Research Report

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

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Abstract.
Background: Depression in individuals with Alzheimer's disease (AD) is common, distressing, difficult to treat, and inadequately understood. It occurs more frequently in AD than in older adults without dementia. The reasons why some patients develop depression during AD and others do not remain obscure.
Objective: We aimed to characterize depression in AD and to identify risk factors.
Methods: We used data from three large dementia focused cohorts: ADNI ($n = 665$ with AD, 669 normal cognition), NACC ($n = 698$ with AD, 711 normal cognition), and BDR ($n = 757$ with AD). Depression ratings were available using the GDS and NPI and in addition for BDR the Cornell. A cut-off of ≥ 8 was used for the GDS and the Cornell Scale for Depression in Dementia, ≥ 6 for the NPI depression sub-scale, and ≥ 2 for the NPI-Q depression sub-scale. We used logistic regression to examine potential risk factors and random effects meta-analysis and an interaction term to look for interactions between each risk factor and the presence of cognitive impairment.
Results: In individual studies there was no evidence of a difference in risk factors for depressive symptoms in AD. In the meta-analysis the only risk factor which increased the risk of depressive symptoms in AD was previous depression, but information on this was only available from one study (OR 7.78 95%CI 4.03–15.03).
Conclusion: Risk factors for depression in AD appear to differ to those for depression per se supporting suggestions of a different pathological process, although a past history of depression was the strongest individual risk factor.

Keywords: Alzheimer's disease, dementia, depression, depressive disorder

INTRODUCTION

Depression and Alzheimer's disease (AD) are both common mental disorders. The incidence of depression is increased in those with AD compared to older people without dementia, it is distressing for patients, and may increase carer burden [1–3]. Up to 16% of individuals with AD develop depression during their illness [4]. Depression in dementia is difficult to treat, appears to have different symptomatology (e.g., less guilt/worthlessness), and currently available anti-depressants are ineffective [5, 6]. Separate

diagnostic criteria have been proposed for depression in AD, but have not been adopted into routine practice [7].

A recent systematic review examining risk factors for depression in AD found only 7 studies, most of which were of relatively low quality. Family and personal history of mental health problems were both found to increase risk [8]. They concluded that the risk factors for depression in AD were largely similar to those for older adults without cognitive impairment, although sex and educational level did not appear to be risk factors for depression in AD. A family history of depression has been one of the most consistently reported risk factors for depression in AD, suggesting a possible genetic predisposition [9, 10].

The underlying biology of depression in AD remains poorly understood. It has been suggested that it may have a vascular component (e.g., [11, 12]). A large case series which used the Hamilton Depression Rating Scale found that depression in AD is not simply a symptom of the dementia [13]. Individuals with depression in AD are more likely than those with AD who are not depressed to develop psychotic symptoms and have also been shown to have increased cortical tangles, which suggests more severe AD pathology [3, 14]. They have also been shown to have reduced perfusion of frontal brain areas and reduced connectivity between the amygdala and the frontal cortex [15, 16].

The reasons why some patients develop depression during AD and others do not remain unknown. The biological mechanisms underlying depression in AD and whether this differs to depression in those without AD also remain unclear.

Aims and objectives

We aimed to characterize depression in individuals with AD using three large cohort studies, to identify risk factors for depression in AD and to assess whether these risk factors differed from those with normal cognition who develop depression.

METHODS

We obtained information from three large dementia focused cohort studies.

National Alzheimer's Co-ordinating Center

The NACC (https://naccdata.org/) was established in 2005 and collates information from Alzheimer's

Disease Research Centers across the USA using uniform data sets. Individuals with AD, mild cognitive impairment (MCI), and normal are included. Each center has its own enrolment protocol. This can include clinician referral, self-referral, active recruitment by community organizations, and recruitment of volunteers with normal cognition. It is therefore not representative of the general US population. Participants are seen approximately annually.

Depressive symptoms were assessed using the Neuropsychiatric Inventory-Questionnaire (NPI-Q) and the Geriatric Depression Scale (GDS) [17, 18]. Unlike Alzheimer's Disease Neuroimaging Initiative (ADNI) individuals with depressive symptoms at baseline were not excluded.

Because the current study was part of a larger analysis which included neuroimaging data [19], individuals were included in this study if they had "at least one MRI scan with calculated volumes available, had at least one visit with information on current/previous depression and either had a diagnosis of AD on at least one occasion, a diagnosis of impaired cognition during follow-up or normal cognition at all visits." [19]. Data was obtained from the September 2019 data freeze.

Alzheimer's Disease Neuroimaging Initiative

The ADNI (http://www.adni-info.org/) was established in 2004 and is a longitudinal study aimed at developing biomarkers and other indicators for the early detection of AD. It has clinical data including PET and MRI on > 800 individuals [20, 21]. Participants included in the trial had either normal cognition, MCI, or early AD at baseline. After the screening visit participants have assessments at 0, 3, 6, and 12 months before the interval between visits increases to every 6 months [20]. ADNI was carried out in phases; ADNI1 in 2004; ADNI-GO in 2009; ADNI 2 in 2011; and ADNI3 in 2016. Many individuals were seen in more than one phase with existing participants included in the recruitment for each successive phase. There are differences in the data collected in each phase. For example, the shorter form NPI-Q was used in ADNI 1 and ADNI-GO whereas the full NPI was used in ADNI 2 & 3. Individuals meeting criteria for depression either at entry to the study or in the 2 years preceding study entry were an excluded, meaning that very few participants had significant depressive symptoms at baseline. Other exclusion criteria included inability to speak English or Spanish, age < 55 or > 90 at study entry, learning disability,

other unstable medical conditions, severe sensory impairment which would impair neuropsychological testing, unwillingness to undergo neuroimaging and lack of a study partner. At study entry participants had to have a Mini-Mental State Examination (MMSE) of > 19.

