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The relationship between severity of Alzheimer's Disease and prevalence of comorbid depressive symptoms and depression: a systematic review

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SUMMARY

OBJECTIVES To gain more insight into the association between severity of Alzheimer's Disease (AD) and prevalence of comborbid depression.

METHODS A systematic literature review based on the Cochrane methodology was performed. PubMed, PsychINFO and EMBASE databases were searched for existing studies that fulfilled predefined inclusion criteria. The studies were divided into: (1) those that analysed the association between severity of AD and prevalence of depressive symptoms ('continuous' approach) and (2) those that investigated the association between severity of AD and diagnosed depression ('categorical' approach). The quality of existing studies was rated and the results were synthesized with a best evidence synthesis.

RESULTS Twenty-four studies fulfilled the inclusion criteria. Nineteen reported results for a continuous approach and seven for a categorical approach. Three of the four high quality studies within the continuous approach did not find a significant association between severity of AD and prevalence of depressive symptoms. None of the three high quality studies using the categorical approach found a significant association between the severity of AD and the prevalence of diagnosed depression.

CONCLUSIONS There is evidence for a lack of association between the severity of AD and the prevalence of comorbid depressive symptoms or diagnosed depression. Until new studies contradict this conclusion, prevention and intervention strategies for comorbid depression in AD should be aimed at all patients irrespective their disease severity.

INTRODUCTION

According to recent studies up to 50% of patients with Alzheimer's Disease (AD) suffer from depression at least once during their disease course (Starkstein et al., 2005). Comorbid depression in patients with AD has been associated with decreased quality of life (Shin et al., 2005), increased need for institutionalization (Steele et al., 1990), greater health care utilization (Kunik et al., 2003), higher mortality rates (Suh et al., 2005) and decreasing caregiver's well being (Kerkstra et al., 1999; Shin et al., 2005). These serious

consequences ask for the development of strategies for prevention, early recognition and intervention for depression in AD. Diagnostic and preventive services should be targeted at those at greatest risk which means that it is important to understand who is most likely to develop depression. In addition, this tells us something about the underlying causes of depression and may help develop preventive and intervention strategies. Within this context, it is important to expand knowledge regarding the relationship between severity of AD and comorbid depression. The results of studies that have examined this relationship are inconsistent (e.g. Harwood et al., 1998; Lopez et al., 2003; Piccininni et al., 2005). Explanations for these diverging results could be multiple, because the studies and study samples differ on many points.

One of the differences between the existing studies is the method used to determine the prevalence of depression: 'continuous' or 'categorical'. Within the continuous method the number of prevalent depressive symptoms is determined without establishing a diagnosis of depression. According to the categorical method, diagnostic criteria for depression are used to determine if a patient suffers from comorbid depression or not. There are various other differences between existing studies that could possibly offer explanations for the diverging results: (1) Many studies group different types of dementia together;

(2) Diagnostic procedures for AD differ between studies;

(3) The assessment instruments for the severity of AD differ;

(4) The instruments used to assess the prevalence of depression are multiple, also within the continuous and categorical approach and

(5) Study samples differ in many relevant aspects, such as severity of AD, living situation, history of depression, or use of psychotropic medication.

In order to gain more insight into the relationship between the prevalence of depression and severity of AD we conducted a systematic literature review by systematically analysing the differences, similarities and methodological quality of existing empirical studies.

The division into studies that use a continuous or a categorical approach forms the main structure around which the results of the review are presented and discussed.

METHODS

The systematic review was conducted in accordance with a predefined research protocol following the guidelines of the Cochrane Collaboration (Clarke and Oxman, 2002) that prescribed the following steps: (1) inclusion criteria; (2) search method; (3) selection method; (4) data extraction; (5) assessment of methodological quality; (6) data synthesis. Steps 3 to 6 were performed independently by the first two authors (RV, JN).

Inclusion criteria

Type of research. This review included naturalistic studies that conducted cross-sectional analyses on the relationship between severity of AD and prevalence of comorbid depressive symptoms or depression.

Patients. Studies had to involve patients who had been diagnosed with AD according to established diagnostic methods and criteria [e.g. NINCDS-ADRDA (McKhann et al., 1984), ICD-10 (World Health Organization, 1992), DSM-III-R or DSM-IV (APA, 1987, 1995) criteria].

Measurement of AD severity. Only studies using a validated measure for AD severity were included.

Scales that just measure degree of cognitive impairment as a measure for the severity of AD [e.g. Mini Mental State Examination (MMSE);

Folstein et al., 1975] as well as scales that also take non-cognitive aspects of AD into account [e.g.

Global Deterioration Scale (GDS); Reisberg et al., 1982] were included.

Measurement of depression. In the case of continuous studies: only studies using an established, validated rating scale for measuring depressive symptomatology were included, regardless of whether the rating scale used was specifically developed to assess depressive symptoms in patients with dementia (e.g. the Cornell Scale for Depression in Dementia (CSDD; Alexopoulos et al., 1988) or not (e.g. the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960).

In the case of categorical studies: those studies were included that either employed established diagnostic criteria for major depressive disorder (MDD) (e.g.
DSM-III-R/-IV or ICD-10 criteria) or used an empirically validated cut-off score on a rating scale for depressive symptoms specifically devised for patients with dementia (e.g. CSDD score>2; Alexopoulos et al., 1988; Lyketsos et al., 1997).

Statistical analysis. Only studies were included that tested the relationship between severity of AD and prevalence of depressive symptoms or depression for statistical significance.

Search method

In March 2006 we searched in three international bibliographical databases, i.e. PubMed, PsychINFO and EMBASE, for all studies that were published in English until that date and potentially fulfilled all five inclusion criteria. The databases were searched using the following strategy that was formulated in PubMed and adapted to the other databases: Dementia [MESH] AND (Depression [MESH] OR Depressive Disorder [MESH]) All literature lists of possibly relevant studies were also screened for additional references.

Selection method

A first selection for inclusion was performed by the first author (RV).On the basis of titles and abstracts all studies that clearly did not meet one of the five inclusion criteria were excluded from the review. If a study appeared to meet the inclusion criteria or if there was any doubt, the full article was read. A second selection was made by two reviewers independently (RV, JN). Based on the full articles both reviewers checked if the studies satisfied all five criteria. Disagreements regarding inclusion status were resolved by discussion. In three cases no consensus could be met and a third reviewer (AF) was consulted.

Data extraction

After the selection procedure, the two reviewers (RV, JN) independently documented the following characteristics of each study:

1. the diagnostic criteria employed to establish presence of AD;
2. the characteristics of the study sample of patients with AD (i.e. size, inpatients or outpatients, sociodemographics, and, if reported, other relevant characteristics such as duration of AD, presence of depression prior to the onset of AD);
3. the rating scale used to measure severity of AD;
4. the rating scale used to measure depressive symptoms or the diagnostic procedure used to establish presence of depression;
5. the dependent and independent variable studied and the statistical technique used to examine their relationship. If a multivariate technique was employed, the included covariates were also documented;
6. a short description of the results (i.e. significant or non-significant relationship, and, if reported, descriptive statistics, test statistics, *p*-value);
7. the direction of the association (in case a significant relationship was found).

