Supplementary Material

Characterization of Depressive Symptoms in Dementia and Examination of Possible Risk Factors

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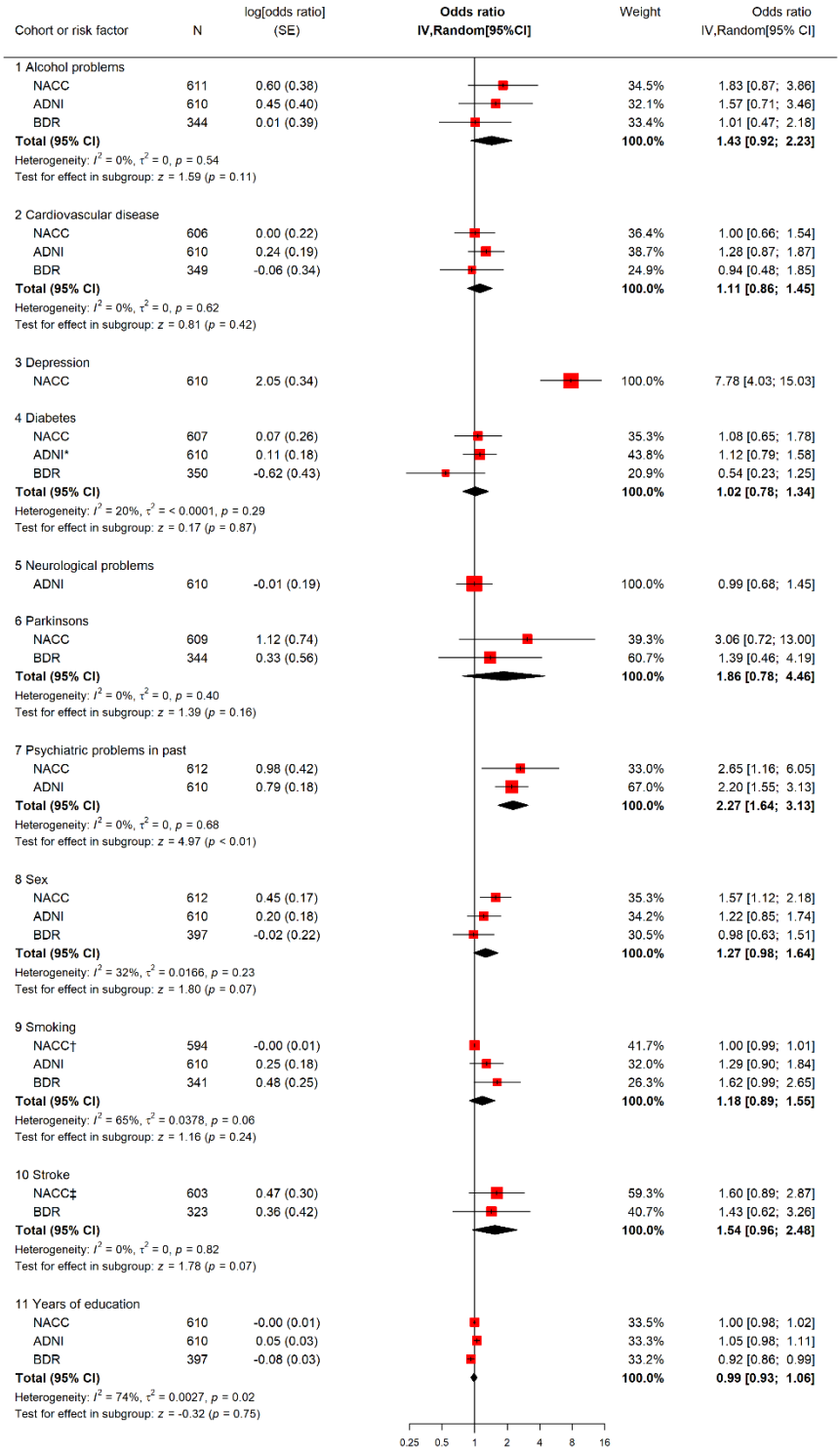


Supplementary Figure 1. Forest plot with previous depression not included as a co-variate. To examine whether depression in the past was acting as a mediator in the NACC results, we repeated the random effects meta-analysis not including previous depression as a co-variate in the NACC data. ADNI and BDR results were identical to the main analysis. As can be seen, once previous depression was not included in the NACC analysis, previous psychiatric problems became a risk factor for depression in AD.

Red boxes represent point estimate (odds ratio) and horizontal lines the 95% confidence intervals. Black diamonds are pooled estimates for each risk factor. Estimates above 1 (on the right-hand side of the y-axis) suggest an increased risk for depression, while estimates below 1 (on the left-hand side of the y-axis) suggests a decreased risk for depression.
*ADNI is endocrine diseases including diabetes. † is smoking as smoking years in NACC, whereas in ADNI and BDR it was smoker versus non-smoker. ‡ Stroke or TIA in NACC.

NACC

Supplementary Table 2. Baseline characteristics of the NACC cohort (AD). Note that restricted only to those who were ever diagnosed with AD and baseline visit was first visit where cognition was noted to be impaired. Individuals prescribed an antidepressant at baseline who were not depressed were excluded from the no depression group. ANOVAs included age and gender as co-variates.

	AD no depression	**AD intermittent depression**	**AD persistent depression**	**Statistical Evidence (Pearson χ^2 or ANOVA)**
	N=393	N=185	N=111	
Age at baseline (mean (SD))	78.2 (8.5)	76.1 (9.4)	74.4 (10.3)	0.935
Gender				0.035
male	221 (56.2%)	89 (48.1%)	49 (44.1%)	
female	172 (43.8%)	96 (51.9%)	62 (55.9%)	
Marital status				0.30
married	256 (65.1%)	124 (67.0%)	78 (70.3%)	
widowed	80 (20.4%)	30 (16.2%)	17 (15.3%)	
divorced	34 (8.7%)	23 (12.4%)	8 (7.2%)	
separated	2 (0.5%)	0 (0.0%)	2 (1.8%)	
never married/annulled	12 (3.1%)	3 (1.6%)	3 (2.7%)	
living with a partner	8 (2.0%)	4 (2.2%)	1 (0.9%)	
unknown or other	1 (0.3%)	1 (0.5%)	2 (1.8%)	
Ethnicity				0.61
White	331 (84.2%)	165 (89.2%)	91 (82.0%)	
Black or African American	44 (11.2%)	13 (7.0%)	16 (14.4%)	
American Indian or Alaskan Native	1 (0.3%)	1 (0.5%)	0 (0.0%)	
Asian	13 (3.3%)	6 (3.2%)	4 (3.6%)	
other	1 (0.3%)	0 (0.0%)	0 (0.0%)	
unknown	3 (0.8%)	0 (0.0%)	0 (0.0%)	
Primary language				0.18
English	364 (92.6%)	169 (91.4%)	94 (84.7%)	
Spanish	18 (4.6%)	10 (5.4%)	10 (9.0%)	
Mandarin	1 (0.3%)	1 (0.5%)	0 (0.0%)	
Japanese	2 (0.5%)	0 (0.0%)	0 (0.0%)	
Other	8 (2.0%)	5 (2.7%)	7 (6.3%)	
Level of independence				0.25
Able to live independently	261 (66.4%)	110 (59.5%)	63 (56.8%)	
Needs assistance with complex tasks	108 (27.5%)	55 (29.7%)	39 (35.1%)	
Needs assistance with basic activities	21 (5.3%)	19 (10.3%)	9 (8.1%)	
Completely dependent	1 (0.3%)	1 (0.5%)	0 (0.0%)	
Unknown	2 (0.5%)	0 (0.0%)	0 (0.0%)	
Accommodation				0.68

