FTLD-tau*p* = 0.002 – FTLD-TDP-43
AD	213 (31.8)	47.1	82.42 (± 8.57)	*P* = 0.001 – CVD*P* = 0.006 – AGD
LBD	65 (9.7)	70.8	84.51 (± 7.89)	*P* = 0.012 – Mixed AD/DLB*P* = 0.027 – FTLD-tau*p* = 0.048 – AGD
Mixed AD/DLB	75 (11.2)	61.3	81.08 (± 8.29)	*P* = 0.031 - LATE-NC*P* = 0.0001 – CVD*P* = 0.001 – AGD
LATE-NC	8 (1.2)	42.9	88.57 (± 7.30)	*P* = 0.016 – FTLD-tau*p* = 0.041 – FTLD-TDP-43
CVD	36 (5.4)	63.9	87.19 (± 7.98)	*P* = 0.002 – FTLD-taup = 0.002 – FTLD-TDP-43
Mixed AD/CVD	18 (2.7)	60	83.87 (± 7.61)	*NS*
FTLD-tau	14 (2.1)	71.4	79.35 (± 8.22)	*P* = 0.003 – AGD
FTLD-TDP43	19 (2.8)	63.6	80.3 (± 8.30)	*P* = 0.001 – AGD
AGD	13 (2.0)	46.2	89.3 (± 6.26)	~
HpSc	4 (0.6)	85.7	83.14 (± 6.57)	~

Abbreviations: AD, Alzheimer's disease; AGD, argyrophilic grain disease; CVD, cerebrovascular disease; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; HpSc, hippocampal sclerosis; IM AD-NC, intermediate Alzheimer's disease neuropathological change; LATE-NC, limbic-predominant age-associated TDP-43 encephalopathy neuropathological change; LBD, Lewy body disease; LowP, low/intermediate level additional pathology.

Table 2. The most frequent neuropathological disease diagnosis was AD, in 31.8% of cases, followed by Mixed AD/DLB, in 11.2% of cases. Intermediate AD neuropathological change (IM AD-NC) was diagnosed in 9.9% closely followed by LBD in 9.7%. CVD and Mixed AD/CVD were diagnosed in 5.4% and 2.8%, respectively; 21.1% of cases were classified as having LowP only. Within this group, the neuropathological criteria for definite primary age-related tauopathy (PART;[32] Braak stage I–IV, Thal Aβ phase 0) were met in 34 cases and for "possible" PART (Braak stage I–IV, Thal Aβ phase 1–2) in 64 cases. All neuropathological stages stratified by neuropathological diagnosis are presented in Table S2. APOE genotype stratified by disease group is presented in Table 3.

3.1 | Frequency of PurP, additional LowP, and mixed SevP

Overall, 22.7% of cases were classified as PurP, 69.9% as additional LowP, and 7.5% as mixed SevP. Figure 1 illustrates each neuropathological diagnosis and the proportionate associated additional LowP, highlighting the high proportion of cases within each neuropathological diagnostic group that have associated additional LowP and the complexity of multimorbidity. Table 4 details the frequency of a PurP and the specific additional LowP, scoring stages and possible combinations in each individual diagnostic group. Within the non-mixed diagnoses, the highest frequency of a PurP was seen in cases with an AD type pathology in which 62.2% of IM AD-NC and 44.5% of AD cases were classified as pure, as were 28.6% of FTLD-tau and 15.8% of FTLD-TDP-43 cases, respectively. Interestingly, no LBD, CVD, LATE-NC, AGD, or HpSc cases were classified as PurP, with all of these cases containing at least one additional LowP. Only 1.0% of the entire cohort exhibited no pathology. The most frequent mixed SevP diagnosis was Mixed AD/DLB, comprising 72.0% of all mixed SevP cases. In non-AD cases, the most common additional LowP was Low/Mod AD-NC seen in 92.3% of LBD, 90.0% of LATE-NC, 84.6% of AGD, and 73.6% of FTLD-TDP-43 cases. In AD cases, additional LATE-NC was by far the most frequent additional LowP, present in 42.7% of Mixed AD/DLB, 34.3% of AD, 27.9% of IM AD-NC, and 16.7% of Mixed AD/CVD cases. In CVD cases, the most frequent additional LowP was Low/Mod AD-NC seen in 80.5% and in 100% of HpSc. Late-NC and α-syn pathology was also present in 22.2% and 5.6% of CVD cases, respectively, but only as a combination together with Low/Mod AD-NC. Aβ pathology was rarely an independent additional LowP (i.e., without Hpτ), seen only in 5.1% of LowP only, 1.5% of LBD, and 2.8% of CVD cases. Furthermore, α-syn pathology was rarely seen as an independent additional LowP, only present in 10.8% of AD. Taking into account all cases with an additional LowP diagnosis ($n = 462$), the majority of cases exhibited only one additional LowP (81.8%), 17.3% exhibited two additional LowP, and 0.9% exhibited three additional LowP. A total of 46 different combinations of a neuropathological diagnosis and additional LowP were recorded.