The findings of the two researchers were compared and disagreements were resolved by discussion. The extracted data is presented for continuous and categorical studies in two separate tables.

Assessment of quality

After the data extraction, the quality of each included study was rated independently by the two researchers (RV, JN), using a set of five predefined criteria (Figure 1). Criteria one to three concerned the internal validity and four and five are statistical criteria. The criteria cover the key domains (1) comparability of subjects (between studies) (2) outcome measurement and (3) statistical analyses that are formulated by the US Agency for Healthcare Research and Quality for observational studies (AHRQ, 2002). Studies were considered to be of ‘high quality’ if at least three quality criteria were met.

[FIGURE 1]

[FIGURE 2]

Several studies examined the relationship between severity of AD and prevalence of depressive symptoms or depression in more than one way—either by employing different statistical techniques or by performing the same analytical technique using the scores of different rating scales for measuring depression symptomatology and/or severity of AD. These so-called 'sub-studies' were evaluated independently.

For each of the five quality criteria scoring positively, a (sub-)study received one 'quality' point. The methodological quality of a (sub-)study was operationalized simply as the sum of all criteria scoring positively and thus potentially ranged from 0–5. There were no disagreements between the two researchers regarding the methodological quality ratings.

Best evidence synthesis

A 'best evidence synthesis' (Slavin, 1995) was conducted to determine the existing evidence for a relationship between severity of AD and prevalence of depressive symptoms and diagnosed depression.

Levels of evidence were based on an earlier review of observational studies (Lievense et al., 2002).

Figure 2 shows the principles of the best evidence synthesis.

RESULTS

Search results and selection of studies

Figure 3 shows the results of each phase in the search method and selection of studies.

Searching the specified databases according to the strategy described above resulted in 5,501 hits. Of these, 208 articles were judged by the first author to be possibly relevant on the basis of titles and abstracts.

Based on full articles found, the first two authors agreed that 21 studies met the four inclusion criteria. A screening of reference lists of all 208 articles resulted in the inclusion of three additional studies. Of the total of 24 included studies, 19 reported results of analyses on the relationship between severity of AD and prevalence of depressive symptoms (continuous approach) and seven on the association between severity of AD and prevalence of diagnosed depression (categorical approach). Two studies used both approaches.

[FIGURE 3]

[TABLE 1]

Data extraction

The extracted data and quality rating of each included study are presented in Table 1 (continuous approach) and Table 2 (categorical approach). Studies were ordered by their methodological quality rating. The 19 'continuous' studies included 34 (sub-)studies, and the seven 'categorical' studies included nine (sub-)studies.

The last column of Table 1 and Table 2 indicates whether or not a significant association was found between the severity of AD and the prevalence of comorbid depressive symptoms or diagnosed depression and, if so, the direction of the association. In studies with a continuous approach eight times a positive association was found, two times a negative association and 24 times no association. In studies with a categorical approach two times a negative association was found and seven times no association.

Best evidence synthesis

Only four studies within the continuous approach and three studies within the categorical approach were rated as being of high methodological quality. Three of these four 'continuous' studies found no association between severity of AD and depressive symptoms and all three 'categorical' studies demonstrated found no relationship between severity of AD and prevalence of diagnosed depression.

Following the principles of the best evidence synthesis within both approaches we found scientific evidence for a lack of association between the severity of AD and the prevalence of depressive symptoms or diagnosed depression.

CONCLUSION AND DISCUSSION

The main conclusion of this systematic review is that, based on current knowledge, evidence exists for a lack of association between the severity of AD and the prevalence of comorbid depressive symptoms or depression.

Earlier non-systematic literature reviews (e.g. Olin et al., 2002) often stated that no conclusions about the relationship between the severity of AD and the prevalence of comorbid depression could be drawn due to large differences between existing studies. In this review we used various methods to overcome this problem: in the first place selection criteria were formulated that make sure that: (1) all study samples consisted of people with AD; and (2) valid assessment methods for depression and severity of AD were used. Secondly, selected studies were categorized into two groups: those that focused on the prevalence of depressive symptoms (continuous approach) and those that examined the prevalence of diagnosed depression (categorical approach). In addition the quality of all selected studies was rated, in order to select the studies with the highest validity.

Limitations of this review are that only studies published in English were included and studies that did not have depression or depressive disorder as a keyword were not identified. We do however not consider it very likely that high quality studies were missed because of this.

The finding that comorbid depressive symptomatology or diagnosed depression is not more prevalent in early, mild or severe AD contrasts with what is often theorized in physiological and psychological theories. These theories hypothesize that the prevalence of depression either decreases (psychological theories) or increases (physiological and psychological theories) with the increasing severity of AD. Interactive theories (Alexopoulos, 2003) do, however, offer a possible explanation for the current findings. According to these theories the neurological and psychosocial factors can reinforce or diminish each other, depending on the specific situation of a patient. Only a longitudinal study could give more insight into the mechanisms underlying the aetiology of depression in AD.

Following the systematic approach of this review and using current knowledge, such a longitudinal study should ideally meet the following criteria: (a) establishing diagnosis of AD according to NINCDS-ADRDA criteria (McKhann et al., 1984); (b) assessing severity of AD with a clinical instrument [e.g. CDR; Hughes et al., (1982) or GDS; Reisberg et al., (1982)]; (c) assessing symptoms of depression with an instrument specifically developed for people with dementia or specifically AD [e.g. CSDD; Alexopoulos et al., (1988) or NPI—Depression Subscale; Cummings et al., (1994)]; (d) establishing diagnosis of depression according to criteria specifically developed for people with AD, such as the Provisional Diagnostic Criteria for Depression of Alzheimer’s Disease (Olin et al., 2002); (e) using multivariate analytic techniques to control for known potentially important confounders (e.g. gender, history of depression, current use of antidepressant or psychotropic medication).

[TABLE 2]

For clinical practice the conclusion of the review shows that the development of specific interventions for signalling, preventing and treating comorbid depression in the different severities of AD should continue.

FIGURES AND TABLES

(1) The diagnosis of AD is established according to the 'golden standard', the NINCDS-ADRDA criteria (McKhann *et al.*, 1984);
(2) Severity of AD is assessed using a clinical instrument that besides cognitive capabilities also takes account of functional and/or clinical factors: (a) CDR (Hughes *et al.*, 1982) or (b) GDS (Reisberg *et al.*, 1982);
(3) Regarding studies that use a continuous approach, depressive symptoms are assessed using a rating scale specifically developed for patients with dementia. In studies with a categorical approach this type of rating scale should be used in combination with established diagnostic criteria for major depressive disorder. The following depression rating scales are specifically developed for demented populations: (a) the CSDD (Alexopoulos *et al.*, 1988); (b) the NPI depression subscale (Cumming *et al.*, 1994); (c) the Dementia Mood Assessment Scale (DMAS; Sunderland *et al.*, 1988); (d) the Revised Memory and Behavior Problem Checklist (RMBPC; Teri *et al.*, 1992);
(4) The statistical analysis controls for the possible influence of at least two of the following confounders known to be associated with comorbid depression: (a) gender; (b) history of depression; (c) history of other psychiatric disorder; (d) current other psychiatric disorder; (e) current use of antidepressant or psychotropic medication; (f) degree of functional impairment;
(5) The sample size of patients with AD is at least as large as the median sample size of all included studies in the review (n=78).