Lives alone	93 (23.7%)	38 (20.5%)	18 (16.2%)	
Lives with spouse or partner	258 (65.6%)	125 (67.6%)	77 (69.4%)	
Lives with relative or friend	36 (9.2%)	18 (9.7%)	15 (13.5%)	
Lives with group	4 (1.0%)	2 (1.1%)	1 (0.9%)	
Other	2 (0.5%)	2 (1.1%)	0 (0.0%)	
Family history of dementia				0.15
None	149 (37.9%)	58 (31.4%)	35 (31.5%)	
At least one family member	218 (55.5%)	113 (61.1%)	62 (55.9%)	
Unknown	26 (6.6%)	14 (7.6%)	14 (12.6%)	
Depression present in last 2 y	39 (10.7%)	70 (41.4%)	62 (59.6%)	<0.001
Prescribed an antidepressant at baseline	0 (0.0%)	59 (31.9%)	38 (34.2%)	<0.001
Total years of smoking	11.3 (14.6)	9.7 (14.4)	11.7 (16.6)	Kwallis p=0.270
NPI total score (mean (SD))	2.2 (2.9)	3.7 (3.6)	5.3(4.7)	Kwallis p=0.012
NPI depression score				<0.001
0	323 (82.2%)	82 (44.3%)	41 (36.9%)	
1	58 (14.8%)	54 (29.2%)	27 (24.3%)	
2	0 (0.0%)	37 (20.0%)	33 (29.7%)	
3	0 (0.0%)	6 (3.2%)	8 (7.2%)	
Missing	12 (3.1%)	6 (3.2%)	2 (1.8%)	
NPI anxiety score				<0.001
0	306 (77.9%)	117 (63.2%)	65 (58.6%)	
1	50 (12.7%)	35 (18.9%)	19 (17.1%)	
2	22 (5.6%)	21 (11.4%)	21 (18.9%)	
3	3 (0.8%)	6 (3.2%)	5 (4.5%)	
Missing	12 (3.1%)	6 (3.2%)	1 (0.9%)	
NPI apathy score				0.002
0	305 (77.6%)	128 (69.2%)	70 (63.1%)	
1	53 (13.5%)	35 (18.9%)	20 (18.0%)	
2	19 (4.8%)	13 (7.0%)	16 (14.4%)	
3	4 (1.0%)	3 (1.6%)	4 (3.6%)	
Missing	12 (3.1%)	6 (3.2%)	1 (0.9%)	

Supplementary Table 3. Neuropsychological test scores at baseline for individuals with AD in NACC

	No depression (n=393)		Intermittent depression (n=183)		Persistent depression (n=111)		Statistical Evidence
Individuals With AD	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
GDS score	1.5	1.5	2.7	2.4	4.4	3.5	KWallis p<0.001
NPI total score	2.2	2.9	3.7	3.6	5.3	4.7	KWallis p<0.001
CDR global score	0.6	0.3	0.6	0.4	0.6	0.3	KWallis p=0.116
CDR sum of boxes	2.4	2.2	2.9	2.7	2.8	2.2	KWallis p=0.016
MMSE score	25.1	3.9	24.8	6.9	25.4	8.2	KWallis p=0.067
Animals named in 1 min	14	5.1	13.5	5.3	13.9	5.1	ANOVA p=0.276
Boston naming test total score	22.9	5.5	22.4	5.5	23.5	5.1	Kwallis p=0.273
Trails A time (s)	81.3	165.1	96.7	195.1	62	94.5	Kwallis p=0.947
Trails B time (s)	234.1	240.8	272	292.2	236.6	242.3	Kwallis p=0.867

Supplementary Table 4. Baseline characteristics of the NACC cohort (normal cognition). Note that restricted only to those who had normal cognition at baseline and during follow-up. ANOVAs included age and gender as co-variates. Note this group just defined using GDS not NPI

	No depression (n=665)		**Intermittent depression (n=23)**		**Persistent depression (n=23)**		**Statistical Evidence (Pearson χ^2, Kwallis or ANOVA)**
Individuals with no cognitive problems	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Age at first visit	67.2	11.3	63.7	16	67.8	12.9	Kwallis p=0.940 χ^2=0.123
Gender							p=0.565
Male	235		11		6		
Female	430		12		17		
Ethnic background							p=0.189
White	580		19		20		
Black/African American	69		2		2		
American Indian or Alaska Native	3		1		0		
Asian	9		1		1		
Other	2		0		0		
Unknown	2		0		0		
Primary language							p<0.001
English							
Spanish	631		19		15		
Mandarin	25		3		7		
Japanese	8		1		1		
Other	1		0		0		
Marital status at baseline							p=0.635
Married	417		17		11		
Widowed	80		1		5		
Divorced/separated	99		0		5		
Never married/annulled	39		4		1		
Living with a partner	25		1		1		
Other/unknown	5		0		0		
Living situation							p=0.614
Lives alone	177		5		9		
Lives with spouse or partner	430		16		10		
Lives with relative or friend	45		2		4		
Lives with group	6		0		0		
Other	7		0		0		
Independence							p=0.011
Able to live independently							
Requires assistance with complex tasks	654		23		23		
Requires assistance with simple tasks	10		0		0		
Completely dependent	1		0		0		
Unknown	0		0		0		
History of first degree relative with cog impairment							p=0.043
No	208		5		13		
Yes	421		16		8		
Unknown	36		2		2		
Years of smoking	9.4	17.2	10.8	16.4	14.7	19.4	Kwallis p=0.046 χ^2=6.159

