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Anxiety in informal dementia carers: a meta-analysis of prevalence

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Conflicts of Interest

The authors declare no conflicts of interest associated with this manuscript.

Abstract

Much of the carer literature has focused on depression and burden as primary outcomes and anxiety appears somewhat neglected. Providing evidence on the prevalence of carer anxiety is critical as it can enhance awareness among professionals, which in turn can lead to improved access to efficacious treatments. This meta-analysis updated the previous review conducted in 2007 to estimate the up-to-date prevalence of anxiety in informal carers for people with dementia. Literature searches were conducted in databases of published and unpublished literature. Events and sample size data were pooled using a random-effects model to obtain an overall prevalence percentage. A total of 10 studies were included, resulting in a pooled estimate of anxiety prevalence at 32.1 percent (95%CI 20.6% to 46.2%, *p*=0.01). Significant heterogeneity was found, which was not reduced following sensitivity analysis. This study suggests anxiety is a prevalent difficulty experienced by dementia carers. Additional research recommendations and clinical implications are discussed.

Keywords

Dementia; Alzheimer's disease; carers; quality of life; well-being

Introduction

Dementia is an umbrella term used to describe a number of illnesses resulting in progressive cognitive decline. Different dementia illnesses can have different symptom profiles that can give rise to different challenges with changes occurring in areas such as memory, attention, mood, and personality[1]. People with dementia are often cared for by informal carers who are usually relatives or friends of the care-recipient[2].

Caregiving often involves providing practical support with daily living tasks in addition to emotional support and assistance in areas such as communication and decision making[3]. Carers are also often required to provide support in the context of changes in personality and behaviours which challenge. Such behaviours can include wandering, shouting, physical aggression towards the carer, and destruction of personal possessions[4]. Furthermore, caregiving is time-consuming and carers often become socially isolated[5]. Caregiving can also place demands on carer's financial resources as they may incur additional costs related to caregiving or may have to reduce time spent in employment to attend to the care-recipient's needs[6].

Whilst there are reports of positive aspects to caregiving, the literature typically demonstrates a negative impact on the psychological wellbeing of carers[7]. Difficulties include clinical levels of depression and anxiety, increased levels of burden and stress, as well as reduced life satisfaction[8-10]. Such difficulties are notable compared to both the non-carer population and to carers of people with non-dementia illnesses[5,11]. Although a negative impact on the psychological wellbeing of carers can be broad, much of the literature has focused on depression and burden as primary outcomes and anxiety appears somewhat neglected. Yet it has been suggested that the majority of depressed carers also experience comorbid anxiety as well as anxiety occurring independently of depression in other carers[12].

It is not clear why comparatively less attention been afforded to anxiety compared to depression in dementia carers. One potential reason may be that many family carers are older people themselves. Anxiety disorders are highly prevalent among older people and

there is evidence that late-life anxiety is associated with increased disability, poor quality of life, and cognitive impairment[13]. Despite these long-term negative consequences of late life anxiety and the fact that it may be more common than later life depression, anxiety disorders are often underestimated, undertreated, and poorly studied in older people[14,15].

The older population tends to present more multiple comorbidities which can complicate the detection and treatment of anxiety. When older people diagnosed with physical illnesses express concerns about their own health, healthcare professionals may mistakenly believe that such worries are part of getting older and anxiety may be neglected and untreated despite its impact on overall well-being. The same can be said for carers of people with dementia. When carers express concerns and worries about their family member with dementia and their own health, this may be considered as an inevitable consequence of caregiving or ageing by professionals or even by carers themselves and may be left untreated.

The current evidence suggests that anxiety in older adults is associated with the increased use of health care services (e.g., hospital admissions) and the increased mortality rate[16]. Previous studies also show that mental health conditions including anxiety are considered to have a significant impact on the overall quality of life of family carers[17]. Given that family carers are such an important resource, it is important to provide evidence on the prevalence of anxiety in this population as it can help researchers and healthcare professionals to have better awareness which in turn can lead to improved access to efficacious treatments.

Indeed, there are two existing reviews focused on the prevalence of anxiety in dementia carers. An earlier meta-analysis conducted by Cooper et al.[18] which measured anxiety diagnoses and clinical level symptoms using valid measurement scales provided an estimate of the prevalence but only included four studies. This meta-analysis was conducted in 2007 and the small number of studies identified clearly highlights the need for an updated review. A more recent meta-analysis again found only four studies reporting the prevalence

though the study focused only on carers for people with Alzheimer's dementia[19]. Thus, there remains a need to establish an accurate estimate of the prevalence of anxiety across the whole population of dementia carers.

The primary aim of this meta-analysis is to provide a synthesized estimate of the prevalence of anxiety, defined as anxiety diagnoses or clinically significant level of symptoms, in the dementia carer population. In addition, several factors are postulated to have an impact on carer wellbeing including carer variables (e.g. gender, ethnicity, coping style), care-recipient factors (e.g. severity of impairment), and environmental factors (e.g. culture; country development status)[20-24]. Therefore, it is important to determine if anxiety is a prevalent difficulty worth examining further in terms of understanding potential mediating and moderating influences. Thus, the second aim of this meta-analysis is to identify potential factors which may have an impact of carer anxiety where appropriate.

Method

Protocol and Registration

The review protocol was published on the PROSPERO international prospective register of systematic reviews (registration number: CRD42018087895; accessed via www.crd.york.ac.uk/PROSPERO).

Search Strategy

A systematic search of published literature was conducted using the electronic databases PsycINFO, MEDLINE, CINAHL, and Scopus. A search of unpublished literature was conducted to address potential publication bias, using Open Grey and ProQuest. Reference lists of key review papers were hand searched. Key search terms included (a) dementia OR Alzheimer* OR "Lewy body" OR "fronto*temporal"; (b) caregiver* OR carer*; (c) anxiety; (d) prevalence preval* OR epidemiol* OR "presence of", with limits placed for English language publications. Sources were searched from the date of database inception to December 31st 2017.

Eligibility Criteria

Articles were eligible if the following criteria were met: (a) Participants are unpaid adult carers (i.e., families, neighbours, and friends) of a person with dementia; (b) the number of participants and current anxiety prevalence rate is reported; (c) anxiety prevalence is assessed as the presence of any anxiety disorder using a reliable and valid anxiety diagnostic tool OR the presence of a clinical level of anxiety symptoms, as assessed using a reliable and valid self-report symptom measure with a clinical cut-off score; (d) the study is reported in English. Dementia diagnosis could be based on a formal diagnosis by a health professional or report of the non-demented participant (i.e., carer).

The main focus of this meta-analysis was the current anxiety prevalence rate and thus studies that only reported incidence or lifetime (or duration of caregiving) prevalence were excluded. Restrictions were not placed on carer demographic details or characteristics as this study aimed to assess the prevalence of anxiety across the whole population of dementia carers.

Selection of Studies

The primary reviewer (LK) conducted the initial search and duplicates were excluded. Potentially relevant articles were identified based on title and abstract. Full articles were obtained and assessed for eligibility mainly by LK. First, two authors (LK, NK) read randomly selected four papers (ten percent of identified articles) and independently completed an electronic screening checklist in order to ensure accurate selection of the eligible papers. Discrepancies were discussed and resolved, and a third reviewer was available for consultation however this was not required. Following this, the first author (LK) completed the assessment of eligibility for the remaining full-text articles.

