Prevalence of depression, anxiety, and apathy symptoms across dementia stages: a systematic review and meta-analysis

Dara K.Y. Leung,[1] W.C. Chan,[2] Aimee Spector,[3] and Gloria H.Y. Wong[1]

[1]Department of Social Work and Social Administration, The University of Hong Kong, Hong Kong; [2]Department of Psychiatry, The University of Hong Kong, Hong Kong; and [3]Division of Psychology and Language Sciences, University College London, UK

Address correspondence to Gloria H.Y. Wong, Department of Social Work and Social Administration, The University of Hong Kong, 5/F, The Jockey Club Tower, The University of Hong Kong, Pokfulam, Hong Kong. E-mail: ghywong@hku.hk

Conflict of interest

None.

Funding

None.

Abstract

Objectives

The present study aimed to resolve inconsistency in reported prevalence of affective symptoms by dementia stage.

Methods/Design

We conducted a meta-analysis of studies with data on dementia stage and prevalence of depression, anxiety, or apathy assessed using validated tools. We performed random-effects meta-analysis and subgroup analysis on symptom prevalence by dementia stage, according to CDR.

Results

The meta-analysis included 5,897 people with dementia from 20 studies. Prevalence rates of depression in mild, moderate, and severe dementia were 38% (95% CI 32-45%), 41% (95% CI 33-49%), and 37% (95% CI 17-56%) respectively. The corresponding prevalence for anxiety was 38% (95% CI 31-45%), 41% (95% CI 31-52%), and 37% (95% CI -8-82%); and 54% (95% CI 45-62%), 59% (95% CI 44-73%), and 43% (95% CI 10-75%) for apathy. The prevalence of depression, anxiety, and apathy did not differ with regard to dementia stage and type. The prevalence of depression in Alzheimer's disease (AD) was significantly lower when it was assessed using diagnostic criteria compared to screening tools. The prevalence of depression in AD was lowest in America, while anxiety in vascular dementia was higher in Europe than Asia.

Conclusions

Depression, anxiety, and apathy symptoms are highly prevalent across dementia stages. There is no evidence of any changes in prevalence of affective symptom as the illness progresses. Evaluation methods and cultural difference may explain some of the variance, suggesting further investigation of factors that may influence the report of symptoms, such as carer psychosocial characteristics, and more cross-cultural studies are needed.

Keywords

Dementia; depression; anxiety; apathy; prevalence; systematic review; meta-analysis; neuropsychiatric symptoms; Alzheimer's disease; vascular dementia

Key points

- Random-effects meta-analysis showed no evidence of any changes in prevalence of depression, anxiety, and apathy as dementia progresses in general dementia, AD and VaD population.
- The variance of prevalence in depression and anxiety may be attributable to symptom evaluation method and region of study conducted.
- Future studies could examine the pattern and management of affective symptoms in relation to carer psychosocial characteristics and across culture.

Introduction

Dementia is a group of neurocognitive conditions affecting over 47 million people globally, and the number is expected to triple by 2050.[1] Cognitive decline affects individuals' functioning and self-care ability, together with the behavioral and psychological symptoms (BPSD) associated with dementia, these put strain on their family members, as well as the society. Depression, anxiety, and apathy are amongst the most frequent and clinically significant BPSD.[2] These symptoms have often been grouped into an affective symptoms cluster,[3] although apathy could also be categorized into a separate subsyndrome in a four-subsyndrome model (i.e., psychosis, affective, apathy, hyperactivity) with overlapping symptoms.[4,5] Affective symptoms including apathy have a negative impact on people with dementia and their carers, including reduced quality of life,[6,7] independence in daily living,[8,9] early institutionalisation,[10] and carer distress.[11]

Psychosocial interventions have been implicated for affective symptoms in people with dementia, including behavioral activation, interpersonal therapy, cognitive behavioural therapy, counselling, and other means to improve communication.[12,13] Evidence on the effectiveness of these psychosocial interventions, however, remains inconclusive.[14] This is potentially due to the diverse target population regarding dementia severity, who may require different intervention design considering factors such as insight and ability to understand verbal communication. Accurate estimates of depression, anxiety, and apathy at different stages of dementia would help identify the best stage to intervene and inform tailored, stage-specific psychosocial intervention design and provide psychoeducation to family carers to develop care plan in advance.

Existing literature reported inconsistent relationship between affective symptoms and dementia severity. One source of inconsistency is the definitions of dementia severity used in these studies. In a systematic review,[15] which included studies using Clinical Dementia Rating

(CDR)[16] and Global Deterioration Scale (GDS)[17] as dementia severity indicator, anxiety was described to be relatively stable across the range of dementia severity, until the profound/terminal stage, where it decreases. Both CDR and GDS are commonly used staging tools that consider both cognitive performance and functioning or self-care ability. Other meta-analyses, however, reported a positive correlation between dementia severity and prevalence of apathy[18], but no effect of dementia severity on the prevalence of depression[18-20] and anxiety.[18] These latter analyses used the mean score on Mini-Mental State Examination (MMSE) as the indicator of dementia severity, which does not take into account functioning or self-care ability, despite their relevance in the development of affective symptoms through self-appraisal when insight allows.

Another source of inconsistency is related to the type of dementia. In a study that explored prevalence of BPSD in four major dementia types, prevalence of depression and anxiety increased significantly with higher CDR scores in AD,[21] while apathy increased significantly with higher CDR scores in AD, dementia with Lewy bodies, vascular dementia, and frontotemporal dementia.[21] In a study that explored the relationship between prevalence of BPSD and dementia severity in AD and dementia with Lewy bodies, anxiety was most prevalent in those with MMSE scores higher than 20 in AD, whereas depression and anxiety were most common in those with MMSE scores less than 10 in vascular dementia.[22] Others reported no significant differences[3,23] or did not report statistical difference across dementia stages in the prevalence of affective symptoms.[22,24]

This study aims to resolve the inconsistency in reported prevalence of depressive, anxiety, and apathy symptoms across dementia stages and by dementia types, to support further development in psychosocial intervention research, through conducting a meta-analysis of studies with data on dementia stage and prevalence of affective symptoms assessed using validated tools.

Method

This meta-analysis protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[26] and was pre-registered at PROSPERO international prospective register of systematic reviews (Ref ID: CRD42019131869).

Search strategy

Systematic searches were conducted in PubMed, EMBASE, Web of Science, and PsycINFO database in November 2020. The text terms and MeSH terms used were "dementia" AND "depression" OR "anxiety" OR "apathy". Detailed search terms are shown in supplementary materials. References were exported and managed using EndNote X8.