Depressive symptoms were measured using the GDS and NPI or NPI-Q [17, 18, 22]. The final dataset used in this analysis was downloaded in May 2021.

Brains for Dementia Research

Data was available for BDR via the Dementia Platforms UK portal (https://portal.dementiasplatform.uk). BDR was set up in 2007 to establish a network of brain bank facilities in England and Wales. Participants in BDR were recruited using advertisements in a wide range of media with support from Alzheimer's Research UK and the Alzheimer's Society. Participants agreed at study entry to donate their brains after their demise. Exclusion criteria included brain trauma/major stroke, healthy controls aged < 65 (except where partner of participant), insufficient command of the English language to be able to complete assessments and "being geographically too remote from an assessment center." [23]. Participants are seen roughly annually by either a psychologist or research nurse. Depressive symptoms were measured using the NPI-Q, the GDS and the Cornell Scale for Depression in Dementia [17, 18, 24].

Definition of depressive symptoms

As in our linked study a cut-off of ≥ 8 was used for the GDS and the Cornell Scale for Depression in Dementia [19]. These cut offs were chosen for the best balance of specificity and sensitivity [25, 26]. NPI sub-scale scores were calculated for depression by multiplying the severity and frequency items for each symptom [22]. A cut-off was used of ≥ 2 for the NPI-Q and ≥ 6 for the NPI depression sub-scale. The NPI cut-off of 6 was chosen to ensure that individuals would have to have had depressive symptoms often/frequently/very frequently and at least of moderate severity. Although the NPI is predominantly a screening tool it has previously been used to define clinically significant behavioral and psychological symptoms of dementia and to diagnose depression [27–29].

Depression caseness was defined as scoring above the threshold on either the NPI, GDS, or Cornell.

Intermittent depression was defined as "one episode above threshold on any scale and persistent as ≥ 2 episodes above threshold on any scale during follow-up" [19].

The GDS is self-rated and thus can only be completed by individuals who are less cognitively impaired and thus are able to understand the content, recall the previous week, and retain the information for long enough to complete the questionnaire. The Cornell is clinician rated and includes information from both patients and carers. While flawed as a diagnostic tool for depression the NPI allowed us to identify individuals with significant depressive symptoms who were unable to complete the GDS as they were too cognitively impaired [30]. The NPI has been previously used in multiple studies to define depression caseness in those with dementia [31–34], and an NPI depression subscale score of 4 or more has been used as a criterion for entry into clinical trials [35].

In those with normal cognition, the NPI was not used to define depression caseness as it has not been validated in this population.

Dataset exclusions

Because we aimed to study persistent depressive symptoms, we excluded participants with only one study visit and those who failed the screening visit. Individuals with treated depression (i.e., taking antidepressants at baseline but who never scored above the GDS threshold during follow-up) were excluded. This comprised 9 individuals in BDR. In NACC, 18 individuals were taking antidepressants at baseline but were not depressed and 105 were taking antidepressants at least 2 timepoints but never met depression caseness criteria. In older adult psychiatry it is common for antidepressants to be prescribed for 2 years to prevent relapse.

In NACC, in which some participants were seen multiple times before they developed cognitive difficulties, visits prior to the time at which they first developed MCI were not considered for the AD group.

Risk factors under investigation

In our risk factor analysis, we considered demographic and clinical variables which have previously been shown to be associated with the risk of an individual developing depression. These included female sex, years of education, smoking, alcohol consumption, stroke, previous psychiatric illness, previous

depression, cardiovascular disease, diabetes, drug use, and neurological illnesses such as Parkinson's disease [36–43]. Data was not available on all risk factors from each of the included studies.

Statistical analysis

All statistical analyses were carried out in STATA 14 except the meta-analysis, which was conducted in R. Chi squared tests were used to assess differences in baseline categorical variables. Parametric analyses were used wherever possible to assess between group differences in continuous variables. Data was examined for normal distribution using histograms, P normal and Q normal plots and where necessary the Shapiro Wilk test. Where data was not normally distributed and could not be transformed, the Kruskal Wallis test was used.

Logistic regression was used to examine the effects of risk factors on the risk of developing clinically significant depressive symptoms, either intermittent or persistent. In NACC age, sex, psychiatric history, history of depression, ethnicity, and years of education were co-variates in this analysis. In ADNI age, sex, ethnicity, psychiatric history, and years of education were used as co-variates. In BDR, age, sex, ethnicity, and years of education were available as co-variates. Random effects meta-analyses were conducted (to allow for between-cohort variations in data collection) to estimate the average effect of each risk factor on depression across the cohorts (where available). Imputation was not possible for any dataset as the data was missing not at random (Older individuals and those with dementia more likely to drop out of the study).

In a second model, to assess whether risk factors for depressive symptoms differed between individuals with AD and normal cognition, cognition (i.e., the presence/absence of dementia) was added to each logistic regression model as an interaction term.