TABLE 3 APOE genotype status of cases stratified by neuropathological diagnosis

	APOE genotype frequency (%)					
Neuropathological diagnosis	**ε4/ε4**	**ε3/ε4**	**ε3/ε3**	**ε2/ε4**	**ε2/ε3**	**ε2/ε2**
All cases (*n* = 606)	**50 (8.3)**	**252 (41.6)**	**236 (38.9)**	**33 (5.4)**	**32 (5.3)**	**3 (0.50)**
LowP only	0 (0)	36 (28.3)	72 (56.7)	4 (2.9)	14 (11)	1 (0.7)
IM AD-NC	4 (6.5)	27 (43.5)	27 (43.5)	1 (1.6)	3 (4.5)	0 (0)
AD	28 (14.4)	106 (54.4)	47 (24.1)	9 (4.6)	4 (2.1)	1 (0.5)
LBD	3 (4.9)	26 (40)	26 (40)	4 (6.6)	2 (3.3)	0 (0)
Mixed AD/DLB	11 (16.4)	32 (47.8)	18 (26.9)	4 (6)	2 (3)	0 (0)
LATE-NC	0 (0)	1 (14.2)	2 (28.6)	2 (28.6)	2 (28.6)	0 (0)
CVD	2 (5.9)	5 (14.7)	18 (52.9)	7 (20.5)	1 (3)	1 (3)
Mixed AD/CVD	1 (7.1)	6 (42.9)	5 (35.7)	2 (14.3)	0 (0)	0 (0)
FTLD-tau	0 (0)	2 (20)	5 (50)	1 (10)	2 (20)	0 (0)
FTLD-TDP-43	0 (0)	6 (33.3)	9 (50)	1 (5.6)	2 (11.1)	0 (0)
AGD	0 (0)	5 (41.7)	5(41.7)	0 (0)	2 (16.7)	0 (0)
HpSc	1 (16.7)	1 (16.7)	4 (66.7)	0 (0)	0 (0)	0 (0)

Abbreviations: AD, Alzheimer's disease; AGD, argyrophilic grain disease; APOE, apolipoprotein E; CVD, cerebrovascular disease; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; HpSc, hippocampal sclerosis; IM AD-NC, intermediate Alzheimer's disease neuropathological change; LATE-NC, limbic-predominant age-associated TDP-43 encephalopathy neuropathological change; LBD, Lewy body disease; LowP, low/intermediate level additional pathology.

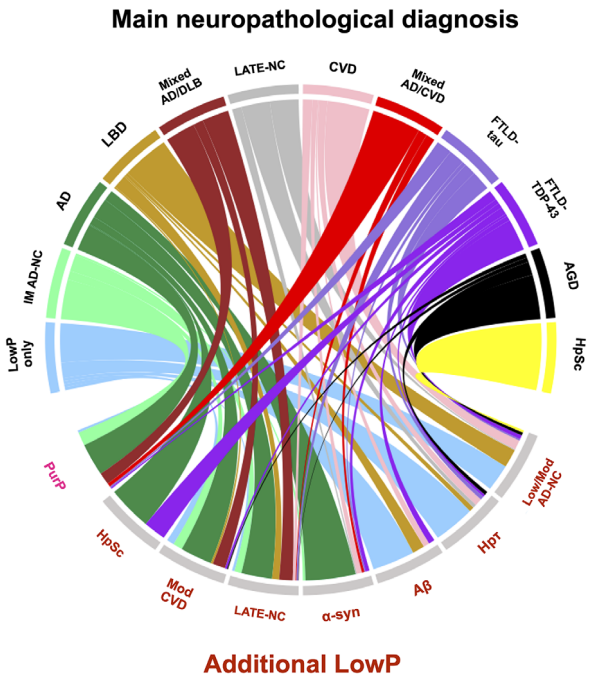

FIGURE 1 A chord diagram illustrating the complex associations and overlap between the main neuropathological diagnosis and additional low pathologies. Each connection is proportional to the frequency of cases presented in Table 4. AD, Alzheimer's disease; AGD, argyrophilic grain disease; CVD, cerebrovascular disease; DLB, dementia with Lewy bodies; FTLD, fronto-temporal lobar degeneration; HpSc, hippocampal sclerosis; IM AD-NC, intermediate Alzheimer's disease neuropathological change; LATE-NC, limbic-predominant age-associated TDP-43 encephalopathy neuropathological change; LBD, Lewy body disease; LowP, low/intermediate-level additional pathology

3.2 | Association of additional LowP and age at death

Age was highly associated with an additional LowP diagnosis (χ^2, df_5, $P = 0.0001$, phi = 0.191). Furthermore, age was associated with an increase in the number of different additional LowP present ($r = 0.207$; $P = 0.0001$). Of cases aged 60–69 years, 54.3% had an additional LowP diagnosis, rising to 85.7% in the group over 100 years of age (Figure 2); in these age groups, 2+ additional LowP were present in 8.9% and 28.6%, respectively (Figure 2).

