

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Savva GM, Wharton SB, Ince PG, et al. Age, neuropathology, and dementia. *N Engl J Med* 2009;360:2302-9.

Supplementary table 1 - Distribution of pathological lesions according to age at death in 426 brains with known dementia status. Column totals are shown in table 1.

		<80				80-84				85-89				90-94				>94				Total			
		No dementia		Dementia		No dementia		Dementia		No dementia		Dementia		No dementia		Dementia		No dementia		Dementia		No dementia		Dementia	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Cortical atrophy Hippocampus	None	41	75.9	10	45.5	22	68.8	12	33.3	25	62.5	19	29.7	22	66.7	19	35.2	7	70	11	28.9	117	69.2	71	33.2
	Mild	9	16.7	4	18.2	8	25	10	27.8	8	20	17	26.6	8	24.2	10	18.5			6	15.8	33	19.5	47	22
	Moderate	4	7.4	8	36.4	2	6.3	12	33.3	6	15	21	32.8	2	6.1	20	37	3	30	17	44.7	17	10.1	78	36.4
	Severe							2	5.6	1	2.5	7	10.9	1	3	5	9.3			4	10.5	2	1.18	18	8.41
	Missing	3		3		3		4		4		6		2		9		2		7		14		29	
Cortical atrophy Neocortex	None	39	69.6	10	41.7	17	51.5	10	25	22	52.4	16	23.9	18	52.9	13	22	5	41.7	8	19.5	101	57.1	57	24.7
	Mild	13	23.2	6	25	11	33.3	13	32.5	11	26.2	15	22.4	12	35.3	13	22	4	33.3	5	12.2	51	28.8	52	22.5
	Moderate	4	7.1	8	33.3	5	15.2	12	30	8	19	26	38.8	4	11.8	25	42.4	3	25	23	56.1	24	13.6	94	40.7
	Severe							5	12.5	1	2.4	10	14.9			8	13.6			5	12.2	1	0.56	28	12.1
	Missing	1		1		2		0		2		3		1		4		0		4		6		12	
Lewy bodies Entorhinal cortex	None	57	100	21	87.5	34	100	33	94.3	41	97.6	60	93.8	34	100	52	88.1	8	88.9	41	100	174	98.9	207	92.8
	Mild			3	12.5			2	5.7	1	2.4	2	3.1			4	6.8	1	11.1			2	1.14	11	4.93
	Moderate											2	3.1			2	3.4					0	0	4	1.79
	Severe															1	1.7					0	0	1	0.45
	Missing	0		1		1		5		2		6		1		4		3		4		7		20	
Lewy bodies Hippocampus	None	57	100	22	91.7	35	100	38	100	43	100	64	95.5	34	100	58	98.3	9	100	43	100	178	100	225	97.4
	Mild			2	8.3							3	4.5			1	1.7					0	0	6	2.6
	Missing	0		1		0		2		1		3		1		4		3		2		5		12	
Lewy bodies Neocortex	None	54	98.2	22	88	34	100	36	94.7	44	100	65	92.9	33	100	53	88.3	11	100	44	100	176	99.4	220	92.8
	Mild	1	1.8	3	12			2	5.3			5	7.1			7	11.7					1	0.56	17	7.17
	Missing	2		0		1		2		0		0		2		3		1		1		6		6	