To assess the effect of persistent low mood, we used trajectory modelling. This accounts for changes in depression scores over time. GDS scores were used as this was the most complete dataset. For the trajectory modelling in the NACC dataset Akaike information criterion (AIC), Bayes information criterion (BIC), and entropy (which assesses model homogeneity) were used to assess the model fit. The model chosen had the lowest AIC, BIC, confidence intervals, no groups with extremely low numbers of participants and an entropy of > 0.7 (see Supplementary Table 5). The odds of correct classification and the average pos-

terior probability for each group were also assessed. Due to missing data, only the first 5 years of time in the study could be modelled in the trajectory analysis. Violin plots and logistic regression were used to assess the influence of trajectory group on NPI-Q sub scale scores. Because ADNI excluded individuals with clinically significant depressive symptoms at study entry and attrition led to missing data on the GDS later in the study, it was not possible to adequately model trajectories of depressive symptoms in ADNI (no model with entropy > 0.7). Due to lower numbers in BDR and individuals completing a mixture of the GDS and Cornell it was again not possible to produce an adequate trajectory model.

The primary outcome was the risk of developing depressive symptoms above the defined threshold. After the a priori analysis, secondary analyses were performed including the analysis of NPI sub scales. These were not included in the power calculation prior to study commencement.

Ethical approvals

All contributing ADCs are required to obtain informed consent from their participants and maintain their own separate IRB review and approval from their institution prior to submitting data to NACC. The NACC database itself is exempt from IRB review and approval.

As this study's use of ADNI and BDR data fell into the category of secondary analysis of anonymized data, under UK law, no separate ethical approval was required for these analyses.

RESULTS

NACC

As shown in Table 1, 698 individuals with AD were included, 111 of whom met criteria for persistent depressive symptoms. Depressed individuals were more to have experienced depression in the last two years, to be female, and to be taking antidepressants. They also had slightly higher baseline NPI anxiety (mean difference 0.30 in persistent depression group) and apathy scores (mean difference 0.31 in persistent depression group). As shown in Supplementary Table 3, at baseline the AD +/– depression groups had similar scores on cognitive tests such as the MMSE.

In the NACC, there were 711 individuals with normal cognition but numbers with either persistent

Table 1

Baseline characteristics of the cohorts in this study. 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 sex as co-variates

	NACC				ADNI				BDR			
	AD no dep N = 393	AD intermittent dep N = 185	AD persistent dep N = 111	Statistical Evidence	AD, no dep n = 447	AD, intermittent dep n = 153	AD, persistent dep n = 66	Statistical Evidence	Dementia no dep n = 490	Dementia intermittent dep n = 185	Dementia persistent dep n = 82	Statistical Evidence
Age at baseline (mean (SD))	78.2 (8.5)	76.1 (9.4)	74.4 (10.3)	$p = 0.935$	74.5 (7.6)	73.8 (7.1)	74.6 (7.1)	$p = 0.579$	80.0 (9.2)	77.8 (9.2)	73.9 (11.3)	$p < 0.001$
Sex				$p = 0.035$				$p = 0.213$				$p = 0.38$
male	221 (56.2%)	89 (48.1%)	49 (44.1%)		58.17%	54.90%	46.97%		54.1%	60.0%	56.1%	
female	172 (43.8%)	96 (51.9%)	62 (55.9%)		41.83%	45.10%	53.03%		45.9%	40.0%	43.9%	
Marital status				$p = 0.30$								$p = 0.24$
married	256 (65.1%)	124 (67.0%)	78 (70.3%)		83.7%	81.7%	83.3%	$p = 0.778$	59.6%	59.5%	62.2%	
widowed	80 (20.4%)	30 (16.2%)	17 (15.3%)		10.1%	10.5%	10.6%		25.1%	25.4%	20.7%	
divorced	34 (8.7%)	23 (12.4%)	8 (7.2%)		3.8%	5.9%	6.1%		3.3%	7.0%	7.3%	
separated	2 (0.5%)	0 (0.0%)	2 (1.8%)									
other	5.4%	4.3%	5.2%		2.5%	2.0%	0.0%		12.0%	8.1%	9.7%	
Ethnicity				$p = 0.61$								$p = 0.33$
White	331 (84.2%)	165 (89.2%)	91 (82.0%)		94.2%	93.5%	92.4%	$p = 0.974$	84.3%	92.0%	98.8%	
Black or African American	44 (11.2%)	13 (7.0%)	16 (14.4%)		3.1%	3.3%	4.6%		0.0%	0.0%	0.0%	
native American/Asian	4.4%	3.7%	3.6%		2.8%	3.3%	3.0%		15.7%	8.0%	1.2%	
Prescribed an antidepressant at baseline	0 (0.0%)	59 (31.9%)	38 (34.2%)	$p < 0.001$	0.0%	2.6%	3.0%	$p = 0.001$	0.0%	4.3%	7.3%	$p = 0.012$
GDS score at baseline	1.5 (1.5)	2.7 (2.4)	4.4 (3.5)	Kwallis $\chi^2 = 77.5$ $p < 0.001$	1.3 (1.1)	2.0 (1.6)	2.4 (1.8)	Kwallis $p < 0.001$	2.5 (2.1)	4.5 (3.0)	5.2 (3.3)	Kwallis $\chi^2 = 47.21$ $p < 0.001$
NPI depression score at baseline	0.1 (0.3)	0.8 (0.9)	1.1 (1.0)	Kwallis $\chi^2 = 161.4$ $p < 0.001$	1.8 (1.0)	2.6 (2.1)	2.4 (1.8)	Kwallis $p = 0.015$				

depressive symptoms (*n* = 23) or intermittent depressive symptoms (*n* = 23) were low (see Supplementary Table 4).