3.3 | Clinicopathological correlations

Cases without CDR or MMSE data were excluded from further clinicopathological analysis. CDR scores were recorded in 508 cases (75.8% of cohort). Overall mean last CDR assessment to death was 11.10 (± 11.6) months. Frequency of CDR and last assessment to death intervals are presented in Table 5. Two hundred thirty-two cases (34.6% of cohort) had more than one MMSE score and time interval(s) between MMSE assessments allowed calculation of overall rate of cognitive decline: (first MMSE–last MMSE)/time interval in years. Clinicopathological analysis was based upon CDR score and not neuropathological classification unless otherwise stated. Hpτ, Aβ plaques, neuritic plaques, and α-syn pathology and the presence of additional LATE-NC were present in significantly more cases with dementia (CDR > 1) than without dementia (CDR < 0.5; Figure 3A and B; all $P < 0.0001$; additional LATE-NC χ^2, df_1, $P = 0.0001$, phi = 0.272). In contrast, CVD and prevalence of additional HpSc (non-TDP-43 associated) did not differ between CDR < 0.5 and CDR > 1 ($P > 0.2$). Apart from CVD and

TABLE 4 Breakdown of pure diagnosis and LowP diagnosis in each diagnostic group

Main neuropathological diagnosis	Pure diagnosis (%)	Singular additional LowP (%)								2+ LowP combinations (%)
		Low AD-NC	IM AD-NC	Hpτ (Braak stage < IV)	Aβ (Thal Aβ Phase 1-4)	α-syn (McKeith Amyg/BS)	aLATE-NC	CVD (mod. VCING)	aHpSc	
LowP only	7 (5.1)	83 (60.6)	~	33 (24.1)	7 (5.1)	0	~	0	0	Low AD-NC + Mod. CVD = 5 (3.6) Hpτ + Mod. CVD = 2 (1.5)
IM AD-NC	41 (60.4)	~	~	~	~	2 (2.9)	16 (23.5)	6 (8.8)	0	aLATE-NC + Mod. CVD = 3 (4.4)
AD	97 (45.5)	~	~	~	~	23 (10.8)	47 (22.1)	15 (7.0)	3 (1.4)	aLATE-NC + α-syn = 13 (6.1) aLATE-NC + Mod. CVD = 11 (5.1) Mod. CVD + α-syn = 1 (0.5) Mod. CVD + aHpSc = 1 (0.5) aLATE-NC + α-syn + CVD = 2 (1.0)
LBD	0	27 (41.5)	16 (24.6)	4 (6.2)	1 (1.5)	~	0	0	0	aLATE-NC + Low AD-NC = 5 (7.7) aLATE-NC + Mod AD-NC = 10 (15.5) Mod AD-NC + Mod. CVD = 1 (1.5) Low AD-NC + aLATE-NC + Mod. CVD = 1 (1.5)
Mixed AD/DLB	36 (48.0)	~	~	~	~	~	27 (36.0)	7 (9.3)	0	LATE + Mod. CVD = 5 (6.7)
LATE-NC	0	3 (37.5)	0	3 (37.5)	0	1 (12.5)	~	0	0	Low AD-NC + aHpSc = 1 (12.5)
CVD	0	16 (44.4)	5 (13.9)	6 (16.7)	1 (2.8)	0	0	~	0	Low AD-NC + aLATE-NC = 4 (11.1) Mod AD-NC + aLATE-NC = 2 (5.5) Low AD-NC + α-syn = 1 (2.8) Low AD-NC + aLATE-NC + α-syn = 1 (2.8)
Mixed AD/CVD	14 (77.8)	~	~	~	~	1 (5.5)	2 (11.2)	~	0	α-syn + aLATE-NC = 1 (5.5)
FTLD-tau	4 (28.6)	3 (21.5)	0	3 (21.5)	0	0	1 (7.1)	0	0	Low AD-NC + α-syn = 1 (7.1) Low AD-NC + aLATE-NC = 1 (7.1) Hpτ + aLATE-NC = 1 (7.1)
FTLD-TDP-43	3 (15.8)	8 (42.1)	2 (10.5)	0	0	0	0	0	0	Low AD-NC + α-syn = 2 (10.5) Low AD-NC + Mod. CVD = 2 (10.5) Hpτ + α-syn = 1 (5.3) Aβ + α-syn = 1 (5.3)
AGD	0	8 (61.5)	1 (7.7)	2 (15.4)	0	0	0	0	0	Low AD-NC + aLATE-NC = 1 (7.7) Low AD-NC + Mod. CVD = 1 (7.7)
HpSc	0	2 (50.0)	0	0	0	0	0	0	~	Low AD-NC + Mod. CVD = 1 (25.0) Mod AD-NC + Mod. CVD = 1 (25.0)

~pathology included in main neuropathological diagnosis so cannot be an additional LowP pathology.

