Anti-hypertensive medications ameliorate Alzheimer disease pathology by slowing its propagation

Andrew J. Affleck[a,b], Perminder S. Sachdev[c], Julia Stevens[d], Glenda M. Halliday[a,e,f]*

[a]Neuroscience Research Australia (NeuRA), Randwick, NSW, Australia

[b]School of Psychiatry, University of New South Wales, NSW, Australia

[c]Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, University of New South Wales, NSW, Australia

[d]Discipline of Pathology, Sydney Medical School, University of Sydney, NSW, Australia

[e]School of Medical Sciences, University of New South Wales, NSW, Australia

[f]Brain and Mind Centre, Sydney Medical School, University of Sydney, NSW, Australia

Supplementary Figure 1. Case selection flow chart
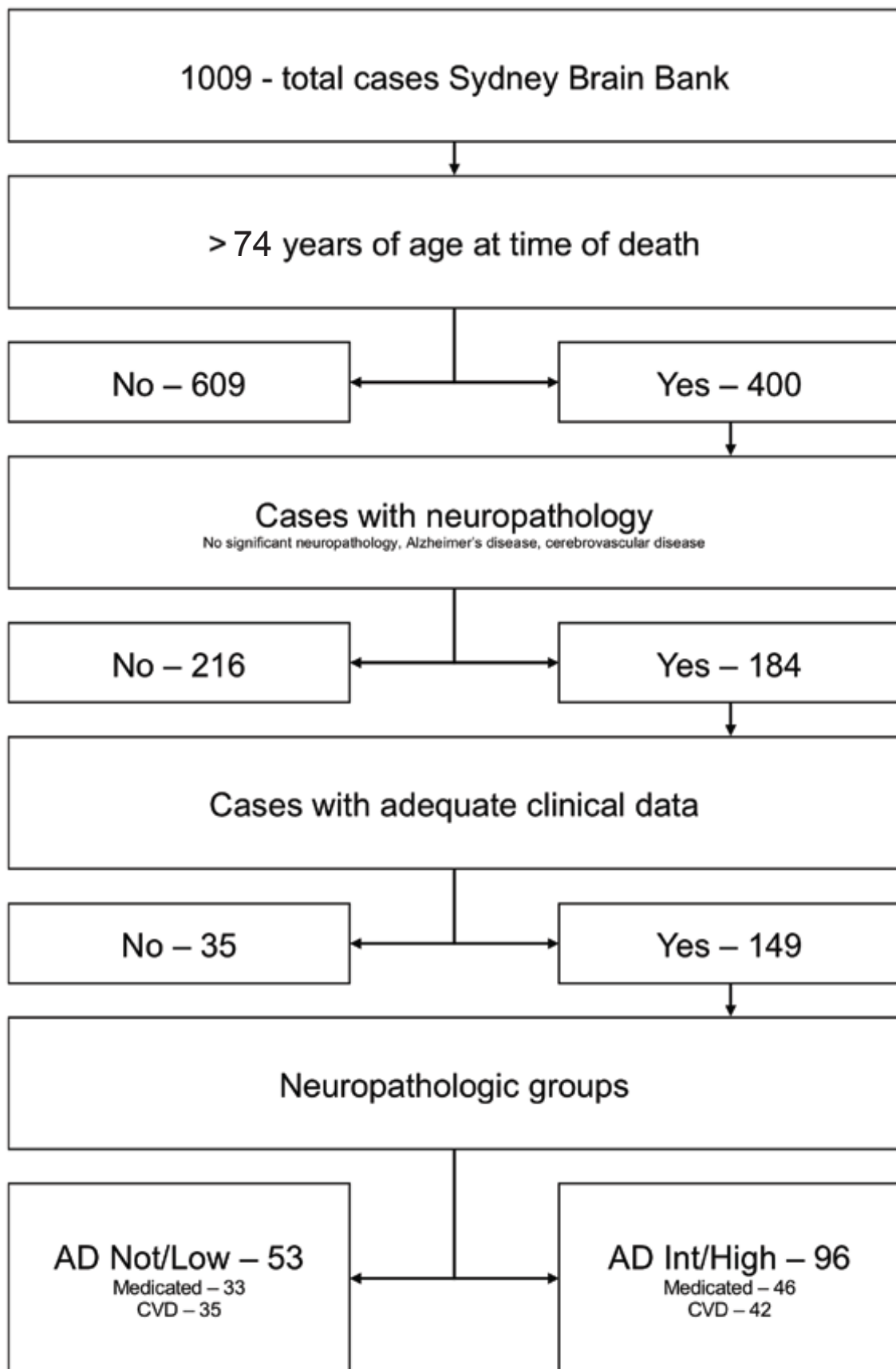
Supplementary Figure 2. Venn diagram illustrating the type and number of cases involved in the study and the overlap with variables of interest (AD Change, CVD presence and antihypertensive medication use).
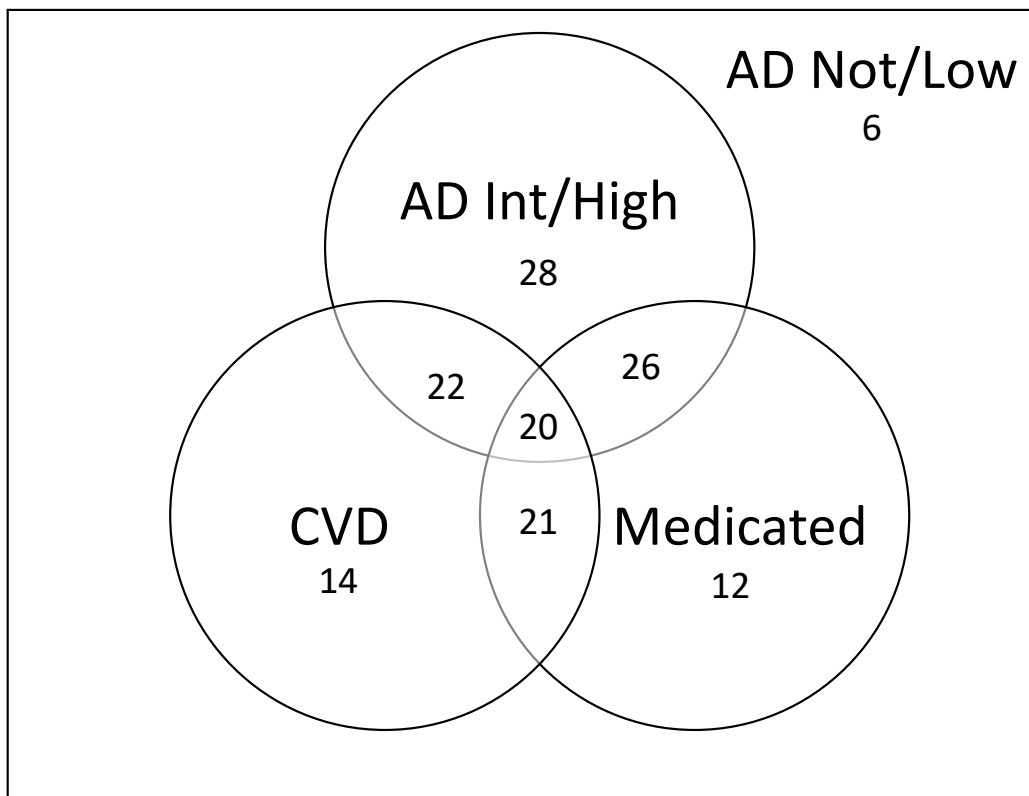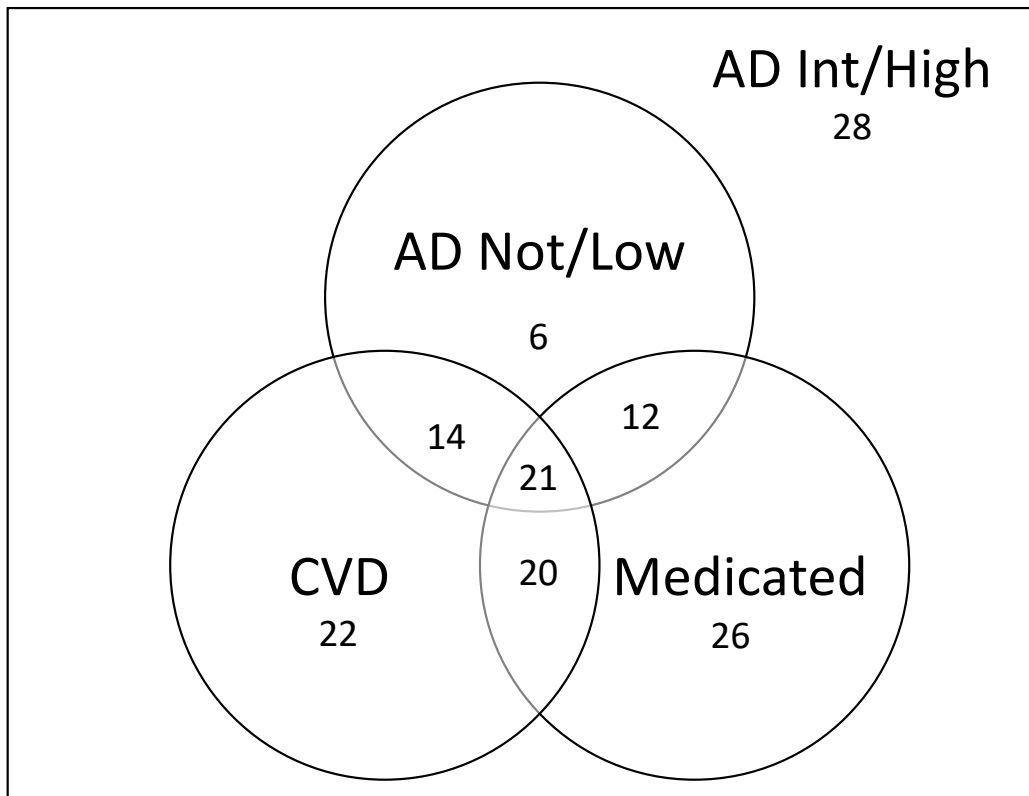
Supplementary Table 1- Further break down of table 1 with accompanying statistics

