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Cognitive behavioural therapy for depression, anxiety and stress in caregivers of dementia patients: a systematic review and meta-analysis

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Abstract

Background

There is limited evidence for the efficacy of cognitive behavioural therapy (CBT) in managing psychological morbidities in caregivers of dementia patients.

Aims

To evaluate changes in dementia caregivers' depression, anxiety and stress following CBT. Also to assess quality of life, intervention adherence/satisfaction and therapy effectiveness using different formats, frequencies and delivery methods.

Methods

Studies were identified through electronic bibliographic searches (MEDLINE, EMBASE, CINAHL, PsycINFO and the Cochrane Library) and from grey literature (Conference Proceedings Citation Index and clinicaltrials.gov). Data was pooled for meta-analysis.

Results

Twenty-five studies were included. Depression (SMD=-0.34; 95% CI -0.47 to -0.21; $p<0.001$) and stress (SMD=-0.36; 95% CI -0.52 to -0.20; $p<0.001$) were significantly reduced after CBT, relative to comparator groups, whilst anxiety was not (SMD=0.10; 95% CI -0.18 to 0.39; $p=0.47$). A subgroup analysis demonstrated that statistically significant reductions in depression and stress were limited to group, but not individual, formats. An additional subgroup analysis revealed that 8 CBT sessions or fewer were equally effective as >8 sessions at significantly reducing depression and stress, relative to comparator groups. Furthermore, analysis with independent samples t-tests demonstrated no statistically significant differences between mean changes in depression (MD= 0.79; 95% CI: -0.45 to 2.03; $p=0.21$) and stress (MD= 0.21; 95% CI: -1.43 to 1.85; $p=0.80$) when directly comparing CBT groups of ≤ 8 and >8 sessions.

Conclusions

Group CBT provides small but significant benefits to caregivers' depression and stress. Therapy cost-effectiveness may be improved by limiting therapy to group formats and 8 sessions.

Declaration of interest

None.

Keywords not in title: Alzheimer's Disease, psychotherapy, mental health

Introduction

Prevalence of dementia in the United Kingdom (UK) is >800,000 and expected to rise to 1 million by 2025; this exponential growth is largely attributed to an ageing population (Knapp et al., 2014). Two thirds of these patients are cared for in the community, at least in part, by a total of 670,000 informal caregivers (Knapp et al., 2014). These caregivers (usually friends or family) save the National Health Service (NHS) £11 billion (\$14.5 billion) per annum and are imperative to the sustained provision of quality care (Knapp et al., 2014). This consideration is not confined to the UK; in 2015, Alzheimer's Disease International estimated global dementia prevalence as 46.8 million, with an annual expenditure of £620 billion (\$818 billion) in healthcare costs (Prince et al., 2015). Given this, it is apparent that dementia is a disease which will affect us all, whether that be through direct personal experiences with the disease, or indirect global healthcare considerations.

There is a range of literature consistent in reporting that informal caregivers of dementia patients experience greater rates of specific psychological morbidities than caregivers of patients with other chronic illnesses (such as cancer, stroke or varied physical/cognitive impairments) (González-Salvador, Arango, Lyketsos, & Barba, 1999; Pinquart & Sörensen, 2003; Schulz, O'Brien, Bookwala, & Fleissner, 1995). These psychological morbidities include somatisation, interpersonal sensitivity, depression, anxiety, stress, distress, burden, obsessive-compulsiveness, hostility, phobia, paranoia, psychoticism and development of dementia. Depression, stress and anxiety are particularly important examples of these; previous research has demonstrated a 20% prevalence of clinically significant anxiety and 10% prevalence of depression in this population (Mahoney, Regan, Katona, & Livingston, 2005). Whilst the literature does not provide a clear estimate of the prevalence of stress in dementia caregivers, previous studies have demonstrated strong associations between caregiver stress, anxiety, depression and dementia severity (Ferrara et al., 2008; González-Salvador et al., 1999). Therefore, there is a strong rationale to investigate these specific morbidities when evaluating management strategies for caregivers of dementia patients.

Cognitive behavioural therapy (CBT) is one of several psychosocial interventions recommended for dementia caregivers by the National Institute for Health and Care Excellence (NICE) (NICE, 2012).

Other examples of these include psychoeducation, peer-support groups, telephone or internet

counselling, training courses and family counselling. Notably, NICE do not recommend that dementia caregivers undergo pharmacological treatments for managing psychological or psychosocial stressors resulting from their caregiving roles (NICE, 2012). The main principle of CBT involves identifying the patient's automatic thoughts and underlying beliefs; these form the basis of abstract mental plans, known as schemas, which serve as frameworks for organising, interpreting and responding to information (Curwen, Palmer, & Ruddell, 2000). Patients use an ABC approach in which they are helped to identify the activating events (A), beliefs (B) and consequences (C) of particular schemas and taught a range of techniques to bring about a change in their thinking and behaviour (Clark & Fairburn, 1997). CBT is conducted by a trained therapist and generally comprises between 5 to 20 one-hour weekly sessions, depending on symptom severity (NHS Choices, 2014). Sessions may be conducted individually or in groups, and either face-to-face, by telephone or, less commonly in the UK, by tele-medicine (for example, pre-recorded videos or real time therapy sessions over video).

Previous evidence has demonstrated the effectiveness of CBT in treating conditions such as depression and stress/anxiety-based disorders in a number of distinct patient populations (Butler, Chapman, Forman, & Beck, 2006; Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; Hofmann & Smits, 2008; Olatunji, Cisler, & Deacon, 2010; Otte, 2011; Stewart & Chambless, 2009). However, only two reviews have previously assessed the efficacy of CBT in managing psychological morbidities in caregivers of dementia patients (Pinquart & Sörensen, 2006; Vernooij-Dassen, Draskovic, McCleery, & Downs, 2011); both of these reviews have notable limitations. The earlier review and meta-analysis of 11 studies demonstrated a significant reduction in dementia caregivers' depression (-0.70; 95% CI -1.10 to -0.30; $P < 0.01$) post-CBT (Pinquart & Sörensen, 2006). However, the review investigated CBT alongside several other psychosocial interventions; consequently, study methods and findings specific to CBT were not described in great detail. Data was not presented using forest plots, therefore there was no clear indication of individual study inclusions, effect sizes, confidence intervals or weightings. Additionally, the number of participants in the pooled depression analysis was modest (11 studies; $n=230$) and no descriptions of study characteristics, quality ratings or risk of bias assessments were provided. In summary, the review's findings were limited by a lack of methodological transparency.

More recently, a Cochrane review investigated the effectiveness of cognitive reframing (a sub-component of CBT) for dementia caregivers (Vernooij-Dassen et al., 2011). This review and meta-analysis included 11 studies to evaluate post-intervention improvements in caregivers' anxiety (4 studies; n=515), depression (6 studies; n=595), burden (3 studies; n=490), coping (4 studies; n=613), stress/distress (4 studies; n=585) and reaction to the dependant's behaviour (3 studies; n=265). Significant reductions were evident for anxiety (SMD=-0.21; 95% CI: -0.39 to -0.04; P=0.02), depression (SMD=-0.66; 95% CI: -1.27 to -0.05; P=0.03) and stress/distress (SMD=-0.24; 95% CI: -0.40 to -0.07; P=0.006) (Vernooij-Dassen et al., 2011). However, the findings were limited by the low number of studies included for each outcome, which was likely the result of focussing on cognitive reframing rather than CBT as a whole. This also contributed to the considerable heterogeneity in the depression analysis ($I^2 = 90\%$); consequently, the authors used a random-effects model, which resulted in wide confidence intervals for this summary effect.

Given its reasonable cost per session (£40-100; \$65-130) (NHS Choices, 2014) and NHS resource scarcity, there is a clear rationale to determine the efficacy of CBT relative to alternative treatments that may prove cheaper and/or more effective. As cost-effectiveness is an important consideration for any healthcare provider – particularly those in the private sector, as is commonplace in the United States – this research is also clearly relevant beyond the scope of the UK. We conducted a systematic review and meta-analysis with the primary outcome of determining the immediate and prolonged effectiveness of CBT in reducing depression, stress and anxiety in caregivers of dementia patients. Secondary outcomes included changes to caregivers' quality of life, caregivers' satisfaction with, and adherence to, CBT, and differences in CBT efficacy using distinct formats (one-to-one versus group sessions), delivery methods (telephone versus in-person sessions) and numbers of sessions (≤ 8 or > 8).

METHODS

Protocol and registration

The protocol was registered with PROSPERO (Hopkinson, Reavell, Lane, & Mallikarjun, 2017) and the systematic review was conducted in accordance with PRISMA guidelines (Knobloch, Yoon, & Vogt, 2011).

Eligibility criteria

This review exclusively included interventional study designs. Randomised controlled trials were the preferred study type, although studies where participants were allocated on a first-come-first-serve or voluntary basis were included, providing participant characteristics were statistically similar ($p > 0.05$) between intervention and comparator groups at baseline. These characteristics included gender, age, mean scores for relevant outcome measures, severity of dependant's dementia and average number of hours caregiving per week. Intention-to-treat analyses were used in preference over as-treated analyses. No exclusions were made on the basis of sample size, since exclusions of smaller studies (which have a tendency to present negative findings) would contribute to publication bias.

Participants were 'informal caregivers' (frequently relatives) of one or more dementia patients. Studies were excluded if they included participants who were carers by employment. No exclusion criteria limited caregivers by gender, age, total duration caregiving or current weekly caregiving hours. However, participants were required to be the primary caregiver of the dementia dependant; this was generally self-reported or determined by study cut-offs detailing a minimum number of required hours caregiving per week. Participants had to demonstrate clinically significant levels of depression, anxiety or stress at baseline by satisfying cut-off scores of symptom severity on validated questionnaires. If studies did not require participants to satisfy cut-off scores of symptom severity, they were only included if the mean scores for both the intervention and control groups satisfied these cut-offs. Study participants did not need to have a clinical diagnosis of depression or an anxiety/stress-related disorder. Secondary outcomes were only assessed in studies reporting data related to the primary outcomes.

