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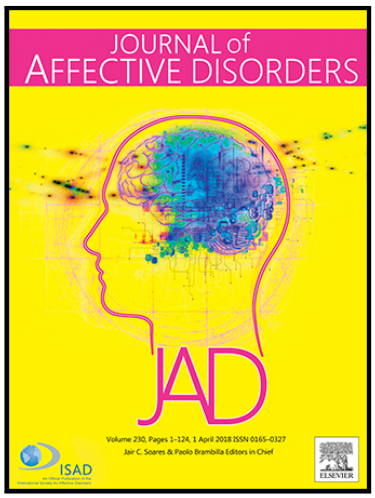

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Highlights:

- Previous psychiatric history increases the odds of depression in people with AD
- Cognitive and functional decline are associated with increased risk of onset of clinically significant symptoms of depression in AD, alongside younger age and neuroticism
- Future research should use either diagnostic criteria or instruments that are validated for depression in this population

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Investigation of possible risk factors for depression in Alzheimer's disease: A systematic review of the evidence

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Abstract

Background: Depression is common in people with Alzheimer's disease (AD), and is associated with increased risk of institutionalisation and mortality. Understanding risk factors for depression in AD is key to its development and treatment.

Methods: We searched the MEDLINE, EMBASE, PsycINFO, and CINAL databases for longitudinal prospective cohort studies that evaluated risk factors for depression in people with AD. Two authors independently selected articles for inclusion and assessed quality of studies using predetermined criteria.

Results: In seven studies that met the inclusion criteria, 2029 participants were followed up for a median of 5 years. Gender and educational attainment were not predictors of depression risk. History of a past psychiatric disorder and greater cognitive impairment predicted increased risk of depression in more than one study. In single studies, younger age, having a family history of psychiatric disorder, neuroticism, functional decline, presence of sleep disturbance and aggression, and increased cardiovascular risk predicted depression risk. Not being within 6 months of dementia onset and, counterintuitively having two comorbid disorders were protective factors in one study.

Limitations: A small number of studies exist overall and only a few have examined the same risk factors. Most of the studies have measured depression using scales that are not validated in AD.

Conclusions: These results inform a preliminary model of depression risk in people with AD. Unlike in the general population, men and women and those with higher and lower educational levels of attainment may be equally at risk of depression. Clinicians should be aware of these possible differences in the risk profile for depression in AD populations,

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to assist detection and enable early treatment. Interventions to delay cognitive and functional decline may reduce depression risk.

Key words: Alzheimer's disease; depression; depressive symptoms; risk factors; protective factors; vulnerability; affective symptoms; affective disorders

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1. Introduction

Alzheimer's disease (AD) is the most common form of dementia and a leading cause of disability in late life (Prince, et al, 2013). Despite cognitive symptoms being the hallmark of the disease, depression is common affecting around half of patients at some point during the illness (Di Iulio, et al, 2010). Systematic review data (Chi, et al, 2015) indicate that estimates of prevalence of major depression in Alzheimer's disease vary by diagnostic approaches, with estimates of 12.7% using DSM-IV criteria (American Psychiatric Association, 1994), versus rates of over 40% in studies employing criteria specific to AD (NIMH-dAD; National Institute of Mental Health – depression in AD; Olin, et al, 2002). Depression in AD is a heterogeneous disorder with differences in research methodology across studies contributing to the complexity of understanding aetiology, course of symptoms and treatment (Lee and Lyketsos, 2003).

Comorbid depression and AD decrease quality of life for people with dementia (Shin, et al, 2005), and are associated with greater impairment in activities of daily living (Starkstein, et al, 2005). Clinically significant symptoms of depression increase mortality (Suh, et al, 2005), moving into care (Lyketsos and Olin, 2002), carer burden and costs of care (Zhu and Sano, 2006). Identifying risk factors for depression can inform its early detection and prevention, reducing overall disability and care costs.