Figure 1. Quality criteria

Evidence:
Provided by consistent outcomes in at least 75% of the studies with a quality score of three or more.

Insufficient evidence:
If less than 75% of the studies with a quality score of three or more have consistent outcomes.

Or

If no studies received a quality score of three or more

Figure 2. Principles of best evidence synthesis

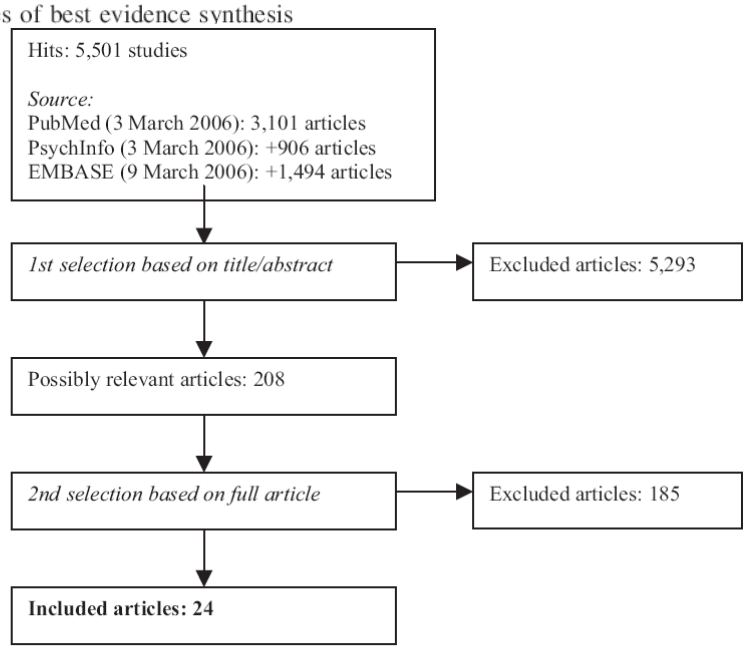

Figure 3. Results of database searches and selection methods

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Table 1. Studies on the association between severity of dementia and prevalence of depressive symptoms in patients with Alzheimer's Disease (AD)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
Piccininni *et al.* (2005)	3	NINCDS-ADRDA criteria for probable AD	$n = 50$ Outpatients Female gender: 76% Age: M (SD) = 69.3 (7.5), range = 53–84 Education: M (SD) = 6.5 (3.9) Duration AD (months): M (SD) = 57.7 (37.3) *Exclusion criteria*: a past history of alcoholism or psychiatric disturbances prior to the onset of dementia; drug abuse or dependence	(1) GDS: Mild (score: 2–3): 28%; Moderate (score: 4–5): 54%; Severe (score:>5): 18% (2) MMSE: M (SD) = 16.8 (5.6)	NPI depression subscale: M (SD) = 3.3 (3.7)	ANOVA: Comparison between mildly, moderately and severely impaired groups regarding NPI-depression score	Mildly impaired group: M (SD) = 3.7 (4.0); Moderately impaired group: M (SD) = 2.7 (3.1); Severely impaired group: M (SD) = 4.7 (5.0); Overall comparison: $p = 0.35$	No significant association
Harwood *et al.* (2000a)	3	NINCDS-ADRDA criteria for possible or probable AD	$n = 114$ Outpatients Female gender: 63%	MMSE: M (SD) = 17.8 (7.2)	RMBPC 9-item depression scale: M (SD) = 8.4 (7.8)	Pearson correlation between RMBPC and MMSE scores	$r = 002$, n.s.	No significant association

(*Continues*)

Table 1. (Continued)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
			Age: M (SD) = 78.8 (6.5), range = 59–92 Education: M (SD) = 11.9 (3.5); range = 2–20 Hispanic: 44% Duration AD: M (SD) = 3.4 (2.5); range = 1–11					
Harwood *et al.* (1998)	3	NINCDS-ADRDA criteria for probable AD	$n = 137$	MMSE: M = 15.6, range = 0–29	CSDD: M = 5.2, range = 0–25; Mild (score: 8–12): 9.5%; Moderate (score: >12): 11.7%	Pearson correlation between CSDD and MMSE scores	$r = -0.25$, $p < 0.01$	More severe depressive symptoms in more severe AD
			Outpatients Female gender: 70% Age: M = 78.2, range = 63–95 Education: M = 10.4, range = 0–20 Hispanic: 50.4% Duration AD: M = 4.1; range = 0–14					
Brodaty and Luscombe (1996)	3 & 2[c]	NINCDS-ADRDA criteria for AD	$n = 208$	*Total sample of patients with dementia*[d]:	HDRS (21-item version): M (SD) = 6.7 (5.3)[e]	(1) Spearman correlations with Bonferroni correction between (a) HDRS and MMSE scores; (b) HDRS and CDR scores	(1a) significant negative correlation; (1b) n.s.	(1a & 2) More severe depressive symptoms in more severe AD

			Outpatients	(1) MMSE: M (SD) = 18.2 (7.2); Mild (score: ≥22); Moderate (score: < 22)	*Total sample of patients with dementia*[d]: MDD (DSM-IV criteria): 6.3%	(2) t test: comparison between mildly and moderately impaired groups (based on MMSE) regarding HDRS scores	(2) mildly impaired group had a significantly lower HDRS score	(1b) No significant association
			Total sample of patients with dementia ($n = 288$)[d]: Female gender: 55% Age: M (SD) = 71.4(7.7) Education: M (SD) = 9.7 (3.4)	(2) CDR: score 0.5: 30.0%; score 1: 48.3%; score 2: 15.7%; score 3: 6.0%				
Müller-Thomsen *et al.* (2005)	2	NINCDS-ADRDA criteria for probable AD	$n = 316$[f]	MMSE: Mild (score: ≥ 18): 49.7%; Moderate-severe (score: <18): 50.3%	(1) GDS (15-item version)	ANOVAs: Comparison between mildly and moderately-severely impaired groups (based on MMSE) regarding:	A: Mildly impaired group; B: Moderately-severely impaired group	(1–3) No significant association
			Outpatients	Mild: M (SD) = 22.3 (2.8); Moderate-severe: M (SD) = 11.6 (4.4)	(2) MADRS	(1) GDS score	(1) A ($n = 140$): M (SD) = 4.5 (3.3); B ($n = 101$): M (SD) = 4.6 (2.6), n.s.	
			Patients with MMSE ≥18 ($n = 157$):		(3) CSDD	(2) MADRS score	(2) A ($n = 120$): M (SD) = 10.1 (6.7); B ($n = 76$): M (SD) = 12. 8 (8.8), $P < 0.10$	
			Female gender: 65%			(3) CSDD score	(3) A ($n = 31$): M (SD) = 6.7 (5.0); B ($n = 16$): M (SD) = 8.1 (5.1), n.s.	
			Age: M (SD) = 72.7 (8.7) *Patients with MMSE <18* ($n = 159$):					