ADNI

We included 666 individuals with AD (see Table 1). As shown in Supplementary Table 9, at baseline the AD +/– depression groups had similar scores on cognitive tests such as the MMSE. Few individuals had depressive symptoms at baseline, and depressive symptoms in this cohort developed during follow-up. There was no evidence of a sex difference in those with depression. Individuals with depressive symptoms had higher baseline MMSE scores, lower Clinical Dementia Rating sum of boxes, and a lower (better) Rey Auditory Verbal Learning Test forgetting score. Unlike the NACC cohort, there was no evidence of a difference in baseline NPI apathy and anxiety scores in individuals with depression.

There were 669 individuals without cognitive impairment (Supplementary Table 9), but above threshold depressive symptoms were again low (*n* = 44 intermittent and *n* = 10 persistent).

BDR

In the BDR cohort, 757 individuals with dementia were included in this study (Table 1). Unlike NACC and ADNI, probable clinical diagnoses are not available and therefore it was not possible to separate individuals with different types of dementia. Depressed individuals were younger (unlike NACC and ADNI), more likely to live alone/with family, had a slightly higher Hachinski Ischemic index score, have higher MMSE score and lower (better) Basic Activities of Daily Living score at baseline.

Risk factors for depressive symptoms in AD/dementia

In the BDR cohort (which included all dementias), there was evidence that being a smoker increased the risk of depressive symptoms but no evidence that years of education or medical co-morbidities altered the risk (Table 2, Supplementary Table 13, and Fig. 1). In the NACC cohort (Supplementary Table 5 and Fig. 1), history of previous depression/psychiatric disease and being female increased the risk of depression. There was again no evidence that years of education increased the risk. Using an interaction term in NACC, there was no evidence that risk factors for depressive symptoms in AD differed from those with normal cognition (Supplementary Tables 5 and 6), but the numbers with normal cognition and depressive symptoms were low. In the ADNI (Fig. 1, Supplementary Tables 1 and 10), there was only evidence that previous psychiatric illness increased the risk of depressive symptoms in AD.

There was again no evidence of an interaction between depressive symptoms and cognitive impairment in any individual study for any of the risk factors examined either in the crude analysis (Supplementary Tables 5, 6, 10, 11, and 14) or when adjustment for co-variates was performed.

For ease of presentation, odds ratios for each risk factor and cohort, as well as pooled estimates from random-effects meta-analyses (where possible) are presented in Fig. 1. For the risk factors where meta-analyses were possible, there was no strong evidence that any risk factor studied increased the risk of depressive symptoms in those with dementia. It was not possible to meta-analyze the effect of previous depression as data on this risk factor was only available from one study (NACC; OR 7.78, 95% CI 4.03 to 15.03). To explore mediation, we removed previous depression as a co-variate from the NACC analysis (Supplementary Figure 1) and re-ran the meta-analyses. Most effect estimates were unchanged, apart from previous psychiatric problems, which increased the risk of depressive symptoms in AD (OR 2.27, 95 % CI 1.64 to 3.13).

Trajectory modelling in the NACC cohort

Using GDS scores, it was possible to model longitudinal depressive symptoms in the NACC cohort. Because GDS completion requires better cognition there may be a bias towards individuals with higher cognitive performance in the groups with higher depression scores. A 5-group model was the best fit (Supplementary Table 7). The two groups with low depression scores throughout appear to be very similar but the model scores for a 4-group model were inferior. Broadly speaking there were individual with low depression scores at baseline whose scores remained low, those with high scores at baseline who remained depressed and individuals whose GDS scores either decreased or increased during 5-year follow-up. Using violin plots (Fig. 2), it appears that individuals with GDS scores that remained high appeared to be more likely to experience apathy (OR 4.30 (95% CI 1.40 to 13.18) *p* = 0.011), anxiety, and depressive symptoms on the NPI during follow-up.