Quality Assessment and Risk of Bias

The quality and risk of bias of included studies was assessed using the Prevalence Critical Appraisal Instrument (PCAI) which is designed specifically for assessing prevalence

studies[25]. Whilst other relevant quality assessment tools exist, the PCAI focuses on assessing the quality of the study methods that were planned and carried out rather than assessing the quality of the written report, which can be misleading[26]. The PCAI consists of ten items regarding the internal and external validity of a study. Each item is rated as either 'yes', 'no', or 'unclear. Furthermore the tool includes a comprehensive usage guide[25].

The items regarding the description of participants and setting and the identification of confounding factors and subgroup differences were further defined to ensure consistent rating for this study. The item regarding the description of participants and setting was rated as 'adequate (i.e., yes)' if a study described over half of twelve characteristics reported to be potentially important in dementia carer outcomes (age; gender; relationship to carer; economic status; ethnicity; education; subjective physical health; use of medication; living arrangement; care-recipient level of impairment; hours spent caregiving; months acting as a carer) with at least one item to be the number of hours caregiving or the number of months acting as a carer[20,27,28]. The item regarding the identification of confounding factors and subgroup differences was rated as 'adequate (i.e., yes)' if over half of the above carer characteristics were accounted for in the analysis.

The PCAI does not provide a quantitative quality level for studies. It was decided that all items on the tool were of equal importance for this review, therefore a study was defined as having a high risk of bias if the total number of 'yes' items achieved was less than half. Two authors (LK, NK) evaluated the methodological quality of one paper from the final dataset in order to ensure accurate understanding of the rating process. Following this, the first author (LK) assessed the methodological quality of the remaining nine articles. Articles defined as low quality were selected for exclusion in sensitivity analysis.

Data Extraction

An electronic form was used to extract study characteristics, participant information, prevalence measurement tool characteristics, and prevalence data as per Cochrane

guidelines[29]. Two authors (LK, NK) read a randomly selected paper from the final dataset and independently completed an electronic data extraction sheet in order to ensure accurate understanding of the coding process. Data extraction was considered reliable as there were no discrepancies found between the two reviewers. Following this, the data for the remaining nine articles were extracted by the first author (LK).

Statistical Analysis

Statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software[30]. The analysis used one-group events and sample size data to calculate a pooled prevalence estimate. A random-effects model was selected to pool the data due to expected variation in participant characteristics and prevalence measurement tools. The random effects model is arguably the most appropriate model as it assumes each study contains its own variance as a result of variation in study characteristics[31].

Heterogeneity and Subgroup Analysis

Heterogeneity was examined visually using a forest plot and the calculation of the I^2 statistic, which shows the percentage of the total variance which can be explained by heterogeneity[32]. Planned sensitivity analysis included the removal of outliers, studies rated as having a high risk of bias, and studies which appeared to meet the inclusion criteria but contained uncertainty (i.e., the use of a higher than usual symptom cut-off score). Remaining heterogeneity was planned to be explored through subgroup analysis using the following moderators: (a) prevalence measurement tool type (diagnostic or self-report); (b) specific prevalence measurement tool; (c) care-recipient dementia type (only where study sample contains a heterogeneous group of care-recipients based on dementia type); (d) country development status, defined as the Human Development Index (HDI) category (low; medium; high; very high) which was determined based on the study country for the purposes of this review[33].

Potentially relevant moderators using summary data (e.g. duration/hours caregiving) were not examined due to potential aggregation bias[34]. Aggregation bias occurs when subgroup analysis or meta-regression is conducted using characteristics of participants summarised at the level of the study (e.g., mean duration of caregiving) that are considered to be varying substantially within studies[29]. In addition, considering not all the studies reported study characteristics of interest (e.g., only three studies reported mean hours of caregiving per day), the quantitative analysis of these moderating factors were not performed, but rather summarised in tables.

Publication Bias

Publication bias was explored visually using a funnel plot and the 'trim and fill' method was applied to estimate prevalence after bias had been taken into account [35,36]. Rosenthal's Fail-safe N was calculated to estimate the number of missing studies which would be required to reduce the *p*-value to below .05[37].

Results

Study Selection

The selection of studies is outlined in Figure 1. The search yielded 768 articles, of which 332 were excluded as duplicates, resulting in 436 articles which were screened based on title and abstract. Thirty-seven articles were subject to full eligibility screening, resulting in a total of ten eligible studies[12,38-46]. The most common reason for exclusion was due to prevalence data not being reported with mean anxiety scores or correlations of anxiety scores with other variables being reported instead (See Supplementary Table 1 for the list of excluded studies with reasons). Of the ten eligible studies, one study was identified for exclusion in sensitivity analysis[45]. Sansoni et al[45] used a higher symptom cut-off score than usual for the anxiety measurement tool used meaning that the study may have underestimated the prevalence rate compared to studies using a lower cut-off score. Furthermore, the study employed a non-typical study design as described below.

Study Characteristics

Participant characteristics

Participant characteristics are summarised in Table 1. The ten studies comprised a total of 918 participants with mean age ranging from 48.7 (SD = 10.1) to 66.7 (SD = 12.6) years. The majority of carer participants were female spouses or adult children of the care-recipient. Only three studies reported the mean hours spent caregiving[39,43,45] and only two reported the mean number of caregiving months[39,45] though another reported the median value[43].

Five of the studies included carers of people with Alzheimer's dementia only[41-45], four studies examined a mixed sample of carers including multiple types of dementia[12,38-40], and one study did not specify details regarding dementia type[46]. Of the four studies using a mixed sample, two reported a majority of Alzheimer's carers[39,40] and the remaining two did not specify percentages for dementia type. The country development status for all studies was categorised at the HDI level 'very high' for all studies apart from Medrano et al[43] which rated at 'high'.

Measurement and design characteristics

Measurement and design characteristics are summarised in Table 2. The majority of studies used self-report symptom measures to determine the prevalence of anxiety with only two studies reporting the prevalence based on a diagnostic tool. Of those employing a self-report symptom measure, four studies used the anxiety subscale from the Hospital Anxiety and Depression Scale (HADS)[47], three used the state subscale of the State-Trait Anxiety Inventory (STAI)[48], one used the Spanish version of the Hamilton Anxiety Rating Scale (HAM-A)[49], and one used the anxiety subscale of the Depression Anxiety Stress Scales (DASS)[50]. Of the two studies using diagnostic tools, one used the Geriatric Mental State Schedule interview[51] and the other used the Structured Clinical Interview – non patient version[52].

Study design was similar across all included studies. Eight studies employed a cross-sectional design and one study used a retrospective case-control design which also reported current cross-sectional prevalence. Another study used a descriptive repeated measures design where the anxiety symptom measure was administered over nine weeks[45]. The authors described the design was chosen to eliminate coincidental bias and as the study reported consistent anxiety scores over the nine-week period it was included in this review

Study Quality and Risk of Bias

The assessment of study quality and bias using the PCAI is presented in Table 3. The quality of included studies varied, with studies achieving between three and seven positive items out of a total of ten. Three studies achieved less than five positive items and were selected for exclusion in sensitivity analysis[43-45].