Abbreviations: a, additional; AD, Alzheimer's disease; AGD, argyrophilic grain disease; LBD, Lewy body disease; CVD, cerebrovascular disease; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; HpSc, hippocampal sclerosis; IM AD-NC, intermediate Alzheimer's disease neuropathological change; LATE-NC, limbic-predominant age-associated TDP-43 encephalopathy neuropathological change; LowP, low/intermediate level additional pathology.

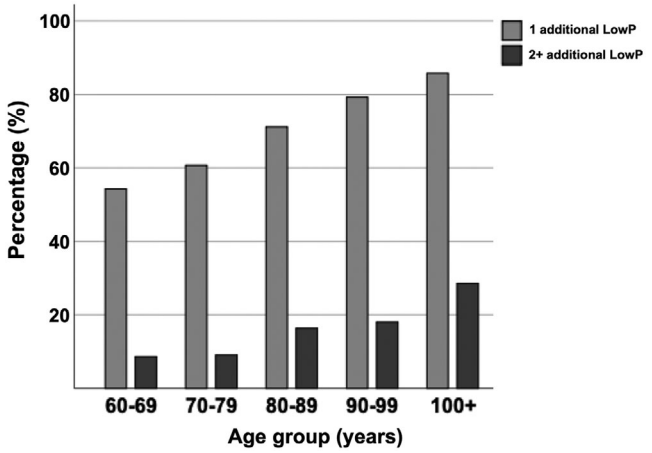

FIGURE 2 The prevalence of and the number of additional LowP increases with age. Of all cases in each age group, the prevalence of an additional LowP diagnosis is 54.3% in the seventh decade, 60.6% in the eighth, 71.2% in the ninth, 79.2% in the hundredth, before peaking at 85.7% at 100 years and over. From the seventh decade the presence of two or more additional LowP increases is 8.6% increasing to 9.0% in the eighth decade, 16.4% in the ninth decade, 18.0% in the hundredth, and peaking at 28.6% at 100 years and over. LowP, low/intermediate-level additional pathology

additional HpSc, all neuropathological stages and the presence of additional LATE-NC were associated with an accelerated rate of cognitive decline: Braak NFT stage ($r = -0.262$; $P = 0.0001$), Thal Aβ phase ($r = -0.266$; $P = 0.0001$), CERAD for neuritic plaques ($r = -0.276$; $P = 0.0001$), McKeith stage ($r = -0.151$; $P = 0.011$), and additional LATE-NC ($r = -0.121$; $P = 0.028$).

3.4 | Effect of main pathological stage, APOE genotype, sex, disease duration, and years of education on the odds of dementia

Forward stepwise binary logistical regression was used to determine the effect of Braak NFT stage, Thal Aβ phase, CERAD for neuritic plaques, and McKeith stage significantly contributed to the odds of having dementia (CDR < 0.5 vs. CDR > 1) or on the odds of having a categorical increase in CDR score (model information is presented in Data S1A in supporting information). Odds ratio (OR) data are presented in Table 6. Briefly, increasing Braak NFT stage was associated with an almost 4-fold increase and Thal Aβ phase and McKeith stage with an almost 3-fold increase in the odds of CDR > 1 versus CDR < 0.5. No neuropathological stage predicted the transition from CDR 0 to CDR 0.5 (model: $P = 0.112$). Increasing Braak NFT stage increased the odds of transitioning from CDR 0.5 to CDR 1 by 75% and the odds of having CDR 2 versus CDR 1 increased more than 2.5 times with increasing neuritic plaque density. Finally, the odds for transitioning from CDR 2 to CDR 3 were increased 57% by Braak NFT stage. APOE genotype status was not found to be significantly associated with the transition from CDR 0 to CDR 0.5 (4/4, $P = 0.102$; 3/4, $P = 0.316$; 3/3, $P = 0.994$; 2/4, $P = 0.243$; 2/3, $P = 0.935$; 2/2, $P = 0.379$). APOE genotype did not significantly influence the OR of neuropathological stages. A longer disease duration (i.e., survival) was associated with being in the CDR < 0.5 group compared to CDR > 1 group (OR = 0.985, 95% CI: 0.976–0.995), but disease duration did not significantly influence OR of neuropathological stages. Sex did not have a significant effect on the odds of being demented ($P = 0.218$) and no effect on OR of neuropathological stages. The number of years of education was significantly higher in the no-cognitive-impairment group compared to the dementia group ($P = 0.003$; mean values no-cognitive-impairment, 13.30 ± 3.8 years; dementia, 12.23 ± 3.41 years); however, due to the marginal difference, as expected this did not significantly influence the odds of being CDR > 1 versus CDR < 0.5 ($P = 0.185$) or the OR of the neuropathological stages.