Inclusion and exclusion criteria

Studies were included that (a) were original research published in scholarly peer-reviewed journals until 2020; (b) focused on dementia using standardized criteria (DSM III or above[27,28], ICD-10 or above[29], NINCDS-ADRDA[30], NINDS-AIREN[31], International consensus criteria for behavioral variant FTD[32], and consensus report of the DLB Consortium[33]), (c) reported dementia stage using CDR or GDS score; (d) reported sufficient information on depression, anxiety, or apathy to calculate the prevalence; (e) assessed depression, anxiety, or apathy symptoms using a validated scale; (f) had a sample size of at least 50, following the criteria suggested by Zhao,[18] in any of the reported dementia stage; and (g) were published in English. For example, if a study had 60 PLwD at mild stage and 10 at severe stage, it would be included in the analysis, but data from severe stage would be excluded. The studies were included regardless of settings.

We excluded studies that were review articles, editorials, commentaries, hypothesis papers, letters without original data, or meta-analysis. Where there was more than one publication reporting data from the same population, the less comprehensive or, if the reported data were equally comprehensive in these publications, the older reports were excluded.

Data extraction and analysis

We extracted the following data from each included study: study characteristics (publication year, country, sample size by CDR or GDS stage, community- or clinic-based setting), population demographics (gender, age, education level, CDR or GDS), condition information (dementia diagnostic criteria, method of affective symptoms assessment, dementia type), and the reported prevalence or information needed to calculate an estimate of affective symptom prevalence. For publications involving multiple assessment time points, only the baseline prevalence was included. Extracted data were entered into an electronic spreadsheet and analyzed using the *meta* and *metafor* packages in R Studio 4.0.2. Crude prevalence was computed for each study. Pooled estimates of prevalence and 95% confidence interval were calculated using random-effects meta-analysis. Analyses of the heterogeneity of prevalence and severity across studies were done with I^2 statistic, with $I^2 \geq 75\%$ indicating high heterogeneity. Subgroup analysis was used to estimate the extent to which measured covariates (dementia severity, assessment tools and study region) could explain the observed heterogeneity in prevalence estimates across studies. Publication bias was examined using Egger's test. For all tests, $p<.050$ was deemed significant.

The reporting quality of all included studies was assessed using the Joanna Briggs Institute Prevalence Critical Appraisal Tool[34]. The instrument was specifically designed to assess the methodological quality of prevalence study and to determine the extent to which the study has addressed the possibility of bias in its design, conduct and analysis. The adequate

sample size was calculated to be 384 assuming the prevalence of affective symptoms was around 20%.

Results

The initial search yielded 12,059 references. A total of 7,370 references remained after deduplication, with an additional seven study identified through reference lists of previous studies. After the initial screen, 319 studies met the criteria for full-text review, of which 299 were excluded based on the inclusion/exclusion criteria. In total, 20 original studies were included in this meta-analysis. Figure 1 outlines our search and screening strategy.

[insert Figure 1]

The key parameters used in the meta-analysis were summarized in Table 1, specific details for each study were shown in Table 2. Among the 20 included studies, less than a third of the studies indicated age, gender, and education year by dementia stage and type. Majority of the studies investigated depression (n=19), followed by apathy (n=13) and anxiety (n=12). All included studies used CDR to assess dementia stage. Three studies reported data on all stages of dementia, six on mild and moderate dementia, ten on mild dementia and one on moderate dementia. Most of the studies were conducted in AD (n=19) and VaD (n=4). One only study reported data on DLB, which was excluded from the subgroup analysis. 17 studies recruited participants from clinic settings, including memory clinics and hospitals, two recruited from community settings such as national survey, and one recruited participants from community centers and hospital. The majority of studies used screening tools to assess depression, anxiety, and apathy symptoms, which included the Neuropsychiatric Inventory[35] (NPI) (n=16), Neuropsychiatric Inventory-Questionnaire[36] (NPI-Q) (n=2), Behavioral

Pathology in Alzheimer's Disease Rating Scale[37] (BEHAVE-AD) (n=1), Behavior Rating Scale for Dementia[38] (BRSD) (n=1). Four studies assessed depression in AD using diagnostic criteria, including National Institute of Mental Health provisional criteria for depression in Alzheimer's Disease[39] (NIMH-dAD) (n=1), Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised[27] (DSM-III-R) (n=2), Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[28] (DSM-IV) (n=1). Two studies assessed self-reported depression from people with dementia using the Geriatric Depression Scale (GDS) and Cornell Scale for Depression in Dementia (CSDD). The studies were conducted in 10 countries and territories: Taiwan (n=3), the USA (n=3), Korea (n=3), Italy (n=2), Hong Kong (n=2), Japan (n=1), Finland (n=1), Norway (n=1), Spain (n=1), and Argentina (n=1).

Half of the studies met more than half of the nine criteria from the Joanna Briggs Institute Prevalence Critical Appraisal Tool[34] (see Supplementary Table 1). One item with low rating was condition measured in a standard, reliable way. Studies scored on this item if they used clinical diagnostic criteria in identifying condition instead of self- or informant-reported scales, however, since we aimed to include affective symptoms identified by both diagnostic criteria and validated scales, the low rating on this item was less likely to have an impact on the current study. Nonetheless, over half of the studies did not report how the assessment was conducted, resulting in a high "unclear" rating. Other items with higher "unclear" rating were adequate response rate and data analysis considering the response rate. These studies reported the number of participants enrolled in the study, but there was insufficient information of the process of recruitment, such as the number of people approached and provided informed consent, to determine the response rate.

[insert Table 1 and 2]

Prevalence of depression

The prevalence of depressive symptoms ranged from 10% to 78%, with an overall pooled prevalence of 39% (95% CI 34-44%; I^2=96%, p<.001). Table 3 shows the random-effects meta-analysis results on prevalence of depression by dementia stage. The average prevalence of depressive symptoms in mild dementia was 38% (range, 10-78%; 96% CI 32-45%; I^2=96%, p<.001); in moderate dementia was 41% (range, 15-61%; 95% CI 17-56%; I^2=93%, p<.001); and 27% in severe dementia (range, 17%-55%; 95% CI 16-39%; I^2=87%, p <.001). In AD, the prevalence of depressive symptoms ranged from 10% to 78%, with an overall pooled prevalence of 38% (95% CI 32-43%; I^2=96%, p<.001). The average prevalence of depressive symptoms in mild AD was 37% (95% CI 30-44%; I^2=96%, p<.001); in moderate AD was 40% (95% CI 31-48%; I^2=97%, p<.001) and 37% (95% CI 16-57%; I^2=93%, p<.001) in severe (see Supplementary Figure 1). Three studies employed more than one criterion to indicate the presence of depression. Two of them identified depression as scoring one or above in the NPI and clinically significant depression as scoring three or above.[40,41] Prevalence of depression was lower than that of clinically significant depression in both studies. Another study identified depression using criteria of minor depressive disorders and major depressive disorders according to DSM-III-R; the prevalence rates reported using the former criteria were higher than those using the latter at moderate and severe AD.[42] Two studies compared self-reported depression with informant-reported and clinical diagnosed depression. Prevalence of self-reported depression was higher than clinically diagnosed or informant-reported significant depression,[41,43] and lower than informant-reported non-clinically significant depression.[41] Seven studies compared prevalence of depression across dementia stages in AD and five did not report significant differences.[3,23,44-46] One reported significantly higher prevalence in moderate above mild dementia,[47] and one reported significant differences across mild, moderate, and severe dementia, with more minor depression in severe stage than the others.[42]