CDR (n)	0-0.5 (60)	1-3 (89)	0 (51)	0.5 (9)	1 (26)	2 (9)	3 (54)
AD Intermediate/High, N (%)	26 (43%)	70 (79%)	21 (41%)	5 (55%)	20 (77%)	5 (55%)	45 (83%)
	$\chi^2(1) = 19.51$, p < .001		$\chi^2(4) = 22.84$, p < .001				
Age at death, mean years (SD) Range	89.0 (6.1) 77 - 103	86.5 (5.3) 76 - 100	89.1 (6.4) 77 - 103	88.3 (4.0) 83 - 93	87.5 (5.5) 76 - 97	86.4 (4.0) 81 - 93	86.0 (5.3) 77 - 100
	$t(147) = 2.66$, p = .02 95% CI = .47, 4.32		$F(4, 144) = 2.09$, p = .09				
Male, n (%)	29 (48)	31 (35)	24 (47)	5 (56)	13 (50)	5 (56)	13 (24)
	$\chi^2(1) = 2.72$, p = .099		$\chi^2(4) = 9.64$, p = .047				
PMD, mean hours (SD)	23 (18)	23 (19)	21 (17)	30 (21)	23 (16)	28 (25)	22 (20)
	$t(147) = -.123$, p = .892 95% CI = .-6.6, 5.59		$F(4, 144) = .609$, p = .657				
Hypertensive, n (%)	33 (55%)	40 (45%)	28 (55%)	5 (56%)	14 (54%)	7 (78%)	19 (35%)
	$\chi^2(1) = 1.45$, p = .228		-				
Hypertension duration, mean years (SD) n/incomplete data	16 (10) 28/5	11 (9) 38/2	16 (11) 23/5	18 (5) 5/0	12 (11) 12/2	8 (9) 7/0	11 (7) 19/0
	$t(64) = 2.307$, p = .024 95% CI = 1.21, 9.48		$F(4, 61) = 1.494$, p = .215				
Hypertensive and medicated*, n (% of hypertensive)	28 (85%)	29 (73%)	25 (89%)	3 (60%)	13 (93%)	3 (43%)	13 (68%)
	$\chi^2(1) = 1.61$, p = .204		-				

