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HUMAN NEUROPATHOLOGY

Subjective memory complaints and neuropathologic changes at age 90 and older: *The 90+ Study*

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Abstract

Background: Subjective Memory Complaints (SMC) are defined as the perception of one's own memory. In several studies SMC are associated with Alzheimer's disease (AD) neuropathologic changes, and only one study has analyzed and found an association of SMC with other neurodegenerative, but not vascular, neuropathologic changes. Yet, the evidence on the association of SMC with non-AD neuropathologic changes is insufficient. We aim to examine the association of SMC with neurodegenerative and vascular neuropathologic changes in individuals age 90 and older (oldest-old) without dementia at death.

Method: The participants of ***The 90+ Study***, a longitudinal study of aging and cognition, who had neuropathologic examination, SMC evaluation, and had no dementia at consensus case conference were included in the analysis. SMC was evaluated with a question from the Geriatric Depression Questionnaire (GDS) "Do you feel you have more problems with memory than most?", consensus case conference diagnosis was normal cognition or Cognitive Impairment No Dementia (CIND). SMC was dichotomized as reported ever vs. never during the study follow-up, and neuropathologic changes were dichotomized as present (see Table 2) vs. absent. We estimated odds ratio [OR] and 95% confidence interval [CI] for presence of each neuropathologic change in those with normal cognition and CIND using logistic regression adjusted for demographics, GDS minus the SMC item averaged across all visits, and MMSE averaged across all visits.

Result: In 238 participants mean age at autopsy was 98 years, 121 (51%) had normal cognition, 67 (28%) have ever reported SMC (Table 1). Those with normal cognition and SMC had higher odds of AD neuropathologic change (OR = 2.9; CI: 1.5-7.9; $p = 0.04$), Lewy Body Disease (LBD) (OR = 3.6; CI: 1.8-11.8; $p = 0.04$), and atherosclerosis (OR = 3.1; CI: 1.2-8.1; $p = 0.02$). There were no significant findings in those with CIND (Figure, Table 2).

Conclusion: In the oldest-old with normal cognition SMC are associated with higher odds of neurodegenerative (AD and LBD) and vascular (atherosclerosis) neuropathologic changes. It is possible that those with normal cognition complain more selectively with respect to neuropathologic changes, compared to those with CIND.

Table 1 Characteristics of participants by case conference cognitive diagnosis and entire group

	Normal cognition	CIND	Total
Total, N	121	117	238
		N (%)	
White	120 (99)	114 (97)	234 (98)
Women	74 (61)	73 (62)	147 (62)
Education			
High school or lower	15 (12)	16 (14)	31 (13)
Vocational school or some college	38 (31)	35 (30)	73 (31)
College or higher	68 (56)	66 (56)	134 (56)
SMC ever	29 (24)	38 (33)	67 (28)
		Mean (SD) [range]	
Age at death, y	97.5 (3.3) [90.1-107.3]	97.5 (4.0) [90.8-108.6]	97.5 (3.6) [90.1-108.6]
Follow-up duration, y	4.2 (2.9) [0.0-12.2]	4.2 (3.0) [0.2-13.4]	4.2 (2.9) [0.0-13.4]
Average MMSE across all visits	28.2 (1.2) [24.0-30.0]	26.4 (2.2) [17.5-30.0]	27.3 (2.0) [17.5-30.0]
Average (GDS minus SMC) across all visits	2.5 (2.0) [0.0-12.0]	2.9 (1.9) [0.3-9.0]	2.7 (2.0) [0.0-12.0]

Notes: CIND=Cognitive Impairment No Dementia; MMSE = Mini-Mental State Examination; SMC=Subjective Memory Complaints; GDS=Geriatric Depression Scale.