In VaD, the prevalence of depressive symptoms ranged from 28% to 72%, with an overall pooled prevalence of 50% (95% CI 36-64%); I^2=91%, p<.001). The average prevalence of depressive symptoms in mild VaD was 48% (95% CI 26-69%, I^2=94%, p<.001), and that in moderate VaD was 55% (95% CI 46-65%, I^2=42%, p=.188) (see Supplementary Figure 2). One study compared prevalence of depression across dementia stages and reported significantly higher prevalence in mild than moderate depression in cortical VaD.[46] Only one study reported data on DLB and the prevalence of depression was 37% in both mild and moderate stage of dementia.

Prevalence of anxiety

The prevalence of anxiety ranged from 13% to 67%, with an overall pooled prevalence of 39% (95% CI 33-45%; I^2=94%, p<.001). Table 3 shows the random-effects meta-analysis results on prevalence of anxiety by dementia stage. The average prevalence of anxiety in mild dementia was 38% (range, 13-67%; 95% CI 31-45%; I^2=94%, p<.001); 41% in moderate dementia (range, 21-65%; 95% CI 31-52%; I^2=91%, p<.001); and 37% in severe dementia (range, 14-60%; 95% CI -0.08-0.82%; I^2=98%, p <.001). In AD, the prevalence of depressive symptoms ranged from 13% to 67%, with an overall pooled prevalence of 38% (95% CI 30-45%); I^2=95%, p<.001). The average prevalence of anxiety in mild AD was 37% (95% CI 28-46%, I^2=95%, p<.001); 38% in moderate AD (95% CI 22-55%, I^2=94%, p <.001) and 37% in severe AD (95% CI 0-82%, I^2=98%, p <.001) (see Supplementary Figure 1). In VaD, the prevalence of anxiety ranged from 26% to 55%, with an overall pooled prevalence of 42% (95% CI 32-53%; I^2=85%, p<.001). The average prevalence anxiety in mild VaD was 41% (95% CI 25-56%, I^2=89%, p<.001), and that in moderate VaD was 46% (95% CI 34-59%, I^2=64%, p=.093) (see Supplementary Figure 2). Only one study reported data on DLB and the prevalence of anxiety were 37% and 48% in mild and moderate stage of dementia, respectively. Four studies

compared prevalence of anxiety across dementia stages in AD and none of them reported significant differences.[3,23,44,46]

Prevalence of apathy

The prevalence of apathy ranged from 24% to 89%, with an overall pooled prevalence of 54% (95% CI 47-61%; I^2=96%, p<.001). Table 3 shows the random-effects meta-analysis results on prevalence of apathy by dementia stage. The average prevalence of apathy in mild dementia was 54% (range, 29-89%; 95% CI 45-62%; I^2=96%, p<.001); 59% in moderate dementia (range, 24-70%; 95% CI 44-73%; I^2=96%, p<.001); and 43% in severe dementia (range, 26-59%; 95% CI 10-75%; I^2=95%, p <.001). In AD, the prevalence of apathy ranged from 24% to 85%, with an overall pooled prevalence of 50% (95% CI 41-59%; I^2=95%, p<.001). The average prevalence of depressive symptoms in mild AD was 50% (95% CI 39-60%; I^2=95%, p<.001); 54% in moderate AD was (95% CI 33-74%, I^2=97%, p <.001) and 43% in severe AD (95% CI 10-75%; I^2=95%, p<.001) (see Supplementary Figure 1). Four studies compared prevalence of anxiety across dementia stages in AD, three did not report significant differences[3,44,46] and one reported significant differences with higher prevalence in moderate and severe as opposed to mild AD.[23] The sample size of the severe group was less than 50 and thus excluded from the current review. In VaD, the prevalence of apathy ranged from 43% to 89%, with an overall pooled prevalence of 60% (95% CI 45-75%; I^2=93%, p<.001). The average prevalence of apathy in mild AD was 60% (95% CI 38-82%; I^2=95%, p<.001), and that in moderate AD was 60% (95% CI 40-80%; I^2=87%, p=.006) (see Supplementary Figure 2). Only one study reported data on DLB and the prevalence of depressive symptoms were 80% and 82 % in mild and moderate stage of dementia, respectively. Two studies compared prevalence of apathy across dementia stages in VaD, one did not report significant difference[46] whereas the other reported significantly higher prevalence in moderate and severe than mild

cortical VaD.[23] However, the severe dementia group had less than 50 participants and thus was not included in the current review.

Publication bias and subgroup analyses

According to Egger's test, there was no evidence of publication bias for depression (p=.781), anxiety (p=.169), but apathy (p<.001). Using the trim and fill method to account for the bias had no effect on the summary estimate of apathy. Significant heterogeneity in the prevalence of depression was observed in all types of dementia. The prevalence of depression, anxiety, and apathy did not differ with regard to dementia stage and type (see Table 3). The prevalence of depression in AD was significantly lower when it was assessed using diagnostic criteria compared to screening tools; no significant difference was observed in self- and informant-reported prevalence. The prevalence of depression and anxiety differ significantly across regions of study, with depression in AD higher in Asia and Europe than America, and anxiety in VaD higher in Europe than Asia (see Table 4).

[insert Table 3 and 4]

Discussion

Main findings

This is the most comprehensive systematic review and meta-analysis to-date examining the prevalence of affective symptoms by dementia stage using established staging criteria. Prevalence rates of depressive symptoms in mild, moderate, and severe dementia were 38%, 41%, and 37% respectively. The corresponding prevalence for anxiety was 38%, 41%, and 37%; and 54%, 59%, and 43% for apathy. Subgroup analysis showed no significant difference in prevalence of affective symptoms between the stages. The prevalence of affective symptoms

also appeared to be higher in mild and moderate stage of VaD than that of AD, but the difference was not significant. It should be noted that significant heterogeneity was observed in all reported prevalence rates. Our findings confirmed that reported affective symptoms vary greatly in the literature, even with the adoption of more stringent staging criteria and when focusing only on AD and VaD.