CDR (n)	0-0.5 (60)	1-3 (89)	0 (51)	0.5 (9)	1 (26)	2 (9)	3 (54)
Normotensive, n (%)	27 (45%)	49 (55%)	23 (45%)	4 (44%)	12 (46%)	2 (22%)	35 (65%)
	$\chi^2(1)$ = 1.45, p = .228	-					
Normotensive and medicated*, N (% of normotensive)	14 (52%)	8 (16%)	12 (52%)	2 (50%)	1 (8%)	0	7 (20%)
	$\chi^2(1)$ = 10.68, p = .001	-					
Cerebrovascular disease and vascular brain injury, n (%)	29 (48%)	48 (54%)	25 (49%)	4 (44%)	15 (58%)	6 (67%)	27 (50%)
	$\chi^2(1)$ = .450, p = .502	-					
Single infarct (non-lobar), n (% of CVD)	12 (41%)	21 (44%)	9 (18%)	3 (33%)	9 (35%)	1 (11%)	11 (20%)
	$\chi^2(1)$ = .041, p = .839	-					
Multiple infarct (non-lobar), n (% of CVD)	17 (59%)	27 (56%)	16 (31%)	1 (11%)	6 (23%)	5 (56%)	16 (30%)
	$\chi^2(1)$ = .041, p = .839	-					

- chi-square expected frequency assumption violated

Supplementary Table 2- Breakdown of anti-hypertensive medications data

Level of AD Neuropathologic Change	Not/Low (53)	Intermediate/High (96)	Total (149)
Age at death, mean years (SD) **Range**	89 (6) 77 - 103	87 (5) 76 - 102	88 (6) 76 - 103
Anti-hypertensive medications, n (%)	33 (62%)	46 (48%)	79 (53%)
Mean no. of medications taken (range)	2.3 (1-4)	2.4 (1-6)	2.3 (1-6)
Mean hypertension duration in yrs (SD)	16 (10)	12 (9)	13 (9)
Diuretics, no. of cases taking (% of anti-hypertensive medicated)	23 (70%)	27 (59%)	50 (63%)
Top 3 most commonly taken Diuretics	Lasix Frusemide Uremide	Lasix Frusemide Natrilix	Lasix Frusemide Natrilix
Mean dose in mg/day (range)	40 (3 – 80) 10 instances of missing dosage data	41 (2.5 – 225) 9 instances of missing dosage data	41 (2.5 – 225) 19 instances of missing dosage data
Total number of diuretics taken	31 (6 cases taking >1)	35 (9 cases taking >1)	66 (15 cases taking >1)
Beta Blockers, no. of cases taking (% of anti-hypertensive medicated)	14 (42%)	20 (44%)	34 (43%)
Top 3 most commonly taken Beta Blockers	Betaloc Metoprolol Atenolol	Betaloc Metoprolol Inderal/Noten/ Tenormin	Betaloc Metoprolol Inderal/Noten/Atenolol
Mean dose in mg/day (range)	49 (1.25 – 100) 1 instances of missing dosage data	68 (5 – 200) 5 instances of missing dosage data	60 (1.25 – 200) 6 instances of missing dosage data
Total number of beta blockers taken	16 (2 cases taking >1)	26 (5 cases taking >1)	42 (7 cases taking >1)
Angiotensin Converting Enzyme Inhibitors (ACE-I), no. of cases taking (% of anti-hypertensive medicated)	14 (42%)	18 (39%)	32 (41%)
Top 3 most commonly taken ACE-Is	Captopril Coversyl/Prinivil/Tritace	Tritace Coversyl Enalpril/Renitec	Tritace Captopril Prinivil/Renitec
Mean dose in mg/day (range)	14 (1.25 – 75) instances of missing dosage data	10 (2.5 – 40) instances of missing dosage data	12 (1.25 – 75) 7 instances of missing dosage data
Total number of ACE-Is taken	15 (1 cases taking >1)	18 (0 cases taking >1)	33 (1 cases taking >1)