Theoretical models of depression in late life propose several interacting vulnerability factors (Fiske, et al, 2009); these include decline in health and function and early or mid-life depression (Fiske, et al, 2009). Consistent with this, longitudinal cohort studies of

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older people living in the community with no cognitive impairment show that chronic disease, functional disability, and psychiatric history increase risk of occurrence of depression (Vink, et al, 2008). Although these models are likely to be relevant to people with dementia, there may be important differences, such as dementia severity, insight, carer factors, and other neuropsychiatric symptoms.

We systematically review evidence reporting on risk factors for incidence of depression in people with AD. We reviewed prospective longitudinal research studies reporting demographic, psychosocial, and clinical risk factors for incident depression in people with AD. We also used this evidence to consider how existing explanatory models for the development of depression in older people might be modified for people with AD to inform future interventions.

2. Methods

2.1. Search strategy and selection of articles

We searched four databases, which included MEDLINE, EMBASE, PsycINFO, and CINAL, up until April 2017. Key search terms included Alzheimer's disease, dementia, depression, depress*, adjustments disorders, mood disorders, affective symptoms, dysthymic disorder, risk factor, risk reduction, vulnerability, and precipitating factors. For the full search term strategy, see Appendix 1. We included studies that met the following inclusion criteria: 1) prospective cohort studies, 2) the whole sample (or a separately analysed sub sample) had a diagnosis of AD (mainly clinical McKhann, et al, 1984), 3) depression diagnosis according to established clinical criteria or a valid and reliable measure assessing depressive symptoms in older people as study outcome (Burns, et al,

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2002). References of all relevant articles and systematic reviews were searched for any additional studies.

2.2. Analysis and assessment of quality of studies

We decided a priori to meta-analyse findings where at least three studies gave results sufficiently homogeneous to combine in a meta-analysis (i.e. used the same diagnostic criteria for depression). To determine the quality of articles, two authors (NS, VO) independently evaluated each study against specific criteria, based on a previous scale that was revised for this review (Tooth, et al, 2005). A study was judged as high quality if the following applied: a) the study reported on a well-defined and representative sample, with a response rate of at least 60%, b) reported a follow-up rate of at least 70%, and c) the criteria for measuring depression were valid (defined as clinical criteria or a validated scale of depression).

3. Results

3.1 Search articles

The search strategy yielded a total of 7,659 articles, of which seven papers met the inclusion criteria (see Figure 1 for details of search results). We found only a few studies using diagnostic criteria or a validated measure of depression. Not all of them provided sufficient data to perform a meta-analysis.

3.2 Description of Included studies

All studies were conducted in the United States or Europe. Three studies excluded individuals who were on antidepressants or had depression at baseline (Arbus, et al, 2011; Gilley, et al, 2004; Spalletta, et al, 2012). The mean age of participants ranged from 72.7 to 84.2 years. Three studies included only people with mild AD (Holtzer, et al, 2005;

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Spalletta, et al, 2012; Steinberg, et al, 2014) and the remaining studies included participants with mild to moderate AD. Two studies (Arbus, et al, 2011; Gilley, et al, 2004) excluded people with a MMSE > 10, and one study (Spalletta, et al, 2012) those with a MMSE > 18. Follow-up periods ranged from 1-14 years, and sample sizes from 133 to 686. Table 1 describes the sample populations, depression measure, follow-up duration and results of included studies. A list of all risk factors examined is presented in Table 2.

Depression diagnosis/assessment of depressive symptoms in included studies

Butt and Strauss, (2001) used DSM-IV criteria for depression (American Psychiatric Association, 1994), whereas the study by Spalletta, et al, (2012) reported depression diagnosis using the NIMH-dAD criteria (Olin, et al, 2002). Gilley, et al, (2004) used the 17-item Hamilton Rating Scale for Depression (HRS-D; Hamilton, 1960), and Holtzer, et al, (2005) the Columbia University Scale for Psychopathology in Alzheimer's disease (CUSPAD; Devanand, 1997). Arbus, et al, (2011), Garre-Olmo, et al, (2003) and Steinberg, et al, (2014) assessed depression using the Neuropsychiatric Inventory (NPI; (Cummings, et al, 1994).