Participants and recruitment

There were no large scale national studies included. Only one study sought a participant sample which could be described as representative of the dementia carer population as a whole[12]. All others did not seek representative samples. For example, Coope et al[38] only included carers of people with mild or moderate dementia and Ervin et al[40] only included rural carers and excluded those which were predicted to be burdened by participating. Several studies limited recruitment based on participant characteristics such as gender[45], dementia type[41-45], or relationship to the care-recipient[39]. Weaving et al[46] only recruited carers who accessed support from voluntary services. However, the majority of studies used appropriate recruitment methods for their chosen samples based on the PCAI guide (e.g., use of random sampling, the full description of how sampling was performed, appropriateness of sampling framework)[25].

A sample size calculation was not conducted before initiation of the study by any of the included studies. Therefore, it was necessary to calculate the minimum sample size required to detect described prevalence rates at a confidence level of 95%[53]. It was noted

that only two studies had used an adequate sample size[38,39]. Furthermore, several studies did not provide an adequate description of participant characteristics neglecting to describe at least six important participant characteristics[12,38,40,41,43,45].

Data measurement and analysis

Only one study was determined to have conducted data analysis with sufficient coverage of the sample[38], two studies had a high proportion of drop-outs[41,45], and all other studies did not report the number of participants that declined to participate or dropped-out. All included studies used objective and reliable prevalence measurement tools, as doing so formed part of the inclusion criteria for this review. All studies were found to use appropriate statistical analysis methods. Only one study gave sufficient consideration to confounding factors and subgroups/moderators[12]. Six studies included analysis of some moderating factors[40,42,43,45,46] though the criteria used to define the moderators was not clear in three of those studies[41-43,45]. Three studies did not give consideration to any moderating factors[38,39,44].

Synthesis of Anxiety Prevalence

Anxiety prevalence rates ranged from 3.7 percent (95% CI 1.4% to 9.4%, $p<0.01$) to 76.5 percent (95% CI 59.5% to 87.8%, $p>0.01$). In meta-analysis, a pooled prevalence estimate of 32.1 percent was achieved (95% CI 20.6% to 46.2%, $p=0.01$). Visual inspection of the forest plot presented in Figure 2 suggested possible heterogeneity between studies which was found to be statistically significant ($I^2=92.9\%$, $p<0.01$).

Publication bias

Visual inspection of the funnel plot for all included studies was inconclusive (Figure 3). Duval and Tweedie's trim and fill method[36] imputed one missing study estimating an adjusted prevalence rate of 27.64 percent (95% CI 16.73% to 42.07%). Rosenthal's fail-safe N[37] calculated 115 missing studies would be required to increase the two-tailed p-value to above .05.

Sensitivity analysis

Sansoni et al[45] met several of the criteria for exclusion in sensitivity analysis. Firstly, the study was identified on the forest plot as a possible outlier (Figure 2). Secondly, the eligibility of Sansoni et al[45] contained some uncertainty due to the use of a higher than usual symptom cut-off score. Thirdly Sansoni et al[45] was rated as having a high risk of bias, achieving only three out of ten positive items. Further two studies were excluded in the sensitivity analysis based on potential risk of bias. Both Medrano et al[43] and Ostojić et al[44] achieved only four out of ten positive items. The sensitivity analysis yielded a reduced though comparable pooled prevalence rate of 27.0 percent (95% CI 15.4% to 42.9%, $p<0.01$). Heterogeneity remained statistically significant ($I^2=94.0\%$, $p<0.01$).

Subgroup analysis

Subgroup analysis was initially conducted using all included studies. A statistically significant difference in prevalence rate between studies grouped by prevalence measurement tool type was identified ($p<0.01$). The pooled prevalence rate as measured by a diagnostic tool was 5.6 percent (95% CI 2.7% to 11.3%, $p<0.01$) with no statistically significant heterogeneity between studies ($I^2=28.2\%$, $p=0.24$). The pooled prevalence rate as measured by a self-report symptom measure was 42.6 percent (95% CI 30.96% to 55.3%, $p<0.25$) with statistically significant heterogeneity between studies ($I^2=89.6\%$, $p<0.01$). The obtained prevalence rates were similar when the subgroup analysis was conducted after sensitivity exclusions (diagnostic tool=5.6% prevalence, 95% CI 2.7% to 11.3%, $p<0.01$; self-report symptom measure=41.2% prevalence, 95% CI 28.6% to 55.1%, $p<0.22$). Further subgroup analysis using individual self-report measures as subgroups was not conducted due to a large variety in the measures used and the small number of studies using each measure.

Subgroup analysis was not conducted using dementia type as there were no studies using a sample of carers for a single dementia type, apart from Alzheimer's dementia.

Furthermore, subgroup analysis was not conducted on HDI category due to all but one study country being rated as ‘very high’.

Discussion

This study synthesized an estimate of the prevalence of anxiety in the dementia carer population defined as anxiety diagnoses or a clinically relevant level of symptoms. The adjusted prevalence rate following publication bias assessment will not be discussed here as it has been suggested that publication bias assessment is not reliable when fewer than 30 studies are included[32].The overall pooled anxiety prevalence rate was 32.1 percent in the current study, which is comparable to the pooled estimate of 31.2 percent for the prevalence of depression obtained by the recent review conducted by Collins and Kishita[54].

Previous studies reported that the prevalence rate of anxiety disorders in older people as measured by diagnostic tools or self-report symptom measures to be 1.2-14 percent[55]. The recent meta-analysis on global prevalence of anxiety symptoms among carers of stroke survivor estimated the prevalence rate at 21.4 percent[56]. These suggest that anxiety is indeed a prevalent psychological difficulty experienced by informal carers of people with dementia. As such anxiety should be afforded as much consideration as depression in the carer literature in terms of developing an understanding of moderating and mediating factors and also with regards to intervention development and assessment.

The pooled prevalence rate contained significant heterogeneity across individual study prevalence rates in the current study. Excluding Sansoni et al[45], Medrano et al[43] and Ostojić et al[44] in sensitivity analysis reduced the prevalence estimate to 27 percent but did not reduce heterogeneity. The individual prevalence rates for both Sansoni et al[45] and Ostojić et al[44] were greater than the overall obtained prevalence rate, whilst Medrano et al[43] obtained a lower prevalence rate. The reduction in prevalence was somewhat unexpected given that Sansoni et al[45] used a higher than usual cut-off score to determine caseness, which was expected to result in an underestimation of prevalence. However, it was noted that Sansoni et al[45] was the only study to include a female only sample. Prior research

suggests that female carers tend to spend more time in caregiving and often have to play multiple conflicting roles[57] resulting in greater psychological distress compared to male carers[11,58,59]. The female gender sample may therefore have resulted in a greater anxiety prevalence rate compared to mixed gender samples.

Diagnostic Tools Versus Self-report Symptom Measures

Subgroup analysis revealed a statistically significant difference in prevalence as measured by diagnostic tools and self-report symptom measures. The pooled prevalence rate when a diagnostic tool was used was 5.6 percent and whilst no significant heterogeneity was found, it is possible that the small number of studies in the diagnostic tool group (n = 2) did not allow for the detection of heterogeneity[32]. The self-report symptom measure prevalence was significantly higher at 42.6 percent with statistically significant heterogeneity between studies. Further exploration of heterogeneity was not conducted as subgroup analysis was limited by the number and characteristics of included studies.