(*Continues*)

Table 1. (Continued)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
			Female gender: 74% Age: M (SD) = 72.6 (9.0)					
Levy *et al.* (1998)	2	NINCDS-ADRDA criteria for probable AD	$n = 30$ Outpatients Female gender: 63% Age: M = 74, range = 54–85	MMSE: M (SD) = 17.5 (7.0)	NPI depression subscale: M (SD) = 1.2 (1.6)	Spearman correlation between NPI-depression and MMSE scores	Nonsignificant trend toward a negative correlation	No significant association
Bungener *et al.* (1996)	2	NINCDS-ADRDA criteria for possible or probable AD	$n = 118$ Outpatients Female gender: 64% Age: M (SD) = 70.1 (7.8), range = 52–86 Education: <6: $n = 49$, 7–11: $n = 38$, ≥12: $n = 29$ Early-onset AD: $n = 61$, Late-onset AD: $n = 55$	(1) MMSE: M (SD) = 19.1 (5.8); range = 3–29 (2) DRS: M (SD) = 104.8 (20.5)	(1) HDRS (17-item version): M (SD) = 8.1 (4.6), range = 0–22 (2) RRS: M (SD) = 9.3 (4.0), range = 3–29 MDD (DSM-III-R criteria): 0% Dysthymia (DSM-III-R criteria): 8.5%	Pearson correlations between (1) HDRS and MMSE scores (2) HDRS and DRS scores (3) RRS and MMSE scores (4) RRS and DRS scores	(1) n.s. (2) n.s. (3) $r = -0.27$, $p = 0.003$ (4) $r = -0.31$, $p < 0.001$	(1 & 2) No significant association (3 & 4) More severe depressive symptoms in more severe AD

Haupt *et al.* (1995)	2	ICD-10 draft criteria for mild to moderate dementia in AD	$n = 78$ Outpatients Female gender: 73% Age: M (SD) = 74.3 (7.5), range = 57–90 Age at symptom onset: M (SD) = 69.4 (7.3) Past history of depression: 0% Antidepressant medication within the 2-year study period: 32%; no patient had to stay on antidepressant medication for >3 weeks	(1) MMSE (2) CAMCOG: M (SD) = 36.2 (24.4) (3) GDS: score 5: 54%; score 6: 35%; score 7: 11%	DMAS mood subscale: M (SD) = 14 (6.6), range = 2–31	Correlations between[g]: (1) DMAS and MMSE scores (2) DMAS and CAMCOG scores	(1) 0.02, n.s. (2) 0.04, n.s.	(1 & 2) No significant association
Verhey *et al.* (1995)	2	NINCDS-ADRDA criteria for possible or probable AD	$n = 48$ Outpatients Female gender: 65%	GDS: M (SD) = 4.8 (0.9); Very mild (score: 3): 8.3%; Mild (score: 4): 25.0%; Moderate (score: 5): 45.8%; Severe (score: 6): 20.8%; Very severe (score: 7): 0%	HDRS (17-item version): M (SD) = 9.4 (9.4) MDD (DSM-III-R criteria): 6.3%	Spearman correlation between HDRS and GDS scores	$r = 0.04$, n.s.	No significant association

(*Continues*)

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			Age: M (SD) = 72.9 (7.6) Education [1(primary school) – 7(university grade)]: 3.6 (1.3) Duration AD: M (SD) = 3.28 (2.4)					
Feher *et al.* (1992)	2	NINCDS-ADRDA criteria for probable AD	$n = 83$		(1) HDRS (17-item version): M (SD) = 4.0 (3.1)	Correlations between:	(1) −0.15, n.s.	(1–3) No significant association
			Outpatients	MMSE: M (SD) = 19.4 (2.9), range = 12–23	(2) GDS (30-item version): M (SD) = 7.8 (5.4)	(1) HDRS and MMSE scores;	(2) −0.15, n.s.	
			Female gender: 49%			(2) GDS and MMSE scores	(3a & b) MMSE score was not a significant predictor of GDS score, $p > 0.10$	
			Age: M (SD) = 65.6 (5.7)			(3) multivariate linear regression: Dependent: GDS score; (a) hierarchical: HDRS scores were entered first; followed by MMSE, memory test and self-awareness scores; (b) simultaneous entry		
			Education: M (SD) = 13.3 (2.8) *Exclusion criteria*: Current psychiatric diagnosis (DSM-III-R criteria); HDRS score >16					

Gottlieb *et al.* (1988)	2	NINCDS-ADRDA criteria for probable AD	$n = 43$ Outpatients Female gender: 67% Age: M (SD) = 72.8 (7.3), range = 55–88 Education: M (SD) = 11.9 (3.6), range = 4–18 *Exclusion criteria*: evidence of other psychiatric disorder; history of significant psychiatric disorder; requiring acute psychiatric intervention at the time of initial presentation	GDS: Low (score: 3–4): 55.8% High (score: ≥5): 44.2%	(1) HDRS (17-item version) (2) SDS	t tests: Comparison between low- and high-impaired groups (based on GDS) regarding (1) HDRS score and (2) SDS score	A: High-impaired group B: Low-impaired group (1) A: M (SD) = 2.2 (3.0), range = 0–10; B: M (SD) = 3.3 (6.1), range = 0–28, $t < 1$, n.s. (2) A: M (SD) = 39.0 (8.6), range = 21–54; B: M (SD) = 36.6 (8.1), range = 23–55, $t < 1$, n.s.	(1 & 2) No significant association
Weiner *et al.* (1997)	1	NINCDS-ADRDA criteria for AD	$n = 30$ Outpatients Age: M (SD) = 72.5 (6.4), range = 6–28	MMSE[h]: M (SD) = 17.3 (6.4), range = 6–28	HDRS (21-item version): (a) Patient's report: M (SD) = 5.7 (3.6), range = 1–12; (b) Caregiver's report: M (SD) = 9.3 (5.2), range = 0–21	Correlations between (1) patient's report HDRS and MMSE scores; (2) caregiver's report HDRS and MMSE scores	(1) n.s. (2) n.s.	(1 & 2) No significant association

(*Continues*)

