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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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.
Investigation of possible risk factors for depression in Alzheimer’s disease 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).


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*


*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.
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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**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.

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References


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Figure 1. Study Flow diagram
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7646 of records identified through database searching

13 of additional records identified through other sources

2009 records remain after duplicates removed

173 of records excluded (not original studies on depression in dementia/AD)

225 of records screened via full text

45 of full-text articles excluded, with reasons:
- 5 longitudinal studies assessing risk factors for depression in people with cognitive impairment/dementia (no separate data on AD)
- 10 longitudinal studies assessing change in depressive symptoms in people with AD, dementia or cognitive impairment
- 16 cross-sectional studies assessing risk factors for depression in AD
- 8 cross-sectional studies assessing risk factors for depression in people with cognitive impairment/dementia
- 5 retrospective review of records studies of factors associated with depression in people with AD
- 1 retrospective review of records study of factors associated with depression in people with dementia

52 of full-text articles assessed for eligibility

7 studies included in the review
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## Table 1 Descriptive characteristics of included studies (prospective longitudinal)

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Follow up (years)</th>
<th>N at baseline</th>
<th>% follow up</th>
<th>Diagnosis of depression/instrument used</th>
<th>Predictors of outcome/summary statistics</th>
<th>Variables controlled for in analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butt &amp; Strauss, 2001</td>
<td>Recruited from AD research registry, USA</td>
<td>Yearly follow-ups (around 3 years)</td>
<td>161</td>
<td>Not reported</td>
<td>RDC &amp; DSM-IV</td>
<td>- 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 &amp; DSM-IV) (OR=2.89, 95% CI: 1.05-7.93)</td>
<td>-age -sex -education -duration of illness -MMSE</td>
</tr>
<tr>
<td>Spalletta 2012</td>
<td>Recruited from memory clinics, Italy</td>
<td>1 year</td>
<td>133</td>
<td>89%</td>
<td>Modified DSM-IV for MDE in AD (Olin et al, 2002)</td>
<td>-Lower MMSE scores (Adjusted: OR=7.3, CI: 1.4-38.1)</td>
<td>-sex -age -education -antidepressants -age at onset -disease duration -baseline MMSE -baseline &amp; follow-up apathy -AChEI dosage -ADL -IADL</td>
</tr>
<tr>
<td>Gilley 2004</td>
<td>Recruited from an AD center, USA</td>
<td>4 years (once every year)</td>
<td>410</td>
<td>88% for year 1</td>
<td>HRS-D Total</td>
<td>- Higher neuroticism (Godberg Adjective Rating Scale) -Neuroticism: (Coefficient= 0.129, SE= 0.053, p=.013)</td>
<td>-sex (*male gender predicted somatic symptoms only) -race -chronic conditions</td>
</tr>
</tbody>
</table>
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- mild to moderate AD (NINCDS-ADRDA; MMSE < 10)
  * reports separate analyses of people with no depressive symptoms at baseline

**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
  - Lower MMSE scores
    - MMSE scores: Coefficient= -0.081, SE= 0.026, \( p =.003 \)
  - Younger age
    - Age: Coefficient= -0.061, SE=0.029, \( p=.036 \)

- Lower function (BDRS scores)
  - (OR=1.01; CI: 1.00-1.01, \( p <.001 \))
- Previous psychiatric history
- sex
- age
- education
- antidepressants
- other health conditions
- MMSE

**Studies using the Neuropsychiatric Inventory**

**Garre-Olmo 2003**
- Recruited from memory hospitals, Spain
- Inclusion criteria:
  - mild to moderate AD (NINCDS-ADRDA)
  - living with carer
  * included people with depressive symptoms at baseline
  - 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**
- 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

- Lower MMSE scores
  - MMSE scores: Coefficient= -0.081, SE= 0.026, \( p =.003 \)
- Younger age
  - Age: Coefficient= -0.061, SE=0.029, \( p=.036 \)