Quality of studies

Quality ratings for each of the studies are reported in Table 3. Only one study met all of the quality criteria specified above and therefore could be rated as high quality (see Methods section for criteria for rating studies as higher quality).

Non-dementia specific factors

Sociodemographic factors: age, sex and education

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Age was assessed as a risk factor in four studies (Arbus, et al, 2011; Garre-Olmo, et al, 2003; Holtzer, et al, 2005; Spalletta, et al, 2012), with one study (Gilley, et al, 2004) reporting younger age to be a significant risk factor for depression (r= 0.092, SE= 0.031, *p*= 0.002). Although in the study by Garre-Olmo, et al, (2003) younger age increased risk, results were not significant (p = 0.055). Neither sex or education were associated with depression risk in any of the studies examining this.

Mental health and psychosocial factors

Personal psychiatric history

Butt and Strauss, (2001) and Garre-Olmo, et al, (2003) found that a personal history of any psychiatric disorder including depression increased odds of depression (using RDC/DSM-IV and NPI respectively). In the study by Butt and Strauss, (2001) prior depression increased odds by 2.89 (95% CI: 1.05-7.93), however baseline depression and antidepressant use were not reported. Garre-Olmo, et al, (2003) found previous psychiatric history to increase odds by 2.94 (chi square= 5.45; *df*= 1; $p < 0.05$; included people with and without depressive symptoms at baseline). In the study by Arbus, et al, (2011) that used the NPI prior depression was not predictive of risk. Use of antidepressants was not significantly associated with future depression risk in two studies (Holtzer, et al, 2005; Spalletta, et al, 2012).

Family history of depression and/or suicide and premorbid personality

Butt and Strauss, (2001) found depressive symptoms, along with suicide within the participants' immediate family increased odds of depression by 3.87 (95% CI: 1.51-9.58). Gilley, et al, (2004) assessed personality as a risk factor (Godberg Adjective Rating

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Scale; Goldberg, et al, 2006) and found neuroticism increased risk of depression (r= 0.149, SE= 0.051, *p*= 0.002). This study excluded participants with depression at baseline.

Dementia-specific risk factors

Cognitive and functional decline and neuropsychiatric symptoms

Spalletta, et al, (2012) and Gilley, et al, (2004) found lower MMSE scores (MMSE; Folstein, et al, 1975) to be significantly associated both with somatic symptoms of depression (HRS-D; effect size= 4.45) and emergence of symptoms (NIMH-dAD criteria; adjusted OR: 7.3; CI: 1.4-38.1). Holtzer, et al, (2005) and Garre-Olmo, et al, (2003) however found that cognitive scores was not a significant predictor of depression risk (used the MMSE and CAMDEX; Roth, et al, 1986 respectively).

Three studies assessed effects of daily function (Garre-Olmo, et al, 2003; Holtzer, et al, 2005; Spalletta, et al, 2012), with only one (Holtzer, et al, 2005) reporting an association between higher functional impairment, rated on the Blessed Dementia Rating Scale and depression risk (Odds ratio: 1.01; CI: 1.00-1.01). Baseline disability (RDRS-2; Rapid Disability Rating Scale; Linn and Linn, 1982) and basic and instrumental activities of daily living (ADL; Katz, et al, 1970; IADLS; Lawton and Brody, 1969) were not significant predictors in the remaining studies (Garre-Olmo, et al, 2003; Spalletta, et al, 2012).

One study tested the effects of neuropsychiatric symptoms (Arbus, et al, 2011), and found that agitation/aggression (RR= 1.96; CI: 1.19-3.23, *p*= 0.0078) and sleep disturbances (RR= 2.65; CI: 1.40-5.00, *p*= 0.00226) significantly increased risk of occurrence of depression. In this study the sample did not have depression/was on antidepressants at baseline.

