Meta-Analysis of the Prevalence of Major Depressive Disorder Among Older Adults With Dementia

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ABSTRACT

Objective: Little is known about the overall prevalence of major depressive disorder (MDD) in persons with dementia (ie, "depression in dementia": DpD). The aim of this systematic review and meta-analysis was to determine the prevalence and factors associated with DpD among older adults (age range 58.7–87.8 years). The protocol was registered in the PROSPERO registry (2015:CRD42015020681).

Data Sources: We searched the following electronic databases: MEDLINE (1946–February 2017), Embase (1980–2017 week 5), and PsycINFO (1967–February 2017) using medical subject headings and free-text search terms for studies in the English language.

Study Selection: We screened 9,421 studies, and 55 met the inclusion criteria (ie, used validated criteria for both MDD and dementia).

Data Extraction: Two independent reviewers extracted data from included studies. Meta-analysis was used to determine the pooled estimates and 95% confidence intervals for the prevalence of DpD. Prevalence across dementia subtypes, study setting, diagnostic criteria, and dementia severity was compared in subgroup analyses.

Results: The prevalence of MDD in all-cause dementia was 15.9% (95% CI, 12.6%–20.1%). The prevalence of MDD was higher among individuals with vascular dementia (24.7%) compared to Alzheimer's disease (14.8%). Studies using the provisional diagnostic criteria for DpD reported a higher prevalence (35.6%) compared to studies using either the *DSM-III-R* (13.2%) or *DSM-IV* (17.3%) criteria.

Conclusions: Depression is common among individuals with dementia, and the type of dementia and diagnostic criteria affect prevalence estimates of DpD. Further studies are required to understand factors that lead to the development of DpD and strategies to prevent and treat DpD.

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With population aging, there will be increasing numbers of older adults with Alzheimer's disease and dementia.[1] Dementia currently affects 24 million individuals worldwide, and its prevalence is expected to quadruple by 2050.[2] While dementia is associated with cognitive changes, behavioral changes such as depression also frequently occur[3] with up to 20% of individuals reporting some degree of clinically significant depressive symptoms.[4] Depressive symptoms are even common in mild cognitive impairment (MCI)–a recent meta-analysis found that the prevalence of depression in MCI was an estimated 32%.[5] Depressive symptoms can have adverse consequences for patients and their care givers,[6] and thus a clear understanding of the prevalence of depression in dementia is warranted.

Individuals with dementia are twice as likely as age-matched controls to be diagnosed with depression[7]; conversely, the presence of chronic depression increases the risk of dementia later in life.[8] As operationalized in the construct mild behavioral impairment,[9] the emergence of new depressive symptoms in older adults is associated with increased risk of cognitive decline and dementia, suggesting that depression may be a prodrome of dementia in addition to a factor associated with poorer outcomes when comorbid with dementia.[10,11] It is hypothesized that depression and dementia may be linked by common risk factors such as vascular disease, hypothalamic-pituitary–axis dysfunction, and increased expression of inflammatory cytokines.[8,12,13] The occurrence of major depressive disorder (MDD) in dementia (ie, "depression in dementia": DpD) may accelerate cognitive and functional decline, lead to poor medical outcomes, hasten admission to long-term care, and increase mortality.[14–21] DpD is also associated with increased burden and depression among caregivers of people with dementia.[14,22]

Although there are known associations between MDD and dementia, the overall prevalence of DpD has not been well described. An estimated 60% of dementia patients with depressive symptoms meet the criteria for MDD, and 1 study reported a prevalence of MDD in dementia of 12.7%.[23] Other studies[12,14,24,25] have observed results that range from 8.0% to 40.0%, with many estimates near the lower end of the range. Possible reasons for the wide range may be due to different diagnostic criteria used to define MDD, methodological variation, and differences in the underlying study populations.

The goal of our study was to conduct a systematic review and meta-analysis to determine the prevalence of DpD among older adults (age range 58.7–87.8 years) in studies that used validated criteria for the diagnosis of both depression and dementia. We also investigated factors associated with DpD including subtype and severity of dementia, clinical setting of studies, and clinical criteria for diagnosing dementia and depression. This information may help us better understand the overall burden of DpD and inform screening, clinical evaluation, and management decisions.

Clinical Points

- Depressive symptoms commonly occur in people with dementia, although the prevalence of major depressive disorder and factors associated with depression in dementia are not well understood.
- For all patients with dementia, particularly those with vascular dementia, clinicians should be alert to the high prevalence of major depressive disorder.

METHODS

Literature Search and Inclusion Criteria

Our review was approved by Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board. Prior to beginning the literature review, our protocol was registered in the PROSPERO registry (2015:CRD42015020681).[26] We searched MEDLINE (1946 to February 2017), Embase (1980 to 2017 week 5) and PsycINFO (1967 to February 2017) databases for relevant articles. We used medical subject headings and free-text search terms to identify studies measuring the prevalence of depression in patients with dementia. See Supplementary Figure 1 for search terms used in the MEDLINE database; these terms were modified slightly for the other databases.

We included prospective and retrospective observational studies published in the English language. Depression was defined as MDD diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition, Revised (*DSM-III-R*) or more recent versions[27] or *International Classification of Diseases, Ninth Edition* (*ICD-9*) or more recent versions.[28] In addition to the generic criteria for MDD, we also included studies that used National Institute of Mental Health provisional criteria for depression in Alzheimer's disease (NIMH-dAD). These criteria were derived from the *DSM-IV* criteria for MDD with some modifications to the duration and frequency of depressive symptoms to reflect unique features of DpD.[29,30] Dementia was defined as all-cause dementia as diagnosed using *DSM-III-R* (or more recent) and *ICD-9* (or more recent) and as specific types of dementia using National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for Alzheimer's disease[31] and National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia.[32]

We excluded studies that only measured depressive symptoms without the criteria for MDD, studies of only Parkinson's disease and frontotemporal dementia, and studies that defined dementia solely using cognitive screening tests. We also excluded studies where the depression or dementia diagnosis was made retrospectively using chart reviews rather than clinical evaluations.

Titles and abstracts of citations that were retrieved from the electronic databases were screened by 2 authors, and relevant studies were retrieved for full-text review. In cases where there was conflict between reviewers, a third author reviewed the citation.

Data Extraction

Two authors used a standardized form to independently extract information from each study regarding the total sample size and proportion of individuals with dementia who met criteria for MDD. Demographic information such as mean age, sex, study setting (eg, community, outpatient, long-term care, inpatient), and study country, when reported, was extracted. Clinical data regarding dementia subtype (eg, Alzheimer's disease, vascular dementia [VaD], mixed dementia types [ie, VaD and Alzheimer's disease], or dementia with Lewy bodies [DLB]), diagnostic criteria for the diagnosis of MDD and dementia, mean scores on cognitive testing (eg, Mini-Mental State Examination [MMSE] or other tests), and dementia severity scales (eg, Clinical Dementia Rating), when reported, were also extracted.

Assessment of Study Quality

Study quality was assessed using the Loney criteria.[33] These criteria assess study bias through 8 characteristics: representativeness of the study population, sampling method, sample size, use of standardized criteria, and unbiased assessment of diagnoses and prevalence. We also considered the presence and size of confidence intervals in the estimates of prevalence. Each characteristic was rated "yes," "no," or "unclear" (see Table 2); "yes" answers indicated a lower risk of bias in the respective characteristics.

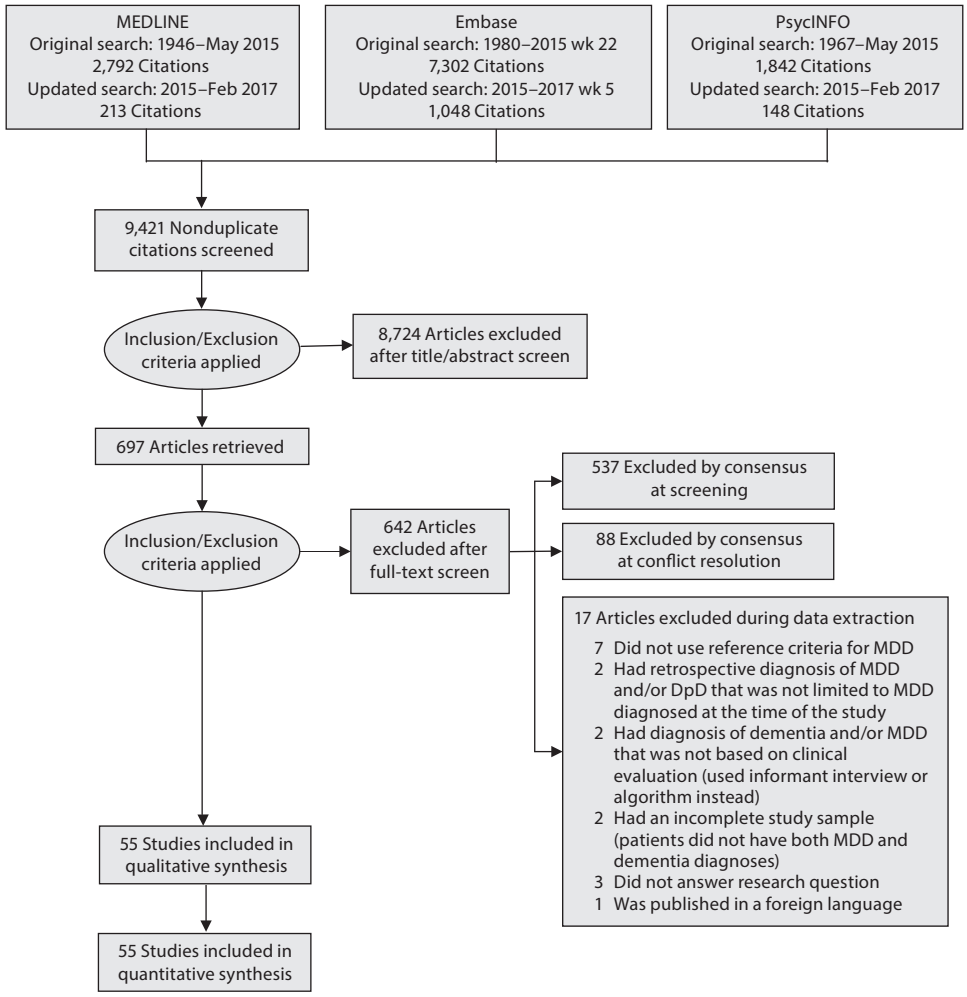
Data Synthesis and Meta-Analysis

Studies were assessed qualitatively to determine appropriateness to combine in meta-analysis. Estimates from clinically homogeneous study populations in individual studies were then combined using the logit transformation in a random-effects meta-analysis to arrive at the pooled estimates and 95% confidence intervals for the prevalence of DpD. We assessed the statistical heterogeneity of studies within the meta-analysis using the Q and I^2 statistics, with evidence of statistical heterogeneity defined as Q (χ^2) statistic P values of $<.1$ or I^2 values $>50\%$. In all analyses, 2-sided P values $<.05$ were used as the threshold for statistical significance. Publication bias was visually assessed using funnel plots. The software package R version 3.2.3 was used for all statistical analyses (R Development Core Team and R Foundation for Statistical Computing, Vienna, Austria).

