Supplementary Material

Cancer and Vascular Comorbidity Effects on Dementia Risk and Neuropathology in the Oldest-Old

Supplementary Tables 1-3. Neuropathologic scoring of cerebrovascular disease.

Supplementary Table 1. Kalaria cerebrovascular disease scale [1, 2]	
Cerebral Cortex (select highest that applies)	
☐ **0** Normal appearance of brain, vessels, white matter, and cortex	
☐ **1** Mild modification of vessel walls, perivascular spaces, or white matter	
☐ **2** Moderate to severe but isolated modification of the vessel (arteriolosclerosis or amyloid angiopathy), usually associated with hemosiderin deposits in the perivascular spaces; and/or Moderate to severe cerebral amyloid angiopathy involving parenchyma	
☐ **3** Moderate to severe perivascular space dilatations either in the deep or the juxtacortical white matter	
☐ **4** Moderate to severe myelin loss; and/or White matter infarct	
☐ **5** Presence of cortical microinfarcts	
☐ **6** Presence of large infarcts and/or cystic infarcts	
Basal ganglia (select highest that applies)	
☐ **0** Normal appearance	
☐ **1** Mild modification of vessel walls or perivascular spaces (or if spaces not noted, but isolated moderate to severe arteriolosclerosis)	
☐ **2** Moderate to severe perivascular space dilatations	
☐ **3** Presence of microinfarcts	
☐ **4** Presence of large infarcts; and/or lacunar infarct	
Kalaria score (Total of cortex and basal ganglia)	**(/10)**

Supplementary Table 2. Strozyk cerebrovascular disease scale [3]	
Large infarct (select highest)	
☐ 0=None	
☐ 1=1	
☐ 2+=2	
Lacunar/Cystic infarcts (select highest)	
☐ 0=None	
☐ 1=1	
☐ 2 or more=2	
Leukoencephalopathy (select highest)	
☐ 0=None	
☐ 1=Mild	
☐ 2=Moderate-to-Severe and/or White matter infarct	
Strozyk score (Total of large, lacunar, and leuko.)	**(/6)**

Supplementary Table 3. Dickson Gestalt for neuropathologic evaluation	
Large infarct (1=1, ≥2=2)	
Lacunar infarct (1=1, ≥2=2)	
Microinfarct (1=1, ≥2=2)	
White matter loss (1=moderate-severe) or White matter infarct	
HpScl-VaD (1=present)	
CAA (1=severe)	
Dickson score (Cumulative score from each pathology)	**(/9)**

Note: Acute lesions do not get scored for any scale.

Supplementary Table 4. Cancer type stratified by in participants without dementia compared to those with dementia

Cancer type	No Dementia	Dementia
None	31/72 (43%)	62/89 (70%)
Skin cancer		
Melanoma	3/72 (4%)	1/89 (1%)
Non-melanoma carcinoma	18/72 (25%)	10/89 (11%)
Non-skin cancer		
Hematological (leukemia)	0/72 (0%)	1/89 (1%)
Solid tumors	16/72 (22%)	14/89 (16%)
Sarcoma	1/72 (1%)	0/89 (0%)
Metastatic	3/72 (4%)	1/89 (1%)

Data are presented as proportions. Cancer history was dichotomized into non-skin cancer and skin cancer [4]. Skin cancers included melanoma and nonmelanoma (basal cell carcinoma, squamous cell carcinoma). Non-skin cancers comprised hematological cancers (leukemia) or solid tumors, including carcinoma (bladder, breast, biliary, colon, esophagus, gastric, kidney, lung, ovary, pancreas, prostate, rectum, uroepithelial, and uterine), sarcoma, and metastatic disease. If a participant had multiple cancers, further sub-analyses prioritized skin cancer when binning cancer history. Note: The No Dementia percentage adds to 99% as several values could not be rounded up.

Supplementary Table 5. Cancer history stratified by dementia type.