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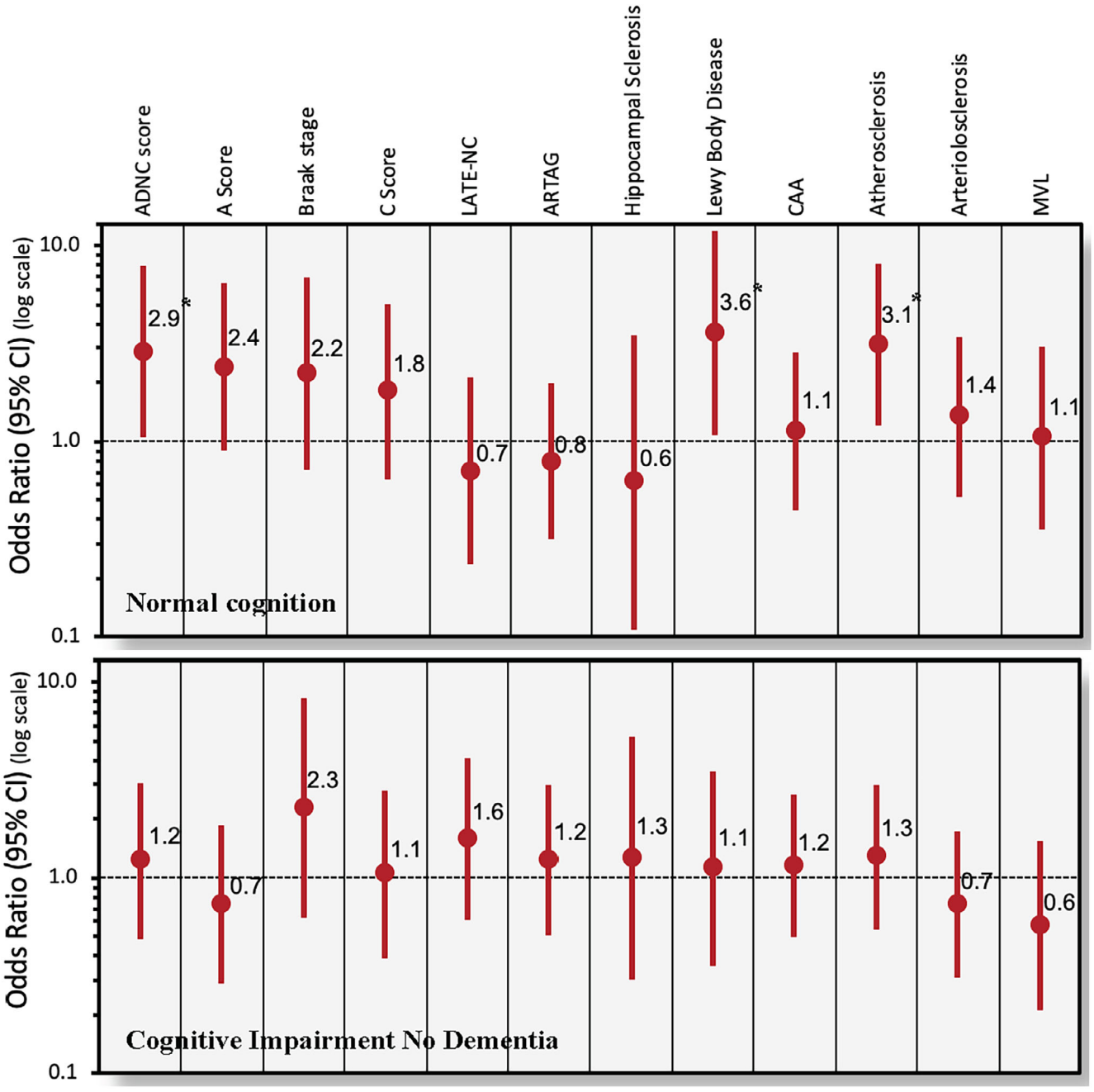
Figure. Association of Subjective Memory Complaints (SMC) with binary neuropathologic change.