Subgroup Analyses

A comparison of the prevalence of depression by dementia subtype (ie, Alzheimer's disease, VaD, mixed dementia types, or DLB), the criteria used to diagnose MDD and dementia, study continent, study setting (eg, community, outpatient, long-term care, inpatient), and severity of cognitive impairment was examined in subgroup analyses. Community setting was defined as participants from epidemiologic samples assessed in a general community setting or at home.

Figure 1. Study Search Results and Flow of Studies Through the Review Process



Abbreviations: DpD = MDD in persons with dementia (ie, "depression in dementia"), MDD = major depressive disorder.

Outpatient setting was defined as outpatients in a hospital or another health-care outpatient setting. Long-term care was defined as participants living in a long-term care or nursing-home facility. Inpatient setting included participants being admitted to a psychiatric inpatient unit at the time of their assessment. The severity of dementia was also examined in subgroup analyses and categorized as "mild" if the mean MMSE score was between 18–24, "moderate" if the mean MMSE score was between 10–17, and "severe" if the mean MMSE score was < 10. We also reported subgroup analyses on the basis of Clinical Dementia Rating scale scores of 0.5, 1, 2, and 3.

Sensitivity Analysis

To determine if study quality had an impact on the estimates of DpD and heterogeneity, we conducted a sensitivity analysis where the primary analysis of DpD was completed after excluding studies with a quality score of < 7 of 8.

RESULTS

Study Selection and Description of Included Studies

A total of 9,421 nonduplicate citations were found, and 8,724 were excluded after review of title and abstract. We included for full-text review 697 studies of which 642 were excluded. The flow diagram and reasons for exclusion are summarized in Figure 1. A total of 55 studies[29,34–87] met inclusion criteria (Table 1). Together, these studies included a total of 13,172 subjects. Thirty studies were conducted in unspecified or mixed outpatient and inpatient settings, 2 studies were conducted in a long-term care setting, 18 were conducted in outpatient settings, 3 were conducted in community settings, and 2 were conducted in inpatient settings.

Assessment of Study Quality

Most studies were found to be of high methodological quality. Of the 55 included studies, 46 studies had a score of

Table 1. Characteristics of Studies Evaluating the Prevalence of MDD in Dementia

Study	Country	Sample Size, n	Setting	Age, mean y	Female (%)	MMSE Score, mean	Dementia Subtype	MDD Criteria	Dementia Criteria	Prevalence of MDD, n (%)
Cummings et al, 1987[34]	United States	Total: 45 AD: 30 VaD: 15	Mixed (inpatient, outpatient)	AD: 70.4 VaD: 71.1	AD: 20.0 VaD: 26.7	AD: 10.7 VaD: 15.9	AD, VaD	*DSM-III-R*	NINCDS-ADRDA	Total: 4 (8.9%) AD: 0 (0%) VaD: 4 (26.7%)
Merriam et al, 1988[35]	United States	175	NA	72	58	NA	AD	*DSM-III-R*	*DSM-III-R*	150 (85.7%)
Rovner et al, 1989[36]	United States	144	Outpatient	66.5	67	9.5	AD	*DSM-III-R*	NINCDS-ADRDA, *DSM-III-R*	24 (16.7%)
Rovner et al, 1990[37]	United States	Total: 253 AD: 172 VaD: 81	LTC	NA	NA	NA	AD, VaD	*DSM-III-R*	*DSM-III-R*	Total: 15 (5.9%) AD: 7 (4.1%) VaD: 8 (9.9%)
Teri et al, 1991[39]	United States	75	Outpatient	74	68	18.1	AD	*DSM-III-R*	*DSM-III-R*	22 (29.3%)
Teri et al, 1991[38]	United States	61	NA	75	68	17.5	AD	*DSM-III-R*	*DSM-III-R*	28 (45.9%)
Skoog, 1993[40]	Sweden	Total: 147 AD: 64 VaD: 69 Other: 14	Mixed (community, institution)	NA	NA	NA	AD, VaD, Other	*DSM-III-R*	NINCDS-ADRDA, *DSM-III-R*	Total: 24 (16.3%) AD: 10 (15.6%) VaD: 11 (15.9%) Other: 3 (21.4%)
Troisi et al, 1993[41]	Italy	26	NA	73.96 (Median)	53.8	NA	AD	*DSM-III-R*	NINCDS-ADRDA, *DSM-III-R*	6 (23.1%)
Forsell et al, 1994[42,a]	Sweden	225	Community	NA	NA	NA	VaD, Other	*DSM-III-R*	*DSM-III-R*	19 (8.4%)
Vida et al, 1994[43]	Canada	26	Mixed (inpatient, outpatient)	70.2	38.5	17.4	AD	RDC	NINCDS-ADRDA	4 (15.4%)
Weiner et al, 1994[44]	United States	264	NA	73.7	67	15.4	AD	*DSM-III-R*	NINCDS-ADRDA	4 (1.5%)
Cummings et al, 1995[45]	United States	33	Mixed (inpatient, outpatient)	71.4	33	17.5	AD	*DSM-III-R*	NINCDS-ADRDA	2 (6.1%)
Migliorelli et al, 1995[46,a]	Argentina	103	NA	71.7	92.0	17.2	AD, Other	*DSM-III-R*	NINCDS-ADRDA	24 (23.3%)
Reichman and Coyne, 1995[47]	United States	Total: 105 AD: 67 VaD: 38	Mixed (outpatient, community)	AD: 77.7 VaD: 74.2	Total: 74.3	AD: 13.6 VaD: 19.9	AD, VaD	*DSM-III-R*	NINCDS-ADRDA, *DSM-III-R*	Total: 18 (17.1%) AD: 7 (10.5%) VaD: 11 (28.9%)
Starkstein et al 1995[48]	Argentina	103	NA	NA	73.7	NA	AD	*DSM-III-R*	NINCDS-ADRDA	80 (77.7%)
Ballard et al, 1996[49,a]	United Kingdom	124	NA	79.65	74.2	NA	AD, VaD, DLB	RDC	NINCDS-ADRDA, *DSM-III-R*	21 (16.9%)
Ballard et al, 1996[50]	United Kingdom	Total: 124 AD: 88 VaD: 20 DLB: 12 Other: 4	Mixed (primarily outpatient)	Total: 79.6	Total: 73.4	NA	AD, VaD, DLB, Other	RDC	NINCDS-ADRDA, *DSM-III-R*	Total: 31 (25.0%) AD: 15 (17.0%) VaD: 9 (45.0%) DLB: 4 (33.3%) Other: 3 (75.0%)
Bungener et al, 1996[51]	France	118	Outpatient	70.1	64	19.1	AD	*DSM-III-R*	NINCDS-ADRDA	0 (0.0%)
Lopez et al, 1996[52]	United States	40	NA	72.8	72.5	19.3	AD	*DSM-III-R*	NINCDS-ADRDA	2 (5.0%)
Lyketsos et al, 1996[53]	United States	137	NA	73.9	89.4	15.4	AD	*DSM-III-R*	NINCDS-ADRDA	38 (27.7%)
Zubenko et al, 1996[54]	United States	208	Inpatient	80.3 (7.0)	72	16.3	AD	*DSM-III-R*	*DSM-III-R*	43 (20.7%)
Ballard et al, 1997[55,a]	United Kingdom	124	Outpatient	79.7	NA	CAMCOG = 46.2	AD, VaD, DLB	*DSM-III-R*	NINCDS-ADRDA, *DSM-III-R*	21 (16.9%)
Lyketsos et al, 1997[56]	United States	120	Outpatient	73.6	68	NA	AD	*DSM-IV*	NINCDS-ADRDA	34 (28.3%)
Lyketsos et al, 1997[57]	United States	109	Mixed (primarily community)	74.4	79	15	NA	*DSM-IV*	NINCDS-ADRDA	24 (22.0%)

(continued)

Table 1 (continued).