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Dementia duration, comorbidity, health and other factors

A longer duration of AD (defined as greater than 6 months) was protective of depression in Arbus et al. (2011) (RR= 0.51; CI: 0.30-0.85, *p*= 0.0102), but duration of dementia did not predict depression in the remaining studies (Garre-Olmo, et al, 2003; Spalletta, et al, 2012; Steinberg, et al, 2014). Garre-Olmo et al. (2003) measured duration of disease in months and Spalletta, et al. (2012) in years, whereas in the study by Steinberg, et al. (2014) no details were provided. Having more than 2 comorbid conditions was found to be protective (RR= 0.45; CI: 0.24-0.83, *p*= 0.0115; Arbus, et al, 2011).

Cardiovascular risk was examined in two studies (Arbus, et al, 2011; Steinberg, et al, 2014) in which one of these reported that vascular risk was not a significant predictor of depression risk (Arbus, et al, 2011). Steinberg et al. (2014) examined a comprehensive set of factors via calculating a vascular index, and although the study found no individual factors affecting depression risk, use of hypertensive medications more than 4 times a week increased NPI affective scores (OR=1.29, *p* =0.05). Other medical conditions (diabetes, hypertension, cancer, and coronary artery disease), nutrition and carer burden were not significant predictors (Gilley, et al, 2004; Steinberg, et al, 2014).

4. Discussion

Summary of main findings

We conducted the first comprehensive systematic review of prospective studies investigating risk factors for depression in people with AD. In the seven studies that met our inclusion criteria, all of which recruited people with mild to moderate AD, only a history of a past psychiatric disorder and greater cognitive impairment predicted

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increased risk of depression in more than one study. In single studies, younger age, being within six months of dementia onset, having a family history of psychiatric disorder, neuroticism, functional decline, presence of sleep disturbance and aggression, and increased cardiovascular risk predicted increased depression risk. Counterintuitively having two comorbid disorders was a protective factor in one study. Two studies found that taking antidepressants did not protect against depression (Holtzer, et al, 2005; Spalletta, et al, 2012).

Our findings that gender and educational attainment were not associated with increased depression risk suggests that risk of depression may operate differently in AD populations compared with the general population (Lorant, et al, 2003; Rai, et al, 2013). By contrast, there was some indication that the relationship between age and depression risk may be similar to that in the general population. While results were inconsistent, two studies reported an association between younger age and increased depression risk that met or approached statistical significance (Garre-Olmo, et al, 2003; Gilley, et al, 2004). Similarly, general population studies have identified increasing age as a protective factor for depression, with an association between older age and resilience to psychological distress a putative cause of this relationship (Jorm, 2000). It may be that people developing dementia at a younger age experience greater distress due to implications for employment or family role expectations, or difficulty accessing services. Alternatively, a relationship between younger age and having early stage dementia may underlie this relationship (Arbus, et al, 2011; Gilley, et al, 2004); because people in the earlier stages of dementia may have more awareness of their illness.

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Arbus, et al, (2011) reported a greater risk of depressive symptoms in people who were within six months of receiving a diagnosis of AD. The same study also found that having more comorbidities present was associated with a decreased risk of depressive symptoms, a finding that might be explained by the lesser likelihood of physical comorbidity in people who were younger and at an earlier stage of their dementia illness.

Our findings that people with AD with a past psychiatric history, family psychiatric history and higher neuroticism are at increased risk of depression are comparable with those in older people without cognitive impairment (Fiske, et al, 2009). They are broadly in line with the model of depression risk postulated for older adults without dementia; that risk is associated with pre-existing vulnerability and onset of frailty (Fiske, et al, 2009; Jylha and Isometsa, 2006; Kendler, et al, 2006; Klein, et al, 2011). The onset of dementia may be conceptualised as a severe biological and emotional stress that is most likely to lead to depression in those with pre-existing vulnerability.

In the populations of people with mild to moderate AD studied, having greater cognitive impairment was predictive of depression. This probably reflects the increased brain pathological load and challenges to living independently with dementia experienced by those with more severe symptoms. The relationship between depressive symptoms and dementia is complex and bidirectional. People with mild cognitive impairment (MCI) are more likely to convert to AD if they have depressive symptoms (Cooper, et al, 2015). Treating depression may therefore improve functional status of people with AD, as well as delaying AD onset through improving functioning in people with MCI.