Studies were only included if their interventions functioned to achieve a change in the caregivers' thoughts, emotions and/or behaviours using CBT or its principles. Therefore, interventions listed as distinct therapeutic models (such as psychoeducation, skills training or problem-solving therapy) were eligible if they utilised CBT principles in their theoretical foundation. Both cognitive and behavioural components had to be described for the study to be included. Studies with significant multicomponent interventions (defined as comprising >25% non-CBT content) were excluded from the review, since this meta-analysis examined the efficacy of CBT. No restrictions were applied to the frequency or duration of intervention sessions. Sessions had to be led by a trained professional, although their format could be individual, group or a mixture. CBT could be delivered via telephone or in-person. Interventions using web or pre-recorded video approaches as the primary delivery method were excluded. The rationale for this was that these formats limit the capacity for participant-therapist interaction; web-based approaches lose the nuance of verbal and non-verbal communication, whilst pre-recorded content does not allow the session to adapt to the participant's individual needs. As telemedicine is not widely employed in the UK, studies using real-time video therapy sessions were also excluded. Studies using third wave CBT interventions such as mindfulness and relaxation were excluded if these components comprised >50% individual sessions or whole programmes. **The 25% and 50% cut-offs used to exclude multicomponent and third wave interventions, respectively, were arbitrary values agreed in consensus by the authors prior to the start of the review.** Comparators comprised waiting-list control, usual treatment or alternative psychotherapeutic interventions.

Search strategy

The search strategies (**Supplementary Resource 1**) were developed by the authors and discussed with an information specialist based at the University of Birmingham. Searches were conducted on MEDLINE (OVID interface, 1946- 26 January 2017), EMBASE (OVID interface, 1974- 26 January 2017), CINAHL (OVID interface, 1937- 26 January 2017), PsycINFO (OVID interface, 1967- 26 January 2017) and the Cochrane Library. Grey literature searches were conducted on the Conference Proceedings Citation Index (28 January 2017) and clinicaltrials.gov (28 January 2017). No language or date restrictions were applied. Additional searches included reference lists of studies identified as eligible for inclusion following full text screening. Citation searches were also conducted on these.

Study selection

Two authors independently screened studies by title and abstract. Full text screening was conducted on remaining studies using the previously defined inclusion and exclusion criteria. Reference searches and citation searches were conducted on studies still eligible after full-text screening. Disagreements of study eligibility were resolved through discussion, mediated by a third author. Where data required to determine eligibility was missing, attempts were made to contact authors for clarification. Foreign language papers were translated by colleagues based at the University of Birmingham, fluent in the appropriate language and with experience in a scientific discipline. Fifteen abstracts required translation from Spanish (n=7), German (n=4), French (n=2), Japanese (n=1) and Korean (n=1); of these, 4 full papers (all Spanish) were fully translated and included in the review (Etxeberria-Arritxabal, Yanguas-Lezaun, Buiza-Bueno, Galdona-Erquicia, & González-Pérez, 2005; Etxeberria Arritxabal et al., 2014; Losada-Baltar, Izal-Fernandez De Troconiz, Montorio-Cerrato, Marquez-Gonzalez, & Perez-Rojo, 2004; Losada, Montorio, Izal, & Marquez Gonzalez, 2005).

Data collection

Data was extracted by the primary author on to a pre-piloted form adapted from the data extraction templates in the Cochrane Protocol Handbook (Cochrane Collaboration, 2011). This form comprised eight sections: general information; eligibility criteria; study procedures; attrition reporting; baseline characteristics; intervention and comparator characteristics; outcomes and measures; and outcome data. A second author independently conducted full data extraction on all included studies' outcome measures and data, and a random 25% (n=6) sample of included studies' characteristics. An agreement rate of >95% was recorded for extracted data and disagreements were resolved through discussion, mediated by a third author.

Risk of bias assessment

Risk of bias was assessed using the Cochrane Collaboration Risk of Bias Tool (Higgins & Green, 2011). This was conducted at the level of the three primary outcomes, rather than for the study as a whole. Study characteristics were rated as 'low risk' (+), 'unclear risk' (?) or 'high risk' (-).

For outcomes with greater than 10 studies, funnel plots were computed by Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, 2014) to assess publication bias through evaluation of power and effect size. Asymmetry was assessed by visual inspection.

Quality assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Higgins & Green, 2011) approach was used to assess the overall quality of evidence for each of the three primary outcomes. Quality ratings comprised rankings of 'very low', 'low', 'moderate' or 'high' for the overall evidence of each outcome.

Data synthesis

Descriptive statistics detailed characteristics for included studies. Outcome measures were combined and a meta-analysis conducted where appropriate. **Where insufficient data was available to conduct a meta-analysis for a specific outcome, individual study results were listed rather than a pooled effect size.** RevMan was used to combine individual study data to determine the pooled effect; the principal summary measures were differences in means (with standard deviations) for depression, stress and anxiety. Since more than one measure was used for each of the primary outcomes, standardised mean differences (SMDs) were used to construct forest plots. Where studies recorded multiple follow-up points for a single outcome, the first data point immediately following completion of the intervention was taken for this purpose. Any additional follow-up measures were used to evaluate prolonged CBT efficacy for short-term (≤ 3 months), medium-term (> 3 months and ≤ 6 months) and long-term (> 6 months) durations. Changes to quality of life were also evaluated through mean differences between pre-post measures from validated questionnaires. Caregiver satisfaction was evaluated through Likert scales with percentages corresponding to each category. Caregiver adherence to the intervention was assessed through the mean session attendance by participants and 5-point Likert scales for homework completion rates (where 0=did not do any homework assignments, 1=did less than half of homework assignments, 2=did half of the homework assignments, 3=did more than half of homework assignments, 4=all homework assignments were done). Changes in CBT efficacy based on differing formats, delivery methods and numbers of sessions were evaluated through subgroup analyses using RevMan forest plots.

Missing data

Mean differences were usually derived from pre and post-intervention data; therefore, pooled standard deviations were estimated using the following formula: $S_{diff} = \sqrt{(S_1^2 + S_2^2 - 2 \times r \times S_1 \times S_2)}$, where S_{diff} is pooled standard deviation, S_1 is baseline standard deviation, S_2 is end-point standard deviation and r is the correlation coefficient between pre-post data (Agency for Healthcare Research and Quality, 2007). A correlation estimate of $r=0.5$ was used where insufficient data was presented; this is a conservative value that the literature advises to reduce the risk of over-estimating intervention (CBT) efficacy (Fu et al., 2008). Average values of $r=0.675$ for intervention group and $r=0.775$ for comparator group were used for the Center for Epidemiologic Studies Depression Scale (CES-D), as data from previous studies provided pooled standard deviations for this measure (Losada, Marquez-Gonzalez, & Romero-Moreno, 2011; Márquez-González, Losada, Izal, Pérez-Rojo, & Montorio, 2007).

Assessment of heterogeneity

The I^2 and Chi square statistics for heterogeneity were calculated using RevMan. Fixed-effects models were preferentially used where outcome studies demonstrated sufficient homogeneity ($I^2 < 50\%$). Where considerable heterogeneity existed between studies ($I^2 > 50\%$), random-effects models were used; this resulted in wider confidence intervals.

Subgroup analyses

Three subgroup analyses were conducted to assess differences in CBT effectiveness based on distinct modalities: in-person versus telephone delivery methods; individual versus group session formats; and low (≤ 8 sessions) versus high (> 8 sessions) number of CBT sessions. A dichotomy of 8 was used for session number, since this was a popular frequency in included studies.

Sensitivity analyses

Where multiple comparators were provided, alternative psychotherapeutic interventions were chosen in preference to waiting-list controls. Therefore, the findings represent CBT efficacy relative to that of a number of different comparator types, including waiting-list control where no alternative intervention was investigated. Consequently, sensitivity analyses were conducted to assess changes to the effect

size from: excluding studies using waiting-list controls; and solely including studies using waiting-list controls. An additional sensitivity analysis was conducted with the exclusion of studies that did not randomize participants to intervention groups.

RESULTS

Electronic and grey literature searches identified 4990 studies. Following the elimination of duplicates and studies with obviously irrelevant titles and abstracts, 164 studies required full text screening. Of these, 22 were eligible for inclusion. Reference and citation searches identified an additional 19 studies; 3 were included following full text screening and the remaining 16 excluded. Therefore, 25 total studies were included in this review (**Figure 1; Table 1**).

Study Characteristics

Studies were conducted across a range of geographical locations, most commonly Spain (n=9) and the USA (n=9), while the remaining studies were conducted in the UK (n=2), Germany (n=2), Canada (n=1), Brazil (n=1) and Italy (n=1). Dates of study publications ranged from 1996 to 2016. Participants were generally family members of dementia patients (often spouses or offspring). Caregiver mean age ranged from 56.6 to 72.6 years. The mean duration of caregiving ranged from 2.2 to 5.5 years and mean caregiving per week from 50.8 to 111.0 hours.

Depression was assessed using 6 different validated questionnaires: Beck Depression Inventory (n=1), Brief Symptom Inventory (n=1), Center for Epidemiologic Studies Depression Scale (n=7), Hopkins Symptom Checklist (n=1), Multiple Affect Adjective Checklist (n=1) and the Patient Health Questionnaire-9 (n=1). Anxiety was also assessed using 6 distinct validated questionnaires: Brief Symptom Inventory (n=1), Hamilton Anxiety Rating Scale (n=1), Hopkins Symptom Checklist (n=1), Hospital Anxiety and Depression Scale (n=2), Profile of Mood States (n=1) and the State-Trait Anxiety Inventory (n=4). Stress was assessed using 2 questionnaires, predominantly the Perceived Stress Scale (n=8) and also the Revised Memory and Behaviour Problems Checklist (n=1).