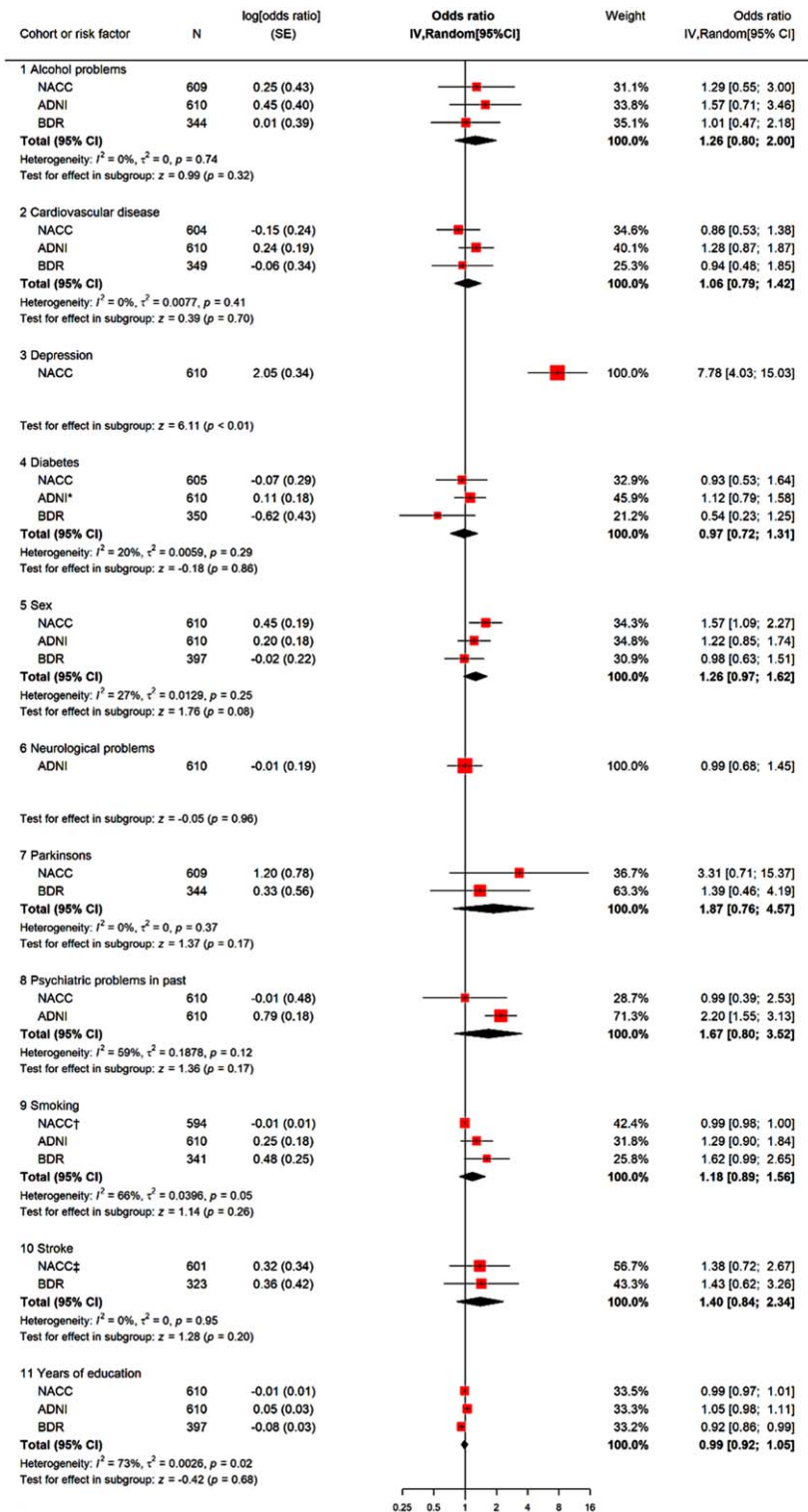| Study	Risk factor	Total N	N depression	N no depression	Odds ratio	Standard error	Lower end of 95% CI	Upper end of 95% CI	Co-variates used
NACC	Cardiovascular disease	604	337	274	0.8569945	0.2088732	0.5315165	1.3817810	age, gender, ethnicity, psych Hx, education years, Hx depression
NACC	Diabetes	605	339	274	0.9279423	0.2682048	0.5266192	1.6351040	age, gender, ethnicity, psych Hx, education years, Hx depression
NACC	Stroke or TIA	601	336	273	1.3818290	0.4637573	0.7157833	2.6676390	age, gender, ethnicity, psych Hx, education years, Hx depression
NACC	Depression	610	341	275	7.7849360	0.4637573	0.7157833	2.6676390	age, gender, ethnicity, education years, Hx depression
NACC	Psychiatric problems in past	610	339	277	0.9937580	0.4731924	0.3908126	2.5269270	age, gender, ethnicity, psych Hx, education years,
NACC	Parkinson's disease	609	340	277	3.3123620	2.5942650	0.7136261	15.3746300	age, gender, ethnicity, psych Hx, education years, Hx depression
NACC	gender female vs. male	610	364	296	1.5745180	0.2928298	1.0935550	2.2670160	age, ethnicity, psych Hx, education years, Hx depression
NACC	alcohol problems yes/no	609	339	277	1.2890680	0.5554154	0.5540159	2.9993660	age, gender, ethnicity, psych Hx, education years, Hx depression
NACC	smoking continuous	594	330	271	0.9913722	0.0064679	0.9787760	1.0041310	age, gender, ethnicity, psych Hx, education years, Hx depression
NACC	years of education	610	364	296	0.9897973	0.0124916	0.9656145	1.0145860	age, gender, ethnicity, psych Hx, education years, Hx depression
ADNI	Psychiatric problems in past	610	399	211	2.2038450	0.3945182	1.5516880	3.1300970	age, gender, ethnicity, education years
ADNI	Neurological problems	610	399	211	0.9912748	0.1927211	0.6771824	1.4510500	age, gender, ethnicity, Psych Hx, education years
ADNI	Endocrine disease incl diabetes	610	399	211	1.1156480	0.1988043	0.7867669	1.5820050	age, gender, ethnicity, Psych Hx, education years
ADNI	Cardiovascular disease	610	399	211	1.2770240	0.2484025	0.8722205	1.8697000	age, gender, ethnicity, Psych Hx, education years
ADNI	alcohol problems yes/no	610	399	211	1.5679050	0.6334404	0.7102816	3.4610580	age, gender, ethnicity, Psych Hx, education years
ADNI	smoker vs. non smoker	610	399	211	1.2875260	0.2334726	0.9024097	1.8369950	age, gender, ethnicity, Psych Hx, education years
ADNI	gender female vs. male	610	399	211	1.2195750	0.2210752	0.8548885	1.7398340	age, gender, ethnicity, Psych Hx, education years
ADNI	years of education	610	399	211	1.0469540	0.0332799	0.9837173	1.1142560	age, gender, ethnicity, Psych Hx, education years
BDR	diabetes	350	259	122	0.5400425	0.2317642	0.2328772	1.2523590	age, gender, ethnicity, education years
BDR	gender female vs. male	397	263	142	0.9781605	0.2181267	0.6318222	1.5143470	age, ethnicity, education years
BDR	smoking mod vs. non	341	227	119	1.5450070	0.4583438	0.8637972	2.7634330	age, gender, ethnicity, education years
BDR	smoking heavy vs. none	341	227	119	1.7359670	0.5995392	0.8822014	3.4159790	age, gender, ethnicity, education years
BDR	alcohol problems yes/no	344	234	115	1.0128510	0.3961941	0.4705255	2.1802570	age, gender, ethnicity, education years
BDR	years of education	397	263	142	0.9210577	0.0319945	0.8604367	0.9859496	age, gender, ethnicity
BDR	Cardiovascular disease	349	234	121	0.9424967	0.3238102	0.4806574	1.8480940	age, gender, ethnicity, education years
BDR	Parkinson's disease	344	232	121	1.3942030	0.7819150	0.4644552	4.1851200	age, gender, ethnicity, education years
BDR	Stroke	323	222	106	1.4276510	0.6023836	0.6244042	3.2642120	age, gender, ethnicity, education years