- Lower function (BDRS scores)
  - (OR=1.01; CI: 1.00-1.01, \( p <.001 \))
- Previous psychiatric history
- sex
- age
- education
- antidepressants
- other health conditions
- MMSE
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<table>
<thead>
<tr>
<th>Study</th>
<th>Recruitment</th>
<th>Inclusion Criteria</th>
<th>Follow-up</th>
<th>NPI</th>
<th>Protective Factors</th>
<th>NPI Affective Symptoms Cluster Score</th>
<th>Use of Antihypertensive Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arbus 2011</strong></td>
<td>Recruited from AD research centers, France</td>
<td>Inclusion criteria:  - mild to moderate AD (NINCDS-ADRDA &amp; DSM-IV, MMSE range 10-26)  - living with carer  *no depressive symptoms/antidepressants at baseline</td>
<td>4 years (every 6 months)</td>
<td>312</td>
<td>71.6% over 4 years</td>
<td>NPI</td>
<td>Agitation/aggression (RR= 1.96; CI: 1.19-3.23, ( p=0.0078 ))</td>
</tr>
<tr>
<td><strong>REAL.FR study</strong></td>
<td>Recruited from AD research centers, France</td>
<td>Inclusion criteria:  - mild to moderate AD (NINCDS-ADRDA &amp; DSM-IV, MMSE range 10-26)  - living with carer  *no depressive symptoms/antidepressants at baseline</td>
<td>4 years (every 6 months)</td>
<td>312</td>
<td>71.6% over 4 years</td>
<td>NPI</td>
<td>Sleep disturbances (RR=2.65; CI: 1.40-5.00, ( p=0.0026 ))</td>
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<tr>
<td><strong>Steinberg 2014</strong></td>
<td>Recruited permanent residents of Cache County, Utah, USA</td>
<td>Inclusion criteria:  - Mild AD (NINCDS-ADRDA)  - ( \geq 65 ) years  * included people with depressive symptoms at baseline</td>
<td>11 years (assessed in three waves)</td>
<td>327</td>
<td>68% across years</td>
<td>NPI Affective symptoms cluster score (only affective cluster and total scores were examined)</td>
<td>Use of antihypertensive medication (( \leq 4 )x per week) (OR=1.29, ( p=0.05 ))</td>
</tr>
<tr>
<td><strong>Cache County Study</strong></td>
<td>Recruited permanent residents of Cache County, Utah, USA</td>
<td>Inclusion criteria:  - Mild AD (NINCDS-ADRDA)  - ( \geq 65 ) years  * included people with depressive symptoms at baseline</td>
<td>11 years (assessed in three waves)</td>
<td>327</td>
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<td>NPI Affective symptoms cluster score (only affective cluster and total scores were examined)</td>
<td>Use of antihypertensive medication (( \leq 4 )x per week) (OR=1.29, ( p=0.05 ))</td>
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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: 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

<table>
<thead>
<tr>
<th>Sociodemographic factors</th>
<th>Mental health factors</th>
<th>Disease specific factors</th>
<th>Physical health factors</th>
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<tbody>
<tr>
<td>Age</td>
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<td>Sex</td>
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<td>Education</td>
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<td>Past psychiatric history</td>
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<td>Familial psychiatric history</td>
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<td>Neuroticism</td>
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<td>Antidepressants</td>
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<td>Cognitive scores</td>
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<tr>
<td>Function</td>
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<tr>
<td>Sleep Disturbances</td>
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<tr>
<td>Aggression/Agitation</td>
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<td>Time since onset/dementia duration</td>
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<tr>
<td>Cardiovascular risk</td>
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<td>Other health conditions</td>
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Diagnosis/standardised instrument

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<th>Age</th>
<th>Sex</th>
<th>Education</th>
<th>Past psychiatric history</th>
<th>Familial psychiatric history</th>
<th>Neuroticism</th>
<th>Antidepressants</th>
<th>Cognitive scores</th>
<th>Function</th>
<th>Sleep Disturbances</th>
<th>Aggression/Agitation</th>
<th>Time since onset/dementia duration</th>
<th>Cardiovascular risk</th>
<th>Other health conditions</th>
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<tr>
<td>Butt &amp; Strauss 2001</td>
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<td>Garre-Olmo 2003</td>
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<td>Arbus 2011</td>
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</tbody>
</table>
Investigation of possible risk factors for depression in Alzheimer’s disease