Years of education	16	6.4	13.9	4.8	16.1	18.5	Kwallis p<0.001 χ^2=18.053
Self-reported depression in the last 2 y							p<0.001
No	569		12		9		
Yes	96		10		14		
Prescribed antidepressant at baseline							p<0.001
No	582		16		14		
Yes	83		7		9		
SSRI	65		6		6		
TCA	3		1		2		
SNRI	13		0		1		
GDS score at baseline	0.7	1	3.5	3.7	7	4.7	Kwallis p<0.001, χ^2=49.039
CDR global score	0	0.1	0.1	0.3	0.2	0.3	Kwallis p<0.001 χ^2=44.76
CDR sum of boxes	0.1	0.4	0.4	1.3	0.4	0.6	Kwallis p=0.415, χ^2=1.758
MMSE score	29.2	3	28.4	1.9	27.5	1.9	Kwallis p<0.001, χ^2=19.629
Animals named in 1 min	23	10	20.5	5.9	32.5	30.6	ANOVA p=0.402
Boston naming test total score	27.8	2.6	27.4	2.9	24.8	4.0	Kwallis p=0.002, χ^2=12.477
Trails A time (s)	45	118.5	39.6	25.7	172.6	328.4	ANOVA p<0.001
Trails B time (s)	97	134.9	161.4	267.6	312.3	374.3	ANOVA p<0.001

Supplementary Table 5. Examination of known risk factors for depression in the elderly as possible co-variates in NACC (individuals with dementia). Note that restricted to those with AD either at baseline, or which developed during study follow-up. Depression was defined as either intermittent or persistent. In this analysis crude odds ratios are presented without the use of co-variates.

Individuals with AD	**No depression (n=393)**	**Intermittent depression (n=185)**	**Persistent depression (n=111)**	**Odds Ratio (95%CI)**
Hx of cardiovascular disease at baseline				0.817 (0.549 to 1.217), p=0.321
No	289	139	86	
Yes	77	30	19	
Hx of diabetes at baseline				0.833 (0.528 to 1.314), p=0.433
No	313	153	86	
Yes	55	16	19	
Hx of stroke/TIA at baseline				1.142 (0.667 to 1.956), p=0.628
No	333	151	95	
Yes	32	18	9	
Hx of previous depression at baseline				6.164 (4.258 to 8.922), p<0.001
No	314	95	36	
Yes	56 (79.9%)	76 (51.4%)	68 (32.4%)	
Hx of previous psychiatric disease at baseline				2.390 (1.118 to 5.109) p=0.025
No	357	163	95	
Yes	11	9	10	
Hx of Parkinson's Disease at baseline				2.701 (0.670 to 10.897), p=0.163
No	366	168	103	
Yes	3	4	2	
Gender				1.471 (1.806 to1.991), p=0.013
Male	221	89	49	
Female	172	96	62	
Hx of alcohol abuse				1.429 (0.746 to 2.733) p=0.280
No	349	160	97	
Yes	19	12	8	
Years of smoking	11.3	9.7	11.7	0.996 (0.985 to 1.006) p=0.397
Years of education	15.8	14.6	16.2	0.977 (0.937 to 1.020) p=0.511

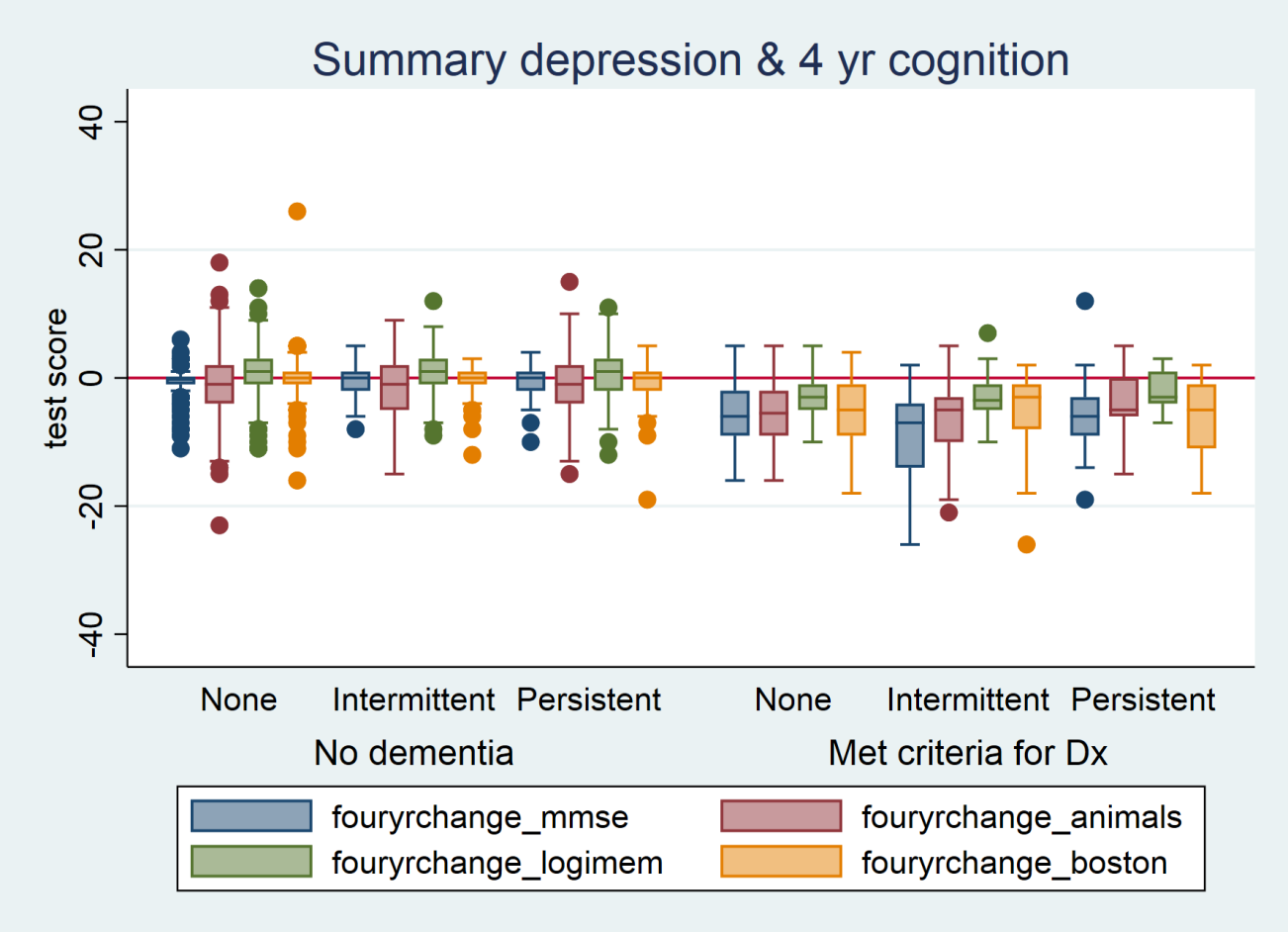
Supplementary Table 6. Examination of known risk factors for depression in the elderly as possible co-variates in NACC (individuals with normal cognition). Note that restricted only to those who had normal cognition at baseline and during follow-up. In this analysis crude odds ratios are presented without the use of co-variates. The possibility of differences between the AD and normal cognition groups was formally tested using an interaction term for cognition in the logistic regression analyses and there was no evidence of difference for any of the possible co-variates. Note this group just defined using GDS not NPI as the NPI was validated for those with dementia.