Variable	Amnestic dementia	Vascular dementia	Lewy body dementia	Uncertain	p
Cancer history					0.40
None	45/61 (74%)	5/7 (71%)	2/5 (40%)	10/16 (62%)	
Cancer present	16/61 (26%)	2/7 (29%)	3/5 (60%)	6/16 (38%)	

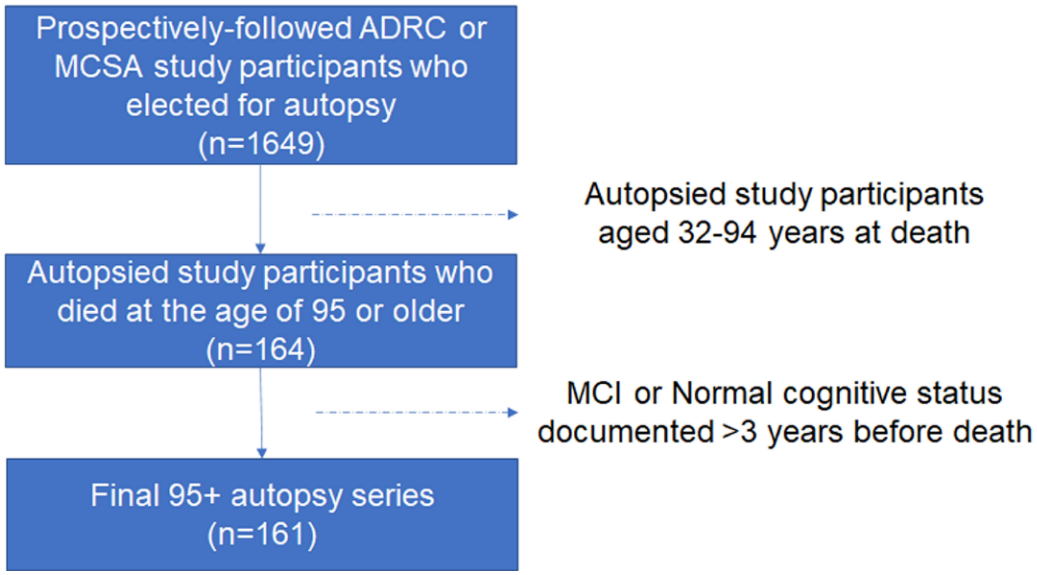
Data are presented as proportions.

Supplementary Table 6. Proposed dysregulated genes and pathways leading to cancer or neurodegeneration.

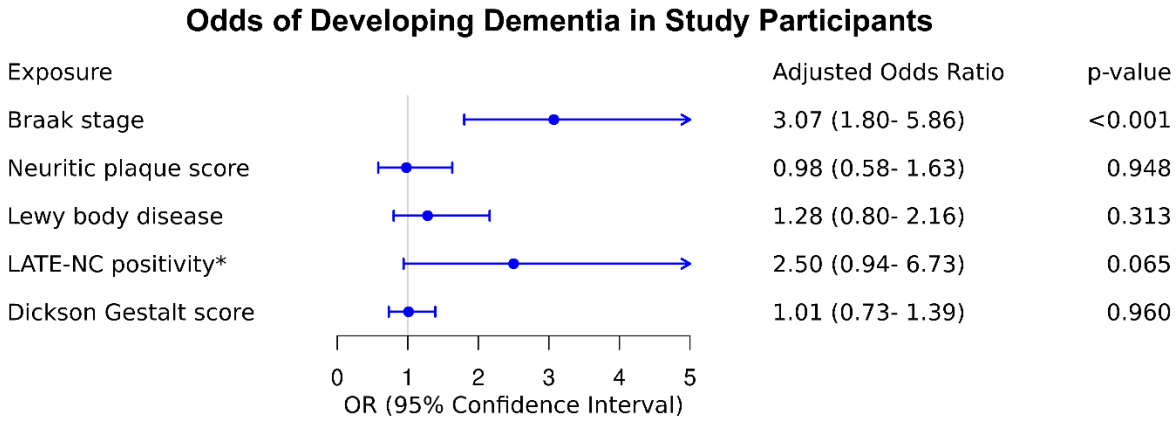
		Cancer	Alzheimer's disease
Protein/Gene/Pathway	**Function**	**Dysregulation by Peripheral Cell**	**Dysregulation by Neurons**
Pin1	enzyme that changes protein structure/function	↑	↓
Wnt	signaling pathway that promotes proliferation	↑	↓
UPS	ubiquitin proteasome system pathway for intracellular protein degradation	↑	↓
p53	a tumor suppressor protein	↓	↑
Outcome Risk		Mitosis/Proliferation	Apoptosis/Degeneration

Table information adapted based on mechanisms reviewed by Driver 2014 [5].