Two studies (Livingston et al., 2014; Wilz, Meichsner, & Soellner, 2016) were only included for follow-up assessments of the primary outcomes, as they were extension papers providing longer follow-up data for two papers already included in this review. Further details concerning study characteristics are outlined in **Table 1**.

Risk of bias assessment

A high risk of bias rating was allocated to all studies' performance bias, since participants could not be blinded to receiving CBT (**Table 2**). Three studies (Losada-Baltar et al., 2004; Losada et al., 2005; Passoni et al., 2014) also received high risk of bias ratings for randomisation, random sequence generation and allocation concealment, since they allowed first-come-first-serve (Losada-Baltar et al., 2004; Losada et al., 2005) and voluntary (Passoni et al., 2014) allocation of participants to CBT groups. Unclear risk ratings for random sequence generation (n=11), allocation concealment (n=11) and blinding of outcome assessment (n=12) were assigned where methods were not adequately detailed. Five studies received high risk of bias ratings for incomplete reporting of outcome data, largely due to a combination of high attrition rates and use of as-treated analyses, whilst none received high risk ratings for selective reporting. 'Other bias' considerations included study conflicts of interest or the inclusion of participants using adjunctive medications such as antidepressants. No studies received high risk of bias ratings for 'other bias'.

Regarding publication bias, funnel plots for depression (**Supplementary Resource 2A**) and anxiety (**Supplementary Resource 2B**) displayed good overall symmetry. As the outcome of 'stress' included fewer than 10 studies, it was not appropriate to construct a forest plot to assess publication bias (Cochrane Collaboration, 2011). However, reporting bias was assessed for all studies included in this outcome using the Cochrane Collaboration Risk of Bias Tool (**Figure 2**).

Quality assessment

Using the GRADE approach, the overall quality of evidence was 'moderate' for depression and stress, but 'very low' for anxiety. Risk of bias was rated as serious for all three outcomes given the proportion of 'high risk' and 'unclear risk' ratings for study procedures. Inconsistency was not rated as serious for depression or stress, but it was for anxiety since studies displayed widely differing estimates of effect size and considerable heterogeneity was identified ($I^2=73\%$). Indirectness was rated as serious for all three outcomes, since CBT interventions varied in content and comparators were considerably different between studies. Imprecision was only rated as serious for anxiety, since its confidence intervals were wider than those for stress or depression and crossed the line of no effect.

Outcomes

Post-intervention changes to depression, anxiety and stress

Caregivers receiving CBT demonstrated statistically significant reductions in depression (n=12; 995 participants; SMD=-0.34; 95% CI -0.47 to -0.21; p<0.001) (Arango-Lasprilla et al., 2014; Coon, Thompson, Steffen, Sorocco, & Gallagher-Thompson, 2003; Gallagher-Thompson et al., 2003; Gendron, Poitras, Dastoor, & Perodeau, 1996; Kamkhagi et al., 2015; Losada-Baltar et al., 2004; Losada et al., 2015, 2011, 2005; Márquez-González et al., 2007; Quayhagen et al., 2000; Wilz & Soellner, 2016) and stress (n=9; 626 participants; SMD=-0.36; 95% CI -0.52 to -0.20; p<0.001) (Arango-Lasprilla et al., 2014; Bourgeois, Schulz, Burgio, & Beach, 2002; Etxeberria-Arritxabal et al., 2005; Etxeberria Arritxabal et al., 2014; Gallagher-Thompson et al., 2007; Gallagher-Thompson, Gray, Dupart, Jimenez, & Thompson, 2008; Losada-Baltar et al., 2004; Losada et al., 2005; Quayhagen et al., 2000) relative to comparator groups immediately after the intervention end-point (**Figure 2A; Figure 2B; Table 3**). There was no significant difference in caregiver anxiety (n=10; 829 participants; SMD=0.10 (95% CI -0.18 to 0.39; p=0.47) (Akkerman & Ostwald, 2004; Bourgeois et al., 2002; Gendron et al., 1996; Gonyea, Lopez, & Velasquez, 2016; Gonzalez, Polansky, Lippa, Gitlin, & Zauszniewski, 2014; Hébert et al., 2003; Livingston, Barber, Rapaport, Knapp, & Griffin, 2013; Losada-Baltar et al., 2004; Passoni et al., 2014; Quayhagen et al., 2000) between those receiving CBT and the comparator groups, immediately following completion of the intervention (**Figure 2C**).

Short-term follow-up demonstrated further reductions in depression in the CBT group within 3-months completion of the intervention (n=3; SMD=-0.99; 95% CI: -1.35 to -0.64; p<0.001) (Arango-Lasprilla et al., 2014; Losada-Baltar et al., 2004; Losada et al., 2005). Conversely, significant reductions in stress were not maintained at short-term follow-up (n=4; SMD=-0.41; 95% CI: -0.90 to 0.09; p=0.11) (Arango-Lasprilla et al., 2014; Bourgeois et al., 2002; Losada-Baltar et al., 2004; Losada et al., 2005). There was insufficient study data to examine medium- and long-term effects on depression and stress.

Quality of life

Only two studies (Kamkhagi et al., 2015; Wilz et al., 2016) investigated changes to caregivers' quality of life between baseline and post-intervention. Both studies used the WHO Quality of Life (WHO-QoL) assessment and detailed mean improvements post-CBT; MD=13.2 (SD=13.36) (Kamkhagi et al., 2015) and MD=0.64 (SD=17.65) (Wilz et al., 2016). Combining study effects did not demonstrate a significant change in quality of life with CBT relative to comparator (SMD=-0.03; 95% CI: -0.40 to 0.33; p=0.86).

Caregiver satisfaction

Four studies (Bourgeois et al., 2002; Losada et al., 2011, 2005; Wilz et al., 2016) presented data on participants' satisfaction using detailed Likert scales. Wilz's study (Wilz et al., 2016) employed a 5-point Likert scale (where 1=very good, 2=good, 3=average, 4=below average, 5=unsatisfactory), with 71.9% of participants rating the intervention as 'very good' and 27% as 'good'. Bourgeois (Bourgeois et al., 2002) incorporated a 3-point scale (where 1=not at all helpful, 2=somewhat helpful, 3=very helpful); of the 89% of participants who received and returned the questionnaires, 46.6% rated the intervention as 'very helpful', 34.4% as 'somewhat helpful' and 4.7% as 'not at all helpful'. Losada's studies (Losada et al., 2011, 2005) used identical scales ranging from 0 ('not satisfied at all') to 10 ('totally satisfied'), with mean scores of 9.40 (SD=0.69) (Losada et al., 2005) and 9.60 (SD=0.68) (Losada et al., 2011).

Intervention adherence

Three studies (Livingston et al., 2013; Losada et al., 2011; Quayhagen et al., 2000) reported mean participant session attendance: 6.42 (SD=2.71) out of 8 sessions (Livingston et al., 2013); 6.9 (SD=1.1) out of 8 sessions (Quayhagen et al., 2000); and 9.2 (SD=2.7) out of 12 sessions (Losada et al., 2011). Only two studies (Losada et al., 2015; Quayhagen et al., 2000) reported on homework completion (rated from 0-4); mean homework completion scores were 2.2 (SD=0.46) (Quayhagen et al., 2000) and 2.29 (SD=1.34) (Losada et al., 2015).

Subgroup Analyses

Telephone versus in-person CBT delivery

Only 3 studies (Gonyea et al., 2016; Wilz et al., 2016; Wilz & Soellner, 2016) used telephone-based CBT interventions; two of these included identical cohorts (Wilz et al., 2016; Wilz & Soellner, 2016) and the third (Gonyea et al., 2016) used telephone calls as a reinforcement for in-person CBT. Therefore, due to an insufficient number of studies investigating telephone CBT interventions, it was not possible to obtain an accurate estimate of CBT effectiveness from this delivery format for any of the three primary outcomes. However, a subgroup analysis was conducted with the exclusion of studies using telephone CBT to assess the efficacy of in-person CBT. Changes to caregivers' depression (SMD=-0.36; 95% CI: -0.50 to -0.22; $p<0.001$) (Arango-Lasprilla et al., 2014; Coon et al., 2003; Gallagher-Thompson et al., 2003; Gendron et al., 1996; Kamkhagi et al., 2015; Losada-Baltar et al., 2004; Losada et al., 2015, 2011, 2005; Márquez-González et al., 2007; Quayhagen et al., 2000) and anxiety (SMD=0.12; 95% CI: -0.20 to 0.43; $p=0.46$) (Akkerman & Ostwald, 2004; Bourgeois et al., 2002; Gendron et al., 1996; Gonzalez et al., 2014; Hébert et al., 2003; Livingston et al., 2013; Losada et al., 2015; Passoni et al., 2014; Quayhagen et al., 2000) evident in the original forest plots were not significantly influenced by these exclusions.