Individuals with no cognitive problems	**No depression (n=665)**	**Intermittent depression (n=23)**	**Persistent depression (n=23)**	**Odds Ratio (95%CI)**	**Evidence for interaction between risk factor and cognitive impairment**
Hx of cardiovascular disease at baseline *No* *Yes*	 597 63	 21 2	 19 4	1.421 (0.580 to 3.484), p=0.442	OR=0.572 (0.180 to 1.818) p=0.344
Hx of diabetes at baseline *No* *Yes*	 556 103	 20 3	 13 9	1.963 (0.981 to 3.927), p=0.057	OR=0.478 (0.175 to 1.307) p=0.151
Hx of stroke/TIA at baseline *No* *Yes*	 627 31	 23 0	 22 1	0.449 (0.060 to 3.368), p=0.436	OR=1.952 (0.221 to 17.251) p=0.548
Hx of previous depression at baseline *No* *Yes*	 503 158	 11 10	 8 15	4.189 (2.247 to 7.808), p<0.001	OR=0.502 (0.225 to 1.119) p=0.092
Hx of previous psychiatric disease at baseline *No* *Yes*	 623 41	 20 3	 20 3	2.279 (0.913 to 5.687), p=0.077	OR=0.992 (0.268 to 3.669) p=0.990
Gender *Male* *Female*	 235 430	 11 12	 6 17	0.932 (0.502 to 1.732), p=0.824	OR=0.890 (0.407 to 1.948) p=0.771
Hx of alcohol abuse *No* *Yes*	 636 29	 21 2	 20 3	2.675 (0.984 to 7.274), p=0.054	OR=0.734 (0.186 to 2.894) p=0.659
Years of smoking	9.4	10.8	14.7	Highest vs. lowest quintile, OR 1.953 (0.965 to 3.951). Overall p=0.124	
Years of education	16	13.9	16.1	Highest vs. lowest quintile, OR 0.304 (0.100 to 0.928) Overall p=0.024	

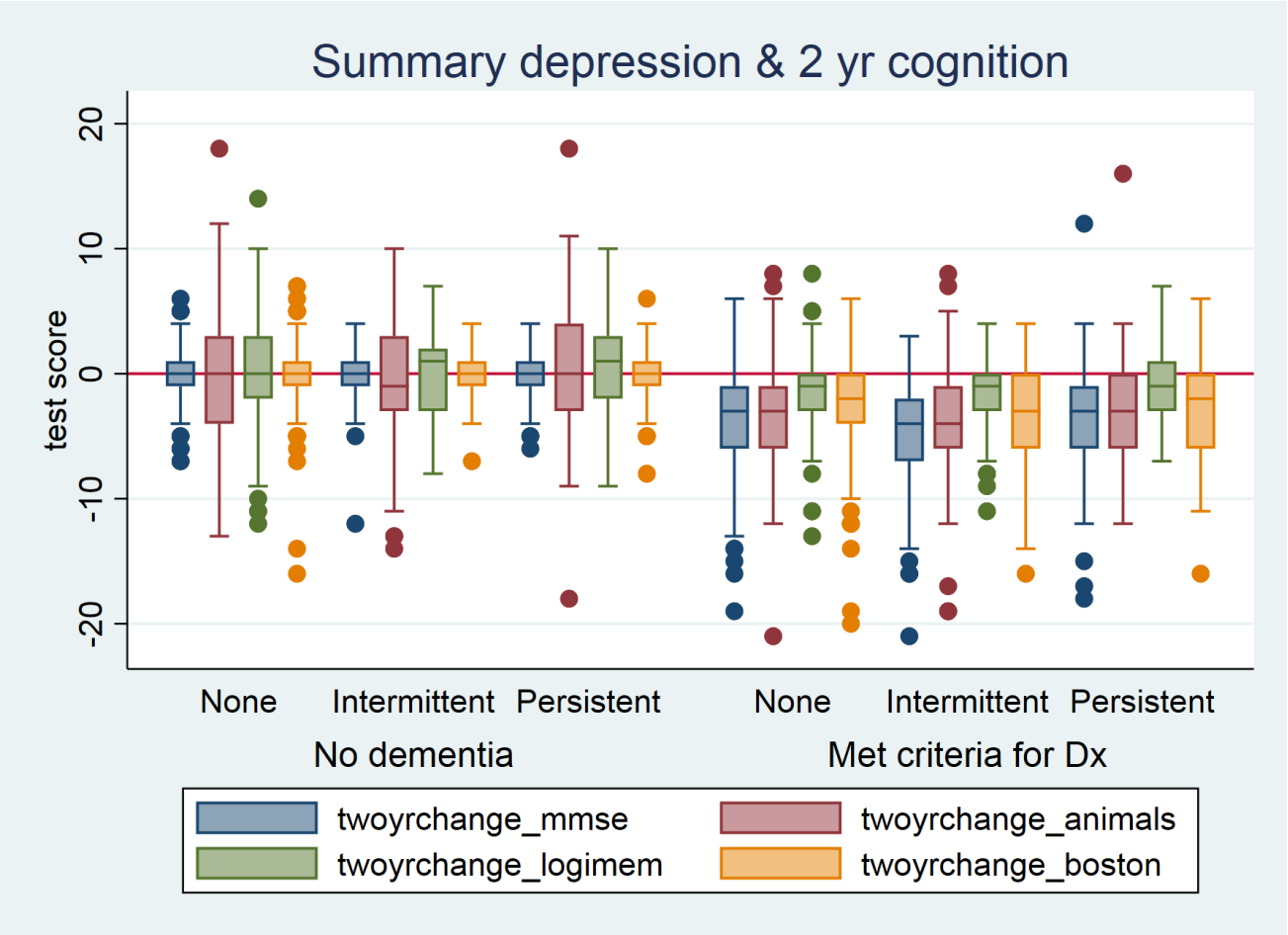
Supplementary Table 7. Trajectory modelling model choice in NACC