Experiencing agitation and aggression, and sleep disturbances increased odds of depression in one study (Arbus, et al, 2011). Agitation and aggressive behavior (along

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with psychosis) have been estimated to occur in 75% of patients, accelerating poor outcomes, increasing dependence, and stress for relatives (Lyketsos and Olin, 2002; Zahodne, et al, 2015). Although limited, these findings indicate that preventing specific neuropsychiatric symptoms such as agitation and sleep disturbances may help treat depression (Lee, et al, 2013).

5. Limitations and future research

Three of the included studies recruited people with mild AD, while four studies involved people with mild to moderate AD. Depression may be more frequent, or more frequently diagnosed in mild AD and risk factors for depression may differ according to dementia severity (Fritze, et al, 2011; Holtzer, et al, 2005). Our findings therefore may not be generalisable to people with more severe dementia, in whom measuring depression may be particularly challenging due to anosognosia and difficulty completing questionnaires. The use of depression scales that are less sensitive to measuring depressive symptoms in AD is a further limitation (Mayer, et al, 2006).

We found few longitudinal studies investigating possible demographic and psychosocial risk factors for depression in AD. The included studies used different diagnostic criteria, follow-up periods and outcome scales, and this lack of homogeneity is a limitation of our review. Most studies are cross-sectional, limiting conclusions of contributions of risk to the incidence of depression.

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6. Conclusions

Our results provide preliminary data to inform a model of depression risk in people with AD; our findings could suggest that previous history of depression is a marker of vulnerability to depression, that may be exacerbated by the brain changes of dementia, or by the psychosocial stresses associated with having dementia, that worsen throughout the mild and moderate stages of the illness. Unlike in the general population, existing studies indicate that men and women and those with higher and lower educational levels of attainment may be equally at risk of depression. Clinicians should be aware of these possible differences in the risk profile for depression in AD populations, to assist detection and enable early treatment. Further studies in the area are warranted.

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Contributors: VO and CC developed the idea for the study. NS VO and CC created the inclusion criteria and reviewed articles. NS, CC, and VO wrote the manuscript. CC led methodological advice. NS, VO, and CC created the quality assessment tool, and revised the paper, all Figures, and Tables. All authors contributed to and read the final manuscript.

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Figure 1. Study Flow diagram