Individual versus group CBT

Relative to the comparator groups, depression was not significantly reduced by individual CBT, but was by group formats; SMD=-0.04; 95% CI: -0.28 to 0.21; $p=0.76$ (Losada et al., 2015; Quayhagen et al., 2000; Wilz & Soellner, 2016) and SMD=-0.45; 95% CI: -0.61 to -0.30; $p<0.001$ (Arango-Lasprilla et al., 2014; Coon et al., 2003; Gallagher-Thompson et al., 2003; Gendron et al., 1996; Kamkhagi et al., 2015; Losada-Baltar et al., 2004; Losada et al., 2011, 2005; Márquez-González et al., 2007), respectively. This finding was similar for stress; individual CBT did not lead to statistically significant reductions relative to comparators (SMD=-0.20; 95% CI: -0.54 to 0.14; $p=0.26$) (Bourgeois et al., 2002; Gallagher-Thompson et al., 2007; Quayhagen et al., 2000), whereas group CBT did (SMD=-0.41; 95% CI: -0.59 to -0.23; $p<0.001$) (Arango-Lasprilla et al., 2014; Etxeberria-Arritxabal et al., 2005; Etxeberria Arritxabal et al., 2014; Gallagher-Thompson et al., 2008; Losada-Baltar et al., 2004; Losada et al., 2005). Neither individual nor group CBT significantly reduced caregivers' anxiety, relative to a comparator treatment; SMD=0.14; 95% CI: -0.05 to 0.33; $p=0.14$ (Bourgeois et al., 2002; Gonyea et al., 2016; Livingston et al., 2013; Losada et al., 2015; Quayhagen et al., 2000) and

SMD=0.00; 95% CI: -0.59 to 0.58; p=0.99 (Akkerman & Ostwald, 2004; Gendron et al., 1996; Gonyea et al., 2016; Gonzalez et al., 2014; Hébert et al., 2003; Passoni et al., 2014), respectively.

Low (≤ 8) versus high (> 8) CBT frequency

CBT interventions comprising ≤ 8 and > 8 total number of sessions both demonstrated statistically significant reductions in depression; SMD=-0.34; 95% CI: -0.61 and -0.07; p=0.01 (Arango-Lasprilla et al., 2014; Gendron et al., 1996; Losada-Baltar et al., 2004; Losada et al., 2015, 2005; Márquez-González et al., 2007; Quayhagen et al., 2000; Wilz & Soellner, 2016) and SMD=-0.38; 95% CI: -0.56 to -0.19; p<0.001 (Coon et al., 2003; Gallagher-Thompson et al., 2003; Kamkhagi et al., 2015; Losada et al., 2011), respectively. Stress was also significantly reduced relative to comparators in both groups receiving ≤ 8 and > 8 CBT sessions; SMD=-0.43; 95% CI: -0.69 to -0.17; p=0.001 (Arango-Lasprilla et al., 2014; Gallagher-Thompson et al., 2007; Losada-Baltar et al., 2004; Losada et al., 2005; Quayhagen et al., 2000) and SMD=-0.32; 95% CI: -0.52 to -0.11; p=0.003 (Bourgeois et al., 2002; Etxeberria-Arritxabal et al., 2005; Etxeberria Arritxabal et al., 2014; Gallagher-Thompson et al., 2008), respectively. The number of CBT sessions did not significantly influence anxiety levels: ≤ 8 sessions (SMD=0.22; 95% CI: -0.14 to 0.59; p=0.23) (Gendron et al., 1996; Gonzalez et al., 2014; Livingston et al., 2013; Losada et al., 2015; Passoni et al., 2014; Quayhagen et al., 2000) and > 8 sessions (SMD= -0.09; 95% CI: -0.58 to 0.40; p=0.71) (Akkerman & Ostwald, 2004; Bourgeois et al., 2002; Gonyea et al., 2016; Hébert et al., 2003).

An analysis assessed whether there was any statistically significant difference in reduction of depression or stress between CBT groups of ≤ 8 and > 8 sessions (rather than relative to comparators). Following independent samples t-tests, reductions were not significantly different for depression (MD= 0.79; 95% CI: -0.45 to 2.03; p=0.21) and stress (MD= 0.21; 95% CI: -1.43 to 1.85; p=0.80) between the groups of ≤ 8 and > 8 sessions.

Sensitivity analyses

By excluding studies using waiting-list control groups, caregivers receiving CBT maintained significantly reduced levels of depression and stress relative to comparators; SMD=-0.31; 95% CI: -0.45 to -0.18; p<0.001 (Arango-Lasprilla et al., 2014; Coon et al., 2003; Gallagher-Thompson et al.,

2003; Gendron et al., 1996; Kamkhagi et al., 2015; Losada-Baltar et al., 2004; Losada et al., 2015, 2011, 2005; Quayhagen et al., 2000; Wilz & Soellner, 2016) and $SMD=-0.32$; 95% CI: -0.49 to -0.15; $p<0.001$ (Arango-Lasprilla et al., 2014; Bourgeois et al., 2002; Etxeberria-Arritxabal et al., 2005; Gallagher-Thompson et al., 2007, 2008; Losada-Baltar et al., 2004; Losada et al., 2005; Quayhagen et al., 2000), respectively. There was no effect on caregiver anxiety when excluding studies using waiting-list controls; $SMD=0.20$; 95% CI: -0.06 to 0.45; $p=0.13$ (Bourgeois et al., 2002; Gendron et al., 1996; Gonyea et al., 2016; Gonzalez et al., 2014; Hébert et al., 2003; Livingston et al., 2013; Losada et al., 2015; Passoni et al., 2014; Quayhagen et al., 2000).

Inclusion of studies only using waiting-list controls also maintained significant reductions in caregiver depression ($SMD=-0.37$; 95% CI: -0.67 to -0.07; $p=0.01$) (Coon et al., 2003; Losada-Baltar et al., 2004; Losada et al., 2015, 2005; Márquez-González et al., 2007; Quayhagen et al., 2000; Wilz & Soellner, 2016) and stress ($SMD=-0.56$; 95% CI: -0.90 to -0.21; $p=0.002$) (Etxeberria Arritxabal et al., 2014; Losada-Baltar et al., 2004; Losada et al., 2005; Quayhagen et al., 2000) relative to all comparators, but not for anxiety ($SMD=-0.40$; 95% CI: -0.90 to 0.11; $p=0.12$) (Akkerman & Ostwald, 2004; Losada et al., 2015; Quayhagen et al., 2000).

By excluding studies that did not randomise participants (Losada-Baltar et al., 2004; Losada et al., 2005; Passoni et al., 2014), results for depression ($SMD=-0.31$; 95% CI: -0.45 to -0.18; $p<0.001$) (Arango-Lasprilla et al., 2014; Coon et al., 2003; Gallagher-Thompson et al., 2003; Gendron et al., 1996; Kamkhagi et al., 2015; Losada et al., 2015, 2011; Márquez-González et al., 2007; Quayhagen et al., 2000; Wilz & Soellner, 2016), stress ($SMD=-0.28$; 95% CI: -0.46 to -0.11; $p=0.001$) (Arango-Lasprilla et al., 2014; Bourgeois et al., 2002; Etxeberria-Arritxabal et al., 2005; Etxeberria Arritxabal et al., 2014; Gallagher-Thompson et al., 2007, 2008; Quayhagen et al., 2000) and anxiety ($SMD=0.16$; -0.13 to 0.46; $p=0.28$) (Akkerman & Ostwald, 2004; Bourgeois et al., 2002; Gendron et al., 1996; Gonyea et al., 2016; Gonzalez et al., 2014; Hébert et al., 2003; Livingston et al., 2013; Losada et al., 2015; Quayhagen et al., 2000) were not significantly different to the original forest plots.

DISCUSSION

This meta-analysis demonstrated that dementia caregivers who received group CBT experienced small but significant reductions in stress and depression, relative to comparator groups. Conversely, CBT did not result in significant reductions in caregiver anxiety, relative to comparators. These findings expand on previous review evidence through inclusion of newer studies published since late 2009, and present narrower 95% confidence intervals than previously reported of CBT efficacy in reducing depression and stress in this population.

Our findings support Pinguart et al's meta-analysis investigating changes to caregiver depression following CBT (-0.70; 95% CI: -1.10 to -0.30; $P < 0.01$) (Pinguart & Sørensen, 2006) and Vernooij-Dassen et al's Cochrane review assessing changes to caregivers' depression (SMD=-0.66; 95% CI -1.27 to -0.05; $p=0.03$) and stress/distress (SMD=-0.24; 95% CI -0.40 to -0.07; $p=0.006$) following cognitive reframing (Vernooij-Dassen et al., 2011). Although medium and long-term assessments of CBT efficacy were not possible, short-term (≤ 3 months) findings demonstrated further reductions in caregivers' depression, but a failure to maintain these significant reductions in stress. An explanation for this might be that the cognitions and behaviours responsible for depressive symptoms are likely to change, whilst stress is more difficult to address due to the ongoing nature of the problems leading to its development.

Our non-significant finding for changes to anxiety post-CBT contradicts Vernooij-Dassen et al's results (SMD=-0.21; 95% CI -0.39 to -0.04; $p=0.02$) (Vernooij-Dassen et al., 2011), in addition to a considerable evidence base supporting CBT's efficacy in the treatment of anxiety-related disorders (Hofmann & Smits, 2008; Olatunji et al., 2010; Otte, 2011; Pinguart & Sørensen, 2006; Stewart & Chambless, 2009). Consequently, this finding should be interpreted with caution, particularly since the GRADE quality of evidence was 'low' for anxiety as an outcome and there were methodological limitations and uncertainties identified across several studies in the risk of bias assessment of this review (**Table 2**). It could be assumed that our non-significant finding resulted from measuring CBT efficacy relative to alternative psychosocial interventions rather than waiting-list controls. However, a sensitivity analysis to account for this also yielded a non-significant effect on anxiety reduction

(SMD=-0.40; 95% CI:-0.90 to 0.11; p=0.12) (**Table 3**). Gonzalez et al propose that non-significant changes in anxiety post-CBT may be attributed to psycho-educative intervention components, which provide caregivers with knowledge of dementia's pathological course and therefore greater anxiety towards future events (Gonzalez et al., 2014). We believe this explanation to be unlikely, since the studies in this review demonstrate no association between the degree of psycho-educative inclusion and intervention efficacy in anxiety reduction. Alternatively, Losada et al suggest that anxiety is treated more effectively through acceptance-coping rather than change-coping strategies, which are more commonly employed in CBT (Losada et al., 2015). Additionally, we noted that only Akkerman et al's (Akkerman & Ostwald, 2004) study investigated a CBT intervention specifically targeted to reduce anxiety, in addition to being the only study to demonstrate its significant reduction post-CBT (SMD=-1.02; 95% CI: -1.73 to -0.31; p=0.005). Therefore, cognitive-behavioural approaches centred on acceptance-coping strategies and specifically tailored to confront anxiety may demonstrate greater efficacy.