The findings of a stable prevalence of affective symptoms were consistent with previous meta-analysis examining the prevalence of depression and anxiety in AD, but not apathy, which was shown to have a positive association with dementia severity.[18] This could be due to how dementia severity was measured and analyzed. Previous meta-analyses used mean MMSE scores as dementia severity indicator while the present divided dementia severity into three stages according to CDR. Mean MMSE scores may not accurately reflect the severity of the sample with PLwD ranging from mild to severe stages. The majority of the studies included in that meta-analysis reported mean MMSE scores between 12 and 23,[18] thus the association between apathy and cognitive impairment might be limited to mild or moderate dementia. Although it is expected that insight is lower in later stage of dementia and thus a higher prevalence of apathy will be reported,[48] the stability of the prevalence rate may suggest the interplay of other attributes to apathy.

Prevalence rates using different assessments

The varying prevalence rates in depression may be attributed to evaluation methods. When diagnostic criteria were employed, the prevalence rate for depression in AD was 27%, compared to 43% using self- or informant-reported screening tools, supporting the findings from previous meta-analysis that lower prevalence rates were associated with more stringent diagnostic criteria than screening tools.[19] The NIMH-dAD, for example, was developed based on DSM-IV and has higher specificity for the diagnosis of depression in AD by requiring the

presence of three depressive symptoms during the same 2-week period which are severe enough to cause significant distress or disruption in social, occupational or psychological functioning, as compared to screening tools, such as HAM-D, which considers the presence of sad mood based on a score of two or more on the item of depressed mood.[49] Therefore, depression may be common among people with dementia, but the symptom severity did not reach clinical significance. Although evaluation methods has been suggested to explain some of the variance in prevalence of anxiety and apathy in AD, none of the included studies employed diagnostic criteria in assessing anxiety and apathy and thus prevented us from examining the association.

It is important to note that, however, while the majority of the included studies used screening tools to assess affective symptoms and hence increased comparability across studies, symptoms are categorized as a "hit" differently across included studies using screening tools, for example, being present in the past month regardless of frequency in NPI and at least three days in the past month in BRSD. One study using BRSD reported higher prevalence in moderate over mild dementia whereas other studies using NPI found no significant differences.[47] Assessment may be a source for the heterogeneity, yet there are insufficient studies to examine the potential correlation.

Furthermore, these screening instruments are mainly self- or informant-reported and reflect symptoms rather than diagnosable disorders. Affective symptoms, as internal states of the PLwD, make modality of measurement pertinent. The significant differences between self-rated and informant-rated prevalence of depression may be attributable to the varying symptoms represented in self-and informant-rated assessment. Informant-based assessment appears to be biased towards capturing the more visible symptoms, such as lack of positive affect, whereas self-rating capture more central symptoms of worthlessness and helplessness.[25] These retrospective self- and informant-reported instruments are also subject to respondents'

cognitive ability and informants' recall bias,[50] and lacking clinician's judgement[51]. Informant-report instruments become increasingly subjective as the people with dementia progress to later stages of the illness when they are unable to tell informants about their mood. The association between BPSD symptoms and severity of dementia can be complicated since BPSD symptoms may influence how the severity of dementia is rated. For instance, presence of apathy may affect the carer's report in relation to the domain of home and hobbies in CDR, which captures whether the people with dementia are engaged in hobbies, overlapping with some measures of apathy (e.g., in NPI-Q).

Prevalence rates in different countries

The variance in prevalence rates of depression and anxiety may be attributable to the diverse study settings, recruitment strategies and data collection methods in different countries, as well as cultural difference. A Western measure may not be as sensitive when being applied in other cultures.[52] Recent reviews revealed that some cultural adaptions of the NPI may ascertain cultural sensitivity more than the others and there appears to be lacking investigation of some aspects of validity of the measure across cultures.[53,54] The presence of BPSD is multifactorial, resulting from the interacting effects of people with dementia, carers, and environmental factors.[55] The need-driven dementia-compromised behavior model[56] considers BPSD as an expression of unmet needs compensating the declining verbal communication ability in people with dementia. Cultural values and resources available to carers may influence how they understand affective symptoms and their choice and use of coping strategies,[57] which may induce varying levels of stress and burden carers experience, and in turn affects how they report BPSD.[58] Stress and depression among carers may also trigger more symptoms in people with dementia.[59]

Heterogeneity of prevalence rate

The significant variance observed in all reported prevalence rates suggested possible heterogeneity in psychopathological process in dementia. The relationship between disease severity and affective symptoms is complicated.[60] Their occurrence is at least partially a direct result of the disease process and brain pathology, while they may also occur as a psychological reaction to the individual's appraisal of the illness and prognosis, the consequential loss of functions, and the changes to one's environment and interpersonal interactions. These appraisals are in turn limited by the person's level of awareness in their ability in activities of daily living, behavioral changes and mood problems. Despite a lacking consensus of the best diagnostic strategy, poor awareness has been suggested to become more frequent with the progression of AD and is associated with more severe apathy and less severe depression and anxiety.[61] Nonetheless, the focus of prevalence rates of affective symptoms in the current meta-analysis may mask the association between the severity of dementia and affective symptoms. The stable prevalence of affective symptoms may suggest that these factors may interact with each other and interfere with well-being differently across dementia stages, for example, insight may play a more important part at earlier stages while environmental factors contribute more in later stages because of cognitive decline and that lowers stress resilience.

Limitations

Although dementia type may influence the prevalence of affective symptoms across dementia stages, there were limited studies conducted in dementia types other than AD and severe dementia populations. Due to the phenomenological overlap between apathy and depression on the predicate of "reduced volition", the prevalence rates of these symptoms, especially those reported by non-professionals, may be inflated. While we suggest there existed a cultural difference in prevalence of affective symptoms, there was a paucity of studies from developing

countries and cross-national studies. The scoop of the literature search was limited with narrow search terms and may subject to selection bias by the only reviewer in the initial screening and data extraction process. The specific type of dementia, such as "Alzheimer's disease", and alternative terms of affective symptoms, such as "neuropsychiatric symptoms" were not used in the current study. Furthermore, the large number of missing data on age, gender, and education year by dementia types and stages limited our understanding of how people with dementia' characteristics might contribute to the prevalence of affective symptoms. While presence of affective symptoms may be affected by external resources, living arrangement and marital status, which may reflect the level of social support received by the person with dementia, were only reported in one included study.[43] Substantially fewer studies were included in this meta-analysis compared to the previous meta-analysis because we only included studies with CDR scores instead of MMSE scores. There was a deviation from the PROSPERO pre-registration with regards to dementia severity assessment from including studies "reported using MMSE, CDR or GDS" to "reported using CDR or GDS". We believe looking at CDR and GDS gave a better picture between affective symptoms and functioning in general in dementia population, not only cognitive functioning.