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

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

*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.*
**Supplementary data Appendix 1: Table of Excluded Studies**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 McCusker 2014</td>
<td>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)</td>
</tr>
<tr>
<td>2 Boorsma 2012</td>
<td>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)</td>
</tr>
<tr>
<td>3 Garavello 2010</td>
<td>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</td>
</tr>
<tr>
<td>4 Bangen 2010</td>
<td>Cross sectional study of the association of stroke risk and cognition in people with AD with or without depression</td>
</tr>
<tr>
<td>5 Wilson 2010</td>
<td>Longitudinal study of change in depressive symptoms in AD; did not examine risk factors</td>
</tr>
<tr>
<td>6 Chan 2008</td>
<td>Cross-sectional analysis of risk factors for clinically significant symptoms of depression in older people with mild forms of cognitive impairment</td>
</tr>
<tr>
<td>7 Wilson 2008</td>
<td>Longitudinal analysis of change of depressive symptoms in AD; did not examine risk factors</td>
</tr>
<tr>
<td>8 Savva 2009</td>
<td>Longitudinal study of risk factors of behavioral and psychological symptoms of dementia (no separate data on AD)</td>
</tr>
<tr>
<td>9 Steinberg 2006</td>
<td>Longitudinal study of risk factors of neuropsychiatric symptoms in people with dementia (no separate data on AD)</td>
</tr>
<tr>
<td>10 Van Winkel 2006</td>
<td>Cross-sectional study of risk factors for depression in AD</td>
</tr>
<tr>
<td>11 Bowirrat 2006</td>
<td>Cross-sectional study of factors associated with depressive symptoms in AD</td>
</tr>
<tr>
<td>12 Regan 2005</td>
<td>Cross-sectional study of exercise and other risk factors associated with depressive symptoms in AD</td>
</tr>
</tbody>
</table>
Investigation of possible risk factors for depression in Alzheimer’s disease