Subgroup analyses revealed that low (≤ 8) and high (> 8 sessions) frequencies of CBT sessions both demonstrated significant reductions in depression and stress relative to comparators. Additional analyses found no significant difference between the mean reduction of either outcome between the two group frequencies. This is an important consideration, particularly for Improving Access to Psychological Therapies (IAPT) services. Referring patients for fewer CBT sessions would result in lower NHS costs and increase the speed and accessibility of service provision without compromising quality of care. Cost effectiveness could be further improved by providing CBT in group rather than individual sessions, particularly since subgroup analyses identified that group CBT formats significantly reduced caregivers' depression and stress relative to comparator, whilst one-to-one formats did not. We propose that this may be accredited to the social and supportive environment which is developed with other members of the therapy group; this may reduce stress or depression in a more holistic manner.

Data on the secondary outcomes of interest were often not reported or were provided in insufficient detail. Pre-post changes to quality of life were only reported in two studies; the pooled effect was non-significant. Findings concerning participant attitudes towards CBT interventions were largely positive,

since participants suggested moderate to high levels of satisfaction in studies reporting this outcome. However, reporting was superficial through Likert-scales; no studies conducted in-depth analyses on attitudes towards specific aspects of CBT, such as accessibility, delivery format, comfortability with therapist or feasibility of homework. Session attendance was high (80%, 86% and 77%), whilst average homework completion was distinctly lower (55% and 57%). Given the low rate of homework completion relative to session attendance, an evaluation of CBT homework content and feasibility is warranted for this population.

Limitations

There was substantial methodological heterogeneity between included studies, predominantly because the primary outcomes were measured using a number of different scales and questionnaires. Study interventions also differed in the individual CBT components that they comprised; importantly, our inclusion criteria also allowed incorporation of some multi-component or third-wave elements. The effect of these elements on overall intervention efficacy was not analysed in our findings, since this would be difficult to achieve given that the degree of component inclusion is not necessarily proportional to its influence on any of the outcomes. Furthermore, the studies were conducted across a wide range of geographic locations, largely comprising Spanish and Hispanic populations across Spain (n=9) and the USA (n=6). Only one study cohort was UK-based (Livingston et al., 2014, 2013); therefore, these findings may not be generalizable to UK-specific populations, given that there are likely to be distinct socioeconomic and cultural differences between these populations. In addition to this, intervention participants differed between studies in regard to their gender proportion, relationship to the dementia patient, duration of caregiving and mean number of hours caregiving per week. These differences may have influenced the relative efficacy of CBT or comparator interventions, and were not considered in the statistical analyses of our data.

There were also notable methodological limitations and uncertainties in a number of studies included in this review (noted in the GRADE and risk of bias assessments in **Table 2**). Specifically, studies were included that: did not specify features of randomisation, blinding or allocation concealment; did not record symptom severity cut-offs for participant inclusion; and did not specify adjunctive use of medications such as antidepressants. These are important factors with the potential to considerably

influence the overall review findings, and should therefore be considered in the interpretation of this review and meta-analysis. Lastly, a number of studies' pooled standard deviations had to be imputed using estimates of pre-post data correlation. In an effort to improve the credibility of statistically significant findings, a conservative correlation estimate of $r=0.5$ was used to reduce the risk of over-estimating intervention (CBT) efficacy (Fu et al., 2008).

Clinical and research implications

General practitioners should consider referral of dementia caregivers to CBT for stress or depression; however, CBT may not be cost-effective for prolonged management of stress in particular. Although this review did not demonstrate improvements to caregivers' anxiety, there is a large evidence base demonstrating that CBT effectively improves anxiety in different patient populations. Therefore, this finding should be interpreted with caution, particularly since it is suggested that tailoring CBT to specifically focus on anxiety or employ acceptance-coping strategies may significantly improve its effectiveness.

Perhaps the most significant findings of this review were that group CBT and interventions comprising ≤ 8 sessions were as effective at reducing depression and stress as individual therapy and those comprising >8 sessions, respectively. Reducing patient referrals (especially for low/moderate symptom severity patients) to 8 sessions and co-ordinating group therapy are strategies that could be utilised by IAPT services to lower NHS costs, reduce strain on CBT services and therefore improve its accessibility.

We recommend that future research should focus on: evaluating differences in effectiveness between tailored and non-tailored CBT interventions, particularly in the treatment of anxiety; evaluation of the prolonged efficacy of CBT in managing depression and stress; qualitative research into dementia caregivers' opinions and attitudes towards CBT accessibility and feasibility; and investigation of CBT effectiveness using alternative delivery methods (particularly telephone or telemedicine), and their suitability for participants exhibiting different symptom severities.

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Supplementary Resources

Supplementary Resource 1: Search strategies used on main electronic databases

Supplementary Resource 2a: Funnel plot of depression studies showing symmetry to discount publication bias

Supplementary Resource 2b: Funnel plot of anxiety studies showing symmetry to discount publication bias

Table 1: Study characteristics for the twenty-five inclusions

			Population Demographics										
Lead Author (Publication Year)	Country	Sample Size	Mean Age	Gender	Ethnicity	Relation	Mean Duration Caregiving	Hours Caring Per Week	Drop-out	Intervention	Comparator	Outcome (Measure)	Outcome Measure Points
(Akkerman & Ostwald, 2004)	USA	38	58.1 (SD=13.8)	Men (13.2%); women (86.8%)	African American (18.4%); Asian (2.6%); Caucasian (65.8%); Hispanic (13.2%)	Family members	3.6y (SD=2.1)	111 (SD=59.4)	3 (7.9%)	'Cognitive behavioural therapy' : Group didactic skills training to address physical, cognitive and behavioral components of caregiver anxiety	Waiting-list control	Anxiety (HAMA)	1. Pre-intervention 2. Post-intervention (week 10) 3. 6-week follow-up (week 16)
(Arango-Lasprilla et al., 2014)	Spain	69	57.5 (SD=11.09)	Men (18.8%); women (81.2%)	Unspecified	Children (52.2%); spouse (18.8%); others (30.0%)	Unspecified	89.3 (SD=51.2)	0 (0%)	'Coping with Frustration' class : Group CBT programme promoting skills such as identification and adaptation of dysfunctional thoughts	Educational control program : Information presented on dementia and its effects on caregiving	Depression (PHQ-9); stress (PSS)	1. Pre-intervention 2. Post-intervention (week 8) 3. 3-month follow-up (week 20).
(Bourgeois et al., 2002)	USA	76	72.6	Men (46.0%); women (54.0%)	White (87.3%); black (12.7%)	Spouse	Unspecified	Unspecified	5 (7.9%)	Patient-change group : 3-hour workshop on antecedent-behaviour-consequence (ABC) relationship, followed by weekly sessions of individual training using the ABC model	1. 'Self-change' group : Workshop on strategies such as increasing pleasant events, problem solving and relaxation techniques 2. Control : General information and referral sources	Anxiety (STAI); stress (PSS)	1. Pre-intervention 2. Post-intervention (week 12) 3. Follow up (3 months after post) 4. Follow up (6 months after post)
(Coon et al., 2003)	USA	169	63.7 (SD=8.4)	Exclusively women	Unspecified	Spouse (56.8%); daughter or in-law (43.2%)	3.3y	Unspecified	39 (33.1%)	Depression management class : Group psychoeducational and skills training, using CBT principles in structure	1. Anger management class : Multicomponent intervention comprising relaxation, cognitive skills and assertiveness training 2. Wait-list control	Depression (MAACL depression subscale)	1. Pre-intervention 2. Post-intervention (4 months) 3. 3-month follow-up (month 7)
(Etxeberria-Arritxabal et al., 2005)	Spain	160	57.5	Men (31.5%); women (68.5%)	Unspecified	Spouse (42.5%); children (49%);	Unspecified	Unspecified	52 (32.5%)	Psychosocial intervention : Group training of skills and strategies aimed at emotional modification	Information course : Psychoeducation strategies for coping with emotions	Stress (PSS)	1. Pre-intervention 2. Post-intervention (1