Number of groups	Trajectory shapes (polynomial order)	BIC (no. of observations)	BIC (no. of participants)	AIC	Entropy
5	5 5 5 5 5	-6274.49	-6253.23	-6168.60	0.708
5	4 4 4 4 4	-6259.88	-6241.66	-6169.12	0.702
5	1 1 4 4 4	-6239.86	-6225.29	-6167.25	0.688
5	2 2 4 4 4	-6244.93	-6229.14	-6166.27	0.701
5	1 1 4 4 1	-6228.16	-6215.40	-6164.62	0.699
5	3 3 3 3 3	-6241.48	-6226.29	6165.84	0.695
5	2 2 2 2 2	-6235.95	-6223.80	6175.44	0.692
5	1 1 1 1 1	-6222.49	-6213.38	-6177.11	0.684
5	0 0 0 0 0	-6203.18	-6197.11	-6172.93	0.709
5	0 0 4 4 1	-6220.56	-6209.02	-6163.08	0.709
5	0 0 4 4 2	-6224.41	-6212.26	-6163.90	0.703
5	**0 0 4 3 1**	**-6216.57**	**-6205.63**	**-6162.11**	**0.703**
5	0 0 3 4 1	-6216.94	-6206.01	-6162.48	0.698
5	0 0 3 3 1	-6213.00	-6202.67	-6161.56	0.698
5	0 0 3 3 2	-6221.98	-6211.05	-6167.52	0.695
4	5 5 5 5	-6281.50	-6264.49	-6196.78	0.715
4	4 4 4 4	-6268.63	-6254.05	-6196.02	0.714
4	0 0 4 4	-6240.27	-6230.55	-6191.86	0.713
4	1 1 4 4	-6247.28	-6236.35	-6192.83	0.710
4	3 3 3 3	-6253.54	-6241.39	6193.03	0.714
4	2 2 2 2	-6240.75	-6231.03	-6192.34	0.714
3	5 5 5	-6346.80	-6334.05	-6283.27	0.679
3	4 4 4	-6336.87	-6325.94	-6282.41	0.672
3	3 3 3	-6325.36	-6316.25	6279.98	0.672

Trajectory Group	Number in group	Ave Posterior probabilities	Odds of correct classification	Weighted posterior probabilities	Proportion in each group
1	213	12.01884	11.29985	0.2228034	0.2336673
2	588	2.867778	3.545866	0.6150628	0.5637509
3	18	224.0012	90.30602	0.0188285	0.0454368
4	108	43.71508	39.61703	0.1129707	0.1232167
5	29	337.7888	300.8925	0.0303347	0.0339283



Supplementary Figure 2. Depression and cognitive measures over a 4-year follow-up in NACC



Supplementary Figure 3. Depression and cognitive measures over a 2-year follow-up in NACC

ADNI

Supplementary Table 8. ADNI cohort baseline demographics and neuropsychological test scores for individuals with AD. Individuals with missing data on depression measures were excluded as were those with only one study visit, those with a maximum GDS score of 5-7 (i.e., possible depression but did not otherwise meet the threshold) and those who did not meet criteria for depression but were taking antidepressant medication

	AD, no depression n=447		AD, intermittent depression n=153		AD, persistent depression n=66		p (ANOVA, Kwallis or Pearson χ^2)
	Mean	SD	Mean	SD	Mean	SD	
Age at study entry (y)	74.524	7.568	73.818	7.144	74.589	7.069	p=0.579
Gender							p=0.213
Female	41.83%		45.10%		53.03%		
Male	58.17%		54.90%		46.97%		
Marital status							p=0.778
Divorced	3.8%		5.9%		6.1%		
Married	83.7%		81.7%		83.3%		
Never married	2.5%		2.0%		0.0%		
Unknown	0.0%		0.0%		0.0%		
Widowed	10.1%		10.5%		10.6%		
Missing							
Ethnicity							p=0.974
Am Indian/Alaskan	0.0%		0.0%		0.0%		
Asian	2.1%		2.6%		1.5%		
Black	3.1%		3.3%		4.6%		
More than one	0.7%		0.7%		1.5%		
Unknown	0.0%		0.0%		0.0%		
White	94.2%		93.5%		92.4%		
Years of education (y)	15.445	2.829	15.797	2.925	15.515	2.868	Kwallis p=0.419
Ever smoked	37.8%		38.5%		49.2%		p=0.225
GDS score	1.325	1.127	2	1.591	2.364	1.751	Kwallis p<0.001
MMSE score	24.703	2.843	25.548	2.542	26.118	2.551	Kwallis p<0.001
Total NPI score	2.283	2.754	3.167	3.311	4.458	5.223	Kwallis p=0.045
NPI depression sub-total	1.785	1.023	2.64	2.099	3.625	2.527	Kwallis p=0.015
NPI anxiety sub-total	2.729	1.647	3.429	2.243	5.167	3.43	Kwallis p=0.225
NPI apathy sub-total	3.284	2.458	4.15	2.207	4.167	2.317	Kwallis p=0.094
Antidepressant prescribed at baseline							p=0.001
No	100.0%		97.4%		97.0%		
Yes	0.0%		2.6%		3.0%		
CDR sum of boxes	3.266	1.974	2.913	1.963	2.451	1.65	Kwallis p=0.009
Logical memory score	2.374	2.988	2.87	3.085	3.98	4.13	Kwallis p=0.469
RAVLT immediate score	25.63	8.201	26.817	8.267	28.647	10.779	ANOVA p=0.051

RAVLT learning score	2.306	2.034	2.826	2.1	2.647	2.528	ANOVA p=0.071
RAVLT % forgetting	84.183	26.28	82.295	25.014	67.573	33.813	ANOVA p=0.005
Number of *APOE* ε4 alleles							
0	34.7%		32.7%		40.9%		p=0.540
1	48.6%		54.3%		43.9%		
2	16.8%		13.1%		15.2%		

Supplementary Table 9. ADNI cohort baseline demographics and neuropsychological test scores for individuals with normal cognition. Individuals with missing data on depression measures were excluded as were those with only one study visit, those with a maximum GDS score of 5-7 (i.e., possible depression but did not meet threshold) and those who did not meet criteria for depression but were taking antidepressant medications.

	Cognitively normal, no depression n=615		Cognitively normal, intermittent depression n=44		Cognitively normal, persistent depression n=10		p (ANOVA, Kwallis or Pearson χ^2)
	Mean	SD	Mean	SD	Mean	SD	
Age at study entry (y)	72.145	6.366	71.948	5.654	72.42	6.322	
Gender							p=0.585
Female	56.6%		61.4%		70.0%		
Male	43.4%		38.6%		30.0%		
Marital status							p=0.127
Divorced	10.9%		25.0%		30.0%		
Married	71.5%		63.6%		70.0%		
Never married	4.9%		2.3%		0.0%		
Unknown	0.2%		0.0%		0.0%		
Widowed	12.5%		9.1%		0.0%		
Ethnicity							p=0.651
Am Indian/Alaskan	0.3%		0.0%		0.0%		
Asian	2.0%		0.0%		10.0%		
Black	6.5%		4.6%		10.0%		
More than one	1.6%		0.0%		0.0%		
Unknown	0.1%		0.0%		0.0%		
White	89.6%		95.5%		80.0%		
Years of education (y)	16.715	2.521	16.523	2.267	16.8	1.687	Kwallis p=0.732
GDS score	0.721	0.975	1.622	1.813	3.1	1.792	Kwallis p=0.008
MMSE score	29.113	1.075	28.913	1.125	29.5	0.548	Kwallis p=0.520
Total NPI score	0.284	0.747	1.176	2.007	0.5	0.548	Kwallis p=0.113
NPI depression sub-total	1.4	0.724	3.667	2.598	4	2.828	Kwallis p=0.018
NPI anxiety sub-total	1.714	1.271	2.833	2.714	N/A	N/A	N/A
NPI apathy sub-total	1.667	1.118	3.5	3.109	5	4.243	N/A as low n
Antidepressant prescribed at baseline							
No	100.0%		95.6%		100.0%		p<0.001
Yes	0.0%		4.4%		0.0%		
CDR sum of boxes	0.048	0.18	0.152	0.317	0	0	Kwallis p=0.488
Logical memory score	13.17	3.399	12.696	4.395	13.333	3.724	p=0.807
RAVLT immediate score	46.192	10.098	46.304	11.542	50.667	9.771	p=0.564
RAVLT learning score	6.254	2.433	5.957	2.383	7.5	1.049	p=0.380