Level of AD Neuropathologic Change	Not/Low (53)	Intermediate/High (96)	Total (149)
Calcium Channel Blockers (CCBs), no. of cases taking (% of anti-hypertensive medicated)	9 (27%)	18 (39%)	27 (34%)
Top 3 most commonly taken CCBs	Adalat Cardizem Isoptin/Anpec	Adalat Isoptin/Norvasc Cardizem/Zanidip	Adalat Cardizem Isoptin
Mean dose in mg/day (range)	150 (90 – 180) 6 instances of missing dosage data	80 (2.5 – 240) 4 instances of missing dosage data	91 (2.5 – 240) 10 instances of missing dosage data
Total number of CCBs taken	9 (0 cases taking >1)	20 (2 cases taking >1)	29 (2 cases taking >1)
Angiotensin Receptor Blockers (ARBs), no. of cases taking (% of anti-hypertensive medicated)	0	11 (24%)	11 (14%)
Top 3 most commonly taken ARBs	-	Avapro Micardis Atacand	Avapro Micardis Atacand
Mean dose in mg/day (range)	-	141 (8 – 450) 2 instances of missing dosage data	141 (8 – 450) 2 instances of missing dosage data
Total number of ARBs taken	-	11 (0 cases taking >1)	11 (0 cases taking >1)

Supplementary Table 3- Demographic and clinic-pathological profile of cases (with statistics) of the main group and experimental laboratory work subsets

	Original		Western analysis		IHC analysis	
Clinical Dementia Rating (n)	0 - 0.5 (60)	1 - 3 (89)	0 - 0.5 (18)	1 - 3 (26)	0 - 0.5 (33)	1 - 3 (25)
AD intermediate/high level change, n (%)	26 (43%)	70 (79%)	4 (22%)	26 (100%)	9 (27%)	15 (60%)
	$\chi^2(1) = 19.51, p < .001$		$\chi^2(1) = 29.66, p < .001$		$\chi^2(1) = 6.28, p = .01$	
Age at death, mean years (SD) Range	89 (6) 77 - 103	87 (5) 76 - 100	88 (6) 78 - 101	88 (8) 75 - 100	89 (6) 77 - 103	90 (5) 80 - 100
	$t(147) = 2.66, p = .02$ [.47, 4.32]		$t(42) = .004, p = 1.00$ [-4.00, 4.20]		$t(56) = -.56, p = .58$ [-3.82, 1.92]	
Male, n (%)	29 (48%)	31 (35%)	7 (39%)	11 (42%)	17 (52%)	10 (40%)
	$\chi^2(1) = 2.72, p = .10$		$\chi^2(1) = .05, p = .82$		$\chi^2(1) = .76, p = .38$	
PMD, mean hours (SD)	23 (18)	23 (19)	19 (12)	15 (10)	25 (20)	17 (13)
	$t(147) = -.12, p = .89$ [-6.60., 5.59]		$t(42) = 1.17, p = .25$ [-2.11, 11.00]		$t(56) = 1.73, p = .09$ [-.89, 16.58]	
Hypertensive, n (%)	33 (55%)	40 (45%)	11 (61%)	12 (46%)	20 (61%)	16 (64%)
	$\chi^2(1) = 1.45, p = .23$		$\chi^2(1) = .95, p = .33$		$\chi^2(1) = .07, p = .79$	

	Original		Western analysis		IHC analysis	
Hypertension duration, mean years (SD)	16 (10)^	11 (9)^	17 (15)	14 (11)	15 (9)	16 (9)
	t(64) = 2.31, p = .03 [.98, 10.01.]		t(21) = .36, p = .72 [-6.87, 11.77]		t(31) = -.25, p = .82 [-8.09, 5.78]	
Hypertensive and medicated*, n (% of hypertensive)	28 (85%)	29 (73%)	10 (91%)	12 (100%)	16 (80%)	13 (81%)
	χ^2(1) = 1.61, p = .20		-		-	
Normotensive, n (%)	27 (45%)	49 (55%)	7 (39%)	14 (54%)	13 (39%)	9 (36%)
	χ^2(1) = 1.45, p = .23		χ^2(1) = .95, p = .33		χ^2(1) = .07, p = .79	
Normotensive and medicated*, n (% of normotensive)	14 (52%)	8 (16%)	0	0	10 (77%)	3 (33%)
	χ^2(1) = 10.68, p = .001		N/A		χ^2(1) = 4.18, p = .04	
Cerebrovascular disease and vascular brain injury, n (%)	29 (48%)	48 (54%)	4 (22%)	7 (27%)	18 (55%)	18 (72%)
	χ^2(1) = .45, p = .50		χ^2(1) = .01, p = .91		χ^2(1) = 1.84, p = .18	