These results may appear to suggest that the different measurement tools were measuring different constructs and that the prevalence of diagnosable anxiety disorders was lower than the prevalence of clinically significant level of symptoms. This is consistent with the results of a recent systematic review on studies of diagnostic accuracy that compared a self-report screening instrument for anxiety disorders with the diagnosis made by a trained clinician[60]. This recent review[60] demonstrated that only limited self-reported measures of anxiety such as Generalised Anxiety Disorder Assessment (GAD-7) have good performance characteristics and are promising as a case-finding instrument. None of included studies used GAD-7 with family carers of people with dementia in the current review. The widespread use of self-report measures of anxiety which may lack in diagnostic specificity and sensitivity needs further consideration in the future studies.

It is also important to highlight that when examining the two studies included in the diagnostic tool group, it was noted that Coope et al[38] did not include carers of people with

'severe' dementia and carers only needed to be in contact with the care-recipient once per week to be included. Furthermore, the Dura et al[39] sample had the lowest number of caregiving hours compared to the other studies which reported caregiving hours. It is possible that the Coope et al[38]and Dura et al[39] participants engaged in less caregiving for people with less severe dementia and both factors postulated to impact on psychological difficulties in carers[5,61].

Care-recipient Dementia Type

The majority of studies included participants caring for a person with Alzheimer's dementia only or used a mixed sample comprising a majority of Alzheimer's carers. Whilst this reflects the prevalence of different types of dementia, it did not allow for the moderating impact of care-recipient dementia type on anxiety prevalence to be explored in this meta-analysis. However, it is possible that prevalence of anxiety is higher or lower in carers of people with different types of dementia given the varying challenges associated with different dementia illnesses[1].

Country Development Status

All of the studies included in this meta-analysis included samples from countries categorised as very highly developed apart from Medrano et al[43] which included a sample from a highly developed country based on the HDI category of each country[33]. It was therefore not possible to examine the moderating impact of country development status. The lack of studies from less developed countries may reflect a lack of research in these areas though it is important to acknowledge that language bias may be a contributing factor as only studies reported in English were included. Given that dementia is a global difficulty and that there may be a greater demand for informal care in less developed countries, it is important that dementia carer research does not neglect the carer population in less developed countries[62].

Additional Clinical and Research Implications

The current national guideline such as the NICE guideline for dementia care in the UK[63] states that healthcare professionals need to be aware that carers of people with dementia are at an increased risk of depression and that they need to familiarise themselves with further guidance on identifying and managing depression. However, the guideline does not refer to the heightened risk of anxiety in this population. There is an urgent need for the guidelines to be updated so that an equal level of attention is warranted to the implementation of assessment and early treatment of anxiety symptoms in family carers.

It is important for future research to focus on identifying factors which moderate anxiety prevalence given the high heterogeneity found in this study. It was not possible to explore the impact of potential moderators such as care-recipient dementia type and country development status in the current study due the number of studies identified. The current literature also highlights that there may be some other potential factors which may have an impact on psychological difficulties experienced by carers such as the time spent on caregiving, role conflicts (e.g., being mother, employee, and carer), and types of caregiving tasks involved (i.e., the level of impairment and independence)[57]. However, exploration of these potential factors is currently not possible due to the limited characteristics of the sample reported in primary studies. Further research on moderating factors can help to both identify carers who may be more vulnerable to experiencing anxiety and achieve a better understanding of potential protective factors.

Given that this study demonstrated anxiety is a prevalent difficulty for dementia carers and that the anxiety prevalence is comparable to that of depression, it would be beneficial for future research to also consider common transdiagnostic factors moderating the range of difficulties experienced by dementia carers. For example, there is a strong evidence that the transdiagonstic factors such as psychological flexibility (the ability to engage in constructive, value-oriented actions despite the presence of unpleasant thoughts and feelings) plays a critical role in explaining the range of difficulties experienced by various populations including chronic pain[64], psychosis[65], and substance use disorders[66]. There is

now emerging evidence that psychological flexibility predicts both anxiety[67] and depression[68] in carers of people with dementia. Indeed, the recent meta-analysis on different types of carer interventions demonstrated that Acceptance and Commitment Therapy which targets psychological flexibility is efficacious for treating both depression and anxiety in carers of people with dementia and that it is particularly beneficial for carers experiencing anxiety symptoms[69]. Should such common factors be identified, it may allow for the development of more resource efficient interventions which are beneficial for a variety of dementia carers regardless of their primary presenting difficulties.

Strengths and Limitations

A strength of this meta-analysis is that it provided an updated pooled estimate of anxiety in carers for all types of dementia. The pooled prevalence rate obtained justifies focusing future research on understanding underlying factors which may moderate anxiety and how interventions may be adapted to address such factors. It also justifies the inclusion of anxiety as an outcome measure in dementia carer intervention research.

An important limitation of this study is the small number of studies included. A total of ten studies were included, which was reduced to seven following exclusion of studies with high risk of bias in sensitivity analysis. Another limitation is the large amount of statistically significant heterogeneity which could not be conclusively explained and thus it was not possible to subsequently draw reliable conclusions with regards to moderating factors. This highlights the need for more research into the prevalence of anxiety in dementia carer populations.

There are also some methodological limitations to this study. The electronic search was limited to English-language articles. The authors did not contact experts in the field for identifying additional studies or seeking unpublished data from the identified studies (e.g., the authors did not seek data from those that reported on carer mean anxiety levels but did not give prevalence data). These may have led to the exclusion of potentially relevant

studies. Data extraction and quality rating were mainly conducted by a single author, which could have led to reporting bias. In addition, studies that identified people with dementia based on a formal diagnosis by a health professional and report of the carer were eligible for the current review which could also have had an impact on the prevalence of anxiety.

Conclusions

Despite the methodological limitations, this meta-analysis highlighted that anxiety is as prevalent as depression in carer of people with dementia and as such warrants a similar level of focus in the research literature and clinical practice. Further research into the prevalence of anxiety in less typically researched groups of dementia carers (e.g. carers residing in less developed countries, carers of people with dementia illnesses other than Alzheimer's dementia) and additional moderating and mediating factors are critical for improved access to evidence based treatments.