3.5 | Additional LowP on the odds of dementia

Forward enter linear regression was used to determine whether the presence of any 1 or 2+ additional LowP significantly contributed to the odds of having dementia (CDR < 0.5 vs. CDR > 1), a categorical increase in CDR score, or the ORs of neuropathological stages (Table 6). The findings are summarized in Data S1B and Table 7. The presence of any additional LowP did not significantly contribute to the odds of being CDR > 1 versus CDR < 0.5 or change the OR of any neuropathological stage. However, the presence of one additional LowP increased the chance of transitioning from CDR 0.5 to CDR 1 almost 20-fold and doubled the influence of Braak NFT stage on the odds of being in the CDR 1 category. The addition of 2+ additional LowP did not further

TABLE 5 Frequencies of each CDR score and mean time interval of last assessment to death

CDR	Frequency (%)	Mean time interval from last CDR assessment to death (months)
CDR 0: No dementia	120 (23.6)	16.5 (± 14.6)
CDR 0.5: MCI	27 (5.3)	10.14 (± 7.2)
CDR > 1: Dementia	361 (71.1)	9.24 (± 9.9)
CDR 1: Mild dementia	50 (13.80)	12.04 (± 11.07)
CDR 2: Moderate dementia	54 (15.0)	9.22 (± 6.54)
CDR 3: Severe dementia	257 (71.2)	8.7 (± 10.180

Abbreviations: CDR, Clinical Dementia Rating; MCI, mild cognitive impairment.

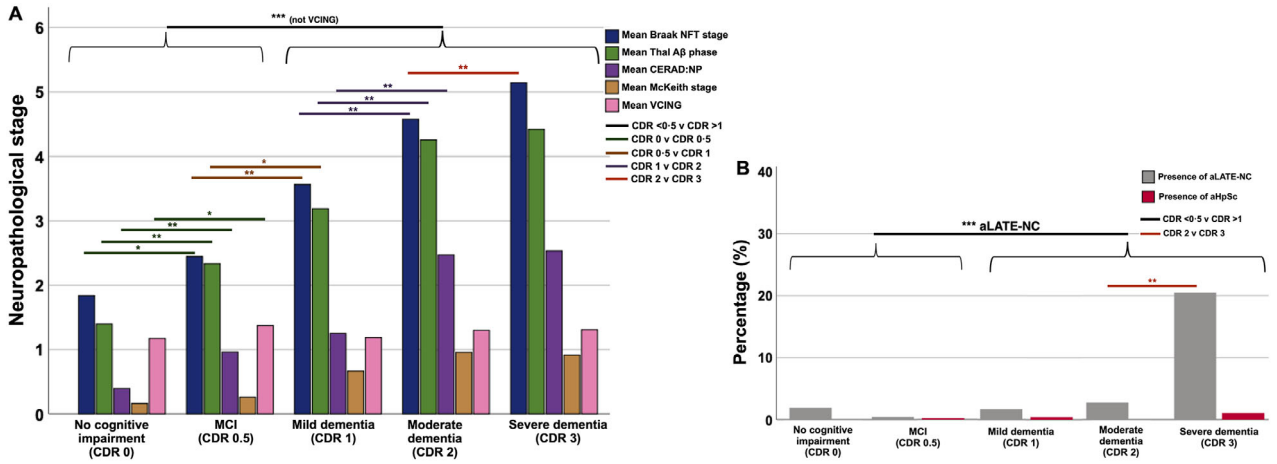

FIGURE 3 Bar charts (A) and (B) indicate significant differences in pathological burden or prevalence of pathologies between no dementia and dementia (CDR < 0.5 vs. CDR > 1) and individual CDR scores. A, Mean neuropathological assessment stages of Hpτ (Braak NFT stage), Aβ plaques (Thal Aβ phase), neuritic plaques (CERAD), α-syn (McKeith stage), and CVD (VCING; moderate or high stage only). B, Percentage of cases presenting with additional LATE-NC or additional HpSc (independent of LATE-NC present) at each CDR score. ***, $P < 0.0001$; **, $P < 0.01$; *, $P < 0.05$. Aβ, amyloid beta; CDR, Clinical Dementia Rating; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CVD, cerebrovascular disease; HpScl, hippocampal sclerosis; LATE-NC, limbic-predominant age-associated TDP-43 encephalopathy neuropathological change; NFT, neurofibrillary tangle; VCING, vascular cognitive impairment neuropathological guidelines

TABLE 6 Odds ratios (OR) and 95% confidence intervals (CI) for categorical increases in CDR scores associated with distinct neuropathological stages

