

Investigation of possible risk factors for depression in Alzheimer's disease

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

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Total number of words: **2,705**

Number of words in the abstract: **279**

Number of Figures: **2**

Number of Tables: **4**

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

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populations, 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*, adjustment 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 Scale; Goldberg, et al, 2006) and found neuroticism increased risk of depression ($r=$

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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.

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

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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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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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Role of funding source: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

Conflict of interest: All authors report no conflict of interest.

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.

Acknowledgments: We would like to thank the Alzheimer's Society who is funding Dr. Vasiliki Orgeta. Dr Claudia Cooper and Dr Vasiliki Orgeta are supported by the UCLH NIHR Biomedical Research Centre.

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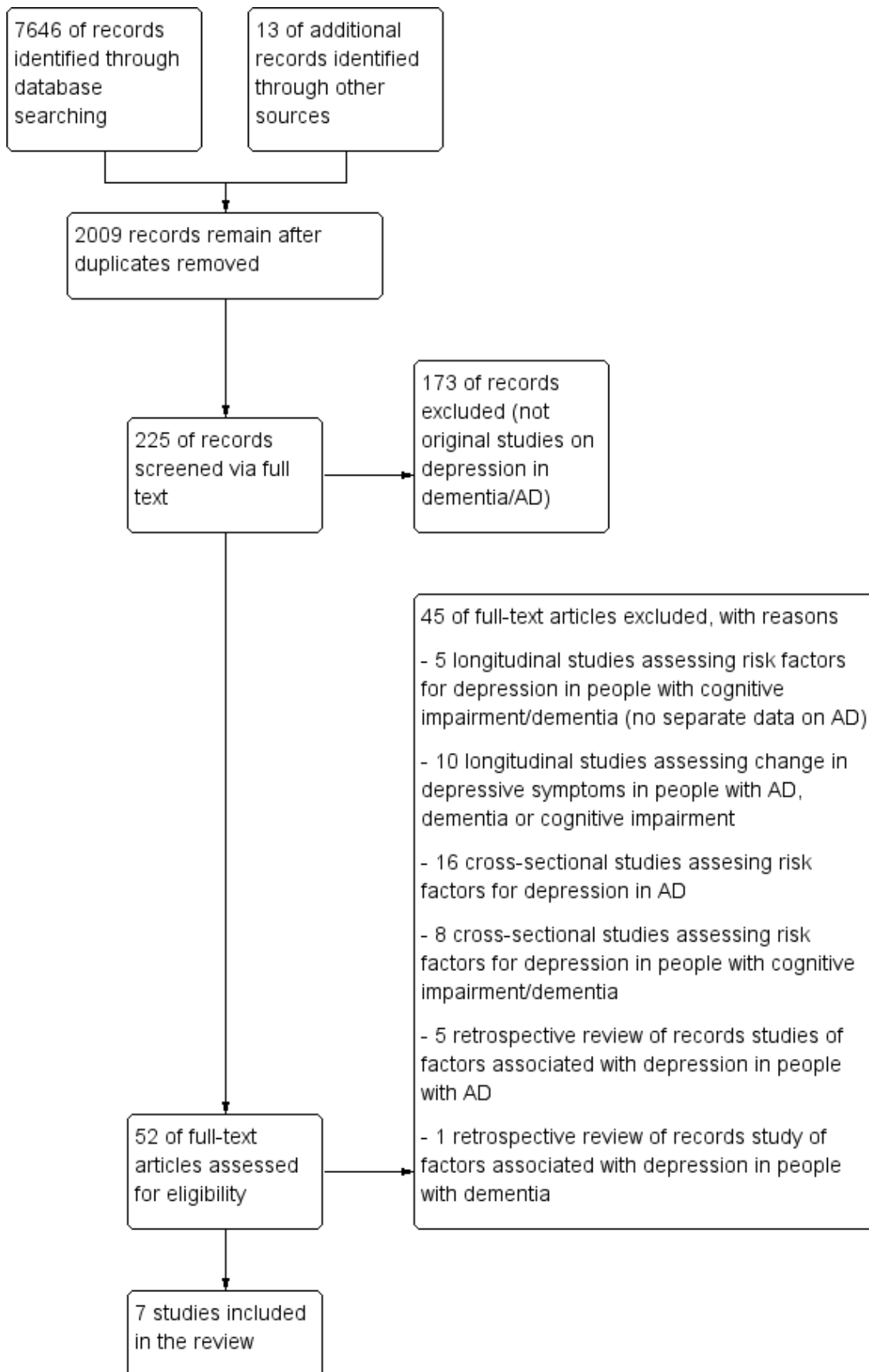
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Figure 1. Study Flow diagram