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Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
Piccininni *et al.* (2005)	3	NINCDS-ADRDA criteria for probable AD	$n = 50$ Outpatients Female gender: 76% Age: M (SD) = 69.3 (7.5), range = 53–84 Education: M (SD) = 6.5 (3.9) Duration AD (months): M (SD) = 57.7 (37.3) *Exclusion criteria*: a past history of alcoholism or psychiatric disturbances prior to the onset of dementia; drug abuse or dependence	(1) GDS: Mild (score: 2–3): 28%; Moderate (score: 4–5): 54%; Severe (score:>5): 18% (2) MMSE: M (SD) = 16.8 (5.6)	NPI depression subscale: M (SD) = 3.3 (3.7)	ANOVA: Comparison between mildly, moderately and severely impaired groups regarding NPI-depression score	Mildly impaired group: M (SD) = 3.7 (4.0); Moderately impaired group: M (SD) = 2.7 (3.1); Severely impaired group: M (SD) = 4.7 (5.0); Overall comparison: $p = 0.35$	No significant association
Harwood *et al.* (2000a)	3	NINCDS-ADRDA criteria for possible or probable AD	$n = 114$ Outpatients Female gender: 63%	MMSE: M (SD) = 17.8 (7.2)	RMBPC 9-item depression scale: M (SD) = 8.4 (7.8)	Pearson correlation between RMBPC and MMSE scores	$r = 002$, n.s.	No significant association

(*Continues*)

Table 1. (Continued)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
			Age: M (SD) = 78.8 (6.5), range = 59–92 Education: M (SD) = 11.9 (3.5); range = 2–20 Hispanic: 44% Duration AD: M (SD) = 3.4 (2.5); range = 1–11					
Harwood *et al.* (1998)	3	NINCDS-ADRDA criteria for probable AD	$n = 137$	MMSE: M = 15.6, range = 0–29	CSDD: M = 5.2, range = 0–25; Mild (score: 8–12): 9.5%; Moderate (score: >12): 11.7%	Pearson correlation between CSDD and MMSE scores	$r = -0.25$, $p < 0.01$	More severe depressive symptoms in more severe AD
			Outpatients Female gender: 70% Age: M = 78.2, range = 63–95 Education: M = 10.4, range = 0–20 Hispanic: 50.4% Duration AD: M = 4.1; range = 0–14					
Brodaty and Luscombe (1996)	3 & 2[c]	NINCDS-ADRDA criteria for AD	$n = 208$	*Total sample of patients with dementia*[d]:	HDRS (21-item version): M (SD) = 6.7 (5.3)[e]	(1) Spearman correlations with Bonferroni correction between (a) HDRS and MMSE scores; (b) HDRS and CDR scores	(1a) significant negative correlation; (1b) n.s.	(1a & 2) More severe depressive symptoms in more severe AD

			Outpatients	(1) MMSE: M (SD) = 18.2 (7.2); Mild (score: ≥22); Moderate (score: < 22)	*Total sample of patients with dementia*[d]: MDD (DSM-IV criteria): 6.3%	(2) t test: comparison between mildly and moderately impaired groups (based on MMSE) regarding HDRS scores	(2) mildly impaired group had a significantly lower HDRS score	(1b) No significant association
			Total sample of patients with dementia ($n = 288$)[d]: Female gender: 55% Age: M (SD) = 71.4(7.7) Education: M (SD) = 9.7 (3.4)	(2) CDR: score 0.5: 30.0%; score 1: 48.3%; score 2: 15.7%; score 3: 6.0%				
Müller-Thomsen *et al.* (2005)	2	NINCDS-ADRDA criteria for probable AD	$n = 316$[f]	MMSE: Mild (score: ≥ 18): 49.7%; Moderate-severe (score: <18): 50.3%	(1) GDS (15-item version)	ANOVAs: Comparison between mildly and moderately-severely impaired groups (based on MMSE) regarding:	A: Mildly impaired group; B: Moderately-severely impaired group	(1–3) No significant association
			Outpatients	Mild: M (SD) = 22.3 (2.8); Moderate-severe: M (SD) = 11.6 (4.4)	(2) MADRS	(1) GDS score	(1) A ($n = 140$): M (SD) = 4.5 (3.3); B ($n = 101$): M (SD) = 4.6 (2.6), n.s.	
			Patients with MMSE ≥18 ($n = 157$):		(3) CSDD	(2) MADRS score	(2) A ($n = 120$): M (SD) = 10.1 (6.7); B ($n = 76$): M (SD) = 12. 8 (8.8), $P < 0.10$	
			Female gender: 65%			(3) CSDD score	(3) A ($n = 31$): M (SD) = 6.7 (5.0); B ($n = 16$): M (SD) = 8.1 (5.1), n.s.	
			Age: M (SD) = 72.7 (8.7) *Patients with MMSE <18* ($n = 159$):					

(*Continues*)

Table 1. (Continued)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
			Female gender: 74% Age: M (SD) = 72.6 (9.0)					
Levy *et al.* (1998)	2	NINCDS-ADRDA criteria for probable AD	$n = 30$ Outpatients Female gender: 63% Age: M = 74, range = 54–85	MMSE: M (SD) = 17.5 (7.0)	NPI depression subscale: M (SD) = 1.2 (1.6)	Spearman correlation between NPI-depression and MMSE scores	Nonsignificant trend toward a negative correlation	No significant association
Bungener *et al.* (1996)	2	NINCDS-ADRDA criteria for possible or probable AD	$n = 118$ Outpatients Female gender: 64% Age: M (SD) = 70.1 (7.8), range = 52–86 Education: <6: $n = 49$, 7–11: $n = 38$, ≥12: $n = 29$ Early-onset AD: $n = 61$, Late-onset AD: $n = 55$	(1) MMSE: M (SD) = 19.1 (5.8); range = 3–29 (2) DRS: M (SD) = 104.8 (20.5)	(1) HDRS (17-item version): M (SD) = 8.1 (4.6), range = 0–22 (2) RRS: M (SD) = 9.3 (4.0), range = 3–29 MDD (DSM-III-R criteria): 0% Dysthymia (DSM-III-R criteria): 8.5%	Pearson correlations between (1) HDRS and MMSE scores (2) HDRS and DRS scores (3) RRS and MMSE scores (4) RRS and DRS scores	(1) n.s. (2) n.s. (3) $r = -0.27$, $p = 0.003$ (4) $r = -0.31$, $p < 0.001$	(1 & 2) No significant association (3 & 4) More severe depressive symptoms in more severe AD