Odds of being CDR > 1 vs. CDR < 0.5 (model $P = 0.001$)		
Neuropathological stage	**OR**	**95% CI**
Braak NFT stage	3.9	2.1–5.5
Thal Aβ phase	2.71	1.51–3.23
CERAD for neuritic plaques	*NS*	~
McKeith stage	3.18	1.85–5.46
Odds of being CDR 0.5 vs. CDR 0 (model $P = 0.112$)		
Odds of being CDR 1 vs. CDR 0.5 (model $P = 0.003$)		
Braak NFT stage	1.75	1.17– 2.62
Thal Aβ phase	*NS*	~
CERAD for neuritic plaques	*NS*	~
McKeith stage	*NS*	~
Odds of being CDR 2 vs. CDR 1 (model $P = 0.0001$)		
Braak NFT stage	*NS*	~
Thal Aβ phase	*NS*	~
CERAD for neuritic plaques	2.62	1.7–4.06
McKeith stage	*NS*	–
Odds of being CDR 2 vs. CDR 3 (model $P = 0.009$)		
Braak NFT stage	1.57	1.09–2.28
Thal Aβ phase	*NS*	~
CERAD for neuritic plaques	*NS*	~
McKeith stage	*NS*	~

Abbreviations: Aβ, amyloid beta; CDR, Clinical Dementia Rating; CERAD, CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NFT, neurofibrillary tangle.

TABLE 7 Odds ratios (OR) and 95% confidence intervals (CI) for categorical increases in CDR scores associated with the presence of additional LowP

Odds of being CDR > 1 vs. CDR < 0.5 (model $P = 0.564$)		
Odds of being CDR 0.5 vs. CDR 0 (model $P = 0.031$)		
Variable	**OR**	**95% CI**
+1/2 additional LowP	19.5	1.31–291.29
Braak NFT stage	3.66	1.46–9.2
Thal Aβ phase	*NC*	*NC*
CERAD for neuritic plaques	*NC*	*NC*
McKeith stage	*NC*	*NC*
Odds of being CDR 1 vs. CDR 0.5 (model $P = 0.116$)		
Odds of being CDR 2 vs. CDR 1 (model $P = 0.248$)		
Braak NFT stage	*NC*	*NC*
Thal Aβ phase	*NC*	*NC*
CERAD for neuritic plaques + 1 LowP	3.17	0.59–6.28
CERAD for neuritic plaques + 2 LowP	4.72	1.39–16.09
McKeith stage	*NC*	*NC*
Odds of being CDR 2 vs. CDR 3 (model $P = 0.172$)		

Abbreviations: Aβ, amyloid beta; CDR, Clinical Dementia Rating; CERAD, CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NFT, neurofibrillary tangle.

significantly contribute to the model or add to the OR of Braak NFT stage. The presence of 1 or 2+ additional LowP did not significantly contribute to the transition from CDR1 to CDR 2; however, the presence of 1 or 2 additional LowP cumulatively increased the OR of neuritic plaque stage almost 2-fold. The presence of 1 or 2+ additional

LowP did not significantly contribute to the transition from CDR 2 to CDR 3 or influence on the OR value of Braak NFT stage.

3.6 | Clinical impact of additional LATE-NC and CVD pathology in AD

The addition of low-level LATE-NC and CVD pathology has been implicated as an important clinical influence on AD. We investigated the influence of additional LATE-NC or CVD on age at death, final MMSE scores, rate of cognitive decline, and disease duration.

3.6.1 | Additional LATE-NC in AD

We selected neuropathological cases diagnosed as PurP AD ($n = 71$; mean age at death 80.35 [± 8.82]), AD with additional LATE-NC (no other additional LowP; $n = 49$; mean age at death 83.74 [± 8.17]), or Mixed AD/DLB (no other additional LowP; n = 25; mean age at death 79.32 [± 7.98]; total $n = 145$). Using Kruskal-Wallis, we compared clinical scores and age at death between the three groups to investigate whether there was any significant decline associated with the presence of additional LATE-NC in AD, and to compare to another AD mixed diagnosis. No significant difference in final MMSE, rate of cognitive decline, or disease duration was seen between groups. Age was shown to be significantly different; post hoc Mann–Whitney *U* analysis indicated that age of death was significantly lower in pure AD ($P = 0.013$) and in Mixed AD/DLB ($P = 0.028$) than in AD with additional LATE-NC.

3.6.2 | Additional CVD pathology in AD

We selected for neuropathological cases diagnosed as having PurP AD (as above), AD with additional CVD ($n = 13$; mean age at death 83.62 [± 6.56]) and Mixed AD/CVD (no additional pathologies; $n = 7$; mean age at death 85.71 [± 6.75]).

We compared age at death and clinical scores between the groups, but no differences were found ($P < 0.099$). However, disease duration was significantly shorter in AD with additional CVD than in PurP AD ($P = 0.038$).

4 | DISCUSSION

It has become increasingly clear that the aged human brain is characterized by the coexistence of multiple neurodegenerative pathologies ranging from minimal additional LowP to mixed SevP. Previous autopsy studies have not clearly defined and differentiated between additional LowP and mixed SevP, and the frequency of true additional LowP and the impact this has on cognition has been unclear. In the present clinicopathological autopsy study, by analyzing the severity of additional pathologies in common age-related neurodegenerative diseases, we have been able to capture the full complexity of multimorbidity and to show that even low amounts of additional pathology, which might have been considered clinically irrelevant, have a statistically significant impact on cognitive decline and the clinical syndrome.