RAVLT % forgetting	31.752	29.249	33.704	32.798	31.688	34.873	Kwallis p=0.834
Number of *APOE* ε4 alleles							p=0.817
0	70.1%		72.3%		70.0%		
1	27.6%		22.7%		30.0%		
2	2.3%		4.6%		0.0%		

Supplementary Table 10. Medical history and other possible risk factors for the development of depression in those with AD in ADNI. In this analysis crude odds ratios are presented without the use of co-variates. Individuals with missing data on depression measures were excluded as were those with only one study visit, those with a maximum GDS score of 5-7 (i.e., possible depression but did not meet threshold) and those who did not meet criteria for depression but were taking antidepressant medications. Using a formal test for interaction there was no evidence of an interaction between depression and cognitive impairment for any of these risk factors.

	AD no depression	**AD intermittent depression**	**AD persistent depression**	**Odds Ratio (95%CI)**	**Interaction term**
	N=510	N=155	N=66		
Gender				OR for male 0.795 (0.575 to 1.101) p=0.167	OR=0.734 (0.313 to 1.714) p=0.474
Male	41.83%	45.10%	53.03%		
Female	58.17%	54.90%	46.97%		
Hx of psychiatric illness				OR=2.134 (1.524 to 2.988) p<0.001	OR=0.514 (0.253 to 1.044) p=0.066
No	56.7%	49.7%	39.4%		
Yes	27.8%	45.8%	56.1%		
Missing	15.5%	4.5%	4.5%		
Hx of neurological illness				OR=1.066 (0.741 to 1.532) p=0.730	OR=0.710 (0.338 to 1.494) p=0.367
No	60.8%	69.0%	63.6%		
Yes	23.7%	26.5%	31.8%		
Missing	15.5%	4.5%	4.5%		
Hx of endocrine/metabolic disease				OR=1.187 (0.852 to 1.653) p=0.312	OR=0.951 (0.475 to 1.900) p=0.886
No	49.2%	52.3%	50.0%		
Yes	35.3%	43.2%	45.5%		
Missing	15.5%	4.5%	4.5%		
Hx of cardiovascular disease				OR=1.289 (0.900 to 1.847) p=0.166	OR =0.954 (0.454 to 2.003)) p=0.901
No	28.6%	31.6%	16.7%		
Yes	55.9%	63.9%	78.8%		
Missing	15.5%	4.5%	4.5%		
Hx of alcohol abuse				OR=1.308 (0.622 to 2.747), p=0.479	OR=2.365 (0.264 to 21.179) p=0.441
No	80.8%	90.3%	89.4%		
Yes	3.7%	5.2%	6.1%		
Missing	15.5%	4.5%	4.5%		
Hx of drug abuse				N/A due to collinearity	
No	83.7%	95.5%	95.5%		
Yes	0.8%	0.0%	0.0%		
Missing	15.5%	4.5%	4.5%		
Hx of smoking				OR =1.153 (0.825 to 1.613) p=0.405	OR=0.892 (0.445 to 1.787) p=0.748
No	52.2%	58.7%	48.5%		
Yes	32.4%	36.8%	47.0%		
Missing	15.5%	4.5%	4.5%		
Years of education	15.147	15.548	15.471	OR=0.962 (0.917 to 1.009) p=0.109	

Supplementary Table 11. Medical history and other possible risk factors for the development of depression in individuals without dementia in ADNI. In this analysis crude odds ratios are presented without the use of co-variates. Individuals with missing data on depression measures were excluded as were those with only one study visit, those with a maximum GDS score of 5-7 (i.e., possible depression but did not meet threshold) and those who did not meet criteria for depression but were taking antidepressant medications. Using a formal test for interaction there was no evidence of an interaction between depression and cognitive impairment for any of these risk factors.

	CN no depression	CN intermittent depression	CN persistent depression	Odds Ratio (95%CI)
	N=615	N=44	N=10	
Gender				OR for male 0.767 (0.431 to 1.362) p=0.365
Male	56.6%	61.4%	70.0%	
Female	43.4%	38.6%	30.0%	
Hx of psychiatric illness				OR=3.535 (1.930 to 6.475) p<0.001
No	41.2%	35.6%	60.0%	
Yes	13.8%	48.9%	40.0%	
Missing	45.1%	15.6%	0.0%	
Hx of neurological illness				OR=1.548 (0.820 to 2.925) p=0.178
No	41.5%	62.2%	40.0%	
Yes	13.4%	22.2%	60.0%	
Missing	45.1%	15.6%	0.0%	
Hx of endocrine/metabolic disease				OR=1.244 (0.685 to 2.261) p=0.473
No	32.7%	42.2%	70.0%	
Yes	22.2%	42.2%	30.0%	
Missing	45.1%	15.6%	0.0%	
Hx of cardiovascular disease				OR =1.443 (0.763 to 2.731) p=0.260
No	21.8%	28.9%	20.0%	
Yes	33.2%	55.6%	80.0%	
Missing	45.1%	15.6%	0.0%	
Hx of alcohol abuse				OR =0.393 (0.052 to 2.969) p=0.365
No	52.1%	82.2%	100.0%	
Yes	2.8%	2.2%	0.0%	
Missing	45.1%	15.6%	0.0%	
Hx of drug abuse				N/A due to collinearity
No	54.1%	84.4%	100.0%	
Yes	0.8%	0.0%	0.0%	
Missing	45.1%	15.6%	0.0%	
Hx of smoking				OR =1.256 (0.691 to 2.282) p=0.455
No	32.8%	46.7%	50.0%	
Yes	22.1%	37.8%	50.0%	
Missing	45.1%	15.6%	0.0%	
Years of education	16.7	16.5	16.8	OR=0.978 (0.876 to 1.092) p=0.689

BDR

Supplementary Table 12. Baseline characteristics of individuals in the BDR Study with Dementia