		<80				80-84				85-89				90-94				>94				Total			
		No dementia		Dementia		No dementia		Dementia		No dementia		Dementia		No dementia		Dementia		No dementia		Dementia		No dementia		Dementia	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Tangles	None	16	28.6	2	8.3	2	5.9	2	5.3	3	6.8	2	3	4	11.4			2	16.7	1	2.3	27	14.9	7	2.98
Entorhinal cortex	Mild	19	33.9	5	20.8	12	35.3	1	2.6	12	27.3	13	19.4	8	22.9	8	12.9	4	33.3	3	6.8	55	30.4	30	12.8
	Moderate	16	28.6	6	25	15	44.1	19	50	24	54.5	27	40.3	17	48.6	24	38.7	5	41.7	22	50	77	42.5	98	41.7
	Severe	5	8.9	11	45.8	5	14.7	16	42.1	5	11.4	25	37.3	6	17.1	30	48.4	1	8.3	18	40.9	22	12.2	100	42.6
	Missing	1		1		1		2		0		3		0		1		0		1		2		8	
	Tangles	None	20	35.7	4	16.7	2	5.7	2	5	5	11.4	4	5.8	4	11.4	1	1.6	3	25	1	2.3	34	18.7	12
Hippocampus	Mild	22	39.3	3	12.5	17	48.6	4	10	16	36.4	15	21.7	12	34.3	8	13.1	1	8.3	9	20.5	68	37.4	39	16.4
	Moderate	11	19.6	5	20.8	10	28.6	13	32.5	17	38.6	22	31.9	11	31.4	15	24.6	4	33.3	17	38.6	53	29.1	72	30.3
	Severe	3	5.4	12	50	6	17.1	21	52.5	6	13.6	28	40.6	8	22.9	37	60.7	4	33.3	17	38.6	27	14.8	115	48.3
	Missing	1		1		0		0		0		1		0		2		0		1		1		5	
	Tangles	None	45	80.4	9	36	19	54.3	9	22.5	24	55.8	26	37.1	19	54.3	22	34.9	7	58.3	15	33.3	114	63	81
Neocortex	Mild	11	19.6	4	16	14	40	13	32.5	14	32.6	20	28.6	16	45.7	9	14.3	4	33.3	17	37.8	59	32.6	63	25.9
	Moderate			6	24	2	5.7	10	25	5	11.6	11	15.7			26	41.3	1	8.3	7	15.6	8	4.42	60	24.7
	Severe			6	24			8	20			13	18.6			6	9.5			6	13.3	0	0	39	16
	Missing	1		0		0		0		1		0		0		0		0		0		2		0	
	Haemorrhage	Absent	54	96.4	23	95.8	30	90.9	36	97.3	37	92.5	63	94	33	97.1	57	96.6	11	100	41	97.6	165	94.8	220
	Present	2	3.6	1	4.2	3	9.1	1	2.7	3	7.5	4	6	1	2.9	2	3.4			1	2.4	9	5.17	9	3.93
	Missing	1		1		2		3		4		3		1		4		1		3		9		14	
Infarct	Absent	47	82.5	13	54.2	23	69.7	25	64.1	32	76.2	41	60.3	21	61.8	46	74.2	11	100	31	72.1	134	75.7	156	66.1
	Present	10	17.5	11	45.8	10	30.3	14	35.9	10	23.8	27	39.7	13	38.2	16	25.8			12	27.9	43	24.3	80	33.9
	Missing	0		1		2		1		2		2		1		1		1		2		6		7	
Lacune	Absent	45	78.9	18	75	28	87.5	30	78.9	37	88.1	50	72.5	28	82.4	47	75.8	8	72.7	28	66.7	146	83	173	73.6
	Present	12	21.1	6	25	4	12.5	8	21.1	5	11.9	19	27.5	6	17.6	15	24.2	3	27.3	14	33.3	30	17	62	26.4
	Missing	0		1		3		2		2		1		1		1		1		3		7		8	
Multiple vascular pathology	Absent	44	77.2	14	56	26	74.3	27	67.5	30	68.2	35	50	24	68.6	38	60.3	9	75	27	60	133	72.7	141	58
	Present	13	22.8	11	44	9	25.7	13	32.5	14	31.8	35	50	11	31.4	25	39.7	3	25	18	40	50	27.3	102	42
	Missing	0		0		0		0		0		0		0		0		0		0		0		0	
Small vessel Disease	Absent	22	41.5	5	21.7	15	48.4	9	26.5	18	41.9	15	22.4	11	31.4	12	19.4	3	27.3	11	25	69	39.9	52	22.6
	Present	31	58.5	18	78.3	16	51.6	25	73.5	25	58.1	52	77.6	24	68.6	50	80.6	8	72.7	33	75	104	60.1	178	77.4
	Missing	4		2		4		6		1		3		0		1		1		1		10		13	