Our findings indicate that only 22.7% of cases were considered a PurP, which is much lower than other community-based and large consortia clinicopathological studies that report a frequency of PurP ranging between 40% and 50%[6,13]. This discrepancy is likely to be due to the more stringent criteria applied in our study to identify cases with additional LowP that would otherwise be classified as a PurP. The AD and IM AD-NC groups had the highest rate of PurP at 44.5% and 62.2%, respectively, which is similar to findings in previous autopsy studies.[7,5,6,33] This is in contrast to a recent combined longitudinal clinicopathological study by Boyle et al.,[8] who reported a pure AD frequency of only 9%; however, the authors considered cerebral amyloid angiopathy (CAA) an additional pathology, while we have chosen not to do so because CAA is seen in 80% to 100% of AD cases.[34]

Overall, 69.9% of the cohort had additional LowP present, which is in line with the mean frequency of 53.6% (range between subgroups of 27% and 81%) reported in a comparative autopsy study by Robinson et al.,[33] and a mixed SevP was reported in the remaining 7.5% of cases. The prevalence of an additional LowP diagnosis as well as the number of additional LowP present were highly associated with increasing age, in agreement with a previous autopsy study that indicated the prevalence of severe mixed pathology and a diagnosis of a mixed disease increased with age.[35] Only one previous autopsy study[5] clearly differentiated between additional LowP and mixed SevP in confirmed AD cases, reporting additional LowP in 31% of cases, which is considerably lower than our reported 44.5%. However, this difference may be due to our inclusion of LATE-NC, which was the most frequent additional LowP and seen in 42.7% of AD cases, in agreement with previous autopsy studies.[18] None of LBD and CVD cases in this study was considered a PurP, with concomitant AD pathology present in 92.3% of LBD cases, and 80.5% of CVD cases, raising important considerations for the management of such patients. Regarding LBD, this universal prevalence of LowP was in contrast to Robinson et al,[33] who reported only 61% of LBD cases contained additional LowP, although this discrepancy may be influenced by the exclusion of CVD/CVL assessment in the Robinson et al. study. Furthermore, the presence of additional LowP was not exclusive to the dementia groups as the second highest prevalence (94.9%) of additional LowP was in the LowP only group; in the vast majority this consisted of low AD neuropathological change or singular Hpτ depositions and Aβ plaques, in line with a previous report.[33] Our frequency of additional LowP in the LowP only was much higher than the 48% frequency reported by a comparative study;[33] however, this is likely due to differing classification of additional pathologies between the two studies. The majority of LowP cases had one additional LowP, but 17.3% of the cohort had two or more additional LowP present. LowP was very heterogeneous: a total 46 LowP combinations/diagnosis were recorded, with predominant pathologies being Hpτ, Aβ, and LATE-NC, in line with a recent autopsy study.[8]

A novel and important finding from our study is that the presence of any single additional LowP increased the odds of transitioning from MCI to mild dementia by 20-fold and doubled the impact of Hpτ pathology on cognitive status; for example, an individual with Braak NFT

stage IV but no additional LowP had half the chance of being mildly demented than did an individual with Braak NFT stage IV and one additional LowP. In addition, the presence of additional LowP doubled the influence of neuritic plaques on the transition from mild to moderate dementia. It has been shown that additional LowP contribute to cognitive decline [13,14,33,36] and our data indicate that the presence of even one additional LowP is crucial in key clinical transitional phases, that is, from MCI to mild dementia, and from mild to moderate dementia. These findings are in agreement with previous clinicopathological studies that found that a clinical diagnosis of MCI was associated with a comorbid diagnosis at autopsy[7] and the number of additional pathologies was associated with clinical dementia[11] or cognitive decline.[12,15] This suggests the presence of additional LowP lowers the threshold for overt cognitive decline, perhaps by lowering brain reserve[37] or promoting synergistic protein interactions. Because of the 46 subcategories describing concomitant pathology, we were unable to investigate the specific impact of individual additional LowP as the analysis would have been statistically underpowered.

A recent example of the clinical impact of additional LowP is additional LATE-NC, which is frequently found in combination with moderate/high AD-NC[38] and present in approximately 50% of AD cases. The presence of LATE-NC in AD is associated with more rapid cognitive decline,[19,39] more pronounced deficits in memory,[40] and greater hippocampal atrophy[41,42] than occur in individuals with AD without additional LATE-NC. However, in our study we found no differences in clinical scores or disease duration between PurP AD and AD with additional LATE-NC, which may reflect the limitations of the dichotomous (present versus absent) assessment of additional LATE-NC in our study. In addition, we compared PurP AD and AD to additional LATE-NC to Mixed AD/DLB and found no differences in clinical scores. Age of death was significantly lower in PurP AD and Mixed AD/LBD than in AD with additional LATE-NC, in keeping with reports that LATE-NC is often seen in the oldest old.[17] The lack of difference in cognitive measures between PurP AD and Mixed AD/DLB in our cohort is in contrast to previous clinicopathological studies that have shown faster cognitive decline in Mixed AD/DLB compared to AD.[43,44] A possible explanation for this discrepancy may be that both PurP AD and Mixed AD/DLB cases in our study were already severely cognitively impaired at baseline assessment and therefore no differences in the rate of cognitive decline could have been detected.