	Dementia no depression n=490 % or mean (SD)	**Dementia intermittent depression** n=185 % or mean (SD)	**Dementia persistent depression** n=82 % or mean (SD)	**Statistical Evidence** Pearson χ^2, ANOVA or Kwallis
Age (y)	80.0 (9.2)	77.8 (9.2)	73.9 (11.3)	p<0.001
Gender				
Female	45.9%	40.0%	43.9%	p=0.38
Male	54.1%	60.0%	56.1%	
Diagnosis at baseline				p= 0.051
Dementia	79.2%	72.4%	70.7%	
Inconclusive	1.8%	0.5%	0.0%	
MCI	11.4%	17.8%	22.0%	
No dementia	7.6%	9.2%	7.3%	
MMSE score	18.6 (9.2)	21.2 (7.7)	20.5 (9.2)	Kwallis χ^2=8.57 p=0.014
MoCA score	21.5 (5.1)	21.7 (4.9)	20.4 (4.7)	Kwallis χ^2=1.28 p=0.529
Bristol activities of daily living score	30.5 (20.2)	23.8 (16.7)	23.2 (17.2)	Kwallis χ^2=20.69 p<0.001
CDR global score	1.9 (1.1)	1.4 (0.9)	1.4 (1.0)	p<0.001
Ethnicity				p=0.33
Any other Asian background	0.0%	0.5%	0.0%	
Any other Ethnic background	0.0%	0.5%	0.0%	
Any other White background	3.9%	1.1%	3.7%	
British English	69.8%	78.9%	79.3%	
British Scottish	1.4%	1.1%	0.0%	
British Welsh	5.5%	7.0%	8.5%	
British other	2.7%	3.2%	7.3%	
Indian	0.4%	0.0%	0.0%	
Irish	1.0%	0.5%	0.0%	
Missing	15.3%	7.0%	1.2%	
Accommodation				p=0.004
Living alone	8.6%	13.0%	12.2%	
Living with family	3.7%	2.7%	6.1%	
Living with friend	0.4%	0.0%	0.0%	
Living with spouse/cohabite	36.5%	47.0%	50.0%	
Other	1.0%	2.2%	2.4%	
Residential/nursing home	34.1%	21.6%	14.6%	
Sheltered accommodation	1.6%	3.8%	2.4%	

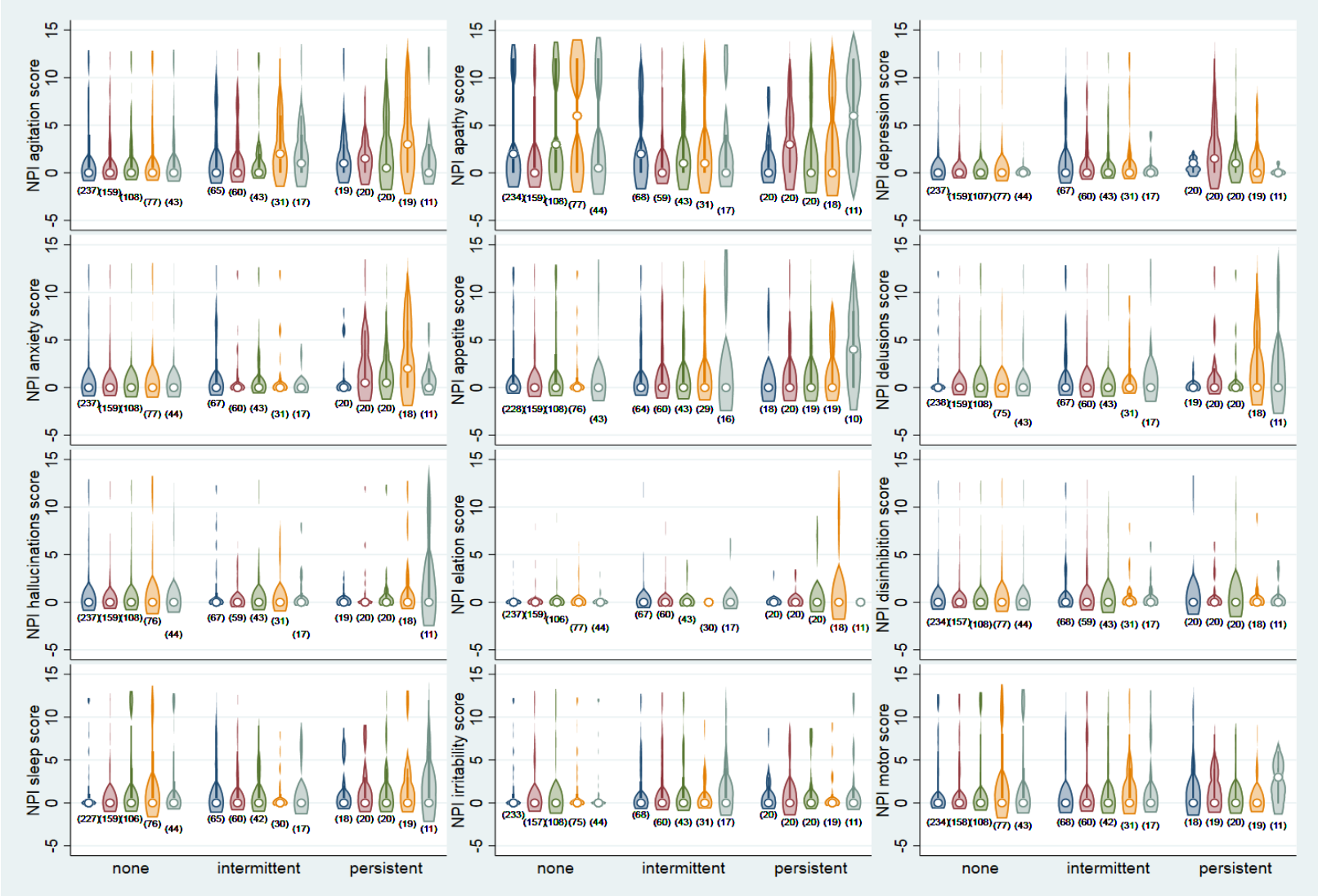
Missing	14.1%	9.7%	12.2%	
Marital Status				p=0.24
Divorced	3.3%	7.0%	7.3%	
Married	59.6%	59.5%	62.2%	
Single	2.4%	3.2%	6.1%	
Unknown	0.8%	0.0%	1.2%	
Widowed	25.1%	25.4%	20.7%	
Missing	8.8%	4.9%	2.4%	
Cornell depression rating scale score	2.5 (1.9)	9.6 (5.6)	10.6 (4.4)	Kwallis χ^2=84.87 p<0.001
Geriatric depression rating scale score	2.5 (2.1)	4.5 (3.0)	5.2 (3.3)	Kwallis χ^2=47.21 p<0.001
Years of education	12.5 (3.6)	12.1 (3)	12.2 (3.3)	Kwallis χ^2=1.78 p=0.411
Hachinski ischemic index score	3.1 (2.3)	4.1 (3.0)	3.4 (2.3)	Kwallis χ^2=7.54 p=0.023
Ever had diabetes				p=0.32
Don't know	0.6%	0.0%	1.2%	
No	70.0%	75.7%	73.2%	
Yes	9.8%	6.5%	6.1%	
Missing	19.6%	17.8%	19.5%	
Smoking status				p=0.003
10-20 / day (for a year or more)	19.2%	26.2%	16.4%	
Heavy smoker (at least 20/day for a year or more)	13.2%	15.4%	29.9%	
No or less than 10 / day	67.6%	58.4%	53.7%	
Ever been a heavy drinker				p=0.45
Don't know	1.8%	0.7%	0.0%	
No	88.0%	85.2%	87.5%	
Yes	10.2%	14.1%	12.5%	
Taking any antidepressant				p=0.012
No	100%	95.7%	92.7%	
Yes	0.0%	4.3%	7.3%	
SSRI				p=0.45
No	100%	97.8%	96.3%	
Yes	0.0%	2.2%	3.7%	
TCA				
No	100%	100%	100%	

Supplementary Table 13. Examination of risk factors for depression in dementia in the BDR cohort. In this analysis crude odds ratios are presented without the use of co-variates.