Supplementary table 2 – Sensitivity analysis of the odds ratios for the associations between neuropathological features and dementia

		At age 75 years at death				At age 95 years at death			
		Primary analysis	¹ Recently assessed	² Adjusted for demographic factors	³ Prevalent cases excluded	Primary analysis	¹ Recently assessed	² Adjusted for demographic factors	³ Prevalent cases excluded
Tangles	Hippocampus	8.6	8.6	7.8	12.1	2.1	2.3	2.0	1.8
	Neocortex	35.2	31.6	31.2	48.8	7.4	9.3	7.3	5.4
	Entorhinal Cortex	4.7	3.5	4.5	7.1	2.9	3.0	2.7	2.6
Neuritic Plaques	Hippocampus	8.6	5.6	7.8	10.4	2.5	3.0	2.4	2.0
	Neocortex	10.2	10.5	9.1	13.1	1.4	1.9	1.4	1.1
	Entorhinal Cortex	7.2	7.5	6.6	8.8	2.3	2.0	2.2	1.8
Diffuse Plaques	Hippocampus	2.4	2.2	2.3	2.9	2.1	1.7	2.1	1.6
	Neocortex	2.7	1.7	2.8	3.4	1.8	2.4	1.9	1.4
	Entorhinal Cortex	2.9	3.4	2.9	3.9	1.2	1.3	1.1	1.0
Cortical atrophy	Hippocampus	8.0	13.2	7.5	11.4	4.2	6.4	3.9	3.1
	Neocortex	5.1	17.0	4.9	6.1	6.1	7.5	6.0	5.4
Vascular pathology	Multiple vascular pathology	2.4	1.9	2.1	2.4	1.6	2.3	1.6	1.5
	Infarcts	2.9	3.0	2.7	2.4	1.1	0.8	1.0	1.1
	Haemorrhage	0.9	0.6	0.6	0.9	0.7	0.4	0.6	1.1
	Lacune	1.4	0.6	1.5	1.7	2.0	7.1	2.4	1.8
	Small vessel disease	2.7	2.5	2.5	3.0	1.8	2.7	1.8	1.6

¹ Includes only the 173 participants assessed within one year of death

² Association adjusted for sex, social class, and the time between last assessment and death

³ Includes only the 400 participants without dementia at baseline

Supplementary Appendix - Diagnosis of Dementia

Dementia status at death for each participant was determined by synthesis of all information available including assessments during the last years of life, informant interview after death where this was possible and death certification.

A study diagnosis of dementia was made if: dementia was present at any assessment, based on the full GMS AGE-CAT diagnostic algorithm equivalent to DSM-III-R (N=188), if dementia was noted on their death certificate (N=20) (unpublished work within CFAS shows that dementia is noted on a death certificate only when it is present in life), or if a detailed retrospective interview with a knowledgeable informant, covering the diagnostic domains required for clinical diagnosis including separation from terminal decline, indicated that dementia was present (N=21).

Participants were considered to have died without dementia if they did not have dementia at their last interview and that interview had been conducted less than six months before death (N=35) or if they did not have dementia at their last interview and the retrospective interview had indicated no dementia at death (N=75).

In individuals where the time since assessment to death was over 6 months and where there was no clear diagnosis possible from a retrospective interview a Bayesian analysis of the probability of dementia was undertaken that modelled the entire cognitive history of an individual. This analysis was combined with all other available information to generate the study diagnosis. This method has been shown to be 94% sensitive and 95% specific to dementia (Matthews 2004). Using this technique it was determined that 73 participants did not have dementia at death, and 14 did have dementia at death. In 30 cases insufficient information close to time of death was available for a reliable clinical diagnosis at the end of life to be made, and these cases were excluded from all analyses.

Matthews FE. Incidence estimation in studies of two-phase two-wave design. A case-control study using the Medical Research Council Cognitive Function and Ageing Study. (PhD Thesis. Cambridge, UK: University of Cambridge, 2004)