Study	Country	Sample Size, n	Setting	Age, mean y	Female (%)	MMSE Score, mean	Dementia Subtype	MDD Criteria	Dementia Criteria	Prevalence of MDD, n (%)
Starkstein et al, 1997[58]	Argentina	116	Outpatient	72.8 (6.8)	92	17.7 (5.8)	AD	*DSM-III-R*	*DSM-III-R*	12 (10.3%)
Forsell and Winblad, 1998[60]	Sweden	306	Mixed	84.6	77.6	NA	AD	*DSM-IV*	*DSM-III-R*	36 (11.8%)
Forsell et al, 1998[59]	Sweden	306	Mixed (inpatient, outpatient)	87.8	83.3	NA	AD	*DSM-IV*	*DSM-III-R*	36 (11.8%)
Ballard et al, 1999[61]	United Kingdom	Total: 184 AD: 92 VaD: 92	Inpatient	AD: 79.1 VaD: 82.2	AD: 62 VaD: 67	NA	AD, VaD	*DSM-III-R*	NINDS-AIREN/ NINCDS-ADRDA	Total: 24 (13.0%) AD: 7 (7.6%) VaD: 17 (18.5%) Other: 5
Janzing et al, 1999[62,b]	Netherlands	91	Mixed (retirement and nursing homes)	NA	NA	NA	NA	*DSM-III-R*	*DSM-III-R*	2 (2.2%)
Liu et al, 1999[63]	Taiwan	141	Outpatient	72.72	55	CASI = 47.84	AD	*DSM-III-R*	NINCDS-ADRDA	7 (5.0%)
Newman, 1999[64]	Canada	621	NA	NA	74.2	NA	AD	*DSM-III-R*	NINCDS-ADRDA	15 (2.4%)
Hargrave et al, 2000[65]	United States	Total: 691 AD: 582 VaD: 48 Mixed: 61	NA	NA	68.71	NA	AD, VaD, Mixed	*DSM-III-R*	NINCDS-ADRDA	Total: 85 (12.3%) AD: 62 (10.7%) VaD: 13 (27.1%) Mixed: 10 (16.4%)
Harwood et al, 2000[66]	United States	55	NA	76.4	82	12.8	AD	*DSM-III-R*	NINCDS-ADRDA	11 (20.0%)
Ballard et al, 2001[67]	United Kingdom	Total: 214 AD: 132 DLB: 82	NA	AD: 76.5 DLB: 81.1	AD: 56 DLB: 56	NA	AD, DLB	*DSM-III-R*	NINCDS-ADRDA, *DSM-III-R*	Total: 26 (12.1%) AD: 13 (9.8%) DLB: 13 (15.9%)
Chemerinski et al, 2001[68]	Argentina	154	Outpatient	72.7	58	19.0	AD	*DSM-III-R*	*DSM-IV*	60 (39.0%)
Kertzman et al, 2002[69]	Israel	Total: 100 AD: 50 VaD: 50	Outpatient	AD: 72 VaD: 71	AD: 66 VaD: 71	AD: 22 VaD: 24	AD, VaD	*DSM-III-R*	NINCDS-ADRDA, *DSM-III-R*	Total: 38 (38.0%) AD: 14 (28.0%) VaD: 24 (48.0%)
Naarding et al, 2002[70]	Netherlands	274	Outpatient	71.1	59.5	18.96	AD	*DSM-IV*	NINCDS-ADRDA	62 (22.6%)
Weiner et al, 2002[71]	United States	586	NA	72.1	67.8	17.7	AD	*DSM-III-R*	NINCDS-ADRDA	28 (4.8%)
Lopez et al, 2003[72]	United States	1155	NA	NA	69.7	16.9	AD	*DSM-IV*	NINCDS-ADRDA	115 (10%)
Zubenko et al, 2003[73]	United States	243	Mixed (outpatient, LTC)	78.4	58.8	18	AD	*DSM-III-R*	NINCDS-ADRDA	44 (18.1%)
Starkstein et al, 2004[74]	Australia	272	Outpatient	71	61	21.8	AD	*DSM-IV*	NINCDS-ADRDA	48 (17.7%)
Landes et al, 2005[75]	United States	131	NA	75.1	53.4	18.5	AD	*DSM-IV*	NINCDS-ADRDA	11 (8.4%)
Østbye et al, 2005[76,a]	Canada	1125	Mixed (community, inpatient)	NA	NA	NA	AD, VaD	*DSM-III-R*	NINCDS-ADRDA, *DSM-III-R*	107 (9.5%)
Starkstein et al, 2005[77]	Argentina	670	Outpatient	72	59	19.2	AD	*DSM-III-R*	NINCDS-ADRDA	177 (26.4%)
Vilalta-Franch et al, 2006[78]	Spain	491	Outpatient	75.2	70.9	17.1	AD	*DSM-IV* *ICD-10* NIMH-dAD	NINCDS-ADRDA	*DSM-IV*: 66 (13.4%) *ICD-10*: 24 (49%) NIMH-dAD: 135 (27.5%)
Park et al, 2007[79]	S. Korea	Total: 216 AD: 108 VaD: 108	NA	AD: 72.37 VaD: 71.45	AD: 50.9 VaD: 50.9	AD: 14.88 VaD: 17.24	AD, VaD	*DSM-IV*	NINCDS-ADRDA, *DSM-IV*	Total: 33 (15.3%) AD: 11 (10.2%) VaD: 22 (20.4%)
Starkstein et al, 2007[80]	Argentina	278	NA	NA	NA	NA	AD	*DSM-IV*	NINCDS-ADRDA	82 (29.5%)
Delano-Wood et al, 2008[81]	United States	323	Outpatient	NA	NA	NA	AD	*DSM-III-R*	NINCDS-ADRDA	8 (2.5%)

(continued)

Table 1 (continued).

Study	Country	Sample Size, n	Setting	Age, mean y	Female (%)	MMSE Score, mean	Dementia Subtype	MDD Criteria	Dementia Criteria	Prevalence of MDD, n (%)
Teng et al, 2008[29]	United States	101	Outpatient	77.7	66	21.0	AD	*DSM-IV* NIMH-dAD	NINCDS-ADRDA	*DSM-IV*: 14 (13.9%) NIMH-dAD: 44 (43.6%)
Leontjevas et al, 2009[82,a]	Netherlands	63	LTC	58.7	52.4	NA	Mixed	NIMH-dAD	*DSM-IV*	12 (19.0%)
Iulio et al, 2010[83]	Italy	119	Outpatient	74.4	67.2	22.6	AD	NIMH-dAD	NINCDS-ADRDA	59 (49.6%)
Winter et al, 2011[84,b]	Germany	98	NA	77.5	65.3	NA	NA	*DSM-IV*	NINCDS-ADRDA	90 (91.8%)
Chiu et al, 2012[85]	Taiwan	302	Outpatient	77.5	72.2	13.0	AD	*DSM-IV* NIMH-dAD	NINCDS-ADRDA, *DSM-III-R*	*DSM-IV*: 28 (9.3%) NIMH-dAD: 90 (29.8%)
El Asmar et al, 2014[86]	Lebanon	162	Community	NA	NA	NA	AD	AGECAT	*DSM-IV*	66 (40.7%)
Benoit et al, 2012[87]	France	695	Outpatient	80	62.0	23.1	AD	NIMH-dAD	NINCDS-ADRDA	332 (47.8%)

[a]These studies did not report a specific prevalence of DpD for each dementia subtype in their sample. Since the prevalence cannot be determined for each subtype, these studies were excluded from the dementia subtype subgroup analysis in Figure 3.
[b]These studies did not report whether their sample contained a mixture of dementia subtypes; therefore, they have "NA" in the Dementia Subtype column and were not included in subgroup analysis in Figure 3.
Abbreviations: AD = Alzheimer's disease; AGECAT = Automated Geriatric Examination for Computer Assisted Taxonomy; CAMCOG = the Cognitive Section of the Cambridge Assessment for Mental Disorders in the Elderly; *CASI* = Cognitive Abilities Screening Instrument; DLB = dementia with Lewy bodies; *DSM-III-R* = *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised; *DSM-IV* = *DSM*, Fourth Edition; *ICD-10* = *International Classification of Diseases, Tenth Revision*; LTC = long-term care; MDD = major depressive disorder; MMSE = Mini-Mental State Examination; NA = not available; NIMH-dAD = National Institute of Mental Health provisional criteria for depression in Alzheimer's disease; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria; NINDS-AIREN = National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria; RDC = Research Diagnostic Criteria; VaD = vascular dementia.

7 or 8 on the quality assessment score. The remaining 9 studies received scores ranging from 4 to 6 (Table 2).

Meta-Analysis of the Prevalence of MDD in Older Adults With Dementia

The prevalence of DpD across all dementia subtypes varied from 0.0% to 91.8% in the individual studies (Figure 2). In meta-analysis, the overall prevalence of DpD for any definition of MDD and all-cause dementia was 15.9% (95% CI, 12.6%–20.1%; Figure 2). There was a high degree of heterogeneity noted in the overall meta-analysis ($I^2 = 98\%$, $P < .01$). There was no evidence of publication bias in this analysis, according to a visual inspection of the funnel plot (Supplementary Figure 2).

Subgroup Analyses

Prevalence of DpD by dementia subtypes. Of the 55 studies, 46 reported on the prevalence of DpD among individuals with Alzheimer's disease and 9 reported similarly among individuals with VaD. Two studies also reported on individuals with DLB. The pooled prevalence of DpD among older adults with AD was 14.8% (95% CI, 11.5–19.1), 24.7% (95% CI, 17.6–34.6) among those with VaD, and 21.5% (95% CI, 10.5–43.9) among those with DLB (Figure 3). There was a statistically significant difference between the 3 groups ($Q = 5.9$, $P = .05$), and pairwise comparisons of each subtype showed a statistical difference between Alzheimer's disease and VaD ($Q = 5.63$, $P = .02$) but none between the other comparisons (Alzheimer's disease vs DLB: $Q = 0.93$, $P = .34$; VaD vs DLB: $Q = 0.12$, $P = .73$). There was evidence of statistical heterogeneity within the Alzheimer's disease ($Q = 2{,}314.2$, $P < .01$, $I^2 = 98\%$) and the VaD subgroups ($Q = 37.3$, $P < .01$, $I^2 = 79\%$).

Prevalence of DpD by diagnostic criteria for MDD. All 55 studies reported at least one diagnostic criterion used to diagnose MDD. In reporting the prevalence of DpD, 34 studies used the *DSM-III-R*, 11 used the *DSM-IV*, 3 used the Research Diagnostic Criteria, 3 used the NIMH-dAD, 3 used multiple diagnostic criteria, and 1 used Automated Geriatric Examination for Computer Assisted Taxonomy to define MDD. Within the *DSM-III-R* and *DSM-IV* subgroups, the pooled prevalence of DpD was 13.2% (95% CI, 9.4%–18.6%) and 17.3% (95% CI, 9.6%–31.4%), respectively. The prevalence of DpD using NIMH-dAD was 35.6% (95% CI, 27.6%–46.0%). The difference between the 3 subgroups was statistically significant ($Q = 22.1$, $P < .01$), and pairwise comparisons of each subgroup showed a statistical difference between *DSM-III-R* and NIMH-dAD ($Q = 20.78$, $P < .01$) and *DSM-IV* and NIMH-dAD ($Q = 4.79$, $P = .03$) but none between *DSM-III-R* and *DSM-IV* ($Q = 0.61$, $P = .43$) (Supplementary Figure 3).