References

1. Johnson DK, Watts AS, Chapin BA, Anderson R, Burns JM. Neuropsychiatric profiles in dementia. *Alzheimer disease and associated disorders.* 2011;25(4):326-332.
2. Friedman EM, Shih RA, Langa KM, Hurd MD. US Prevalence And Predictors Of Informal Caregiving For Dementia. *Health affairs (Project Hope).* 2015;34(10):1637-1641.
3. Alzheimer's Research UK. *Dementia in the Family [Internet].* London, UK: Alzheimer's Research UK; n.d [cited 2019 February 7] Available from https://www.alzheimersresearchuk.org/wp-content/uploads/2015/12/Dementia-in-the-Family-The-impact-on-carers.pdf.
4. Andrews GJ. Managing challenging behaviour in dementia. *BMJ (Clinical research ed.).* 2006;332(7544):741.
5. Brodaty H, Donkin M. Family caregivers of people with dementia. *Dialogues In Clinical Neuroscience.* 2009;11(2):217-228.
6. Janssen A. *Patient and spouse perceptions of cognitive and neuropsychiatric symptoms in parkinson's disease: implications for distress, quality of life and relationship satisfaction [Thesis]*. London, UK: Doctor of Clinical Psychology, King's College London; 2013.
7. Roff LL, Burgio LD, Gitlin L, et al. Positive aspects of Alzheimer's caregiving: the Role of race. *The Journals of Gerontology: Series B: Psychological Sciences and Social Sciences.* 2004;59(4):185-190.
8. Dahlrup B, Ekstrm H, Nordell E, Elmsthl S. Coping as a caregiver: A question of strain and its consequences on life satisfaction and health-related quality of life. *Archives of Gerontology and Geriatrics.* 2015;61(2):261-270.
9. Sörensen S, Conwell Y. Issues in dementia caregiving: effects on mental and physical health, intervention strategies, and research needs. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* 2011;19(6):491-496.

10. Schulz R, Obrien AT, Bookwala J, Fleissner K. Psychiatric and Physical Morbidity Effects of Dementia Caregiving: Prevalence, Correlates, and Causes. *The Gerontologist.* 1995;35(6):771-791.

11. Mausbach BT, Chattillion EA, Roepke SK, Patterson TL, Grant I. A comparison of psychosocial outcomes in elderly Alzheimer caregivers and noncaregivers. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* 2013;21(1):5-13.

12. Mahoney R, Regan C, Katona C, Livingston G. Anxiety and depression in family caregivers of people with Alzheimer Disease: the LASER-AD study. *American Journal of Geriatric Psychiatry.* 2005;13(9):795-801.

13. Bower ES, Wetherell JL, Mon T, Lenze EJ. Treating anxiety disorders in older adults: Current treatments and future directions. *Harvard Review of Psychiatry.* 2015;23(5):329-342.

14. Alwahhabi F. Anxiety Symptoms and Generalized Anxiety Disorder in the Elderly: A Review. *Harvard Review of Psychiatry (Taylor & Francis Ltd).* 2003;11(4):180.

15. Bryant C, Jackson H, Ames D. The prevalence of anxiety in older adults: Methodological issues and a review of the literature. *Journal of Affective Disorders.* 2008;109(3):233-250.

16. Schuurmans J, van Balkom A. Late-life Anxiety Disorders: A Review. *Current Psychiatry Reports.* 2011;13(4):267-273.

17. Farina N, Page TE, Daley S, et al. Factors associated with the quality of life of family carers of people with dementia: A systematic review. *Alzheimer's & Dementia: The Journal Of The Alzheimer's Association.* 2017.

18. Cooper C, Balamurali TBS, Livingston G. A systematic review of the prevalence and covariates of anxiety in caregivers of people with dementia. *International Psychogeriatrics.* 2007;19(02):175-195.

19. Sallim A, Sayampanathan A, Cuttilan Aa. Prevalence of mental health disorders among caregivers of patients with Alzheimer Disease. *Journal of the American Medical Directors Association.* 2015;16(12):1034-1041.

20. Covinsky KE, Newcomer R, Fox P, et al. Patient and caregiver characteristics associated with depression in caregivers of patients with dementia. *Journal of General Internal Medicine.* 2003;18(12):1006-1014.

21. Janevic MR, Connell CM. Racial, ethnic, and cultural differences in the dementia caregiving experience. *The Gerontologist.* 2001;41(3):334-347.

22. Shaji KS. Dementia care in developing countries: the road ahead. *Indian journal of psychiatry.* 2009;51 Suppl 1(Suppl1):5-7.

23. Snyder CM, Fauth E, Wanzek J, et al. Dementia caregivers' coping strategies and their relationship to health and well-being: The Cache County Study. *Aging \& Mental Health.* 2015;19(5):390-399.

24. Wong C, Merrilees J, Ketelle R, Barton C, Wallhagen M, Miller B. The experience of caregiving: differences between behavioral variant of frontotemporal dementia and Alzheimer disease. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* 2012;20(8):724-728.

25. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *International journal of health policy and management.* 2014;3(3):123-128.

26. Harder T. Some notes on critical appraisal of prevalence studies: Comment on: The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence . *International journal of health policy and management.* 2014;3(5):289-290.

27. Cooper C, Balamurali TBS, Selwood A, Livingston G. A systematic review of intervention studies about anxiety in caregivers of people with dementia. *International Journal of Geriatric Psychiatry.* 2007;22(3):181--188.

28. Cosseddu M, Alberici A, Pelizzola S, Padovani A, Borroni B. The other face of the coin: The caregiver burden in frontotemporal lobar degeneration. *International Journal of Geriatric Psychiatry.* 2013;28(6):655--657.

29. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].* The Cochrane Collaboration, Available from http://handbook.cochrane.org.; 2011.

30. Borenstein M, Hedges L, Higgins J, Rothstein H. *Comprehensive Meta-Analysis Version 3.* Englewood, NJ 2013.

31. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods.* 2010;1(2):97-111.

32. Cuijpers P. *Meta-analyses in mental health research . A practical guide.* Vrije Universiteit Amsterdam 2016.

33. United Nations Development Programme. Human Development Report 2016 Human Development for Everyone [Internet]. 2016 [cited 2019 February 12]. Available from: http://hdr.undp.org/en/content/human-development-report-2016-human-development-everyone.

34. Kaufmann E, Reips U-Da. Avoiding methodological biases in meta-analysis. *Zeitschrift für Psychologie.* 2016;224(3):157-167.

35. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Criticisms of Meta Analysis. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, eds. *Introduction to Meta Analysis*. West Sussex, UK: John Wiley & Sons, Ltd.; 2009:377-387.

36. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics.* 2000;56(2):455-463.

37. Rosenthal R. The file drawer problem and tolerance for null results. *Psychological Bulletin.* 1979;86(3):638-641.

38. Coope B, Ballard C, Saad K, et al. The prevalence of depression in the carers of dementia sufferers. *International Journal of Geriatric Psychiatry.* 1995;10(3):237-242.

39. Dura JR, Stukenberg KW, Kiecolt-Glaser JK. Anxiety and depressive disorders in adult children caring for demented parents. *Psychology and aging.* 1991;6(3):467-473.

40. Ervin K, Pallant J, Reid C. Caregiver distress in dementia in rural Victoria. *Australasian Journal on Ageing.* 2015;34(4):235-240.

41. Garca-Alberca JM, Cruz B, Lara JP, Garrido V, Lara A, Gris E. Anxiety and depression are associated with coping strategies in caregivers of Alzheimer's disease patients: Results from the MÁLAGA-AD study. *International Psychogeriatrics.* 2012;24(8):1325-1234.

42. Garca-Alberca JM, Lara JP, Luis Berthier M. Anxiety and depression in caregivers are associated with patient and caregiver characteristics in Alzheimer's disease. *International Journal of Psychiatry in Medicine.* 2011;41(1):57-69.