						others (8.5%)					through CBT theory		year)	
(Etxeberria Arritxabal et al., 2014)	Spain	52	54.8	Men (20.5%); women (79.5%)	Unspecified	Spouse (40.6%); children (57.6%); other (1.8%)	4.9y	50.8	Unspecified		Psychoeducational intervention: Group sessions to aid coping strategies, based on CBT theory	Waiting-list control	Stress (PSS)	1. Pre-intervention 2. Post-intervention (week 10)
(Gallagher-Thompson et al., 2003)	USA	213	57.2	Exclusively women	Latino (42.7%); Anglo (57.3%)	Spouse (37.6%); non-spouse (62.4%)	5y	Unspecified	Unspecified		'Coping with Caregiving': Group CBT mood management skills training	Enhanced support control group: Developed using notions outlined by the Alzheimer's Association, principled on peer support	Depression (CES-D)	1. Pre-intervention 2. Post-intervention (3 months after end of intervention)
(Gallagher-Thompson et al., 2007)	USA	55	61.5	Exclusively women	Exclusively Chinese	Spouse (25.5%); non-spouse (56.4%)	3.7y	Unspecified	10 (18.1%)		'In home behavioural management program': Individual modules including 'behaviour management', 'unhelpful thoughts' and 'communication issues' to help with caregiving stress	Telephone support condition: 12-20 minute support calls over 2 week intervals	Stress (PSS)	1. Pre-intervention 2. Post-intervention (4 months)
(Gallagher-Thompson et al., 2008)	USA	184	57.8	Exclusively women	Hispanic (48.3%); non-Hispanic (51.7%)	Spouse (38.1%); non-spouse (61.9%)	Unspecified	Unspecified	28 (15%)		'Coping with Caregiving' group: Group skills-based sessions using cognitive-behavioural principles	Telephone support condition: 12-20 minute support calls over 2 week intervals	Stress (PSS)	1. Pre-intervention 2. Post-intervention (6 months from baseline)
(Gendron et al., 1996)	USA	35	66.2 (SD=9.5)	Men (34.5%); women (65.7%)	Unspecified	Unspecified	2.2y (SD=16.9)	Unspecified	9 (25.7%)		Cognitive-behavioural skills training group: Group assertion training, problem-solving and cognitive restructuring	Information support group: Video presentations (e.g. health and aging, dementia, respite services) and Q&A sessions with relevant speakers	Depression (HSC); anxiety (HSC); satisfaction with intervention	1. Pre-intervention 2. Post-intervention (8 weeks) 3. Follow-up (3 months) 4. Follow-up (6 months)
(Gonyea et al., 2016)	USA	67	55.7	Men (4.5%); women (95.5%)	Puerto Rican (46.3%); Dominican (41.8%); other (11.9%)	Spouse (25.4%); children (56.7%); other (17.9%)	Unspecified	Unspecified	3 (4.5%)		Cognitive-behavioural therapy group intervention: Group sessions teaching the rationale and use of antecedents-behaviours-consequences; problem-solving approach	Psychoeducational control: Education about memory loss, progression of Alzheimer's disease, home safety and communication	Anxiety (STAI)	1. Pre-intervention 2. Post-intervention (Week 5) 3. Follow-up (3 months)
(Gonzalez et al., 2014)	Spain	102	60.2	Exclusively women	White (43.1%); African	Spouse (23.5%);	Unspecified	Unspecified	9 (8.8%)		Resourcefulness training group: Group cognitive-	Standard care: Received a binder with information on	Anxiety (STAI)	1.Pre-intervention

					American (56.9%)	non-spouse (76.5%))	behavioural skills such as problem identification, coping strategies and decision making	community resources and Alzheimer's educational information		2. Post-intervention (week 6) 3. Follow-up (3 months)
(Hébert et al., 2003)	Canada	144	59.8	Men (20.1%); women (79.8%)	Unspecified	Spouse (61.1%); others (38.9%)	2.8yrs	Unspecified	26 (18.1%)	'Psychoeducative program' : Group cognitive appraisal and coping strategies to improve caregivers' abilities in coping with caregiving-related stress	Support group control: Identical support programme offered by the Alzheimer Society	Anxiety (STAI)	1. Pre-intervention 2. Post-intervention (week 16)
(Kamkhagi et al., 2015)	Brazil	37	59.2	Men (24.3%); women (75.7%)	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified	Psychodynamic group psychotherapy: Group sessions confronting emotions and reinforcing resilience	Body awareness therapy: Psychophysiological reconditioning through touch and movement	Depression (BDI); quality of life (WHO-QoL)	1. Pre-intervention 2. Post-intervention (week 14)
(Livingston et al., 2013)	UK	260	69.0	Men (23.8%); women (68.5%)	White UK (75.4%); white others (5.8%); black and minority (18.5%)	Spouse (41.9%); children (43.5%); other (10.8%)	Unspecified	Unspecified	23 (8.8%)	'Strategies for relatives' program: Individual coping intervention based on cognitive and behavioural training and support	Treatment as usual: Assessment, diagnosis and management following NICE guidance	Anxiety (HADS-A); adherence to intervention	1. Pre-intervention 2. Post-intervention (4 months)
(Livingston et al., 2014)	UK	260	69.0	Men (23.8%); women (68.5%)	White UK (75.4%); white others (5.8%); black and minority (18.5%)	Spouse (41.9%); children (43.5%); other (10.8%)	Unspecified	Unspecified	33 (12.7%)	'Strategies for relatives' program: Individual coping intervention based on cognitive and behavioural training and support	Treatment as usual: Assessment, diagnosis and management following NICE guidance	Anxiety (HADS-A); adherence to intervention	1. Follow-up (20 months after post-intervention)
(Losada-Baltar et al., 2004)	Spain	75	61.1 (SD=1.5)	Men (12.9%); women (87.1%)	Unspecified	Spouses (41.9%); children (48.4%); others (9.7%)	3.8y	83.3	44 (58.7%)	Cognitive behavioural intervention: Individual modification of dysfunctional thoughts for coping with caregiving	1. Problem solving program: Teaching caregivers strategies to deal with daily problems and manage their emotions 2. Waiting-list control	Depression (CES-D); stress (PSS); intervention satisfaction	1. Pre-intervention 2. Post-intervention (week 8) 3. Follow-up (week 20)
(Losada et al., 2005)	Spain	120	62.0	Men (16.4%); women (83.6%)	Unspecified	Spouse (22%); children (70.5%); others (7.5%)	Unspecified	Unspecified	54 (45%)	Cognitive behavioural intervention: Individual modification of dysfunctional thoughts for coping with caregiving	1. Problem solving program: Teaching caregivers strategies to deal with daily problems and manage their emotions 2. Waiting-list control	Depression (CES-D); stress (PSS); intervention satisfaction	1. Pre-intervention 2. Post-intervention (week 8) 3. Follow-up (week 20)
(Losada et al., 2011)	Spain	167	60	Men (17.2%); women (82.8%)	Unspecified	Spouse (35%); children (59.2%); others (5.7%)	4.6y	76.3	49 (29.3%)	Cognitive-behavioural intervention: Group skills training to analyse and change maladaptive thoughts/behaviours	Usual care control: Social and health care centre support	Depression (CES-D)	1. Pre-intervention 2. Post-intervention (week 12)

(Losada et al., 2015)	Spain	135	61.8	Men (15.5%); women (84.5%)	Unspecified	Spouses (40.7%); children (50.4%); others (8.9%)	4y	105.1	41 (30.4%)	Cognitive behavioural therapy: Individual modules of cognitive restructuring, assertive skills, relaxation and increasing pleasant activities	1. Acceptance and commitment therapy: teaches acceptance of internal events, values and actions towards these 2. Minimal support control: 2 hour workshop	Depression (CES-D); anxiety (POMS subscale); intervention satisfaction	1. Pre-intervention 2. Post-intervention (week 8) 3. Follow-up (6 months)
(Márquez-González et al., 2007)	Spain	74	56.6	Men (20.3%); women (79.7%)	Unspecified	Spouse (48.1%); children (46.1%); others (5.8%)	4.2y	34.3	35 (47%)	'Modification of Dysfunctional Thoughts about Caregiving Intervention': Group modules; dysfunctional thoughts/behavioural skills	Waiting-list control	Depression (CES-D)	1. Pre-intervention 2. Post-intervention (week 8)
(Passoni et al., 2014)	Italy	102	58.6	Men (31.4%); women (68.6%)	Unspecified	Unspecified	Unspecified	Unspecified	Unspecified	Cognitive behavioural therapy group: Psychoeducational approach through a manual and group identification/control of dysfunctional thoughts using cognitive restructuring	1. 'Manual only' condition: Received a manual with information on dementia and advice for coping in the home environment 2. Control	Anxiety (STAI)	1. Pre-intervention 2. Post-intervention (6 months from baseline)
(Quayhagen et al., 2000)	USA	98	71.8 (SD=8.1)	Men (38.8%); women (61.2%)	White (93.2%); Hispanic (3.9%); African-American (1.9%); Asian (1.0%)	Exclusively spouses	Unspecified	Unspecified	Unspecified	Dyadic counselling group: Systems and cognitive behavioural approach to assist problem identification, stress reduction, frustration management, communication and conflict resolution	1. Dual seminar group: Group discussion, support and problem solving 2. Early day care group: Respite care and education 3. Waiting-list control	Depression (BSI); anxiety (BSI); stress (BSI)	1. Pre-intervention 2. Post-intervention (week 8)
(Wilz & Soellner, 2016)	Germany	229	62 (SD=9.3)	Men (17.8%); women (82.2%)	Unspecified	Spouse (39.8%); daughters (39.3%); others (20.9%)	5.5y (SD=4.4)	Unspecified	47 (20.5%)	'TeleTAnDem' intervention*: Telephone-based cognitive behaviour therapy sessions (problem-solving, emotional regulation skills, cognitive restructuring)	1. Progressive muscle relaxation group: Written information, DVD and telephone calls teaching relaxation techniques 2. Untreated control group	Depression (CES-D)	1. Pre-intervention 2. Post-intervention (3 months) 3. Follow-up (6 months post-intervention)
(Wilz et al., 2016)	Germany	229	62 (SD=9.3)	Men (17.8%); women (82.2%)	Unspecified	Spouse (39.8%); daughters (39.3%); others (20.9%)	5.5y (SD=4.4)	Unspecified	124 (54.1%)	'TeleTAnDem' intervention*: Telephone-based cognitive behaviour therapy sessions (problem-solving, emotional regulation skills, cognitive restructuring)	1. Progressive muscle relaxation group: Written information, DVD and telephone calls teaching relaxation techniques 2. Untreated control group	Depression (CES-D); quality of life (WHO-QOL-BREF)	1. Pre-intervention 2. Follow-up (2 years)

Table Legend: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BSI, Brief Symptom Inventory; CES-D, Center for Epidemiological Studies Depression Scale; HADS-A, Hospital Anxiety and Depression Scale (anxiety subscale); HADS-D, Hospital Anxiety and Depression Scale (depression subscale); HAMA, Hamilton Anxiety Rating Scale; HSC, Hopkins Symptom Checklist; MBPC, The Revised Memory and Behavior Problems Checklist; PHQ-9, Patient Health Questionnaire-9; POMS, Profile of Mood States; PSS, Perceived Stress Scale; STAI, State-Trait Anxiety Inventory; WHO-QOL, WHO Quality of Life Scale.