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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
<i>Studies using diagnostic criteria or a standardised instrument of depression</i>							
Butt & Strauss, 2001	Recruited from AD research registry, USA <u>Inclusion criteria:</u> -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 <u>Inclusion criteria:</u> - 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
Gilley 2004	Recruited from an AD center, USA <u>Inclusion criteria:</u>	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, $p=.013$)	-sex (*male gender predicted somatic symptoms only) -race -chronic conditions

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- mild to moderate AD (NINCDS-ADRDA; MMSE < 10)
* reports separate analyses of people with no depressive symptoms at baseline

- Lower MMSE scores
-MMSE scores: Coefficient= -0.081, SE= 0.026, $p=.003$

- Younger age
- Age: Coefficient= -0.061, SE=0.029, $p=.036$

-previous psychiatric history

Holtzer 2005 Recruited via memory research centers/general hospital, Europe & USA 14 years (every 6 months) 536 94.5% (24.2% had a complete 5 year follow-up) CUSPAD

Inclusion criteria:
-Mild probable AD (NINCDS-ADRDA)
-19-21% were on antidepressants
* separate analyses of those with no depressive symptoms at baseline

-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 Recruited from memory hospitals, Spain 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
-baseline cognition (CAMCOG)
-baseline disability (RDRS-2)
-baseline NPI

EDAC study - mild to moderate AD (NINCDS-ADRDA)
- living with carer
* included people with depressive symptoms at baseline

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Arbus 2011	Recruited from AD research centers France	4 years (every 6 months)	312	71.6% over 4 years	NPI	- Agitation/aggression (RR= 1.96; CI: 1.19-3.23, $p=0.0078$)	-sex -age -education
REAL.FR study	<u>Inclusion criteria:</u> -mild to moderate AD (NINCDS-ADRDA & DSM-IV, MMSE range 10- 26) -living with carer *no depressive symptoms/ antidepressants at baseline					- Sleep disturbances (RR=2.65; CI: 1.40-5.00, $p=0.0026$) <i>Protective factors</i> - 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, $p=0.0115$)	-living arrangement -caregiver status -time since diagnosis -history of depression -cardiovascular risk -MMSE -caregiver burden -nutritional status
Steinberg 2014	Recruited permanent residents of Cache County Utah, USA	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 ($\leq 4x$ per week) (OR=1.29, $p=0.05$)	-sex -education -age at onset -dementia duration -APOE genotype
Cache County Study	<u>Inclusion criteria:</u> -Mild AD (NINCDS- ADRDA) - ≥ 65 years *included people with depressive symptoms at baseline						

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: Acetylcholinesterase 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
<i>Diagnosis/standardised instrument</i>													
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
<i>Neuropsychiatric inventory</i>													
Garre-Olmo 2003	0	0	+				0	0			0		
Arbus 2011	0	0	0	0					+	+	-	0	-
Steinberg 2014	0	0									0	+	

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

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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
<i>Study</i>			
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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Supplementary data Appendix 1: Table of Excluded Studies

	Studies	Reason for exclusion
1	McCusker 2014	Observational prospective study of risk factors for depression in older people in long-term care facilities (of which some had cognitive impairment, no separate data on AD)
2	Boorsma 2012	Naturalistic cohort study of risk factors of depression in older people living in nursing and residential care homes (of which some had a diagnosis of dementia, no separate data on AD)
3	Garavello 2010	Retrospective study looking at medical records with a follow-up stage on depression in AD comparing those with or without depression on measures of cognition, function and caregiver stress
4	Bangen 2010	Cross sectional study of the association of stroke risk and cognition in people with AD with or without depression
5	Wilson 2010	Longitudinal study of change in depressive symptoms in AD; did not examine risk factors
6	Chan 2008	Cross-sectional analysis of risk factors for clinically significant symptoms of depression in older people with mild forms of cognitive impairment
7	Wilson 2008	Longitudinal analysis of change of depressive symptoms in AD; did not examine risk factors
8	Savva 2009	Longitudinal study of risk factors of behavioral and psychological symptoms of dementia (no separate data on AD)
9	Steinberg 2006	Longitudinal study of risk factors of neuropsychiatric symptoms in people with dementia (no separate data on AD)
10	Van Winkel 2006	Cross-sectional study of risk factors for depression in AD
11	Bowirrat 2006	Cross-sectional study of factors associated with depressive symptoms in AD
12	Regan 2005	Cross-sectional study of exercise and other risk factors associated with depressive symptoms in AD