Haupt *et al.* (1995)	2	ICD-10 draft criteria for mild to moderate dementia in AD	$n = 78$ Outpatients Female gender: 73% Age: M (SD) = 74.3 (7.5), range = 57–90 Age at symptom onset: M (SD) = 69.4 (7.3) Past history of depression: 0% Antidepressant medication within the 2-year study period: 32%; no patient had to stay on antidepressant medication for >3 weeks	(1) MMSE (2) CAMCOG: M (SD) = 36.2 (24.4) (3) GDS: score 5: 54%; score 6: 35%; score 7: 11%	DMAS mood subscale: M (SD) = 14 (6.6), range = 2–31	Correlations between[g]: (1) DMAS and MMSE scores (2) DMAS and CAMCOG scores	(1) 0.02, n.s. (2) 0.04, n.s.	(1 & 2) No significant association
Verhey *et al.* (1995)	2	NINCDS-ADRDA criteria for possible or probable AD	$n = 48$ Outpatients Female gender: 65%	GDS: M (SD) = 4.8 (0.9); Very mild (score: 3): 8.3%; Mild (score: 4): 25.0%; Moderate (score: 5): 45.8%; Severe (score: 6): 20.8%; Very severe (score: 7): 0%	HDRS (17-item version): M (SD) = 9.4 (9.4) MDD (DSM-III-R criteria): 6.3%	Spearman correlation between HDRS and GDS scores	$r = 0.04$, n.s.	No significant association

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Table 1. (Continued)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
			Age: M (SD) = 72.9 (7.6) Education [1(primary school) – 7(university grade)]: 3.6 (1.3) Duration AD: M (SD) = 3.28 (2.4)					
Feher *et al.* (1992)	2	NINCDS-ADRDA criteria for probable AD	$n = 83$		(1) HDRS (17-item version): M (SD) = 4.0 (3.1)	Correlations between:	(1) −0.15, n.s.	(1–3) No significant association
			Outpatients	MMSE: M (SD) = 19.4 (2.9), range = 12–23	(2) GDS (30-item version): M (SD) = 7.8 (5.4)	(1) HDRS and MMSE scores;	(2) −0.15, n.s.	
			Female gender: 49%			(2) GDS and MMSE scores	(3a & b) MMSE score was not a significant predictor of GDS score, $p > 0.10$	
			Age: M (SD) = 65.6 (5.7)			(3) multivariate linear regression: Dependent: GDS score; (a) hierarchical: HDRS scores were entered first; followed by MMSE, memory test and self-awareness scores; (b) simultaneous entry		
			Education: M (SD) = 13.3 (2.8) *Exclusion criteria*: Current psychiatric diagnosis (DSM-III-R criteria); HDRS score >16					

Gottlieb *et al.* (1988)	2	NINCDS-ADRDA criteria for probable AD	$n = 43$ Outpatients Female gender: 67% Age: M (SD) = 72.8 (7.3), range = 55–88 Education: M (SD) = 11.9 (3.6), range = 4–18 *Exclusion criteria*: evidence of other psychiatric disorder; history of significant psychiatric disorder; requiring acute psychiatric intervention at the time of initial presentation	GDS: Low (score: 3–4): 55.8% High (score: ≥5): 44.2%	(1) HDRS (17-item version) (2) SDS	t tests: Comparison between low- and high-impaired groups (based on GDS) regarding (1) HDRS score and (2) SDS score	A: High-impaired group B: Low-impaired group (1) A: M (SD) = 2.2 (3.0), range = 0–10; B: M (SD) = 3.3 (6.1), range = 0–28, $t < 1$, n.s. (2) A: M (SD) = 39.0 (8.6), range = 21–54; B: M (SD) = 36.6 (8.1), range = 23–55, $t < 1$, n.s.	(1 & 2) No significant association
Weiner *et al.* (1997)	1	NINCDS-ADRDA criteria for AD	$n = 30$ Outpatients Age: M (SD) = 72.5 (6.4), range = 6–28	MMSE[h]: M (SD) = 17.3 (6.4), range = 6–28	HDRS (21-item version): (a) Patient's report: M (SD) = 5.7 (3.6), range = 1–12; (b) Caregiver's report: M (SD) = 9.3 (5.2), range = 0–21	Correlations between (1) patient's report HDRS and MMSE scores; (2) caregiver's report HDRS and MMSE scores	(1) n.s. (2) n.s.	(1 & 2) No significant association

(*Continues*)

Table 1. (Continued)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
			Education: M (SD) = 12.6 (4.0), range = 3–20					
Fitz and Teri (1994)	1	DSM-III-R criteria for AD	$n = 91$		HDRS (17-item version)	(1) Pearson correlation between HDRS and DRS scores	(1 & 2) n.s.	(1 & 2) No significant association
			Outpatients	DRS: M (SD) = 102 (18.8), range = 56–139; Mild (score: >102): 50.5%; Moderate (score: <103): 49.5%	MDD (DSM-III-R criteria): 50.5%	(2) Comparison between mildly and moderately impaired groups (based on DRS) regarding HDRS score		
			Female gender: 55%					
			Age: range = 46–90					
Troisi *et al.* (1993)	1	NINCDS-ADRDA criteria for probable AD	$N = 26$		HDRS (17-item version): Mild-moderate (score: 10–16): 30.8%; Marked (score: ≥17): 7.7%	ANOVA and PLSD	(1) Overall comparison: $p < 0.05$	(1 & 2) More severe depressive symptoms in more severe AD
			Outpatients	(1) MMSE: mild-moderate (score: 16–23): 50%; severe (score: ≤15): 50%	MDD (DSM-III-R criteria): 23.1%	posthoc tests: (1) comparison between mildly-moderately and severely impaired groups (based on MMSE) regarding HDRS score	Posthoc comparison: severely impaired group had significantly higher HDRS score than mildly-moderately impaired group ($p < 0.05$)	
			Female gender: 54%	(2) DSM-III-R: Mild: 26.9%; Moderate: 42.3%; Severe: 30.8%		(2) comparison between mildly, moderately and severely impaired groups (based on DSM-III-R) regarding HDRS score	(2) Overall comparison: $p = 0.01$	

			Age: M (SD) = 74.0 (5.5), range = 65–84 Education: M (SD) = 7.15 (5.0), range = 0–19				Posthoc comparisons: severely impaired group had significantly higher HDRS score than mildly ($p < 0.01$) and moderately impaired ($p < 0.05$) groups	
Sultzer *et al.* (1992)	1	NINCDS-ADRDA criteria for probable AD	$N = 61$ Outpatients (majority) and inpatients Female gender: 5% Age: M (SD) = 73.0 (7.8), range = 53–88 Education: M (SD) = 13.0 (3.2), range = 7–20 Duration: M (SD) = 5.8 (3.7), range = 1–20 *Exclusion criteria*: history of psychotic disorder prior to onset of dementia; evidence of psychoactive substance use disorder	MMSE: M (SD) = 10.0 (8.5), range = 0–28	HDRS (17-item version): M = 10.3, range = 1–22	Pearson correlation between HDRS and MMSE scores	$r = -0.38$, $p = 0.003$	More severe depressive symptoms in more severe AD

(*Continues*)