Future studies

Considering the potential influence of carers' subjective bias on the heterogeneity of symptom prevalence, studies could explore the association between carers' psychological characteristics, such as carer self-efficacy and burden, and informant-reported prevalence rate, and how well-being could be improved in both people with dementia and their carers. Cross-cultural studies are needed to establish a better understanding how BPSD are presented and managed with consideration of cultural values and resources. The current meta-analysis found different prevalence rates between self- or informant-reported and clinically diagnosed depression,

future studies could investigate whether discrepancy exists in anxiety and apathy. While this study has in the strength of incorporating cross-cultural and heterogeneous study settings in estimating the prevalence of affective symptoms, future studies should also consider including open-access datasets, many of which include variables needed for the current research question (e.g., the National Alzheimer's Coordinating Center dataset and the Global Alzheimer's Association Interactive Network). With the large sample size of these datasets across countries and regions, albeit focusing mainly on Alzheimer's disease, can inform further the prevalence of affective symptoms in dementia. The current findings can potentially be updated in the near future by incorporating these massive unanalyzed data.

Conclusion

The overall prevalence of depression, anxiety and apathy is high and stable across stages in AD and VaD population, thus affective symptoms are an important treatment target throughout the course of dementia. Symptom evaluation method and cultural difference may explain some of the variance in the prevalence of affective symptoms. The findings suggest further investigation of factors influencing report of affective symptoms, such as carer psychosocial characteristics, and more cross-cultural studies examining the pattern and management of affective symptoms.

References

1. World Health Organisation. *Risk reduction of cognitive decline and dementia - WHO guidelines.* 2019.
2. Frisoni G, Rozzini L, Gozzetti A, et al. Behavioral syndromes in Alzheimer's disease: description and correlates. *Dementia and Geriatric Cognitive Disorders.* 1999;10(2):130-138.
3. Lyketsos CG, Sheppard JM, Steinberg M, et al. Neuropsychiatric disturbance in Alzheimer's disease clusters into three groups: the Cache County study. *International journal of geriatric psychiatry.* 2001;16(11):1043-1053.
4. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. *Front Neurol.* 2012;3:73.
5. Aalten P, Verhey FR, Boziki M, et al. Neuropsychiatric syndromes in dementia. Results from the European Alzheimer Disease Consortium: part I. *Dement Geriatr Cogn Disord.* 2007;24(6):457-463.
6. Hongisto K, Hallikainen I, Selander T, et al. Quality of Life in relation to neuropsychiatric symptoms in Alzheimer's disease: 5-year prospective ALSOVA cohort study. *International journal of geriatric psychiatry.* 2018;33(1):47-57.
7. Karttunen K, Karppi P, Hiltunen A, et al. Neuropsychiatric symptoms and quality of life in patients with very mild and mild Alzheimer's disease. *International journal of geriatric psychiatry.* 2011;26(5):473-482.
8. Riley RJ, Burgener S, Buckwalter KC. Anxiety and stigma in dementia: a threat to aging in place. *The Nursing clinics of North America.* 2014;49(2):213-231.
9. Schulz R, Martire LM. Family caregiving of persons with dementia: prevalence, health effects, and support strategies. *Am J Geriatr Psychiatry.* 2004;12(3):240-249.

10. Dorenlot P, Harboun M, Bige V, Henrard JC, Ankri J. Major depression as a risk factor for early institutionalization of dementia patients living in the community. *International journal of geriatric psychiatry.* 2005;20(5):471-478.
11. Mukherjee A, Biswas A, Roy A, Biswas S, Gangopadhyay G, Das SK. Behavioural and Psychological Symptoms of Dementia: Correlates and Impact on Caregiver Distress. *Dementia and geriatric cognitive disorders extra.* 2017;7(3):354-365.
12. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet.* 2017;390(10113):2673-2734.
13. National Institute for Health and Care Excellence (NICE). *Dementia: assessment, management and support for people living with dementia and their carers.* London2018.
14. Abraha I, Rimland JM, Trotta FM, et al. Systematic review of systematic reviews of non-pharmacological interventions to treat behavioural disturbances in older patients with dementia. The SENATOR-OnTop series. *BMJ Open.* 2017;7(3):e012759.
15. Seignourel PJ, Kunik ME, Snow L, Wilson N, Stanley M. Anxiety in dementia: a critical review. *Clin Psychol Rev.* 2008;28(7):1071-1082.
16. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993;43(11):2412-2414.
17. Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. *American Journal of Psychiatry.* 1982;139(9):1136-1139.
18. Zhao Q, Tan L, Wang H, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *Journal of Affective Disorders.* 2016;190:264-271.

19. Kuring JK, Mathias JL, Ward L. Prevalence of Depression, Anxiety and PTSD in People with Dementia: a Systematic Review and Meta-Analysis. *Neuropsychol Rev.* 2018;28:393-416.

20. Chakrabarty T, Sepehry AA, Jacova C, Hsiung GY. The prevalence of depressive symptoms in frontotemporal dementia: a meta-analysis. *Dement Geriatr Cogn Disord.* 2015;39(5-6):257-271.

21. Kazui H, Yoshiyama K, Kanemoto H, et al. Differences of behavioral and psychological symptoms of dementia in disease severity in four major dementias. *PLoS One.* 2016;11(8).

22. Ballard C, Neill D, O'Brien J, McKeith IG, Ince P, Perry R. Anxiety, depression and psychosis in vascular dementia: prevalence and associations. *J Affect Disord.* 2000;59(2):97-106.

23. Fuh JL, Wang SJ, Cummings JL. Neuropsychiatric profiles in patients with Alzheimer's disease and vascular dementia. *Journal of neurology, neurosurgery, and psychiatry.* 2005;76(10):1337-1341.

24. Steffens DC, Maytan M, Helms MJ, Plassman BL. Prevalence and clinical correlates of neuropsychiatric symptoms in dementia. *Am J Alzheimers Dis Other Demen.* 2005;20(6):367-373.

25. Saari TT, Hallikainen I, Hintsa T, Koivisto AM. Network structures and temporal stability of self- and informant-rated affective symptoms in Alzheimer's disease. *Journal of Affective Disorders.* 2020;276:1084-1092.

26. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 2009;6(7):e1000097.

27. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (3th ed., revised).* Washington, DC: Author; 1987.

28. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (4th ed., text rev.).* Washington, DC: Author; 2000.

29. World Health Organization. *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines.* Geneva: World Health Organization; 1992.

30. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34(7):939-944.

31. Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology.* 1993;43(2):250-260.

32. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain.* 2011;134(9):2456-2477.

33. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology.* 2017;89(1):88-100.

34. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. *Int J Evid Based Healthc.* 2015;13(3):147-153.

35. Cummings J, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology.* 1994;44:2308-2314.

36. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a Brief Clinical Form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci.* 2000;12(2):233-239.

37. Reisberg B, Borenstein J, Salob SP, Ferris SH, Franssen E, Georgotas A. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. *J Clin Psychiatry.* 1987;48(5,suppl).