Notes: ADNC score=Alzheimer's Disease Neuropathologic Change score, A score, Braak stage, C score according to the NIA-AA criteria; LATE-NC=Limbic Predominant Age-Related TDP-43 Encephalopathy Neuropathologic Change; ARTAG=Aging-Related Tau Astroglyopathy; CAA=Cerebral Amyloid Angiopathy; MVL=Microvascular Lesions. Odds Ratios (OR) and 95% Confidence Intervals (95% CI) from logistic regression separate for normal cognition and CIND, with neuropathologic changes (present vs. absent) as outcomes and Subjective Memory Complaints as predictor, adjusted for age at death, length of follow-up, sex, education, (Geriatric Depression Scale minus SMC) averaged across all visits, and MMSE averaged across all visits. Asterisk (*) identifies significant findings.

Table 2. Association of Subjective Memory Complaints with binary neuropathologic change

	N	OR	95% CI	*p*-value
Normal cognition, N=121				
ADNC score, Intermediate/high	74	**2.88**	**1.05-7.92**	**0.04**
A score, 2/3	72	2.40	0.90-6.44	0.08
Braak stage, IV-VI	89	2.23	0.72-6.92	0.16
C score, Sparse/moderate/frequent	84	1.80	0.64-5.10	0.27
LATE-NC, Amygdala/hippocampus/frontal cortex	30	0.71	0.24-2.12	0.53
ARTAG, Occasional/numerous	68	0.80	0.32-1.98	0.62
Hippocampal sclerosis, Present	10	0.63	0.11-3.55	0.60
LBD, Brainstem/amygdala/limbic/neocortical	18	**3.56**	**1.07-11.83**	**0.04**
CAA, Mild/ moderate/severe	60	1.12	0.44-2.84	0.81
Atherosclerosis, Moderate/severe	39	**3.13**	**1.21-8.09**	**0.02**
Arteriolosclerosis, Moderate/severe	69	1.35	0.53-3.46	0.53
MVL, 1-3	26	1.05	0.36-3.10	0.93
CIND, N=117				
ADNC score, Intermediate/high	77	1.23	0.49-3.10	0.66
A score, 2/3	76	0.74	0.29-1.85	0.51
Braak stage, IV-VI	96	2.27	0.63-8.23	0.21
C score, Sparse/moderate/frequent	85	1.05	0.39-2.82	0.92
LATE-NC, Amygdala/hippocampus/frontal cortex	30	1.57	0.61-4.08	0.35
ARTAG, Occasional/numerous	68	1.24	0.51-3.01	0.64
Hippocampal sclerosis, Present	10	1.28	0.31-5.32	0.74
LBD, Brainstem/amygdala/limbic/neocortical	20	1.13	0.36-3.55	0.84
CAA, Mild/ moderate/severe	56	1.16	0.50-2.69	0.74
Atherosclerosis, Moderate/severe	54	1.29	0.55-3.03	0.56
Arteriolosclerosis, Moderate/severe	62	0.73	0.31-1.72	0.47
MVL, 1-3	32	0.57	0.21-1.55	0.27

Notes: N=number of participants with neuropathologic change present included in the analysis; ADNC score=Alzheimer's Disease Neuropathologic Change score, A score, Braak stage, C score according to the NIA-AA criteria; LATE-NC=Limbic Predominant Age-Related TDP-43 Encephalopathy Neuropathologic Change; ARTAG=Aging-Related Tau Astroglyopathy; LBD=Lewy Body Disease; CAA=Cerebral Amyloid Angiopathy; MVL=Microvascular Lesions.

Odds Ratios (OR), 95% Confidence Intervals (95% CI), and *p*-values from logistic regression separate for normal cognition and CIND, with neuropathologic changes (present vs. absent) as outcomes and Subjective Memory Complaints (SMC) as predictor, adjusted for age at death, length of follow-up, sex, education, (Geriatric Depression Scale minus SMC) averaged across all visits, and MMSE averaged across all visits.