Cohort or risk factor	N	log[odds ratio] (SE)	Weight	Odds ratio IV,Random[95% CI]
1 Alcohol problems				
NACC	609	0.25 (0.43)	31.1%	1.29 [0.55; 3.00]
ADNI	610	0.45 (0.40)	33.8%	1.57 [0.71; 3.46]
BDR	344	0.01 (0.39)	35.1%	1.01 [0.47; 2.18]
Total (95% CI)			100.0%	1.26 [0.80; 2.00]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.74$				
Test for effect in subgroup: $z = 0.99$ ($p = 0.32$)				
2 Cardiovascular disease				
NACC	604	-0.15 (0.24)	34.6%	0.86 [0.53; 1.38]
ADNI	610	0.24 (0.19)	40.1%	1.28 [0.87; 1.87]
BDR	349	-0.06 (0.34)	25.3%	0.94 [0.48; 1.85]
Total (95% CI)			100.0%	1.06 [0.79; 1.42]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0077$, $p = 0.41$				
Test for effect in subgroup: $z = 0.39$ ($p = 0.70$)				
3 Depression				
NACC	610	2.05 (0.34)	100.0%	7.78 [4.03; 15.03]
Test for effect in subgroup: $z = 6.11$ ($p < 0.01$)				
4 Diabetes				
NACC	605	-0.07 (0.29)	32.9%	0.93 [0.53; 1.64]
ADNI*	610	0.11 (0.18)	45.9%	1.12 [0.79; 1.58]
BDR	350	-0.62 (0.43)	21.2%	0.54 [0.23; 1.25]
Total (95% CI)			100.0%	0.97 [0.72; 1.31]
Heterogeneity: $I^2 = 20\%$, $\tau^2 = 0.0059$, $p = 0.29$				
Test for effect in subgroup: $z = -0.18$ ($p = 0.86$)				
5 Sex				
NACC	610	0.45 (0.19)	34.3%	1.57 [1.09; 2.27]
ADNI	610	0.20 (0.18)	34.8%	1.22 [0.85; 1.74]
BDR	397	-0.02 (0.22)	30.9%	0.98 [0.63; 1.51]
Total (95% CI)			100.0%	1.26 [0.97; 1.62]
Heterogeneity: $I^2 = 27\%$, $\tau^2 = 0.0129$, $p = 0.25$				
Test for effect in subgroup: $z = 1.76$ ($p = 0.08$)				
6 Neurological problems				
ADNI	610	-0.01 (0.19)	100.0%	0.99 [0.68; 1.45]
Test for effect in subgroup: $z = -0.05$ ($p = 0.96$)				
7 Parkinsons				
NACC	609	1.20 (0.78)	36.7%	3.31 [0.71; 15.37]
BDR	344	0.33 (0.56)	63.3%	1.39 [0.46; 4.19]
Total (95% CI)			100.0%	1.87 [0.76; 4.57]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.37$				
Test for effect in subgroup: $z = 1.37$ ($p = 0.17$)				
8 Psychiatric problems in past				
NACC	610	-0.01 (0.48)	28.7%	0.99 [0.39; 2.53]
ADNI	610	0.79 (0.18)	71.3%	2.20 [1.55; 3.13]
Total (95% CI)			100.0%	1.67 [0.80; 3.52]
Heterogeneity: $I^2 = 59\%$, $\tau^2 = 0.1878$, $p = 0.12$				
Test for effect in subgroup: $z = 1.36$ ($p = 0.17$)				
9 Smoking				
NACC†	594	-0.01 (0.01)	42.4%	0.99 [0.98; 1.00]
ADNI	610	0.25 (0.18)	31.8%	1.29 [0.90; 1.84]
BDR	341	0.48 (0.25)	25.8%	1.62 [0.99; 2.65]
Total (95% CI)			100.0%	1.18 [0.89; 1.56]
Heterogeneity: $I^2 = 66\%$, $\tau^2 = 0.0396$, $p = 0.05$				
Test for effect in subgroup: $z = 1.14$ ($p = 0.26$)				
10 Stroke				
NACC‡	601	0.32 (0.34)	56.7%	1.38 [0.72; 2.67]
BDR	323	0.36 (0.42)	43.3%	1.43 [0.62; 3.26]
Total (95% CI)			100.0%	1.40 [0.84; 2.34]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.95$				
Test for effect in subgroup: $z = 1.28$ ($p = 0.20$)				
11 Years of education				
NACC	610	-0.01 (0.01)	33.5%	0.99 [0.97; 1.01]
ADNI	610	0.05 (0.03)	33.3%	1.05 [0.98; 1.11]
BDR	397	-0.08 (0.03)	33.2%	0.92 [0.86; 0.99]
Total (95% CI)			100.0%	0.99 [0.92; 1.05]
Heterogeneity: $I^2 = 73\%$, $\tau^2 = 0.0026$, $p = 0.02$				
Test for effect in subgroup: $z = -0.42$ ($p = 0.68$)				