Risk Factor	**Dementia no depression** n=490 % or mean (SD)	**Dementia intermittent depression** n=185 % or mean (SD)	**Dementia persistent depression** n=82 % or mean (SD)	Odds ratio (95% CI)
Gender				Female
Female	45.9%	40.0%	43.9%	0.83 (0.61 to 1.12)
Male	54.1%	60.0%	56.1%	p=0.212
Diabetes				0.61 (0.34 to 1.08)
No	70.0%	75.7%	73.2%	p=0.092
Yes	9.8%	6.5%	6.1%	
Smoking				Heavy smoker vs. non
10-20/day	19.2%	26.2%	16.4%	1.80 (1.13 to 2.85)
>20/day	13.2%	15.4%	29.9%	p=0.013
No or <10/day	67.6%	58.4%	53.7%	
Heavy drinking				1.37 (0.82 to 2.28)
No	88.0%	85.2%	87.5%	p=-0.230
Yes	10.2%	14.1%	12.5%	
Previous stroke				1.06 (0.61 to 1.82)
No	87.0%	84.7%	95.0%	p=0.827
Yes	10.1%	13.9%	3.3%	
Parkinson's disease				1.26 (0.53 to 3.01)
No	96.4%	92.2%	95.4%	p=0.596
Yes	3.3%	5.2%	3.6%	
Cardiovascular disease (MI or angina)				1.05 (0.65 to 1.71) p=0.836
No	86.3%	83.8%	91.0%	
Yes	12.9%	15.6%	9.0%	
Years of education	12.5 (3.6)	12.1 (3)	12.2 (3.3)	Highest versus lowest 0.64 (0.35 to 1.18) p=0.155

Supplementary Table 16. Odds using logistic regression of an individual scoring above the threshold of 6 for any individual NPI sub-scale after 5 years in BDR. Age, gender, accommodation status at baseline, and smoking status at baseline were included as co-variates. Pathological diagnosis category (none, AD/mixed, other neurodegenerative disease) was included as a covariate in model 2.

NPI Symptom	Dementia no depression (comparison group) OR (95% CI)	Dementia intermittent depression Model 1	Dementia intermittent depression Model 2 + pathological diagnosis	Dementia persistent depression Model 1	Dementia persistent depression Model 2 + pathological diagnosis	AD versus other pathologies
Apathy	1	1.50 (0.97 to 2.30), p=0.066	1.34 (0.75 to 2.40), p=0.318	2.99 (1.53 to 5.83), p=0.001	1.81(0.66 to 4.94), p=0.249	1.77 (0.99 to 3.19), p=0.055
Agitation	1	1.78 (1.15 to 2.76), p=0.010	1.87 (1.07 to 3.27), p=0.028	4.66 (2.51 to 8.66), p<0.001	4.13 (1.59 to 10.77), p=0.004	2.56 (1.31 to 5.01), p=0.006
Depression	1	3.90 (2.40 to 6.32), p<0.001	4.10 (2.20 to 7.61), p<0.001	6.12 (3.29 to 11.41), p<0.001	5.07 (1.95 to 13.17), p=0.001	1.24 (0.57 to 2.68), p=0.584
Appetite	1	1.94 (1.38 to 2.93), p=0.002	2.00 (1.17 to 3.41), p=0.011	2.81 (1.56 to 5.06), p=0.001	2.61 (1.06 to 6.42), p=0.037	0.97 (0.54 to 1.73), p=0.920
Sleep	1	1.28 (0.84 to 1.96), p=0.257	1.11 (0.64 to 1.91), p=0.713	3.42 (1.90 to 6.13), p<0.001	3.84 (1.54 to 9.56), p=0.004	1.43 (0.77 to 2.65), p=0.252
Irritability	1	1.48 (0.94 to 2.33), p=0.091	1.16 (0.65 to 2.09), p=0.614	3.39 (1.87 to 6.14), p<0.001	2.12 (0.85 to 5.26), p=0.107	2.69 (1.26 to 5.72), p=0.011
Anxiety	1	1.96 (1.21 to 3.17), p=0.006	1.61 (0.87 to 2.97), p=0.130	4.37 (2,.39 to 8.02), p<0.001	5.12 (2.00 to 13.01), p=0.001	2.05 (0.97 to 4.36), p=0.061
Motor	1	1.11 (0.72 to 1.73), p=0.643	1.33 (0.77 to 2.31), p=0.310	2.33 (1.31 to 4.16), p=0.004	1.65 (0.68 to 3.98) p=0.265	1.69 (0.90 to 3.18), p=0.106
Delusions	1	2.01 (1.25 to 3.24), 0=0.004	1.92 (1.04 to 3.55), p=0.036	1.76 (0.91 to 3.41), p=0.094	1.51 (0.56 to 4.09), p=0.410	5.21 (1.96 to 13.91), p=0.001
Hallucinations	1	1.82 (1.07 to 3.10), p=0.027	1.90 (0.94 to 3.83), p=0.073	1.31 (0.61 to 2.80), p=0.494	0.81 (0.21 to 3.12) p=0.758	3.50 (1.28 to 9.52), p=0.014
Disinhibition	1	1.65 (0.87 to 3.12), p=0.123	1.61 (0.84 to 3.10), p=0.148	2.92 (1.14 to 7.38), p=0.026	2.83 (1.05 to 7.62), p=0.039	0.85 (0.41 to 1.76), p=0.656
Elation	1	2.78 (0.70 to 10.98), p=0.145	2.89 (0.71 to 11.74), p=0.137	16.72 (3.96 to 70.60), p<0.001	21.28 (4.46 to 101.63), p<0.001	0.58 (0.15 to 2.20), p=0.421



Supplementary Figure 4. NPI symptoms during 5-year follow-up in those with no depression, intermittent depression and persistent depression in the BDR cohort. Note that the NPI was used so the threshold for clinical significance is at least 4 (most authors) or 6 (this study). The numbers in brackets under each plot are the number of individuals in each group with information on that NPI symptom.