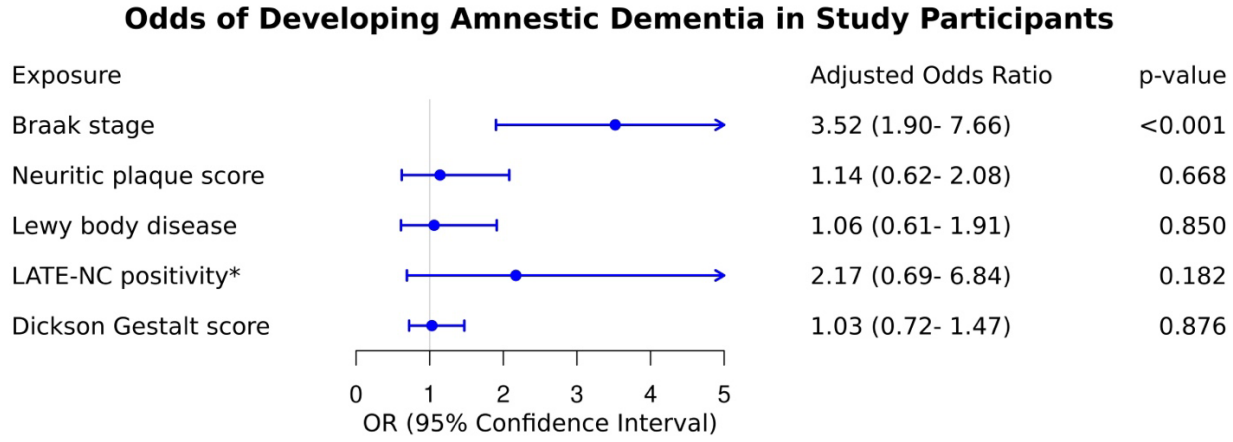
Supplementary Figure 1. The Mayo Clinic brain bank of neurodegenerative diseases was queried to identify participants from the Alzheimer's Disease Research Center or Mayo Clinic Study of Aging who came to autopsy at ≥95 years-old (95+ series). Individuals younger than 95 were excluded. Clinical records were reviewed to confirm cognitively normal or mild cognitive impairment clinical status within three years of death, which resulted in a further exclusion of three individuals. ADRC, Alzheimer's Disease Research Center; MCI, mild cognitive impairment; MCSA, Mayo Clinic Study of Aging.



Supplemental Figure 2. Odds of dementia given exposure to neuropathologic variables. Results of multivariable logistic regression depicting odds of dementia given exposure to neuropathologic variables including Braak stage (0-VI), neuritic plaque score (0-3), Lewy body disease (0=none, 1=brainstem, 2=transitional, 3=diffuse), LATE-NC positivity in amygdala* (0=none, 0.5=insufficient for positivity, 1=positive), and Dickson Gestalt score (0-5). The adjusted odds ratio is provided for each variable to contextualize independent association after controlling for other variables in the model. LATE-NC, Limbic predominant age-related TDP-43 neuropathologic change in amygdala.



Supplementary Figure 3. Odds of amnestic dementia given exposure to neuropathologic variables. Results of multivariable logistic regression depicting odds of amnestic dementia given exposure to neuropathologic variables including Braak stage (0-VI), neuritic plaque score (0-3), Lewy body disease (0=none, 1=brainstem, 2=transitional, 3=diffuse), LATE-NC positivity in amygdala* (0=none, 0.5=insufficient for positivity, 1=positive), and Dickson Gestalt score (0-5). The adjusted odds ratio is provided for each variable to contextualize independent association after controlling for other variables in the model. AD, Alzheimer's disease; LATE-NC, Limbic predominant age-related TDP-43 neuropathologic change in amygdala.



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