43. Medrano M, Rosario RL, Payano AN, Capelln NR. Burden, anxiety and depression in caregivers of Alzheimer patients in the Dominican Republic. *Dementia & Neuropsychologia.* 2014;8(4):384-388.

44. Ostojić D, Vidović D, Baceković A, Brecić P, Jukić V. Prevalence of anxiety and depression in caregivers of alzeheimer's dementia patients. *Acta Clinica Croatica.* 2014;53(1):17-21.

45. Sansoni J, Vellone E, Piras G. Anxiety and depression in community-dwelling, Italian Alzheimer's disease caregivers. *International Journal of Nursing Practice.* 2004;10(2):93-100.

46. Weaving J, Orgeta V, Orrell M, Petrides KV. Predicting anxiety in carers of people with dementia: the role of trait emotional intelligence. *International Psychogeriatrics.* 2014;26(7):1201-1209.

47. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica.* 1983;67(6):361-370.

48. Spielberger CD, Gorsuch RL, Lushene RE. *Manual for the State-Trait Anxiety Inventory.* Palo Alto, CA: Consulting Psychologists Press; 1970.

49. Lobo A, Chamorro L, Luque A, et al. Validation of the Spanish versions of the Montgomery-Asberg depression and Hamilton anxiety rating scales [Article in Spanish]. *Medicina Clínica.* 2002;118(13):493-499.

50. Ng F, Trauer T, Dodd S, Callaly T, Campbell S, Berk M. The validity of the 21-item version of the Depression Anxiety Stress Scales as a routine clinical outcome measure. *Acta Neuropsychiatrica.* 2007;19(5):304-310.

51. Copeland JRM, Dewey ME, Henderson AS, et al. The geriatric mental state (GMS) used in the community: Replication studies of the computerized diagnosis AGECAT. *Psychological medicine.* 1988;18(1):219-223.

52. Riskind JH, Beck AT, Berchick RJ, Brown G, Steer RA. Reliability of DSM-III diagnoses for major depression and generalized anxiety disorder using the Structured Clinical Interview for DSM-III. *Archives of General Psychiatry.* 1987;44(9):817-820.

53. Naing L, Winn T, Rusli BN. Practical Issues in Calculating the Sample Size for Prevalence Studies. *Archives of Orofacial Sciences.* 2006;1:9-14.

54. Collins R, Kishita N. Prevalence of depression and burden among informal caregivers of people with dementia. *Ageing & Society.* 2018:Accepted for publication.

55. Remes O, Brayne C, van der Linde R, Lafortune L. A systematic review of reviews on the prevalence of anxiety disorders in adult populations. *Brain and behavior.* 2016;6(7):e00497-e00497.

56. Loh AZ, Tan JS, Zhang MW, Ho RC. The Global Prevalence of Anxiety and Depressive Symptoms Among Caregivers of Stroke Survivors. *Journal of the American Medical Directors Association.* 2017;18(2):111-116.

57. Sharma N, Chakrabarti S, Grover S. Gender differences in caregiving among family - caregivers of people with mental illnesses. *World Journal Of Psychiatry.* 2016;6(1):7-17.

58. Borsje P, Hems MAP, Lucassen PLBJ, Bor H, Koopmans RTCM, Pot AM. Psychological distress in informal caregivers of patients with dementia in primary care: course and determinants. *Family Practice.* 2016;33(4):374-381.

59. Pillemer S, Davis J, Tremont G. Gender effects on components of burden and depression among dementia caregivers. *Aging & Mental Health.* 2018;22(9):1162-1167.

60. Herr NR, Williams JW, Jr., Benjamin S, McDuffie J. Does This Patient Have Generalized Anxiety or Panic Disorder?: The Rational Clinical Examination Systematic ReviewScreening for Generalized Anxiety or Panic DisorderScreening for Generalized Anxiety or Panic Disorder. *JAMA.* 2014;312(1):78-84.

61. Gaugler JE, Jarrott SE, Zarit SH, Stephens M-AP, Townsend A, Greene R. Adult day service use and reductions in caregiving hours: effects on stress and psychological well-being for dementia caregivers. *International Journal of Geriatric Psychiatry.* 2003;18(1):55-62.

62. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association.* 2013;9(1):63-75.

63. National Institute for Health and Care Excellence. NICE guideline [NG97] Dementia: assessment, management and support for people living with dementia and their carers [Internet]. 2018 [cited 2019 February 5] Available from https://www.nice.org.uk/guidance/ng97.

64. Lin J, Klatt LI, McCracken LM, Baumeister H. Psychological flexibility mediates the effect of an online-based acceptance and commitment therapy for chronic pain: an investigation of change processes. *Pain.* 2018;159(4):663-672.

65. Spidel A, Lecomte T, Kealy D, Daigneault I. Acceptance and commitment therapy for psychosis and trauma: Improvement in psychiatric symptoms, emotion regulation, and treatment compliance following a brief group intervention. *Psychology and psychotherapy.* 2018;91(2):248-261.

66. Luoma JB, Kohlenberg BS, Hayes SC, Fletcher L. Slow and steady wins the race: a randomized clinical trial of acceptance and commitment therapy targeting shame in substance use disorders. *Journal of Consulting and Clinical Psychology.* 2012;80(1):43-53.

67. Romero-Moreno R, Losada A, Márquez-González M, Mausbach BT. Stressors and anxiety in dementia caregiving: multiple mediation analysis of rumination, experiential avoidance, and leisure. *International Psychogeriatrics.* 2016;28(11):1835-1844.

68. Spira AP, Beaudreau SA, Jimenez D, et al. Experiential avoidance, acceptance, and depression in dementia family caregivers. *Clinical Gerontologist.* 2007;30(4):55-64.

69. Kishita N, Hammond L, Dietrich C, Mioshi E. Which intervention work for dementia family carers?: An updated systematic review of randomised controlled trials of carer interventions. *International Psychogeriatrics.* 2018;30(11):1679-1696.

Figure legend

Figure 1. Systematic literature search flow chart

Figure 2. Forest plot for meta-analysis of anxiety prevalence

Figure 3. Publication bias assessment funnel plot for anxiety prevalence studies

Table 1. Characteristics of participants for each study

Study	Country	Total N	Mean age (SD)	% female	Relationship to care-recipient (%)	Mean hours caregiving per day (SD)	Mean number of months caregiving (SD)	Care-recipient dementia type (%)
Coope et al. (1995)	UK	109	NR	62	Spouse (42); Adult child (39.5); Sibling (4.6); Distant relative/friend (14.7)	NR	NR	Any mild or moderate Dementia (NR)
Dura et al. (1991)	USA	78	48.74 (10.11)	84.6	Adult child (100)	4.61 (4.94)	48.83 (40.22)	Alzheimer's disease (80.77); Multi-infarct dementia (3.85); Huntingdon's dementia (3.85); Parkinson's dementia (7.69); Unspecified dementia (3.85)
Ervin et al. (2015)	Australia	39	NR	77	Daughter (28); Wife (28); Husband (18); Other family member/friend (21)	NR	NR	Not specified dementia (43); Alzheimer's disease (46); Other (Parkinson's dementia, Vascular dementia, Cerebral amyloidosis) (10)
García-Alberca et al. (2011)	Spain	125	61.41 (11.03)	79.2	Adult child (44); Spouse (41.9); Sibling (6.4); Other relative (8)	NR	NR	Alzheimer's disease (100)
García-Alberca et al. (2012)	Spain	80	62.15 (10.37)	77.5	Adult child (43.8); Spouse (38.8); Sibling (7.4); Other relative (10)	NR	NR	Alzheimer's disease (100)
Mahoney et al. (2005)	UK	153	64 (3.3)	69.9	Spouse (44.4); Adult child (44.4); Friend (4.6)	NR	NR	Alzheimer's disease (NR); Dementia (NR)
Medrano et al. (2014)	Dominican Republic	67	61 (NR)	84	Adult child (55); Spouse (15); Grandchild (12); Sibling (9); Other relative (9)	NR	NR	Alzheimer's disease (100)
Ostojić et al. (2014)	Croatia	30	57.6	73.3	Adult child (63.3); Spouse (26.7)	16.43 (9.93)	NR	Alzheimer's disease (100)