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year</th>
<th>Methodology</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Dorenlot 2005</td>
<td>Longitudinal study</td>
<td>Assessing the association of major depression as a risk factor for institutionalisation in people with dementia</td>
</tr>
<tr>
<td>14</td>
<td>Kim 2002</td>
<td>Cross-sectional study</td>
<td>On stroke and vascular risk factors for depression in cognitively impaired older people</td>
</tr>
<tr>
<td>15</td>
<td>Harwood 2000</td>
<td>Cross-sectional study</td>
<td>Of factors associated with depressive symptoms in AD</td>
</tr>
<tr>
<td>16</td>
<td>Liu 1999</td>
<td>Cross-sectional study</td>
<td>Of factors associated with depression in AD</td>
</tr>
<tr>
<td>17</td>
<td>Li 2001a</td>
<td>Longitudinal study</td>
<td>Of change in depressive symptoms in cognitively impaired older people</td>
</tr>
<tr>
<td>18</td>
<td>Li 2001b</td>
<td>Cross-sectional study</td>
<td>Of factors associated with depressive symptoms in AD</td>
</tr>
<tr>
<td>19</td>
<td>Morawetz 1996</td>
<td>Cross-sectional study</td>
<td>Of risk factors associated with depressive symptoms in people with cognitive impairment and dementia</td>
</tr>
<tr>
<td>20</td>
<td>Giebel 2015</td>
<td>Cross-sectional study</td>
<td>Of risk factors associated with depressive symptoms in people with severe dementia</td>
</tr>
<tr>
<td>21</td>
<td>Harwood 2000</td>
<td>Cross-sectional study</td>
<td>Of clinical correlates of depression and psychosis in AD</td>
</tr>
<tr>
<td>22</td>
<td>Borza 2015</td>
<td>Longitudinal study</td>
<td>Of factors associated with change in depressive symptoms in nursing home residents of which most had dementia (no separate data on AD)</td>
</tr>
<tr>
<td>23</td>
<td>Bidzan 2014</td>
<td>Cross-sectional study</td>
<td>Comparing AD patients with mild vascular pathology vs severe vascular pathology in neuropsychiatric symptoms</td>
</tr>
<tr>
<td>24</td>
<td>Thielscher 2013</td>
<td>Longitudinal study</td>
<td>Of risk factors of developing depression in patients with neurological diseases including dementia (no separate data on AD)</td>
</tr>
<tr>
<td>25</td>
<td>Majic 2012</td>
<td>Cross-sectional study</td>
<td>Examining correlates of depression in nursing home residents with dementia</td>
</tr>
<tr>
<td>26</td>
<td>Bergdahl 2011</td>
<td>Cross-sectional study</td>
<td>Of factors associated with depression among very old people with dementia</td>
</tr>
<tr>
<td>27</td>
<td>Lovheim 2009</td>
<td>Cross-sectional study</td>
<td>Examining the association between gender and depressive symptoms in people with dementia</td>
</tr>
</tbody>
</table>
## Investigation of possible risk factors for depression in Alzheimer’s disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methodology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>28 Archer 2007</td>
<td>Cross-sectional study</td>
<td>of the association of premorbid personality and depressive symptoms in AD</td>
</tr>
<tr>
<td>29 Steffens 2005</td>
<td>Cross-sectional study</td>
<td>of the association of preexisting medical conditions and neuropsychiatric symptoms in AD and dementia</td>
</tr>
<tr>
<td>30 Chan 2003</td>
<td>Cross-sectional study</td>
<td>of correlates of depressive symptoms in people with dementia</td>
</tr>
<tr>
<td>31 Janzing 2000</td>
<td>Longitudinal study</td>
<td>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</td>
</tr>
<tr>
<td>32 Harwood 1999</td>
<td>Cross-sectional study</td>
<td>investigating premorbid history of depression as a risk for depression in AD</td>
</tr>
<tr>
<td>33 Jost 1996</td>
<td>Retrospective medical records review study</td>
<td>on evolution of psychiatric symptoms in AD but not investigating risk factors</td>
</tr>
<tr>
<td>34 Migliorelli 1995</td>
<td>Cross-sectional study</td>
<td>of risk factors for depression in AD</td>
</tr>
<tr>
<td>35 Pearlson 1990</td>
<td>Retrospective medical review charts study</td>
<td>of association of family history of depression with depression in AD</td>
</tr>
<tr>
<td>36 Maxwell 2014</td>
<td>Longitudinal study</td>
<td>investigating the correlates of persistent symptoms of depression in people living with dementia in care homes</td>
</tr>
<tr>
<td>37 Ponomareva 2014</td>
<td>Longitudinal study</td>
<td>of development of AD with and without depressive disorder; did not evaluate risk factors</td>
</tr>
<tr>
<td>38 Anor 2014</td>
<td>Cross-sectional study</td>
<td>of the association of neuropsychiatric symptoms with hypertension, hypercholesterolemia, and diabetes in AD</td>
</tr>
<tr>
<td>39 Zubenko 1996</td>
<td>Cross-sectional study</td>
<td>examining the association of premorbid rates of major depression and concurrent syndrome of depression in inpatients with AD</td>
</tr>
<tr>
<td>40 Carpenter 1995</td>
<td>Retrospective review</td>
<td>of medical charts on the prevalence of personal history of depression in people with major depression and AD versus major depression but no dementia</td>
</tr>
</tbody>
</table>
Investigation of possible risk factors for depression in Alzheimer’s disease

<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
<th>Study Description</th>
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<tr>
<td>41</td>
<td>Stroud 2008</td>
<td>Retrospective charts review of the association of health-related and social factors with depressive symptoms in people with cognitive impairment and dementia</td>
</tr>
<tr>
<td>42</td>
<td>Moon 2014</td>
<td>Retrospective review of medical charts examining the association of vascular risk factors and neuropsychiatric symptoms (including depressive symptoms) in AD</td>
</tr>
<tr>
<td>43</td>
<td>Apostolova 2014</td>
<td>Cross-sectional study of risk factors for neuropsychiatric symptoms (including depressive symptoms) in AD</td>
</tr>
<tr>
<td>44</td>
<td>Klugman 2009</td>
<td>Retrospective review of medical notes examining the association of cerebrovascular pathology and depressive symptoms in AD</td>
</tr>
<tr>
<td>45</td>
<td>Barca 2017</td>
<td>Longitudinal study of progression of Alzheimer’s disease examining trajectories of depressive symptoms; did not examine risk factors</td>
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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]
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14. Risk reduction.mp. [mp]
15. Risk factor*.mp. [mp]
16. exp Risk Reduction Behavior/
17. Vulnerability.mp.
18. exp Precipitating Factors/