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13	Dorenlot 2005	Longitudinal study assessing the association of major depression as a risk factor for institutionalisation in people with dementia
14	Kim 2002	Cross-sectional study on stroke and vascular risk factors for depression in cognitively impaired older people
15	Harwood 2000	Cross-sectional study of factors associated with depressive symptoms in AD
16	Liu 1999	Cross-sectional study of factors associated with depression in AD
17	Li 2001a	Longitudinal study of change in depressive symptoms in cognitively impaired older people
18	Li 2001b	Cross-sectional study of factors associated with depressive symptoms in AD
19	Morawetz 1996	Cross-sectional study of risk factors associated with depressive symptoms in people with cognitive impairment and dementia
20	Giebel 2015	Cross-sectional study of risk factors associated with depressive symptoms in people with severe dementia
21	Harwood 2000	Cross-sectional study of clinical correlates of depression and psychosis in AD
22	Borza 2015	Longitudinal study of factors associated with change in depressive symptoms in nursing home residents of which most had dementia (no separate data on AD)
23	Bidzan 2014	Cross-sectional study comparing AD patients with mild vascular pathology vs severe vascular pathology in neuropsychiatric symptoms
24	Thielscher 2013	Longitudinal study of risk factors of developing depression in patients with neurological diseases including dementia (no separate data on AD)
25	Majic 2012	Cross-sectional study examining correlates of depression in nursing home residents with dementia
26	Bergdahl 2011	Cross-sectional study of factors associated with depression among very old people with dementia
27	Lovheim 2009	Cross-sectional study examining the association between gender and depressive symptoms in people with dementia

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28	Archer 2007	Cross-sectional study of the association of premorbid personality and depressive symptoms in AD
29	Steffens 2005	Cross-sectional study of the association of preexisting medical conditions and neuropsychiatric symptoms in AD and dementia
30	Chan 2003	Cross-sectional study of correlates of depressive symptoms in people with dementia
31	Janzing 2000	Longitudinal study of depression in nursing home residents with and without dementia (no separate data on AD) investigating the influence of baseline diagnosis on outcome of depression
32	Harwood 1999	Cross-sectional study investigating premorbid history of depression as a risk for depression in AD
33	Jost 1996	Retrospective medical records review study on evolution of psychiatric symptoms in AD but not investigating risk factors
34	Migliorelli 1995	Cross-sectional study of risk factors for depression in AD
35	Pearlson 1990	Retrospective medical review charts study of association of family history of depression with depression in AD
36	Maxwell 2014	Longitudinal study investigating the correlates of persistent symptoms of depression in people living with dementia in care homes
37	Ponomareva 2014	Longitudinal study of development of AD with and without depressive disorder; did not evaluate risk factors
38	Anor 2014	Cross-sectional study of the association of neuropsychiatric symptoms with hypertension, hypercholesterolemia, and diabetes in AD
39	Zubenko 1996	Cross-sectional study examining the association of premorbid rates of major depression and concurrent syndrome of depression in inpatients with AD
40	Carpenter 1995	Retrospective review of medical charts on the prevalence of personal history of depression in people with major depression and AD versus major depression but no dementia

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41	Stroud 2008	Retrospective charts review of the association of health-related and social factors with depressive symptoms in people with cognitive impairment and dementia
42	Moon 2014	Retrospective review of medical charts examining the association of vascular risk factors and neuropsychiatric symptoms (including depressive symptoms) in AD
43	Apostolova 2014	Cross-sectional study of risk factors for neuropsychiatric symptoms (including depressive symptoms) in AD
44	Klugman 2009	Retrospective review of medical notes examining the association of cerebrovascular pathology and depressive symptoms in AD
45	Barca 2017	Longitudinal study of progression of Alzheimer's disease examining trajectories of depressive symptoms; did not examine risk factors

Supplementary data Appendix 1 Search Strategy

Medline search strategy

1. exp Alzheimer Disease/
2. Alzheimer Disease.mp. [mp]
3. exp Dementia/
4. Dementia.mp. [mp]
5. Depress*.mp.
6. exp Depressive Disorder/ or exp Dysthymic Disorder/ or exp Depressive Disorder, Major/
7. exp Adjustment Disorders/
8. exp Mood Disorders/
9. exp Affective Symptoms/
10. exp Depressive Disorder, Major/
11. depressive disorder.mp. [mp]
12. dysthymic disorder.mp. [mp]
13. exp Risk Factors/
14. Risk reduction.mp. [mp]
15. Risk factor*.mp. [mp]
16. exp Risk Reduction Behavior/
17. Vulnerability.mp.
18. exp Precipitating Factors/