Sansoni et al. (2004)	Italy	34	59.21 (9.62)	100	Wife (73.53); Sister (1.94); Daughter (11.76); Other relative (8.82); Friend (2.94)	19.38 (4.75)	47.76 (34.08)	Alzheimer's disease (100)
Weaving et al. (2014)	UK	203	66.71 (12.64)	69.8	Spouse (61.5); Adult child (33.5); Other relative/friend/partner (5)	NR	NR	NR

Note. NR = Not reported.

Table 2. Characteristics of measurements and design for each study

Study	Study design	Anxiety measurement type and tool	Cut-off point/criteria for caseness	Prevalence Caseness % (N)
Coope et al. (1995)	Cross-sectional	Diagnostic - GMS-AGECAT	Level ≥3	3.67 (4)
Dura et al. (1991)	Retrospective case-control incl. cross sectional data	Diagnostic - SCID-NP	Meets DSM-III-R diagnostic criteria for Generalized Anxiety Disorder, Social Phobia or Panic Disorder	7.69 (6)
Ervin et al. (2015)	Cross-sectional	Self-report symptom measure - DASS-21	≥10 (incl. moderate (10-14); severe(15-19); extremely severe (≥20))	26 (10)
García-Alberca et al. (2011)	Cross-sectional	Self-report symptom measure - STAI-S	≥28	53 (66)
García-Alberca et al. (2012)	Cross-sectional	Self-report symptom measure - STAI-S	≥28	56.6 (45)
Mahoney et al. (2005)	Cross-sectional	Self-report symptom measure - HADS-A	≥11	23.5 (36)
Medrano et al. (2014)	Cross-sectional	Self-report symptom measure - HARS Spanish version	≥6 (incl. mild 6-14; moderate/severe ≥15)	19 (13)
Ostojić et al. (2014)	Cross-sectional	Self-report symptom measure – HADS-A Croatian version	≥11	46.7 (14)
Sansoni et al. (2004)	Descriptive correlational repeated measures	Self-report symptom measure - STAI-S	>40	76.47 (26)
Weaving et al. (2014)	Cross-sectional	Self-report symptom measure - HADS	≥11	49.2 (100)

Note. NR = Not reported; GMS-AGECAT = Geriatric Mental State Schedule interview - Automated Geriatric Examination for Computer Assisted Taxonomy; SCID-NP = Structured Clinical Interview - non-patient version; DASS-21 = Depression Anxiety Stress Scales; STAI-S = State-Trait Anxiety

Table 3. Assessment of quality and risk of bias using the Prevalence Critical Appraisal Instrument for each study

Study	Coope et al. (1995)	Dura et al. (1991)	Ervin et al. (2015)	García-Alberca et al. (2011)	García-Alberca et al. (2012)	Mahoney et al. (2005)	Medrano et al. (2014)	Ostojić et al. (2014)	Sansoni et al. (2004)	Weaving et al. (2014)
Item 1: Sample representative of target population?	No	No	No	No	No	Yes	No	No	No	No
Item 2: Appropriate recruitment method?	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes
Item 3: Adequate sample size?	Yes	Yes	No	No	No	No	No	No	No	No
Item 4: Detailed description of participants and setting?	No	Yes	No	Yes	No	No	No	Yes	No	Yes
Item 5: Data analysis conducted with sufficient coverage of sample?	Yes	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear	No	Unclear
Item 6: Objective and standard measurement criteria used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Item 7: Reliable measurement used?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Item 8: Appropriate statistical analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Item 9: Confounding factors/subgroups/differences identified and accounted for?	No	No	No*	No*	No*	Yes	No*	No	No*	No*
Item 10: Subpopulations identified using objective criteria	N/A	N/A	Yes	Unclear	Yes	Yes	Unclear	N/A	Unclear	Yes
Total number of 'Yes' items	6	6	5	5	5	7	3	4	4	6

Note. *Some factors/subgroups/differences identified and accounted for, but below level sufficient to rate as ‘yes’; N/A = Not applicable.