0.25 0.5 1 2 4 8 16

Fig. 1. (*Continued*)

Principal component analysis in the NACC cohort

In our previous study, we used polychoric principal component analysis including NPI and GDS scores to allow for the semi categorical nature of the NPI three factors emerged: factor 1 (the majority of the NPI sub scales), factor 2 (NPI depression, anxiety, and some loading for apathy) and factor 3 (GDS depression) [19].

Although it was not possible to perform trajectory modelling in either ADNI or BDR, it was possible to examine NPI symptoms during follow-up in the BDR cohort (Supplementary Figure 4). The same effect on apathy and anxiety was not seen. This may be because BDR includes many different types of dementia, or a true non replication. Using logistic regression to examine models to examine risk factors for clinically significant NPI symptoms in BDR (Supplementary Table 14), almost all NPI sub-scales were more likely to be clinically significant in those with persistent depression, with some evidence that pathological diagnosis altered this relationship.

DISCUSSION

We have examined three large dementia focused cohorts to identify risk factors for depressive symptoms in AD. In individual studies, using interaction terms, we found no evidence that the risk factors differed from depression per se. A history of previous depression was the risk factor with the best evidence of effect but data on this was only available from one study. There were differences between cohorts (Table 4) that may have been due to recruitment criteria. Although our formal test for whether risk factors for depression differed between those with and without AD was not significant, in the random effects meta-analysis only previous depression increased the risk of depressive symptoms in AD. Information on this was only however available from one study. Other risk factors under examination which have been shown to increase the risk of depression, did not increase the risk of depressive symptoms in AD in the current study.

A previous systematic review which included over 2200 individuals found that only previous psychiatric history and greater cognitive impairment were predictive of depression in dementia. Like us they found no evidence that sex, diabetes, or cardiovascular risk increased the risk of depression [8]. Our study adds to the evidence that risk factors for depression appear to be different to the wider older adult population. For example, female sex, alcohol use, and stroke are well established as risk factors for depression in the general population.

We have not formally commented on the rates of depression in each cohort as they are not representative of the general population. It was noticeable, however, that depression was more common in those with AD in each cohort, but as controls in these cohorts are volunteers who may differ from the wider population (e.g., more highly educated), this may account for some of the difference observed.

In our previous study, we found evidence using a *post hoc* principal component analysis that depression in AD may be linked to apathy and anxiety more than other NPI sub scales [19]. In the current study, we demonstrated in the BDR cohort that almost all NPI sub scales were more likely to be clinically significant in those with depressive symptoms. Depressive symptoms have been previously shown to vary during follow-up [44, 45]. It has also previously been demonstrated that factor analysis may yield different combinations at baseline to during follow-up [46, 47]. It has been suggested that future research should consider pairs or small groups of symptoms when attempting to understand the underlying biology.

Strengths of this study include the use of multiple cohorts, the use of higher thresholds than some previous studies to define depression so that only clinically significant depressive symptoms were included, the larger size compared to some previous studies and the length of follow-up data available. This allowed a more longitudinal view of depression in AD. Limitations include the relatively low numbers of individuals without dementia who developed depressive symptoms (although this is consistent with the known prevalence) and the low numbers of individuals with persistent depressive symptoms in ADNI