38. Tariot PN, Mack JL, Patterson MB, et al. The Behavior Rating Scale for dementia of the consortium to establish a registry for Alzheimer's Disease. The behavioral pathology committee of the consortium to establish a registry for Alzheimer's Disease. *Am J Psychiatry.* 1995;152:1349-1357.

39. Teng E, Ringman JM, Ross LK, et al. Diagnosing depression in Alzheimer disease with the national institute of mental health provisional criteria. *The American Journal of Geriatric Psychiatry.* 2008;16(6):469-477.

40. Vik-Mo AO, Giil LM, Ballard C, Aarsland D. Course of neuropsychiatric symptoms in dementia: 5-year longitudinal study. *International journal of geriatric psychiatry.* 2018;33(10):1361-1369.

41. Kwak YT, Yang Y, Pyo SJ, Koo MS. Clinical characteristics according to depression screening tools in patients with Alzheimer's disease: view from self, caregiver-reported and drug-intervention pattern. *Geriatrics & gerontology international.* 2014;14(3):660-666.

42. Starkstein SE, Jorge R, Mizrahi R, Robinson RG. The construct of minor and major depression in Alzheimer's disease. *The American journal of psychiatry.* 2005;162(11):2086-2093.

43. Porta-Etessam J, Tobaruela-González JL, Rabes-Berendes C. Depression in patients with moderate Alzheimer disease: a prospective observational cohort study. *Alzheimer disease and associated disorders.* 2011;25(4):317-325.

44. Cheng ST, Kwok T, Lam LC. Neuropsychiatric symptom clusters of Alzheimer's disease in Hong Kong Chinese: prevalence and confirmatory factor analysis of the Neuropsychiatric Inventory. *International psychogeriatrics.* 2012;24(9):1465-1473.

45. Liu CY, Fuh JL, Teng EL, et al. Depressive disorders in Chinese patients with Alzheimer's disease. *Acta Psychiatrica Scandinavica.* 1999;100(6):451-455.

46. Manso-Calderón R, Cacabelos-Pérez P, Sevillano-García MD, Herrero-Prieto ME, González-Sarmiento R. The impact of vascular burden on behavioural and psychological symptoms in older adults with dementia: the BEVASDE study. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology.* 2020;41(1):165-174.

47. Youn JC, Lee DY, Jhoo JH, Kim KW, Choo IH, Woo JI. Prevalence of neuropsychiatric syndromes in Alzheimer's disease (AD). *Archives of gerontology and geriatrics.* 2011;52(3):258-263.

48. Horning SM, Melrose R, Sultzer D. Insight in Alzheimer's disease and its relation to psychiatric and behavioral disturbances. *International journal of geriatric psychiatry.* 2014;29(1):77-84.

49. Novais F, Starkstein S. Phenomenology of Depression in Alzheimer's Disease. *Journal of Alzheimer's Disease.* 2015;47:845-855.

50. Lai CKY. The merits and problems of Neuropsychiatric Inventory as an assessment tool in people with dementia and other neurological disorders. *Clin Interv Aging.* 2014;9:1051-1061.

51. Lyketsos CG, Carrillo MC, Ryan JM, et al. Neuropsychiatric Symptoms in Alzheimer's Disease. *Alzheimers Dement.* 2011;7(5).

52. Rogler LH. Methodological sources of cultural insensitivity in mental health research. *The American psychologist.* 1999;54(6):424-433.

53. Saari T, Koivisto A, Hintsa T, Hänninen T, Hallikainen I. Psychometric Properties of the Neuropsychiatric Inventory: A Review. *Journal of Alzheimer's disease : JAD.* 2020.

54. Perrault A, Oremus M, Demers L, Vida S, Wolfson C. Review of Outcome Measurement Instruments in Alzheimer's Disease Drug Trials: Psychometric Properties of Behavior and Mood Scales. *Journal of Geriatric Psychiatry and Neurology.* 2000;13(4):181-196.

55. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ.* 2015;350:h369.

56. Algase DL, Beck C, Kolanowski A, et al. Need-driven dementia-compromised behavior: An alternative view of disruptive behavior. *American Journal of Alzheimer's disease.* 1996;11(6):10-19.

57. Knight BG, Sayegh P. Cultural values and caregiving: The updated sociocultural stress and coping model. *The Journals of Gerontology: Series B.* 2010;65(1):5-13.

58. Norton MC, Piercy KW, Rabins PV, et al. Caregiver-recipient closeness and symptom progression in Alzheimer disease. The Cache County Dementia Progression Study. *The Journals of Gerontology Series B, Psychological Sciences and Social Sciences.* 2009;64(5):560-568.

59. de Vugt ME, Stevens F, Aalten P, et al. Do caregiver management strategies influence patient behaviour in dementia? *International journal of geriatric psychiatry.* 2004;19(1):85-92.

60. Judge KS, Menne HL, Whitlatch CJ. Stress process model for individuals with dementia. *Gerontologist.* 2010;50(3):294-302.

61. Starkstein SE. Anosognosia in Alzheimer's disease: diagnosis, frequency, mechanism and clinical correlates. *Cortex; a journal devoted to the study of the nervous system and behavior*. 2014;61:64-73.

Table 1. Summary of key parameters used in the meta-analysis by dementia severity.

	Mild (CDR = 1)			Moderate (CDR = 2)			Severe (CDR = 3)		
Dementia subtype	N_{study}	$N_{participants}$	Mean / %	N_{study}	$N_{participants}$	Mean / %	N_{study}	$N_{participants}$	Mean / %
AD	18	2709	-	10	2330	-	3	243	-
Age (years)	6	1234	76.95	2	1443	78.05	-	-	-
Female (%)	6	1234	66.75	2	1443	71.23	-	-	-
Education (years)	6	1234	8.64	1	194	10.00	-	-	-
Marital status (% married)	-	-	-	1	1249	49.76	-	-	-
Affective symptoms									
Depression	17	2593	96	10	2330	100	3	243	93
Diagnostic criteria	4	594	22	4	1612	69	1	71	29
Screening tool	14	2115	74	7	1967	31	2	172	71
Informant-reported	14	2115	78	6	718	31	-	-	-
Self-reported	1	104	4	1	1249	54	-	-	-
Anxiety †	12	1996	74	5	657	28	2	172	66
Apathy †	13	2079	77	5	657	28	2	172	66
Setting									
Community	2	175	6	1	50	2	1	69	28
Clinic	16	2604	96	8	2157	93	2	174	72
Mixed	1	101	4	1	123	5	-	-	-
Area of study									
America	4	711	26	2	267	11	2	140	58
Asia	9	1283	47	6	631	27	-	-	-
Europe	5	715	26	2	1432	61	1	103	42
VaD	4	352	-	2	192	-	-	-	-
Age (years)	1	72	75.90	-	-	-	-	-	-