Table 2: Risk of bias assessments using the Cochrane Collaboration Risk of Bias Tool

	Randomisation	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting bias (reporting bias)	Other bias
Akkerman 2004	+	?	?	-	+	+	?	?
Arango-Lasprilla 2014	+	+	+	-	+	+	?	?
Bourgeois 2002	+	?	+	-	+	+	?	?
Coon 2003	+	?	?	-	+	-	?	?
Etxeberria Arritxabal 2005	+	?	?	-	?	-	?	?
Etxeberria Arritxabal 2014	+	?	?	-	?	?	?	?
Gallagher-Thompson 2003	+	+	+	-	+	+	+	?
Gallagher-Thompson 2007	+	?	?	-	?	+	+	?
Gallagher-Thompson 2008	+	+	+	-	+	+	+	?
Gendron 1996	+	?	?	-	+	+	?	?
Gonyea 2016	+	?	?	-	?	+	?	?
Gonzalez 2014	+	?	?	-	?	+	?	?
Hebert 2003	+	+	+	-	+	+	?	?
Kamkhagi 2015	+	?	?	-	+	?	?	?
Livingston 2013	+	+	+	-	+	+	+	?
Livingston 2014	+	+	+	-	+	+	+	?
Losada 2005	-	-	-	-	?	-	?	?
Losada 2011	+	+	+	-	+	+	?	?
Losada 2015	+	+	?	-	+	+	?	?
Losada-Baltar 2004	-	-	-	-	?	-	?	?
Marquez-Gonzalez 2007	+	+	+	-	?	+	?	?
Passoni 2014	-	-	?	-	?	+	?	?
Quayhagen 2000	+	?	?	-	?	+	?	?
Wilz & Soellner 2016	+	+	+	-	?	+	?	?
Wilz 2016	+	+	+	-	?	-	+	?

Table 3: Summary of meta-analysis results for depression, anxiety and stress outcomes

Outcome/Focus	Number of Studies	SMD (95% CI)	p value
Depression			
Original plot	12	-0.34 (-0.47 to -0.21)	<0.001
Short-term follow-up	3	-0.99 (-1.35 to -0.64)	<0.001
Medium-term follow-up	-	-	-
Long-term follow-up	-	-	-
Sensitivity analyses			
1. No waiting-list comparators	11	-0.31 (-0.45 to -0.18)	<0.001
2. Waiting-list comparators	7	-0.37 (-0.67 to -0.07)	0.01
3. Only including studies that randomised participants	10	-0.31 (-0.45 to -0.18)	<0.001
Subgroup analyses			
1. Telephone	-	-	-
In-person	11	-0.36 (-0.50 to -0.22)	<0.001
2. Individual	3	-0.04 (-0.28 to 0.21)	0.76
Group	9	-0.45 (-0.61 to -0.30)	<0.001
3. ≤8 sessions	8	-0.34 (-0.61 to -0.07)	0.01
>8 sessions	4	-0.38 (-0.56 to -0.19)	<0.001
Anxiety			
Original plot	10	0.10 (-0.18 to 0.39)	0.47
Short-term follow-up	3	0.11 (0.18 to 0.40)	0.46
Medium-term follow-up	4	-0.01 (-0.20 to 0.19)	0.93
Long-term follow-up	-	-	-
Sensitivity analyses			
1. No waiting-list comparators	9	0.20 (-0.06 to 0.45)	0.13
2. Waiting-list comparators	3	-0.40 (-0.90 to 0.11)	0.12
3. Only including studies that randomised participants	9	0.16 (-0.13 to 0.46)	0.28
Subgroup analyses			
1. Telephone	-	-	-
In-person	9	0.12 (-0.20 to 0.43)	0.46
2. Individual	5	0.14 (-0.05 to 0.33)	0.14
Group	5	0.00 (-0.59 to 0.58)	0.99
3. ≤8 sessions	6	0.22 (-0.14 to 0.59)	0.23
>8 sessions	4	-0.09 (-0.58 to 0.40)	0.71
Stress			
Original plot	9	-0.36 (-0.52 to -0.20)	<0.001
Short-term follow-up	4	-0.41 (-0.90 to 0.09)	0.11
Medium-term follow-up	-	-	-
Long-term follow-up	-	-	-
Sensitivity analyses			
1. No waiting-list comparators	8	-0.32 (-0.49 to -0.15)	<0.001
2. Waiting-list comparators	4	-0.56 (-0.90 to -0.21)	0.002
3. Only including studies that randomised participants	7	-0.28 (-0.46 to -0.11)	0.001

Subgroup analyses			
1. Telephone	-	-	-
In-person	9	-0.36 (-0.52 to -0.20)	<0.001
2. Individual	3	-0.20 (-0.54 to 0.14)	0.26
Group	6	-0.41 (-0.59 to -0.23)	<0.001
3. ≤8 sessions	5	-0.43 (-0.69 to -0.17)	0.001
>8 sessions	4	-0.32 (-0.52 to -0.11)	0.003

Figure 1: PRISMA flow diagram demonstrating the identification, screening and eligibility assessments of studies preceding review inclusion

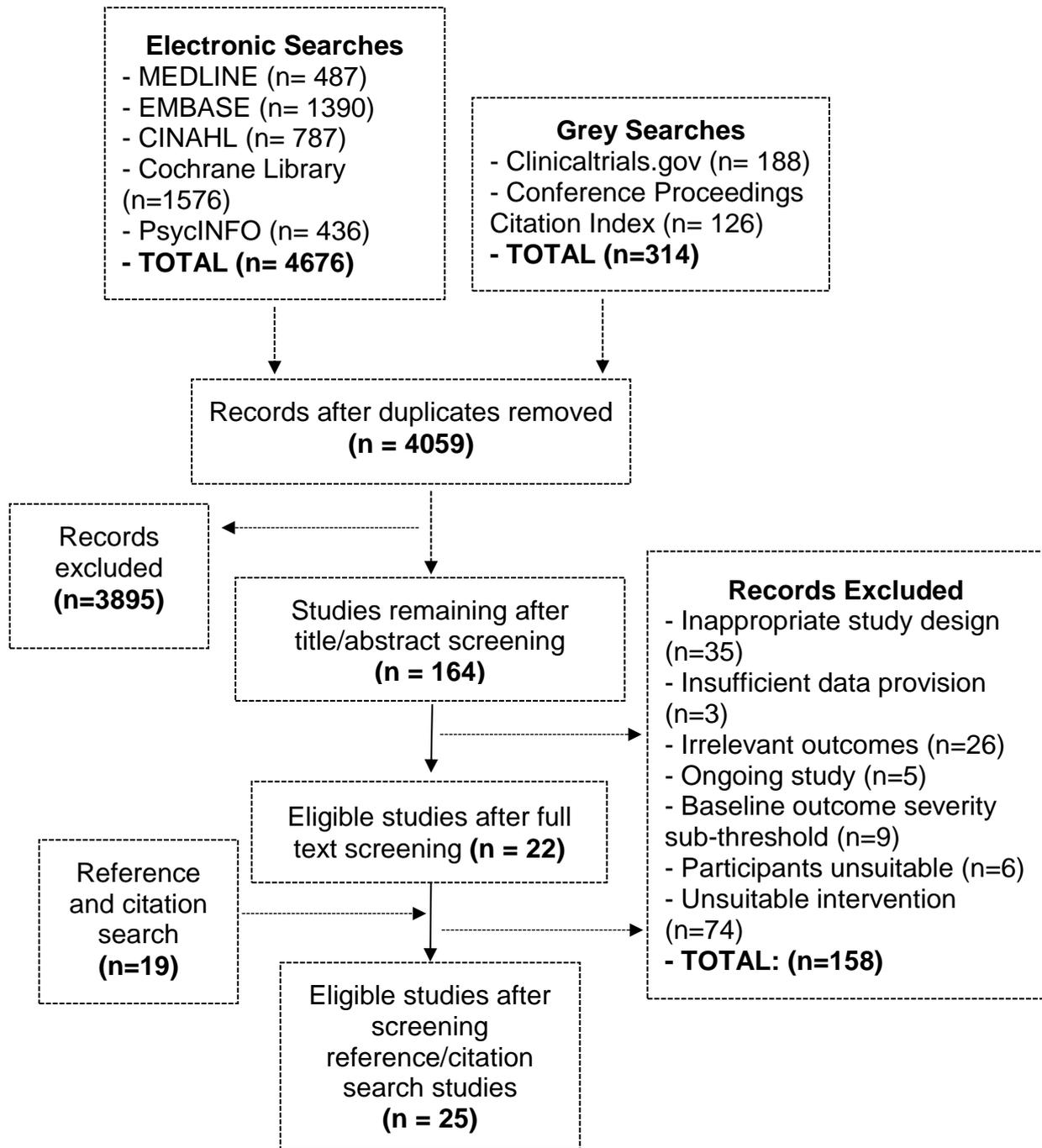


Figure 2A: Forest plot demonstrating a significant reduction in CBT group depression relative to comparator