Table 1. (Continued)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
Fischer *et al.* (1990)	1	NINCDS-ADRDA criteria for probable AD	$N = 55$		HDRS (17-item version): M (SD) = 12.4 (5.8), range = 2–27	(1) Kruskal-Wallis rank test: comparison between mildly, moderately and severely impaired groups (based on MMSE) regarding HDRS score	(1) Mildly impaired group: M (SD) = 13.1 (6.5); Moderately impaired group: M (SD) = 14.3 (5.2); Severely impaired group: M (SD) = 9.9 (3.9)	(1 & 2) Less severe depressive symptoms in more severe AD
			Inpatients	MMSE: M (SD) = 11.5 (9.1), range = 0–23; Mild (score: 16–23): 41.8%; Moderate (score: 6–15): 23.6%; Severe (score: < 6): 34.5%		(2) Spearman correlation between HDRS and MMSE scores	Overall comparison: $p < 0.05$	
			Female gender: 87% Age: M (SD) = 79.4 (8.8), range = 58–93 No patient received antidepressants at the time of investigation or for 2 weeks previously				(2) $r = 0.27$, $p < 0.05$	
Shuttleworth *et al.* (1987)	1	NINCDS-ADRDA criteria for AD	$n = 22$		SDS: M = 41.2	ANOVA: comparison between mildly, moderately and severely impaired groups (based on MMSE) regarding SDS score	Mildly impaired group: M = 41.4; Moderately impaired group: M = 41.6; Severely impaired group: M = 40.6; Overall comparison: F 0.98, df = 2 and 19, n.s.	No significant association

			Outpatients Female gender: 59% Age: M = 67.1 Education: M = 14.5	MMSE: Mild (score: 20–25): 31.8%; Moderate (score: 15–19): 36.4%; Severe (score: 5–14): 31.8%	MDD (DSM-III criteria): 41%			
Galynker *et al.* (1995)	0	DSM-III-R criteria for AD	$n = 26$ Outpatients Female gender: 58% Age: M (SD) = 78.8 (6.45), range = 63–89 Antipsychotic medication: 26.9% Benzodiazepines: 23.1% Antidepressants: 15.4%	MMSE: M (SD) = 16.8 (7.52), range = 1–28	HDRS (17-item version): M (SD) = 10.5 (5.73), range = 2–24	Pearson correlation with Bonferroni correction between HDRS and MMSE scores	$r = -0.33$, n.s.	No significant association

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Table 1. (Continued)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Severity of depressive symptoms[b]	Statistical analysis	Results	Direction of association
Teri and Wagner (1991)	0	DSM-III-R criteria for AD	$n = 75$	(1)MMSE: M (SD) = 18.1 (5.7), range = 4–27; Mild (score: >21): 30.7%; Moderate (score: 21-16): 37.3%; Severe (score: < 16): 32.0%	HDRS (17-item version): (a) patient's report: M (SD) = 5.0 (5.2), range = 0–26; (b) caregiver's report: M (SD) = 7.6 (6.9), range = 0–30; (c) clinician's evaluation: M (SD) = 8.2 (6.9), range = 0–30	3(source) × 3(severity of AD) repeated measures MANOVA: Dependent: HDRS score; *Severity of AD*: mild, moderate, severe (based on MMSE); *Source*: patient, caregiver or clinician	No significant effect of severity of AD	No significant association
			Outpatients	(2) GDS: M (SD) = 4.6 (1.0), range = 2–6	MDD (DSM-III-R criteria): 29%			
			Female gender: 68% Age: M (SD) = 74.0 (7.4), range = 46–89 Education: ≤12th grade: 72%, >12th grade: 28%					

CAMCOG = Cambridge Cognitive Examination; CDR = Clinical Dementia Rating Scale (Morris, 1993); CSDD = Cornell Scale for Depression in Dementia (Alexopolous *et al*., 1988); df = degrees of freedom DMAS = Dementia Mood Assessment Scale (Sunderland *et al*., 1988); DRS = Mattis Dementia Rating Scale (Mattis, 1976); DSM = Diagnostic and Statistical Manual of Mental Disorders, third revised (DSM-III-R) or fourth (DSM-IV) edition (American Psychiatric Association, 1987, 1994); GDS = Geriatric Depression Scale (Yesavage *et al*., 1982–1983; Sheikh and Yesavage, 1985); GDS = Global Deterioration Scale (Reisberg *et al*., 1982); HDRS = Hamilton Depression Rating Scale (Hamilton, 1960; Williams, 1988); ICD-10 = International Classification of Diseases, tenth edition (World Health Organization, 1987); MADRS = Montgomery and Åsperg Depression Scale (Montgomery and Åsberg, 1979); MDD = Major Depressive Disorder; MMSE = Mini-Mental State Examination (Folstein *et al*., 1975); NINCDS-ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (McKhann *et al*., 1984); NPI = Neuropsychiatric Inventory (Cummings *et al*., 1994); n.s. = not significant; PLSD = Fisher's Protected Least Significant Difference; RMBPC = Revised Memory and Behavior Problem Checklist (Teri *et al*., 1992); RRS = Retardation Rating Scale (Widlocher, 1983; Roth *et al*., 1986); SDS = Zung Self-Rating Depression Scale (Zung, 1965).

[a]Data concerning education and duration of AD are presented in years, unless stated otherwise. Only psychiatric exclusion criteria are presented.

[b]If available data on prevalence of major depression or dysthymia are also presented.

[c]This study had two different quality scores because separate analyses were performed using scores on different scales to assess severity of AD.

[d]No (further) data concerning the sample of patients with AD were reported.

[e]Missing data for 6 patients, $n = 202$.

[f]Depression scales were not performed in every patient with AD for various reasons.

[g]Results concern those at baseline.

[h]Missing data for 2 patients, $n = 28$.

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Table 2. Studies on the association between severity of dementia and prevalence of diagnosed depression in patients with Alzheimer's Disease (AD)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Prevalence of depression[b]	Statistical analysis	Results	Direction of association
Harwood *et al.* (2000b)	3	NINCDS-ADRDA criteria for possible or probable AD	$n = 96$	MMSE:	Depression (CSDD score: ≥7): 39.6%	Multivariate logistic regression: Dependent: depression (0/1); Independent: MMSE score; Covariates: age, education, gender, marital status, functional status and psychosis	OR (95% CI) = 0.9 (0.9–1.0), $p = 0.25$	No significant association
			Outpatients Female gender: 70% Age: M (SD) = 74.9 (6.8) Education: M (SD) = 9.9 (5.2) Cuban American: 100% Functional status (BDS): M (SD) = 5.8 (4.2) Presence of delusions/ hallucinations: 32.3%	M (SD) = 15.9 (6.5)	CSDD (all AD patients): M (SD) = 7.4 (6.9), range = 0–28			
Lyketsos *et al.* (1997)	3	NINCDS-ADRDA criteria for probable AD	$n = 109$	(1) CDR:	(a) MDD (DSM-IV criteria): 22%; (b) Minor depression (depressed mood, crying spells, or anhedonia according to CSDD and CSDD score: >6): 27%; (c) remaining patients: 51%			