Prevalence of DpD by severity of cognitive impairment. A total of 10 studies reported on the prevalence of DpD among individuals with mild dementia (MMSE, 18–24) and 9 studies reported on individuals with moderate dementia (MMSE, 10–17). The pooled prevalence of DpD among those with mild dementia was 22.1% (95% CI, 15.7%–30.9%). The pooled prevalence of DpD among those with moderate dementia was 11.6% (95% CI, 6.9%–19.7%). The difference between the 2 subgroups did not meet the threshold for statistical significance ($Q = 4.03$, $P = .04$)

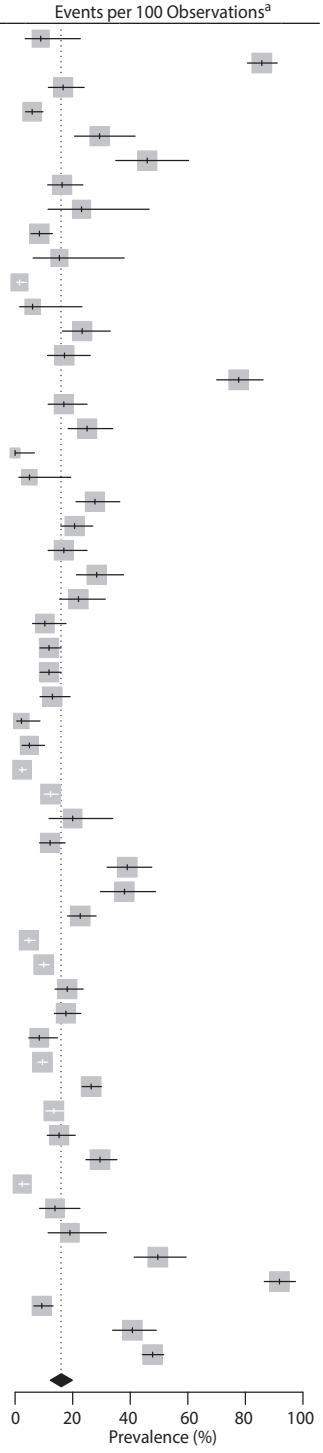
Table 2. Risk of Bias Assessment for Studies Included in the Review

Study	Are the study design and sampling method appropriate for the research question?	Is the sampling frame appropriate?	Is the sample size adequate?	Are objective, suitable, and standard criteria used for measurement of the health outcome?	Is the health outcome measured in an unbiased fashion?	Is the response rate adequate? Are the refusers described?	Are the estimates of prevalence or incidence given with confidence intervals and in detail by subgroup, if appropriate?	Are the study subjects and the setting described in detail and similar to those of interest to you?	**Quality Assessment Score**
Cummings et al, 1987[34]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Merriam et al, 1988[35]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Rovner et al, 1989[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Rovner et al, 1990[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Teri et al, 1991[39]	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	6
Teri et al, 1991[38]	No	No	No	Yes	Yes	Yes	Yes	Yes	5
Skoog, 1993[40]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	7
Troisi et al, 1993[41]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Forsell et al, 1994[42]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Vida et al, 1994[43]	No	No	No	Yes	Yes	Unclear	Yes	Yes	4
Weiner et al, 1994[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Cummings et al, 1995[45]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Migliorelli et al, 1995[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Reichman and Coyne, 1995[47]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Starkstein et al, 1995[48]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	6
Ballard et al, 1996[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Ballard et al, 1996[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Bungener et al, 1996[51]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Lopez et al, 1996[52]	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Yes	5
Lyketsos et al, 1996[53]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Zubenko et al, 1996[54]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Ballard et al, 1997[55]	Yes	Yes	No	Yes	Unclear	Unclear	Yes	Unclear	4
Lyketsos et al, 1997[56]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Lyketsos et al, 1997[57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Starkstein et al, 1997[58]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Forsell et al, 1998[59]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Forsell and Winblad, 1998[60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Ballard et al, 1999[61]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	7
Janzing et al, 1999[62]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Liu et al, 1999[63]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Newman, 1999[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Hargrave et al, 2000[65]	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	6
Harwood et al, 2000[66]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Ballard et al, 2001[67]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	7
Chemerinski et al, 2001[68]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Kertzman et al, 2002[69]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Naarding et al, 2002[70]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Weiner et al, 2002[71]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Lopez et al, 2003[72]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Zubenko et al, 2003[73]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Starkstein et al, 2004[74]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Landes et al, 2005[75]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Ostbye et al, 2005[76]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	7
Starkstein et al, 2005[77]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Vilalta-Franch et al, 2006[78]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Park et al, 2007[79]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Starkstein et al, 2007[80]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Delano-Wood et al, 2008[81]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Teng et al, 2008[29]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	7
Leontjevas et al, 2009[82]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Iulio et al, 2010[83]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Winter et al, 2011[84]	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Yes	5
Chiu et al, 2012[85]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Asmar et al, 2014[86]	Yes	Yes	Yes	Yes	Unclear	Unclear	No	Yes	5
Benoit et al, 2012[87]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8

Figure 2. Prevalence of MDD Among Older Adults With Any Type of Dementia

Study	Sample Size	Dep Dx (n)	Prevalence (%)	95% CI	Weight (%)
Cummings et al, 1987[34]	45	4	8.89	3.49–22.65	1.5
Merriam et al, 1988[35]	175	150	85.71	80.68–91.06	2.0
Rovner et al, 1989[36]	144	24	16.67	11.57–24.01	1.9
Rovner et al, 1990[37]	253	15	5.93	3.63– 9.69	1.8
Teri et al, 1991[39]	75	22	29.33	20.64–41.68	1.9
Teri et al, 1991[38]	61	28	45.90	34.96–60.28	1.9
Skoog, 1993[40]	147	24	16.33	11.32–23.54	1.9
Troisi et al, 1993[41]	26	6	23.08	11.44–46.55	1.7
Forsell et al, 1994[42]	225	19	8.44	5.49–12.98	1.9
Vida et al, 1994[43]	26	4	15.38	6.25–37.90	1.5
Weiner et al, 1994[44]	264	4	1.52	0.57– 4.01	1.5
Cummings et al, 1995[45]	33	2	6.06	1.58–23.22	1.2
Migliorelli et al, 1995[46]	103	24	23.30	16.41–33.08	1.9
Reichman and Coyne, 1995[47]	105	18	17.14	11.26–26.10	1.9
Starkstein et al, 1995[48]	103	80	77.67	70.03–86.14	2.0
Ballard et al, 1996[49]	124	21	16.94	11.47–25.01	1.9
Ballard et al, 1996[50]	124	31	25.00	18.43–33.91	1.9
Bungener et al, 1996[51]	118	0	0.00	0.03– 6.71	0.5
Lopez et al, 1996[52]	40	2	5.00	1.30–19.30	1.2
Lyketsos et al, 1996[53]	137	38	27.74	21.17–36.34	1.9
Zubenko et al, 1996[54]	208	43	20.67	15.84–26.98	1.9
Ballard et al, 1997[55]	124	21	16.94	11.47–25.01	1.9
Lyketsos et al, 1997[56]	120	34	28.33	21.32–37.66	1.9
Lyketsos et al, 1997[57]	109	24	22.02	15.47–31.35	1.9
Starkstein et al, 1997[58]	116	12	10.34	6.05–17.68	1.8
Forsell et al, 1998[59]	306	36	11.76	8.66–15.99	1.9
Forsell and Winblad, 1998[60]	306	36	11.76	8.66–15.99	1.9
Ballard et al, 1999[61]	184	24	13.04	8.98–18.94	1.9
Janzing et al, 1999[62]	91	2	2.20	0.56– 8.65	1.2
Liu et al, 1999[63]	141	7	4.96	2.41–10.22	1.7
Newman, 1999[64]	621	15	2.42	1.47– 3.98	1.8
Hargrave et al, 2000[65]	691	85	12.30	10.08–15.01	2.0
Harwood et al, 2000[66]	55	11	20.00	11.79–33.93	1.8
Ballard et al, 2001[67]	214	26	12.15	8.47–17.42	1.9
Chemerinksi et al, 2001[68]	154	60	38.96	31.97–47.48	2.0
Kertzman et al, 2002[69]	100	38	38.00	29.58–48.81	1.9
Naarding et al, 2002[70]	274	62	22.63	18.18–28.17	2.0
Weiner et al, 2002[71]	586	28	4.78	3.33– 6.86	1.9
Lopez et al, 2003[72]	1,155	115	9.96	8.37–11.84	2.0
Zubenko et al, 2003[73]	243	44	18.11	13.86–23.66	1.9
Starkstein et al, 2004[74]	272	48	17.65	13.65–22.81	1.9
Landes et al, 2005[75]	131	11	8.40	4.77–14.78	1.8
Østbye et al, 2005[76]	1,125	107	9.51	7.94–11.39	2.0
Starkstein et al, 2005[77]	670	177	26.42	23.28–29.98	2.0
Vilalta-Franch et al, 2006[78]	491	66	13.44	10.74–16.82	2.0
Park et al, 2007[79]	216	33	15.28	11.16–20.91	1.9
Starkstein et al, 2007[80]	278	82	29.50	24.59–35.38	2.0
Delano-Wood et al, 2008[81]	323	8	2.48	1.25– 4.91	1.7
Teng et al, 2008[29]	101	14	13.86	8.52–22.54	1.8
Leontjevas et al, 2009[82]	63	12	19.05	11.45–31.69	1.8
Iulio et al, 2010[83]	119	59	49.58	41.36–59.43	2.0
Winter et al, 2011[84]	98	90	91.84	86.57–97.42	2.0
Chiu et al, 2012[85]	302	28	9.27	6.52–13.19	1.9
El Asmar et al, 2014[86]	162	66	40.74	33.84–49.06	2.0
Benoit et al, 2012[87]	695	332	47.77	44.20–51.63	2.0
Random effects model			**15.90**	**12.58–20.10**	**100.0**

Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.7167$, $P < .01$



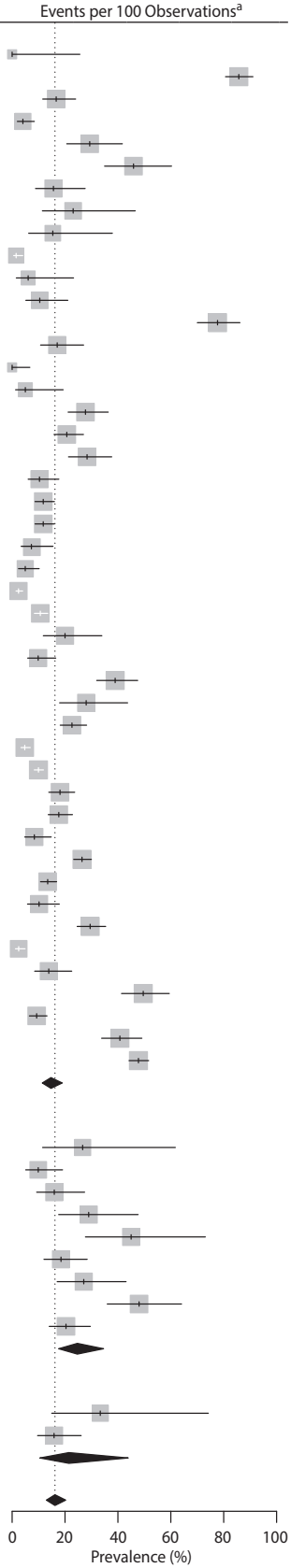
[a]The size of the square of each prevalence estimate reflects its precision based on the random effects meta-analysis. Confidence intervals that lie within that range are denoted by white crosshairs.
Abbreviations: Dep Dx (n) = number of individuals with a diagnosis of MDD, MDD = major depressive disorder.