Female (%)	1	72	45.21	-	-	-	-	-	-
Education (years)	1	72	11.00	-	-	-	-	-	-
Affective symptoms									
Depression †	4	352	100	2	192	100	-	-	-
Anxiety †	4	352	100	2	192	100	-	-	-
Apathy †	4	352	100	2	192	100	-	-	-
Setting									
Clinic	4	352	100	2	192	100	-	-	-
Area of study									
Asia	2	154	44	1	59	30	-	-	-
Europe	2	198	56	1	133	69	-	-	-
DLB	1	109	-	1	62	-	-	-	-
Age (years)	1	109	78.00	1	62	79.90	-	-	-
Female (%)	1	109	60.55	1	62	58.06	-	-	-
Education (years)	1	109	10.50	1	62	10.60	-	-	-
Affective symptoms									
Depression †	1	109	100	1	62	100	-	-	-
Anxiety †	1	109	100	1	62	100	-	-	-
Apathy †	1	109	100	1	62	100	-	-	-
Setting									
Clinic	1	109	100	1	62	100	-	-	-
Area of study									
Asia	1	109	100	1	62	100	-	-	-

Note: AD = Alzheimer's disease, DLB = dementia with Lewy bodies, VaD = vascular dementia.
† Symptoms measured using screening tools.

Table 2. Summary details for individual studies that examined the prevalence of depression, anxiety, or apathy.

Author	Country (Region)	Setting	Dementia			N	Female (%)	Age (years)	Education (years)	Affective symptoms		
			Type	Assessment	Stage					Symptom	Assessment	Prevalence (%)
Cheng (2012)	Hong Kong (Asia)	Mixed	AD	NINCDS-ADRDA	Mild	101	-	-	-	Depression	NPI-12	35
										Anxiety	NPI-12	24
										Apathy	NPI-12	29
					Moderate	123	-	-	-	Depression	NPI-12	40
										Anxiety	NPI-12	21
										Apathy	NPI-12	37
Chiu (2012)	Taiwan (Asia)	Clinic-based	AD	NINCDS-ADRDA	Mild	87	-	-	-	Depression	NIMH-dAD	24
					Moderate	87	-	-	-	Depression	NIMH-dAD	46
D'Onofrio (2012)	Italy (Europe)	Clinic-based	AD	DSM-IV, NINCDS-ADRDA	Mild	51	-	-	-	Depression	NPI	39
										Anxiety	NPI	47
										Apathy	NPI	49
			VaD	DSM-IV, NINDS-AIREN	Mild	63	-	-	-	Depression	NPI	51
										Anxiety	NPI	54
										Apathy	NPI	44
Di Iulio (2010)	Italy (Europe)	Clinic-based	AD	NINCDS-ADRDA	Mild	119	67.2	74.4 (7.0)	7.8 (4.7)	Depression	NPI	78
										Anxiety	NPI	66
										Apathy	NPI	85
Fuh (2005)	Taiwan (Asia)	Clinic-based	AD	DSM-IV	Mild	188	-	-	-	Depression	NPI	46
										Anxiety	NPI	33
										Apathy	NPI	43
					Moderate	107	-	-	-	Depression	NPI	44
										Anxiety	NPI	43
										Apathy	NPI	55

Author	Country (Region)	Setting	Dementia			N	Female (%)	Age (years)	Education (years)	Affective symptoms		
			Type	Assessment	Stage					Symptom	Assessment	Prevalence (%)
			VaD	DSM-IV	Mild	82	-	-	-	Depression	NPI	39
										Anxiety	NPI	28
										Apathy	NPI	42
					Moderate	59	-	-	-	Depression	NPI	49
										Anxiety	NPI	38
										Apathy	NPI	49
Kazui (2016)	Japan (Asia)	Clinic-based	AD	DSM-III-R, NINCDS-ADRDA	Mild	479	68.9	77.2 (8.0)	10.9 (2.9)	Depression	NPI	33
										Anxiety	NPI	27
										Apathy	NPI	78
					Moderate	195	74. 4	78.3 (8.6)	10.0 (2.7)	Depression	NPI	38
										Anxiety	NPI	38
										Apathy	NPI	84
			DLB	DSM-III-R, the Consortium on DLB International Workshop	Mild	109	60.6	78.0 (6.1)	10.5 (2.8)	Depression	NPI	37
										Anxiety	NPI	37
										Apathy	NPI	80
					Moderate	62	58. 1	79.9 (6.2)	10.6 (2.8)	Depression	NPI	37
										Anxiety	NPI	48
										Apathy	NPI	82
			VaD	DSM-III-R, NINDS-AIREN	Mild	73	45.2	75.9 (8.8)	11.0 (2.7)	Depression	NPI	27
										Anxiety	NPI	26
										Apathy	NPI	88
Kwak (2014)	Korea (Asia)	Clinic-based	AD	NINCDS-ADRDA	Mild	104	-	-	-	Depression	NPI	11
										Depression	NPI	63
										Depression	GDS	36
Lam			AD		Mild	96	93.8	84.3 (6.0)	1.24 (3.21)	Depression	NPI	29

Author	Country (Region)	Setting	Dementia			N	Female (%)	Age (years)	Education (years)	Affective symptoms		
			Type	Assessment	Stage					Symptom	Assessment	Prevalence (%)
(2007)	Hong Kong (Asia)	Community-based		NINCDS-ADRDA						Apathy	NPI	46
Landes (2005)	Ohio (America)	Clinic-based	AD	NINCDS-ADRDA	Mild	62	-	-	-	Depression	DSM-IV	10
										Apathy	DAIR	53
Liu (1999)	Taiwan (Asia)	Clinic-based	AD	DSM-III-R, NINCDS-ADRDA	Mild	63	-	-	-	Depression	DSM-III-R	21
					Moderate	59	-	-	-	Depression	DSM-III-R	15
Liu (2007)	Taiwan (Asia)	Clinic-based	AD	DSM-IV, NINCDS-ADRDA	Mild	75	-	-	-	Depression	BEHAVE-AD	37
										Anxiety	BEHAVE-AD	45
Lyketsos (2001)	USA (America)	Community-based	AD	NINCDS-ADRDA	Mild	79	-	-	-	Depression	NPI	22
										Anxiety	NPI	13
										Apathy	NPI	30
					Moderate	50	-	-	-	Depression	NPI	20
										Anxiety	NPI	24
										Apathy	NPI	24
					Severe	69	-	-	-	Depression	NPI	17
										Anxiety	NPI	15
										Apathy	NPI	26
Manso-Calderon (2020)	Spain (Europe)	Clinic-based	AD	NIN-AA	Mild	193	-	-	-	Depression	NPI	67
										Anxiety	NPI	67
										Apathy	NPI	55
					Moderate	183	-	-	-	Depression	NPI	67
										Anxiety	NPI	65
										Apathy	NPI	67
					Severe	103	-	-	-	Depression	NPI	60