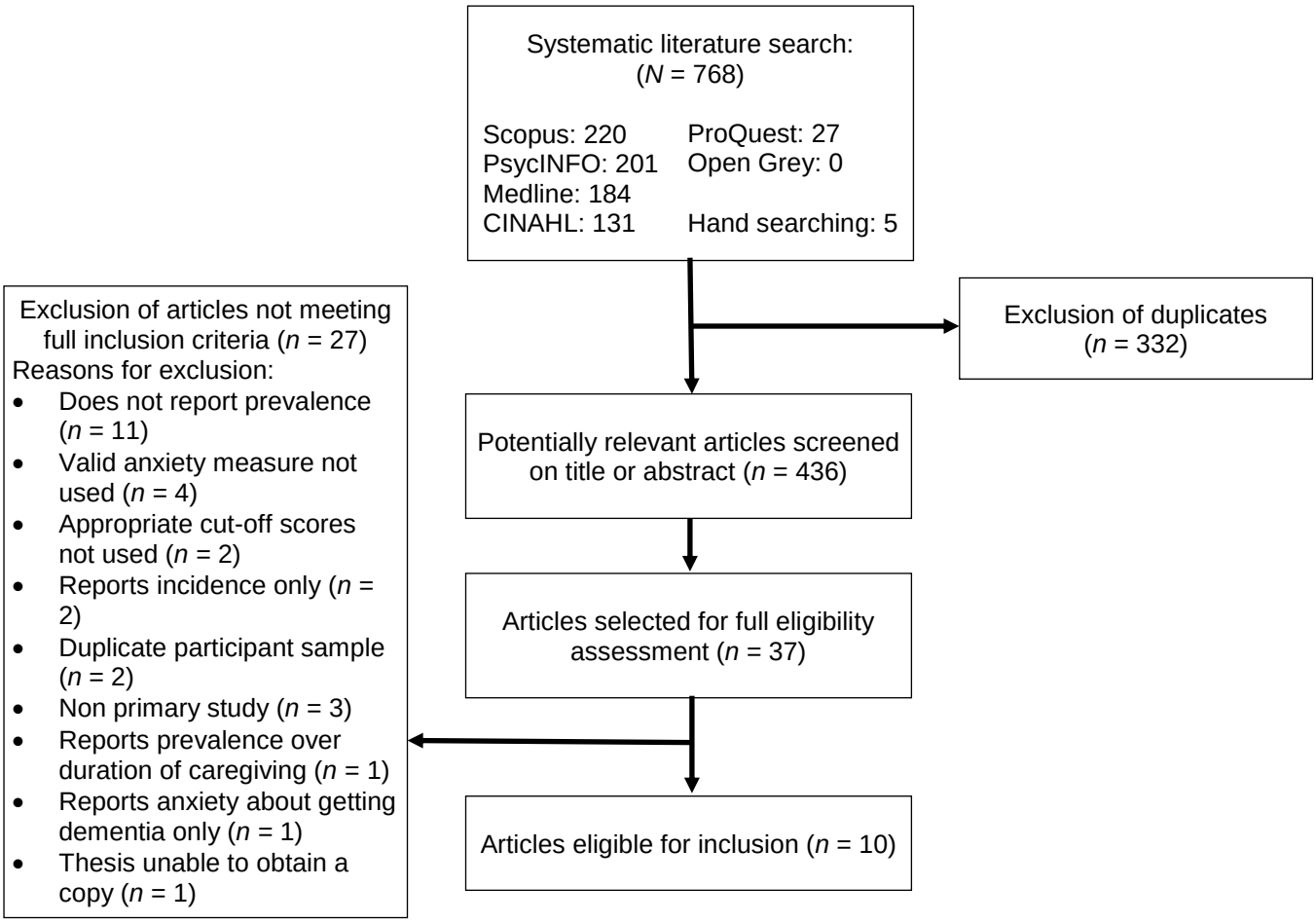

Figure 1 Systematic literature search flow chart

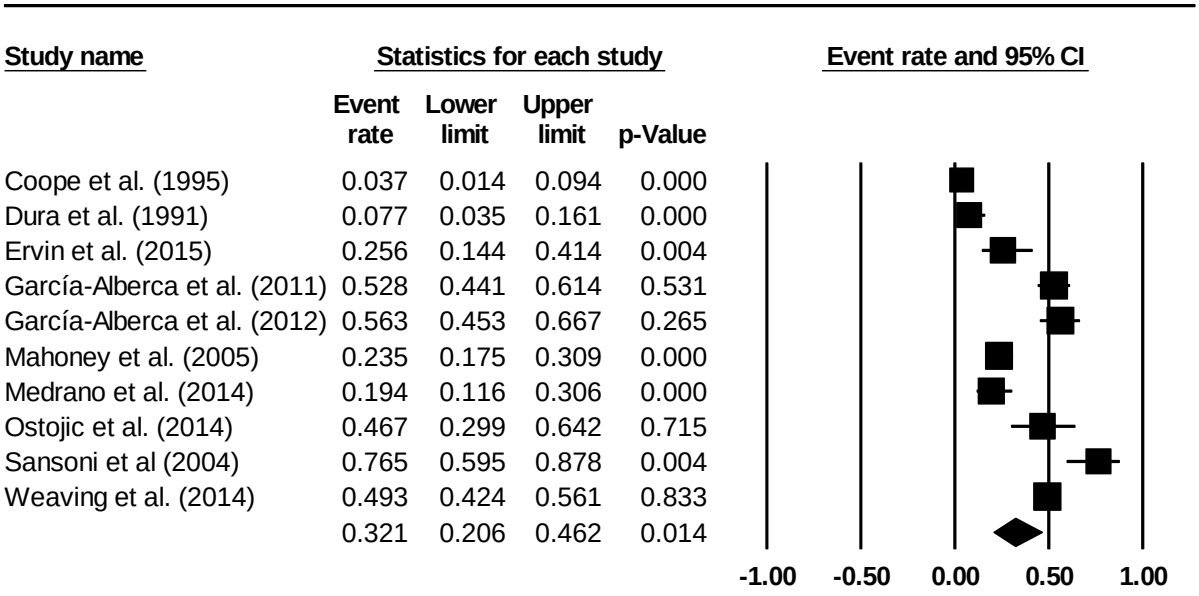

Figure 2 Forest plot for meta-analysis of anxiety prevalence

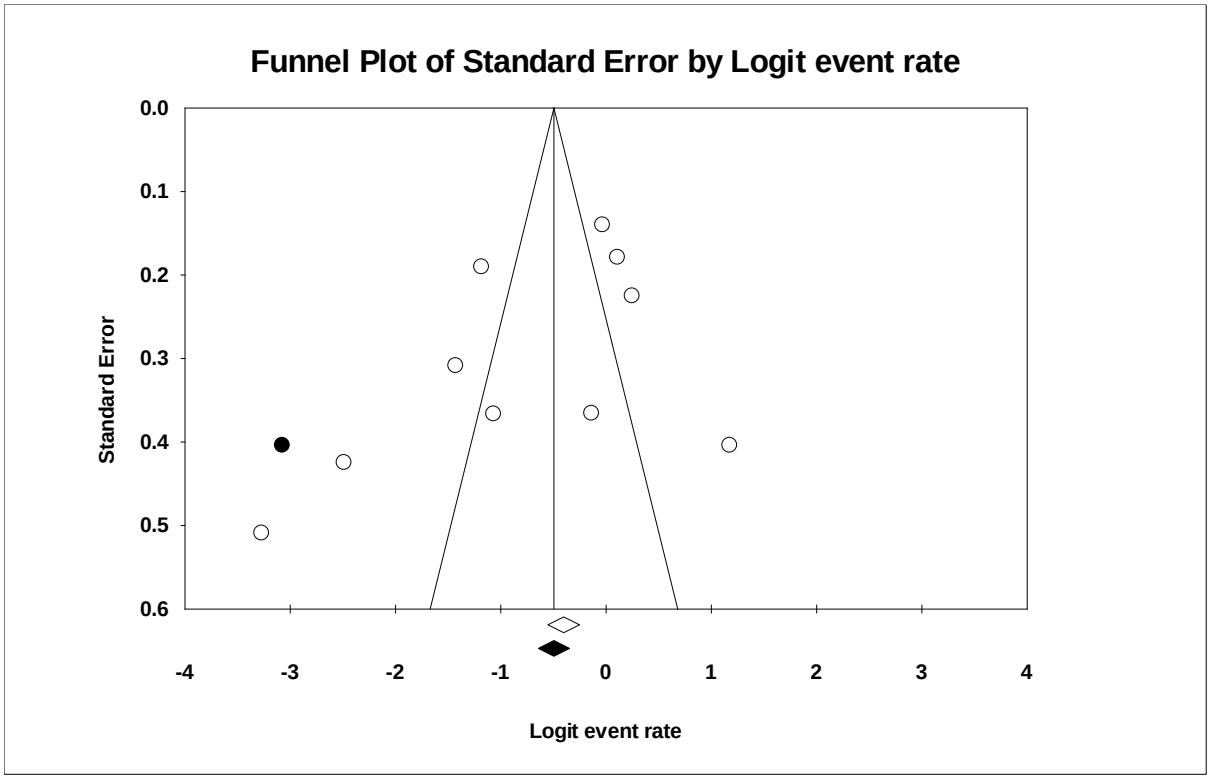

Figure 3 Publication bias assessment funnel plot for anxiety prevalence studies