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Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Prevalence of depression[b]	Statistical analysis	Results	Direction of association
Harwood *et al.* (2000b)	3	NINCDS-ADRDA criteria for possible or probable AD	$n = 96$	MMSE:	Depression (CSDD score: ≥7): 39.6%	Multivariate logistic regression: Dependent: depression (0/1); Independent: MMSE score; Covariates: age, education, gender, marital status, functional status and psychosis	OR (95% CI) = 0.9 (0.9–1.0), $p = 0.25$	No significant association
			Outpatients Female gender: 70% Age: M (SD) = 74.9 (6.8) Education: M (SD) = 9.9 (5.2) Cuban American: 100% Functional status (BDS): M (SD) = 5.8 (4.2) Presence of delusions/ hallucinations: 32.3%	M (SD) = 15.9 (6.5)	CSDD (all AD patients): M (SD) = 7.4 (6.9), range = 0–28			
Lyketsos *et al.* (1997)	3	NINCDS-ADRDA criteria for probable AD	$n = 109$	(1) CDR:	(a) MDD (DSM-IV criteria): 22%; (b) Minor depression (depressed mood, crying spells, or anhedonia according to CSDD and CSDD score: >6): 27%; (c) remaining patients: 51%			

			Outpatients Female gender: 79% Age: M (SD) = 74.4 (7.9) History of depressive disorder: 17.4%.	Early (score: 0.5): 9.8%; Mild (score: 1): 38.2%; Moderate (score: 2): 29.4%; Severe (score: 3): 21.6% (2) MMSE: M (SD) = 15.0 (6.5), range = 0–28	CSDD (all AD patients): M (SD) = 8.0 (7.2), range = 0–28	Chi-square test: Distribution of the 3 depression groups across CDR scores	$\chi 2 = 5.86$, df = 4, $p = 0.21$	No significant association
Ballard *et al.* (1996)	3	NINCDS-ADRDA criteria for possible or probable AD	$n = 88$	CAMCOG:	MDD (depressive symptoms were rated using the CSDD; next, diagnosis was made according to the RDC criteria): 17.0%	Bivariate logistic regression:	Wald chi-square test = 0.63, $p = 0.43$	No significant association
			Outpatients *Total sample of patients with dementia* ($n = 124$)[c]: Female gender: 73% Age: M = 79.6 *Exclusion criteria*: fulfilment of the CAMDEX criteria for severe dementia	*Total sample of patients with dementia*[c]: M = 43.9	CSDD (all AD patients): M = 9.2	Dependent: depression (0/1); Independent: CAMCOG score		

(*Continues*)

Payne *t al.* (1998)	2	NINCDS-ADRDA criteria for possible or probable AD	$n = 151$	MMSE:	Depression (CSDD score: >12): 17%	(1) bivariate logistic regression:	(1) OR (95% CI) = 1.03 (0.97–1.09)	(1) No significant association
			Outpatients	M (SD) = 14.7 (7.3)	CSDD (all AD patients):	Dependent: depression (0/1); Independent: MMSE score	(2) OR (95% CI) = 1.09 (1.01–1.19)	(2) Lower likelihood of depression in more severe AD
			Female gender: 81%		M (SD) = 6.6 (6.1), range = 0–25	(2) multivariate logistic regression:		
			Age: M (SD) = 8.1(7.9) Caucasian: 80.7% Functional status (PGDRS-P): M (SD) = 7.5 (7.5)			Covariate: functional status		
Fitz and Teri (1994)	1	DSM-III-R criteria for AD	$n = 91$	DRS:	MDD (DSM-III-R criteria): 50.5%	Comparison between mildly and moderately impaired groups (based on DRS) regarding frequency of MDD	MDD:	No significant association
			Outpatients	M (SD) = 102 (18.8), range = 56–139; Mild (score: < 103): 49.5%; Moderate (score: >102): 50.5%			Mildly impaired group:	
			Female gender: 55%				56.5%; Moderately impaired group: 44.4%; n.s.	
			Age: Range: 46-90					

(*Continues*)

Table 2. (Continued)

Study	Quality	Diagnostic criteria for AD	Characteristics of AD patients[a]	Severity of AD	Prevalence of depression[b]	Statistical analysis	Results	Direction of association
Troisi *et al.* (1993)	1	NINCDS-ADRDA criteria for probable AD	$n = 26$	(1) MMSE:	MDD (DSM-III-R criteria): 23.1%	Chi-square tests:	(1) MDD: mildly-moderately impaired group: 7.7%; severely impaired group: 38.5%; control group: 11.5%; $\chi 2 = 5.51$, df = 2, $p = 0.06$	(1&2) No significant association
			Outpatients	mild-moderate (score: 16–23): 50%;		(1) comparison between control, mildly-moderately and severely impaired groups (based on MMSE) regarding frequency of MDD	(2) MDD: Mildly impaired group: 0%; Moderately impaired group: 11.5%; Severely impaired group: 11.5%; Control group: 11.5%; $\chi 2 = 5.11$, d.f. = 3, n.s.	
			Female gender: 54%	severe (score: ≤15): 50%		(2) comparison between control, mildly, moderately and severely impaired groups (based on DSM-III-R criteria) regarding frequency of MDD		
			Age: M (SD) = 74.0 (5.53), range = 65–84 Education: M (SD) = 7.15 (5.03), range = 0–19	(2) DSM-III-R: Mild: 26.9% Moderate: 42.3% Severe: 30.8%				

ADRDA = National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (McKhann *et al.*, 1984); BDS = Blessed Dementia Scale (Blessed *et al.*, 1968); BRSD = Behavioral Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Tariot *et al.*, 1995); CAMCOG = Cambridge Cognitive Examination (Roth *et al.*, 1986); CAMDEX = Cambridge Mental Disorders in the Elderly Examination (Roth *et al.*, 1986); CDR = Clinical Dementia Rating Scale (Morris, 1993); CI = Confidence Interval; CSDD = Cornell Scale for Depression in Dementia (Alexopolous *et al.*, 1988); df = degrees of freedom; DRS = Mattis Dementia Rating Scale (Mattis, 1988); DSM = *Diagnostic and Statistical Manual of Mental Disorders*, third (DSM-III), third revised (DSM-III-R) or fourth (DSM-IV) edition (American Psychiatric Association, 1980, 1987, 1994); HDRS = Hamilton Depression Rating Scale (Hamilton, 1960); MDD = Major Depressive Disorder; NINCDS—MMSE = Mini-Mental State Examination (Folstein *et al.*, 1975); n.s. = not significant; OR = Odds Ratio; PGDRS-P = Psychogeriatric Dependency Rating Scale- Physical dependency scale (Wilkinson and Graham-White, 1980); RDC = Research Diagnostic Criteria (Spitzer *et al.*, 1978).

[a]Data concerning education and duration of AD are presented in years, unless stated otherwise. Only psychiatric exclusion criteria are presented.

[b]If available scores on depression rating scales for the sample of patients with AD are also presented.

[c]No (further) data concerning the sample of patients with AD were reported.

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