Author	Country (Region)	Setting	Dementia			N	Female (%)	Age (years)	Education (years)	Affective symptoms		
			Type	Assessment	Stage					Symptom	Assessment	Prevalence (%)
										Anxiety	NPI	60
										Apathy	NPI	59
			VaD	NINDS-AIREN	Mild	135	-	-	-	Depression	NPI	72
										Anxiety	NPI	55
										Apathy	NPI	64
					Moderate	133	-	-	-	Depression	NPI	59
										Anxiety	NPI	52
										Apathy	NPI	70
Park (2015)	Korea (Asia)	Clinic-based	AD	DSM-IV, NINCDS-ADRDA	Mild	171	-	-	-	Anxiety	K-NPI	42
										Apathy	NPI	55
Porta-Etessam (2011)	Spain (Europe)	Clinic-based	AD	NINCDS-ADRDA	Moderate	1249	68.1	77.8 (6.7)	-	Depression	CSDD	56
										Depression	DSM-IV	39
Saari (2019)	Finland (Europe)	Clinic-based	AD	DSM-IV, NINCDS-ADRDA	Mild	236	51.2	75.2 (6.5)	7.6 (3.3)	Depression	NPI-12	37
										Anxiety	NPI-12	26
										Apathy	NPI-12	48
Starkstein (2005)	Argentina (America)	Clinic-based	AD	NINCDS-ADRDA	Mild	382	-	-	-	Depression	DSM-III-R (MDD)	26
										Depression	DSM-III-R (MnDD)	26
					Moderate	217	-	-	-	Depression	DSM-III-R (MDD)	29
										Depression	DSM-III-R (MnDD)	21
					Severe	71	-	-	-	Depression	DSM-III-R (MDD)	24
										Depression	DSM-III-R (MnDD)	45
Vik-Mo (2018)	Norway (Europe)	Clinic-based	AD	ICD-10,	Mild	116	71	75.3 (7.8)	9.6 (2.9)	Depression	NPI (score > 0)	58

Author	Country (Region)	Setting	Dementia			N	Female (%)	Age (years)	Education (years)	Affective symptoms		
			Type	Assessment	Stage					Symptom	Assessment	Prevalence (%)
				NINCDS-ADRDA						Depression	NPI (score > 3)	24
										Anxiety	NPI (score > 0)	41
										Anxiety	NPI (score > 3)	19
										Apathy	NPI (score > 0)	53
										Apathy	NPI (score > 3)	37
Wadsworth (2012)	USA (America)	Clinic-based	AD	NINCDS-ADRDA	Mild	188	48.4	75.3 (7.5)	14.7 (3.1)	Depression	NPI-Q	34
										Anxiety	NPI-Q	35
										Apathy	NPI-Q	34
Youn (2011)	Korea (Asia)	Clinic-based	AD	NINCDS-ADRDA	Mild	90	-	-	-	Depression	BRSD	58
					Moderate	61	-	-	-	Depression	BRSD	61

AD, Alzheimer's disease; BRSD, Behaviour Rating Scale for Dementia; DAIR, Dementia Apathy Interview and Rating; DSM, The Diagnostic and Statistical Manual of Mental Disorders; FTD, frontotemporal dementia; ICD, International Classification of Diseases; LBD, Lewy bodies dementia; MDD, Major depressive disorders; MnDD, Minor depressive disorders; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for Alzheimer's disease; NPI, Neuropsychiatric Inventory; NPI-Q, Neuropsychiatric Inventory-Questionnaire; VaD, vascular dementia.

Table 3. Prevalence of depression, anxiety, and apathy in general dementia, AD and VaD according to dementia stage.

	Depression				Anxiety				Apathy			
	Prevalence (%)	95% CI	I^2 (%)	*p*	Prevalence (%)	95% CI	I^2 (%)	*p*	Prevalence (%)	95% CI	I^2 (%)	*p*
All dementia	39	34 - 44	96	<.001	39	33 - 45	94	<.001	54	47 - 61	96	<.001
Mild	38	32 - 45	96	<.001	38	31 - 45	94	<.001	54	45 - 62	95	<.001
Moderate	41	33 - 49	96	<.001	41	31 - 52	91	<.001	59	44 - 73	96	<.001
Severe	37	17 - 56	93	<.001	37	-8 - 82	98	<.001	43	10 - 75	95	<.001
AD	38	32 - 43	96	<.001	38	30 - 45	95	<.001	50	41 - 59	95	<.001
Mild	37	30 - 44	96	<.001	37	28 - 46	95	<.001	50	39 - 60	95	<.001
Moderate	40	31 - 48	97	<.001	38	22 - 55	95	<.001	54	33 - 74	97	<.001
Severe	37	16 - 57	93	<.001	37	0 - 82	98	<.001	43	10 - 75	95	<.001
VaD	50	36 - 64	90	<.001	42	32 - 53	85	<.001	60	45 - 75	93	<.001
Mild	48	26 - 69	93	<.001	41	25 - 56	89	<.001	60	38 - 82	95	<.001
Moderate	55	46 - 65	42	0.188	46	34 - 59	64	0.093	60	40 - 80	87	0.006

AD, Alzheimer's disease; VaD, vascular dementia.

Table 4. Prevalence of depression, anxiety, and apathy in AD and VaD according to evaluation method and region of study.

	Depression				Anxiety				Apathy			
	Prevalence (%)	95% CI	I^2 (%)	*p*	Prevalence (%)	95% CI	I^2 (%)	*p*	Prevalence (%)	95% CI	I^2 (%)	*p*
AD												
Evaluation method												
Diagnosis	27	21 - 33	91	<.001	-	-	-	-	-	-	-	-
Screening tools	43	38 - 49	95	<.001	-	-	-	-	-	-	-	-
Informant-reported	42	35 - 50	95	<.001	-	-	-	-	-	-	-	-
Self-reported	46	27 - 66	94	<.001	-	-	-	-	-	-	-	-
Region of study												
America	25	20 - 17	77	<.001	21	10 - 33	87	<.001	33	25 - 42	72	<.001
Asia	37	30 - 44	92	<.001	34	28 - 40	84	<.001	53	39 - 68	97	<.001
Europe	53	43 - 62	97	<.001	49	34 - 64	97	<.001	57	46 - 68	93	<.001
VaD												
Region of study												
Asia	38	26 - 50	70	0.004	30	23 - 37	24	0.270	43	32 - 93	97	<.001
Europe	61	50 - 73	79	<.001	53	48 - 59	0	0.89	60	47 - 73	83	<.001

AD, Alzheimer's disease; VaD, vascular dementia.