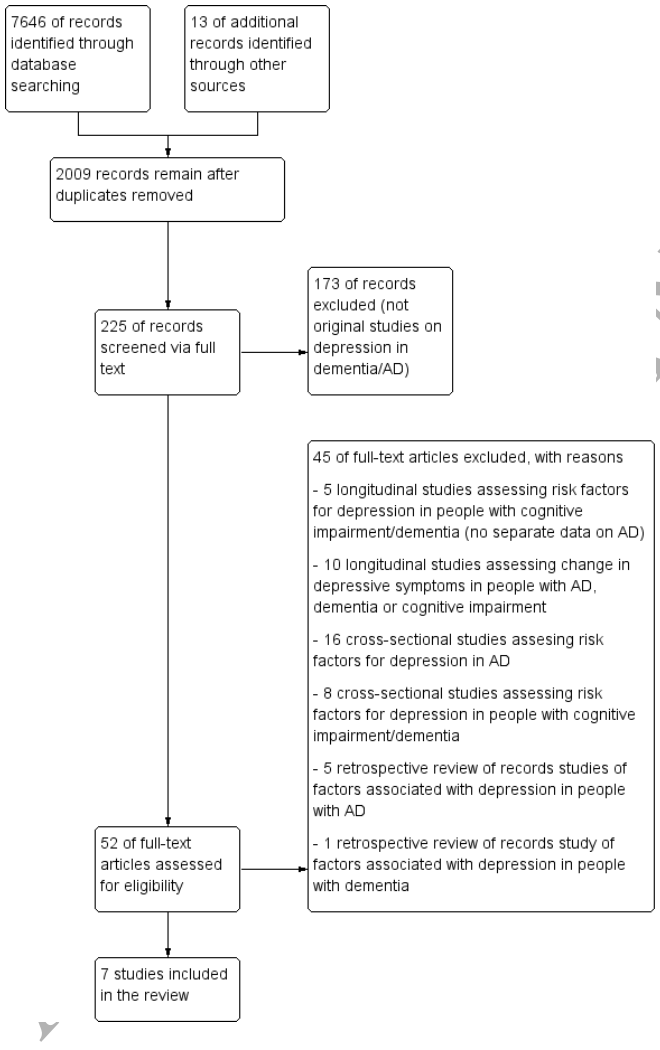

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Table 1 Descriptive characteristics of included studies (prospective longitudinal)

Study	Sample	Follow up (years)	N at baseline	% follow up	Diagnosis of depression/instrument used	Predictors of outcome/summary statistics	Variables controlled for in analyses
Studies using diagnostic criteria or a standardised instrument of depression							
Butt & Strauss, 2001	Recruited from AD research registry, USA Inclusion criteria: -probable/possible mild to moderate AD (NINCDS-ADRDA and DSM-III-R) -living in the community	Yearly follow-ups (around 3 years)	161	Not reported	RDC & DSM-IV	- Family history of depression/suicide (Family History Research Diagnostic criteria) (OR= 3.87, 95% CI:1.51-9.58) - Prior personal history of depression (RDC & DSM-IV) (OR=2.89, 95% CI: 1.05-7.93)	-age -sex -education -duration of illness -MMSE
Spalletta 2012	Recruited from memory clinics, Italy Inclusion criteria: - mild AD (NINCDS-ADRDA; MMSE < 18; CDR < 1) -having a carer -no medical illness/psychiatric disorder	1 year	133	89%	Modified DSM-IV for MDE in AD (Olin et al, 2002)	-Lower MMSE scores (Adjusted: OR=7.3, CI: 1.4-38.1)	-sex -age -education -antidepressants -age at onset -disease duration -baseline MMSE -baseline & follow-up apathy -AChEI dosage -ADL -IADL

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Gilley 2004	Recruited from an AD center, USA Inclusion criteria: - mild to moderate AD (NINCDS-ADRDA; MMSE < 10) * reports separate analyses of people with no depressive symptoms at baseline	4 years (once every year)	410	88% for year 1	HRS-D Total	- Higher neuroticism (Godberg Adjective Rating Scale) -Neuroticism: (Coefficient= 0.129, SE= 0.053, *p*=.013 - Lower MMSE scores -MMSE scores: Coefficient= -0.081, SE= 0.026, *p*=.003 - Younger age - Age: Coefficient= -0.061, SE=0.029, *p*=.036)	-sex (*male gender predicted somatic symptoms only) -race -chronic conditions -previous psychiatric history
Holtzer 2005	Recruited via memory research centers/general hospital, Europe & USA Inclusion criteria: -Mild probable AD (NINCDS-ADRDA) -19-21% were on antidepressants * separate analyses of those with no depressive symptoms at baseline	14 years (every 6 months)	536	94.5% (24.2% had a complete 5 year follow-up)	CUSPAD	-Lower function (BDRS scores) (OR=1.01; CI: 1.00-1.01, *p* <.001)	-sex -age -education -antidepressants -other health conditions -MMSE
Studies using the Neuropsychiatric Inventory							
Garre-Olmo 2003 EDAC study	Recruited from memory hospitals, Spain Inclusion criteria: - mild to moderate AD	1 year	150	Not reported	NPI	- Previous psychiatric history (CAMDEX) Chi square= 2.05; *df*= 1; *p* < 0.05) (OR: 3.70)	-sex -age -education -time since onset of AD