All neuropathological lesions, with the exception of CVD, were associated with cognitive decline; in particular Hpτ-, Aβ-, and α-synrelated pathology were associated with up to a 3-fold increase in the odds of dementia, in agreement with previous clinicopathological studies.[8,45,46] Our study provided novel information regarding the specific neuropathologies that significantly contributed to the progression and severity of the clinical dementia, namely Hpτ pathology in the conversion from MCI to mild dementia and moderate to severe dementia, and neuritic plaques in the transition from mild to moderate dementia. This highlights the impact of Hpτ, and subsequent AD-associated neuropathological change, on cognitive function, as has been previously recognized.[47]

Perhaps surprisingly, no case was classified as pure CVD, that is, CVD without any LowP, in contrast to previous studies that reported the frequency of pure CVD between 2% and 11%.[5] Additionally, a diagnosis of Mixed AD/CVD was present in only 2.8% of cases—lower than reported frequencies within community-based clinicopathological studies from the United States[13] and the UK[4] but in line with previous reports from the Vienna consecutive autopsy series.[5] Furthermore, CVD was not associated with cognitive decline or an increased risk of cognitive impairment or dementia, contrary to other large clinicopathological studies (for reviews please see Kapasi and Schneider[48] and Kapasi et al. [49]) but in agreement with a previous autopsy study.[11] This study also found that the addition of LowP CVD in AD did not impact clinical scores when compared to pure AD in contrast to previous studies.[4,16,50,51] However, this study did reveal that individuals with AD and additional CVD had a shorter disease duration, suggesting accelerated disease progression. These differences in prevalence and clinical contribution may be affected by selection bias, as exclusion criteria for BDR recruitment includes major stroke, and the use of the VCING criterion for the neuropathological assessment of CVD limits CVD assessments to low, moderate, or high likelihood of contributing to cognitive impairment. However, the VCING criteria reflect a validated neuropathological assessment of CVD in relation to the predicted probabilities of vascular cognitive impairment; therefore, our study may reflect a truer representation of the prevalence of clinically relevant CVD within this UK cohort. On the other hand, VCING criteria are relatively crude and do not have the accuracy of neuropathological criteria used for the assessment of neurodegenerative proteinopathies. The detailed assessment of CVD is challenging, as CVD-associated brain damage does not progress in a stereotyped topographical manner and therefore large areas of the *post mortem* brain would need to be assessed to get a complete picture of CVD-associated brain damage. In addition, *post mortem* delay may result in autolytic changes that may mask microscopic hypoxic tissue damage. Hence, the use of VCING criteria may lead to an underestimation of the contribution of CVD to cerebral multimorbidity.

The exact pathomechanisms of cerebral multimorbidity are still poorly understood, but it is assumed that both age-associated failures of basic cellular mechanisms and protein—protein interactions play a crucial role (please see Spires-Jones et al.[52] for review). The accumulation of misfolded proteins and CVD/CVL in the human brain are clearly associated with advanced age; dysfunction of the complex and interrelating systems of basic cellular homeostatic regulation, DNA damage repair, autophagy regulation, and oxidative stress response are all associated with cellular dysfunction in aging, and some individual genetic variability, leaving cells vulnerable to further insults. Due to the complexity and heterogeneity of neuropathological lesions in the aged brain, future classification should move away from rigid categorization of neurodegeneration into distinct disease subtypes only (e.g., AD, LBD) and be inclusive of the presence, severity, and location of LowP. This will provide a more precise picture of neurodegeneration in general and unravel subtle clinicopathological phenotypes and may be transferable to future biomarkers and *intra vitam* diagnosis allowing

for accurate clinical trials design and interpretation, as well as targeted and personalized therapeutics.

5 | CONCLUSIONS

More than three quarters of aged individuals have multiple brain pathologies, of which the vast majority are LowP. No case of LBD or CVD was without additional LowP. The presence of even one LowP significantly affects cognitive decline, increasing the risk of transitioning from MCI to dementia 20-fold and augmenting the influence of other pathologies on cognitive decline. The progression of clinical dementia was significantly attributed to Hpτ pathology. The high prevalence of multimorbidity in the aged brain should be accounted for in neuropathological assessment and clinicopathological studies and be at the forefront of consideration in dementia research, in particular in the design and interpretation of clinical studies.

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CONFLICTS OF INTEREST

The authors report no declarations of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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