(Supplementary Figure 4). There were also no differences in prevalence of DpD according to the Clinical Dementia Rating scale scores in the 4 studies reporting this information (Supplementary Figure 5).

Prevalence of DpD by study setting. A total of 18 studies reported on the prevalence of DpD in outpatient settings, 2 reported on those examined in long-term care, 3 reported on those in the community, and 2 reported on those sampled from inpatient settings. Studies in outpatient clinical settings reported a pooled prevalence estimate of DpD of 18.4% (95% CI, 13.9%–24.4%). The pooled prevalence of DpD among individuals in long-term care was 10.6% (95%

Figure 3. Prevalence of MDD Among Older Adults by Different Subtypes of Dementia

Study	Sample Size	Dep Dx (n)	Prevalence (%)	95% CI	Weight (%)
Dementia subtype = AD					
Cummings et al, 1987[34]	30	0	0.00	0.10–25.62	0.5
Merriam et al, 1988[35]	175	150	85.71	80.68–91.06	2.0
Rovner et al, 1989[36]	144	24	16.67	11.57–24.01	1.9
Rovner et al, 1990[37]	172	7	4.07	1.97–8.41	1.6
Teri et al, 1991[39]	75	22	29.33	20.64–41.68	1.9
Teri et al, 1991[38]	61	28	45.90	34.96–60.28	1.9
Skoog, 1993[40]	64	10	15.63	8.84–27.61	1.8
Troisi et al, 1993[41]	26	6	23.08	11.44–46.55	1.7
Vida et al, 1994[43]	26	4	15.38	6.25–37.90	1.5
Weiner et al, 1994[44]	264	4	1.52	0.57–4.01	1.4
Cummings et al, 1995[45]	33	2	6.06	1.58–23.22	1.2
Reichman and Coyne, 1995[47]	67	7	10.45	5.18–21.06	1.7
Starkstein et al, 1995[48]	103	80	77.67	70.03–86.14	2.0
Ballard et al, 1996[50]	88	15	17.05	10.75–27.03	1.8
Bungener et al, 1996[51]	118	0	0.00	0.03–6.71	0.5
Lopez et al, 1996[52]	40	2	5.00	1.30–19.30	1.2
Lyketsos et al, 1996[53]	137	38	27.74	21.17–36.34	1.9
Zubenko et al, 1996[54]	208	43	20.67	15.84–26.98	1.9
Lyketsos et al, 1997[56]	120	34	28.33	21.32–37.66	1.9
Starkstein et al, 1997[58]	116	12	10.34	6.05–17.68	1.8
Forsell et al, 1998[59]	306	36	11.76	8.66–15.99	1.9
Forsell & Winblad, 1998[60]	306	36	11.76	8.66–15.99	1.9
Ballard et al, 1999[61]	92	7	7.61	3.73–15.51	1.7
Liu et al, 1999[63]	141	7	4.96	2.41–10.22	1.6
Newman, 1999[64]	621	15	2.42	1.47–3.98	1.8
Hargrave et al, 2000[65]	582	62	10.65	8.42–13.48	1.9
Harwood et al, 2000[66]	55	11	20.00	11.79–33.93	1.8
Ballard et al, 2001[67]	132	13	9.85	5.88–16.50	1.8
Chemerinksi et al, 2001[68]	154	60	38.96	31.97–47.48	2.0
Kertzman et al, 2002[69]	50	14	28.00	17.95–43.67	1.8
Naarding et al, 2002[70]	274	62	22.63	18.18–28.17	1.9
Weiner et al, 2002[71]	586	28	4.78	3.33–6.86	1.9
Lopez et al, 2003[72]	1155	115	9.96	8.37–11.84	2.0
Zubenko et al, 2003[73]	243	44	18.11	13.86–23.66	1.9
Starkstein et al, 2004[74]	272	48	17.65	13.65–22.81	1.9
Landes et al, 2005[75]	131	11	8.40	4.77–14.78	1.8
Starkstein et al, 2005[77]	670	177	26.42	23.28–29.98	2.0
Vilalta-Franch et al, 2006[78]	491	66	13.44	10.74–16.82	1.9
Park et al, 2007[79]	108	11	10.19	5.82–17.83	1.8
Starkstein et al, 2007[80]	278	82	29.50	24.59–35.38	2.0
Delano-Wood et al, 2008[81]	323	8	2.48	1.25–4.91	1.7
Teng et al, 2008[29]	101	14	13.86	8.52–22.54	1.8
Iulio et al, 2010[83]	119	59	49.58	41.36–59.43	2.0
Chiu et al, 2012[85]	302	28	9.27	6.52–13.19	1.9
El Asmar et al, 2014[86]	162	66	40.74	33.84–49.06	2.0
Benoit et al, 2012[87]	695	332	47.77	44.20–51.63	2.0
Random effects model (AD)			**14.79**	**11.48–19.05**	**80.5**
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.6805$, $\chi^2_{45} = 2{,}314.21$ ($P < .01$)					
Dementia subtype = VaD					
Cummings et al, 1987[34]	15	4	26.67	11.52–61.72	1.6
Rovner et al, 1990[37]	81	8	9.88	5.12–19.07	1.7
Skoog, 1993[40]	69	11	15.94	9.27–27.41	1.8
Reichman and Coyne, 1995[47]	38	11	28.95	17.59–47.64	1.8
Ballard et al, 1996[50]	20	9	45.00	27.72–73.05	1.8
Ballard et al, 1999[61]	92	17	18.48	12.03–28.38	1.8
Hargrave et al, 2000[65]	48	13	27.08	17.03–43.08	1.8
Kertzman et al, 2002[69]	50	24	48.00	35.97–64.05	1.9
Park et al, 2007[79]	108	22	20.37	14.03–29.58	1.9
Random effects model (VaD)			**24.66**	**17.59–34.58**	**16.1**
Heterogeneity: $I^2 = 79\%$, $\tau^2 = 0.2009$, $\chi^2_8 = 37.31$ ($P < .01$)					
Dementia subtype = DLB					
Ballard et al, 1996[50]	12	4	33.33	14.98–74.20	1.6
Ballard et al, 2001[67]	82	13	15.85	9.63–26.10	1.8
Random effects model (DLB)			**21.46**	**10.49–43.91**	**3.4**
Heterogeneity: $I^2 = 58\%$, $\tau^2 = 0.1604$, $\chi^2_1 = 2.39$ ($P = .12$)					
Random effects model (all subtypes)			**16.27**	**13.01–20.35**	**100.0**
Heterogeneity: $I^2 = 98\%$, $\tau^2 = 0.6561$, $\chi^2_{56} = 2{,}384.83$ ($P < .01$)					
Test for subgroup differences: $\chi^2_2 = 5.88$ ($P = .05$)					



[a]The size of the square of each prevalence estimate reflects its precision based on the random effects meta-analysis. Confidence intervals that lie within that range are denoted by white crosshairs. Abbreviations: AD = Alzheimer's disease, Dep Dx (n) = number of individuals with a diagnosis of MDD, DLB = dementia with Lewy bodies, MDD = major depressive disorder, VaD = vascular dementia.

CI, 3.4%–33.3%), in the community was 20.0% (95% CI, 8.3%–48.0%), and in inpatient samples was 16.7% (95% CI, 10.7%–26.3%). There was no significant difference between subgroups ($Q = 1.0$, $P = .81$) (Supplementary Figure 6).

Prevalence of DpD by continent of study sample. We pooled the studies by continent for subgroup analysis: 5 were from Asia, 1 from Australia, 19 from Europe, 25 from North America, and 5 from South America. The pooled prevalence of DpD from studies in Asia was 17.0% (95% CI, 8.8%–32.7%); in Australian studies, 17.7% (95% CI, 13.7%–22.8%); in European studies, 18.1% (95% CI, 12.4%–26.5%); in North American studies, 12.2% (95% CI, 7.5%–19.8%); and in South American studies, 29.5% (95% CI, 16.1%–54.1%). The differences between subgroups were not statistically significant ($Q = 5.1$, $P = .28$) (Supplementary Figure 7).

Sensitivity Analysis

After excluding studies with a quality score of less than 7, the prevalence of DpD from the remaining 46 studies was 14.1% (95% CI, 10.9%–18.3%), and heterogeneity remained high ($Q = 2{,}364.5$, $P < .01$, $I^2 = 98\%$).

DISCUSSION

Our review found that MDD is common among older adults with dementia with a prevalence of 15.9%. There was a high degree of heterogeneity in the estimates of the prevalence of DpD. Some of the factors that were associated with the prevalence of DpD included type of dementia as well as the diagnostic criteria used for dementia. We did not observe that study setting or dementia severity had a significant impact on the prevalence of DpD. The findings from our review are consistent with a previous meta-analysis[23] of DpD, which reported a prevalence of 12.7%, although this study included only 25 studies as compared to the 55 studies that were included in our review. Overall, our review provides evidence supporting a high prevalence of DpD, highlighting its clinical importance in this population.

Our review indicates that individuals with dementia have an increased prevalence of MDD when compared to individuals without dementia, where depression prevalence is approximately 1.8%.[88] The reasons for this difference in prevalence are most likely multifactorial. Neurodegenerative changes associated with dementia may lead to alterations in neurotransmitters that contribute to the increased prevalence of depression.[79,89] Depression or depressive symptoms, common among individuals with MCI,[5] may also be a prodrome of dementia in many individuals,[10,12] and the presence of symptoms may be associated with an increased risk of subsequent conversion to dementia.[90] Chronic depression has also been identified as a risk factor for the development of dementia[91,92] and may contribute to the high prevalence of DpD. Individuals with dementia also frequently experience stressful life events and limited social supports that further contribute to the increased risk of depression.[93] There are quite likely multiple pathways that lead to the development of DpD, and further studies are required to understand how these different factors contribute.