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	(NINCDS-ADRDA) - living with carer * included people with depressive symptoms at baseline						-baseline cognition (CAMCOG) -baseline disability (RDRS-2) -baseline NPI
Arbus 2011 REAL.FR study	Recruited from AD research centers France Inclusion criteria: -mild to moderate AD (NINCDS-ADRDA & DSM-IV, MMSE range 10-26) -living with carer *no depressive symptoms/ antidepressants at baseline	4 years (every 6 months)	312	71.6% over 4 years	NPI	- Agitation/aggression (RR= 1.96; CI: 1.19-3.23, *p*=0.0078) - Sleep disturbances (RR=2.65; CI: 1.40-5.00, *p*=0.0026) *Protective factors* - Longer duration of disease (over 6 months) (RR=0.51; CI: 0.30-0.85, *p*= 0.0102) -Number of comorbid conditions (2+ comorbid conditions) (RR=0.45; CI: 0.24-0.83, *p*=0.0115)	-sex -age -education -living arrangement -caregiver status -time since diagnosis -history of depression -cardiovascular risk -MMSE -caregiver burden -nutritional status
Steinberg 2014 Cache County Study	Recruited permanent residents of Cache County Utah, USA Inclusion criteria: -Mild AD (NINCDS-ADRDA) - ≥ 65 years *included people with depressive symptoms at baseline	11 years (assessed in three waves)	327	68% across years	NPI Affective symptoms cluster score (only affective cluster and total scores were examined)	-Use of antihypertensive medication (≤ 4x per week) (OR=1.29, *p*=0.05)	-sex -education -age at onset -dementia duration -APOE genotype

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Notes. NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders; RDC: Research Diagnostic Criteria; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; MMSE: Mini Mental State Examination; CDR: Clinical Dementia Rating; MDE: Major Depressive Episode; AChEI: Acetylcholinestaerase inhibitors; ADL: Activities of daily living; IADL: Instrumental activities of daily living; HRSD: Hamilton Rating Scale Depression; CUSBAD: Columbia Scale for Psychopathology in Alzheimer's Disease; BDRS: Blessed Dementia Rating Scale; NPI: Neuropsychiatric Inventory; CAMDEX: Cambridge Mental Disorders of the Elderly Examination criteria; RDRS-2: Rapid Disability Rating Scale.

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Table 2
Risk factors examined in included studies

	Sociodemographic factors			Mental health factors				Disease specific factors					Physical health factors	
	Age	Sex	Education	Past Psychiatric history	Familial psychiatric history	Neuroticism	Anti-depressants	Cognitive scores	Function	Sleep Disturbances	Aggression/Agitation	Time since onset/ dementia duration	Cardio-vascular risk	Other health conditions
Diagnosis/standardised instrument														
Butt & Strauss 2001		0	0	+	+									
Spalletta 2012	0	0	0				0	+	0			0		
Gilley 2004	+	0				+		+						0
Holtzer 2005	0	0	0				0	0	+					0
Neuropsychiatric inventory														
Garre-Olmo 2003		0	0	+				0	0			0		
Arbus 2011	0	0	0	0						+	+	-	0	-

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Steinberg 2014	0	0			0	+

A plus sign indicates a risk factor; a minus sign indicates a protective factor; a zero sign indicates the factor was not significant.

Table 3 Quality assessment of included studies

Quality Assessment	Representative population and response rate < 60% eligible participants	At least 70% follow up	Valid outcome measure
Study			
Butt & Strauss 2001	No	Not Specified	Yes - DSM-IV
Spalletta 2012	No	Yes	Yes - DSM-IV for MDE in AD
Gilley 2004	Yes - Response rate: 83%	Yes	Yes - HRSD
Holtzer 2005	Yes - Response rate: not specified	Yes	Yes – CUSPAD
Garre-Olmo 2003	Yes - Response rate: 71.8%	Yes	No – NPI
Arbus 2011	Yes - Response rate: not specified	Yes	No – NPI
Steinberg 2014	Yes - Response rate: 90%	No (68% follow up)	No - NPI

Note: DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; HRSD: Hamilton Depression Rating Scale; CUSPAD: Columbia University Scale for Psychopathology in Alzheimer's Disease; NPI: Neuropsychiatric Inventory.

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