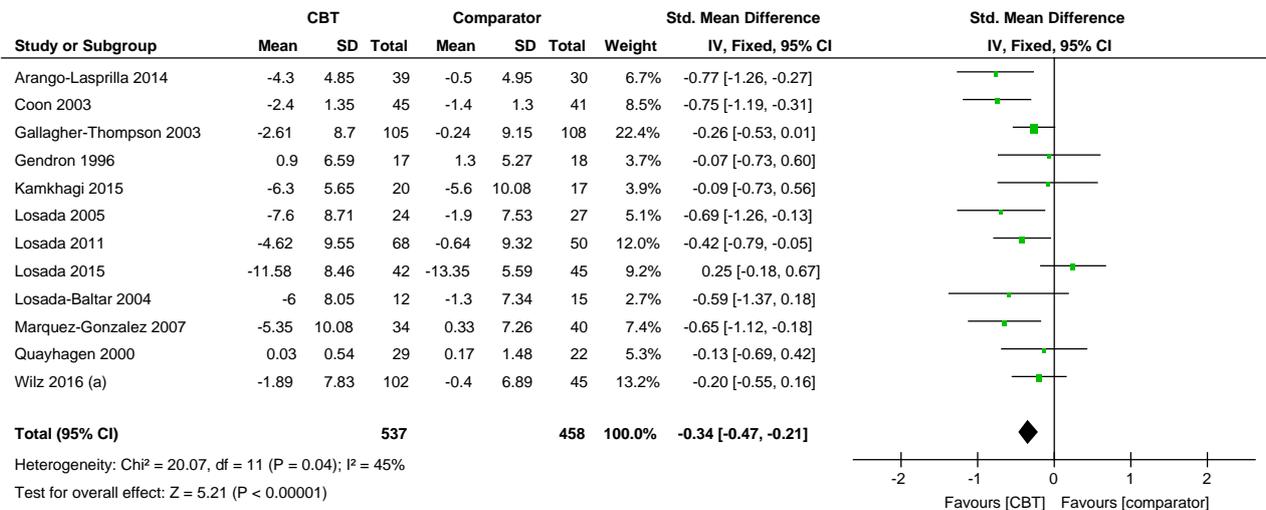


Figure 2B: Forest plot demonstrating a significant reduction in CBT group stress relative to comparator

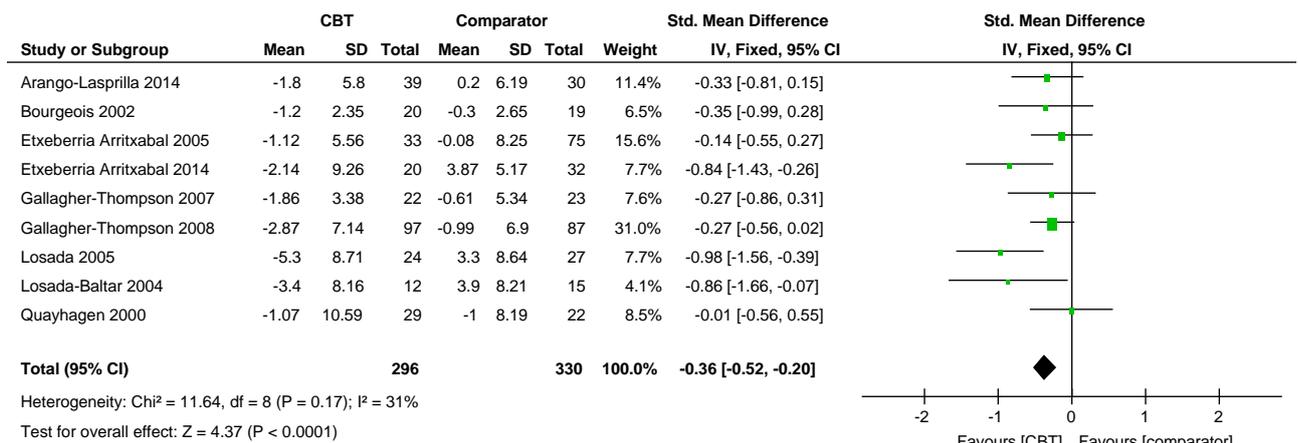
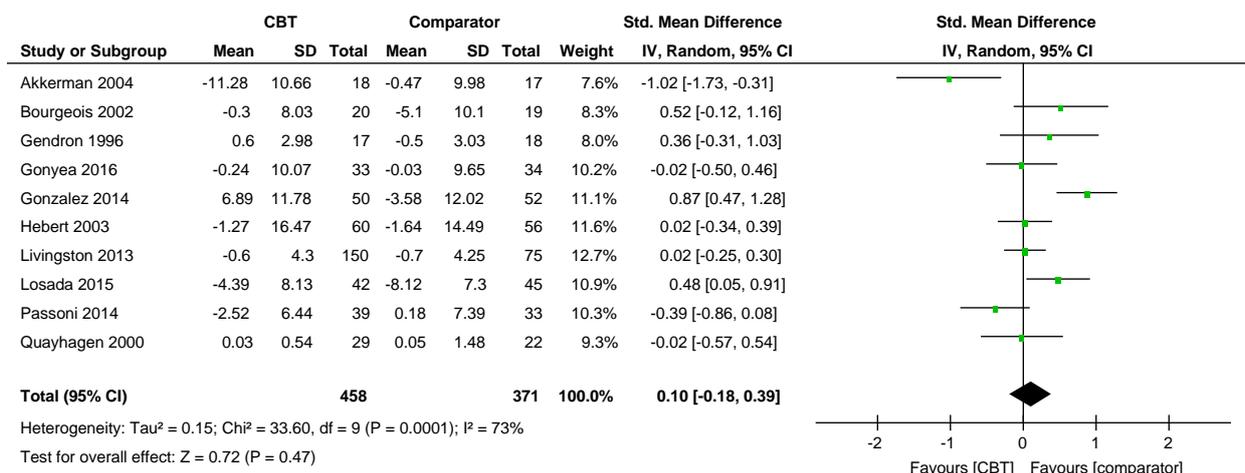


Figure 2C: Forest plot demonstrating no difference in CBT group anxiety relative to comparator



Supplementary Resource 1: Search strategies used on main electronic databases

MEDLINE, EMBASE AND PSYCINFO:

#1.	Exp Dementia
#2.	dement* or alzheimer* or frontotemporal degenerat* or cerebral autosomal recessive arteriopathy or cadasil or carasil or huntington* or korsakoff* or binswanger* or creutzfeld jacob* or creutzfeld jakob or hiv associated neurocognitive disorder* or hiv-associated neurocognitive disorder* or kluver-bucy* or lewy body or pick disease or picks disease or pick's disease or primary progressive aphasia or sundown syndrome or sundowning or cognitively impaired or cognitive impairment
#3.	1 or 2
#4.	Exp Cognitive therapy
#5.	Exp Behavior therapy
#6.	cbt or cognitive behav* or cognitive-behav* or cognitive therap* or behav* therap* or cognitive training or behav* training or cognitive intervention or counsel* or psychosocial intervention or psychosocial therap* or psychosocial support or skills therap* or psychotherap* or support group
#7.	4 or 5 or 6
#8.	carer* or caregiv* or care-giv* or relative or famil* or friend or spouse-caregiver or informal care*
#9.	Exp Depression
#10.	stress or anxi* or psychological morbidit*
#11.	9 or 10
#12.	"3 and 7 and 8 and 11"

CINAHL AND COCHRANE:

#1.	Exp Dementia
#2.	Alzheimer's Disease
#3.	1 or 2
#4.	Exp Cognitive therapy
#5.	Exp Behavior therapy
#6.	CBT
#7.	Cognitiv* behavio#r
#8.	Cognitiv* therap*
#9.	Counsel*
#10.	Support*
#11.	Psychosocial intervention
#12.	Psychosocial therap*
#13.	Psychotherap*
#14.	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
#15.	Carer*
#16.	Caregiv*
#17.	Care-giv*
#18.	Relative
#19.	Famil*
#20.	Friend*
#21.	Spouse
#22.	Informal care*
#23.	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
#24.	Exp Depression
#25.	Stress
#26.	Anxi*
#27.	Psychological morbidit*
#28.	24 or 25 or 26 or 27

#29. | 3 and 14 and 23 and 28

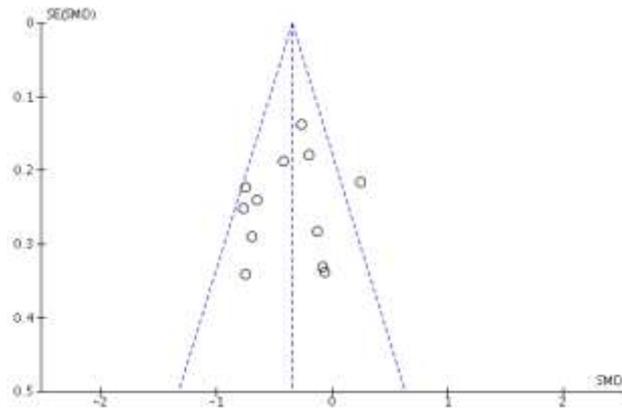
CLINICALTRIALS.GOV:

- #1 | Advanced search
- #2 | Search terms: dementia OR Alzheimer OR carer OR caregiver OR care-giver
- #3 | Conditions: dementia OR Alzheimer
- #4 | Interventions: cognitive behaviour therapy OR cognitive behavior therapy OR cbt OR psychotherapy OR psychosocial OR support OR therapy OR intervention
- #5 | Outcome measures: stress OR anxiety OR depression

CONFERENCE PROCEEDINGS CITATION INDEX:

- #1 | Dementia or Alzheimer
- #2 | Carer OR caregiver
- #3 | Cognitive behaviour therapy OR cognitive behavior therapy OR cbt OR psychotherapy OR psychosocial OR support OR therapy OR intervention
- #4 | Stress OR anxiety OR depression OR psychosocial OR morbidity
- #5 | 1 AND 2 AND 3 AND 4

Supplementary Resource 2A: Funnel plot of depression studies showing symmetry to discount publication bias



Supplementary Resource 2B: Funnel plot of anxiety studies showing symmetry to discount publication bias