One challenge with accurately diagnosing DpD is that depression itself is associated with cognitive impairment.[94] Individuals with major depression can display clinically significant cognitive deficits, particularly in measures of executive functioning and attention, both during depressive episodes and in the euthymic state.[94] The presence of cognitive deficits in depression can also be a marker of poor response to antidepressant treatment.[95] Our review focused on the diagnosis of MDD and dementia using validated diagnostic criteria, and as such, misclassification of individuals as having dementia when these cognitive deficits may have been caused by depression should have been minimal. However, additional studies are required to identify both neuropsychological profiles[94,96] and imaging biomarkers,[97] which may be useful in distinguishing between cognitive deficits caused by depression versus those of early dementia. In clinical practice, actively treating depression and other comorbidities that may be contributing to cognitive impairment would be recommended for individuals presenting with clinically significant depressive symptoms and cognitive impairment prior to establishing a diagnosis of dementia.

In our review, the prevalence of MDD in older adults with VaD (24.7%) was significantly higher than in those with Alzheimer's disease (14.8%). While there may be multiple reasons for this difference, it is most likely due to the direct relationship between cerebrovascular disease pathology and the risk of developing depression. Cerebrovascular disease is known to be an independent risk factor for depression among individuals without dementia; therefore, the higher rate of DpD in VaD is consistent with the increased risk of depression.[98] VaD is also a heterogeneous disease, and specific patterns of cerebrovascular disease in VaD (eg, multiinfarct dementia vs large cortical infarct) may be associated with different rates of MDD prevalence.[99] Our study suggests that individuals with VaD may be at particularly high risk of depression, and clinicians should carefully monitor mood symptoms in this population.

We found that the NIMH-dAD provisional diagnostic criteria for DpD were associated with higher prevalence estimates for DpD when compared to MDD criteria that are not specific to dementia. The NIMH-dAD criteria were derived from *DSM-IV* criteria with modifications that include reducing the number of core depressive symptoms from 5 to 3 symptoms, omitting the concentration criteria, and allowing symptoms to be present at any point within a 2-week period, which is in contrast to the *DSM-IV* requirement that all the symptoms be present for most of the time in a 2-week period.[30] Our review found that the NIMH-dAD criteria are quite likely more sensitive to detecting depression in older adults with dementia than the *DSM-IV* criteria, although the increased sensitivity may be associated with a loss of specificity.[29] Whether the NIMH-dAD is susceptible to false positives or the *DSM-III-R* or *DSM-IV*

is susceptible to false negatives is unknown, and whether 1 set of criteria is preferred or more accurate than another requires further study. Clinicians should be aware that the diagnostic criteria used to identify DpD may impact the case definition and prevalence estimates, and the criteria most relevant for clinical application may depend on the specific situation and intended clinical purpose such as screening or confirmation of diagnosis.

The estimated prevalence of DpD according to dementia severity was numerically higher among those with milder dementia than moderate dementia, although this was not statistically significant. While a recent meta-analysis[100] showed no association between dementia severity and frequency of depressive symptoms, another review[23] of DpD found a higher prevalence of MDD among individuals with milder severity of dementia. It is likely that depression criteria are more accurate among individuals with mild dementia where awareness of symptoms is preserved to a greater extent than among individuals with more advanced dementia.[101] Whether the accuracy of depression criteria differs across severities of dementia requires further study. Although not statistically significant, the prevalence of depression among individuals in long-term care was lower than in other settings. This may in part be related to the severity of dementia, which tends to be higher among long-term care residents, although other factors may also play a potential role in these differences as well.

The high prevalence of DpD has important clinical implications[14–21] and supports recommendations that clinicians should be vigilant for MDD in dementia.[102] Given the relatively high baseline probability of depression in dementia and the availability of screening tools with good diagnostic test properties,[103] screening for depression in dementia may be clinically feasible. Once depression is identified, guidelines recommend nonpharmacologic and supportive measures for all individuals with dementia,[104,105] and there is increasing evidence for specific psychotherapies for treatment of DpD.[106] Guidelines also recommend a trial of antidepressants when there is an inadequate response to nonpharmacologic management of MDD,[104,105] although the efficacy of antidepressants in treating DpD is controversial.[107]

Our study used rigorous review methods and included only studies that used standardized criteria for both MDD and dementia. Most of the included studies were of high methodological quality. However, significant statistical heterogeneity was observed in our meta-analyses. While we could identify some potential contributors to this heterogeneity, additional differences in underlying methodologies and study populations very likely contributed to this heterogeneity. There are some limitations to our review. Although our review was focused on MDD among individuals with dementia, subsyndromal symptoms of depression are also common in dementia and associated with poor outcomes.[4] The prevalence of subsyndromal depression and factors associated with these symptoms have been evaluated in mild cognitive impairment,[5] and examination of depressive symptoms more broadly among individuals with dementia should also be considered as a separate topic for meta-analysis. Information on the use of antidepressants was not reported in the majority of studies included in our review, although antidepressant use has been reported to be common among individuals with dementia.[108] The effectiveness of antidepressants for treating DpD is currently questionable,[18] and whether antidepressant treatment impacts the prevalence estimates is unknown.

CONCLUSION

MDD is common among individuals with dementia, and the prevalence of DpD varies with the type of dementia and depression criteria. Persons with dementia, caregivers, and health care providers should be aware of the high prevalence of MDD in dementia. Further research is needed to clarify the relationships between dementia and depression as well as to develop optimal strategies to identify and manage depression in individuals with dementia once it develops.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Geriatric Psychiatry section. Please contact Jordan F. Karp, MD, at jkarp@psychiatrist.com, or Gary W. Small, MD, at gsmall@psychiatrist.com.

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Supplementary Material

Article Title: Meta-Analysis of the Prevalence of Major Depressive Disorder Among Older Adults With Dementia

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List of Supplementary Material for the article

1. **Figure 1** Search Terms Used in Electronic Database Search
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4. **Figure 4** Forest Plot of Prevalence of Major Depressive Disorder in Dementia by Dementia Severity
5. **Figure 5** Forest Plot of the Prevalence of Major Depressive Disorder according to Clinical Dementia Rating Scale Scores.
6. **Figure 6** Forest Plot of the Prevalence of Major Depressive Disorder in Dementia by Setting of Study
7. **Figure 7** Forest Plot of the Prevalence of Major Depressive Disorder in Dementia by Continent of Study

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Supplementary eFigure 1: Search Terms Used in Electronic Database Search

1. exp Depressive Disorder/di [Diagnosis]

2. exp Depressive Disorder/ep [Epidemiology]

3. exp Depression/et [Etiology]

4. exp Depressive Disorder, Major/di [Diagnosis]

5. exp Depressive Disorder/et [Etiology]

6. exp Depressive Disorder, Major/ep [Epidemiology]

7. exp Depression/di [Diagnosis]

8. exp Depression/ep [Epidemiology]

9. exp Depression/cl [Classification]

10. depression.mp.

11. "major depression".mp.

12. "major depressive disorder".mp.

13. exp Alzheimer Disease/co [Complications]

14. exp Alzheimer Disease/di [Diagnosis]

15. exp Alzheimer Disease/ep [Epidemiology]

16. exp Dementia/di [Diagnosis]

17. exp Dementia/ep [Epidemiology]

18. exp Dementia, Vascular/di [Diagnosis]

19. exp Dementia, Vascular/ep [Epidemiology]

20. exp Dementia, Multi-Infarct/di [Diagnosis]

21. exp Dementia, Multi-Infarct/ep [Epidemiology]

22. exp Dementia/co [Complications]

23. exp Dementia/cl [Classification]

24. Alzheimer.mp.

25. dementia.mp.

26. "dementia with Lewy bodies".mp.

27. "Lewy body dementia".mp.

28. "Parkinson's disease dementia".mp.

29. exp Prevalence/

30. exp Retrospective Studies/

31. exp Cross-Sectional Studies/

32. prevalence.mp.

33. frequency.mp.

34. exp Incidence/

35. incidence.mp.

36. exp Epidemiology/

37. "prevalence studies".mp.

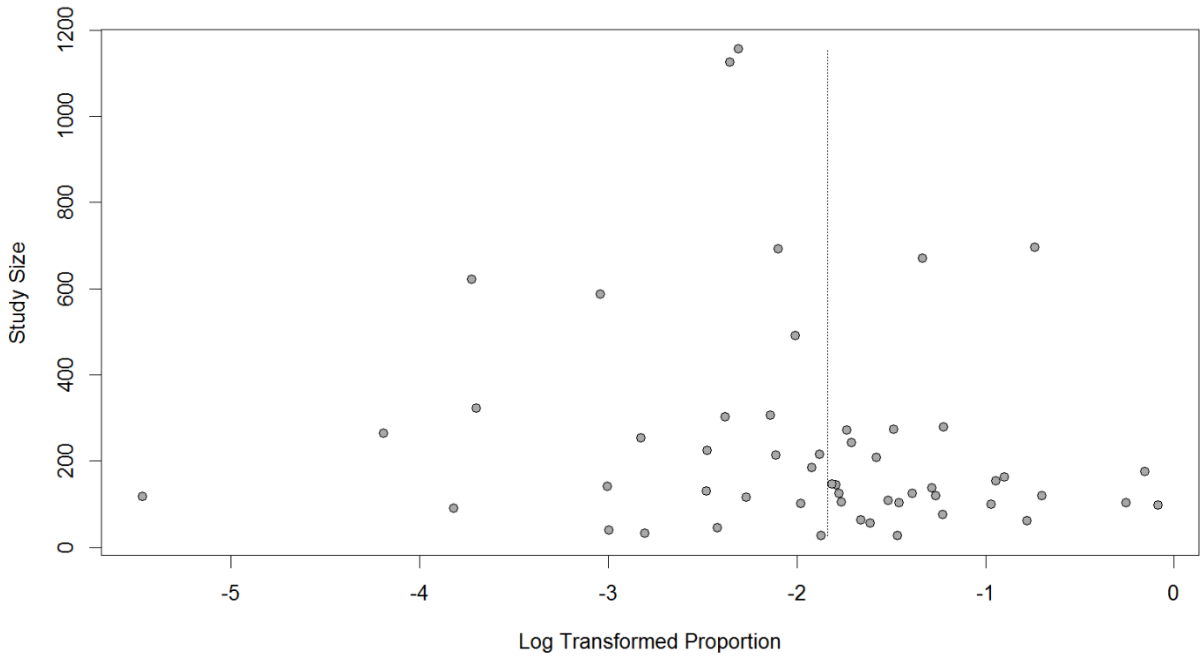
38. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12

39. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

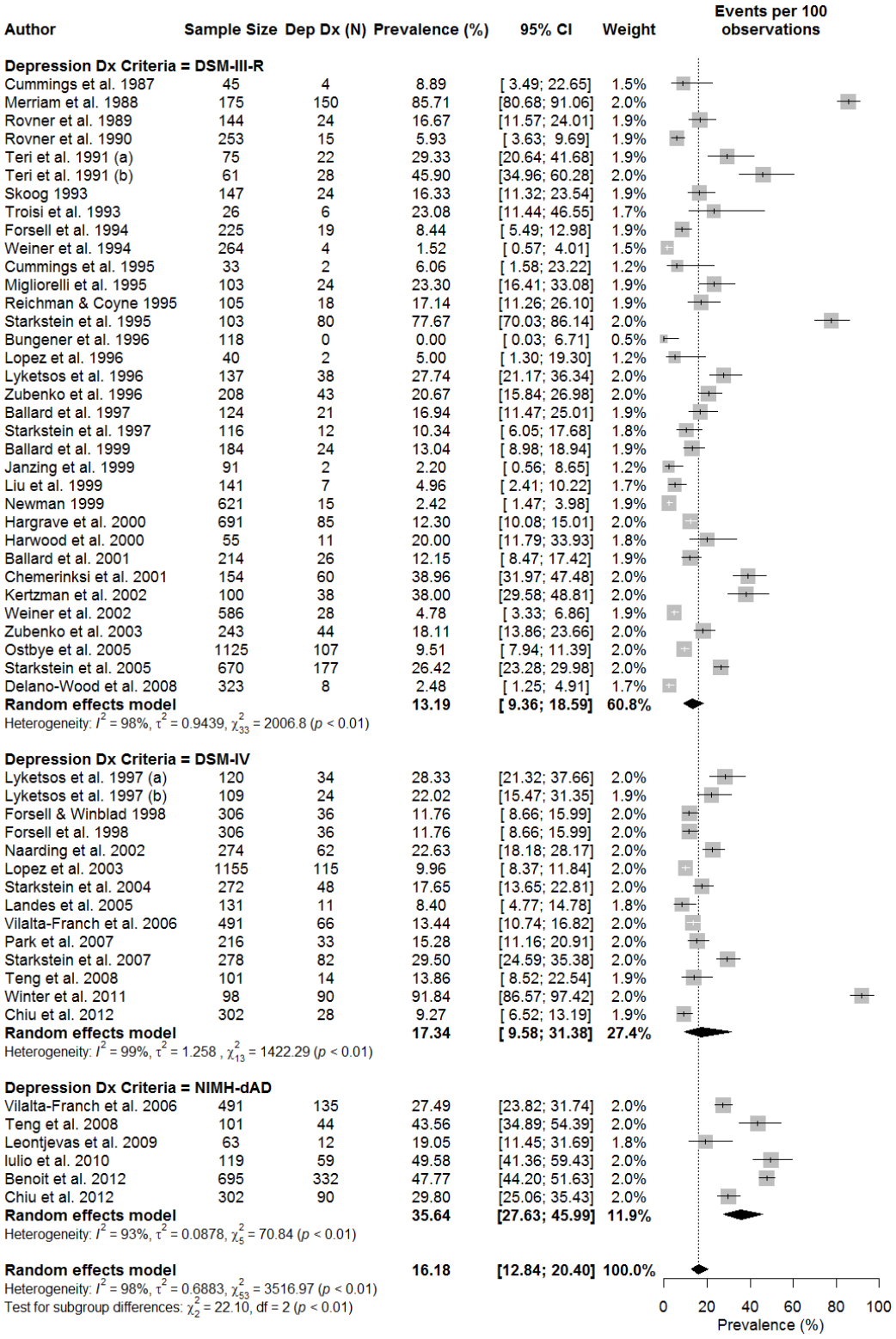
40. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37

41. 38 and 39 and 40

Supplementary eFigure 2: Funnel Plot of the Prevalence of Major Depressive Disorder in Dementia

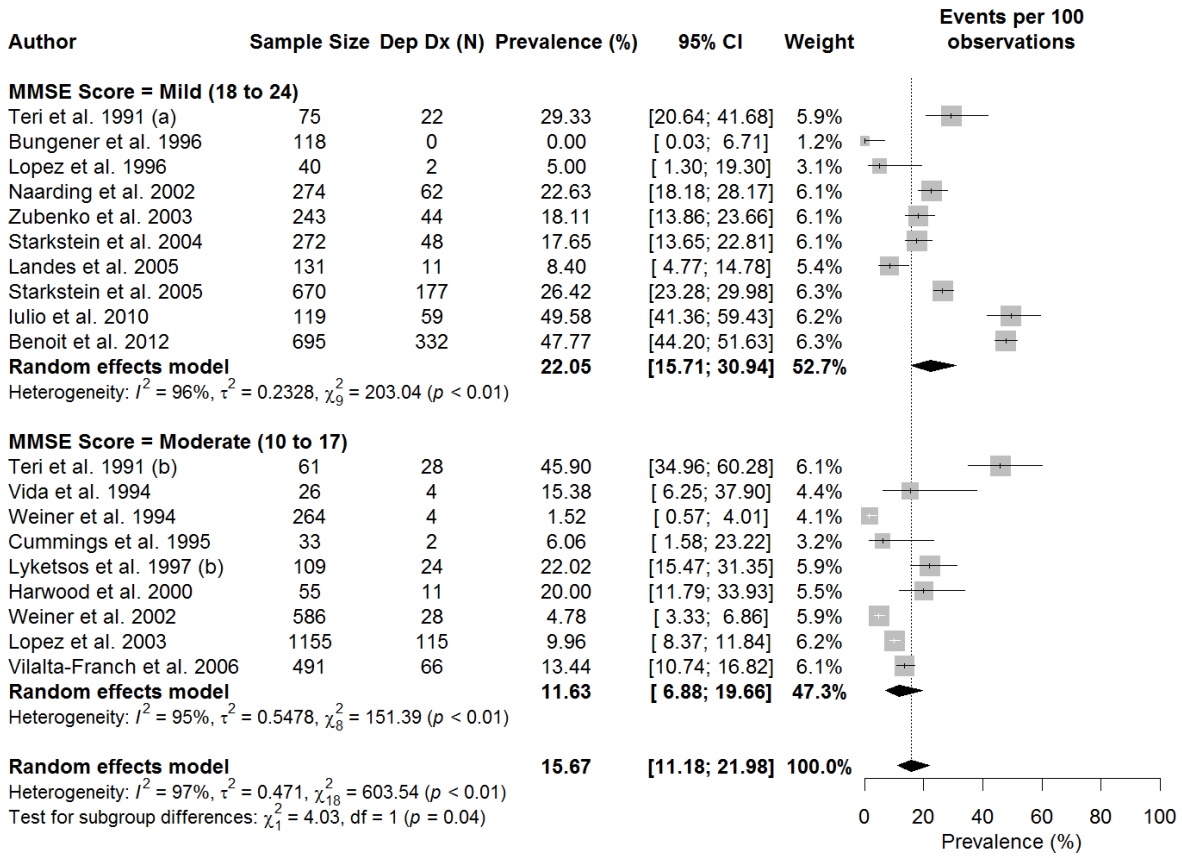


Supplementary eFigure 3: Forest Plot of the Prevalence of Major Depressive Disorder (MDD) in Dementia by Diagnostic Criteria for MDD.



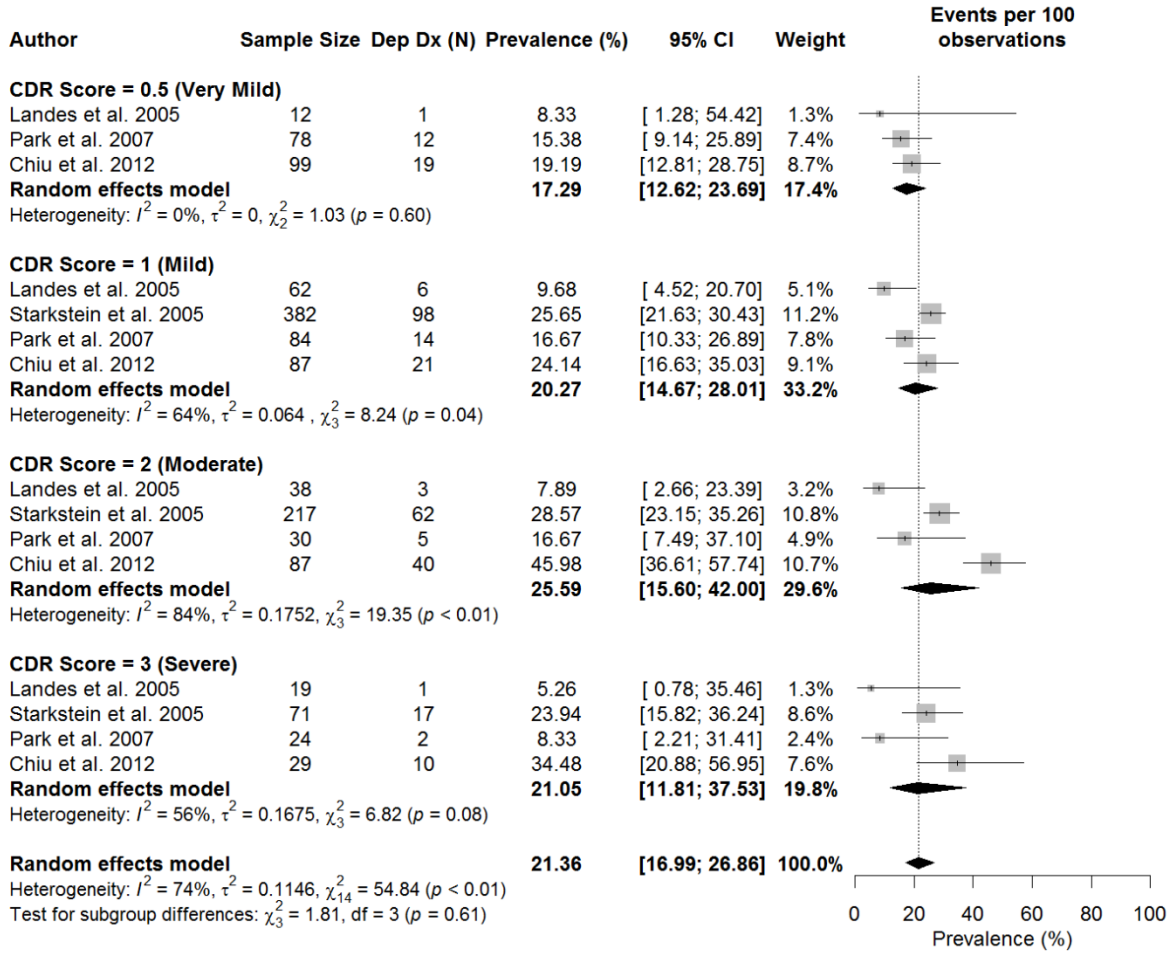
Note: Dep Dx (N): Number of individuals with a depression diagnosis; Depression Dx Criteria: Criteria used to diagnosis depression; DSM-III-R: Diagnostic and Statistics Manual of Mental Disorders, 3rd edition, Revised; DSM-IV: Diagnostic and Statistics Manual of Mental Disorders, 4th edition; NIMH-dAD: National Institute of Mental Health provisional criteria for depression in Azheimer's disease.