Fig. 1. Random effects meta-analysis of the effect of risk factors under investigation for their effect on the development of depression (either intermittent or persistent) in AD from the NACC, ADNI and BDR cohorts. Data was not available for all risk factors in each study. 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.
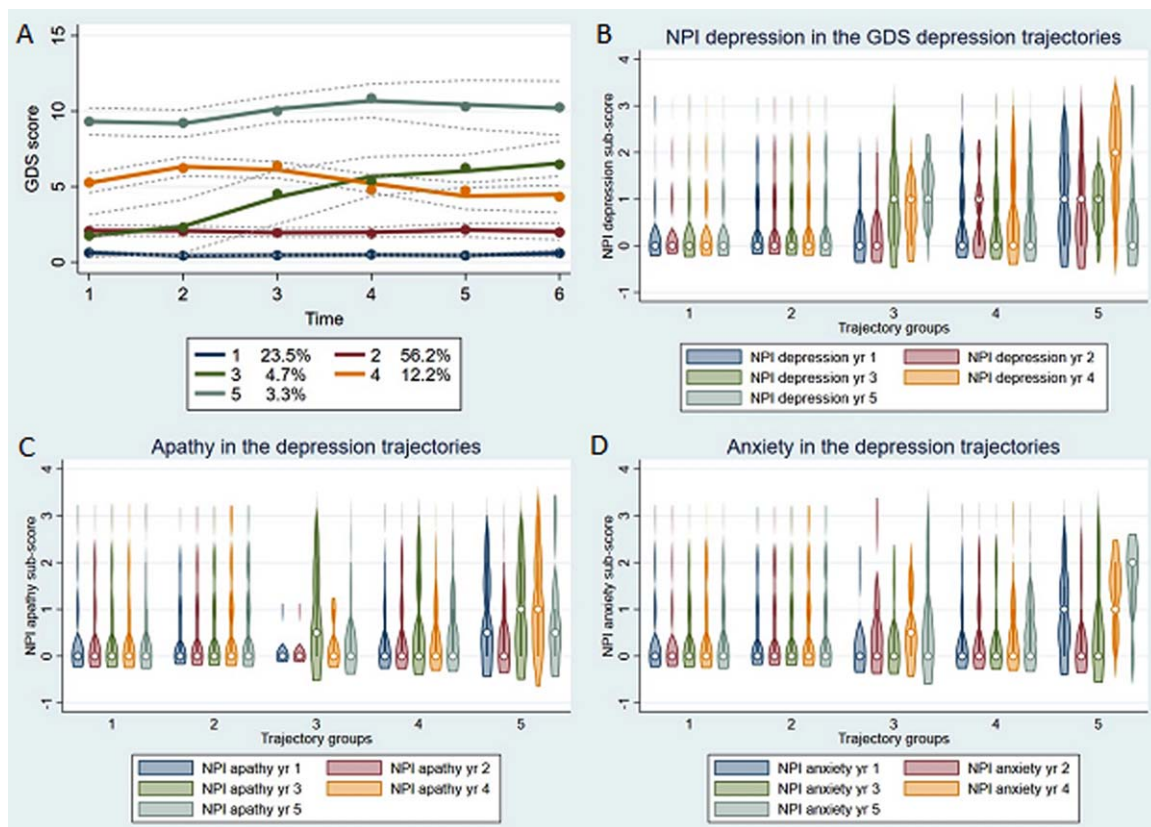
Fig. 2. GDS trajectory analysis in NACC (A). Individuals with persistent depressive symptoms during follow-up (group 5) appeared to have more apathy (C), anxiety (D), and NPI rated depression (B) during 5-year follow-up.

(due to the study entry criteria). Due to nature of recruitment for NACC, BDR, and ADNI, individuals with normal cognition in these studies are likely not to be representative of the normal population. In addition, low numbers of individuals with normal cognition, including those with normal cognition and depressive symptoms, are likely to have limited the power of some of our analyses, particularly the analysis using the presence/absence of dementia as an interaction term to assess whether the risk factors for depressive symptoms differed between those with and without dementia. Numbers were especially low for those with normal cognition and depression in ADNI. This limits our conclusions on whether the risk factors for depressive symptoms truly differ between those with and without AD. While we have carried out some secondary, *post hoc* analyses we have clearly identified which analyses these were and have advised that the results be treated with caution until replicated.

Future work should include a more detailed examination of depression in AD in relation to vascular risk factors in larger cohorts or in a meta-analysis, examination of regional atrophy and examination of the genetic underpinnings of depression in AD.

To conclude, we have used data from three large cohorts to study depression in AD. We have identified that a past history of depression is the strongest risk factor for the development of depressive symptoms in AD.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

LS has no relevant conflicts of interest to disclose. She has previously received a travel award from the RCPsych/Gatsby Foundation and is the finance office for the Academic Faculty of the Royal College of Psychiatrists. She has received research funding in the past from the Mason Medical Research Foundation, the David Telling Charitable Trust, BRACE Alzheimer's Research and the British Neuropathological Society.

ML has no relevant conflicts of interest to disclose. He has received research funding from the MS Society, Parkinson's UK and the NIHR HTA.

JP has no relevant conflicts of interest to disclose.

During the last 3 years, Clive Ballard has received consulting fees from Acadia pharmaceutical company, AARP, Addex pharmaceutical company, Eli Lily, Enterin pharmaceutical company, GWPharm, H.Lundbeck pharmaceutical company, Novartis pharmaceutical company, Janssen Pharmaceuticals, Johnson and Johnson pharmaceuticals, Novo Nordisk pharmaceutical comapny, Orion Corp pharmaceutical company, Otsuka America Pharm Inc, Sunovion Pharm. Inc, Suven pharmaceutical company, Roche

DATA AVAILABILITY

The data used in this study was obtained from ADNI (www.loni.ucla.edu/ADNI), the NACC (https://naccdata.org/), and Dementia Platforms UK (https://portal.dementiasplatform.uk). Data is available free of charge to bona fide researchers who submit a research proposal.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/ADR-239000.

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