	Original		Western analysis		IHC analysis	
Single infarct (non-lobar), n (% of infarct)	12 (41%)	21 (44%)	3 (75%)	0	8 (44%)	5 (28%)
	$\chi^2(1) = .04$, $p = .84$		-		$\chi^2(1) = 1.08$, $p = .30$	
Multiple infarcts (non-lobar), n (% of infarct)	17 (59%)	27 (56%)	1 (25%)	7 (100%)	10 (56%)	13 (72%)
	$\chi^2(1) = .04$, $p = .84$		-		$\chi^2(1) = 1.08$, $p = .30$	

"–" chi-square expected frequency assumption violated

Supplementary Table 4- Multinomial logistic regression statistics

	b (SE)	95% CI for Odds Ratio		
		Lower	Odds Ratio	Upper
A0/A1 (none/cortical abeta deposition) vs. Reference category - A3 (cortical, striatal and nigral abeta deposition)				
Medicated**	2.01 (0.68)	1.98	7.43	27.87
Hypertensive	-0.18 (0.58)	0.27	0.84	2.59
CVD	0.95 (0.56)	0.87	2.59	7.73
Age	0.06 (0.05)	0.96	1.06	1.17
Gender (Male)	0.50 (0.54)	0.57	1.66	4.80
Post mortem delay	0.02 (0.01)	1.00	1.02	1.05
Intercept*	-9.30 (4.56)			
A2 (cortical and striatal abeta deposition) vs. Reference category- A3 (cortical, striatal and nigral abeta deposition)				
Medicated*	1.12 (0.54)	1.05	3.05	8.86
Hypertensive	0.02 (0.52)	0.37	1.02	2.80
CVD*	1.11 (0.50)	1.15	3.02	7.98
Age*^	0.09 (0.04)	1.01	1.10	1.19
Gender (male)	0.28 (0.48)	0.52	1.33	3.40
Post mortem delay	0.00 (0.01)	0.98	1.00	1.03
Intercept**	-10.98 (3.84)			

Note. R^2 = .19 (Cox & Snell), .23 (Nagelkerke). Model $\chi^2(12)$ = 30.92, p = .002, *$p < .05$, ** $p < .01$, *** $p < .001$, ^ = no main effect.

	b (SE)	95% CI for Odds Ratio		
		Lower	Odds Ratio	Upper
B0 (none) vs. Reference category B3 (Braak NFT stage V or VI)				
Medicated*	1.46 (0.67)	1.15	4.30	16.03
Hypertensive	-0.84 (0.68)	0.12	0.43	1.64
CVD	0.13 (0.58)	0.36	1.14	3.58
Age*^	0.11 (0.05)	1.01	1.12	1.23
Gender (male)	0.89 (0.63)	0.70	2.43	8.40
Post mortem delay	0.05 (0.02)	0.98	1.01	1.04
Intercept*	-11.58 (4.58)			
B1 (Braak NFT stage I or II) vs. Reference category B3 (Braak NFT stage V or VI)				
Medicated*	1.18 (0.59)	1.01	3.24	10.37
Hypertensive	0.32 (0.58)	0.44	1.37	4.28
CVD	1.09 (0.56)	0.99	2.96	8.85
Age	0.09 (0.05)	0.99	1.09	1.20
Gender (male)*	1.42 (0.56)	1.39	4.14	12.35
Post mortem delay	0.01 (0.01)	0.98	1.01	1.04
Intercept*	-10.54 (4.33)			
		95% CI for Odds Ratio		
	b (SE)	Lower	Odds Ratio	Upper

B2 (Braak NFT stage III or IV) vs. Reference category B3 (Braak NFT stage V or VI)				
Medicated*	1.33 (0.52)	1.37	3.77	10.37
Hypertensive	0.20 (0.50)	0.45	1.22	3.27
CVD	0.06 (0.45)	0.44	1.06	2.57
Age	0.06 (0.04)	0.98	1.06	1.15
Gender (male)**	1.575(0.49)	1.81	4.72	12.33
Post mortem delay	-0.01 (0.01)	0.97	0.99	1.02
Intercept	-6.37 (3.66)			

Note. R^2 = .25 (Cox & Snell), .27 (Nagelkerke). Model $\chi^2(18)$ = 42.41, p = .001, *p < .05, ** p < .01, *** p < .001, ^ = no main effect.