Supplementary eFigure 4: Forest Plot of Prevalence of Major Depressive Disorder in Dementia by Dementia Severity.



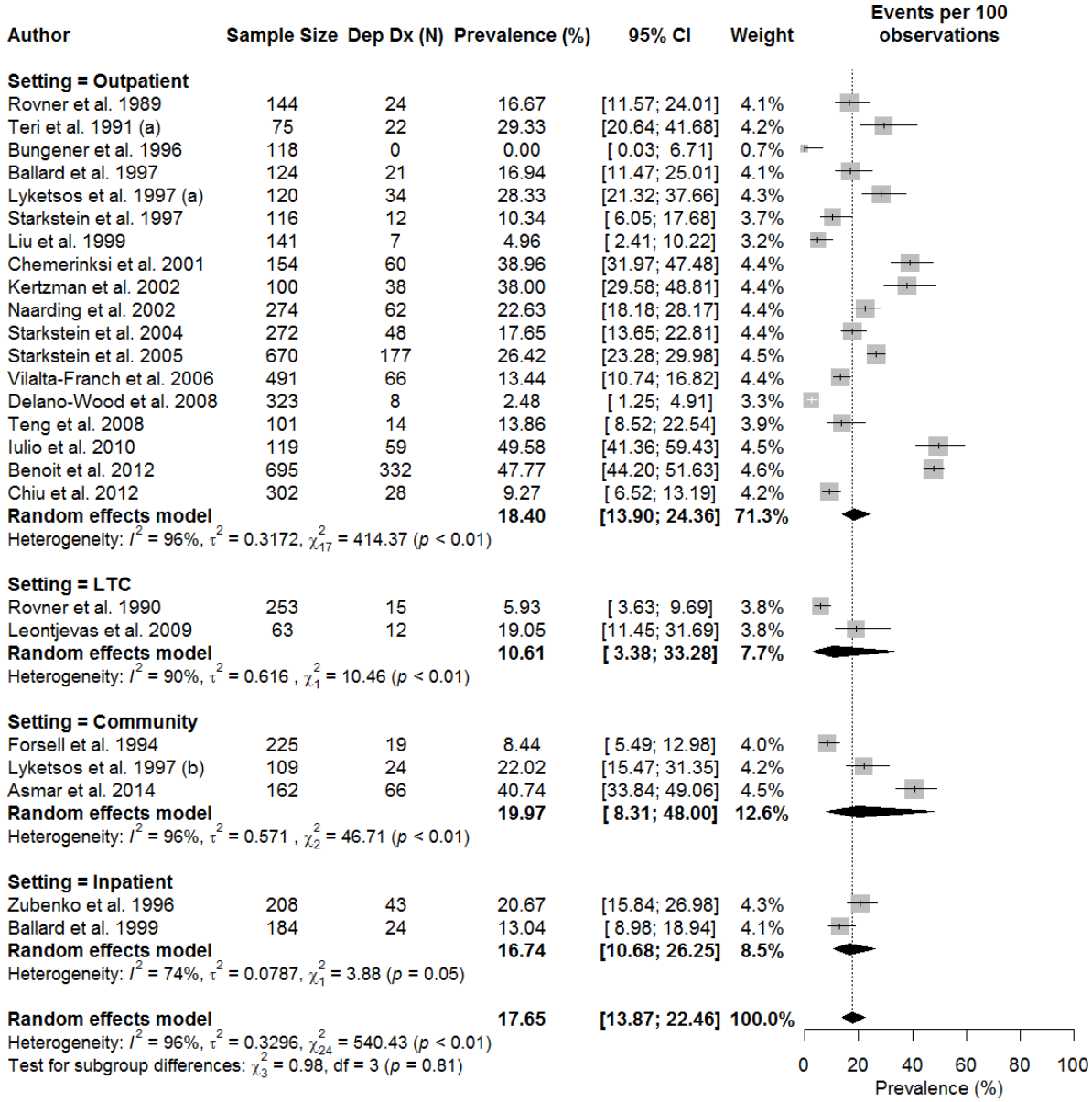
Note: Dep Dx (N): Number of individuals with a depression diagnosis; MMSE: Mini-Mental State Examination

Supplementary eFigure 5: Forest Plot of the Prevalence of Major Depressive Disorder according to Clinical Dementia Rating Scale Scores.



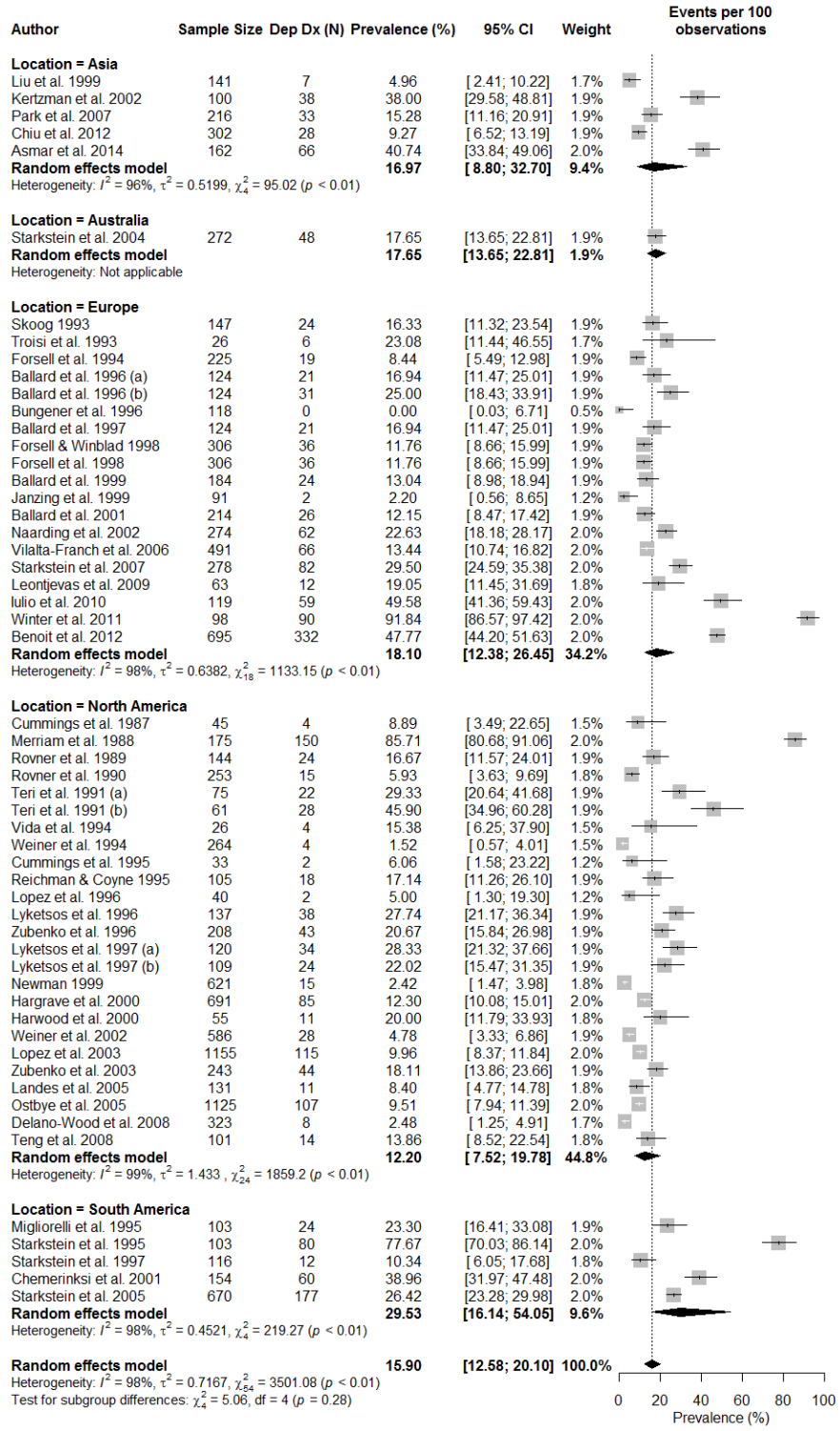
Abbreviations: CDR: Clinical Dementia Rating; Dep Dx (N): Number of individuals with a depression diagnosis.

Supplementary eFigure 6: Forest Plot of the Prevalence of Major Depressive Disorder in Dementia by Setting of Study.



Note: Dep Dx (N): Number of individuals with a depression diagnosis; LTC: Long-term care.

Supplementary eFigure 7: Forest Plot of the Prevalence of Major Depressive Disorder in Dementia by Continent of Study.



Note: Dep Dx (N): Number of individuals with a depression diagnosis.